ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2024 February 26; 12(6): 1039-1195

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

PUBLICATION DATE

February 26, 2024

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2024 February 26; 12(6): 1039-1044

DOI: 10.12998/wjcc.v12.i6.1039

ISSN 2307-8960 (online)

EDITORIAL

Lateral clavicle fracture-plating options and considerations

Sathish Muthu, Saravanan Annamalai, Velmurugan Kandasamy

Specialty type: Orthopedics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Jiang N, China

Received: October 19, 2023
Peer-review started: October 19, 2023
First decision: December 19, 2023
Revised: December 21, 2023
Accepted: January 12, 2024
Article in press: January 12, 2024
Published online: February 26, 2024

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Abstract

Clavicle fractures are among the most prevalent types of fractures with numerous treatment strategies that have evolved over time. In the realm of lateral-third clavicle fracture management, several surgical methods are available, with plate and screw constructs being one of the most frequently employed options. Within this construct, numerous choices exist for fixing the fracture. This editorial provides an overview of the common plate options utilized in the management of distal third clavicle fractures underscoring the critical considerations and approaches that guide clinicians in selecting the most appropriate fixation techniques, considering the complex landscape of clavicle fractures and their challenging management.

Key Words: Clavicle fracture; Surgical management; Distal clavicle plating; Superior plating; Anterior plating

Core Tip: The common options utilized in the management of the lateral end of the clavicle remain plate and screw construct. Among the myriad options available, anatomical precontoured locking plates with and without coracoclavicular suture reconstruction remain the commonly used implant. However, considering the cost and ease of molding non-locking reconstruction plates, hook plates have also been used. Among the plate positions, both superior and anterior placement provide similar clinical outcomes with their advantages and disadvantages.

Citation: Muthu S, Annamalai S, Kandasamy V. Lateral clavicle fracture-plating options and considerations. *World J Clin Cases* 2024; 12(6): 1039-1044
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1039.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1039

INTRODUCTION

A clavicle fracture stands out as one of the most frequently occurring fractures, with an overall incidence rate of 64 cases per 100000 individuals each year[1,2]. Over time, a multitude of treatment approaches have been developed to address this issue. Extensive investigation into the therapeutic techniques for clavicle fractures has been conducted, comparing a range of treatment options from conservative to surgical management in numerous studies[3-5]. Furthermore, a mounting body of high-quality evidence from randomized controlled trials has suggested that non-surgical methods may lead to increased initial fracture displacement, higher non-union rates, and longer recovery times, fostering a growing consensus that surgical treatment may be more beneficial for individuals with clavicle fractures especially when it occurs in the lateral one-third[6-8].

Several surgical methods are available for lateral-third clavicle fracture management, with plate and screw constructs representing one of the most employed options[4]. There are a multitude of choices to fix the fracture using this construct. This editorial outlined the key plating choices employed in the management of distal third clavicle fractures and the fixation methods involved in them.

ANATOMICAL PRECONTOURED LOCKING PLATES

Locking plates remain one of the most utilized in the management of fractures due to their advantages, such as strong fixation resulting from the screw-plate locking mechanism and minimal contact with cortical bone, which preserves blood supply[9,10]. The current implementation of the minimally invasive technology that allows plating by percutaneous methods combined with locking plates is considered ideal for bone fixation as it minimizes periosteal stripping and promotes rapid healing[10]. The recent array of region-specific tailor-made locking plates is considered less conspicuous even after the bone union, and its implant removal rates are lower compared to the traditional plates[11]. Numerous anatomically contoured plates available in the market are equipped with lateral screw clusters, designed to secure even small lateral fragments effectively as shown in Figure 1A. In most of these cluster designs, the lateral fragment needs to be around 10 mm to 15 mm in size to accommodate three screws. Some plates come with features such as suture holes or provisions for snugly incorporating a suture button considering the additional option to add a coracoclavicular (CC) suspensory fixation as shown in Figure 1B.

The consideration to incorporate CC fixation along with the plated constructs is decided based on their efficacy demonstrated in various studies. For instance, in a study conducted by Furuhata *et al*[12], it was observed that using a locking plate as the sole treatment for injuries involving ligamentous injury demonstrated an increase in the CC distance, while those without the CC ligament injury did not show this pattern. This finding implied that locking plates on their own may not provide adequate vertical stability when CC ligaments are compromised. From this finding, one might conclude that CC fixation could be bundled with the traditional locking plates in cases with CC ligament injury. However, it is worth noting that no disparities in function scores, union rates, or complications were noted between the two groups. We also have studies reporting comparable results using either of the techniques for injuries with CC ligament injury[13]. In summary, we understand that incorporation of the CC fixation augments the biomechanics of the repair construct in distal clavicular fractures. It is indicated in cases with partial or complete CC ligament injury (Neer 2B and 5), whereas it might not be indicated in cases with intact ligaments (Neer 2A).

Celestre *et al*[14] conducted a study to understand the effect of localization of the plate in the management of midshaft clavicular fractures. They compared anterior *vs* superior locking plates and standard *vs* locking plates. Their findings indicated that resistance to failure due to bending along with axial compression/torsion stiffness was found at its best in the superior location of the locking plate. Hence, a similar positioning and plating option is commonly used for lateral end clavicle fractures. Locked plating has certain limitations, including the potential challenge of achieving sufficient grip when there is lateral comminution and the possibility of implant prominence. In a retrospective analysis encompassing 16 cases of distal clavicle fractures treated with plates and screws, 50% of cases required hardware removal[15]. However, there are also other studies with lower hardware removal rates[16-18]. Hence, caution should be exercised in the selection of these high-profile plates that might necessitate future surgery for implant removal.

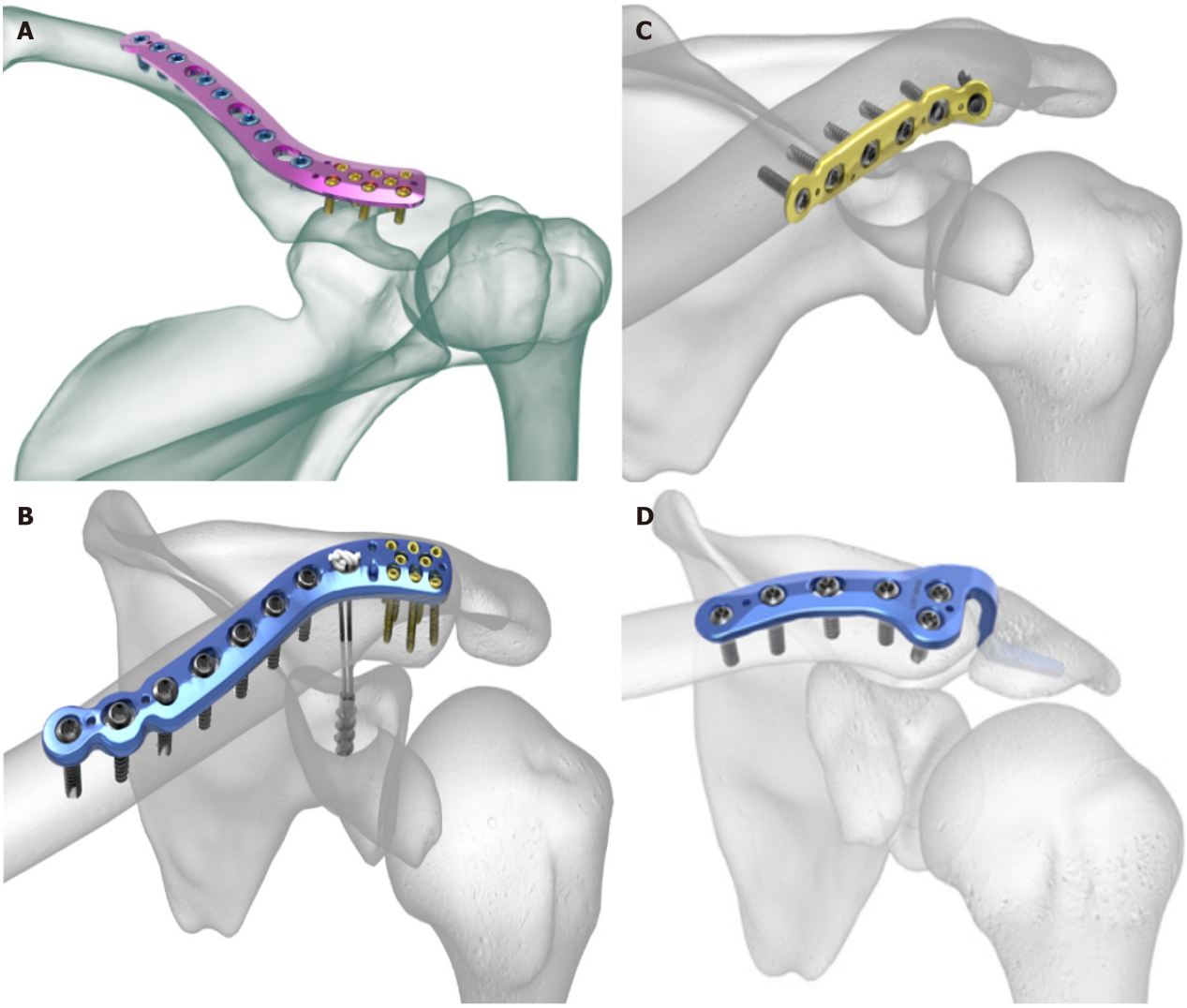

Figure 1 Common plating options in the management of distal end of clavicle fracture. A: Anatomical precontoured locking plate in superior positioning; B: Anatomical precontoured locking plate with coracoclavicular suture construct; C: Anteroinferior positioning of dynamic compression plates; D: Hook plate.

NON-LOCKING PLATES

Apart from the precontoured anatomical locking plates for lateral end clavicle fractures, several other plate types used in surgical management include reconstruction plates, limited-contact dynamic compression plates, and T-plates with comparable clinical results[19-21]. However, clinical results comparing them with the locking plates in the fixation of the lateral end of the clavicle are limited. To enhance the rate and quality of bone union, several factors need to be considered when selecting an implant, including the location of the fracture, level of comminution, quality of the bone, demand, and compliance of the patient. Clavicle bridging plating in osteoporotic bone, while achieving stable fixation, may not provide the same level of rigidity. It is noted that in elderly patients more complications are noted in plated constructs compared to intramedullary pin fixation (Knowles pinning)[22]. Plate loosening is the drawback of dynamic compression plate fixation, especially in patients with poor bone quality. The locking plate technology mitigates this complication of the plate and screws loosening with a robust fixation construct even in osteopenic bone[22].

HOOK PLATES

Hook plates are a construct with a hook placed in the lateral aspect beneath the acromion process anchored to the medial clavicle fragment with cortical screws as shown in Figure 1C. This approach offers a means of stabilizing fracture of the distal end of the clavicle with small lateral fragments which is not sufficient for locking compression plates to act upon. In addition to the horizontal stability, the hook plates ensure vertical stability so that they can be used in fractures with CC ligament injury with coracoid fractures where CC fixation is impractical. Another additional advantage is noted in cases of sustaining type 2B fractures where there is no need for extensive dissection around the trapezoid ligament. A 98% fusion rate and comparable functional outcomes were noted in patients using hook plates and other fixation methods

based on a recent meta-analysis[23].

However, there are concerns related to the use of hook plates. The hook can potentially cause erosion in the inferior aspect of the acromion, which was noted in 27% of cases[23]. There are some reported cases of acromial fractures[24,25]. As a result, it is generally recommended to remove the implant after the fracture has fully healed, adding to the overall treatment burden. Factors that increase the risk of acromion osteolysis include the placement of the hook in a position that points anteriorly by remaining posterior to the acromioclavicular joint[26], hook misalignment where it does not match with the slope of the acromion that results in point loading instead of even distribution of the load across the entire hook[27], and allowing shoulder abduction and flexion of more than 90 degrees before plate removal. Further, delayed removal of the implant after the fracture has fully healed (*e.g.*, due to noncompliance or loss to follow-up) is a consideration with hook plates. Furthermore, it is advisable to exercise caution when contemplating the use of hook plates in cases where preexisting acromial erosion is noted as seen in cuff tear arthropathy, weak bone due to osteoporosis, or the presence of an os acromiale[28].

The mismatch noted between the hook and the acromion slope can be mitigated by pliable plates that could be manually contoured or the utilization of recent plates with a 15-degree inferior angulation[29]. The posterior aspect of the acromioclavicular joint capsule can be used as a reference point during the surgical procedure to make sure that the hook is placed in the ideal anterior position. Other noted complications with this device include arthrosis of the acromioclavicular joint (22%), fractures of the clavicle just medial to the plate (22%), and shoulder stiffness or subacromial impingement (47%)[23]. We also noted reports of tears in the rotator cuff muscles in a magnetic resonance imaging study. However, they did not find any complete tears among the 39 cases investigated[30]. Finally, another study noted that 66% of demanding athletes did not return to sports with the utilization of the hook plates[31]. Although this inference is from a single study, one could reserve the utilization of the hook plates in select cases of elite athletes rather than for everyone.

PLATE POSITIONING

One key component in the utilization of the plating for the lateral end of the clavicle is the choice of plate position. The two commonly involved plate positioning methods include anterior inferior plating and superior plating as shown in Figure 1A and D, respectively. Multiple studies have sought to compare the merits of these two approaches for clavicle fractures. However, the optimal positioning of the plate and choice of the plate type remains a subject of debate. Zlowodzki *et al*[3] reported an association between superior plating and increased postoperative symptoms. In contrast, Robertson *et al*[8] argued in favor of superior plating over anterior inferior plating, citing advantages in fracture fixation for routine activities[32]. Furthermore, previous research has highlighted the superior biomechanical stability of superior plating[14]. Conversely, evidence has suggested a reduced risk of implant prominence and injury to the neurovascular bundle with anterior inferior plating[33-35].

COMPARATIVE STUDIES

In general, comparable results were noted in studies comparing the locked plating or CC fixation or hook plates in the management of lateral clavicular fractures with respect to the bone union and final functional outcomes. Despite removing the events of hardware removal, hook plates did not perform well in early functional outcomes and complications compared to the other two[23]. When coming to the locking plates with and without the addition of the CC constructs, either comparable results or results favoring additional CC fixation were noted[16,36].

Upon analyzing 59 studies with 2284 patients in a meta-analysis comparing different distal clavicle fixation techniques, hook plates did not perform well in Constant scores compared to CC fixation. However, in comparison to locking plates and K-wire constructs no difference was noted. All the included constructs gave comparable union rates[13]. Maximum complications including hardware failure, infection, and wound complications were noted in the K-wire constructs in the form of tension banding followed by hook plates with the second-highest rate of complications. Similar results were noted in another systematic review comparing the complications with hook plates compared to locked plating and CC fixation[23]. Their recommendation was to make a surgical fixation using CC fixation alone, followed closely by a locking plate with CC fixation.

Recent case reports on using reconstruction plates in the anteroinferior position for lateral end clavicle fracture without comminution with a single screw in the lateral fragment added to the interest[37]. Recently published biomechanical studies showcased the superiority of lateral locking plates with orthogonal anteroposterior locking screw placement in the lateral fragment to negate the need for CC stabilization[38]. Further, clinical trial results demonstrated comparable clinical outcomes at 1 year in hook plate and locking plate constructs[17]. However, quicker recovery was noted in the locking plate fixation[39]. Similar results were noted between the locking and non-locking plate constructs[40].

CONCLUSION

This literature review provided recommendations on implant selection in the management of lateral end clavicle fractures. Wherever possible, utilization of fixation techniques such as CC fixation and trans-osseous suturing should be instigated to avoid complications due to hardware prominence since similar union rates were recorded compared to other

plating techniques. We did not note sufficient evidence to recommend arthroscopic-assisted CC fixation or adding CC fixation to the traditional locking plates over the commonly performed open fixation techniques. However, considering the evidence from the biomechanical studies, addition of CC fixation could be considered in high-demand athletes. On the other hand, one should not consider K-wires and tension bands as their first choice due to the inferior results compared to other techniques. In fracture patterns with small lateral fragments that could not be stabilized by other means, hook plates remain an ideal candidate. However, due to the higher complication rate compared to other techniques hook plates are less suitable for routine use. Hence, the selection of the ideal fixation construct is determined by the size of the lateral fragment and the status of CC ligaments.

FOOTNOTES

Author contributions: Muthu S performed the conceptualization, data curation, data analysis, manuscript writing, and revision of the manuscript; Annamalai S performed the data analysis, manuscript writing, and revision of the manuscript; Kandasamy V performed data analysis, manuscript writing, and revision of the manuscript.

Conflict-of-interest statement: The authors declare having no conflicts of interest.

Country/Territory of origin: India

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S-Editor: Chen YL
L-Editor: Filipodia
P-Editor: Xu ZH

REFERENCES

1 **Nordqvist A**, Petersson C. The incidence of fractures of the clavicle. *Clin Orthop Relat Res* 1994; 127-132 [PMID: 8131324]
2 **Postacchini F**, Gumina S, De Santis P, Albo F. Epidemiology of clavicle fractures. *J Shoulder Elbow Surg* 2002; **11**: 452-456 [PMID: 12378163 DOI: 10.1067/mse.2002.126613]
3 **Zlowodzki M**, Zelle BA, Cole PA, Jeray K, McKee MD; Evidence-Based Orthopaedic Trauma Working Group. Treatment of acute midshaft clavicle fractures: systematic review of 2144 fractures: on behalf of the Evidence-Based Orthopaedic Trauma Working Group. *J Orthop Trauma* 2005; **19**: 504-507 [PMID: 16056089 DOI: 10.1097/01.bot.0000172287.44278.ef]
4 **McKee RC**, Whelan DB, Schemitsch EH, McKee MD. Operative versus nonoperative care of displaced midshaft clavicular fractures: a meta-analysis of randomized clinical trials. *J Bone Joint Surg Am* 2012; **94**: 675-684 [PMID: 22419410 DOI: 10.2106/JBJS.J.01364]
5 **Robinson CM**, Goudie EB, Murray IR, Jenkins PJ, Ahktar MA, Read EO, Foster CJ, Clark K, Brooksbank AJ, Arthur A, Crowther MA, Packham I, Chesser TJ. Open reduction and plate fixation versus nonoperative treatment for displaced midshaft clavicular fractures: a multicenter, randomized, controlled trial. *J Bone Joint Surg Am* 2013; **95**: 1576-1584 [PMID: 24005198 DOI: 10.2106/JBJS.L.00307]
6 **Robinson CM**, Court-Brown CM, McQueen MM, Wakefield AE. Estimating the risk of nonunion following nonoperative treatment of a clavicular fracture. *J Bone Joint Surg Am* 2004; **86**: 1359-1365 [PMID: 15252081 DOI: 10.2106/00004623-200407000-00002]
7 **Hill JM**, McGuire MH, Crosby LA. Closed treatment of displaced middle-third fractures of the clavicle gives poor results. *J Bone Joint Surg Br* 1997; **79**: 537-539 [PMID: 9250733 DOI: 10.1302/0301-620x.79b4.7529]
8 **Robertson GA**, Wood AM. Return to sport following clavicle fractures: a systematic review. *Br Med Bull* 2016; **119**: 111-128 [PMID: 27554280 DOI: 10.1093/bmb/ldw029]
9 **Perren SM**. Evolution and rationale of locked internal fixator technology. Introductory remarks. *Injury* 2001; **32** Suppl 2: B3-B9 [PMID: 11718733 DOI: 10.1016/s0020-1383(01)00120-6]
10 **Haidukewych GJ**. Innovations in locking plate technology. *J Am Acad Orthop Surg* 2004; **12**: 205-212 [PMID: 15473672 DOI: 10.5435/00124635-200407000-00001]
11 **Jiang H**, Qu W. Operative treatment of clavicle midshaft fractures using a locking compression plate: comparison between mini-invasive plate osteosynthesis (MIPPO) technique and conventional open reduction. *Orthop Traumatol Surg Res* 2012; **98**: 666-671 [PMID: 23000038 DOI: 10.1016/j.otsr.2012.02.011]
12 **Furuhata R**, Matsumura N, Udagawa K, Oki S, Morioka H. Residual coracoclavicular separation after plate fixation for distal clavicle fractures: comparison between fracture patterns. *JSES Int* 2021; **5**: 840-845 [PMID: 34505093 DOI: 10.1016/j.jseint.2021.04.017]
13 **Uittenbogaard SJ**, van Es LJM, den Haan C, van Deurzen DFP, van den Bekerom MPJ. Outcomes, Union Rate, and Complications After Operative and Nonoperative Treatments of Neer Type II Distal Clavicle Fractures: A Systematic Review and Meta-analysis of 2284 Patients. *Am J Sports Med* 2023; **51**: 534-544 [PMID: 34779668 DOI: 10.1177/03635465211053336]
14 **Celestre P**, Roberston C, Mahar A, Oka R, Meunier M, Schwartz A. Biomechanical evaluation of clavicle fracture plating techniques: does a locking plate provide improved stability? *J Orthop Trauma* 2008; **22**: 241-247 [PMID: 18404033 DOI: 10.1097/BOT.0b013e31816c7bac]
15 **Davis BP**, Shybut TB, Coleman MM, Shah AA. Risk factors for hardware removal following operative treatment of middle- and distal-third

clavicular fractures. *J Shoulder Elbow Surg* 2021; **30**: e103-e113 [PMID: 32663568 DOI: 10.1016/j.jse.2020.06.034]

16 **Zhang C**, Huang J, Luo Y, Sun H. Comparison of the efficacy of a distal clavicular locking plate versus a clavicular hook plate in the treatment of unstable distal clavicle fractures and a systematic literature review. *Int Orthop* 2014; **38**: 1461-1468 [PMID: 24728348 DOI: 10.1007/s00264-014-2340-z]

17 **Orlandi TV**, Rogers NS, Burger MC, King PR, Lamberts RP. A prospective randomized controlled trial comparing plating augmented with coracoclavicular fixation and hook plate fixation of displaced distal-third clavicle fractures. *J Shoulder Elbow Surg* 2022; **31**: 906-913 [PMID: 35158065 DOI: 10.1016/j.jse.2022.01.114]

18 **Gutman MJ**, Joyce CD, Patel MS, Lazarus MD, Horneff JG. Outcomes Following Different Fixation Strategies of Neer Type IIB Distal Clavicle Fractures. *Arch Bone Jt Surg* 2022; **10**: 160-165 [PMID: 35655745 DOI: 10.22038/ABJS.2021.54472.2718]

19 **Kaipel M**, Majewski M, Regazzoni P. Double-plate fixation in lateral clavicle fractures-a new strategy. *J Trauma* 2010; **69**: 896-900 [PMID: 20093980 DOI: 10.1097/TA.0b013e3181bedf28]

20 **Teimouri M**, Ravanbod H, Farrokhzad A, Sabaghi J, Mirghaderi SP. Comparison of hook plate versus T-plate in the treatment of Neer type II distal clavicle fractures: a prospective matched comparative cohort study. *J Orthop Surg Res* 2022; **17**: 369 [PMID: 35907856 DOI: 10.1186/s13018-022-03261-8]

21 **Kingsly P**, Sathish M, Ismail NDM. Comparative analysis of functional outcome of anatomical precontoured locking plate versus reconstruction plate in the management of displaced midshaft clavicular fractures. *J Orthop Surg (Hong Kong)* 2019; **27**: 2309499018820351 [PMID: 30798707 DOI: 10.1177/2309499018820351]

22 **Lee YS**, Lin CC, Huang CR, Chen CN, Liao WY. Operative treatment of midclavicular fractures in 62 elderly patients: knowles pin versus plate. *Orthopedics* 2007; **30**: 959-964 [PMID: 18019991 DOI: 10.3928/01477447-20071101-13]

23 **Asadollahi S**, Bucknill A. Hook Plate Fixation for Acute Unstable Distal Clavicle Fracture: A Systematic Review and Meta-analysis. *J Orthop Trauma* 2019; **33**: 417-422 [PMID: 31335567 DOI: 10.1097/BOT.0000000000001481]

24 **Chiang CL**, Yang SW, Tsai MY, Kuen-Huang Chen C. Acromion osteolysis and fracture after hook plate fixation for acromioclavicular joint dislocation: a case report. *J Shoulder Elbow Surg* 2010; **19**: e13-e15 [PMID: 20303294 DOI: 10.1016/j.jse.2009.12.005]

25 **Lee SJ**, Eom TW, Hyun YS. Complications and Frequency of Surgical Treatment with AO-Type Hook Plate in Shoulder Trauma: A Retrospective Study. *J Clin Med* 2022; **11** [PMID: 35207299 DOI: 10.3390/jcm11041026]

26 **Shimpuku E**, Uchiyama Y, Imai T, Takatori N, Watanabe M. Relationship Between Subacromial Bone Erosion and Hook Position of Clavicular Plate in Distal Clavicle Fractures. *J Orthop Trauma* 2022; **36**: e243-e249 [PMID: 34744153 DOI: 10.1097/BOT.0000000000002301]

27 **Kirsch JM**, Blum L, Hake ME. Distal Clavicle Fractures: Open Reduction and Internal Fixation With a Hook Plate. *J Orthop Trauma* 2018; **32** Suppl 1: S2-S3 [PMID: 29985889 DOI: 10.1097/BOT.0000000000001214]

28 **Sun Q**, Cai M, Wu X. Os acromiale may be a contraindication of the clavicle hook plate: case reports and literature review. *BMC Musculoskelet Disord* 2021; **22**: 969 [PMID: 34809638 DOI: 10.1186/s12891-021-04841-1]

29 **Li G**, Liu T, Shao X, Liu Z, Duan J, Akileh R, Cao S, Jin D. Fifteen-degree clavicular hook plate achieves better clinical outcomes in the treatment of acromioclavicular joint dislocation. *J Int Med Res* 2018; **46**: 4547-4559 [PMID: 30092651 DOI: 10.1177/0300060518786910]

30 **Hackenberger J**, Schmidt J, Altmann T. [The effects of hook plates on the subacromial space--a clinical and MRT study]. *Z Orthop Ihre Grenzgeb* 2004; **142**: 603-610 [PMID: 15472772 DOI: 10.1055/s-2004-832323]

31 **Bhatia DN**, Page RS. Surgical treatment of lateral clavicle fractures associated with complete coracoclavicular ligament disruption: Clinico-radiological outcomes of acromioclavicular joint sparing and spanning implants. *Int J Shoulder Surg* 2012; **6**: 116-120 [PMID: 23493665 DOI: 10.4103/0973-6042.106224]

32 **Hulsmans MH**, van Heijl M, Houwert RM, Timmers TK, van Olden G, Verleisdonk EJ. Anteroinferior versus superior plating of clavicular fractures. *J Shoulder Elbow Surg* 2016; **25**: 448-454 [PMID: 26671776 DOI: 10.1016/j.jse.2015.09.005]

33 **Collinge C**, Devinney S, Herscovici D, DiPasquale T, Sanders R. Anterior-inferior plate fixation of middle-third fractures and nonunions of the clavicle. *J Orthop Trauma* 2006; **20**: 680-686 [PMID: 17106378 DOI: 10.1097/01.bot.0000249434.57571.29]

34 **Kloen P**, Sorkin AT, Rubel IF, Helfet DL. Anteroinferior plating of midshaft clavicular nonunions. *J Orthop Trauma* 2002; **16**: 425-430 [PMID: 12142833 DOI: 10.1097/00005131-200207000-00011]

35 **Sinha A**, Edwin J, Sreeharsha B, Bhalaik V, Brownson P. A radiological study to define safe zones for drilling during plating of clavicle fractures. *J Bone Joint Surg Br* 2011; **93**: 1247-1252 [PMID: 21911537 DOI: 10.1302/0301-620X.93B9.25739]

36 **Salazar BP**, Chen MJ, Bishop JA, Gardner MJ. Outcomes after locking plate fixation of distal clavicle fractures with and without coracoclavicular ligament augmentation. *Eur J Orthop Surg Traumatol* 2021; **31**: 473-479 [PMID: 32949271 DOI: 10.1007/s00590-020-02797-x]

37 **Zhao XL**, Liu YQ, Wang JG, Liu YC, Zhou JX, Wang BY, Zhang YJ. Distal clavicle fractures treated by anteroinferior plating with a single screw: Two case reports. *World J Clin Cases* 2023; **11**: 7502-7507 [PMID: 37969449 DOI: 10.12998/wjcc.v11.i30.7502]

38 **Jo OI**, Almond M, Rupansinghe HS, Ackland DC, Ernstbrunner L, Ek ET. Biomechanical analysis of plating techniques for unstable lateral clavicle fractures with coracoclavicular ligament disruption (Neer type IIB). *J Shoulder Elbow Surg* 2023; **32**: 695-702 [PMID: 36535559 DOI: 10.1016/j.jse.2022.11.008]

39 **Wang HK**, Liang LS, He RG, Su YB, Mao P, Hu JZ. Comparative analysis of locking plates versus hook plates in the treatment of Neer type II distal clavicle fractures. *J Int Med Res* 2020; **48**: 300060520918060 [PMID: 32314621 DOI: 10.1177/0300060520918060]

40 **Uchiyama Y**, Handa A, Omi H, Hashimoto H, Shimpuku E, Imai T, Takatori N, Watanabe M. Locking versus nonlocking superior plate fixations for displaced midshaft clavicle fractures: A prospective randomized trial comparing clinical and radiografic results. *J Orthop Sci* 2021; **26**: 1094-1099 [PMID: 33176960 DOI: 10.1016/j.jos.2020.09.017]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2024 February 26; 12(6): 1045-1049

DOI: 10.12998/wjcc.v12.i6.1045

ISSN 2307-8960 (online)

EDITORIAL

Tumor deposits in axillary adipose tissue in patients with breast cancer: Do they matter?

Muhammed Mubarak, Rahma Rashid, Shaheera Shakeel

Specialty type: Pathology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Gu GL, China; Jiang L, China

Received: November 13, 2023
Peer-review started: November 13, 2023
First decision: January 9, 2024
Revised: January 10, 2024
Accepted: January 31, 2024
Article in press: January 31, 2024
Published online: February 26, 2024

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Abstract

Tumor deposits (TDs) are defined as discrete, irregular clusters of tumor cells lying in the soft tissue adjacent to but separate from the primary tumor, and are usually found in the lymphatic drainage area of the primary tumor. By definition, no residual lymph node structure should be identified in these tumor masses. At present, TDs are mainly reported in colorectal cancer, with a few reports in gastric cancer. There are very few reports on breast cancer (BC). For TDs, current dominant theories suggest that these are the result of lymph node metastasis of the tumor with complete destruction of the lymph nodes by the tumor tissue. Even some pathologists classify a TD as two lymph node metastases for calculation. Some pathologists also believe that TDs belong to the category of disseminated metastasis. Therefore, regardless of the origin, TDs are an indicator of poor prognosis. Moreover, for BC, sentinel lymph node biopsy is generally used at present. Whether radical axillary lymph node dissection should be adopted for BC with TDs in axillary lymph nodes is still inconclusive. The present commentary of this clinical issue has certain guiding significance. It is aimed to increase the awareness of the scientific community towards this under-recognized problem in BC pathology.

Key Words: Breast cancer; Tumor deposits; Lymph node metastasis; Staging

Core Tip: In this editorial, we comment on a case report by Li *et al* published in the recent issue of the *World Journal of Clinical Cases*. According to the authors of this article, the objective of presenting this case was to bring to attention the detection and reporting of tumor deposits (TDs) in breast cancer. TDs are being increasingly detected and reported in many other types of surgically resected cancers, but in this editorial article, we will focus specifically on the significance of TDs in primary breast carcinoma.

Citation: Mubarak M, Rashid R, Shakeel S. Tumor deposits in axillary adipose tissue in patients with breast cancer: Do they matter? *World J Clin Cases* 2024; 12(6): 1045-1049
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1045.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1045

INTRODUCTION

In this editorial, we comment on a case report by Li *et al*[1] published in the recent issue of the *World Journal of Clinical Cases*. According to the authors of this article, the objective of presenting this case was to bring to attention the detection and reporting of tumor deposits (TDs) in breast cancer (BC). TDs are being increasingly detected and reported in many other types of surgically resected cancers, but in this editorial article, we will focus specifically on the significance of TDs in primary BC.

TDs are defined as discrete, irregular clusters of tumor cells lying in the soft tissue adjacent to but separate from the primary tumor (PT), and are usually found in the draining lymphatic area of the PT. By convention, no remaining lymph node (LN) structure should be discernible in these TDs. These can only be diagnosed on histopathological examination (Figures 1-3). These are an important prognostic feature in a variety of malignant tumors. Their origin, classification, and significance are still not completely understood. Moreover, their definitions have also changed, particularly in colorectal cancer (CRC). They are often thought to be derived from metastasis by the lymphatic route, but origins from venous and perineural pathways of tumor spread have also been suggested. Some pathologists even classify a TD as two LN metastases (LNMs) for calculation. Other pathologists believe that TDs belong to the category of disseminated metastases. In the vast majority of cases of TDs, the origin is not discernible at the time of their detection. Regardless of their origin, development, or evolution, TDs serve as an indicator of poor prognosis.

TDs were first described by Gabriel *et al*[2] in 1935 in CRC. However, these were not given due importance for staging or prognostic purposes for CRC or other tumor types for a considerable time. The interest in TDs was revived around the late 1990s and early 2000s when several studies were conducted on the significance of TDs in CRCs and gastric cancer (GC) reporting a significant adverse effect on prognosis[3-6]. TDs have also been detected in many other malignant tumors, particularly of the gastrointestinal tract[7-10]. More recently, these have also been studied in head and neck cancers [11].

In GC and CRC, TDs in the LN drainage area have been identified as independent prognostic factors. In CRC, TDs have been incorporated into the TNM staging system[12]. However, the categorization, and incorporation in staging, of TDs have changed considerably in each TNM Edition since their original description in TNM 5, and the terminology remains controversial. Currently, these are assigned N1c in the absence of associated LNMs[13]. Currently, TDs are not included in the clinical or pathological staging of any other cancer including BC.

BC is the most common malignant tumor in women throughout the world[14]. BC staging is performed using the TNM staging system and is a major determinant of prognosis. According to the most recent TNM staging updates, invasive tumor masses within axillary fat distinct from identifiable LN structure, are designated as regional LNMs (pN)[15]. However, such lesions appear to be analogous to TDs of carcinomas of other tissues described in the literature, and they may represent TDs of BCs. In BC, very few studies have been done on this pathological lesion.

Li *et al*[1] have done a commendable job in reporting this case of isolated TD in the axillary area in a 70-year-old female patient with primary BC. However, given the clinical course and follow-up of this particular patient, TD does not fulfill the role of a prognostic marker in this case as the follow-up is short and no adverse outcome occurred till the last follow-up in this patient. However, they have succeeded in provoking thoughts and consideration of this lesion in BC through their case study and literature review.

In an interesting study on TDs in BC, Durak *et al*[16] retrospectively reviewed 145 cases of BC, detected and managed between 2001 and 2006 at a single center for determining the frequency of TDs. TDs were found in 42 (29%) of cases. After exclusion of TDs from the number of metastatic LNs, the pN stage of nine patients changed. On multivariate exploration, the presence of TDs was independently and significantly associated with distant metastases. The probability of distant metastases was 3.3-fold higher in patients with TDs. TDs were also associated with shortened patient survival time as compared to those patients without TDs, although this was not statistically significant. The results from the study by Durak *et al*[16] show that TDs are found in a significant proportion of patients with BC and that their presence should alert the clinician regarding the possibility of distant metastases. They concluded that the presence of TDs, the study of which is neither time-consuming nor requires additional sophisticated tests, should be included in the pathology reports for possible use in clinical practice and future research. There is a need for more such studies, particularly multicenter studies, to reflect better on the importance of TDs in BC patients.

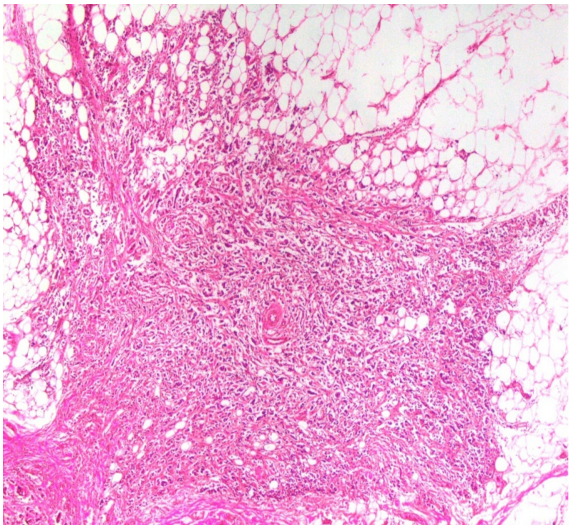

Figure 1 An irregular mass of tumor tissue in the axillary adipose tissue. There is no lymphoid tissue at the periphery or within the tumor mass. This will qualify for designation of tumor deposits in axillary fat (H&E, × 40).

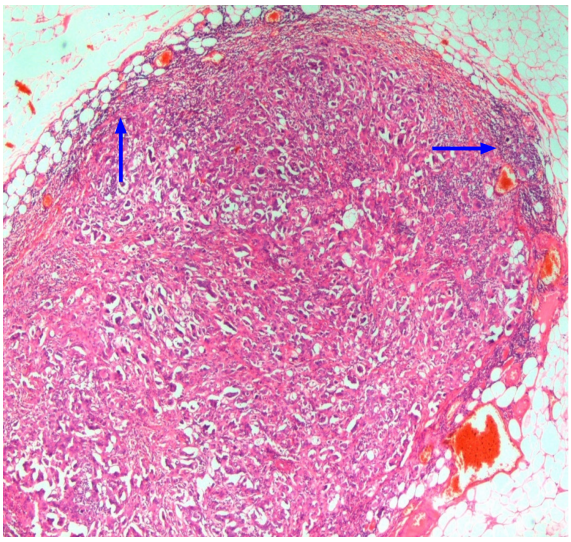

Figure 2 In this case, the tumor mass is exhibiting ovoid or reniform configuration consistent with lymph node metastasis. Focally, some lymphoid tissue can be seen at the periphery of the tumor mass (arrows). This will not qualify for the designation of tumor deposits (H&E, × 40).

In another large single-center study, Mamtani *et al*[17] studied the clinical significance of extranodal TDs (ETDs) in 1114 consecutive patients with T1T2cN0 invasive BCs. Overall, 113 (10.1%) patients had ETDs in this study. It was found that among T1-T2cN0 patients with sentinel LNMs, ETDs in axillary fat were strongly associated with ≥ 4 positive non-sentinel lymph nodes at axillary LN dissection (ALND). They concluded that even among the patients who may otherwise meet the criteria for the omission of ALND, the detection of ETDs in axillary fat warrants consideration of ALND.

More similar studies are warranted by other investigators on patients with BC to delineate the long-term prognosis of TDs in this type of malignancy. At the same time, a modified Delphi process can also be initiated to streamline the diagnostic approach to TDs detection in BCs as in CRCs[18].

CONCLUSION

In summary, in this era of precision diagnostics and personalized medicine, the interest has been rekindled in TDs in many types of malignant tumors including BC. There is a need to report these and perform large, multicenter, prospective studies to detect their clinical significance in improving patient care.

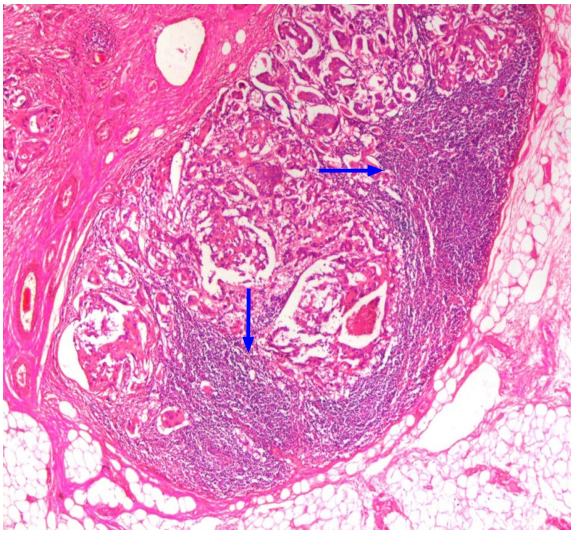

Figure 3 Another example of lymph node metastasis in the axilla. A variably thick rim of lymphoid tissue can be seen at the periphery of the tumor mass (arrows). This will also not qualify for tumor deposits designation (H&E, ×40).

FOOTNOTES

Author contributions: All authors contributed equally to the preparation of this manuscript; Mubarak M conceived the idea; Mubarak M and Rashid R did literature search; Mubarak M wrote the preliminary draft; Mubarak M, Rashid R, and Shakeel S critically reviewed and approved the manuscript.

Conflict-of-interest statement: All authors declare that they have no conflict-of-interest.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Li T**, Zhang WH, Liu J, Mao YL, Liu S. Isolated axillary tumor deposit consistent with primary breast carcinoma: A case report. *World J Clin Cases* 2023; **11**: 7718-7723 [PMID: 38078126 DOI: 10.12998/wjcc.v11.i31.7718]
2 **Gabriel WB**, Dukes C, Bussey HJR. Lymphatic spread in cancer of the rectum. *Br J Surg* 1935; **1**: 395-413 [DOI: 10.1002/bjs.1800239017]
3 **Nagtegaal ID**, Knijn N, Hugen N, Marshall HC, Sugihara K, Tot T, Ueno H, Quirke P. Tumor Deposits in Colorectal Cancer: Improving the Value of Modern Staging-A Systematic Review and Meta-Analysis. *J Clin Oncol* 2017; **35**: 1119-1127 [PMID: 28029327 DOI: 10.1200/JCO.2016.68.9091]
4 **Kobayashi T**, Ishida M, Miki H, Hatta M, Hamada M, Hirose Y, Sekimoto M. Significance of desmoplastic reactions on tumor deposits in patients with colorectal cancer. *Oncol Lett* 2023; **25**: 1 [PMID: 36419753 DOI: 10.3892/ol.2022.13587]
5 **Pu H**, Pang X, Fu J, Zheng R, Chen Y, Zhang D, Fang X. Significance of tumor deposits combined with lymph node metastasis in stage III colorectal cancer patients: a retrospective multi-center cohort study from China. *Int J Colorectal Dis* 2022; **37**: 1411-1420 [PMID: 35595975 DOI: 10.1007/s00384-022-04149-z]
6 **Zheng P**, Lai C, Yang W, Chen Z. Prognostic Significance of Tumor Deposits in Combination with Lymph Node Metastasis in Stage III Colon Cancer: A Propensity Score Matching Study. *Am Surg* 2020; **86**: 164-170 [PMID: 32167047]
7 **Mirkin KA**, Kulaylat AS, Hollenbeak CS, Messaris E. Prognostic Significance of Tumor Deposits in Stage III Colon Cancer. *Ann Surg Oncol* 2018; **25**: 3179-3184 [PMID: 30083832 DOI: 10.1245/s10434-018-6661-9]
8 **Liang Y**, Wu L, Liu L, Ding X, Wang X, Liu H, Meng J, Xu R, He D, Liang H. Impact of extranodal tumor deposits on prognosis and N stage in gastric cancer. *Surgery* 2019; **166**: 305-313 [PMID: 31221435 DOI: 10.1016/j.surg.2019.04.027]
9 **Liang Y**, Chang S, Guo H, Man Q, Zang F, Gao S. Presence of tumor deposits is an indicator of poor prognosis in patients with pancreatic ductal adenocarcinoma. *Am J Cancer Res* 2023; **13**: 1970-1984 [PMID: 37293176]

10 **Zhou M**, Yang W, Zou W, Yang J, Zhou C, Zhang Z, Wang Y, Zhang J, Li G, Xia F. Prognostic significance of tumor deposits in radically resected gastric cancer: a retrospective study of a cohort of 1915 Chinese individuals. *World J Surg Oncol* 2022; **20**: 304 [PMID: 36138439 DOI: 10.1186/s12957-022-02773-1]

11 **González-Vallejo L**, Blanco-Sainzdelamaza J, Querejeta-Ayerra A, Chiesa-Estomba C. Extracapsular nodal extension and tumor deposits in head and neck squamous cell carcinoma. *Cancer Rep (Hoboken)* 2023; **6**: e1897 [PMID: 37700458 DOI: 10.1002/cnr2.1897]

12 **Chen P**, Zuo ZL, Feng LB, Chen XL, Hu XY, Liu Q, Xia D. Questioning the staging of tumor deposits of colorectal cancer in the eighth edition of the TNM classification: validation by prognosis. *Int J Clin Exp Pathol* 2019; **12**: 4309-4318 [PMID: 31933832]

13 Delattre JF, Selcen Oguz Erdogan A, Cohen R, Shi Q, Emile JF, Taieb J, Tabernero J, André T, Meyerhardt JA, Nagtegaal ID, Svrcek M. A comprehensive overview of tumour deposits in colorectal cancer: Towards a next TNM classification. *Cancer Treat Rev* 2022; **103**: 102325 [PMID: 34954486 DOI: 10.1016/j.ctrv.2021.102325]

14 **Sapna F**, Athwal PSS, Kumar M, Randhawa S, Kahlon S. Therapeutic Strategies for Human Epidermal Receptor-2 Positive Metastatic Breast Cancer: A Literature Review. *Cureus* 2020; **12**: e9522 [PMID: 32905036 DOI: 10.7759/cureus.9522]

15 Teichgraeber DC, Guirguis MS, Whitman GJ. Breast Cancer Staging: Updates in the AJCC Cancer Staging Manual, 8th Edition, and Current Challenges for Radiologists, From the AJR Special Series on Cancer Staging. *AJR Am J Roentgenol* 2021; **217**: 278-290 [PMID: 33594908 DOI: 10.2214/AJR.20.25223]

16 **Durak MG**, Canda T, Yilmaz B, Seker NS, Kokkoz SE, Alicikus ZA, Akturk N, Gorken IB, Ellidokuz H, Sevinc AI, Saydam S, Sarioglu S. Prognostic Importance of Tumor Deposits in the Ipsilateral Axillary Region of Breast Cancer Patients. *Pathol Oncol Res* 2019; **25**: 577-583 [PMID: 30368727 DOI: 10.1007/s12253-018-0515-4]

17 **Mamtani A**, Barrio AV, Goldman DA, Wen HY, Vincent A, Morrow M. Extranodal Tumor Deposits in the Axillary Fat Indicate the Need for Axillary Dissection Among T1-T2cN0 Patients with Positive Sentinel Nodes. *Ann Surg Oncol* 2020; **27**: 3585-3592 [PMID: 32488512 DOI: 10.1245/s10434-020-08632-1]

18 **Lord A**, Brown G, Abulafi M, Bateman A, Frankel W, Goldin R, Gopal P, Kirsch R, Loughrey MB, Märkl B, Moran B, Puppa G, Rasheed S, Shimada Y, Snaebjornsson P, Svrcek M, Washington K, West N, Wong N, Nagtegaal I. Histopathological diagnosis of tumour deposits in colorectal cancer: a Delphi consensus study. *Histopathology* 2021; **79**: 168-175 [PMID: 33511676 DOI: 10.1111/his.14344]

World Journal of Clinical Cases

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World J Clin Cases 2024 February 26; 12(6): 1050-1062

DOI: 10.12998/wjcc.v12.i6.1050

ISSN 2307-8960 (online)

MINIREVIEWS

New strategies in the diagnosis and treatment of immune-checkpoint inhibitor-mediated colitis

Tsvetelina Velikova, Boris Krastev, Milena Gulinac, Miroslav Zashev, Vasko Graklanov, Milena Peruhova

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Tulassay Z, Hungary; Zheng L, China

Received: October 27, 2023
Peer-review started: October 27, 2023
First decision: December 6, 2023
Revised: December 20, 2023
Accepted: January 19, 2024
Article in press: January 19, 2024
Published online: February 26, 2024

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Abstract

Immune-checkpoint inhibitor-mediated colitis (IMC) is an increasingly recognized adverse event in cancer immunotherapy, particularly associated with immune checkpoint inhibitors (ICIs) such as anti-cytotoxic T-lymphocyte antigen-4 and anti-programmed cell death protein-1 antibodies. As this revolutionary immunotherapy gains prominence in cancer treatment, understanding, diagnosing, and effectively managing IMC becomes paramount. IMC represents a unique challenge due to its immune-mediated nature and potential for severe complications. However, a precise picture of IMC pathophysiology is currently unavailable. Therefore, we aimed to summarize the existing data while acknowledging the need for further research. This comprehensive review explores the mechanisms underlying ICIs, gastrointestinal adverse effects, and, in particular, IMC's incidence, prevalence, and features. Our review also emphasizes the importance of recognizing IMC's distinct clinical and histopathological features to differentiate it from other forms of colitis. Furthermore, this paper highlights the urgent

need for evolving diagnostic methods, therapeutic strategies, and a multidisciplinary approach to effectively manage IMC.

Key Words: Immune-checkpoint inhibitors; Immune-checkpoint inhibitor-mediated colitis; Inhibitor-mediated colitis management; Immunotherapy-associated colitis; Checkpoint inhibitor-induced colitis; Gastrointestinal adverse effects; Checkpoint inhibitor toxicity; Inhibitor-mediated colitis therapy

Core Tip: Diagnosing and managing immune-checkpoint inhibitor-mediated colitis (IMC) is essential for optimizing the benefits of cancer immunotherapy. This review underscores the importance of accurate diagnosis, differentiating IMC from other forms of colitis, and tailoring treatment strategies for optimal outcomes. Multidisciplinary approaches, including endoscopy, histopathology, and immune profiling, are crucial in diagnosing IMC. Treatment options range from corticosteroids to immunosuppressants, and a personalized approach is often required. Collaborative efforts between oncologists, gastroenterologists, and pathologists are critical to effectively manage this emerging immune-related adverse event.

Citation: Velikova T, Krastev B, Gulinac M, Zashev M, Graklanov V, Peruhova M. New strategies in the diagnosis and treatment of immune-checkpoint inhibitor-mediated colitis. *World J Clin Cases* 2024; 12(6): 1050-1062
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1050.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1050

INTRODUCTION

Over the past two decades, immune checkpoint inhibitors (ICIs) have transformed the landscape of cancer treatment, offering a glimmer of hope for patients battling a spectrum of malignancies[1]. By targeting immune checkpoint molecules like cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein-1 (PD-1), these immunotherapies harness their own defenses to combat cancer cells. The clinical success of ICIs is nothing short of remarkable, ushering in an era where some individuals previously deemed incurable experience profound and durable remissions[2].

However, this therapeutic paradigm shift has not been without its challenges. While ICIs show great promise, they also constrain immune-related adverse events (irAEs)[3]. These irAEs can affect nearly any organ or system, ranging from skin rashes to endocrine dysfunction. Gastrointestinal (GI) toxicities are the most common and clinically significant. Immune-checkpoint inhibitor-mediated colitis (IMC) stands out as a prominent and often formidable challenge[4,5].

IMC is characterized by inflammation of the colonic mucosa and presents as one of the most frequent irAEs associated with ICIs[6]. This inflammatory condition arises when the delicate balance between immune activation and tolerance in the gut is disrupted, leading to dysregulated immune responses. The exact pathophysiological mechanisms of IMC are still under intense investigation, but emerging evidence indicates that gut mucosal immunity plays a pivotal role in its development[7]. Figure 1 presents some of the hypothesized immunological mechanisms of IMC development.

Precise incidence and prevalence of IMC can be challenging to ascertain, primarily due to variations in rates between different ICIs and the absence of standardized reporting mechanisms. However, some estimates have provided insights. Contemporary studies suggest that the incidence of GI irAEs, including IMC, occurs in 0.3% to 7.0% of treated patient, approximately 15%-25% of patients treated with anti-CTLA-4 agents and 5%-10% of patients treated with anti-PD-1/PD-L1 agents[8,9]. The prevalence of IMC may be underestimated, as not all cases reach clinical significance[10].

The clinical features of IMC are broad and varied, encompassing a spectrum of presentations from mild diarrhea to severe colitis. The diversity of symptoms and the potential for rapid progression underscore the need for early detection and prompt intervention. Clinicians, oncologists, and researchers must comprehensively understand IMC to optimize patient care[7,11].

This review aims to present the mechanisms of action of ICIs and existing data on IMC risk factors, diagnosis, clinical, endoscopic, and serologic features, and treatment strategies, including medications, biologics, fecal microbiota transplantation (FMT), surgery, *etc*, and the emergence of novel biomarkers and treatments, leading to more effective management of this irAE and improved patient outcomes.

SEARCH STRATEGY

We conducted a comprehensive literature review to identify relevant studies focusing on IMC diagnosis and treatment. The search was performed in key databases, including PubMed, Scopus, and Medline. A combination of Medical Subject Headings (MESH) terms and free-text words was used to maximize the search results.

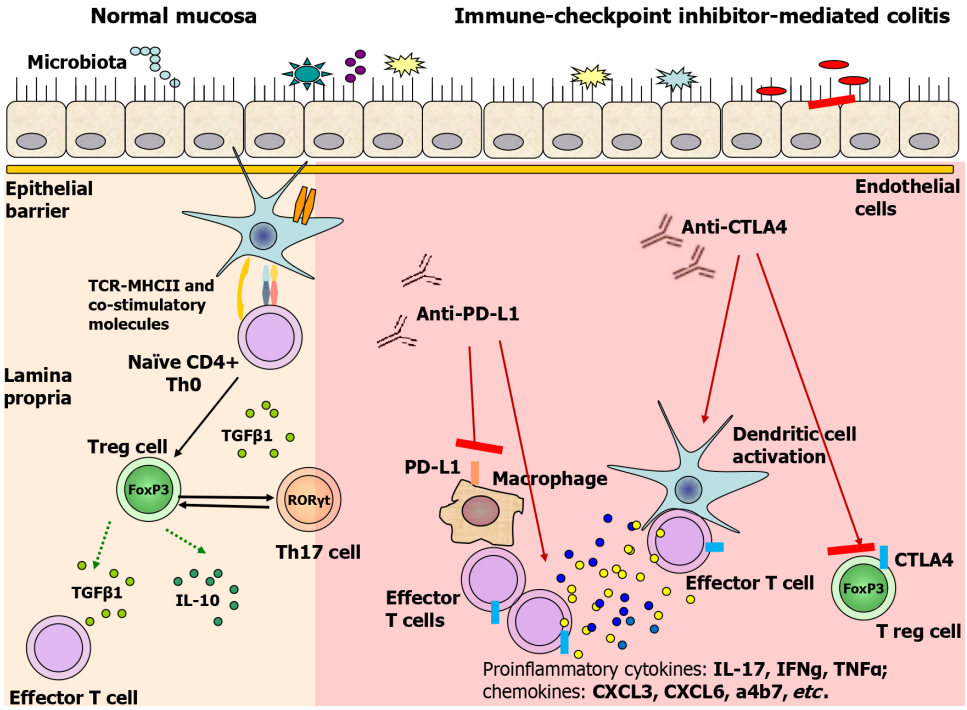

Figure 1 Proposed immune-mediated pathways of immune checkpoint inhibitor-mediated colitis. In normal mucosa, T regulatory cells are fully capable of inducing tolerance while balancing pro-inflammatory cells and molecules (*i.e.* Th17 cells) and anti-inflammatory molecules (*i.e.* IL-10, TGFb, *etc*). By blocking cytotoxic T-lymphocyte antigen-4 (CTLA-4) or programmed cell death ligand-1, immune checkpoint inhibitors promote pro-inflammatory cytokines, chemokine production, Treg differentiation inhibition, and suppression of IL-10 and TGFb secretion. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier (https://smart.servier.com/) is licensed under a Creative Commons Attribution 4.0 Unported License (Supplementary material). CTLA-4: Cytotoxic T-lymphocyte antigen-4; PD-L1: Programmed cell death ligand-1.

The search terms used were as follows: ("Immune-Checkpoint Inhibitor" OR "Checkpoint Inhibitor") AND ("Colitis"); ("Immune-Checkpoint Inhibitor-Mediated Colitis" OR "Immunotherapy-Associated Colitis") AND ("Diagnosis Strategies" OR "Diagnostic Approaches"); ("Immune-Checkpoint Inhibitor" OR "Checkpoint Inhibitor") AND ("Gastrointestinal Adverse Effects" OR "Immune-Related Colitis"); ("Immune-Checkpoint Inhibitor-Mediated Colitis" OR "Immunotherapy-Associated Colitis") AND ("Treatment Approaches" OR "Management"). The search strategy aimed to identify papers discussing IMC diagnosis and treatment in the context of immunotherapy and ICIs. Relevant articles were screened based on titles, abstracts, and full text to ensure their alignment with the paper's objectives. The flow chart of identification, screening, and inclusion of retrieved papers is shown in Figure 2, following the PRISM guidelines.

The retrieved papers were further filtered to include only original research, reviews, clinical trials, and case studies that provided valuable insights into the topic. The publication date was limited to the most recent literature, primarily from the last ten years.

This systematic search strategy gathered a comprehensive selection of literature to form the basis for our review of new strategies for diagnosing and treating IMC. We wrote a modified form of a narrative review, following the recent guidelines[12].

RISK FACTORS FOR THE DEVELOPMENT OF IMMUNE-CHECKPOINT INHIBITOR-MEDICATED COLITIS

The risk of IMC among cancer patients depends on various factors with external and intrinsic nature. One of the most significant determinants of IMC occurrence is the type of checkpoint inhibitor treatment. While both anti-CTLA4 and PD1 inhibitors have the potential to cause immune-mediated bowel inflammation and diarrhea, this toxicity is up to three times more common among patients treated with anti-CTLA4 compared to those who have received anti-PD1 or anti-PD-L1 agents[13,14]. The risk of IMC and diarrhea becomes most pronounced with checkpoint inhibitor combinations.

A meta-analysis on the incidence of immune-related diarrhea among patients treated with combinations of anti-CTLA4 and anti-PD1 or anti-CTLA1 and anti-PD-L1 reports the incidence of IMC almost three times higher in the anti-CTLA4 and anti-PD1 cohort: 40.4% for anti-CTLA4 and anti-PD-L1 *vs* 13.2% for the anti-CTLA4 and anti-PD1 combination[15]. Monotherapies with anti-PD1-L1 or anti-PD-1 posed the slightest risk of such GI complications, with occurrence rates of 11.0% and 9.1% for each drug subclass, respectively. Whether higher doses of ICIs are associated with more IMC is not yet clear. While it is considered more relevant to drugs like nivolumab and ipilimumab, the dose seems less significant for pembrolizumab[16].

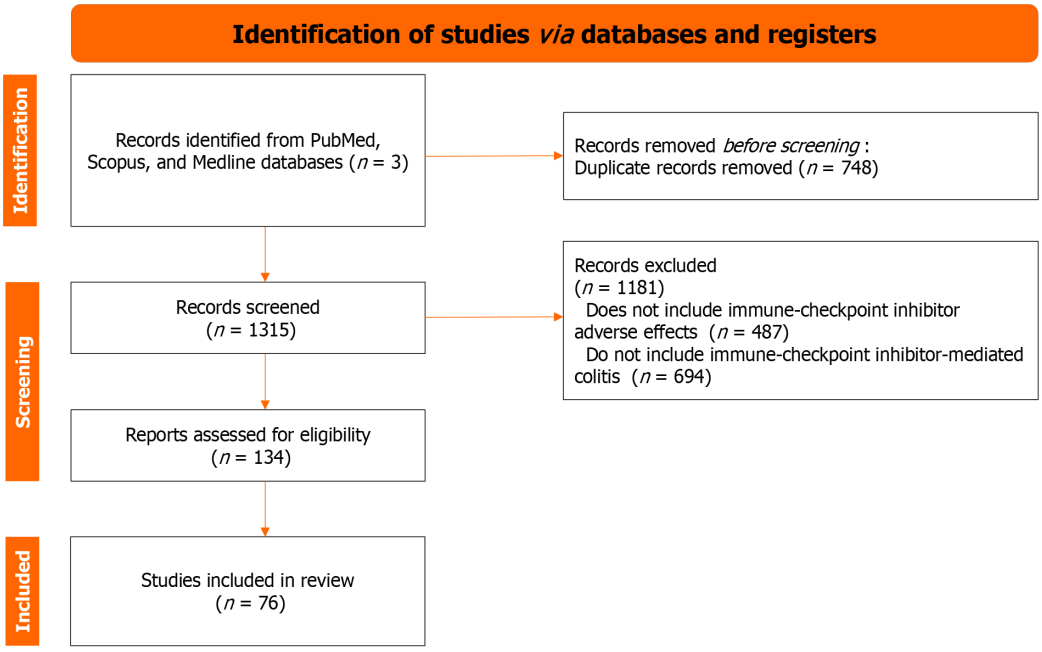

Figure 2 PRISMA-guided flow chart of the papers screened and included in the manuscript.

Genetic predisposition to the occurrence of IMC has also been a subject of research and speculation. A report on the association of human leucocyte antigen (HLA) variation and immunotherapy-related adverse events revealed a significant association between *HLA-DQB1*03:01* and colitis[17]. As this HLA class II variant is also found with higher prevalence among inflammatory bowel disease (IBD) patients, it further supports a potential role in the pathogenesis of immune-mediated bowel inflammation like the one observed with IMC. Clinical similarities between IMC and IBD led to the investigation of a polygenic risk score, primarily developed for ulcerative colitis, in IMC[18]. The score effectively identified subjects at risk of all grades and severe IMC in a cohort of more than 1300 non-small cell lung cancer patients receiving ICIs[18].

DIAGNOSIs OF IMMUNE-CHECKPOINT INHIBITOR-MEDIATED COLITIS

Clinical presentation

Most commonly, ICI-related GI irAEs manifest as colitis, characterized by watery diarrhea, abdominal pain, blood or mucus in the stool, and nocturnal bowel movements. IMC is the second most common irAE, which appears 6 wk to 8 wk after initial treatment with ICIs[19,20].

It was estimated that more frequently, GI irAEs emerged in patients treated with anti-CTLA-4 monotherapy than with PD-1/PD-L1 inhibitors. More specifically, as reported above, many studies reported that 30% to 40% of patients treated with CTLA-4 blockers developed diarrhea. Moreover, combined therapy of PD-1/PD-L1 inhibitor and CTLA-4 blockade leads to the highest rate of ICI-mediated diarrhea[14,21].

The evaluation of IMC typically involves a combination of clinical, endoscopic, histopathological, and laboratory assessments to determine the severity, extent, and underlying cause of the condition.

The clinical presentation of IMC can vary from person to person but often includes the following symptoms: diarrhea, abdominal pain, rectal bleeding, urgency tenesmus, and weight loss[7]. To rule out infectious enterocolitis, the patients should be initially tested for infections such as *Salmonella*, *Shigella*, *Campylobacter*, parasites, *and Clostridium difficile* before the diagnosis of IMC is accepted. Another important diagnostic test in patients with diarrhea includes a fecal PCR test to exclude *cytomegalovirus* colitis[22]. Computer tomography (CT) with oral and intravenous contrast should be performed in patients with diarrhea and abdominal pain to evaluate bowel inflammation and other intra-abdominal disorders. Long-lasting IMC could lead to severe complications such as ileus, toxic megacolon, and intestinal perforation[23].

It must be highlighted that symptom severity and duration could vary widely in patients. Clinical manifestation could present with mild, intermittent symptoms in some patients, while others could have severe symptoms that require urgent medical treatment. The exact medical evaluation and early detection of IMC are essential for better outcomes[24].

In line with this, Common Terminology Criteria for Adverse Events (CTCAE) provides a widely recognized system for evaluating the intensity of IMC[7]. IMC severity is categorized on a scale ranging from 1 (mild symptoms) to 5 (the most severe cases), taking into account symptomatology, endoscopic observations, and treatment protocols. Based on the grading, different treatment options are available (Figure 3).

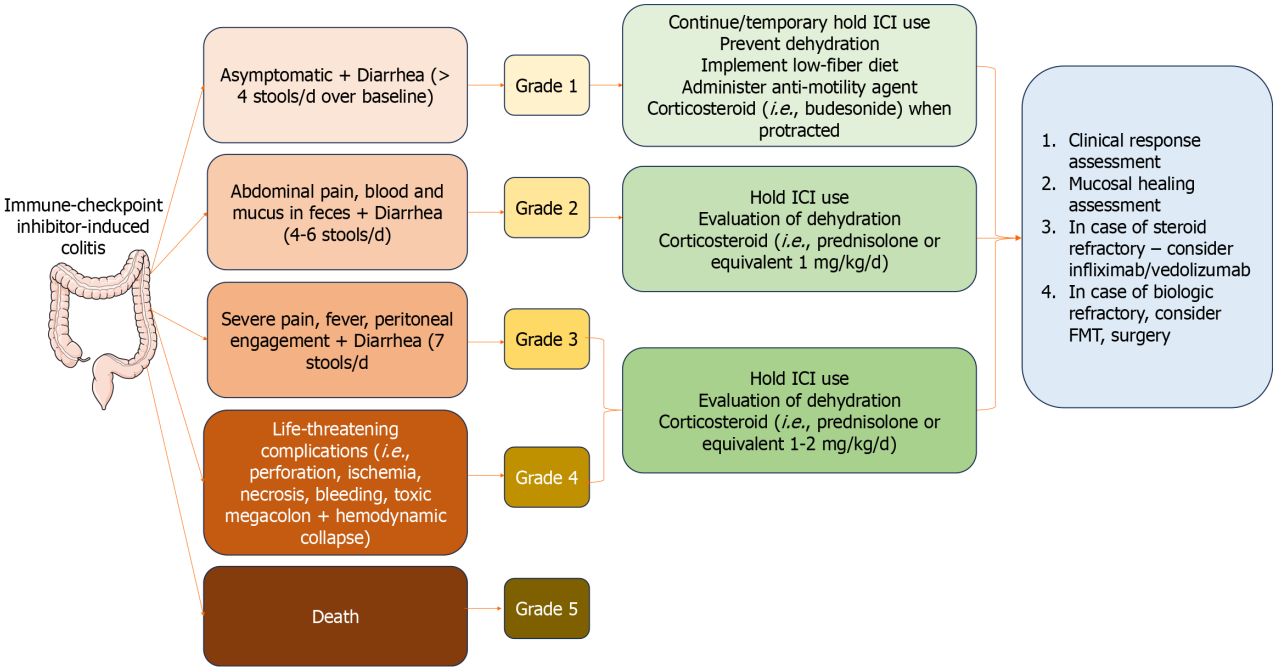

Figure 3 Grading the severity of immune checkpoint inhibitor-induced colitis and diarrhea and management. After discontinuing immune checkpoint inhibitors, clinical response and mucosal healing assessment are needed, and then biologics, fecal microbiota transplantation or surgery are introduced. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier (https://smart.servier.com/) is licensed under a Creative Commons Attribution 4.0 Unported License (Supplementary material). FMT: Fecal microbiota transplantation; ICI: Immune checkpoint inhibitors.

Endoscopic features of immune-mediated colitis

It should be noted that the precise evaluation of colonic mucosa during the colonoscopy is essential for distinguishing the IMC from other GI disorders, such as IBD or infections colitis. After detailed analysis of many factors, such as clinical manifestation, endoscopic appearance, and histopathological examination of the tissue biopsies, the diagnosis of IMC could be accepted[25].

So far, there is no established grading scale for endoscopic evaluation of IMC. However, in clinical practice, the Mayo Endoscopic Score for Ulcerative Colitis and the Simple Endoscopic Score for Crohn's disease (CD) could be used[24].

In line with this, endoscopic evaluation is essential in diagnosing and assessing the severity of IMC. The endoscopic features of IMC could be diverse, depending on the underlying cause and extent of inflammation. Some of the major endoscopic features typical for IMC include mucosal inflammation, erythema, edema, and loss of vascular pattern of the mucosa[26]. Most commonly, in clinical practice, patients on a high dose or combination of immunotherapy are diagnosed with mild colitis[27].

Many publications indicate that colonic ulcerations observed during endoscopy in patients with ipilimumab-mediated enterocolitis may be a clinical indicator of a more severe and potentially steroid-refractory disease. Extensive ulcerations suggest a more significant degree of tissue damage and inflammation. Patients with such endoscopic findings may be at higher risk of not responding well to standard steroid therapy[28].

A single-center study by Wang *et al*[29] demonstrated the connection between endoscopic and histologic features of ICI-related GI toxicities with long-term follow-up. The authors established that patients with more extensive and higher-grade colitis with ulcers on endoscopy and histological findings of acute inflammation have better outcomes. Another important conclusion is the correlation between endoscopic inflammation and the higher grade of colitis but not with higher-grade diarrhea.

Pathologic and histologic features of IMC

Today, as oncology emphasizes personalized therapy, the identification of PD-L1 on tumor cells and tumor-infiltrating immune cells by histological and immunohistochemical examination is a great step forward. However, it is vital to determine whether it can be used a predictive tissue biomarker for scientific research and leverage the potential for antitumor immunotherapy in patients. Although PD-L1 expression represents a measure of the potential of the patient's immune system to recognize the tumor and mount an effective antitumor immune response, ICIs produce various side effects[30]. According to literature data, only 4.9% to 22.0% of patients treated with ICIs report mild immune-related side effects and 4%-8% reported severe side effects that required treatment discontinuation[30]. The most commonly reported side effects are fatigue (affecting more than 36% of patients), opportunistic infections (in more than 38% of cases), disorders in the function of the thyroid gland as thyroiditis, hyper- and hypothyroidism (mainly when treated with anti-PD-1), adrenal insufficiency, hepatitis (proceeding with jaundice and asymptomatic elevation of transaminases and/or bilirubin) and diarrhea. Diarrhea is the most frequent mild side effect in patients with IMC, and perforation is rare but causes severe complications. The incidence of immune-related diarrhea is 1.3%-13.6% based on the specific agent, dose and combination of treatment for patients taking anti-PD1 and anti-PD-L1 medication[31,32]. Colitis is an immune-related

adverse event of anti-PD1 (Nivolumab and Pembrolizumab) and anti-PD-L1 medications (Atezolizumab, Avelumab, and Durvalumab)[32].

Histologic assessment is a valuable tool for confirming the diagnosis of IMC and guiding treatment decisions. Depending on the severity and extent of inflammation, treatment may include corticosteroids, immunosuppressive agents, or temporary discontinuation of the ICI[20], as shown in Figure 3.

It is important to note that the histological features of IMC can overlap with those of other forms of colitis, such as IBD. Therefore, a careful evaluation of clinical history, endoscopic findings, and histopathological features is necessary to differentiate ICI-related colitis from other causes. A hallmark feature of IMC is the presence of a dense inflammatory infiltrate within the colonic mucosa[32].

According to our experience, in just 1 mo, we had 6 patients (3/6 men and 3/6 women), aged between 27-51 years. The patients are had relapse/refractory Hodgkin's lymphoma (4/6 with nodular sclerosis and 2/6 with mixed cellularity) and were treated with PDL-1 therapy as 4th line. All patients developed immune-related colitis after treatment with Nivolumab (4/6) and Pembrolizumab (2/6). One of the patients also had immune-related hepatitis and immune-related arthritis, and one died during therapy. The observed IMCs were grade 2 (5 of the patients) and grade 3 (1 patient). We performed fibro colonoscopy (FCS) in 1 patient with grade 3 colitis (Figure 4) and with grade 1-2 colitis (Figure 5) to evaluate mucosal involvement. We provide a histological evaluation of the biopsies (Figures 4 and 5). All patients had grade 3 diarrhea, which was treated with corticosteroids and cessation of checkpoint inhibitors.

Recent reports suggest that ICI-induced diarrhea/colitis may occur at different periods of therapy, but in most cases, occurs after an average of three infusions. However, it can occur immediately after the first infusion[33,34].

Although IMC is one of the most common side effects, there is little information on the pathological features of anti-PD-1/PD-L1 colitis. Chen *et al*[35] described the most common histopathologic findings in 8 patients who developed colitis while on monotherapy with ICIs. The most common injury pattern they observed (5/8 cases) was an active colitis with neutrophilic crypt microabscesses and prominent crypt epithelial cell apoptosis and crypt atrophy/dropout. The remaining cases (3/8) showed a lymphocytic colitis-like pattern characterized by increased intraepithelial lymphocytes and surface epithelial injury without crypt atrophy[35].

Interestingly, the authors reported that recurrent colitis was observed in patients several months after completion of ICI therapy[34,35]. Unfortunately, in our practice, patients with immune-related colitis are rarely biopsied, thus significantly reducing the awareness of anti-PD-1/PD-L1 colitis among pathologists and making it difficult to diagnose and treat it timely.

Nevertheless, precisely because of the non-specific morphological features of IMC and the similar changes in other colitis (*i.e*. *cytomegalovirus*-associated colitis, acute graft *vs* host disease, IBD; chemotherapy-induced colitis), further evaluation with endoscopy and biopsy could confirm the diagnosis.

Biomarkers and serological markers

Effective management of IMC is liable on early diagnosis, as prompt intervention can mitigate the severity of colitis. To facilitate this, there is growing interest in identifying serological and fecal biomarkers that can aid in the early detection and monitoring of IMC[36].

These markers can be obtained from circulation, target organs, *etc*. For CTLA-4 inhibitors, the following are discussed: from blood (*i.e*. T cell repertoires, T regulatory cells, eosinophils, IL-6, IL-17, serum proteins, and gene expression profiles, *etc*), from target organs (*i.e*. ectopic expression of CTLA-4, baseline gut microbiota, muscle attenuation) and from the host. On the other hand, for PD-1/PD-L1 inhibitor-related toxicity, there are some routine blood tests (*i.e*. complete blood count, CD4+ Th1 cells, serum autoantibodies, soluble serum proteins, HLA genotypes), *etc*[37-40].

Because IMC involves complex immune system dysregulation, IL-17, a pro-inflammatory cytokine implicated in several autoimmune and inflammatory conditions, has also been explored. While IL-17's role in IMC remains an area of active investigation, its elevated levels in the serum and colon tissue may signify the immunological milieu and contribute to IMC pathogenesis. Monitoring IL-17 levels could provide insights into disease progression and therapeutic responses[41-43].

Fecal calprotectin is another biomarker whose usefulness is under investigation for IMC diagnosis and management. Elevated fecal calprotectin levels are associated with various GI disorders, including IBD. For IMC, a rise in fecal calprotectin levels may indicate an inflammatory process in the colon. However, more research is needed to establish the sensitivity and specificity of fecal calprotectin as a reliable biomarker for IMC. Its use is limited by the possibility of false-positive results in the context of irAEs and immunotherapy, making its interpretation challenging[44-46].

Despite potential biomarkers, it is essential to acknowledge that serological markers for IMC are not yet validated for routine clinical use. Current research primarily consists of small-scale studies and case reports, and there is a lack of standardized cutoff values to define IMC. Moreover, serological markers may not be exclusive to IMC, making differential diagnosis complex[37]. However, the search for reliable biomarkers for IMC continues. By identifying distinct serological profiles associated with IMC, clinicians may be better equipped to diagnose and manage these emerging irAEs. Prospective studies with larger cohorts, exploring a spectrum of potential markers, and their correlation with clinical outcomes are vital for establishing their clinical utility. Furthermore, understanding the interplay between these serological markers and the evolving immune responses during immunotherapy will provide deeper insights into the immunopathogenesis of IMC[38].

In conclusion, some established biomarkers, such as fecal calprotectin and IL-17, represent promising avenues for improving the diagnosis and management of IMC. While these markers hold potential, further research and standardization are required before they can be integrated into clinical practice. By leveraging the collective expertise of oncologists, gastroenterologists, and immunologists, the quest for biomarkers specific to IMC is a collaborative effort that underscores the need for precision medicine in the era of cancer immunotherapy.

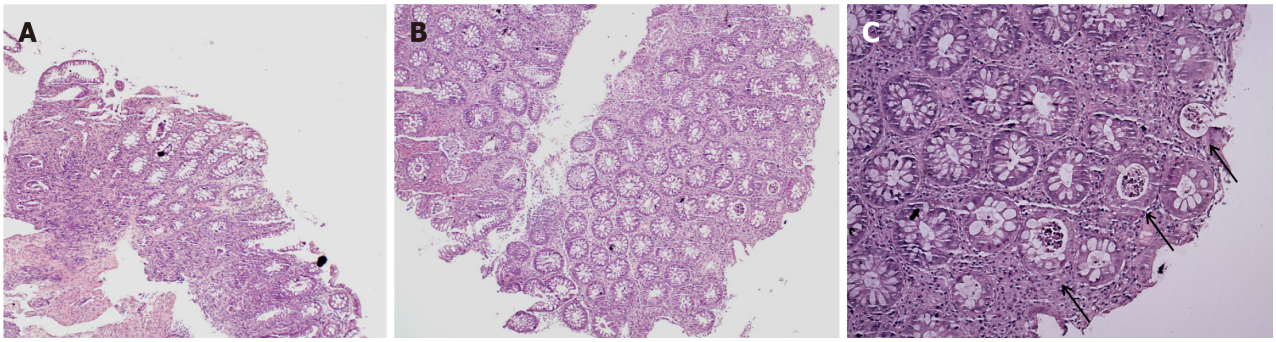

Figure 4 This colonic biopsy shows severe colitis highlighted by cryptitis and focal crypt microabscess (C-marked with an arrows), and surface epithelial injury without crypt atrophy. A: Hematoxylin and eosin (H&E) × 20; B: H&E × 50; C: H&E × 100.

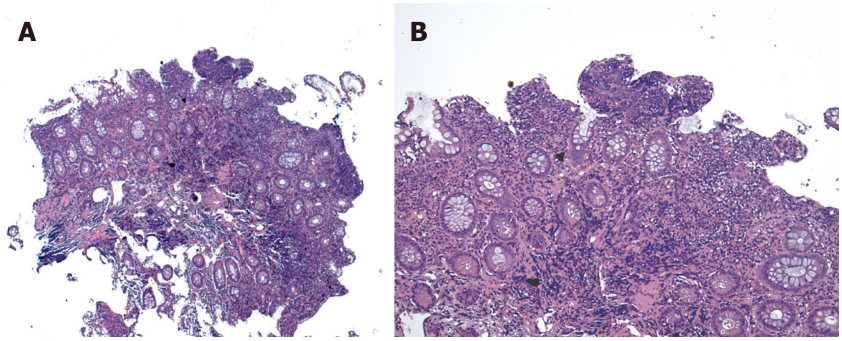

Figure 5 Hematoxylin and eosin staining. A and B: This colonic biopsy shows increased intraepithelial lymphocytes (lymphocytic colitis pattern of injury), mild focal active colitis and surface epithelial injury. Hematoxylin and eosin × 50 (A), × 100 (B).

MANAGEMENT OF IMMUNE-CHECKPOINT INHIBITOR-MEDIATED COLITIS

Treatment options

The grade of the GI irAE is determined by the severity of the diarrhea (*i.e.* a rise in the number of stool movements per day relative to baseline) and the existence and seriousness of additional colitis symptoms.

Management of grade 1 and 2 IMC

Current guidelines recommend that patients with grade 1 diarrhea (< 4 bowel movements per day) without other additional symptoms of colitis be treated conservatively with hydration and loperamide or diphenoxylate/atropine[47].

In patients with more than four bowel movements per day (grade 2), treatment should start with oral corticosteroid (1-2 mg/kg) with tapering in 4-6 wk. In such cases, ICI therapy should be discontinued immediately (Figure 3). If this therapy fails, intravenous corticosteroids should be initiated. The efficacy of the treatment must be evaluated regularly every 3-5 d. In cases where the general condition of the patient deteriorates and the severity of diarrhea does not improve, a colonoscopy should be performed[48]. The results from the endoscopic assessment can give valuable information about the activity of colon inflammation and its extent. According to many retrospective clinical studies, half of the patients treated with systemic corticosteroids have improved ICI-related diarrhea[24].

However, in certain situations, corticosteroids cannot control the symptoms, and the deterioration of diarrhea may become even life-threatening without more aggressive immunosuppressant treatment. Current guidelines recommend adding infliximab or vedolizumab to corticosteroid treatment in such cases.

Initially, infliximab has been recommended in steroid-refractory IMC. Infliximab is a monoclonal antitumor necrosis factor alpha (TNF-α) antibody, which has a comprehensive implication in the treatment of various autoimmune diseases such as ulcerative colitis, CD, rheumatoid and psoriatic arthritis, and psoriasis[49]. There have been reported data concerning the implication of infliximab for treating severe steroid-refractory IMC associated with ipilimumab[50,51].

Another immunosuppressant agent used in steroid-refractory IMC cases is vedolizumab, which represents an integrin antagonist that binds to α4β7 integrin. In general, the mechanism of action of vedolizumab includes limiting the migration of T-lymphocytes into the gut mucosa, which leads to the alleviation of gut inflammation. Vedolizumab can provide a more specific immunosuppression impact over inflamed gut mucosa by remodeling antitumor immune responses[52,53].

It must be pointed out that both immunosuppressants have several weaknesses, such as drug-induced comorbidities and increased risk of infections[54,55].

Management of severe (grade 3-4) IMC

In cases with severe IMC (grade 3-4), patients should be hospitalized, and specific treatment must be initiated. Intravenous corticosteroids (1-2 mg/kg/d) should be started until symptoms improve. The duration of corticosteroid treatment usually continues over 4-6 wk with tapering of corticosteroid dosage[56].

The current guidelines recommend combined therapy with steroids and infliximab or vedolizumab, preferably within 2 wk of onset, especially for patients with high-risk endoscopic features if no improvement is seen after 2 d to 3 d of intravenous methylprednisolone (1-2 mg/kg/d) therapy[57].

There is no consensus on the length of treatment with TNF-blockers (infliximab) or integrin blockers (vedolizumab). The likelihood of endoscopic/histologic remission is correlated with the treatment duration. It was estimated that the risk of recurrence is decreased by using up to three doses (at weeks 0, 2, and 6)[58].

The choice between which immunosuppressive regimen (infliximab or vedolizumab) should be administrated depends on many factors. Of great importance is to properly evaluate the risk of infections, other comorbidities, and malignancy [59].

Data related to treating colitis resistant to immunosuppressive medication with fecal transplantation has been published. Of course, the expertise of the center and the institutional availability are of great importance for the success of the procedure[60].

Fecal transplantation in immune-mediated colitis

The impaired homeostasis of the gut microbiome plays an essential role in developing IMC. In recent decades, FMT has been used in clinical practice as a treatment method for patients with recurrent *Clostridium difficile* infection and IBD. FMT aims to restructure the gut microbiota to its normal composition. This medical process is characterized by transferring fecal matter obtained from a healthy donor into the GI tract of the patient[61]. The first case series concerning the implication of FMT for successfully treated patients with IMC was published by Wang *et al*[60]. The authors concluded that modulation of the gut microbiome could lead to improvement of the IMC.

Recently, many data represent fascinating results concerning the effect of FMT in the treatment of refractory to corticosteroids and immunosuppression therapy. A current study by Halsey *et al*[62] reveals 92% achieving clinical remission in patients with grade 3 or 4 ICM-related diarrhea. The authors also made a 16S rRNA sequencing of patient stool samples. They found a complete remission of the patient's microbiota after the FMT with increases in abundance of *Collinsella* and *Bifidobacterium*.

A study by Wang *et al*[63] represents data on managing IMC with FMT as a first-line treatment. The results from the study demonstrate that FMT as a first-line treatment leads to quick relief of symptoms in most patients; thus, the use of steroids and immunosuppression could be avoided. Furthermore, the study revealed that first-line FMT treatment of IMC could replace the current treatment standards.

Surgical treatment

In situations where IMC fails to adequately respond to medical treatment and becomes severe, surgical intervention becomes necessary[64,65]. The surgical procedure can vary, contingent upon factors such as the severity and extent of the colitis, the patient's overall health, and specific clinical considerations. Surgery is particularly indicated when complications arise, such as colonic perforation, toxic megacolon, or severe bleeding.

Fortunately, such complications are rare. In a phase III clinical trial comprising 511 patients who underwent ipilimumab treatment for malignant melanoma, only 1% had perforation as a side effect, while 5% needed hospitalization for severe enterocolitis[66]. A difference in the frequency of colonic perforation or need for colectomy is observed among patients treated for renal cell carcinoma, with an incidence of 6.6%[67].

The preferred surgical approach is a subtotal colectomy because the colonic lesions tend to be extensive. Opting for segmental colonic resection often leads to significant inflammation of the remaining colon during the postoperative period[68].

In non-perforative cases, particularly in critically ill patients, an alternative option is the creation of a diverting ileostomy. This can help reduce the duration of the surgery and minimize complications[69]. An ileostomy should be considered at an earlier stage, as this surgical intervention tends to be less aggressive than a colectomy. Additionally, an early ileostomy allows for the potential resumption of ICI therapy sooner[70]. Due to the possibility of relapsing with severe colitis, which in some cases can be much more severe than the initial type, the ileostomy closure period must be carefully planned[71].

Postoperative complications vary depending on the surgical procedure and patient comorbidities. At short-term follow-up (< 30 d), complications may occur in 21% of patients, often presenting as postoperative infection and intestinal obstruction. In the long term, the complication rate can vary by 39%, mainly due to fecal incontinence and small bowel obstruction[72].

Due to the lack of early warning symptoms of colitis development after ICI use, multidisciplinary team monitoring and quick action are advised[73].

FUTURE DIRECTIONS AND PERSPECTIVES FOR IMC

As the field of immunotherapy rapidly evolves, ongoing research in diagnosing and managing IMC is essential to ensure the best possible care for patients. Several promising future directions can be explored to enhance our understanding and handling of this specific immunotherapy-related adverse event[74].

The development of these future directions relies on robust, large-scale studies, interdisciplinary collaboration, and the exchange of knowledge across the fields of oncology, immunology, and gastroenterology. A collective effort among researchers, clinicians, and pharmaceutical companies is vital to enhance our ability to diagnose and manage IMC, ultimately improving patient outcomes and the safety of cancer immunotherapy[75,76].

Personalized risk profiling

Precision medicine proposed tools to predict individual susceptibility to IMC, such as genomics, immunogenetics, and immune profiling, allowing for risk assessment before immunotherapy initiation.

Early biomarker panels

Identifying specific serological and molecular markers for IMC is a priority. However, the search for reliable, high-sensitivity assays that can identify IMC earlier in treatment, allowing for timely intervention, is ongoing.

Multidisciplinary guidelines

It is important to create comprehensive, multidisciplinary guidelines to offer oncologists, gastroenterologists, and other healthcare providers a standardized approach to the diagnosis, management, and monitoring of IMC.

Tailored therapies

Investigating tailored therapies for individual patient responses to different treatment modalities, including immunosuppressive agents, ICI discontinuation, and monoclonal antibodies, is essential for optimizing care.

Combination of immunotherapies

More research is needed to understand the specific risk profiles for IMC and establish guidelines for managing complex cases.

Telemedicine and remote monitoring

These allow for regular monitoring of patients, enabling the early detection of IMC symptoms and swift intervention.

Shared decision-making

Future clinical practice should embrace shared decision-making models, allowing patients to actively participate in treatment decisions while understanding the risks and benefits of certain immunotherapy.

Immunomodulation strategies

Novel immunomodulation strategies are needed that target and modulate immune responses and induce immune tolerance.

CONCLUSION

IMC is an emerging and complex clinical entity associated with the expanding use of cancer immunotherapies. In this comprehensive review, we have delved into the mechanisms, clinical features, diagnosis, management of IMC and promising future directions, focusing on evolving biomarker-based diagnostics.

The importance of early recognition and accurate diagnosis of IMC to ensure prompt and effective management of the condition was emphasized. Incorporating established or novel biomarkers for IMC into clinical practice holds promise for swift, accurate, and non-invasive identification of cases, enabling clinicians to intervene in a timely manner.

Nevertheless, managing IMC requires a multidisciplinary approach and tailored treatment strategies that balance effective ICI administration with the potential risk of IMC. Medical professionals from different fields must collaborate to optimize patient care while minimizing adverse effects. Overall, as immunotherapy continues to revolutionize cancer treatment, IMC remains a challenge but also represents a growing opportunity for research and innovation. The future directions we have outlined open avenues for more personalized care, early biomarker-based diagnosis, and novel treatment strategies, fostering a safer and more effective landscape for cancer immunotherapy.

FOOTNOTES

Author contributions: Peruhova M and Velikova T contributed to conceptualization; Krastev B and Gulinac M contributed to methodology; Zashe M contributed to software; Peruhova M and Graklanov V contributed to resources; Zashev M and Graklanov V contributed to data curation; Velikova T, Gulinac M, and Peruhova M contributed to visualization; Peruhova M, Krastev B, Gulinac M, and Zashev M wrote the original draft; Velikova T contributed to review and editing the manuscript, English language proofreading, funding acquisition, and supervision; all authors revised and approved the final version of the manuscript prior to submission.

Supported by the European Union-NextGenerationEU, through the National Recovery and Resilience Plan of the Republic of Bulgaria, No. BG-RRP-2.004-0008.

Conflict-of-interest statement: The authors declare having no conflicts of interest.

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S-Editor: Chen YL
L-Editor: Filipodia
P-Editor: Zhao S

REFERENCES

1 **Iranzo P**, Callejo A, Assaf JD, Molina G, Lopez DE, Garcia-Illescas D, Pardo N, Navarro A, Martinez-Marti A, Cedres S, Carbonell C, Frigola J, Amat R, Felip E. Overview of Checkpoint Inhibitors Mechanism of Action: Role of Immune-Related Adverse Events and Their Treatment on Progression of Underlying Cancer. *Front Med (Lausanne)* 2022; **9**: 875974 [PMID: 35707528 DOI: 10.3389/fmed.2022.875974]

2 **Perdyan A**, Sobocki BK, Balihodzic A, Dąbrowska A, Kacperczyk J, Rutkowski J. The Effectiveness of Cancer Immune Checkpoint Inhibitor Retreatment and Rechallenge-A Systematic Review. *Cancers (Basel)* 2023; **15** [PMID: 37444600 DOI: 10.3390/cancers15133490]

3 **Esfahani K**, Meti N, Miller WH Jr, Hudson M. Adverse events associated with immune checkpoint inhibitor treatment for cancer. *CMAJ* 2019; **191**: E40-E46 [PMID: 30642824 DOI: 10.1503/cmaj.180870]

4 **Ramos-Casals M**, Brahmer JR, Callahan MK, Flores-Chávez A, Keegan N, Khamashta MA, Lambotte O, Mariette X, Prat A, Suárez-Almazor ME. Immune-related adverse events of checkpoint inhibitors. *Nat Rev Dis Primers* 2020; **6**: 38 [PMID: 32382051 DOI: 10.1038/s41572-020-0160-6]

5 **Velikova T**, Krastev B, Lozenov S, Gencheva R, Peshevska-Sekulovska M, Nikolaev G, Peruhova M. Antibiotic-Related Changes in Microbiome: The Hidden Villain behind Colorectal Carcinoma Immunotherapy Failure. *Int J Mol Sci* 2021; **22** [PMID: 33578709 DOI: 10.3390/ijms22041754]

6 **Yin Q**, Wu L, Han L, Zheng X, Tong R, Li L, Bai L, Bian Y. Immune-related adverse events of immune checkpoint inhibitors: a review. *Front Immunol* 2023; **14**: 1167975 [PMID: 37304306 DOI: 10.3389/fimmu.2023.1167975]

7 **Som A**, Mandaliya R, Alsaadi D, Farshidpour M, Charabaty A, Malhotra N, Mattar MC. Immune checkpoint inhibitor-induced colitis: A comprehensive review. *World J Clin Cases* 2019; **7**: 405-418 [PMID: 30842952 DOI: 10.12998/wjcc.v7.i4.405]

8 **Prieux-Klotz C**, Dior M, Damotte D, Dreanic J, Brieau B, Brezault C, Abitbol V, Chaussade S, Coriat R. Immune Checkpoint Inhibitor-Induced Colitis: Diagnosis and Management. *Target Oncol* 2017; **12**: 301-308 [PMID: 28540478 DOI: 10.1007/s11523-017-0495-4]

9 **Weingarden AR**, Rubin SJS, Gubatan J. Immune checkpoint inhibitor-mediated colitis in gastrointestinal malignancies and inflammatory bowel disease. *World J Gastrointest Oncol* 2021; **13**: 772-798 [PMID: 34457186 DOI: 10.4251/wjgo.v13.i8.772]

10 **Tang L**, Wang J, Lin N, Zhou Y, He W, Liu J, Ma X. Immune Checkpoint Inhibitor-Associated Colitis: From Mechanism to Management. *Front Immunol* 2021; **12**: 800879 [PMID: 34992611 DOI: 10.3389/fimmu.2021.800879]

11 **Alorfi NM**, Alourfi MM. Biologic Therapy for Refractory Immune Checkpoint Inhibitor Colitis. *Biologics* 2022; **16**: 119-127 [PMID: 35957978 DOI: 10.2147/BTT.S367675]

12 **Gasparyan AY**, Ayvazyan L, Blackmore H, Kitas GD. Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. *Rheumatol Int* 2011; **31**: 1409-1417 [PMID: 21800117 DOI: 10.1007/s00296-011-1999-3]

13 **Soularue E**, Lepage P, Colombel JF, Coutzac C, Faleck D, Marthey L, Collins M, Chaput N, Robert C, Carbonnel F. Enterocolitis due to immune checkpoint inhibitors: a systematic review. *Gut* 2018; **67**: 2056-2067 [PMID: 30131322 DOI: 10.1136/gutjnl-2018-316948]

14 **Tandon P**, Bourassa-Blanchette S, Bishay K, Parlow S, Laurie SA, McCurdy JD. The Risk of Diarrhea and Colitis in Patients With Advanced Melanoma Undergoing Immune Checkpoint Inhibitor Therapy: A Systematic Review and Meta-Analysis. *J Immunother* 2018; **41**: 101-108 [PMID: 29401166 DOI: 10.1097/CJI.0000000000000213]

15 **Bishay K**, Tandon P, Bourassa-Blanchette S, Laurie SA, McCurdy JD. The risk of diarrhea and colitis in patients with lung cancer treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *Curr Oncol* 2020; **27**: e486-e494 [PMID: 33173388 DOI: 10.3747/co.27.6251]

16 **Gong Z**, Wang Y. Immune Checkpoint Inhibitor-Mediated Diarrhea and Colitis: A Clinical Review. *JCO Oncol Pract* 2020; **16**: 453-461 [PMID: 32584703 DOI: 10.1200/OP.20.00002]

17 **Hasan Ali O**, Berner F, Bomze D, Fässler M, Diem S, Cozzio A, Jörger M, Früh M, Driessen C, Lenz TL, Flatz L. Human leukocyte antigen variation is associated with adverse events of checkpoint inhibitors. *Eur J Cancer* 2019; **107**: 8-14 [PMID: 30529903 DOI: 10.1016/j.ejca.2018.11.009]

18 **Middha P**, Thummalapalli R, Betti MJ, Yao L, Quandt Z, Balaratnam K, Bejan CA, Cardenas E, Falcon CJ, Faleck DM; Princess Margaret Lung Group, Gubens MA, Huntsman S, Johnson DB, Kachuri L, Khan K, Li M, Lovly CM, Murray MH, Patel D, Werking K, Xu Y, Zhan LJ, Balko JM, Liu G, Aldrich MC, Schoenfeld AJ, Ziv E. Polygenic risk score for ulcerative colitis predicts immune checkpoint inhibitor-mediated colitis. *medRxiv* 2023 [PMID: 37292751 DOI: 10.1101/2023.05.15.23289680]

19 **Weber JS**, Dummer R, de Pril V, Lebbé C, Hodi FS; MDX010-20 Investigators. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. *Cancer* 2013; **119**: 1675-1682 [PMID: 23400564 DOI: 10.1002/cncr.27969]

20 **Wang Y**, Abu-Sbeih H, Mao E, Ali N, Qiao W, Trinh VA, Zobniw C, Johnson DH, Samdani R, Lum P, Shuttlesworth G, Blechacz B, Bresalier R, Miller E, Thirumurthi S, Richards D, Raju G, Stroehlein J, Diab A. Endoscopic and Histologic Features of Immune Checkpoint Inhibitor-Related Colitis. *Inflamm Bowel Dis* 2018; **24**: 1695-1705 [PMID: 29718308 DOI: 10.1093/ibd/izy104]

21 **Pernot S**, Ramtohul T, Taieb J. Checkpoint inhibitors and gastrointestinal immune-related adverse events. *Curr Opin Oncol* 2016; **28**: 264-268 [PMID: 27138569 DOI: 10.1097/CCO.0000000000000292]

22 **McCutcheon JL**, McClain CM, Puzanov I, Smith TA. Infectious Colitis Associated With Ipilimumab Therapy. *Gastroenterology Res* 2014; **7**: 28-31 [PMID: 27785266 DOI: 10.14740/gr594e]

23 **Shah R**, Witt D, Asif T, Mir FF. Ipilimumab as a Cause of Severe Pan-Colitis and Colonic Perforation. *Cureus* 2017; **9**: e1182 [PMID: 28533998 DOI: 10.7759/cureus.1182]

24 **Geukes Foppen MH**, Rozeman EA, van Wilpe S, Postma C, Snaebjornsson P, van Thienen JV, van Leerdam ME, van den Heuvel M, Blank CU, van Dieren J, Haanen JBAG. Immune checkpoint inhibition-related colitis: symptoms, endoscopic features, histology and response to management. *ESMO Open* 2018; **3**: e000278 [PMID: 29387476 DOI: 10.1136/esmoopen-2017-000278]

25 **Menon T**, Afzali A. Immune-Mediated Colitis. *Curr Treat Options Gastroenterol* 2019; **17**: 506-523 [PMID: 31741212 DOI: 10.1007/s11938-019-00263-0]

26 **Verschuren EC**, van den Eertwegh AJ, Wonders J, Slangen RM, van Delft F, van Bodegraven A, Neefjes-Borst A, de Boer NK. Clinical, Endoscopic, and Histologic Characteristics of Ipilimumab-Associated Colitis. *Clin Gastroenterol Hepatol* 2016; **14**: 836-842 [PMID: 26748223 DOI: 10.1016/j.cgh.2015.12.028]

27 **Larkin J**, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, Ferrucci PF, Hill A, Wagstaff J, Carlino MS, Haanen JB, Maio M, Marquez-Rodas I, McArthur GA, Ascierto PA, Long GV, Callahan MK, Postow MA, Grossmann K, Sznol M, Dreno B, Bastholt L, Yang A, Rollin LM, Horak C, Hodi FS, Wolchok JD. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med* 2015; **373**: 23-34 [PMID: 26027431 DOI: 10.1056/NEJMoa1504030]

28 **Eggermont AM**, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, Schmidt H, Hamid O, Robert C, Ascierto PA, Richards JM, Lebbé C, Ferraresi V, Smylie M, Weber JS, Maio M, Bastholt L, Mortier L, Thomas L, Tahir S, Hauschild A, Hassel JC, Hodi FS, Taitt C, de Pril V, de Schaetzen G, Suciu S, Testori A. Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. *N Engl J Med* 2016; **375**: 1845-1855 [PMID: 27717298 DOI: 10.1056/NEJMoa1611299]

29 **Wang Y**, Abu-Sbeih H, Mao E, Ali N, Ali FS, Qiao W, Lum P, Raju G, Shuttlesworth G, Stroehlein J, Diab A. Immune-checkpoint inhibitor-induced diarrhea and colitis in patients with advanced malignancies: retrospective review at MD Anderson. *J Immunother Cancer* 2018; **6**: 37 [PMID: 29747688 DOI: 10.1186/s40425-018-0346-6]

30 **Baxi S**, Yang A, Gennarelli RL, Khan N, Wang Z, Boyce L, Korenstein D. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. *BMJ* 2018; **360**: k793 [PMID: 29540345 DOI: 10.1136/bmj.k793]

31 **Wang PF**, Chen Y, Song SY, Wang TJ, Ji WJ, Li SW, Liu N, Yan CX. Immune-Related Adverse Events Associated with Anti-PD-1/PD-L1 Treatment for Malignancies: A Meta-Analysis. *Front Pharmacol* 2017; **8**: 730 [PMID: 29093678 DOI: 10.3389/fphar.2017.00730]

32 **Wang DY**, Ye F, Zhao S, Johnson DB. Incidence of immune checkpoint inhibitor-related colitis in solid tumor patients: A systematic review and meta-analysis. *Oncoimmunology* 2017; **6**: e1344805 [PMID: 29123955 DOI: 10.1080/2162402X.2017.1344805]

33 **Mooradian MJ**, Wang DY, Coromilas A, Lumish M, Chen T, Giobbie-Hurder A, Johnson DB, Sullivan RJ, Dougan M. Mucosal inflammation predicts response to systemic steroids in immune checkpoint inhibitor colitis. *J Immunother Cancer* 2020; **8** [PMID: 32414860 DOI: 10.1136/jitc-2019-000451]

34 **Nishida T**, Iijima H, Adachi S. Immune checkpoint inhibitor-induced diarrhea/colitis: Endoscopic and pathologic findings. *World J Gastrointest Pathophysiol* 2019; **10**: 17-28 [PMID: 31559106 DOI: 10.4291/wjgp.v10.i2.17]

35 **Chen JH**, Pezhouh MK, Lauwers GY, Masia R. Histopathologic Features of Colitis Due to Immunotherapy With Anti-PD-1 Antibodies. *Am J Surg Pathol* 2017; **41**: 643-654 [PMID: 28296676 DOI: 10.1097/PAS.0000000000000829]

36 **Xu Y**, Fu Y, Zhu B, Wang J, Zhang B. Predictive Biomarkers of Immune Checkpoint Inhibitors-Related Toxicities. *Front Immunol* 2020; **11**: 2023 [PMID: 33123120 DOI: 10.3389/fimmu.2020.02023]

37 **Li N**, Hou X, Huang S, Tai R, Lei L, Li S, Abuliz A, Wang G, Yang S. Biomarkers related to immune checkpoint inhibitors therapy. *Biomed Pharmacother* 2022; **147**: 112470 [PMID: 35074251 DOI: 10.1016/j.biopha.2021.112470]

38 **Les I**, Martínez M, Pérez-Francisco I, Cabero M, Teijeira L, Arrazubi V, Torrego N, Campillo-Calatayud A, Elejalde I, Kochan G, Escors D. Predictive Biomarkers for Checkpoint Inhibitor Immune-Related Adverse Events. *Cancers (Basel)* 2023; **15** [PMID: 36900420 DOI: 10.3390/cancers15051629]

39 **Jia XH**, Geng LY, Jiang PP, Xu H, Nan KJ, Yao Y, Jiang LL, Sun H, Qin TJ, Guo H. The biomarkers related to immune related adverse events caused by immune checkpoint inhibitors. *J Exp Clin Cancer Res* 2020; **39**: 284 [PMID: 33317597 DOI: 10.1186/s13046-020-01749-x]

40 **Bai R**, Lv Z, Xu D, Cui J. Predictive biomarkers for cancer immunotherapy with immune checkpoint inhibitors. *Biomark Res* 2020; **8**: 34 [PMID: 32864131 DOI: 10.1186/s40364-020-00209-0]

41 **Callahan MK**, Yang A, Tandon S, Xu Y, Subudhi SK, Roman RA, Heine AI, Pogoriler E, Kuk D, Panageas K, Yuan JD, Allison JP, Wolchok JD. Evaluation of Serum IL-17 Levels During Ipilimumab Therapy: Correlation With Colitis. *J Clin Oncol* 2011; **29**: 2505 [DOI: 10.1200/jco.2011.29.15_suppl.2505]

42 **Bamias G**, Delladetsima I, Perdiki M, Siakavellas SI, Goukos D, Papatheodoridis GV, Daikos GL, Gogas H. Immunological Characteristics of Colitis Associated with Anti-CTLA-4 Antibody Therapy. *Cancer Invest* 2017; **35**: 443-455 [PMID: 28548891 DOI: 10.1080/07357907.2017.1324032]

43 **Westdorp H**, Sweep MWD, Gorris MAJ, Hoentjen F, Boers-Sonderen MJ, van der Post RS, van den Heuvel MM, Piet B, Boleij A, Bloemendal HJ, de Vries IJM. Mechanisms of Immune Checkpoint Inhibitor-Mediated Colitis. *Front Immunol* 2021; **12**: 768957 [PMID: 34777387 DOI: 10.3389/fimmu.2021.768957]

44 **Zou F**, Wang X, Glitza Oliva IC, McQuade JL, Wang J, Zhang HC, Thompson JA, Thomas AS, Wang Y. Fecal calprotectin concentration to assess endoscopic and histologic remission in patients with cancer with immune-mediated diarrhea and colitis. *J Immunother Cancer* 2021; **9** [PMID: 33436487 DOI: 10.1136/jitc-2020-002058]

45 **Abu-Sbeih H**, Ali FS, Alsaadi D, Jennings J, Luo W, Gong Z, Richards DM, Charabaty A, Wang Y. Outcomes of vedolizumab therapy in patients with immune checkpoint inhibitor-induced colitis: a multi-center study. *J Immunother Cancer* 2018; **6**: 142 [PMID: 30518410 DOI: 10.1186/s40425-018-0461-4]

46 **Kennedy LC**, Grivas P. Immunotherapy-Related Colitis: An Emerging Challenge and a Quest for Prospective Data. *JCO Oncol Pract* 2020; **16**: 464-465 [PMID: 32780983 DOI: 10.1200/OP.20.00620]

47 **Thompson JA**, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, Budde LE, Costa L, Davies M, Dunnington D, Ernstoff MS, Frigault M, Kaffenberger BH, Lunning M, McGettigan S, McPherson J, Mohindra NA, Naidoo J, Olszanski AJ, Oluwole O, Patel SP, Pennell N, Reddy S, Ryder M, Santomasso B, Shofer S, Sosman JA, Wang Y, Weight RM, Johnson-Chilla A, Zuccarino-Catania G, Engh A. NCCN Guidelines Insights: Management of Immunotherapy-Related Toxicities, Version 1.2020. *J Natl Compr Canc Netw* 2020; **18**: 230-241 [PMID: 32135517 DOI: 10.6004/jnccn.2020.0012]

48 **Brahmer JR**, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, Chau I, Ernstoff MS, Gardner JM, Ginex P, Hallmeyer S, Holter Chakrabarty J, Leighl NB, Mammen JS, McDermott DF, Naing A, Nastoupil LJ, Phillips T, Porter LD, Puzanov I, Reichner CA, Santomasso BD, Seigel C, Spira A, Suarez-Almazor ME, Wang Y, Weber JS, Wolchok JD, Thompson JA; National Comprehensive Cancer Network. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2018; **36**: 1714-1768 [PMID: 29442540 DOI: 10.1200/JCO.2017.77.6385]

49 **Sfikakis PP**. The first decade of biologic TNF antagonists in clinical practice: lessons learned, unresolved issues and future directions. *Curr Dir Autoimmun* 2010; **11**: 180-210 [PMID: 20173395 DOI: 10.1159/000289205]

50 **Postow MA**, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. *N Engl J Med* 2018; **378**: 158-168 [PMID: 29320654 DOI: 10.1056/NEJMra1703481]

51 **Friedman CF**, Proverbs-Singh TA, Postow MA. Treatment of the Immune-Related Adverse Effects of Immune Checkpoint Inhibitors: A Review. *JAMA Oncol* 2016; **2**: 1346-1353 [PMID: 27367787 DOI: 10.1001/jamaoncol.2016.1051]

52 **Bergqvist V**, Hertervig E, Gedeon P, Kopljar M, Griph H, Kinhult S, Carneiro A, Marsal J. Vedolizumab treatment for immune checkpoint inhibitor-induced enterocolitis. *Cancer Immunol Immunother* 2017; **66**: 581-592 [PMID: 28204866 DOI: 10.1007/s00262-017-1962-6]

53 **Hsieh AH**, Ferman M, Brown MP, Andrews JM. Vedolizumab: a novel treatment for ipilimumab-induced colitis. *BMJ Case Rep* 2016; **2016** [PMID: 27539137 DOI: 10.1136/bcr-2016-216641]

54 **Youssef J**, Novosad SA, Winthrop KL. Infection Risk and Safety of Corticosteroid Use. *Rheum Dis Clin North Am* 2016; **42**: 157-176, ix [PMID: 26611557 DOI: 10.1016/j.rdc.2015.08.004]

55 **Siegel CA**, Hur C, Korzenik JR, Gazelle GS, Sands BE. Risks and benefits of infliximab for the treatment of Crohn's disease. *Clin Gastroenterol Hepatol* 2006; **4**: 1017-24; quiz 976 [PMID: 16843733 DOI: 10.1016/j.cgh.2006.05.020]

56 **Thompson JA**, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, Budde LE, Costa L, Davies M, Dunnington D, Ernstoff MS, Frigault M, Hoffner B, Hoimes CJ, Lacouture M, Locke F, Lunning M, Mohindra NA, Naidoo J, Olszanski AJ, Oluwole O, Patel SP, Reddy S, Ryder M, Santomasso B, Shofer S, Sosman JA, Wahidi M, Wang Y, Johnson-Chilla A, Scavone JL. Management of Immunotherapy-Related Toxicities, Version 1.2019. *J Natl Compr Canc Netw* 2019; **17**: 255-289 [PMID: 30865922 DOI: 10.6004/jnccn.2019.0013]

57 **Abu-Sbeih H**, Ali FS, Luo W, Qiao W, Raju GS, Wang Y. Importance of endoscopic and histological evaluation in the management of immune checkpoint inhibitor-induced colitis. *J Immunother Cancer* 2018; **6**: 95 [PMID: 30253811 DOI: 10.1186/s40425-018-0411-1]

58 **Abu-Sbeih H**, Ali FS, Wang X, Mallepally N, Chen E, Altan M, Bresalier RS, Charabaty A, Dadu R, Jazaeri A, Lashner B, Wang Y. Early introduction of selective immunosuppressive therapy associated with favorable clinical outcomes in patients with immune checkpoint inhibitor-induced colitis. *J Immunother Cancer* 2019; **7**: 93 [PMID: 30940209 DOI: 10.1186/s40425-019-0577-1]

59 **Evangelatos G**, Bamias G, Kitas GD, Kollias G, Sfikakis PP. The second decade of anti-TNF-a therapy in clinical practice: new lessons and future directions in the COVID-19 era. *Rheumatol Int* 2022; **42**: 1493-1511 [PMID: 35503130 DOI: 10.1007/s00296-022-05136-x]

60 **Wang Y**, Wiesnoski DH, Helmink BA, Gopalakrishnan V, Choi K, DuPont HL, Jiang ZD, Abu-Sbeih H, Sanchez CA, Chang CC, Parra ER, Francisco-Cruz A, Raju GS, Stroehlein JR, Campbell MT, Gao J, Subudhi SK, Maru DM, Blando JM, Lazar AJ, Allison JP, Sharma P, Tetzlaff MT, Wargo JA, Jenq RR. Fecal microbiota transplantation for refractory immune checkpoint inhibitor-associated colitis. *Nat Med* 2018; **24**: 1804-1808 [PMID: 30420754 DOI: 10.1038/s41591-018-0238-9]

61 **Abu-Sbeih H**, Wang Y. Gut Microbiome and Immune Checkpoint Inhibitor-Induced Enterocolitis. *Dig Dis Sci* 2020; **65**: 797-799 [PMID: 32040664 DOI: 10.1007/s10620-020-06103-x]

62 **Halsey TM**, Thomas AS, Hayase T, Ma W, Abu-Sbeih H, Sun B, Parra ER, Jiang ZD, DuPont HL, Sanchez C, El-Himri R, Brown A, Flores I, McDaniel L, Ortega Turrubiates M, Hensel M, Pham D, Watowich SS, Hayase E, Chang CC, Jenq RR, Wang Y. Microbiome alteration *via* fecal microbiota transplantation is effective for refractory immune checkpoint inhibitor-induced colitis. *Sci Transl Med* 2023; **15**: eabq4006 [PMID: 37315113 DOI: 10.1126/scitranslmed.abq4006]

63 **Wang YH**, Varatharajalu K, Shatila M, Campbell MT, Msaouel P, Kovitz CA. First-line treatment of fecal microbiota transplantation for immune-mediated colitis. *J Clini Onco* 2023; **41** Suppl 16: 2510 [DOI: 10.1200/JCO.2023.41.16_suppl.2510]

64 **Samaan MA**, Pavlidis P, Papa S, Powell N, Irving PM. Gastrointestinal toxicity of immune checkpoint inhibitors: from mechanisms to management. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 222-234 [PMID: 29512649 DOI: 10.1038/nrgastro.2018.14]

65 **Mitchell KA**, Kluger H, Sznol M, Hartman DJ. Ipilimumab-induced perforating colitis. *J Clin Gastroenterol* 2013; **47**: 781-785 [PMID: 23632354 DOI: 10.1097/MCG.0b013e31828f1d51]

66 **Hodi FS**, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbé C, Peschel C, Quirt I, Clark JI, Wolchok JD, Weber JS, Tian J, Yellin MJ, Nichol GM, Hoos A, Urba WJ. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; **363**: 711-723 [PMID: 20525992 DOI: 10.1056/NEJMoa1003466]

67 **Beck KE**, Blansfield JA, Tran KQ, Feldman AL, Hughes MS, Royal RE, Kammula US, Topalian SL, Sherry RM, Kleiner D, Quezado M, Lowy I, Yellin M, Rosenberg SA, Yang JC. Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. *J Clin Oncol* 2006; **24**: 2283-2289 [PMID: 16710025 DOI: 10.1200/jco.2005.04.5716]

68 **Marthey L**, Mateus C, Mussini C, Nachury M, Nancey S, Grange F, Zallot C, Peyrin-Biroulet L, Rahier JF, Bourdier de Beauregard M, Mortier L, Coutzac C, Soularue E, Lanoy E, Kapel N, Planchard D, Chaput N, Robert C, Carbonnel F. Cancer Immunotherapy with Anti-CTLA-4 Monoclonal Antibodies Induces an Inflammatory Bowel Disease. *J Crohns Colitis* 2016; **10**: 395-401 [PMID: 26783344 DOI: 10.1093/ecco-jcc/jjv227]

69 **Le KDR**, Choy KT, Roth S, Heriot AG, Kong JCH. Immune mediated colitis: a surgical perspective. *ANZ J Surg* 2023; **93**: 1495-1502 [PMID: 37088921 DOI: 10.1111/ans.18485]

70 **Portenkirchner C**, Kienle P, Horisberger K. Checkpoint Inhibitor-Induced Colitis-A Clinical Overview of Incidence, Prognostic Implications and Extension of Current Treatment Options. *Pharmaceuticals (Basel)* 2021; **14** [PMID: 33923423 DOI: 10.3390/ph14040367]

71 **Horisberger K**, Portenkirchner C, Rickenbacher A, Biedermann L, Gubler C, Turina M. Complete Recovery of Immune Checkpoint Inhibitor-induced Colitis by Diverting Loop Ileostomy. *J Immunother* 2020; **43**: 145-148 [PMID: 32028372 DOI: 10.1097/CJI.0000000000000309]

72 **Peyrin-Biroulet L**, Germain A, Patel AS, Lindsay JO. Systematic review: outcomes and post-operative complications following colectomy for ulcerative colitis. *Aliment Pharmacol Ther* 2016; **44**: 807-816 [PMID: 27534519 DOI: 10.1111/apt.13763]

73 **Nakamura Y**. Biomarkers for Immune Checkpoint Inhibitor-Mediated Tumor Response and Adverse Events. *Front Med (Lausanne)* 2019; **6**: 119 [PMID: 31192215 DOI: 10.3389/fmed.2019.00119]

74 **Terrin M**, Migliorisi G, Dal Buono A, Gabbiadini R, Mastrorocco E, Quadarella A, Repici A, Santoro A, Armuzzi A. Checkpoint Inhibitor-Induced Colitis: From Pathogenesis to Management. *Int J Mol Sci* 2023; **24** [PMID: 37511260 DOI: 10.3390/ijms241411504]

75 **Cai X**, Zhan H, Ye Y, Yang J, Zhang M, Li J, Zhuang Y. Current Progress and Future Perspectives of Immune Checkpoint in Cancer and Infectious Diseases. *Front Genet* 2021; **12**: 785153 [PMID: 34917131 DOI: 10.3389/fgene.2021.785153]

76 **Del Gaudio A**, Di Vincenzo F, Petito V, Giustiniani MC, Gasbarrini A, Scaldaferri F, Lopetuso LR. Focus on Immune Checkpoint Inhibitors-related Intestinal Inflammation: From Pathogenesis to Therapeutical Approach. *Inflamm Bowel Dis* 2023 [PMID: 37801695 DOI: 10.1093/ibd/izad229]

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World J Clin Cases 2024 February 26; 12(6): 1063-1075

DOI: 10.12998/wjcc.v12.i6.1063

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Correlative factors of poor prognosis and abnormal cellular immune function in patients with Alzheimer's disease

Hua Bai, Hong-Mei Zeng, Qi-Fang Zhang, Yue-Zhi Hu, Fei-Fei Deng

Specialty type: Neurosciences

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Velázquez-Soto H, Mexico

Received: October 26, 2023
Peer-review started: October 26, 2023
First decision: December 15, 2023
Revised: December 21, 2023
Accepted: January 29, 2024
Article in press: January 29, 2024
Published online: February 26, 2024

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Abstract

BACKGROUND

Alzheimer's disease (AD) is a serious disease causing human dementia and social problems. The quality of life and prognosis of AD patients have attracted much attention. The role of chronic immune inflammation in the pathogenesis of AD is becoming more and more important.

AIM

To study the relationship among cognitive dysfunction, abnormal cellular immune function, neuroimaging results and poor prognostic factors in patients.

METHODS

A retrospective analysis of 62 hospitalized patients clinical diagnosed with AD who were admitted to our hospital from November 2015 to November 2020. Collect cognitive dysfunction performance characteristics, laboratory test data and neuroimaging data from medical records within 24 h of admission, including Mini Mental State Examination Scale score, drawing clock test, blood T lymphocyte subsets, and neutrophils and lymphocyte ratio (NLR), disturbance of consciousness, extrapyramidal symptoms, electroencephalogram (EEG) and head nucleus magnetic spectroscopy (MRS) and other data. Multivariate logistic regression analysis was used to determine independent prog-nostic factors. the modified Rankin scale (mRS) was used to determine whether the prognosis was good. The correlation between drug treatment and prognostic mRS score was tested by the rank sum test.

RESULTS

Univariate analysis showed that abnormal cellular immune function, extrapyramidal symptoms, obvious disturbance of consciousness, abnormal EEG, increased NLR, abnormal MRS, and complicated pneumonia were related to the poor prognosis of AD patients. Multivariate logistic regression analysis showed that the decrease in the proportion of T lym-phocytes in the blood after abnormal cellular immune function (odd ratio: 2.078, 95% confidence interval: 1.156-3.986, $P < 0.05$) was an independent risk factor for predicting the poor prognosis of AD. The number of days of donepezil treatment to improve cognitive function was negatively correlated with mRS score ($r = 0.578$, $P < 0.05$).

CONCLUSION

The decrease in the proportion of T lymphocytes may have predictive value for the poor prognosis of AD. It is recommended that the proportion of T lymphocytes < 55% is used as the cut-off threshold for predicting the poor prog-nosis of AD. The early and continuous drug treatment is associated with a good prognosis.

Key Words: Alzheimer's disease; Cellular immunity; Prognosis; T lymphocytes; Magnetic resonance spectroscopy

Core Tip: Abnormal cellular immune function, extrapyramidal symptoms, abnormal electroencephalogram, increased neutrophils and lymphocyte ratio, abnormal magnetic spectroscopy, and complicated pneumonia were related to the poor prognosis of Alzheimer's disease (AD) patients. The decrease in the proportion of T lymphocytes in the blood after abnormal cellular immune function was an independent risk factor for predicting the poor prognosis of AD. The number of days of donepezil treatment to improve cognitive function was negatively correlated with modified Rankin scale score. The decrease in the proportion of T lymphocytes may have predictive value for the poor prognosis of AD.

Citation: Bai H, Zeng HM, Zhang QF, Hu YZ, Deng FF. Correlative factors of poor prognosis and abnormal cellular immune function in patients with Alzheimer's disease. *World J Clin Cases* 2024; 12(6): 1063-1075
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1063.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1063

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease with severe cognitive dysfunction. The prominent clinical manifestations are memory loss, confusion of thinking and logic, and abnormal mental behavior. It accounts for about 40%-60% of dementia patients[1,2]. At present, it is also inclined to think that AD is a chronic inflammatory disease mediated by abnormal autoimmune function. Mononuclear RNA sequencing and transcriptomics analysis show that the abnormal changes in microglia in the brain of AD patients induce a series of abnormal immune function. The activation of abnormal inflammasome represented by nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor protein 3 (NLRP3) inflammasome mediates the secretion of many immune inflammatory factors and subsequent cascades of chronic cascades reactions in immune inflammation[3,4]. The amyloid β (Aβ) peptide produced by abnormal neurons precipitates and aggregates outside the cell. The hyperphosphorylation of tau protein can also easily cause aggregation, leading to neuron and nerve synaptic dysfunction and cell death, especially small glial cells. Reactive proliferation of glial cells often causes secondary cytopathological reactions in diseased brain regions[5]. The activation of NLRP3 inflammasome promotes the aggregation of Aβ protein and the pathological formation of AD. The activation of NLRP3 inflammasome also contributes to the phosphorylation of tau protein and the accelerated development of AD. The interaction between Aβ and tau protein promotes the progression of AD. The onset and development of AD are usually mediated by abnormal immune function[6-8].

At present, the diagnostic criteria of AD mostly depend on the screening of cognitive function scale and the exclusion of similar diseases. Although there are some biochemical markers of dementia in serum or cerebrospinal fluid (CSF), their specificity and sensitivity are not high[9,10]. Combining some biochemical markers in blood or CSF for early diagnosis of AD may be a direction of future efforts, among which some biochemical markers related to immunity have great research prospects. Some scholars have combined the detection results of magnetic resonance spectroscopy (MRS) with blood biochemical markers and achieved good results[11]. On the other hand, the research on the factors affecting the prognosis of AD also has important clinical and social significance. Some AD patients may have a long life, but whether this longevity has social value is worth exploring. Longevity with obvious lack of quality of life and heavy burden on families may not be worth advocating. We need to make AD patients live a healthy life and return to society as much as possible [12,13].

The role of chronic immune inflammation in the pathogenesis of AD is becoming more and more important. The ratio of neutrophil to lymphocyte (NLR) in blood is an important systemic inflammatory biomarker. NLR is calculated by absolute counting of neutrophils divided by absolute counts of lymphocytes. NLR has been reported to be increased in

diabetes, hypertension, myocardial infarction. stroke and some tumor patients, which may be a new index to evaluate the prognosis of these patients[14-16]. The detection of T lymphocytes, B lymphocytes and natural killer cells in blood by flow cytometry can evaluate whether the immune function of AD patients is abnormal[17]. Combined with the detection of relevant biochemical markers and electroencephalogram (EEG) wave indexes by cranial MRS, it has great clinical significance for the early diagnosis and prognosis evaluation of AD patients. As far as we know, little research work has been carried out in this regard[18-20]. Therefore, this study focuses on the correlation between abnormal immune function and adverse prognostic factors in AD patients, and hope to find some valuable clues.

MATERIALS AND METHODS

Case study

This retrospective case study was reviewed and approved by the Medical Ethics Committee of the Third Affiliated Hospital of Guizhou Medical University in China. AD patients and their families hospitalized in the Department of Neurology and Psychiatry of the Third Affiliated Hospital of Guizhou Medical University were told to participate in the study and signed an informed consent form in accordance with the Declaration of Helsinki. The researchers checked the electronic medical records of 229 patients initially diagnosed with various types of dementia. These cases were patients who were discharged from the hospital between November 2015 and November 2020. The researchers re-evaluated the basis for the diagnosis of dementia in these cases, first confirmed or ruled out dementia through the Mini Mental State Examination Scale (MMSE) and the Cognitive Function Screening Scale, and then based on the medical history, clinical manifestations, and laboratory test results. In the diagnosis of AD, pay special attention to the use of the Harkinski Ischemic Scale to identify AD. Excluded 14 patients with incomplete data and 7 patients lacking the basis for the diagnosis of dementia scales. The remaining 208 patients with various types of dementia were further differentiated, and 87 patients with vascular dementia (VD) and 53 patients with other non-AD dementia were excluded. AD is roughly equivalent to the dementia of phlegm obstruction in Chinese medicine. VD is roughly equivalent to the dementia of qi stagnation and blood stasis in Chinese Medicine.

The 68 patients in this retrospective study are all clinically diagnosed AD patients. The 68 AD patients who met the needs of this study were selected for follow-up. After the patients are discharged from the hospital, they will be followed up and followed up by family members or guardians by telephone every 3 months. The prognosis will be assessed after detailed inquiries, and semi-quantitative according to the classic scale.

Data collection

Collect the following medical history and clinical data: Age of onset, gender, chief complaint, duration of disease, first symptoms, other symptoms, main positive signs, cranial magnetic resonance imaging (MRI), cranial MRS, EEG, blood routine, blood immunity Results of cell examination and drug treatment. The main metabolites detected by MRS include N-acetylaspartate (NAA), creatine (Cr), choline (Cho), inositol (MI), *etc.* NAA/Cr ratio and MI/Cr ratio were collected as key analysis indicators. Regarding EEG data, it is mainly to pay attention to the abnormal β wave and slow wave (θ wave and δ wave), especially the ratio of (θ + δ) to (α + β) in the whole brain [(θ + δ)/(α + β)]. We also pay attention to the ratio of neutrophils to lymphocytes (NLR) in the blood. The percentage values of T lymphocytes, B lymphocytes, and natural killer (NK) cells detected by flow cytometry are also collected. As the value of Aβ protein and tau protein in the blood in the diagnosis of AD is controversial sometimes, this study was not collected. The decrease of Aβ42 protein in the CSF and the increase of phosphorylated tau protein do have certain value in the diagnosis of AD, but there are many lacks of data in this group of cases, and they have not been collected. In addition, we collected MMSE score data and cognitive function screening scale scores for AD patients.

Prognosis assessment

The modified rankin scale (mRS) was used to assess neurological function at admission, discharge, and follow-up. There are 6 grades of mRS score: 0 score is for full recovery; a score of 1 score is defined as having no apparent dysfunction or being able to perform daily life and work tasks despite symptoms; 2 score is mild disability, but basically able to complete daily life and work tasks independently; 3 score is moderate disability, unable to complete all previous activities, difficult to handle own affairs independently; 4 score is severely disabled and needs to be cared for by someone else; 5 score is severe disability who require intensive care by medical staff; and 6 score is defined as death case.

According to the mRS during the follow-up period, all patients were divided into two groups: Those with mRS score of 0-2 scores were defined as "good prognosis"; 3-6 scores was defined as "poor prognosis".

Flow cytometry to detect cellular immune indicators

The FC500 automatic flow cytometer was used to perform the detection by direct immunofluorescence. The percentage of quantitative counts of T lymphocytes, B lymphocytes, and NK cells in the blood of patients was measured at one time. FITC-labeled anti-CD mAbs and normal mouse IgG were prepared. Cell wash with 2% BSA, 0.1% NaN and PBS. The fixative was prepared to a volume of 100 mL with 25% glutaraldehyde 3.2 mL, 2 g glucose, and BSA-free cell wash. Debug the flow cytometer. 10^6 PBMC were added to each experimental tube, centrifuged at 1500 r/min for 3 min, and the supernatant was discarded. Add 20 mL of fluorescein-labeled anti-CD mAb, mix well; incubate at 4 °C for 60 min, add cell wash, centrifuge at 1500 r/min for 3 min, wash repeatedly 3 times; use cell wash to restore volume to 0.5 mL, add fixative 20 mL, mix; carefully check on the machine.

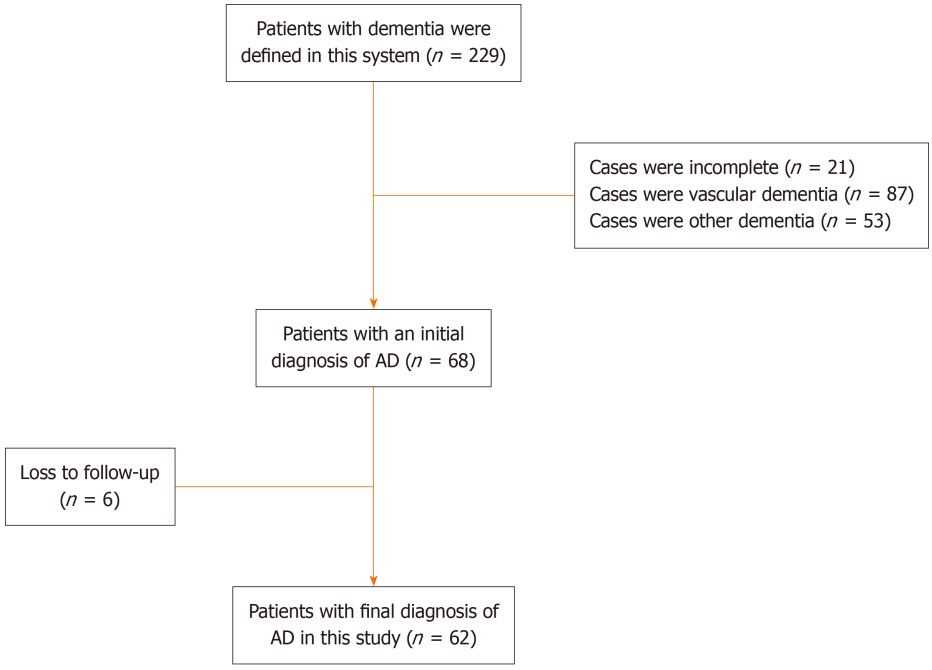

Figure 1 Flowchart of the study. AD: Alzheimer's disease.

Statistical analysis

SPSS software was used for statistical analysis (version 17.0). The data collected are expressed as mean ± SD or median (range). Count data is expressed as a ratio or percentage. Univariate correlation analysis was used to compare the differences between the two groups. Student *t* test or Mann Whitney test is used for measurement data, *t* test is used for variables with normal distribution, and Mann Whitney test is used for variables with non normal distribution. The counting data were compared by chi square test. Logistic regression analysis was used to determine the independent risk factors of poor prognosis. Differences in mRS scores between two groups were determined using Spearman rank correlation test. The best cut-off value of NAA/Cr as a prognostic index of AD was determined by the analysis of receptor working curve (ROC). *P* values less than 0.05 (bilateral) were considered statistically significant.

RESULTS

Basic information of clinical data

Through the electronic medical records database of the inpatient department and medical record room of the hospital, 229 cases of patients with clinical diagnosis of single or combined dementia were collected, including 87 cases of VD, 68 cases of AD, and 53 cases of other dementia. These patients with other types of dementia included 3 cases of frontotemporal dementia, 2 cases of Lewy body dementia, 5 cases of Parkinson's disease dementia, 10 cases of chronic alcoholism dementia, 3 cases of dementia after carbon monoxide poisoning, 2 cases of dementia after AIDS infection, 3 cases of hypothyroid dementia, 2 cases of neurosyphilis paralytic dementia cases, 4 cases of dementia after hydrocephalus, 1 case of dementia after heavy metal poisoning, 3 cases of dementia after organic pesticide poisoning, 6 cases of dementia after intracranial infection, and 9 cases of mixed dementia. Another 7 patients did not meet the criteria for diagnosing dementia according to international standards, and the clinical data of 14 patients were incomplete. Of the 68 patients diagnosed with AD, 6 patients had incomplete data or lost contact during the follow-up of this study (Figure 1 provides a schematic diagram of the process for selecting patients). The clinical diagnostic criteria of AD are verified in accordance with the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association. Among the 62 patients with complete follow-up of AD, 7 had a family history of dementia, including 4 with *APP* gene mutation, 2 with *PS-1* gene mutation, and 1 with *PS-2* gene mutation.

The 62 patients in this follow-up study were 55 to 92 years old (71.0 years old ± 8.7 years old), 24 males and 38 females. All of them had chronic insidious onset and were sent to the hospital for treatment after they were found to have abnormal symptoms by their families. These patients had no history of major mental trauma, no history of head trauma, no history of drug abuse and toxicosis. The first symptoms were as follows: 19 cases (30.6%) of memory loss, 15 cases (24.2%) of personality changes, and 28 cases (45.1%) of abnormal mental behavior. The time from onset to hospital admission ranges from 5 d to 1.5 years. Initially, 35 patients (56.5%) were misdiagnosed as depression, schizophrenia, personality disorder, menopausal syndrome, affective psychological disorder and insomnia, *etc*. Throughout the course of the disease, all patients had obvious clinical manifestations of memory loss and abnormal mental behavior. The 54 patients had obvious short-term memory deficits, 34 patients had abnormal personality, 26 patients hallucinated, 20 patients had significant depression, 19 patients had persecuted delusions, 12 patients had autonomic dysfunction, and 10 patients

had varying degrees of consciousness disturbances, including special disturbances of consciousness, delirium, and stupor. Follow-up was interrupted for 6 patients, two of whom died of complicated pneumonia and respiratory failure, one of whom died of complicated lung cancer metastasis and spread, one of whom died of complicated arrhythmia, and two of whom had family members who were unwilling to cooperate with follow-up. The clinical characteristics and other basic information of the AD patients studied were summarized (Table 1).

Auxiliary inspection results

The data of Cranial MRI, MRS, EEG, blood routine, and blood immune cell tests were available for all patients. There were 52 cases with abnormal brain MRI, including 43 (69.4%) with brain atrophy, 22 (35.5%) with demyelinating lesions around the ventricle (white matter osteoporosis), and 36 (25.8%) with abnormal T2 signals in the hippocampus (Figure 2). There were 60 cases with abnormal brain MRS, including 59 cases with decreased NAA/Cr (95.1%) and 56 cases with increased MI/Cr (90.3%). There were 48 cases (77.4%) with abnormal EEG examination, including 18 patients with high-amplitude β waves, 17 patients with more theta waves, 13 patients with δ waves, and the ratio of (θ + δ)/(α + β) is greater than 1.8 in 42 patients. Among the AD patients in this study, only 5 patients had mild abnormalities in routine blood tests, while the NLR value exceeded 4.5 in 20 patients and exceeded 4.0 in 46 patients. Blood immune cell examination found abnormal in 38 cases, mainly the proportion of T lymphocytes or NK cells decreased. The proportion of T lymphocytes was (55.4% ± 6.3%) in AD patients. The partial results of detecting lymphocyte subsets using flow cytometry are shown in Figure 3.

The relevant situation of the treatment effect

All patients were treated with medications, mainly medications that may improve cognitive function. Among them, 48 patients were treated with Donepezil (5-10 mg/d), 7 patients were treated with nicergoline, 5 patients were treated with Galantamine. Huperzine A was used in 2 cases. In addition, piracetam, oxiracetam, adenosine triphosphate, coenzyme Q10, vitamin E and other drugs were used for treatment. Risperidone, or olanzapine, or clozapine was used at the same time to control mental symptoms. All patients were not treated with transcranial magnetic therapy, acupuncture therapy, music therapy, psychotherapy, and other treatment methods. The average follow-up time is 10 months (6-24 months). At the end of the follow-up, 16 patients (25.8%) had a good prognosis, 19 patients (30.6%) had a moderate prognosis, and 27 patients (43.6%) had a poor prognosis. mRS score: 5 points for 3 cases, 4 points for 7 cases, 3 points for 4 cases, 2 points for 17 cases, 1 point for 23 cases, and 0 points for 8 cases. Among them, 28 cases were treated with risperidone alone to control their psychiatric symptoms, and the follow-up mRS score was 1-5 (3.00 ± 0.72) points. Four patients died during the follow-up period, and 40 patients were hospitalized again during the follow-up period.

Prognosis and predictive factors

Univariate analysis showed that there were significant differences in five indexes in the corresponding auxiliary examination test values between the groups with good prognosis and poor prognosis, including hallucination (P = 0.025), abnormal EEG (P = 0.003), the ratio of (θ + δ)/(α + β) by EEG (P = 0.019), abnormality of hippocapus (P = 0.001), the proportion of T lymphocytes obtained by flow cytometry (P = 0.008). We found that the proportion of T lymphocytes < 55% can be used as the cut-off threshold for predicting the poor prognosis of AD. We also found that the ratio of (θ + δ)/(α + β) was usually greater than or equal to 1.8 in the poor prognosis group. In addition, patients with severe depressive symptoms, moderate or severe brain atrophy, severe abnormal EEG, and significantly reduced ratios of T lymphocytes or NK cells were associated with poor prognosis in AD patients (Tables 2 and 3).

The NLR ratio in blood, the severity of memory impairment and the time of drug treatment had no significant correlation with the prognosis of AD patients. The ROC analysis of NAA/Cr obtained by MRS can predict the adverse prognosis of AD patients, and the area under the curve is 0.825 (95% confidence interval: 0.126-0.958; P < 0.01). According to the ROC curve, the best intercept value is 1.52, the sensitivity is 85.6%, and the specificity is 89.3% (Figure 3). Subsequently, spearman correlation analysis or the Rank Sum test was performed. The correlation between the NAA/Cr ratio and mRS score after the treatment of donepezil in 28 patients was analyzed, and it was found that there was a positive correlation between the two group (r = 0.609, P < 0.05); the number of days of donepezil treatment to improve cognitive function was negatively correlated with mRS score (r = 0.578, P < 0.05).

DISCUSSION

In this project, we retrospectively studied the subsequent prognosis of patients initially diagnosed with AD. We analyzed the clinical features, blood examination results, imaging data, EEG results and flow cytometry results. It also focused on the factors that are closely related to the poor prognosis. This study showed that the median T lymphocyte percentage in the poor prognosis group was significantly lower than that in the good prognosis group. The percentage of T lymphocytes in the blood to the total lymphocytes is an important indicator reflecting the cellular immune function. There have been studies by scholars supporting that reduced cellular immune function may promote the onset of AD[21], our research results suggest that the reduced cellular immune function further makes the prognosis of AD patients worse. T lymphocytes are the main cells of cellular immunity. After being stimulated by antigens, T lymphocytes transform into sensitized T cells. They have direct killing effect on the invading antigen and the synergistic killing effect of cytokines released by sensitized T cells[22,23]. In anti-infective immunity, cellular immunity is the main force of anti-infective immunity to participate in immune protection. In neurodegenerative diseases, the decrease of cellular immune function is more likely due to the reduction of the body's own immunity[24]. After a transgenic AD mouse lacking T lymphocytes

Table 1 Clinical data and related characteristics of the Alzheimer's disease patients

Characteristics	Patients
Sex (male/female)	24/38
Age, mean, range (yr)	71 (55-92)
Interval between onset and hospitalization	87, 5-547
Mean, range (d)	
Initial symptom	
Hypomnesis, *n* (%)	19 (30.6)
Apparent personality change	15 (24.2)
Abnormal mental behavior	28 (45.1)
Personality abnormality, *n* (%)	34 (54.8)
Recent memory deficits, *n* (%)	54 (87.1)
Hallucination, *n* (%)	26 (41.9)
Delusion of victimization, *n* (%)	19 (30.6)
Disturbance of consciousness, *n* (%)	10 (16.1)
Depressed, *n* (%)	20 (32.2)
Abnormal EEG results, *n* (%)	48 (77.4)
(θ + δ)/(α + β) more than 1.8, *n* (%)	42 (67.7)
Abnormal brain MRI results, *n* (%)	52 (83.9)
Encephalatrophy, *n* (%)	43 (69.4)
Abnormality of hippocampus, *n* (%)	36 (58.1)
Ratio of NAA/Cr decreased, *n* (%)	59 (95.2)
NLR (median interquartile)	2.25 (1.59-2.97)
Proportion of T lymphocytes in blood	0.55 (0.47-0.63)
Proportion of B lymphocytes in blood	0.13 (0.09-0.18)
Proportion of NK cell in blood	0.11 (0.07-0.17)

EEG: Electroencephalogram; MRI: Magnetic resonance imaging; NLR: Neurtrophil-to-lymphocyte ratio; NAA: N-acetylaspartate; Cr: Creatine; NK: Natural killer.

was cultured for 6 months, Marsh *et al*[25] found that the accumulation of beta amyloid in the brains of these mice was more than twice that of AD mice with intact immune systems. In addition, the neuroinflammation of Rag5xfad mice with immunodeficiency was significantly increased, which is manifested by changes in the phenotype of microglia, increased production of cytokines, and decreased phagocytic ability. Regulatory T cells are important factors in maintaining immune tolerance of the body, and they may have a protective effect on the pathogenesis of AD[17]. It is speculated that the decline of cellular immune function is not only closely related to the onset of AD, but also has a greater relationship with the poor prognosis of AD. There is increasing evidence that the occurrence of AD is closely related to slow immune inflammation, and the changes of lymphocytes in the blood may be directly related to this slow immune inflammation. Therefore, in this study, data from lymphocyte subsets were collected and analyzed.

MRS is an imaging technique that uses the principle of magnetic resonance and chemical shift phenomena to perform imaging and quantitative analysis of specific nuclei and related compounds[26,27]. In the normal human brain, there are 5 resonance spectrum peaks in the MRS examination: NAA peak, Cho peak, Cr peak, inositol peak, and glutamate peak. The decrease in NAA peak can be used as a sign of neuron loss or damage in the brain. The content of Cr in the gray matter of the brain is higher than that of the white matter, and it is a high energy phosphoric acid reserve substance for ATP/ADP conversion[28]. This research found that the NAA/Cr ratio of the AD poor prognosis group was significantly lower than the NAA/Cr ratio of the good prognosis group. The decrease in NAA/Cr ratio indicates that there is more loss of bilateral hippocampal neurons, which can be used as a biomarker for the transition from mild cognitive impairment to AD. Zhang *et al*[29] found that the NAA/Cr ratio of the posterior cingulate gyrus of MCI patients who progressed to AD dementia was lower than that of patients who progressed to Lewy body dementia (DLB). The prognosis of AD type dementia and DLB. Kantarci *et al*[30] tested the cranial MRS of AD, VD, and DLB patients and found that NAA/Cr in AD and VD patients were lower than normal. AD patients had NAA/Cr lower than DLB patients. The

Table 2 Univariate analysis of prognostic factors associated with Alzheimer's disease

Variables	Good prognosis (*n* = 27)	Poor prognosis (*n* = 35)	*P* value
Age (yr)	71.2 ± 15.3	70.6 ± 16.7	0.829
Sex, *n* (%)			
Male	11 (40.7)	15 (42.9)	0.867
Female	16 (59.3)	20 (57.1)	
Duration from onset to admission, *n* (%)			
< 90 d	18 (66.7)	22 (62.9)	0.755
≥ 90 d	9 (33.3)	13 (37.1)	
Personality abnormality			
Yes	15	19	0.092
No	12	16	
Recent memory deficits			
Yes	22	32	0.247
No	5	3	
Hallucination			
Yes	7	19	0.025
No	20	16	
Delusion of victimization			
Yes	5	14	0.069
No	22	21	
Disturbance of consciousness			
Yes	2	8	0.101
No	25	27	
Depressed			
Yes	8	12	0.698
No	19	23	
Abnormal EEG results			
Yes	16	32	0.003
No	11	3	
(θ + δ)/(α + β) from EEG			
≥ 1.8	14	28	0.019
< 1.8	13	7	
Abnormal brain MRI results			
Yes	24	28	0.346
No	3	7	
Encephalatrophy			
Yes	20	23	0.479
No	7	12	
Abnormality of hippocampus			
Yes	8	28	0.001
No	19	7	
NAA/Cr ratio decreased			

Yes	25	34	0.408
No	2	1	
NLR (median IQR)	2.19 (1.51-2.87)	2.34 (1.62-3.28)	0.379
Proportion of T lymphocytes in blood	0.63 (0.38-0.77)	0.37 (0.24-0.49)	0.008
Proportion of B lymphocytes in blood	0.11 (0.08-0.18)	0.14 (0.10-0.23)	0.282
Proportion of NK cell in blood	0.15 (0.08-0.19)	0.10 (0.06-0.16)	0.075

AD: Alzheimer's disease; SD: Standard deviation; IQR: Interquartile range; EEG: Electroencephalogram; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; NLR: Neutrophil-to-lymphocyte ratio; NAA: N-acetyl aspartate; Cr: Creatine; NK: Natural killer. *P* values < 0.05 are considered statistically significant.

Table 3 Multivariate analysis of factors associated with a poor prognosis

Variables	OR	95%CI	*P* value
Hallucination	2.961	0.265-18.397	0.723
Abnormal EEG results	1.983	0.079-7.531	0.682
Abnormal brain MRI results	12.369	0.592-39.127	0.849
Abnormality of hippocampus	5.394	0.275-78.364	0.231
NAA/Cr ratio decreased	1.398	0.056-135.284	0.816
Proportion of T lymphocytes in blood	3.265	1.156-5.681	0.038

95%CI: 95% confidence interval; OR: Odds ratio; EEG: electroencephalogram; NAA: N-acetylaspartate; Cr: Creatine.

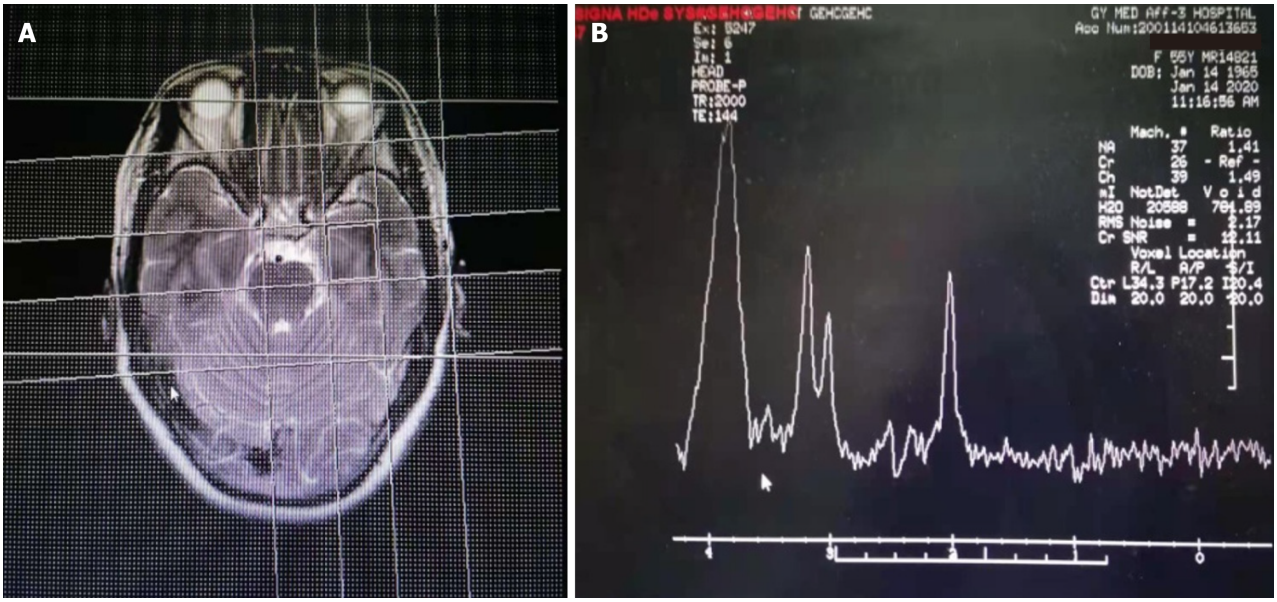

Figure 2 Magnetic resonance imaging and corresponding magnetic spectroscopy images of an Alzheimer's disease patient. The patient was a 55-year-old female with a 4-year course of disease and a Mini Mental State Examination Scale score of 14 points. A: Magnetic resonance imaging images (axial view) of the patient showed mild degeneration and atrophy in the hippocampus, deepening of multiple cerebral sulcus, suggesting mild brain atrophy; B: The corresponding magnetic spectroscopy pictures of the patient showed N-acetylaspartate 37mmol/L, creatine 26 mmol/L, and choline 39 mmol/L, indicating that there was a metabolic disorder of brain neurotransmitters.

Cho/Cr ratio of AD and DLB patients was higher than normal. The researcher believes that in dementia characterized by neuronal loss, NAA/Cr ratio is reduced, and in dementia characterized by severe cholinergic insufficiency, Cho/Cr ratio is elevated. By examining the cranial MRS of AD patients, it can not only be used to diagnose AD, but also be used to evaluate the prognosis of AD patients.

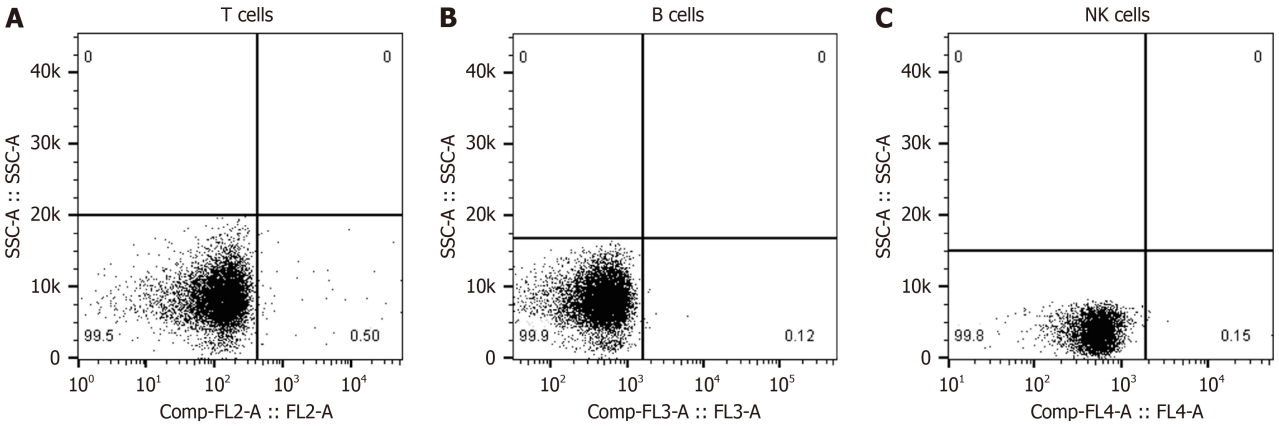

Figure 3 Lymphocyte subsets in the blood of Alzheimer's disease patients were detected by flow cytometry. A: T cell was detected by using Anti-human CD3e-PE (ebioscience); B: B cells were detected by using Anti-Human CD19-PerCP (BioLegend); C: Natural killer cells were detected by using anti-human CD56-APC (ebioscience). NK: Natural killer.

EEG examination is mainly used for differential diagnosis of epilepsy, as well as auxiliary diagnosis of encephalitis and certain encephalopathy[31]. This study also found that the prognosis of AD patients with a ratio of $(\theta + \delta)/(\alpha + \beta)$ greater than or equal to 1.8 obtained by EEG was poor, suggesting that careful EEG analysis also has a certain value in judging the prognosis of AD. Engedal *et al*[32] used statistical pattern recognition quantitative EEG to predict the conversion rate of dementia in patients with subjective cognitive decline (SCD) and MCI, and conducted follow-up. Of the 200 participants with complete data, 70 cases progressed from other conditions to dementia, and 52 cases developed to AD. Based on the EEG test results, the receiver operating characteristics analysis showed that the area under the curve was 0.78, the corresponding sensitivity was 71%, and the specificity was 69%. Researcher believe these SCD and MCI patients are at high risk of developing dementia within five years. Our study also found that the clinical prognosis of AD patients with severe depressive symptoms, moderate or severe brain atrophy, and severe abnormal EEG is poor. These aspects need to be grasped as a whole and further analyzed. Olichney *et al*[4] believed that when abnormal N400 and P600 repeat effects were detected by cognitive event related potential (ERP) in AD patients, it indicated that the synaptic plasticity in the brain of the patients had been significantly abnormal. Abnormalities of P600 or N400 in MCI patients are significantly associated with an increased risk of subsequent conversion to AD, and ERP test could provide a useful biomarker for the diagnosis of AD patients.

NLR is considered to be an easy to detect and operate systemic inflammatory index, which is related to the abnormal cellular immune function. Based on the above considerations, we analyzed the impact of NLR on the prognosis of AD patients. The results showed that there was no significant correlation between the ratio of NLR in blood and the prognosis of AD patients. Rembach *et al*[33] found that the sensitivity of NLR itself is not enough to diagnose AD. There is indeed a certain correlation between NLR and neocortical amyloid load in the cross section, but this relationship disappeared after longitudinal analysis. Moreover, the association between NLR and cognitive decline is also limited. They believe that NLR may only reflect the peripheral blood related inflammatory process, which is greatly affected by age and gender. These research results and views are basic consistent with our conclusion. Under normal circumstances, a small number of activated T cells enter the brain and participate in immune monitoring, but the infiltration of a large number of T cells usually occurs in the case of severe chronic immune inflammation in AD. Macrophages rather than microglia are the main phagocytes in the brain. These infiltrating cells are the key to the repair process. Giving anti-inflammatory treatment at the appropriate time of the disease can reduce the risk of Aβ pathological damage caused by deposition[34-36].

However, our research had some limitations. First, this study was a retrospective analysis, and it is difficult to control confounding factors. Second, the items related to the detection of cellular immune function were incomplete, and lymphocyte transformation test and immunoglobulin test were not carried out. Third, the sample size of this study is relatively small, and it is a single institution study, and the popularization value of the conclusion is limited. Nevertheless, this research still has some valuable findings in predicting the correlation between abnormal cellular immune function and poor prognosis in AD patients.

CONCLUSION

The decrease in the proportion of T lymphocytes may have predictive value for the poor prognosis of AD (Figure 4). It is suggested that the proportion of T lymphocytes less than 55% should be used as the cut-off threshold for predicting the poor prognosis of AD. In addition, MRS combined with EEG detection is also worthy of recognition in predicting the poor prognosis of AD. Yet the early and continuous drug treatment that improve cognitive function is associated with a good prognosis.

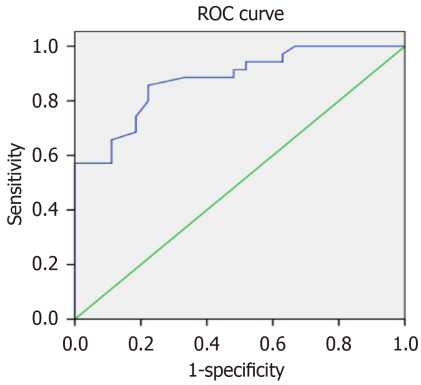

Figure 4 Receptor working curve of the predictive value of N-acetylaspartate/creatine ratio of magnetic spectroscopy for poor prognosis of Alzheimer's disease. ROC: Receptor working curve.

ARTICLE HIGHLIGHTS

Research background

Alzheimer's disease (AD) is a neurodegenerative disease with severe cognitive dysfunction. The prominent clinical manifestations are memory loss, confusion of thinking and logic, and abnormal mental behavior. At present, it is also inclined to think that AD is a chronic inflammatory disease mediated by abnormal autoimmune function. Mononuclear RNA sequencing and transcriptomics analysis show that the abnormal changes in microglia in the brain of AD patients induce a series of abnormal immune function. The activation of abnormal inflammasome represented by nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor protein 3 (NLRP3) inflammasome mediates the secretion of many immune inflammatory factors and subsequent cascades of chronic cascades reactions in immune inflammation. The amyloid β (Aβ) peptide produced by abnormal neurons precipitates and aggregates outside the cell. The hyperphosphorylation of tau protein can also easily cause aggregation, leading to neuron and nerve synaptic dysfunction and cell death, especially small glial cells. Reactive proliferation of glial cells often causes secondary cytopathological reactions in diseased brain regions.

Research motivation

The role of chronic immune inflammation in the pathogenesis of AD is becoming more and more important. The ratio of NLR in blood is an important systemic inflammatory biomarker. NLR is calculated by ab-solute counting of neutrophils divided by absolute counts of lymphocytes. NLR has been reported to be increased in diabetes, hypertension, myocardial infarction. stroke and some tumor patients, which may be a new index to evaluate the prognosis of these patients. The detection of T lymphocytes, B lymphocytes and natural killer cells in blood by flow cytometry can evaluate whether the immune function of AD patients is abnormal. Combined with the detection of relevant biochemical markers and EEG wave indexes by cranial magnetic spectroscopy (MRS), it has great clinical significance for the early diagnosis and prognosis evaluation of AD patients. As far as we know, little research work has been carried out in this regard.

Research objectives

To explore the correlation between abnormal immune function and adverse prognostic factors in AD patients, and hope to find some valuable clues.

Research methods

A retrospective analysis of 62 hospitalized patients clinical diagnosed with AD who were admitted to our hospital from November 2015 to November 2020. Collect cognitive dysfunction performance characteristics, laboratory test data and neuroimaging data from medical records within 24 h of admission, including MMSE score, drawing clock test, blood T lymphocyte subsets, and NLR, disturbance of consciousness, extrapyramidal symptoms, electroencephalogram (EEG) and head nucleus MRS and other data. Multivariate logistic regression analysis was used to determine independent prognostic factors. the modified Rankin scale (mRS) was used to determine whether the prognosis was good. The correlation between drug treatment and prognostic mRS score was tested by the rank sum test.

Research results

Univariate analysis showed that abnormal cellular immune function, extrapyramidal symptoms, obvious disturbance of consciousness, abnormal EEG, increased NLR, abnormal MRS, and complicated pneumonia were related to the poor prognosis of AD patients. Multivariate logistic regression analysis showed that the decrease in the proportion of T lymphocytes in the blood after abnormal cellular immune function (odd ratio: 2.078, 95% confidence interval: 1.156-3.986, $P < 0.05$) was an independent risk factor for predicting the poor prognosis of AD. The number of days of donepezil treatment to improve cognitive function was negatively correlated with mRS score ($r = 0.578$, $P < 0.05$).

Research conclusions

The decrease in the proportion of T lymphocytes may have predictive value for the poor prognosis of AD. It is suggested that the proportion of T lymphocytes less than 55% should be used as the cut-off threshold for predicting the poor prognosis of AD. In addition, MRS combined with EEG detection is also worthy of recognition in predicting the poor prognosis of AD. Yet the early and continuous drug treatment that improve cognitive function is associated with a good prognosis.

Research perspectives

It is speculated that the decline of cellular immune function is not only closely related to the onset of AD, but also has a greater relationship with the poor prognosis of AD. There is increasing evidence that the occurrence of AD is closely related to slow immune inflammation, and the changes of lymphocytes in the blood may be directly related to this slow immune inflammation. In a word, this research still has some valuable findings in predicting the correlation between abnormal cellular immune function and poor prognosis in AD patients.

FOOTNOTES

Author contributions: Bai H contributed to study design, fundraising, and manuscript preparation; Bai H, Zeng HM, Hu YZ, and Deng FF contributed to investigation and data collection; Zeng HM, Zhang QF, and Bai H contributed to results analysis and discussion; all authors approved the final version of this manuscript.

Supported by the National Natural Science Foundation of China, No. 3206080019 and No. 32060182; Science and Technology Support Plan of Guizhou Province in China, No. [2020]4Y129; and Qiannan Prefecture Science and Technology Plan Project, No. [2022]01.

Institutional review board statement: The study was reviewed and approved by the Third Affiliated Hospital of Guizhou Medical University (Approval No. 20162160).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at baih2020@gmc.edu.cn.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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S-Editor: Chen YL
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Jacus JP**, Mayelle A, Voltzenlogel V, Cuervo-Lombard CV, Antoine P. Modelling Awareness in Alzheimer's Disease. *J Alzheimers Dis* 2020; **76**: 89-95 [PMID: 32417778 DOI: 10.3233/JAD-200017]

2 **Scheltens P**, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, Van der Flier WM. Alzheimer's disease. *Lancet* 2016; **388**: 505-517 [PMID: 26921134 DOI: 10.1016/S0140-6736(15)01124-1]

3 **Lee JY**, Jin HK, Bae JS. Sphingolipids in neuroinflammation: a potential target for diagnosis and therapy. *BMB Rep* 2020; **53**: 28-34 [PMID: 31818364 DOI: 10.5483/BMBRep.2020.53.1.278]

4 **Olichney JM**, Taylor JR, Gatherwright J, Salmon DP, Bressler AJ, Kutas M, Iragui-Madoz VJ. Patients with MCI and N400 or P600 abnormalities are at very high risk for conversion to dementia. *Neurology* 2008; **70**: 1763-1770 [PMID: 18077800 DOI: 10.1212/01.wnl.0000281689.28759.ab]

5 **Ising C**, Venegas C, Zhang S, Scheiblich H, Schmidt SV, Vieira-Saecker A, Schwartz S, Albasset S, McManus RM, Tejera D, Griep A, Santarelli F, Brosseron F, Opitz S, Stunden J, Merten M, Kayed R, Golenbock DT, Blum D, Latz E, Buée L, Heneka MT. NLRP3 inflammasome activation drives tau pathology. *Nature* 2019; **575**: 669-673 [PMID: 31748742 DOI: 10.1038/s41586-019-1769-z]

6 **Li L**, Ismael S, Nasoohi S, Sakata K, Liao FF, McDonald MP, Ishrat T. Thioredoxin-Interacting Protein (TXNIP) Associated NLRP3 Inflammasome Activation in Human Alzheimer's Disease Brain. *J Alzheimers Dis* 2019; **68**: 255-265 [PMID: 30741672 DOI: 10.3233/JAD-180814]

7 **Olsen I**, Singhrao SK. Inflammasome Involvement in Alzheimer's Disease. *J Alzheimers Dis* 2016; **54**: 45-53 [PMID: 27314526 DOI: 10.3233/JAD-160197]

8 **Stancu IC**, Cremers N, Vanrusselt H, Couturier J, Vanoosthuyse A, Kessels S, Lodder C, Brône B, Huaux F, Octave JN, Terwel D, Dewachter I. Aggregated Tau activates NLRP3-ASC inflammasome exacerbating exogenously seeded and non-exogenously seeded Tau pathology in vivo. *Acta Neuropathol* 2019; **137**: 599-617 [PMID: 30721409 DOI: 10.1007/s00401-018-01957-y]

9 **Cable J**, Holtzman DM, Hyman BT, Tansey MG, Colonna M, Kellis M, Brinton RD, Albert M, Wellington CL, Sisodia SS, Tanzi RE. Alternatives to amyloid for Alzheimer's disease therapies-a symposium report. *Ann N Y Acad Sci* 2020; **1475**: 3-14 [PMID: 32472577 DOI: 10.1111/nyas.14371]

10 **Egan MF**, Kost J, Voss T, Mukai Y, Aisen PS, Cummings JL, Tariot PN, Vellas B, van Dyck CH, Boada M, Zhang Y, Li W, Furtek C, Mahoney E, Harper Mozley L, Mo Y, Sur C, Michelson D. Randomized Trial of Verubecestat for Prodromal Alzheimer's Disease. *N Engl J Med* 2019; **380**: 1408-1420 [PMID: 30970186 DOI: 10.1056/NEJMoa1812840]

11 **Mielke MM**, Hagen CE, Xu J, Chai X, Vemuri P, Lowe VJ, Airey DC, Knopman DS, Roberts RO, Machulda MM, Jack CR Jr, Petersen RC, Dage JL. Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography. *Alzheimers Dement* 2018; **14**: 989-997 [PMID: 29626426 DOI: 10.1016/j.jalz.2018.02.013]

12 **Reitz C**. Genetic diagnosis and prognosis of Alzheimer's disease: challenges and opportunities. *Expert Rev Mol Diagn* 2015; **15**: 339-348 [PMID: 25634383 DOI: 10.1586/14737159.2015.1002469]

13 **Wang M**, Peng IF, Li S, Hu X. Dysregulation of antimicrobial peptide expression distinguishes Alzheimer's disease from normal aging. *Aging (Albany NY)* 2020; **12**: 690-706 [PMID: 31907335 DOI: 10.18632/aging.102650]

14 **Hamelin L**, Lagarde J, Dorothée G, Potier MC, Corlier F, Kuhnast B, Caillé F, Dubois B, Fillon L, Chupin M, Bottlaender M, Sarazin M. Distinct dynamic profiles of microglial activation are associated with progression of Alzheimer's disease. *Brain* 2018; **141**: 1855-1870 [PMID: 29608645 DOI: 10.1093/brain/awy079]

15 **Kim MS**, Kim Y, Choi H, Kim W, Park S, Lee D, Kim DK, Kim HJ, Hyun DW, Lee JY, Choi EY, Lee DS, Bae JW, Mook-Jung I. Transfer of a healthy microbiota reduces amyloid and tau pathology in an Alzheimer's disease animal model. *Gut* 2020; **69**: 283-294 [PMID: 31471351 DOI: 10.1136/gutjnl-2018-317431]

16 **Sayed A**, Bahbah EI, Kamel S, Barreto GE, Ashraf GM, Elfil M. The neutrophil-to-lymphocyte ratio in Alzheimer's disease: Current understanding and potential applications. *J Neuroimmunol* 2020; **349**: 577398 [PMID: 32977249 DOI: 10.1016/j.jneuroim.2020.577398]

17 **Speciale L**, Calabrese E, Saresella M, Tinelli C, Mariani C, Sanvito L, Longhi R, Ferrante P. Lymphocyte subset patterns and cytokine production in Alzheimer's disease patients. *Neurobiol Aging* 2007; **28**: 1163-1169 [PMID: 16814429 DOI: 10.1016/j.neurobiolaging.2006.05.020]

18 **Bregman N**, Kavé G, Zeltzer E, Biran I; Alzheimer's Disease Neuroimaging Initiative. Memory impairment and Alzheimer's disease pathology in individuals with MCI who underestimate or overestimate their decline. *Int J Geriatr Psychiatry* 2020; **35**: 581-588 [PMID: 32011757 DOI: 10.1002/gps.5274]

19 **Fani L**, Georgakis MK, Ikram MA, Ikram MK, Malik R, Dichgans M. Circulating biomarkers of immunity and inflammation, risk of Alzheimer's disease, and hippocampal volume: a Mendelian randomization study. *Transl Psychiatry* 2021; **11**: 291 [PMID: 34001857 DOI: 10.1038/s41398-021-01400-z]

20 **Fohner AE**, Sitlani CM, Buzkova P, Doyle MF, Liu X, Bis JC, Fitzpatrick A, Heckbert SR, Huber SA, Kuller L, Longstreth WT, Feinstein MJ, Freiberg M, Olson NC, Seshadri S, Lopez O, Odden MC, Tracy RP, Psaty BM, Delaney JA, Floyd JS. Association of Peripheral Lymphocyte Subsets with Cognitive Decline and Dementia: The Cardiovascular Health Study. *J Alzheimers Dis* 2022; **88**: 7-15 [PMID: 35527553 DOI: 10.3233/JAD-220091]

21 **Bonotis K**, Krikki E, Holeva V, Aggouridaki C, Costa V, Baloyannis S. Systemic immune aberrations in Alzheimer's disease patients. *J Neuroimmunol* 2008; **193**: 183-187 [PMID: 18037502 DOI: 10.1016/j.jneuroim.2007.10.020]

22 **Lodygin D**, Hermann M, Schweingruber N, Flügel-Koch C, Watanabe T, Schlosser C, Merlini A, Körner H, Chang HF, Fischer HJ, Reichardt HM, Zagrebelsky M, Mollenhauer B, Kügler S, Fitzner D, Frahm J, Stadelmann C, Haberl M, Odoardi F, Flügel A. β-Synuclein-reactive T cells induce autoimmune CNS grey matter degeneration. *Nature* 2019; **566**: 503-508 [PMID: 30787438 DOI: 10.1038/s41586-019-0964-2]

23 **Regen F**, Hellmann-Regen J, Costantini E, Reale M. Neuroinflammation and Alzheimer's Disease: Implications for Microglial Activation. *Curr Alzheimer Res* 2017; **14**: 1140-1148 [PMID: 28164764 DOI: 10.2174/1567205014666170203141717]

24 **Hur JY**, Frost GR, Wu X, Crump C, Pan SJ, Wong E, Barros M, Li T, Nie P, Zhai Y, Wang JC, Tcw J, Guo L, McKenzie A, Ming C, Zhou X, Wang M, Sagi Y, Renton AE, Esposito BT, Kim Y, Sadleir KR, Trinh I, Rissman RA, Vassar R, Zhang B, Johnson DS, Masliah E, Greengard P, Goate A, Li YM. The innate immunity protein IFITM3 modulates γ-secretase in Alzheimer's disease. *Nature* 2020; **586**: 735-740 [PMID: 32879487 DOI: 10.1038/s41586-020-2681-2]

25 **Marsh SE**, Abud EM, Lakatos A, Karimzadeh A, Yeung ST, Davtyan H, Fote GM, Lau L, Weinger JG, Lane TE, Inlay MA, Poon WW, Blurton-Jones M. The adaptive immune system restrains Alzheimer's disease pathogenesis by modulating microglial function. *Proc Natl Acad Sci U S A* 2016; **113**: E1316-E1325 [PMID: 26884167 DOI: 10.1073/pnas.1525466113]

26 **Chaney A**, Williams SR, Boutin H. In vivo molecular imaging of neuroinflammation in Alzheimer's disease. *J Neurochem* 2019; **149**: 438-451 [PMID: 30339715 DOI: 10.1111/jnc.14615]

27 **Chandra A**, Dervenoulas G, Politis M; Alzheimer's Disease Neuroimaging Initiative. Magnetic resonance imaging in Alzheimer's disease and mild cognitive impairment. *J Neurol* 2019; **266**: 1293-1302 [PMID: 30120563 DOI: 10.1007/s00415-018-9016-3]

28 **Joe E**, Medina LD, Ringman JM, O'Neill J. (1)H MRS spectroscopy in preclinical autosomal dominant Alzheimer disease. *Brain Imaging Behav* 2019; **13**: 925-932 [PMID: 29907927 DOI: 10.1007/s11682-018-9913-1]

29 **Zhang B**, Ferman TJ, Boeve BF, Smith GE, Maroney-Smith M, Spychalla AJ, Knopman DS, Jack CR Jr, Petersen RC, Kantarci K. MRS in mild cognitive impairment: early differentiation of dementia with Lewy bodies and Alzheimer's disease. *J Neuroimaging* 2015; **25**: 269-274 [PMID: 25039916 DOI: 10.1111/jon.12138]

30 **Kantarci K**, Petersen RC, Boeve BF, Knopman DS, Tang-Wai DF, O'Brien PC, Weigand SD, Edland SD, Smith GE, Ivnik RJ, Ferman TJ, Tangalos EG, Jack CR Jr. 1H MR spectroscopy in common dementias. *Neurology* 2004; **63**: 1393-1398 [PMID: 15505154 DOI: 10.1212/01.wnl.0000141849.21256.ac]

31 **Bagattini C**, Mutanen TP, Fracassi C, Manenti R, Cotelli M, Ilmoniemi RJ, Miniussi C, Bortoletto M. Predicting Alzheimer's disease severity

by means of TMS-EEG coregistration. *Neurobiol Aging* 2019; **80**: 38-45 [PMID: 31077959 DOI: 10.1016/j.neurobiolaging.2019.04.008]

32 **Engedal K**, Barca ML, Høgh P, Bo Andersen B, Winther Dombernowsky N, Naik M, Gudmundsson TE, Øksengaard AR, Wahlund LO, Snaedal J. The Power of EEG to Predict Conversion from Mild Cognitive Impairment and Subjective Cognitive Decline to Dementia. *Dement Geriatr Cogn Disord* 2020; **49**: 38-47 [PMID: 32610316 DOI: 10.1159/000508392]

33 **Rembach A**, Watt AD, Wilson WJ, Rainey-Smith S, Ellis KA, Rowe CC, Villemagne VL, Macaulay SL, Bush AI, Martins RN, Ames D, Masters CL, Doecke JD; AIBL Research Group. An increased neutrophil-lymphocyte ratio in Alzheimer's disease is a function of age and is weakly correlated with neocortical amyloid accumulation. *J Neuroimmunol* 2014; **273**: 65-71 [PMID: 24907904 DOI: 10.1016/j.jneuroim.2014.05.005]

34 **Laurent C**, Buée L, Blum D. Tau and neuroinflammation: What impact for Alzheimer's Disease and Tauopathies? *Biomed J* 2018; **41**: 21-33 [PMID: 29673549 DOI: 10.1016/j.bj.2018.01.003]

35 **Lee JY**, Han SH, Park MH, Baek B, Song IS, Choi MK, Takuwa Y, Ryu H, Kim SH, He X, Schuchman EH, Bae JS, Jin HK. Neuronal SphK1 acetylates COX2 and contributes to pathogenesis in a model of Alzheimer's Disease. *Nat Commun* 2018; **9**: 1479 [PMID: 29662056 DOI: 10.1038/s41467-018-03674-2]

36 **Long H**, Zhong G, Wang C, Zhang J, Zhang Y, Luo J, Shi S. TREM2 Attenuates Aβ1-42-Mediated Neuroinflammation in BV-2 Cells by Downregulating TLR Signaling. *Neurochem Res* 2019; **44**: 1830-1839 [PMID: 31134514 DOI: 10.1007/s11064-019-02817-1]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2024 February 26; 12(6): 1076-1083

DOI: 10.12998/wjcc.v12.i6.1076

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Bipolar hip arthroplasty using conjoined tendon preserving posterior lateral approach in treatment of displaced femoral neck fractures

Ting-Xin Yan, Sheng-Jie Dong, Bo Ning, Yu-Chi Zhao

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ng BW, Malaysia

Received: November 20, 2023
Peer-review started: November 20, 2023
First decision: December 15, 2023
Revised: December 30, 2023
Accepted: January 27, 2024
Article in press: January 27, 2024
Published online: February 26, 2024

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Abstract

BACKGROUND

Hip fractures account for 23.8% of all fractures in patients over the age of 75 years. More than half of these patients are older than 80 years. Bipolar hemiarthroplasty (BHA) was established as an effective management option for these patients. Various approaches can be used for the BHA procedure. However, there is a high risk of postoperative dislocation. The conjoined tendon-preserving posterior (CPP) lateral approach was introduced to reduce postoperative dislocation rates.

AIM

To evaluate the effectiveness and safety of the CPP lateral approach for BHA in elderly patients.

METHODS

We retrospectively analyzed medical data from 80 patients with displaced femoral neck fractures who underwent BHA. The patients were followed up for at least 1 year. Among the 80 patients, 57 (71.3%) were female. The time to operation averaged 2.3 d (range: 1-5 d). The mean age was 80.5 years (range: 67-90 years), and the mean body mass index was 24.9 kg/m^2 (range: 17-36 kg/m^2). According to the Garden classification, 42.5% of patients were type III and 57.5% of patients were type IV. Uncemented bipolar hip prostheses were used for all patients. Torn conjoined tendons, dislocations, and adverse complications during and after surgery were recorded.

RESULTS

The mean postoperative follow-up time was 15.3 months (range: 12-18 months). The average surgery time was 52 min (range: 40-70 min) with an average blood loss of 120 mL (range: 80-320 mL). The transfusion rate was 10% (8 of 80 patients).

The gemellus inferior was torn in 4 patients (5%), while it was difficult to identify in 2 patients (2.5%) during surgery. The posterior capsule was punctured by the fractured femoral neck in 3 patients, but the conjoined tendon and the piriformis tendon remained intact. No patients had stem varus greater than 3 degrees or femoral fracture. There were no patients with stem subsidence more than 5 mm at the last follow-up. No postoperative dislocations were observed throughout the follow-up period. No significance was found between preoperative and postoperative mean Health Service System scores (87.30 ± 2.98 *vs* 86.10 ± 6.10, $t = 1.89$, $P = 0.063$).

CONCLUSION

The CPP lateral approach can effectively reduce the incidence of postoperative dislocation without increasing perioperative complications. For surgeons familiar with the posterior lateral approach, there is no need for additional surgical instruments, and it does not increase surgical difficulty.

Key Words: Conjoined tendon preserving; Bipolar hip arthroplasty; Femoral neck fractures; Postoperative dislocation; Posterolateral approach

Core Tip: We evaluated the effectiveness and safety of the conjoined tendon-preserving posterior (CPP) approach for bipolar hemiarthroplasty (BHA) during a short-term follow-up. We retrospectively evaluated 80 patients who underwent CPP BHA implanted with cementless femoral protheses. We protected the posterior structures of the hip joint. We made a partial incision in the quadratus femoris muscle to increase exposure, thus making the surgical procedure more feasible. There was no dislocation or other adverse events observed during the early follow-up period. The CPP approach can effectively reduce dislocation after BHA and improve postoperative hip joint stability.

Citation: Yan TX, Dong SJ, Ning B, Zhao YC. Bipolar hip arthroplasty using conjoined tendon preserving posterior lateral approach in treatment of displaced femoral neck fractures. *World J Clin Cases* 2024; 12(6): 1076-1083
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1076.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1076

INTRODUCTION

Hip fractures account for 23.8% of all fractures in patients over the age of 75 years[1]. More than half of these patients are older than 80 years[2]. A substantial proportion of hip fractures are femoral neck fractures, which puts the femoral head at risk of osteonecrosis and nonunion due to the vulnerable blood supply[3]. Bipolar hemiarthroplasty (BHA) was established as an effective management option that results in excellent pain relief, early mobilization, a short operation time, similar revision rate to total hip replacement within 5 years, and good long-term return to function in inactive elderly patients[4,5].

Various approaches can be used for the BHA procedure. The conventional posterolateral approach is the most widely used technique because it provides easy exposure, a short operation time, and a low incidence of postoperative gait disturbances[6]. However, it also leads to a higher postoperative dislocation rate than the anterior and lateral approaches [7,8]. Surgeons modified the posterolateral approach and reduced the incidence of postoperative dislocation by retaining the piriformis tendon and short external rotators with varying degrees[9-11].

Tetsunaga *et al*[12] reported a BHA technique using the conjoined tendon-preserving posterior (CPP) approach. For this technique, only the external obturator muscle is dissected in geriatric patients. Good outcomes with no cases of postoperative dislocation have been reported. Our department started using the CPP approach for BHA for displaced femoral neck fractures in 2021. This retrospective study was conducted to evaluate the effectiveness and safety of the CPP approach for BHA in elderly patients with femoral neck fractures.

MATERIALS AND METHODS

Population

This retrospective cohort study was approved by the institutional review board of our hospital. A prospectively compiled database was used to recruit patients who underwent cementless BHA for a displaced femoral neck fracture at our hospital from February 2021 to May 2022. A total of 103 consecutive patients were identified. One year after the surgery, 23 patients were lost to follow-up or died due to causes unrelated to the BHA. A total of 80 patients were included in this study.

Surgical procedure and postoperative rehabilitation

All operations were performed by a single senior surgeon (Yu-Chi Zhao), who performs at least 200 hip arthroplasty surgeries annually. The patients underwent BHA in the lateral decubitus position, and the iliac crest and sacrum were fixed anteriorly and posteriorly, respectively, to obtain a stable pelvis. A 45° incision about 10 cm in length was made posteriorly with the apex of the greater trochanter as the center. The gluteus maximus was bluntly separated along its fibers. Then, self-retaining retractors were placed under the deep fascia layer of the gluteus maximus. The pericapsular fat was resected using electrocautery to expose the posterior margin of the gluteus medius and the short external rotator muscles. The sciatic nerve was identified and protected during the operation. The piriformis tendon was palpable in the superior aspect of the wound deep to the gluteus Medius muscle. The gemellus superior, internal obturator, gemellus inferior, external obturator muscles, and quadratus femoris were identified caudally (Figure 1A). The obturator externus and proximal quadratus femoris were sectioned at the bony insertion site along the posterior aspect of the greater trochanter (Figure 1B).

It is important to coagulate the deep medial circumflex femoral artery, which is almost always at the proximal margin of the quadratus femoris muscle. The inferior portion of the joint capsule was incised in an "L" shape that started from the caudal margin of the gemellus inferior muscle. The arthrotomy was extended distally along the posterior border of the femur while preserving the posterior labrum. Then, No. 1 Ethicon was used to mark and invert the dissected capsule (Figure 1C). After the femoral neck was cut along the planned osteotomy line, the femoral head was removed using a corkscrew (Figure 1D). The femoral head was measured to select the appropriate outer head. The hip joint was flexed, adducted, and internally rotated to manipulate the femur in a similar way to the classical approach. Next, femoral broaching and insertion of instruments and femoral components were performed while preserving the piriformis muscle and conjoined tendon. An inner head and outer head of appropriate lengths were put in place to perform reduction. Manual reduction was performed according to a previous report[12]. This often requires a greater hip flexion degree than the conventional posterolateral approach. Then, the reduction was completed by pushing the outer head to the acetabulum. At this time, the suture on the capsule was retracted to prevent the capsule from embedding into the acetabulum (Figure 1E). After testing the hip stability and determining that there was no discrepancy in leg length, the joint was irrigated by a pulse flusher. The capsule, obturator externus, and proximal quadratus femoris was repaired to the trochanter by two transosseous tunnels, and the proximal capsule incision was repaired side to side (Figure 1F). All patients began full weight-bearing exercises assisted by a walker on postoperative day 1. A pillow was recommended to avoid excessive adduction for 3 wk.

Statistical analysis

The primary outcome was postoperative dislocation and adverse event rates. We also collected demographic data, including age, sex, and body mass index, perioperative data, including time to operation, operation time, preservation of short external rotator muscles, bleeding volume, transfusion, and the type of the prosthesis used, and postoperative data, including prosthesis alignment and femoral stem subsidence during follow-up. The Health Service System (HSS) score [13] was used to evaluate the hip function.

SPSS software (IBM Corp., Armonk, NY, United States) was used for statistical analysis, and continuous variables were represented by mean ± SD. The paired *t* test was used to compare HSS scores before surgery and 1 year after surgery. *P* values < 0.05 were considered significant.

RESULTS

Among the 80 patients, 57 (71.3%) were female. The time to operation averaged 2.3 d (range: 1-5 d). The mean age was 80.5 years (range: 67-90 years), and the mean body mass index was 24.9 kg/m^2 (range: 17-36 kg/m^2). According to the Garden classification, 42.5% of patients were type III and 57.5% of patients were type IV.

General data

The mean postoperative follow-up time was 12.3 months (range: 10-18 months). Uncemented bipolar hip prostheses were used for all patients: 31 hips with Self-Centering Bipolar and HA-coated Corail® stem (Depuy, Warsaw, IN, United States); and 49 hips with Cocr Ball Head & Bipolar Head and tapered HA-coated CL stem (AKMEDICAL, Beijing, China). The average surgery time was 52 min (range: 40-70 min) with an average blood loss of 120 mL (range: 80-320 mL).

Soft tissue damage during operation

The gemellus inferior was torn in 4 patients (5%), while it was difficult to identify in 2 patients (2.5%) during surgery. The posterior capsule was punctured by the fractured femoral neck in 3 patients, but the conjoined tendon and the piriformis tendon remained intact. The transfusion rate was 10% (8 of 80 patients). No patients had stem varus greater than 3 degrees or femoral fractures.

Adverse events and HSS score

There were no patients with stem subsidence more than 5 mm at the last follow-up. There were also no postoperative dislocations throughout the follow-up period. No significance was found between preoperative and postoperative mean HSS scores (87.30 ± 2.98 *vs* 86.10 ± 6.10, $t = 1.89$, $P = 0.063$).

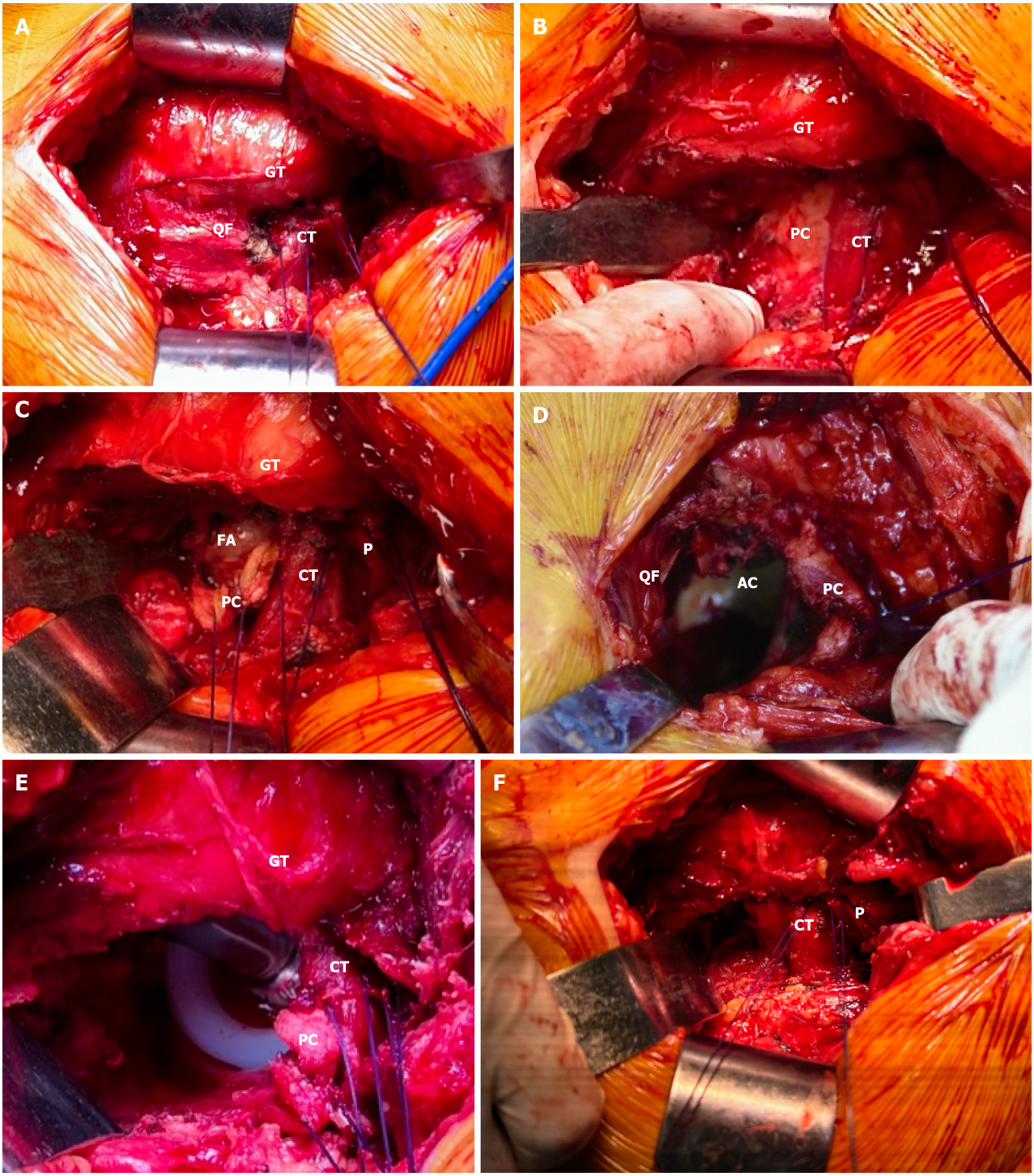

Figure 1 Shows the exposure of left hip joint, protection of the external external rotator muscles and piriformis tendon during bipolar hip arthroplasty using conjoined tendon preserving posterior lateral approach. A: After self-retaining retractors were placed under the deep fascia layer of the gluteus maximus, the piriformis and conjoined tendon were marked by two No. 1 Ethicon sutures. Expose the greater trochanter and quadratus femoris muscle; B: The partial quadratus femoris muscle was incised and retracted by a Hohmann retractor. The posterior capsule was exposed; C: The bottom half of the posterior capsule was incised and inverted by two sutures. Expose the femoral head D: After removing the femoral head, the acetabulum was exposed. A Hohmann retractor was placed behind the posterior-inferior wall to better observe the acetabulum; E: The prosthesis was implanted, and the marking sutures remained in place; F: The posterior capsule was reattached at the trochanteric insertion site. The conjoined tendon and piriformis marked by sutures remained intact. GT: Greater trochanter; CT: Conjoined tendon; PC: Posterior capsule; FA: Femoral head; QF: Quadratus femoris muscle; AC: Acetabulum; P: Piriformis.

DISCUSSION

Hemiarthroplasty has been widely used for the treatment of displaced intracapsular fractures of the femoral neck with favorable clinical outcomes[14,15]. However, postoperative dislocation in patients who underwent the conventional posterolateral approach remains a seemingly inevitable complication[8,16]. The lateral approach[6] and direct anterior approach (DAA)[17] were introduced for hemiarthroplasty in recent years. Compared to the posterolateral approach,

significantly lower dislocation rates and early functional mobility were observed[18].

Recently, Maratt *et al*[19] reported that there was no difference in the dislocation rate after total hip arthroplasty (THA) between patients undergoing a DAA (0.84%) and a modern posterior approach with repair of the capsule (0.79%). Christensen *et al*[20] conducted a retrospective review of 13335 primary THA procedures and found that patients in the posterior approach group had a slightly higher dislocation rate compared to the DAA and lateral groups (1.1% *vs* 0.7% *vs* 0.5%, respectively). Differences in dislocation rates for different approaches may be due to improved protocols and surgical techniques, larger bearing heads, and dual mobility constructs to avoid prosthetic impingement and dislocations that have occurred over the past decade. Furthermore, there is still a learning curve for the different approaches, even for surgeons who are already familiar with the posterolateral approach. In addition, perioperative complications such as femoral fracture, nerve palsy, and prosthesis malposition will still inevitably occur in the early stages of the learning curve[21,22].

The conventional posterolateral approach usually requires excision of the insertion point of the piriformis tendon, and short external rotators are released from their insertion on the posterior margin of the greater trochanter. The posterior capsule is incised as far superior and inferior as feasible for exposure of the acetabulum and intraoperative dislocation of the femoral head from acetabulum[23]. Due to instability after surgery, Pellicci *et al*[24] advocated that posterior soft tissue should be repaired to reduce the dislocation rate. However, Stähelin *et al*[25] reported that the repair failure rate of short external rotator muscles was as high as 70%. Stangl-Correa *et al*[26] reported that the incidence of failure of the reinsertion of short external rotators and the posterior capsule was 16.2% based on ultrasound findings conducted 6-8 wk after surgery.

Pellicci *et al*[27] used magnetic resonance imaging to evaluate the integrity of the posterior soft tissue repair after primary THA. They found that in 90% of patients the posterior capsule remained intact. They also observed that 43% of piriformis tendons and 57% of conjoined tendons had a gap > 25 mm between the hypointense tendon end and the greater trochanter. Additionally, they found atrophy of the piriformis muscle and the obturator internus muscle. The different results from these studies may be due to different assessment methods. However, they demonstrate that there is still a possibility of failure and compromised muscle function even after repair. Therefore, it is better to maintain continuity during surgery instead of repairing after cutting. Maintaining continuity can maintain a greater degree of integrity and physiological function of the soft tissues.

Several authors have reported that the modified posterior approach can preserve some of the short external rotators of the hip. Khan *et al*[28] reported lower mean blood loss, greater improvement in Western Ontario McMaster Osteo-Arthritis Index scores, and no dislocations for the less invasive approach compared to the standard posterior approach. They preserved the piriformis tendon and released the posterior capsule and tendons of the gemelli and obturator internus. Repair of the posterior capsule was suggested. Kim *et al*[9] reported excellent results in a series of 220 patients using external rotator preservation, in which they preserved the piriformis, superior gemelli, and obturator internus with complete posterior capsulectomy.

Roger and Hill[10] adopted a posterosuperior approach, which detaches and repairs the piriformis or conjoined tendon. Penenberg *et al*[29] introduced a percutaneously assisted THA, which is similar to the approach reported by Roger and Hill[10]. These two approaches need specialized instruments to complete the operation procedure. The CPP approach we adopted in this study uses traditional posterior lateral approach instruments without the need for specialized instruments, making it easy to implement in clinical practice. Moreover, surgical records show that the integrity of short external rotator muscles and piriformis tendon is well preserved during surgery, without increasing the exposure difficulty.

For BHA, it is not often necessary to expose the acetabulum like in a THA. In BHA, removing the femoral head, exposing the femoral medullary cavity, and completing the joint reduction after implanting the prosthesis are required. This allows the preservation of more of the joint capsule and external rotators. Tetsunaga *et al*[12] performed BHA in 40 geriatric patients aged ≥ 80 years using the CPP approach, which dissects only the external obturator muscle and preserves the gemellus inferior muscle. No cases of intraoperative fracture or postoperative dislocation were observed in the study. Nakamura *et al*[30] conducted a prospective multicenter clinical study of 322 patients who underwent BHA using the CPP approach. They also resected the proximal part of the quadratus femoris and external obturator muscles. No postoperative dislocations were detected throughout the 9.1 ± 1.5 months (range: 6-17 months) follow-up.

We have performed BHA using the CPP approach since 2021. Two different brands of prostheses have been implanted. Both have reduced shoulder design, which allows the prosthesis to be implanted in a neutral alignment while reducing the risk of injury to the conjoined tendons. In addition to preserving short external rotators and the piriformis tendon, we also focus on preserving the integrity of the posterior upper joint capsule (ischiofemoral ligament). This can form a soft tissue wall that blocks the posterior upper dislocation. Moreover, it can preserve the wrapping effect on the large outer head, which can reduce the abnormal increase in mobility after joint replacement surgery[31]. We do not emphasize the integrity of the quadratus femoris muscle. To avoid damaging the short external rotator muscles, caudal exposure is necessary to make the removal of the femoral head and the procedure of the medullary cavity easier. In addition, electrocoagulation reduces intraoperative blood loss compared to intraoperative blunt injury of the ascending branch of the medial circumflex femoral artery in the quadriceps femoris muscle caused by traction.

Although no cases of postoperative dislocation and femoral fracture were detected, 4 cases of gemellus inferior tears were detected during surgery, which mainly occurred in the early stage. No cases needed total posterior capsulotomy, but we observed puncture of the posterior capsule by the fractured femoral neck in 3 cases. This may be due to the lack of preoperative immobilization, such as transcutaneous traction. Postoperative rehabilitation for these patients was the same as the other patients.

Our study had some limitations. First, our study was retrospective despite using prospectively compiled data. Second, there was no comparative group *via* conventional posterolateral approach during the same period. Because there is very little risk of posterior dislocation after utilizing the CPP approach, we have avoided performing BHA using the conventional posterolateral approach during the study period. However, the dislocation rate in this study was significantly lower than that at our institution from 2019-2020 [0% (0/80) *vs* 4.32% (6/139)]. Third, the follow-up time was short. Since dislocation after hip arthroplasty usually occurs within 3 months, the length of follow-up in our study also has some degree of clinical significance.

CONCLUSION

This retrospective study revealed that the CPP approach for BHA is a safe and effective approach for treatment of femoral neck fractures with fully coated cementless femoral stem. For surgeons who are familiar with the posterolateral approach, no special instrumentation is required and the learning curve is minimal. Compared with the traditional posterolateral approach, the CPP approach can preserve the conjoined tendon, piriformis tendon, and partial posterior joint capsule, providing greater hip stability and significantly reducing the postoperative dislocation rate without increasing perioperative complications.

ARTICLE HIGHLIGHTS

Research background

The traditional posterior lateral approach for hip replacement carries a high risk of hip dislocation. Surgeons have reduced the incidence of dislocation after hip replacement by modifying the surgical approach. Reducing the dislocation rate after bipolar hemiarthroplasty (BHA) surgery will greatly improve patient satisfaction and quality of life.

Research motivation

To improve the stability of the hip joint and reduce the postoperative dislocation rate through modifying the posterior lateral approach by preserving the conjoined tendon, piriformis tendon, and partial posterior joint capsule.

Research objectives

To explore the effectiveness and safety of the conjoined tendon-preserving posterior lateral (CPP) approach for BHA in patients with a fractured femoral neck.

Research methods

This retrospective study included adult inpatients from single hospital who underwent BHA with the CPP approach. Paired *t* test was used to compare the Health Service System scores before surgery and 1 year after surgery.

Research results

No dislocation was found during the follow-up period. No serious postoperative complications occurred.

Research conclusions

The CPP approach can significantly reduce postoperative dislocation after BHA in femoral neck fracture patients.

Research perspectives

This study provided evidence for how to reduce the dislocation rate after hip replacement surgery and emphasized the importance of the soft tissue integrity around the hip joint.

FOOTNOTES

Author contributions: Zhao YC designed the report; Yan TX collected the patients' clinical data; Dong SJ analyzed the data, Yan TX and Ning B wrote the paper; All authors read and approved the final manuscript.

Institutional review board statement: The Clinical Trial Ethics Committee of Yantaishan Hospital provided approval for this study (IRB No. LL-2023-161-L).

Informed consent statement: During outpatient follow-up, the patients signed an informed consent form to be included in the study.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The data that support the findings of this study are available on request from the corresponding author at zhaoyuchizyc@163.com. The data are not publicly available due to privacy or ethical restrictions.

STROBE statement: The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

Country/Territory of origin: China

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S-Editor: Li L
L-Editor: A
P-Editor: Zheng XM

REFERENCES

1 **Veldman HD**, Heyligers IC, Grimm B, Boymans TA. Cemented versus cementless hemiarthroplasty for a displaced fracture of the femoral neck: a systematic review and meta-analysis of current generation hip stems. *Bone Joint J* 2017; **99-B**: 421-431 [PMID: 28385929 DOI: 10.1302/0301-620X.99B4.BJJ-2016-0758.R1]
2 **Sing CW**, Lin TC, Bartholomew S, Bell JS, Bennett C, Beyene K, Bosco-Levy P, Bradbury BD, Chan AHY, Chandran M, Cooper C, de Ridder M, Doyon CY, Droz-Perroteau C, Ganesan G, Hartikainen S, Ilomaki J, Jeong HE, Kiel DP, Kubota K, Lai EC, Lange JL, Lewiecki EM, Lin J, Liu J, Maskell J, de Abreu MM, O'Kelly J, Ooba N, Pedersen AB, Prats-Uribe A, Prieto-Alhambra D, Qin SX, Shin JY, Sørensen HT, Tan KB, Thomas T, Tolppanen AM, Verhamme KMC, Wang GH, Watcharathanakij S, Wood SJ, Cheung CL, Wong ICK. Global Epidemiology of Hip Fractures: Secular Trends in Incidence Rate, Post-Fracture Treatment, and All-Cause Mortality. *J Bone Miner Res* 2023; **38**: 1064-1075 [PMID: 37118993 DOI: 10.1002/jbmr.4821]
3 **Miyamoto RG**, Kaplan KM, Levine BR, Egol KA, Zuckerman JD. Surgical management of hip fractures: an evidence-based review of the literature. I: femoral neck fractures. *J Am Acad Orthop Surg* 2008; **16**: 596-607 [PMID: 18832603 DOI: 10.5435/00124635-200810000-00005]
4 **Schmidt AH**, Leighton R, Parvizi J, Sems A, Berry DJ. Optimal arthroplasty for femoral neck fractures: is total hip arthroplasty the answer? *J Orthop Trauma* 2009; **23**: 428-433 [PMID: 19550230 DOI: 10.1097/BOT.0b013e3181761490]
5 **Ekhtiari S**, Gormley J, Axelrod DE, Devji T, Bhandari M, Guyatt GH. Total Hip Arthroplasty Versus Hemiarthroplasty for Displaced Femoral Neck Fracture: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Bone Joint Surg Am* 2020; **102**: 1638-1645 [PMID: 32732709 DOI: 10.2106/JBJS.20.00226]
6 **Kristensen TB**, Vinje T, Havelin LI, Engesæter LB, Gjertsen JE. Posterior approach compared to direct lateral approach resulted in better patient-reported outcome after hemiarthroplasty for femoral neck fracture. *Acta Orthop* 2017; **88**: 29-34 [PMID: 27805460 DOI: 10.1080/17453674.2016.1250480]
7 **Spina M**, Luppi V, Chiappi J, Bagnis F, Balsano M. Direct anterior approach versus direct lateral approach in total hip arthroplasty and bipolar hemiarthroplasty for femoral neck fractures: a retrospective comparative study. *Aging Clin Exp Res* 2021; **33**: 1635-1644 [PMID: 32910422 DOI: 10.1007/s40520-020-01696-9]
8 **Jobory A**, Kärrholm J, Hansson S, Åkesson K, Rogmark C. Dislocation of hemiarthroplasty after hip fracture is common and the risk is increased with posterior approach: result from a national cohort of 25,678 individuals in the Swedish Hip Arthroplasty Register. *Acta Orthop* 2021; **92**: 413-418 [PMID: 33821752 DOI: 10.1080/17453674.2021.1906517]
9 **Kim YS**, Kwon SY, Sun DH, Han SK, Maloney WJ. Modified posterior approach to total hip arthroplasty to enhance joint stability. *Clin Orthop Relat Res* 2008; **466**: 294-299 [PMID: 18196409 DOI: 10.1007/s11999-007-0056-8]
10 **Roger DJ**, Hill D. Minimally invasive total hip arthroplasty using a transpiriformis approach: a preliminary report. *Clin Orthop Relat Res* 2012; **470**: 2227-2234 [PMID: 22215476 DOI: 10.1007/s11999-011-2225-z]
11 **Yoo JH**, Kwak D, Lee Y, Ma X, Yoon J, Hwang J. Clinical results of short external rotators preserving posterolateral approach for hemiarthroplasty after femoral neck fractures in elderly patients. *Injury* 2022; **53**: 1164-1168 [PMID: 35034776 DOI: 10.1016/j.injury.2021.12.049]
12 **Tetsunaga T**, Tetsunaga T, Yamada K, Sanki T, Kawamura Y, Ozaki T. Bipolar Hip Arthroplasty Using a Conjoined Tendon-preserving Posterior Approach in Geriatric Patients. *Acta Med Okayama* 2021; **75**: 25-30 [PMID: 33649610 DOI: 10.18926/AMO/61430]
13 **Harris WH**. Traumatic arthritis of the hip after dislocation and acetabular fractures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation. *J Bone Joint Surg Am* 1969; **51**: 737-755 [PMID: 5783851]
14 **Jonas SC**, Shah R, Al-Hadithy N, Norton MR, Sexton SA, Middleton RG. Displaced intracapsular neck of femur fractures in the elderly: bipolar hemiarthroplasty may be the treatment of choice; a case control study. *Injury* 2015; **46**: 1988-1991 [PMID: 26239422 DOI: 10.1016/j.injury.2015.06.047]
15 **Viswanath A**, Malik A, Chan W, Klasan A, Walton NP. Treatment of displaced intracapsular fractures of the femoral neck with total hip arthroplasty or hemiarthroplasty. *Bone Joint J* 2020; **102-B**: 693-698 [PMID: 32475248 DOI: 10.1302/0301-620X.102B6.BJJ-2019-1459.R1]
16 **Svenøy S**, Westberg M, Figved W, Valland H, Brun OC, Wangen H, Madsen JE, Frihagen F. Posterior versus lateral approach for hemiarthroplasty after femoral neck fracture: Early complications in a prospective cohort of 583 patients. *Injury* 2017; **48**: 1565-1569 [PMID: 28465004 DOI: 10.1016/j.injury.2017.03.024]
17 **Ferguson TA**, Eastman JG. Anterior approach hip arthroplasty. *Curr Orthop Pract* 2011; **22**: 39-45 [DOI: 10.1097/BCO.0b013e3182059ba6]
18 **Neyisci C**, Erdem Y, Bilekli AB, Bek D. Direct Anterior Approach Versus Posterolateral Approach for Hemiarthroplasty in the Treatment of Displaced Femoral Neck Fractures in Geriatric Patients. *Med Sci Monit* 2020; **26**: e919993 [PMID: 31961830 DOI: 10.12659/MSM.919993]

19 **Maratt JD**, Gagnier JJ, Butler PD, Hallstrom BR, Urquhart AG, Roberts KC. No Difference in Dislocation Seen in Anterior Vs Posterior Approach Total Hip Arthroplasty. *J Arthroplasty* 2016; **31**: 127-130 [PMID: 27067754 DOI: 10.1016/j.arth.2016.02.071]

20 **Christensen TH**, Egol A, Pope C, Shatkin M, Schwarzkopf R, Davidovitch RI, Aggarwal VK. How Does Surgical Approach Affect Characteristics of Dislocation After Primary Total Hip Arthroplasty? *J Arthroplasty* 2023; **38**: S300-S305 [PMID: 37236286 DOI: 10.1016/j.arth.2023.05.034]

21 **Lee GC**, Marconi D. Complications Following Direct Anterior Hip Procedures: Costs to Both Patients and Surgeons. *J Arthroplasty* 2015; **30**: 98-101 [PMID: 26118568 DOI: 10.1016/j.arth.2015.03.043]

22 **Nairn L**, Gyemi L, Gouveia K, Ekhtiari S, Khanna V. The learning curve for the direct anterior total hip arthroplasty: a systematic review. *Int Orthop* 2021; **45**: 1971-1982 [PMID: 33629172 DOI: 10.1007/s00264-021-04986-7]

23 **White RE Jr**, Forness TJ, Allman JK, Junick DW. Effect of posterior capsular repair on early dislocation in primary total hip replacement. *Clin Orthop Relat Res* 2001; 163-167 [PMID: 11764346 DOI: 10.1097/00003086-200112000-00019]

24 **Pellicci PM**, Bostrom M, Poss R. Posterior approach to total hip replacement using enhanced posterior soft tissue repair. *Clin Orthop Relat Res* 1998; 224-228 [PMID: 9917607 DOI: 10.1097/00003086-199810000-00023]

25 **Stähelin T**, Vienne P, Hersche O. Failure of reinserted short external rotator muscles after total hip arthroplasty. *J Arthroplasty* 2002; **17**: 604-607 [PMID: 12168177 DOI: 10.1054/arth.2002.32187]

26 **Stangl-Correa P**, Stangl-Herrera W, Correa-Valderrama A, Ron-Translateur T, Cantor EJ, Palacio-Villegas JC. Postoperative Failure Frequency of Short External Rotator and Posterior Capsule With Successful Reinsertion After Primary Total Hip Arthroplasty: An Ultrasound Assessment. *J Arthroplasty* 2020; **35**: 3607-3612 [PMID: 32684400 DOI: 10.1016/j.arth.2020.06.065]

27 **Pellicci PM**, Potter HG, Foo LF, Boettner F. MRI shows biologic restoration of posterior soft tissue repairs after THA. *Clin Orthop Relat Res* 2009; **467**: 940-945 [PMID: 18813893 DOI: 10.1007/s11999-008-0503-1]

28 **Khan RJ**, Fick D, Khoo P, Yao F, Nivbrant B, Wood D. Less invasive total hip arthroplasty: description of a new technique. *J Arthroplasty* 2006; **21**: 1038-1046 [PMID: 17027549 DOI: 10.1016/j.arth.2006.01.010]

29 **Penenberg BL**, Bolling WS, Riley M. Percutaneously assisted total hip arthroplasty (PATH): a preliminary report. *J Bone Joint Surg Am* 2008; **90** Suppl 4: 209-220 [PMID: 18984733 DOI: 10.2106/JBJS.H.00673]

30 **Nakamura T**, Yamakawa T, Hori J, Goto H, Nakagawa A, Takatsu T, Naoki Osamura, Saito A, Keisuke Hagio, Mouri K. Conjoined tendon preserving posterior approach in hemiarthroplasty for femoral neck fractures: A prospective multicenter clinical study of 322 patients. *J Orthop Surg (Hong Kong)* 2021; **29**: 23094990211063963 [PMID: 34920684 DOI: 10.1177/23094990211063963]

31 **van Arkel RJ**, Ng KCG, Muirhead-Allwood SK, Jeffers JRT. Capsular Ligament Function After Total Hip Arthroplasty. *J Bone Joint Surg Am* 2018; **100**: e94 [PMID: 30020129 DOI: 10.2106/JBJS.17.00251]

World Journal of Clinical Cases

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World J Clin Cases 2024 February 26; 12(6): 1084-1093

DOI: 10.12998/wjcc.v12.i6.1084

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Association of preschool children behavior and emotional problems with the parenting behavior of both parents

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Specialty type: Pediatrics

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Shahriari M, Iran

Received: September 22, 2023
Peer-review started: September 22, 2023
First decision: December 22, 2023
Revised: December 29, 2023
Accepted: January 25, 2024
Article in press: January 25, 2024
Published online: February 26, 2024

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Abstract

BACKGROUND

Parental behaviors are key in shaping children's psychological and behavioral development, crucial for early identification and prevention of mental health issues, reducing psychological trauma in childhood.

AIM

To investigate the relationship between parenting behaviors and behavioral and emotional issues in preschool children.

METHODS

From October 2017 to May 2018, 7 kindergartens in Ma'anshan City were selected to conduct a parent self-filled questionnaire - Health Development Survey of Preschool Children. Children's Strength and Difficulties Questionnaire (Parent Version) was applied to measures the children's behavioral and emotional performance. Parenting behavior was evaluated using the Parental Behavior Inventory. Binomial logistic regression model was used to analyze the association between the detection rate of preschool children's behavior and emotional problems and their parenting behaviors.

RESULTS

High level of parental support/participation was negatively correlated with conduct problems, abnormal hyperactivity, abnormal total difficulty scores and abnormal prosocial behavior problems. High level of maternal support/participation was negatively correlated with abnormal emotional symptoms and abnormal peer interaction in children. High level of parental hostility/coercion was positively correlated with abnormal emotional symptoms, abnormal conduct

problems, abnormal hyperactivity, abnormal peer interaction, and abnormal total difficulty scores in children (all $P < 0.05$). Moreover, paternal parenting behaviors had similarly effects on behavior and emotional problems of preschool children compared with maternal parenting behaviors (all $P > 0.05$), after calculating ratio of odds ratio values.

CONCLUSION

Our study found that parenting behaviors are associated with behavioral and emotional issues in preschool children. Overall, the more supportive or involved the parents are, the fewer behavioral and emotional problems the children experience; conversely, the more hostile or controlling the parents are, the more behavioral and emotional problems the children face. Moreover, the impact of fathers' parenting behaviors on preschool children's behavior and emotions is no less significant than that of mothers' parenting behaviors.

Key Words: Children; Preschool age; Parenting; Behavioral; Parenting problems

Core Tip: Seven kindergartens in Ma'anshan City were selected to conduct a questionnaire survey. The purpose of this study was to analyze the behavioral and emotional problems of preschool children in Ma'anshan City and to explore the relationship between parenting behavior and behavior and emotional problems of preschool children. The emotional and behavioral problems of preschool children in Ma'anshan City are high, and the parenting style is closely related to the emotional and behavioral problems of children. Targeted health education should be carried out to encourage the active participation of fathers to ensure the healthy physical and mental development of children.

Citation: Wang SM, Yan SQ, Xie FF, Cai ZL, Gao GP, Weng TT, Tao FB. Association of preschool children behavior and emotional problems with the parenting behavior of both parents. *World J Clin Cases* 2024; 12(6): 1084-1093
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1084.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1084

INTRODUCTION

In recent years, children's behavior and emotional problems has been the focus of research at home and abroad, and its main behavioral problems (externalized) such as aggressive behavior, illegal and criminal behavior, emotional problems (internalized) such as anxiety, depression[1-3]. Parenting behaviors play a crucial role in shaping children's psychological and behavioral development. Different parenting styles, such as authoritative, authoritarian, permissive, and uninvolved, have been linked to various outcomes in children[4-6]. It is alarming that more than half of the psycho behavioral problems originate in early childhood[7,8], in which the pre-school years are the key period of psychological development and personality formation[9].

World Health Organization (WHO) underscores the critical significance of early education and nurturing in shaping the psychological and behavioral well-being of children, particularly within the pivotal initial five years of their lives[10]. Education guidance and support for parents and caregivers are instrumental in fostering children's mental health and developmental progress[11]. Currently, programs that concentrate on parenting techniques and the dynamics of parent-child interactions, like the parent skills training programme, are designed to assist parents in cultivating appropriate educational approaches and enhancing their parenting skills[12]. The international community stresses the importance of preventing child abuse and violence in order to protect children's mental health[13,14].

Children's behavioral and emotional problems can negatively affect their daily lives and mental health in adolescence and even adulthood. Preschoolers are in the early stage of growth and development, and are susceptible to the family environment, and children's behavioral and emotional problems is closely related to the parenting style. Therefore, researching the influence of parental behaviors on the psychological and behavioral growth of children is advantageous both for society and parents. Our study aids in the early detection and prevention of mental health concerns in children, ultimately contributing to the minimization of psychological trauma during their developmental years.

MATERIALS AND METHODS

Object

Using a random cluster sampling method, from October 2017 and May 2018, seven kindergartens were randomly selected from those directly jurisdiction by Ma'anshan City. All preschool children in the kindergartens were selected as the survey participants, and their parents were investigated with the questionnaire - Survey on the Health Development of Preschool Children, developed by Anhui Medical University. The survey included a total of 75 classes, with 2427

questionnaires distributed and 2253 valid questionnaires collected, resulting in a 92.83% response rate. Among the respondents, there were 1200 boys and 1053 girls. All parents of the preschool children signed an informed consent form prior to the survey.

Research content and methods

Basic information of children: The basic information of children includes the gender, age, residence, family economic status, whether the only child, father's education level, father's age, mother's education level, mother's age, *etc.*

Behavioural and emotional problems in children: Children's Strength and Difficulties Questionnaire (Parent Version) [15] was utilized to measures the children's behavioral and emotional performance. This scale encompasses five domains: emotional problems, conduct problems, hyperactivity problems, peer interaction problems, and pro-social behavior, with a total of 25 items. Each item is scored based on the child's performance over the past 6 months, with ratings of 0, 1, and 2 points assigned for responses categorized as inconsistent, somewhat consistent, and completely consistent, respectively. Notably, the scoring for the pro-social behavior dimension is done in a reverse manner. The total score of emotional problems was 0-3 as normal, 4 as marginal, and 5-10 as abnormal. The total score of conduct problems was 0-2 as normal, 3 as marginal, and 4-10 as abnormal. The total score of hyperactivities was 0-5 as normal, 6 as marginal, and 7-10 as abnormal. The total score of peer interaction problems was 0-2 as normal, 3 as marginal, and 4-10 as abnormal. The total score of difficult problems is 0-13 for normal, 14-16 for marginal, and 17-40 for abnormal. The total score of prosocial behavior was 6-10 normal, 5 marginal, and 0-4 abnormal.

Parenting behavior: Using the Parental Behavior Inventory, from CNKI (national knowledge infrastructure, www.cnki.net) to evaluate the parenting behavior of the parents of preschool children. The scale is closely related to the evaluation of parents' emotions, parenting pressure, and children's behavior problems, and has good reliability and validity. The scale was divided into 2 dimensions: support/participation and hostility/coercion, including 10 entries each. According to the frequency of occurrence in daily life, each entry was scored as never, occasionally, sometimes, medium, regular, and always, with 0, 1, 2, 3, 4, and 5 points. The score range of each dimension is 0-50 points, the higher the score, the deeper the degree of this dimension. The total score for father and mother in both dimensions was calculated separately and then grouped by percentiles: ≤ P_{25} for low levels, P_{25}-P_{75} for the moderate level, ≥ P_{75} for a high level.

Survey method: The survey organizers provided unified training for city-level investigators and kindergarten healthcare teachers, and thoroughly explained the purpose and significance of the study to both the kindergartens and the parents. All the questionnaires were uniformly distributed to the main caregivers by the kindergarten and collected by the head teacher after completion. Subsequently, the three-level quality control was carried out by the class teacher, the health care teacher, and the municipal quality controller. If problems are found, return to inquiry and correct in time.

Statistical analyses

Epi Data 3.0 was used to establish a database for double data entry. Statistics and Logistic regression analyses were performed using the SPSS 20.0 statistical software. mean ± SD and n (%) were used to describe the continuous and categorical variables, respectively. The distribution of behavioral and emotional problem detection rates in preschool children with different sociodemographic characteristics was determined to use χ^2 tests were performed for comparison. A binomial logistic regression model was used to analyze the association of parenting behavior and preschool children behavior and emotional problems by controlling for their age, sex, residence, family economic status, parental education, and age. Odds ratio (OR) was used to calculate ratio of OR[16] to compare the differences between parents in the association between high level of support/participation and high level of hostility/coercive parenting behavior and children's behavior and emotional problems. The test level was a two-sided test of $\alpha = 0.05$.

RESULTS

General information

A total of 2253 preschool children were included in this study. Children aged 3, 4, 5 and 6 accounted for 28.5%, 32.6%, 33.6% and 5.3% of the total, respectively. Boys accounted for 53.3%. Urban preschool children accounted for 84.5%. The only child accounted for 75.8%.

Detection of behavioral and emotional problems in preschool children

Among 2253 preschool children, 167 (7.4%) had abnormal emotional problems, 178 (7.9%) had abnormal conduct problems, 396 (17.6%) had abnormal hyperactivity, 528 (23.4%) had abnormal peer interaction, 232 (10.3%) had abnormal total difficulty scores, and 235 (10.4%) had abnormal prosocial behavior problems. Among them, the abnormal proportion of peer interaction problems was the highest, followed by hyperactivity problems and prosocial behavior problems.

As is shown in Table 1, our results showed that the detection rate of abnormal emotional problems in children with parents with lower education level was higher, and the difference was statistically significant ($P < 0.05$). The abnormal detection rate of conduct problems was higher in boys, children with lower education level of parents and children with younger mothers ($P < 0.05$ or $P < 0.001$). The prevalence of hyperactivity was higher in children with poor family economic status, lower educational level of father and younger parents ($P < 0.05$ or $P < 0.001$). The detection rate of abnormal peer communication was higher in children with younger age and living in non-urban areas ($P < 0.05$ or $P <$

Table 1 Distribution of behavioral and emotional problems detection rates in preschoolers with different demographic characteristics, *n* (%)

Feature	*n*	Emotional problem	Conduct problem	Hyperactivity	Peer interaction	Total score of difficulty	Pro-social behavior question
Age							
3	642	45 (7.0)	59 (9.2)	114 (17.8)	185 (28.8)	76 (11.8)	88 (13.7)
4	734	57 (7.8)	60 (8.2)	134 (18.3)	174 (23.7)	76 (10.4)	77 (10.5)
5	757	55 (7.3)	48 (6.3)	129 (17.0)	147 (19.4)	69 (9.1)	63 (8.3)
6	120	10 (8.3)	11 (9.2)	19 (15.8)	22 (18.3)[b]	11 (9.2)	7 (5.8)[a]
Sex							
Male	1200	90 (7.5)	113 (9.4)	251 (20.9)	322 (26.8)	144 (12.0)	141 (11.8)
Female	1053	77 (7.3)	65 (6.2)[a]	145 (13.8)[b]	206 (19.6)[b]	88 (8.4)[a]	94 (8.9)[a]
Domicile							
City proper	1903	126 (6.6)	133 (7.0)	333 (17.5)	423 (22.2)	178 (9.4)	187 (9.8)
Non-urban	350	41 (11.7)[b]	45 (12.9)[b]	63 (18.0)	105 (30.0)[a]	54 (15.4)[b]	48 (13.7)[a]
Family economic status							
Range	136	15 (11.0)	15 (11.0)	32 (23.5)	40 (29.4)	29 (21.3)	20 (14.7)
Same as	1870	135 (7.2)	147 (7.9)	333 (17.8)	431 (23.0)	183 (9.8)	188 (10.1)
Preferably	247	17 (6.9)	16 (6.5)	31 (12.6)[a]	57 (23.1)	20 (8.1)[b]	27 (10.9)
Single-child							
Yes	1707	126 (7.4)	133 (7.8)	309 (18.1)	400 (23.4)	180 (10.5)	175 (10.3)
No	546	41 (7.5)	45 (8.2)	87 (15.9)	128 (23.4)	52 (9.5)	60 (11.0)
Father's education level							
Junior high school and below	267	30 (11.2)	31 (11.6)	48 (18.0)	82 (30.7)	40 (15.0)	34 (12.7)
High school/technical secondary school	911	71 (7.8)	74 (8.1)	182 (20.0)	227 (24.9)	107 (11.7)	94 (10.3)
College degree or above	1075	66 (6.1)[a]	73 (6.8)[a]	166 (15.4)[a]	219 (20.4)[b]	85 (7.9)[a]	107 (10.0)
Father age							
≤ 24	355	59 (8.0)	68 (9.2)	152 (20.5)	170 (23.0)	89 (12.0)	77 (10.4)
25-29	977	67 (8.3)	61 (7.6)	146 (18.2)	184 (22.9)	90 (11.2)	89 (11.1)
≥ 30	911	41 (5.8)	49 (6.9)	98 (13.8)[a]	174 (24.5)	53 (7.5)[a]	69 (9.7)
Maternal education level							
Junior high school and below	349	33 (9.5)	46 (13.2)	68 (19.5)	99 (28.4)	49 (14.0)	45 (12.9)
High school/technical secondary school	884	75 (8.5)	68 (7.7)	180 (20.4)	232 (26.2)	106 (12.0)	91 (10.3)
College degree or above	1020	59 (5.8)[a]	64 (6.3)[b]	148 (14.5)	197 (19.3)[b]	77 (7.5)[b]	99 (9.7)
Maternal age							
≤ 24	631	60 (9.5)	66 (10.5)	142 (22.5)	151 (23.9)	79 (12.5)	63 (10.0)
25-29	1099	64 (6.8)	66 (7.0)	159 (17.0)	214 (22.8)	100 (10.7)	104 (11.1)
≥ 30	523	43 (6.3)	46 (6.7)[a]	95 (13.9)[b]	163 (23.8)	53 (7.7)[a]	68 (9.9)

[a]$P < 0.05$.
[b]$P < 0.01$.

0.001). The abnormal detection rate of total difficulty score of boys, children with poor family economic status, parents with lower education level and younger parents was higher ($P < 0.05$ or $P < 0.001$). The abnormal detection rate of prosocial behavior problems was higher in children with younger age, boys and living in non-urban areas, and the difference was statistically significant ($P < 0.05$; Table 1).

Relationship between parenting behavior and children's emotional and behavioral problems

As is shown in Table 2, after adjusting the confounding factors of children's age, gender, residence, family economic status, parental education level and age confounding, the low-level group of each dimension was used as the reference. The analysis results revealed that high-level of father support/participation (OR = 0.35, 95%CI: 0.21-0.57) was inversely related to children's conduct problems; High-level of father support/participation (OR = 0.68, 95%CI: 0.49-0.93) was negatively correlated with hyperactivity abnormalities in children; Medium-level of father support/participation (OR = 0.64, 95%CI: 0.47-0.88) and high-level support/participation (OR = 0.42, 95%CI: 0.28-0.64) was inversely associated with abnormal total difficulty score in children; Father-medium horizontal support/participation (OR = 0.5, 95%CI: 0.37-0.68) and high-level support/participation (OR = 0.26, 95%CI: 0.17-0.40) was negatively correlated with abnormal prosocial behavior problems in children; High level of maternal support/participation (OR = 0.63, 95%CI: 0.40-0.99) was inversely associated with abnormal emotional symptoms in children; Maternal intermediate horizontal support/participation (OR = 0.54, 95%CI: 0.38-0.77) and high-level support/participation (OR = 0.33, 95%CI: 0.20-0.54) was inversely related to abnormal children's conduct problems; High level of maternal support/participation (OR = 0.53, 95%CI: 0.38-0.74) was inversely correlated with hyperactivity abnormalities in children; Maternal intermediate horizontal support/participation (OR = 0.60, 95%CI: 0.48-0.76) and high-level support/participation (OR = 0.53, 95%CI: 0.40-0.70) was negatively associated with abnormal peer communication in children; Maternal intermediate horizontal support/participation (OR = 0.60, 95%CI: 0.44-0.82) and high-level support/participation (OR = 0.41, 95%CI: 0.27-0.63) was inversely related with abnormal total score in children; Maternal intermediate horizontal support/participation (OR = 0.44, 95%CI: 0.33-0.60) and high-level support/participation (OR = 0.24, 95%CI: 0.15-0.37) was negatively associated with abnormal prosocial behavior problems in children; Father with high-level hostility/coercion (OR = 2.00, 95%CI: 1.30-3.08) was positively correlated with abnormal emotional symptoms in children; Fathers intermediate horizontal hostility/coercion (OR = 1.66, 95%CI: 1.04-2.65) and high levels of hostility/coercion (OR = 3.27, 95%CI: 2.03-5.25) was positively related with children's conduct problems; Fathers intermediate horizontal hostility/coercion (OR = 1.48, 95%CI: 1.10-2.00) and high level of hostility/coercion (OR = 2.29, 95%CI: 1.66-3.15) was positively correlated with hyperactivity in children; Father with a high level of hostility/coercion (OR = 1.92, 95%CI: 1.45-2.54) was positively associated with abnormal peer interaction in children; Fathers intermediate horizontal hostility/coercion (OR = 1.63, 95%CI: 1.08-2.46) and high levels of hostility/coercion (OR = 3.25, 95%CI: 2.14-4.94) was positively correlated with the abnormal total difficulty score of children; High level of maternal hostility/coercion (OR = 2.08, 95%CI: 1.36-3.19) was positively correlated with abnormal emotional symptoms in children; Maternal intermediate horizontal hostility/coercion (OR = 2.03, 95%CI: 1.27-3.22) and a high level of hostility/coercion (OR = 3.24, 95%CI: 2.04-5.15) was positively related with children's conduct problems; Maternal intermediate horizontal hostility/coercion (OR = 1.63, 95%CI: 1.20-2.20) and a high level of hostility/coercion (OR = 2.87, 95%CI: 2.11-3.89) was positively correlated with hyperactivity in children; Maternal intermediate horizontal hostility/coercion (OR = 1.38, 95%CI: 1.07-1.78) and high levels of hostility/coercion (OR = 1.90, 95%CI: 1.46-2.48) was positively associated with abnormal peer communication in children; Maternal intermediate horizontal hostility/coercion (OR = 1.60, 95%CI: 1.08-2.38) and high levels of hostility/coercion (OR = 2.99, 95%CI: 2.03-4.42) was positively correlated with the abnormal total difficulty score of children.

Differences between parents in the associations of children's behavioral and emotional problems with parenting behaviors

As is shown in Table 3, after comparing the risk ratio of high level of parental support/involvement, high level of parental hostility/coercive parenting behavior and children's behavior and emotional problems, it was found that there was no significant difference in the correlation between parental parenting behavior and children's behavior and emotional problems between fathers and mothers ($P > 0.05$).

DISCUSSION

The WHO estimates that about 10% to 20% of children worldwide suffer from one or more psychological problems[10]. Preschoolers' psychological development is not mature, they are easily affected by internal and external factors and produce psychological behavioral problems[17,18]. Usually, the causes of behavior and emotional problems in preschool children are mainly related to the combination of genetic[19], biological environment[20], family and social factors, among which the family environment mainly includes parent-child relationship, parental relationship and family intimacy[21,22].

There are four parenting styles: authoritative (high warmth and control), authoritarian (low warmth, high control), permissive (high warmth, low control), and uninvolved (low warmth and control)[23]. It is now generally accepted that authoritative parenting, characterized by warmth, responsiveness, and appropriate levels of control, has been associated with positive child outcomes such as higher self-esteem, better academic performance, and lower rates of behavioral problems[24,25]. Permissive parenting, defined by its high levels of warmth but low levels of control, may lead to children exhibiting poor impulse control, diminished academic performance, and an increased propensity to partake in risky behaviors[26]. Uninvolved parenting, marked by low levels of warmth and control, has been linked to negative

Table 2 Logistic regression analysis of the relationship between parenting behavior and behavior and mood problems in preschoolers, OR (95%CI)

Parenting behavior dimension	Emotional symptoms	Conduct problem	Hyperactivity	Peer interaction	Total score of difficulty	Pro-social behavior question
Father with support/participation						
Low level	1.00	1.00	1.00	1.00	1.00	1.00
Medium level	0.89 (0.62, 1.29)	0.77 (0.54, 1.09)	0.94 (0.72, 1.22)	0.59 (0.46, 0.75)[b]	0.64 (0.47, 0.88)[a]	0.50 (0.37, 0.68)[b]
High tone	0.64 (0.40, 1.01)	0.35 (0.21, 0.57)[b]	0.68 (0.49, 0.93)[a]	0.61 (0.47, 0.81)[b]	0.42 (0.28, 0.64)[b]	0.26 (0.17, 0.40)[b]
Mother with the support/participation						
Low level	1.00	1.00	1.00	1.00	1.00	1.00
Medium level	0.72 (0.50, 1.04)	0.54 (0.38, 0.77)[b]	0.92 (0.71, 1.19)	0.60 (0.48, 0.76)[b]	0.60 (0.44, 0.82)[a]	0.44 (0.33, 0.60)[b]
High tone	0.63 (0.40, 0.99)[a]	0.33 (0.20, 0.54)[b]	0.53 (0.38, 0.74)[b]	0.53 (0.40, 0.70)[b]	0.41 (0.27, 0.63)[b]	0.24 (0.15, 0.37)[b]
Father is hostile/coercive						
low level	1.00	1.00	1.00	1.00	1.00	1.00
Medium level	0.97 (0.64, 1.49)	1.66 (1.04, 2.65)[a]	1.48 (1.10, 2.00)[a]	1.25 (0.97, 1.62)	1.63 (1.08, 2.46)[a]	1.18 (0.84, 1.66)
High tone	2.00 (1.30, 3.08)[a]	3.27 (2.03, 5.25)[b]	2.29 (1.66, 3.15)[b]	1.92 (1.45, 2.54)[b]	3.25 (2.14, 4.94)[b]	1.12 (0.76, 1.65)
Mother is hostile/coercive						
Low level	1.00	1.00	1.00	1.00	1.00	1.00
Medium level	1.31 (0.85, 2.01)	2.03 (1.27, 3.22)[a]	1.63 (1.20, 2.20)[a]	1.38 (1.07, 1.78)[a]	6.01 (1.08, 2.38)[a]	1.28 (0.91, 1.79)
High tone	2.08 (1.36, 3.19)[a]	3.24 (2.04, 5.15)[b]	2.87 (2.11, 3.89)[b]	1.90 (1.46, 2.48)[b]	2.99 (2.03, 4.42)[b]	1.28 (0.89, 1.85)

[a]$P < 0.05$.

[b]$P < 0.01$.

The child's age, gender, residence, family economic status, parental education level, and age were adjusted.

outcomes such as low self-esteem, poor academic performance, and increased risk of delinquency[27]. In summary, the role of parental behaviors is paramount in shaping children's psychological and behavioral growth. It is crucial for parents to recognize the implications of their parenting styles and aim for a balanced method, integrating warmth, responsiveness, and suitable levels of discipline. Such an approach is key to nurturing well-rounded and healthy development in children.

In our study, we compared the results of the survey data from CNKI in China. 232 children with abnormal total difficulty scores, accounting for 10.3%, which was similar to the examination rate of psychological and behavioral problems of preschool children in Xuzhou reported by Han *et al*[28] and in Xuzhou reported by Xu *et al*[29] (9.8%), and higher than the 7.76% reported by Deng *et al*[30] in Shanghai and 8.72% reported by Yu *et al*[31] in Wuhu. It is slightly lower than the 11.8% reported by Zeng *et al*[32] in Liuzhou and 11.6% reported by Huang *et al*[33] in Hunan Province. It shows that the detection rate of behavior problems among preschool children varies in different regions, but the incidence of emotional and behavioral problems in preschool children in Ma'anshan is at a relatively high level.

Preschool is a key period for the development of children's emotional, conduct, peer interaction and other functions. If the child's growth and development are neglected at this time, it may lead to a series of emotional and behavioral problems. The highest incidence of issues among children was in abnormal peer interactions, followed by hyperactivity. Notably, the rate of abnormal emotional problems was the lowest, mirroring the findings observed in Wuhu city. It shows that the behavior and emotional problems of preschool children in our city cannot be ignored, especially to pay attention to the problem of peers interaction and hyperactivity. It also suggests that parents and nurseries should attach great importance to the hyperactivity and peer interaction of preschool children, especially boys, and strengthen reasonable guidance and health education.

Fathers and mothers' rearing patterns also known as parenting style, which refers to the relatively stable behavior style that parents think, feel and show when raising their children, and is a combination of emotional behaviors when

Table 3 Comparison of the associations between parenting behavior and behavioral and emotional problems in preschool children, OR (95%CI)

Parenting behavior dimension	Emotional symptoms	Conduct problem	Hyperactivity	Peer interaction	Total score of difficulty	Pro-social behavior question
Father with a high-level of support/participation	0.64 (0.40, 1.01)	0.35 (0.21, 0.57)	0.68 (0.49, 0.93)	0.61 (0.47, 0.81)	0.42 (0.28, 0.64)	0.26 (0.17, 0.40)
High-level level of maternal support/participation	0.63 (0.40, 0.99)	0.33 (0.20, 0.54)	0.53 (0.38, 0.74)	0.53 (0.40, 0.70)	0.41 (0.27, 0.63)	0.24 (0.15, 0.37)
ROR	1.02 (0.53, 1.94)	1.06 (0.52, 2.14)	1.28 (0.81, 2.04)	1.15 (0.78, 1.70)	1.02 (0.57, 1.85)	1.08 (0.58, 2.02)
P value	0.962	0.870	0.291	0.480	0.936	0.801
Father with a high level of hostility/coercion	2.00 (1.30, 3.08)	3.27 (2.03, 5.25)	2.29 (1.66, 3.15)	1.92 (1.45, 2.54)	3.25 (2.14, 4.94)	1.12 (0.76, 1.65)
Mother with a high level of hostility/coercion	2.08 (1.36, 3.19)	3.24 (2.04, 5.15)	2.87 (2.11, 3.89)	1.90 (1.46, 2.48)	2.99 (2.03, 4.42)	1.28 (0.89, 1.85)
ROR	0.96 (0.52, 1.76)	1.01 (0.52, 1.96)	0.80 (0.51, 1.24)	1.01 (0.69, 1.49)	1.09 (0.61, 1.92)	0.88 (0.51, 1.49)
P value	0.899	0.978	0.318	0.958	0.775	0.623

ROR: Ratio of odds ratio.

interacting with their children[34]. The current study supports that parenting styles are associated with children's physical and mental health and have lasting effects as well as internalizing and externalizing problems[35]. Positive parenting style lays a good foundation for children's emotional and behavioral capacity building, and bad or ineffective parenting style and children's behavioral problems promotes each other[36]. Fatherhood-rearing is essential for children to complete the transition from within the family to the outside world[37]. Related studies have shown that early mother and child paternity can partly predict whether child behavior is problematic[38,39]. Indeed, the parenting behaviors of both parents distinctly influence the internalized behaviors of preschool children[40,41]. Furthermore, inconsistencies in parenting styles can hinder children's ability to regulate their emotions effectively. This inconsistency can heighten the risk of poor peer relationships, aggressive behavior, and diminished independence among other negative outcomes. Therefore, family parenting style is closely related to preschool children's behavior and emotional problems. It is of great significance to the early development of children to master the knowledge of child rearing, clearly recognize the value of parenting, and fully realize the love, encouragement, understanding and tolerance of parents, among which the role of father should not be ignored.

CONCLUSION

In conclusion, the emotional and behavioral problems of preschool children in Ma'anshan city are relatively high and affected by various factors, among which the parenting style is closely related to children's emotional and behavioral problems, so targeted health education should be carried out, especially to encourage fathers to be actively involved, to ensure the physical and mental health development of children.

ARTICLE HIGHLIGHTS

Research background

Parental actions are vital in molding children's mental and behavioral growth, essential for early detection and prevention of mental health problems, minimizing childhood psychological trauma.

Research motivation

To investigate the relationship between parenting behaviors and behavioral and emotional issues in preschool children. Targeted health education should be carried out to encourage the active participation of fathers to ensure the healthy physical and mental development of children.

Research objectives

Between October 2017 and May 2018, a survey in seven Ma'anshan kindergartens used random sampling. Parents of all preschoolers completed Anhui Medical University's health questionnaire, yielding 2253 valid responses (92.83%) from 75

classes, including 1200 boys and 1053 girls, with prior parental consent.

Research methods

From October 2017 to May 2018, in Ma'anshan City, parents in 7 kindergartens completed the "Health Development Survey of Preschool Children," including the Strengths and Difficulties Questionnaire and Parental Behavior Inventory to assess children's behavior, emotions, and parenting impacts, analyzed using binomial logistic regression.

Research results

Greater parental support reduces children's conduct issues, hyperactivity, total difficulties, and prosocial behavior problems. Maternal support particularly lessens children's emotional symptoms and peer issues. Conversely, parental hostility increases these problems (all $P < 0.05$). Paternal behavior impacts children's behavior and emotions similarly to maternal behavior ($P > 0.05$), as shown by odds ratio comparisons.

Research conclusions

Our research indicates a link between parenting styles and preschoolers' behavioral and emotional issues. Generally, increased parental support or involvement leads to fewer such problems in children, while greater hostility or control from parents results in more issues. Additionally, fathers' influence on children's behavior and emotions is equally significant as that of mothers.

Research perspectives

This research perspectives of this article focus on understanding the influence of parenting behaviors on preschool children's emotional and behavioral development. It emphasizes the significance of both supportive and coercive parenting styles, examining how each uniquely impacts a child's psychological well-being. The study also brings attention to the equally important roles of both fathers and mothers in shaping their children's behavior and emotions. By conducting a detailed analysis through questionnaires in multiple kindergartens, the research provides insights into how different parenting approaches can foster or hinder a child's emotional and behavioral health, underlining the necessity for balanced and supportive parenting in early childhood development.

FOOTNOTES

Author contributions: Wang SM, Yan SQ, Gao GP and Tao FB contributed to the conceptualization; Weng TT contributed to the data curation, formal analysis, and investigation; Yan SQ, Cai ZL and Tao FB contributed to the funding acquisition; Wang SM contributed to the methodology and writing-original draft; Yan SQ contributed to the project administration and supervision; Yan SQ, Xie FF, Cai ZL and Tao FB contributed to the resources; Tao FB contributed to the software; Wang SM and Yan SQ contributed to the validation; Cai ZL contributed to the visualization; Wang SM, Yan SQ and Gao GP contributed to the writing-review & editing.

Supported by the National Natural Science Foundation of China, No. 81330068.

Institutional review board statement: The study was approved by Institutional Review Board of Ma'anshan Maternal and Child Health Center.

Informed consent statement: All the study subjects provided informed consent.

Conflict-of-interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

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S-Editor: Zhang H
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Miller KN**, Jacobson KC. The Differential Impact of Parenting on Adolescent Externalizing Behaviors in the Context of Maternal Stress. *J Youth Adolesc* 2023; **52**: 1459-1470 [PMID: 36807232 DOI: 10.1007/s10964-023-01747-0]

2 **Leuba AL**, Meyer AH, Kakebeeke TH, Stülb K, Arhab A, Zysset AE, Leeger-Aschmann CS, Schmutz EA, Kriemler S, Jenni OG, Puder JJ, Munsch S, Messerli-Bürgy N. The relationship of parenting style and eating behavior in preschool children. *BMC Psychol* 2022; **10**: 275 [PMID: 36419113 DOI: 10.1186/s40359-022-00981-8]

3 **Kaiser T**, Li J, Pollmann-Schult M, Song AY. Poverty and Child Behavioral Problems: The Mediating Role of Parenting and Parental Well-Being. *Int J Environ Res Public Health* 2017; **14** [PMID: 28867777 DOI: 10.3390/ijerph14090981]

4 **St George SM**, Wilson DK. A qualitative study for understanding family and peer influences on obesity-related health behaviors in low-income African-American adolescents. *Child Obes* 2012; **8**: 466-476 [PMID: 23061501 DOI: 10.1089/chi.2012.0067]

5 **Jago R**, Wood L, Zahra J, Thompson JL, Sebire SJ. Parental control, nurturance, self-efficacy, and screen viewing among 5- to 6-year-old children: a cross-sectional mediation analysis to inform potential behavior change strategies. *Child Obes* 2015; **11**: 139-147 [PMID: 25584518 DOI: 10.1089/chi.2014.0110]

6 **Del Puerto-Golzarri N**, Azurmendi A, Carreras MR, Muñoz JM, Braza P, Vegas O, Pascual-Sagastizabal E. The Moderating Role of Surgency, Behavioral Inhibition, Negative Emotionality and Effortful Control in the Relationship between Parenting Style and Children's Reactive and Proactive Aggression. *Children (Basel)* 2022; **9** [PMID: 35053729 DOI: 10.3390/children9010104]

7 **Bele SD**, Bodhare TN, Valsangkar S, Saraf A. An epidemiological study of emotional and behavioral disorders among children in an urban slum. *Psychol Health Med* 2013; **18**: 223-232 [PMID: 22783928 DOI: 10.1080/13548506.2012.701751]

8 **Kassing F**, Godwin J, Lochman JE, Coie JD; Conduct Problems Prevention Research Group. Using Early Childhood Behavior Problems to Predict Adult Convictions. *J Abnorm Child Psychol* 2019; **47**: 765-778 [PMID: 30280365 DOI: 10.1007/s10802-018-0478-7]

9 **Sanefuji W**, Haryu E. Preschoolers' Development of Theory of Mind: The Contribution of Understanding Psychological Causality in Stories. *Front Psychol* 2018; **9**: 955 [PMID: 29946286 DOI: 10.3389/fpsyg.2018.00955]

10 Diabetes. In: Word Health Organization. [cited 2023 Aug 20]. Available from: https://www.who.int/westernpacific/health-topics/diabetes

11 **Haine-Schlagel R**, Martinez JI, Roesch SC, Bustos CE, Janicki C. Randomized Trial of the Parent And Caregiver Active Participation Toolkit for Child Mental Health Treatment. *J Clin Child Adolesc Psychol* 2018; **47**: S150-S160 [PMID: 27442606 DOI: 10.1080/15374416.2016.1183497]

12 **Fursland A**, Freeman J. Proceedings of the 2014 Australia and New Zealand Academy for Eating Disorders (ANZAED) Conference. *J Eat Disord* 2014; **2**: I1-P14 [PMID: 25467931 DOI: 10.1186/2050-2974-2-S1-O36]

13 **Doyle JJ Jr**, Aizer A. Economics of Child Protection: Maltreatment, Foster Care, and Intimate Partner Violence. *Annu Rev Econom* 2018; **10**: 87-108 [PMID: 31007830 DOI: 10.1146/annurev-economics-080217-053237]

14 **Crombach A**, Bambonyé M. Intergenerational violence in Burundi: Experienced childhood maltreatment increases the risk of abusive child rearing and intimate partner violence. *Eur J Psychotraumatol* 2015; **6**: 26995 [PMID: 26679146 DOI: 10.3402/ejpt.v6.26995]

15 **Famodu OO**, Adebayo AM, Adebayo BE. Child labor and mental health status of in-school adolescents in a municipal local government area of Lagos state, Nigeria. *Int J Adolesc Med Health* 2018; **33** [PMID: 30367800 DOI: 10.1515/ijamh-2018-0075]

16 **Altman DG**, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003; **326**: 219 [PMID: 12543843 DOI: 10.1136/bmj.326.7382.219]

17 **Kim SW**, Jeon HR, Kim JY, Kim Y. Heart Rate Variability Among Children With Acquired Brain Injury. *Ann Rehabil Med* 2017; **41**: 951-960 [PMID: 29354571 DOI: 10.5535/arm.2017.41.6.951]

18 **Wang S**, Agius M. The use of Music Therapy in the treatment of Mental Illness and the enhancement of Societal Wellbeing. *Psychiatr Danub* 2018; **30**: 595-600 [PMID: 30439854]

19 **Gundersen C**, Mahatmya D, Garasky S, Lohman B. Linking psychosocial stressors and childhood obesity. *Obes Rev* 2011; **12**: e54-e63 [PMID: 21054757 DOI: 10.1111/j.1467-789X.2010.00813.x]

20 **Ylijoki MK**, Ekholm E, Ekblad M, Lehtonen L. Prenatal Risk Factors for Adverse Developmental Outcome in Preterm Infants-Systematic Review. *Front Psychol* 2019; **10**: 595 [PMID: 30971974 DOI: 10.3389/fpsyg.2019.00595]

21 **Staff RT**, Hogan MJ, Whalley LJ. The influence of childhood intelligence, social class, education and social mobility on memory and memory decline in late life. *Age Ageing* 2018; **47**: 847-852 [PMID: 30084877 DOI: 10.1093/ageing/afy111]

22 **Runge RA**, Soellner R. Measuring children's emotional and behavioural problems: are SDQ parent reports from native and immigrant parents comparable? *Child Adolesc Psychiatry Ment Health* 2019; **13**: 46 [PMID: 31798684 DOI: 10.1186/s13034-019-0306-z]

23 **Elinder LS**, Patterson E, Nyberg G, Norman Å. A Healthy School Start Plus for prevention of childhood overweight and obesity in disadvantaged areas through parental support in the school setting - study protocol for a parallel group cluster randomised trial. *BMC Public Health* 2018; **18**: 459 [PMID: 29625599 DOI: 10.1186/s12889-018-5354-4]

24 **Wong RSM**, Yu EYT, Guo VY, Wan EY, Chin WY, Wong CKH, Fung CSC, Tung KTS, Wong WH, Ip P, Tiwari AFY, Lam CLK. A prospective cohort study to investigate parental stress and child health in low-income Chinese families: protocol paper. *BMJ Open* 2018; **8**: e018792 [PMID: 29472262 DOI: 10.1136/bmjopen-2017-018792]

25 **Steinsbekk S**, Bonneville-Roussy A, Fildes A, Llewellyn CH, Wichstrøm L. Child and parent predictors of picky eating from preschool to school age. *Int J Behav Nutr Phys Act* 2017; **14**: 87 [PMID: 28679411 DOI: 10.1186/s12966-017-0542-7]

26 **Mukherjee SB**. Autism Spectrum Disorders - Diagnosis and Management. *Indian J Pediatr* 2017; **84**: 307-314 [PMID: 28101829 DOI: 10.1007/s12098-016-2272-2]

27 **He Y**, Liu C, Luo R. Emotional Warmth and Rejection Parenting Styles of Grandparents/Great Grandparents and the Social-Emotional Development of Grandchildren/Great Grandchildren. *Int J Environ Res Public Health* 2023; **20** [PMID: 36674323 DOI: 10.3390/ijerph20021568]

28 **Han B**, Huang H, Yao X, Li X, Li S, Yan H. The relationship between screen time and emotional behavior problems in preschool children in Ezhou City. *Zhongguo Xuexiao Weisheng* 2019; **40**: 1669-1671 [DOI: 10.16835/j.cnki.1000-9817.2019.11.019]

29 **Xu G**, Gong X, Zhu Z, Jiang L, Geng M, Wu X, Tao F, Chu Y, Peng L. The mediating effect of sleep disorders in preschool children on behavioral and emotional problems and parenting styles. *Zhongguo Gonggong Weisheng* 2020; **4**: 1143-1146 [DOI: 10.11847/zgggws1122985]

30 **Deng Y**, Ji J, Fan J, Jiang Y, Chen H, Chen Z. Investigation and analysis of behavioral and emotional problems among 23,325 preschool children in Shanghai. *Zhongguo Shequ Yishi* 2019; **35**: 159-160,163 [DOI: 10.3969/j.issn.1007-614x.2019.11.114]

31 **Yu M**, Wang R, He H, Zhang A, Ning M. Investigation and analysis of emotional and behavioral problems in preschool children in Wuhu city. *Shiyong Yufang Yixue* 2021; **28**: 309-312 [DOI: 10.3969/j.issn.1006-3110.2021.03.016]

32 **Zeng P**, Feng Y, Zeng T, Zhang H, Li H. Liuzhou school-age children's emotional and behavioral problems analysis. *Zhongguo Ertong Baojian Zazhi* 2019; **27**: 1005-1007 [DOI: 10.11852/zgetbjzz2018-1506]

33 **Huang G**, Wu H, Liu Z, Du Q, Huang Q, Fang J. Investigation on emotional and behavioral problems in 1280 children aged 3 to 6 years. *Zhongguo Ertong Baojian Zazhi* 2012; **20**: 595-597,603

34 **Shloim N**, Edelson LR, Martin N, Hetherington MM. Parenting Styles, Feeding Styles, Feeding Practices, and Weight Status in 4-12 Year-Old Children: A Systematic Review of the Literature. *Front Psychol* 2015; **6**: 1849 [PMID: 26696920 DOI: 10.3389/fpsyg.2015.01849]

35 **Berkien M**, Louwerse A, Verhulst F, van der Ende J. Children's perceptions of dissimilarity in parenting styles are associated with internalizing and externalizing behavior. *Eur Child Adolesc Psychiatry* 2012; **21**: 79-85 [PMID: 22222568 DOI: 10.1007/s00787-011-0234-9]

36 **Bögels S**, Phares V. Fathers' role in the etiology, prevention and treatment of child anxiety: a review and new model. *Clin Psychol Rev* 2008; **28**: 539-558 [PMID: 17854963 DOI: 10.1016/j.cpr.2007.07.011]

37 **Pinquart M**. Associations of parenting dimensions and styles with externalizing problems of children and adolescents: An updated meta-analysis. *Dev Psychol* 2017; **53**: 873-932 [PMID: 28459276 DOI: 10.1037/dev0000295]

38 **Crocetti E**, Moscatelli S, Van der Graaff J, Keijsers L, van Lier P, Koot HM, Rubini M, Meeus W, Branje S. The Dynamic Interplay among Maternal Empathy, Quality of Mother-Adolescent Relationship, and Adolescent Antisocial Behaviors: New Insights from a Six-Wave Longitudinal Multi-Informant Study. *PLoS One* 2016; **11**: e0150009 [PMID: 26990191 DOI: 10.1371/journal.pone.0150009]

39 **Noergaard B**, Johannessen H, Fenger-Gron J, Kofoed PE, Ammentorp J. Participatory Action Research in the Field of Neonatal Intensive Care: Developing an Intervention to Meet the Fathers' Needs. A Case Study. *J Public Health Res* 2016; **5**: 744 [PMID: 28083521 DOI: 10.4081/jphr.2016.744]

40 **Kim P**, Leckman JF, Mayes LC, Newman MA, Feldman R, Swain JE. Perceived quality of maternal care in childhood and structure and function of mothers' brain. *Dev Sci* 2010; **13**: 662-673 [PMID: 20590729 DOI: 10.1111/j.1467-7687.2009.00923.x]

41 **Allen KB**, Tan PZ, Sullivan JA, Baumgardner M, Hunter H, Glovak SN. An Integrative Model of Youth Anxiety: Cognitive-Affective Processes and Parenting in Developmental Context. *Clin Child Fam Psychol Rev* 2023; **26**: 1025-1051 [PMID: 37819403 DOI: 10.1007/s10567-023-00458-z]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2024 February 26; 12(6): 1094-1103

DOI: 10.12998/wjcc.v12.i6.1094

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Assessment of the triglyceride glucose index in adult patients with chronic diarrhea and constipation

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Herrero-Fresneda I, Spain

Received: December 8, 2023
Peer-review started: December 8, 2023
First decision: December 20, 2023
Revised: January 3, 2024
Accepted: January 19, 2024
Article in press: January 19, 2024
Published online: February 26, 2024

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Abstract

BACKGROUND

Accumulating evidence suggests that the gut microbiome is involved in the pathogenesis of insulin resistance (IR). However, the link between two of the most prevalent bowel disorders, chronic diarrhea and constipation, and the triglyceride glucose (TyG) index, a marker of IR, has not yet been investigated.

AIM

To investigate the potential association between TyG and the incidence of chronic diarrhea and constipation.

METHODS

This cross-sectional study enrolled 2400 participants from the National Health and Nutrition Examination Survey database from 2009-2010. TyG was used as an exposure variable, with chronic diarrhea and constipation as determined by the Bristol Stool Form Scale used as the outcome variables. A demographic investigation based on TyG quartile subgroups was performed. The application of multivariate logistic regression models and weighted generalized additive models revealed potential correlations between TyG, chronic diarrhea, and constipation. Subgroup analyses were performed to examine the stability of any potential associations.

RESULTS

In the chosen sample, chronic diarrhea had a prevalence of 8.00%, while chronic constipation had a prevalence of 8.04%. In multiple logistic regression, a more prominent positive association was found between TyG and chronic diarrhea, particularly in model 1 (OR = 1.45; 95%CI: 1.17-1.79, P = 0.0007) and model 2 (OR = 1.40; 95%CI: 1.12-1.76, P = 0.0033). No definite association was observed bet-

ween the TyG levels and chronic constipation. The weighted generalized additive model findings suggested a more substantial positive association with chronic diarrhea when TyG was less than 9.63 (OR = 1.89; 95%CI: 1.05-3.41, *P* = 0.0344), and another positive association with chronic constipation when it was greater than 8.2 (OR = 1.74; 95%CI: 1.02-2.95, *P* = 0.0415). The results of the subgroup analyses further strengthen the extrapolation of these results to a wide range of populations.

CONCLUSION
Higher TyG levels were positively associated with abnormal bowel health.

Key Words: Triglyceride glucose index; National Health and Nutrition Examination Survey; Chronic diarrhea; Chronic constipation; Cross-sectional study; Bowel health

Core Tip: Chronic diarrhea and constipation are two common conditions that interfere with daily life. Herein, we identified a positive association between the triglyceride glucose index, a marker of insulin resistance (IR), and chronic diarrhea in the National Health and Nutrition Examination Survey database. These results suggest that early and comprehensive management of IR may be beneficial for maintaining normal bowel health. Further investigations should be conducted on the underlying pathological mechanisms.

Citation: Zhu JY, Liu MY, Sun C. Assessment of the triglyceride glucose index in adult patients with chronic diarrhea and constipation. *World J Clin Cases* 2024; 12(6): 1094-1103
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1094.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1094

INTRODUCTION

Chronic diarrhea and chronic constipation are prevalent disorders that can severely impact a patient's quality of life[1,2]. Incomplete statistics have estimated that functional bowel disorders, as defined by the Rome Standard IV, result in more than four million medical visits per year in the United States[3]. Abnormal stool consistency is assessed as a part of the evaluation metrics in clinical practice[4,5]. The Bristol Stool Form Scale (BSFS)[6] was used to quantify these symptoms in the National Health and Nutrition Examination Survey (NHANES). Extensive research has been conducted using epidemiological data based on these criteria[7-10]. In the NHANES 2005-2010 sample population, the frequency of chronic diarrhea was higher in patients diagnosed with metabolic syndrome and nonalcoholic fatty liver disease than in patients with chronic constipation, or in the normal population[9]. Patients with chronic diarrhea and constipation have an increased prevalence of selected cancers, cardiovascular diseases, and risk of all-cause mortality[8]. Additionally, chronic diarrhea is more common in diabetic patients than non-diabetic patients, and the two are strongly inter-correlated [10]. According to epidemiological evidence, abnormal bowel habits are closely associated with chronic and metabolic diseases.

Insulin resistance (IR) is a metabolic condition believed to be a precursor of type 2 diabetes[11], and a manifestation of metabolic syndrome involving pathophysiological mechanisms[12,13]. Metagenomic research tools and animal experiments have recently uncovered the effects of the gut microbiota on host energy metabolism and their potential causal role in metabolic disorders[14-16]. Furthermore, there is a clear link between chronic diarrhea, constipation, and the gut microbiota. The triglyceride glucose (TyG) index is a useful and simple method for assessing IR. As such, we hypothesized that the TyG index is associated with abnormalities in bowel function. Many studies have previously demonstrated the applicability of TyG in clinical settings, as well as its accessibility to community-based primary care hospitals[17]. With this in mind, in the present study, we investigated the TyG index profile of patients with chronic diarrhea and constipation using data from the NHANES 2009-2010 database.

MATERIALS AND METHODS

Study population

Participants for this cross-sectional study were selected from the NHANES 2009-2010 database, for which informed written consent was obtained from all participants prior to engagement, and which contained no personal patient information. The dataset utilized a complex multistage probability sampling design that included, but was not limited to demographics, dietary habits, and test examinations.

All selected participants responded to the Bowel Health Questionnaire, which investigated standard stool types, and provided data on their fasting blood glucose and triglyceride levels. We further excluded participants who self-reported as having inflammatory bowel disease, celiac disease, or colon cancer. Ultimately, the study included 2400 individuals aged 20 years or older. Figure 1 depicts the sample selection process.

Bowel Health Questionnaire and TyG index

Responses to a general question about stool type were provided in the Bowel Health Questionnaire of the NHANES 2009-2010 database. In this system, stool types 1-7 are classified based on the BSFS criteria, which primarily assess the shape and consistency of the stools; these criteria are widely implemented in clinical practice[7]. Specifically, stools were described as changing in shape and consistency in a stepwise manner from type 1 (separate hard lumps resembling nuts) to type 7 (watery, no solid pieces). Chronic diarrhea was defined as type 6 or 7; chronic constipation as type 1 or type 2; and the remaining types were considered to indicate healthy bowels.

In this study, TyG, which comprises fasting blood glucose and triglycerides, was chosen as the exposure variable. The calculation to obtain Ln [fasting triglyceride (mg/dL) fasting glucose (mg/dL)/2] is straightforward and rapid to implement.

Covariates

Based on similar previous studies, the following covariates were considered and included: Age, sex, race, education (adults 20+), ratio of family income to poverty, body mass index (BMI), laxatives, alcohol, self-reported hypertension, diabetes mellitus, and hypercholesterolemia. All the above covariates were considered in the fully adjusted model. Table 1 presents the breakdown conditions for each covariate.

Statistical analyses

The population was segmented according to TyG quartiles ranging from low to high, and discrepancies in demographic information were measured. Three generalized linear regression models, adjusted for covariates, were used to explore the relationship between TyG and chronic diarrhea or constipation. The non-linear relationship was analyzed using smooth curve fitting and generalized additivity models, and the presence and importance of the inflection points were investigated by applying two-stage linear models and log-likelihood ratios. Subgroup analyses were conducted to assess the consistency of this association across varying age groups, sexes, and BMI ranges, and among individuals with hypertension and diabetes. All preceding research stages were conducted using Empower software and R version 3.4.3.

RESULTS

Baseline characteristics of the study participants

Table 1 presents the primary demographic features of the cohort of 2400 patients, which comprised 48.21% males and 51.79% females enrolled in the study. The mean age and TyG index values were 49.35 ± 17.60 and 8.68 ± 0.64 respectively. For assessment purposes, participants were categorized into four groups. The overall incidence of chronic constipation was 8.04% among all participants, while the incidences of chronic constipation in the population stratified by TyG quartiles were as follows: Quartile 1 (Q1) (6.89-8.24): 8.85%; Q2 (8.25-8.62), 8.15%; Q3 (8.62-9.04), 7.33%, and Q4 (9.04-12.34), 7.83%, with a P value of 0.806. The prevalence of chronic diarrhea was 8.00% in all participants, and the prevalence of chronic diarrhea in the population grouped by TyG quartiles was Q1, 6.00%; Q2, 6.16%; Q3, 7.33%; and Q4, 7.83%, (P = 0.004). Compared to individuals in Q1-3, Q4 exhibited the highest range of TyG indices, including a higher proportion of males, an increase in the percentage of low-educated and poor people, an indication of overweight and obesity based on BMI, and a significant increase in the percentage of self-reported hypertension, diabetes mellitus, and hypercholesterolemia.

Association between TyG index and bowel health

Table 2 presents the association between TyG index and bowel health. Our findings indicated that elevated levels of TyG were positively correlated with the risk of chronic diarrhea, particularly in the crude model (OR = 1.45; 95%CI: 1.17-1.79, P = 0.0007) and partly adjusted model 2 (OR = 1.40; 95%CI: 1.12-1.76, P = 0.0033). This relationship became less significant in model 3 after full variable control (OR = 1.35; 95%CI: 0.85-2.13, P = 0.2071). Nevertheless, no correlation between the TyG index and chronic constipation were found, with ORs (95%CIs) of 0.96 (0.76-1.21), 1.10 (0.86-1.40), and 1.50 (0.95-2.37) for models 1, 2, and 3, respectively.

TyG levels were subsequently split into quartiles to further examine changes in the tendency of relationships. In models 1 and 2, positive correlation patterns emerged for chronic diarrhea. In a crude model, for example, when the TyG index increased by one standard deviation, participants in the top TyG quartile exhibited a 1.88-fold greater likelihood of suffering from chronic diarrhea than those in the bottom quartile (OR = 1.88; 95%CI: 1.23-2.86, P for trend = 0.0007). In model 3, individuals in the upper quartile of TyG were more likely to experience chronic diarrhea than those in the lower quartile, although statistical difference was not reached (OR = 1.52; 95%CI: 0.65-3.56, P for trend = 0.2268). None of the trend tests between TyG and chronic constipation showed statistical significance (P > 0.05) in models 1-3.

After considering all the covariates, smooth curve fitting and a generalized additivity model were used (Figure 2). Regarding chronic diarrhea, a two-stage linear model was applied, resulting in an inflection point of 9.63, which showed statistical significance on the log-likelihood ratio test (P = 0.047). When the TyG index fell below 9.63, the chances of

Table 1 Demographics and characteristics of participants by quartiles of triglyceride glucose index, from the National Health and Nutrition Examination Surveys 2009-2010

	Q1, *n* = 599 (6.89-8.24)	Q2, *n* = 601 (8.25-8.62)	Q3, *n* = 600 (8.62-9.04)	Q4, *n* = 600 (9.04-12.34)	*P* value
Age (yr), mean ± SD	43.47 ± 16.99	49.03 ± 17.81	51.93 ± 17.77	52.95 ± 16.24	< 0.001[c]
Triglyceride (mg/dL), mean ± SD	62.00 ± 13.32	94.21 ± 15.25	131.68 ± 22.99	246.43 ± 186.73	< 0.001[c]
Fasting glucose (mg/dL), mean ± SD	92.59 ± 10.28	100.66 ± 16.57	106.19 ± 18.46	129.96 ± 51.53	< 0.001[c]
Gender, *n* (%)					< 0.001[c]
Male	219 (36.56)	277 (46.09)	327 (54.50)	334 (55.67)	
Female	380 (63.44)	324 (53.91)	273 (45.50)	266 (44.33)	
Race, *n* (%)					< 0.001[c]
Mexican American	77 (12.85)	108 (17.97)	116 (19.33)	160 (26.67)	
Other Hispanic	67 (11.19)	60 (9.98)	58 (9.67)	83 (13.83)	
Non-Hispanic white	291 (48.58)	286 (47.59)	313 (52.17)	276 (46.00)	
Non-Hispanic black	135 (22.54)	124 (20.63)	74 (12.33)	60 (10.00)	
Other races	29 (4.84)	23 (3.83)	39 (6.50)	21 (3.50)	
Levels of education, *n* (%)					< 0.001[c]
≤ High school	108 (18.03)	156 (25.96)	172 (28.76)	237 (39.83)	
> High school	491 (81.97)	445 (74.04)	426 (71.24)	358 (60.17)	
Ratio of family income to poverty, *n* (%)					0.008[b]
≤ 1	97 (17.86)	113 (20.14)	128 (23.23)	137 (25.95)	
> 1	446 (82.14)	448 (79.86)	423 (76.77)	391 (74.05)	
Body mass index, *n* (%)					< 0.001[c]
Under/normal weight	294 (49.33)	178 (29.82)	125 (20.94)	71 (11.97)	
Overweight	176 (29.53)	218 (36.52)	212 (35.51)	208 (35.08)	
Obese	126 (21.14)	201 (33.67)	260 (43.55)	314 (52.95)	
Diabetes, *n* (%)					< 0.001[c]
Yes	20 (3.37)	48 (8.18)	65 (11.05)	145 (25.09)	
No	573 (96.63)	539 (91.82)	523 (88.95)	433 (74.91)	
Hypertension, *n* (%)					< 0.001[c]
Yes	128 (21.37)	204 (33.94)	237 (39.50)	283 (47.17)	
No	471 (78.63)	397 (66.06)	363 (60.50)	317 (52.83)	
High cholesterol level, *n* (%)					< 0.001[c]
Yes	114 (28.22)	162 (39.71)	183 (41.78)	276 (61.47)	
No	290 (71.78)	246 (60.29)	255 (58.22)	173 (38.53)	
Alcohol, *n* (%)					< 0.001[c]
≥ 1, < 8	419 (96.54)	418 (94.36)	385 (92.55)	331 (88.74)	
≥ 8	15 (3.46)	25 (5.64)	31 (7.45)	42 (11.26)	
Chronic diarrhea, *n* (%)					0.004[b]
Yes	37 (6.18)	37 (6.16)	52 (8.67)	66 (11.00)	
No	562 (93.82)	564 (93.84)	548 (91.33)	534 (89.00)	
Chronic constipation, *n* (%)					0.806
Yes	53 (8.85)	49 (8.15)	44 (7.33)	47 (7.83)	

No	546 (91.15)	552 (91.85)	556 (92.67)	553 (92.17)

[a]*P* < 0.05.
[b]*P* < 0.01.
[c]*P* < 0.001.

Table 2 ORs (95%CI) for the relationship between the triglyceride glucose index and chronic diarrhea and chronic constipation, from the National Health and Nutrition Examination Survey 2009-2010

TyG		OR (95%CI)	
		Chronic constipation	Chronic diarrhea
Model 1 continuous		0.96 (0.76, 1.21)	1.45 (1.17, 1.79)
Q1	6.89-8.24	1.0 (reference)	1.0 (reference)
Q2	8.25-8.62	0.91 (0.61, 1.37)	1.00 (0.62, 1.59)
Q3	8.62-9.04	0.82 (0.54, 1.24)	1.44 (0.93, 2.23)
Q4	9.04-12.34	0.88 (0.58, 1.32)	1.88 (1.23, 2.86)
P for trend		0.4591	0.0007[a]
Model 2 continuous		1.10 (0.86, 1.40)	1.40 (1.12, 1.76)
Q1	6.89-8.24	1.0 (reference)	1.0 (reference)
Q2	8.25-8.62	1.00 (0.66, 1.52)	0.95 (0.59, 1.53)
Q3	8.62-9.04	1.00 (0.65, 1.55)	1.38 (0.88, 2.18)
Q4	9.04-12.34	1.06 (0.68, 1.64)	1.71 (1.10, 2.65)
P for trend		0.8026	0.0044[b]
Model 3 continuous		1.50 (0.95, 2.37)	1.35 (0.85, 2.13)
Q1	6.89-8.24	1.0 (reference)	1.0 (reference)
Q2	8.25-8.62	1.07 (0.50, 2.28)	0.92 (0.39, 2.14)
Q3	8.62-9.04	1.86 (0.89, 3.90)	1.18 (0.52, 2.66)
Q4	9.04-12.34	1.76 (0.76, 4.07)	1.52 (0.65, 3.56)
P for trend		0.0999	0.2268

[a]*P* < 0.05.
[b]*P* < 0.01.
Model 1: No covariates were adjusted; Model 2: Adjusted for gender, age, and race; Model 3: Adjusted for age, gender, race, education (adults 20+), ratio of family income to poverty. Body mass index, laxatives, alcohol, self-reported hypertension, diabetes mellitus, and hypercholesterolemia. TyG: Triglyceride glucose.

suffering from chronic diarrhea rose by 89% with each one-SD increase in the TyG index (OR = 1.89; 95%CI: 1.05-3.41, *P* = 0.0344). Conversely, no association was seen above 9.63 (OR = 0.24; 95%CI: 0.03-2.22, *P* = 0.2080), and the curve tended to flatten. Regarding chronic constipation, a positive correlation was found between TyG and chronic constipation only when the TyG value exceeded 8.2 (OR = 1.74; 95%CI: 1.02-2.95, *P* = 0.0415), but the *P* value of the log-likelihood ratio did not meet the required significance (*P* = 0.321).

Subgroup analysis

Initially, we aimed to investigate the impact of a range of factors on the risk of chronic diarrhea. First, in models 1 and 3, we examined the subgroups categorized by age, sex, BMI, diabetes, and hypertension. Despite an intermittent lack of positive correlation between TyG and chronic diarrhea in some subgroups in the crude model, the interaction test confirmed that the association remained unaffected by these factors. Furthermore, this positive correlation was consistent across different age groups and hypertensive conditions. In summary, model 1 demonstrated that the variables mentioned above did not affect the occurrence of chronic diarrhea. For the subgroup analysis of model 3, the *P* value of the interaction test was greater than 0.05, supporting the inference that the connection between TyG and chronic diarrhea was similar across populations.

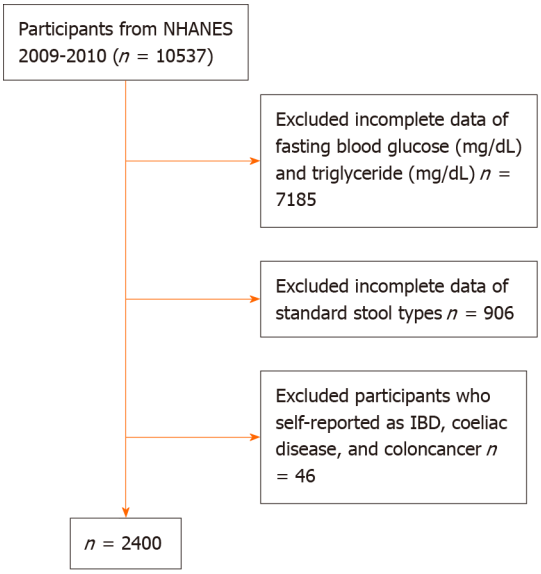

Figure 1 Flowchart of the selection of participants from the National Health and Nutrition Examination Survey 2009-2010. NHANES: National Health and Nutrition Examination Survey; IBD: Inflammatory bowel disease.

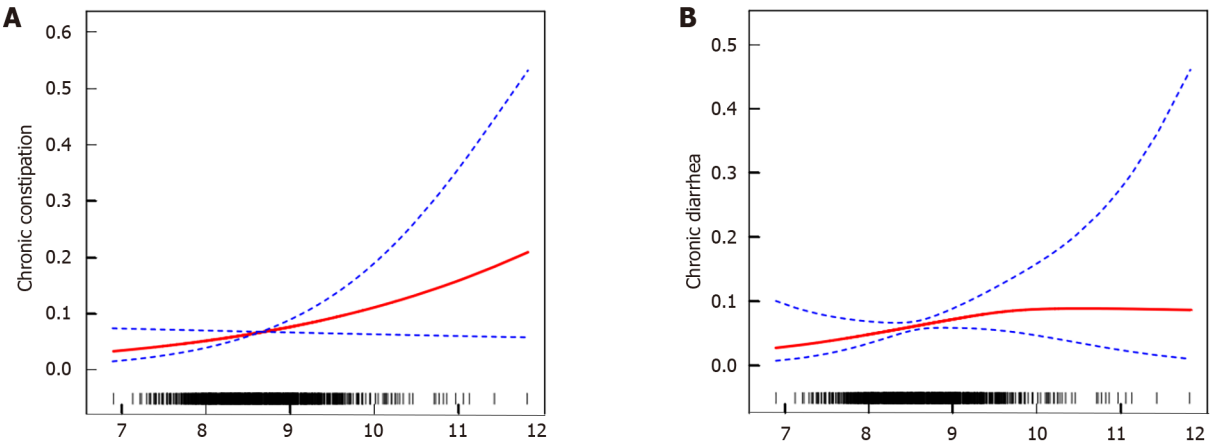

Figure 2 The non-linear associations between triglyceride glucose and chronic diarrhea and chronic constipation. A: The non-linear associations between triglyceride glucose (TyG) and chronic constipation; B: The non-linear associations between TyG and chronic diarrhea. TyG: Triglyceride glucose.

Subsequently, further subgroup analyses were performed using model 3 to check the robustness of the relationship between TyG levels and chronic constipation. It is worth noting that higher TyG scores were found to be correlated with an increased risk of chronic constipation in the hypertensive population (OR = 2.53; 95%CI: 1.19-5.37, P = 0.0159), but not in the non-hypertensive population, indicating that this association may be stronger in hypertensive individuals. However, no connections with P values for interactions were found to fulfill the statistically significant interaction criteria, emphasizing that the association between TyG and chronic constipation is dependent.

DISCUSSION

In this cross-sectional study encompassing 2400 participants, our findings demonstrated a heightened risk of chronic diarrhea with elevated TyG levels. This non-linear connection demonstrated that TyG was positively correlated with chronic diarrhea and constipation at distinct value bands. Subgroup analysis further indicated that this relationship persisted irrespective of sex, age, BMI, hypertension, or diabetes status.

To our knowledge, this is the first study to evaluate the correlation between TyG index and abnormal gut health. The TyG formula indicated that an elevated value reflected anomalies in glucose and lipid levels. The gut microbiota is a primary regulator of the host's metabolic energy and substrate metabolism[18,19]. Bäckhed *et al*[20] previously showed that hyperglycemia directly and specifically shaped intestinal barrier failure and increased the susceptibility to intestinal infections. They also discovered that hyperglycemia affects intestinal epithelial cells *via* the bidirectional glucose

transporter receptor GLU2, causing the intracellular recording of metabolism-related genes. Disturbances in the composition of the gut microbiota can disrupt the immune system, leading to inflammation, oxidative stress, and IR. Certain prebiotics and probiotics have further been proven to regulate fat metabolism, enhance insulin sensitivity, and control intestinal inflammation and oxidative stress in mice, as evidenced by animal models. Cranberry extracts enriched with phenolic compounds, green tea powder, and *Lactobacillus plantarum* have also demonstrated positive effects on metabolic phenotypes. Specifically, these substances have been observed to increase the proportion of gut bacteria belonging to the genus *Akkermansia*. Additionally, the expression of various modulators of inflammation was found to be lowered following their administration[21,22]. Similarly, the probiotic *Lactobacillus acidophilus* has also been demonstrated to alter gut microbial abundance and diversity; suppress the TLR4/NF-κB signaling pathway; and improve energy, glucose, and lipid metabolism[23]. Dysbiosis of gut microbes, in turn, facilitates the pathology of a variety of intestinal disorders, including chronic diarrhea and chronic constipation[24], through mechanisms that primarily include the production of large amounts of toxins by certain opportunistic pathogenic bacteria[25], altered metabolic function of bile acids[26,27], and involvement in the regulation of gastrointestinal motility through the production and uptake of 5-hydroxytryptamine[28,29]. Overall, gut microbes seem to play a joint role in the development of IR and abnormal gut health, but it has not been directly established whether IR causally mediates chronic diarrhea through modulation of the gut microbes. Smoothed curve-fitting results have indicated that TyG impacts chronic diarrhea and constipation at two relatively separate intervals, with chronic diarrhea in the antecedent half of the curve, and chronic constipation in the subsequent half. This indicates that the pathogenic mechanisms underlying TyG, chronic diarrhea, and constipation may differ. Additionally, the results of this research could provide further insights into subsequent basic experiments investigating the influence of metabolic factors on the pathological mechanisms of abnormal gut health.

In prior studies, abnormal gut health and several chronic diseases have been associated with the dietary inflammation index and C-reactive protein levels. The inflammatory response and oxidative stress are undoubtedly involved in the intrinsic evolution of a variety of disease states. However, this study was unable to provide further evidence of the precise mechanisms by which TyG may mediate chronic diarrhea or constipation. In addition to IR, higher TyG indices are indicative of a poor health status and have been implicated in cardiovascular disease[30], obesity[31], diabetes[32], hypertension[33], metabolic syndrome[34], and lipid metabolism[35]. In the present study, the positive link between TyG and diarrhea remained after controlling for basic demographic characteristics, but disappeared in the fully adjusted model, indicating that TyG may be inextricably linked to physical conditions and personal aggregates. However, the interaction reached statistical significance in the subgroup analyses for models 1 and 3, which included sex, age, BMI, hypertension, and diabetes. TyG levels are closely correlated with constipation in individuals with hypertension. To the best of our knowledge, only one study has reported that hypertension (22%) is the most frequent comorbidity in patients with chronic constipation[36].

Overall, the present study contributes to our understanding of the relationship between IR and chronic diarrhea, indicating that timely co-management may be critical. Similar to previous studies on abnormal gut health and type 2 diabetes, chronic diarrhea seems to be more strongly linked to other diseases than chronic constipation[37]. It is also worth noting that while the results for TyG and chronic constipation lacked statistical significance, this did not rule out the role of TyG in chronic constipation. There is a current pressing need for a reliable indicator of intestinal dysfunction for the co-treatment of chronic illnesses. Given the lack of more detailed data on disease progression in the NHANES database, such as the temporal relationship between elevated TyG levels and the emergence of abnormal gut health. Thus, a well-designed randomized controlled trial is necessary to determine whether TyG could be applied as a reliable predictor of chronic diarrhea and constipation, as well as to assess its potential use in practice.

This study has several shortcomings. Firstly, the definitions of persistent constipation and diarrhea did not follow the most recent Rome criteria. As this was only a cross-sectional study, it is important to consider that the causal relationships and mechanisms underlying the association between TyG and chronic diarrhea and constipation require further investigation through prospective studies with larger sample sizes and basic experiments. Such further investigation will aid in the future application of TyG in clinical practice.

CONCLUSION

Overall, the present analysis of subjects enrolled in the NHANES 2009-2010 database indicated a correlation between a higher TyG index and an increased likelihood of chronic diarrhea. Further studies are required to understand the pathological mechanisms underlying TyG and abnormal gut health. Improving the treatment and management of IR may reduce the incidence of abnormal bowel health.

ARTICLE HIGHLIGHTS

Research background

Triglyceride glucose (TyG) was associated with a variety of chronic diseases. However, there is currently a lack of research regarding their association with abnormal gut health.

Research motivation

The National Health and Nutrition Examination Survey (NHANES) provides national-level data on the health and

nutritional status of the United States population. The gut microbiome and pathogenesis of insulin resistance (IR) has been intensively studies using this data. As TyG as a marker of IR, we decided to explore the association between TyG and abnormal gut health using the NHANES database.

Research objectives

To study the association between TyG and the incidence of chronic diarrhea and constipation in United States adults.

Research methods

This cross-sectional study was conducted among adults with complete data on TyG, chronic diarrhea, and constipation included in the 2009-2010 NHANES. TyG was calculated using the following equation: Ln [fasting triglyceride (mg/dL) fasting glucose (mg/dL)/2]. Chronic diarrhea and constipation were assessed using the Bristol Stool Form Scale. Weighted multivariate regression and subgroup analyses were conducted to explore the independent relationship between TyG, chronic diarrhea, and constipation.

Research results

In this cross-sectional study encompassing 2400 participants, our findings demonstrated a heightened risk of chronic diarrhea with elevated TyG levels. The non-linear connection demonstrated that TyG positively correlated with chronic diarrhea and constipation at distinct value bands. Subgroup analysis indicated that this relationship persisted irrespective of sex, age, BMI, hypertension, or diabetes status.

Research conclusions

A total of 2400 participants were included in this cross-sectional study, which revealed a correlation between elevated TyG levels and a heightened risk of chronic diarrhea.

Research perspectives

Further research is required to establish the exact causal relationship between TyG and abnormal gut health, which will contribute to the prediction, co-management, and treatment of subsequent diseases.

FOOTNOTES

Author contributions: All contributors participated in study formulation and design. Zhu JY prepared the initial draft of the manuscript; Liu MY prepared, collected, and analyzed the data; Sun C revised and reviewed the manuscript; the manuscript was accepted for publication after final approval from the authors.

Institutional review board statement: The NHANES is a publicly available database, and this research was reviewed and approved by the Research Ethics Review Board of the National Center for Health Statistics.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Data sharing statement: The dataset supporting the conclusions of this article is available in the NHANES repository: NHANES-National Health and Nutrition Examination Survey Homepage (cdc.gov).

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S-Editor: Zhang H
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 **Araki M**, Shinzaki S, Yamada T, Arimitsu S, Komori M, Shibukawa N, Mukai A, Nakajima S, Kinoshita K, Kitamura S, Murayama Y, Ogawa H, Yasunaga Y, Oshita M, Fukui H, Masuda E, Tsujii M, Kawai S, Hiyama S, Inoue T, Tanimukai H, Iijima H, Takehara T. Psychologic stress and disease activity in patients with inflammatory bowel disease: A multicenter cross-sectional study. *PLoS One* 2020; **15**: e0233365 [PMID: 32453762 DOI: 10.1371/journal.pone.0233365]

2 **Gîlc-Blanariu GE**, Ștefnescu G, Trifan AV, Moscalu M, Dimofte MG, Ștefnescu C, Drug VL, Afrsnie VA, Ciocoiu M. Sleep Impairment and Psychological Distress among Patients with Inflammatory Bowel Disease-beyond the Obvious. *J Clin Med* 2020; **9** [PMID: 32698475 DOI:

10.3390/jcm9072304]
3 **Ma C**, Congly SE, Novak KL, Belletrutti PJ, Raman M, Woo M, Andrews CN, Nasser Y. Epidemiologic Burden and Treatment of Chronic Symptomatic Functional Bowel Disorders in the United States: A Nationwide Analysis. *Gastroenterology* 2021; **160**: 88-98.e4 [PMID: 33010247 DOI: 10.1053/j.gastro.2020.09.041]
4 **Koyama T**, Nagata N, Nishiura K, Miura N, Kawai T, Yamamoto H. Prune Juice Containing Sorbitol, Pectin, and Polyphenol Ameliorates Subjective Complaints and Hard Feces While Normalizing Stool in Chronic Constipation: A Randomized Placebo-Controlled Trial. *Am J Gastroenterol* 2022; **117**: 1714-1717 [PMID: 35971232 DOI: 10.14309/ajg.0000000000001931]
5 **Hamad A**, Fragkos KC, Forbes A. A systematic review and meta-analysis of probiotics for the management of radiation induced bowel disease. *Clin Nutr* 2013; **32**: 353-360 [PMID: 23453637 DOI: 10.1016/j.clnu.2013.02.004]
6 **O'Donnell LJ**, Virjee J, Heaton KW. Detection of pseudodiarrhoea by simple clinical assessment of intestinal transit rate. *BMJ* 1990; **300**: 439-440 [PMID: 2107897 DOI: 10.1136/bmj.300.6722.439]
7 **Ballou S**, Katon J, Singh P, Rangan V, Lee HN, McMahon C, Iturrino J, Lembo A, Nee J. Chronic Diarrhea and Constipation Are More Common in Depressed Individuals. *Clin Gastroenterol Hepatol* 2019; **17**: 2696-2703 [PMID: 30954714 DOI: 10.1016/j.cgh.2019.03.046]
8 **Peng Y**, Liu F, Qiao Y, Wang P, Ma B, Li L, Si C, Wang X, Zhang M, Song F. Association of abnormal bowel health with major chronic diseases and risk of mortality. *Ann Epidemiol* 2022; **75**: 39-46 [PMID: 36116757 DOI: 10.1016/j.annepidem.2022.09.002]
9 **Shin A**, Xu H, Imperiale TF. Associations of chronic diarrhoea with non-alcoholic fatty liver disease and obesity-related disorders among US adults. *BMJ Open Gastroenterol* 2019; **6**: e000322 [PMID: 31523443 DOI: 10.1136/bmjgast-2019-000322]
10 **Sommers T**, Mitsuhashi S, Singh P, Hirsch W, Katon J, Ballou S, Rangan V, Cheng V, Friedlander D, Iturrino J, Lembo A, Nee J. Prevalence of Chronic Constipation and Chronic Diarrhea in Diabetic Individuals in the United States. *Am J Gastroenterol* 2019; **114**: 135-142 [PMID: 30410038 DOI: 10.1038/s41395-018-0418-8]
11 **Kahn SE**, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 2006; **444**: 840-846 [PMID: 17167471 DOI: 10.1038/nature05482]
12 **Brown AE**, Walker M. Genetics of Insulin Resistance and the Metabolic Syndrome. *Curr Cardiol Rep* 2016; **18**: 75 [PMID: 27312935 DOI: 10.1007/s11886-016-0755-4]
13 **da Silva AA**, do Carmo JM, Li X, Wang Z, Mouton AJ, Hall JE. Role of Hyperinsulinemia and Insulin Resistance in Hypertension: Metabolic Syndrome Revisited. *Can J Cardiol* 2020; **36**: 671-682 [PMID: 32389340 DOI: 10.1016/j.cjca.2020.02.066]
14 **Aron-Wisnewsky J**, Vigliotti C, Witjes J, Le P, Holleboom AG, Verheij J, Nieuwdorp M, Clément K. Gut microbiota and human NAFLD: disentangling microbial signatures from metabolic disorders. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 279-297 [PMID: 32152478 DOI: 10.1038/s41575-020-0269-9]
15 **Cao GT**, Dai B, Wang KL, Yan Y, Xu YL, Wang YX, Yang CM. Bacillus licheniformis, a potential probiotic, inhibits obesity by modulating colonic microflora in C57BL/6J mice model. *J Appl Microbiol* 2019; **127**: 880-888 [PMID: 31211897 DOI: 10.1111/jam.14352]
16 **Liu J**, Yue S, Yang Z, Feng W, Meng X, Wang A, Peng C, Wang C, Yan D. Oral hydroxysafflor yellow A reduces obesity in mice by modulating the gut microbiota and serum metabolism. *Pharmacol Res* 2018; **134**: 40-50 [PMID: 29787870 DOI: 10.1016/j.phrs.2018.05.012]
17 **Tahapary DL**, Pratisthita LB, Fitri NA, Marcella C, Wafa S, Kurniawan F, Rizka A, Tarigan TJE, Harbuwono DS, Purnamasari D, Soewondo P. Challenges in the diagnosis of insulin resistance: Focusing on the role of HOMA-IR and Tryglyceride/glucose index. *Diabetes Metab Syndr* 2022; **16**: 102581 [PMID: 35939943 DOI: 10.1016/j.dsx.2022.102581]
18 **Dao MC**, Everard A, Aron-Wisnewsky J, Sokolovska N, Prifti E, Verger EO, Kayser BD, Levenez F, Chilloux J, Hoyles L; MICRO-Obes Consortium, Dumas ME, Rizkalla SW, Doré J, Cani PD, Clément K. Akkermansia muciniphila and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. *Gut* 2016; **65**: 426-436 [PMID: 26100928 DOI: 10.1136/gutjnl-2014-308778]
19 **Bäckhed F**, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci U S A* 2004; **101**: 15718-15723 [PMID: 15505215 DOI: 10.1073/pnas.0407076101]
20 **Saad MJ**, Santos A, Prada PO. Linking Gut Microbiota and Inflammation to Obesity and Insulin Resistance. *Physiology (Bethesda)* 2016; **31**: 283-293 [PMID: 27252163 DOI: 10.1152/physiol.00041.2015]
21 **Anhê FF**, Roy D, Pilon G, Dudonné S, Matamoros S, Varin TV, Garofalo C, Moine Q, Desjardins Y, Levy E, Marette A. A polyphenol-rich cranberry extract protects from diet-induced obesity, insulin resistance and intestinal inflammation in association with increased Akkermansia spp. population in the gut microbiota of mice. *Gut* 2015; **64**: 872-883 [PMID: 25080446 DOI: 10.1136/gutjnl-2014-307142]
22 **Axling U**, Olsson C, Xu J, Fernandez C, Larsson S, Ström K, Ahrné S, Holm C, Molin G, Berger K. Green tea powder and Lactobacillus plantarum affect gut microbiota, lipid metabolism and inflammation in high-fat fed C57BL/6J mice. *Nutr Metab (Lond)* 2012; **9**: 105 [PMID: 23181558 DOI: 10.1186/1743-7075-9-105]
23 **Kang Y**, Kang X, Yang H, Liu H, Yang X, Liu Q, Tian H, Xue Y, Ren P, Kuang X, Cai Y, Tong M, Li L, Fan W. Lactobacillus acidophilus ameliorates obesity in mice through modulation of gut microbiota dysbiosis and intestinal permeability. *Pharmacol Res* 2022; **175**: 106020 [PMID: 34896249 DOI: 10.1016/j.phrs.2021.106020]
24 **Altomare A**, Di Rosa C, Imperia E, Emerenziani S, Cicala M, Guarino MPL. Diarrhea Predominant-Irritable Bowel Syndrome (IBS-D): Effects of Different Nutritional Patterns on Intestinal Dysbiosis and Symptoms. *Nutrients* 2021; **13** [PMID: 33946961 DOI: 10.3390/nu13051506]
25 **Zhong W**, Lu X, Shi H, Zhao G, Song Y, Wang Y, Zhang J, Jin Y, Wang S. Distinct Microbial Populations Exist in the Mucosa-associated Microbiota of Diarrhea Predominant Irritable Bowel Syndrome and Ulcerative Colitis. *J Clin Gastroenterol* 2019; **53**: 660-672 [PMID: 29210899 DOI: 10.1097/MCG.0000000000000961]
26 **Slattery SA**, Niaz O, Aziz Q, Ford AC, Farmer AD. Systematic review with meta-analysis: the prevalence of bile acid malabsorption in the irritable bowel syndrome with diarrhoea. *Aliment Pharmacol Ther* 2015; **42**: 3-11 [PMID: 25913530 DOI: 10.1111/apt.13227]
27 **Dior M**, Delagrèverie H, Duboc H, Jouet P, Coffin B, Brot L, Humbert L, Trugnan G, Seksik P, Sokol H, Rainteau D, Sabate JM. Interplay between bile acid metabolism and microbiota in irritable bowel syndrome. *Neurogastroenterol Motil* 2016; **28**: 1330-1340 [PMID: 27060367 DOI: 10.1111/nmo.12829]
28 **Cao H**, Liu X, An Y, Zhou G, Liu Y, Xu M, Dong W, Wang S, Yan F, Jiang K, Wang B. Dysbiosis contributes to chronic constipation development *via* regulation of serotonin transporter in the intestine. *Sci Rep* 2017; **7**: 10322 [PMID: 28871143 DOI: 10.1038/s41598-017-10835-8]
29 **Agus A**, Planchais J, Sokol H. Gut Microbiota Regulation of Tryptophan Metabolism in Health and Disease. *Cell Host Microbe* 2018; **23**: 716-724 [PMID: 29902437 DOI: 10.1016/j.chom.2018.05.003]

30 **Tao LC**, Xu JN, Wang TT, Hua F, Li JJ. Triglyceride-glucose index as a marker in cardiovascular diseases: landscape and limitations. *Cardiovasc Diabetol* 2022; **21**: 68 [PMID: 35524263 DOI: 10.1186/s12933-022-01511-x]

31 **Sheng G**, Lu S, Xie Q, Peng N, Kuang M, Zou Y. The usefulness of obesity and lipid-related indices to predict the presence of Non-alcoholic fatty liver disease. *Lipids Health Dis* 2021; **20**: 134 [PMID: 34629059 DOI: 10.1186/s12944-021-01561-2]

32 **Park B**, Lee HS, Lee YJ. Triglyceride glucose (TyG) index as a predictor of incident type 2 diabetes among nonobese adults: a 12-year longitudinal study of the Korean Genome and Epidemiology Study cohort. *Transl Res* 2021; **228**: 42-51 [PMID: 32827706 DOI: 10.1016/j.trsl.2020.08.003]

33 **Huang Z**, Ding X, Yue Q, Wang X, Chen Z, Cai Z, Li W, Chen G, Lan Y, Wu W, Wu S, Chen Y. Triglyceride-glucose index trajectory and stroke incidence in patients with hypertension: a prospective cohort study. *Cardiovasc Diabetol* 2022; **21**: 141 [PMID: 35897017 DOI: 10.1186/s12933-022-01577-7]

34 **Mirr M**, Skrypnik D, Bogdański P, Owecki M. Newly proposed insulin resistance indexes called TyG-NC and TyG-NHtR show efficacy in diagnosing the metabolic syndrome. *J Endocrinol Invest* 2021; **44**: 2831-2843 [PMID: 34132976 DOI: 10.1007/s40618-021-01608-2]

35 **Zhao J**, Fan H, Wang T, Yu B, Mao S, Wang X, Zhang W, Wang L, Zhang Y, Ren Z, Liang B. TyG index is positively associated with risk of CHD and coronary atherosclerosis severity among NAFLD patients. *Cardiovasc Diabetol* 2022; **21**: 123 [PMID: 35778734 DOI: 10.1186/s12933-022-01548-y]

36 **Bruce Wirta S**, Hodgkins P, Joseph A. Economic burden associated with chronic constipation in Sweden: a retrospective cohort study. *Clinicoecon Outcomes Res* 2014; **6**: 369-379 [PMID: 25143749 DOI: 10.2147/CEOR.S61985]

37 **Fagherazzi G**, Gusto G, Balkau B, Boutron-Ruault MC, Clavel-Chapelon F, Bonnet F. Functional gastrointestinal disorders and incidence of type 2 diabetes: Evidence from the E3N-EPIC cohort study. *Diabetes Metab* 2016; **42**: 178-183 [PMID: 26738848 DOI: 10.1016/j.diabet.2015.11.006]

World Journal of Clinical Cases

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World J Clin Cases 2024 February 26; 12(6): 1104-1110

DOI: 10.12998/wjcc.v12.i6.1104

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Acute pancreatitis as a complication of acute COVID-19 in kidney transplant recipients

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Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Gong F, China

Received: December 7, 2023
Peer-review started: December 7, 2023
First decision: December 17, 2023
Revised: December 18, 2023
Accepted: January 31, 2024
Article in press: January 31, 2024
Published online: February 26, 2024

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Abstract

BACKGROUND

Acute pancreatitis is a rare extrapulmonary manifestation of coronavirus disease 2019 (COVID-19) but its full correlation with COVID-19 infection remains unknown.

AIM

To identify acute pancreatitis' occurrence, clinical presentation and outcomes in a cohort of kidney transplant recipients with acute COVID-19.

METHODS

A retrospective observational single-centre cohort study from a transplant centre in Croatia for all adult renal transplant recipients with a functioning kidney allograft between March 2020 and August 2022 to record cases of acute pancreatitis during acute COVID-19. Data were obtained from hospital electronic medical records. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was proven by a positive SARS-CoV-2 real-time reverse transcriptase-polymerase chain reaction on the nasopharyngeal swab.

RESULTS

Four hundred and eight out of 1432 (28.49%) patients who received a renal allograft developed COVID-19 disease. The analyzed cohort included 321 patients (57% males). One hundred and fifty patients (46.7%) received at least one dose of the anti-SARS-CoV-2 vaccine before the infection. One hundred twenty-five

(39.1%) patients required hospitalization, 141 (44.1%) developed pneumonia and four patients (1.3%) required mechanical ventilation. Treatment included immunosuppression modification in 233 patients (77.1%) and remdesivir in 53 patients (16.6%), besides the other supportive measures. In the study cohort, only one transplant recipient (0.3%) developed acute pancreatitis during acute COVID-19, presenting with abdominal pain and significantly elevated pancreatic enzymes. She survived without complications with a stable kidney allograft function.

CONCLUSION
Although rare, acute pancreatitis may complicate the course of acute COVID-19 in kidney transplant recipients. The mechanism of injury to the pancreas and its correlation with the severity of the COVID-19 infection in kidney transplant recipients warrants further research.

Key Words: Acute pancreatitis; COVID-19; Kidney transplant; Angiotensin-converting enzyme-2 receptor; Immunosuppressive agents

Core Tip: The attention to the effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus on pancreatic tissue has been arising. It is hypothesized that the SARS-CoV-2 virus can directly affect pancreatic tissue *via* angiotensin-converting enzyme 2 receptors which are heavily expressed in pancreatic cells. Our single-centre retrospective study aimed to identify the occurrence of acute pancreatitis, clinical presentation and outcomes in a cohort of kidney transplant recipients with acute coronavirus disease 2019 (COVID-19) between March 2020 and August 2022. 28.49% of transplant recipients developed COVID-19 disease and only 0.3% developed acute pancreatitis during the acute COVID-19 presenting with abdominal pain and elevated pancreatic enzymes with no imaging features. The mechanism of injury to the pancreas and its correlation with the severity of the COVID-19 infection in kidney transplant recipients warrants further research.

Citation: Basic-Jukic N, Juric I, Katalinic L, Furic-Cunko V, Sesa V, Mrzljak A. Acute pancreatitis as a complication of acute COVID-19 in kidney transplant recipients. *World J Clin Cases* 2024; 12(6): 1104-1110
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1104.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1104

INTRODUCTION

Acute pancreatitis is an acute inflammation of the pancreas characterized by typical upper abdominal pain, vomiting and nausea. Clinical, biochemical and/or radiologic findings are required to establish a diagnosis[1]. The most common causes of pancreatitis are gallstones, alcohol, hypertriglyceridemia, post-endoscopic retrograde cholangiopancreatography pancreatitis, medications and pancreatic duct injury[2]. Since March 2020, when the WHO declared the novel coronavirus disease 2019 (COVID-19) outbreak a global pandemic[3], many studies investigated its effect on different organ systems and tissues, showing that 15% of patients with acute COVID-19 infection develop digestive symptoms[4]. COVID-19-associated pancreatic injury has been suggested, but its correlation with pancreatic disease remains unclear. It is hypothesized that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus affects pancreatic tissue *via* angiotensin-converting enzyme 2 receptors, which are heavily expressed in pancreatic cells and indirectly by locoregional inflammation as a part of systemic inflammation[5]. A recent United States study on a total of 1659040 hospitalized COVID-19 patients showed that the incidence of pancreatitis is 0.6% and that is followed by worse in-hospital outcomes, including increased episodes of septic shock, acute kidney injury and requirement for hemodialysis compared to patients without pancreatitis, but without increased mortality[6]. In the COVID-19 setting, transplanted patients carry an additional disease burden due to immunosuppression; however, the data on the transplant population on acute COVID-19 and pancreatitis is lacking. Therefore, this study aims to identify the occurrence of acute pancreatitis, its clinical presentation and outcomes in a cohort of kidney transplant recipients with acute COVID-19.

MATERIALS AND METHODS

Study design

A retrospective observational single-centre cohort study recruited study participants from the largest kidney transplant centre in Croatia to record cases of acute pancreatitis during acute COVID-19 infection. Data were retrospectively obtained from hospital charts and records. The study included all adult renal transplant recipients with a functioning kidney allograft between March 2020 and August 2022.

SARS-CoV-2 infection

SARS-CoV-2 infection was proven by a positive SARS-CoV-2 real-time reverse transcriptase-polymerase chain reaction (RT-PCR) on the nasopharyngeal swab. No data on SARS-CoV-2 genotyping were available.

Acute pancreatitis

The diagnosis of acute pancreatitis was based on the fulfilment of two of three criteria: (1) Upper abdominal pain; (2) serum amylase and/or lipase of at least three times the upper limit of normal; and/or (3) findings consistent with acute pancreatitis on imaging studies (abdominal ultrasound, computed tomography or magnetic resonance imaging)[1]. The study was approved by the University Hospital Center Zagreb Ethics committee.

RESULTS

In the study period, 408 out of 1432 (28.49%) patients who received a renal allograft at our institution developed COVID-19 disease, proved by the positive SARS-CoV-2 RT-PCR on the nasopharyngeal swab. Twenty-five patients died in the period during or after the infection and 62 patients had not been assessed in our clinic and were therefore excluded from the study population, which finally included 321 patients (57% males) (Table 1). One hundred and fifty patients (46.7%) received at least one dose of the anti-SARS-CoV-2 vaccine before the infection. Regarding the severity of SARS-COV-2 infection, 21 (6.6%) patient was completely asymptomatic, while 125 (39.1%) patients required hospitalization, 141 (44.1%) developed pneumonia and 4 patients (1.3%) required mechanical ventilation. The most common presenting symptom was febrility (76.6%), followed by respiratory symptoms (71.9%) and diarrhoea (12.2%).

Treatment included immunosuppression modification in 233 patients (77.1%) and remdesivir in 53 patients (16.6%), besides the other supportive measures. Additionally, thirteen patients (4.4%) received intravenous immunoglobulins, eight (2.5%) received convalescent plasma and 30 patients (9.4%) received hyperimmune anti- cytomegalovirus (CMV) globulin (in exchange for convalescent plasma) as a passive immune augmentation. Three patients (0.9%) were treated with tocilizumab. In the study cohort only one patient (0.3%) developed acute pancreatitis during acute COVID-19.

COVID-19 and acute pancreatitis-a case description

A 68-year-old female with a kidney allograft from a deceased donor 127 months ago due to end-stage renal disease caused by rapidly progressive glomerulonephritis presented with a three-week history of productive cough, inapatency, abdominal pain, vomiting and diarrhoea. Her immunosuppressive regimen included cyclosporine, mycophenolate mofetil and steroids. The posttransplant course was complicated with new-onset diabetes after transplantation and an episode of *E. coli* sepsis. At admission, her abdomen was tender and painful on palpation. SARS-CoV-2 polymerase chain reaction was tested positive by RT-PCR on the nasopharyngeal swab and laboratory investigations revealed elevated serum amylase (187 IU/L, reference range 23-91 IU/L) and lipase (179 IU/L, reference range 13-60 IU/L). Her temperature was 37.5 ℃, O_2 saturation was 98%, and her blood pressure was 158/82 mmHg. Chest X-rays revealed bilateral COVID-19 pneumonia. Over the following days, serum amylase increased to 1203 IU/L and lipase to 1489 IU/L with C-reactive protein within the normal range. Computerized tomography did not show any changes in the pancreatic or peripancreatic tissue.

Treatment included hydration, broad-spectrum antibiotics, proton pump inhibitors and low molecular weight heparin with temporary cessation of mycophenolate. She recovered entirely without complications with a stable allograft function.

DISCUSSION

Our retrospective analysis shows that acute pancreatitis in a COVID-19 setting is a rare (0.3%) complication in kidney transplant recipients. Data on the transplant population are scarce and are based only on a few case reports from which no data about the incidence and characteristics of this specific group of patients can be extracted[7].

Also, in a non-COVID-19 setting, acute pancreatitis is rare after kidney transplantation and is mainly associated with the use of steroids and other immunosuppressive drugs[8] without traditional risk factors like gallstones and alcohol consumption. Furthermore, as renal transplant recipients are immunocompromised, they are more vulnerable to viral infections such as CMV, Epstein-Barr virus and varicella zoster, which can cause viral pancreatitis[9].

During acute SARS-CoV-2 infection, acute pancreatitis was diagnosed in only one kidney transplant recipient from our cohort. Current guidelines recommend monitoring the presence of systemic inflammatory response syndrome or organ failure at admission for a minimum of 48 h to predict the development of a severe course of the disease[1]. Her symptoms were present at the hospital admission; however the three-week history disables precise determination of the timing between the SARS-CoV-2 infection and the development of acute pancreatitis.

In the non-transplant population, the literature demonstrates cases of acute pancreatitis at COVID-19's initial presentation and those that developed during hospitalization[10,11]. In the study of Wang *et al*[12], 17% of the patients with severe COVID infection had elevated levels of serum amylase and lipase, indicating pancreatic injury. Elevated levels of pancreatic enzymes in intensive care unit COVID-19 patients were reported in several studies[13,14], however, there were no reporting details on the clinical data or radiological imaging for evaluating pancreatitis severity and treatment. The prevalence of acute pancreatitis among critically ill patients presenting with COVID-19 is significantly higher (7.9%)

Table 1 Coronavirus disease 2019 kidney transplant recipients characteristics (*n* = 321)

Characteristics	Number (%) of patients	Range
Sex		
Male/female	183/138 (57/43)	
Age (yr) [Median (IQR)]	55 (44-64)	22-81
Primary kidney disease		
Glomerulonephritis	9 + 8 (30.6)	
Diabetic nephropathy	12 (3.8)	
ADPKD	48 (15)	
Pyelonephritis	26 (8.1)	
Nephroangiosclerosis	26 (8.1)	
Other	110 (34.4)	
Time from transplantation (months) [Median (IQR)]	94.5 (52-135.8)	1-368
Height (cm) [Median (IQR)]	171 (163-180)	124-199
Body weight (kg) [Median (IQR)]	79 (67-92)	42-150
BMI [Median (IQR)]	26.5 (23.9-29.2)	17.36-45.79
Nutritional status		
Underweight (BMI < 18.5)	4 (1.3)	
Normal weight	105 (32.8)	
Pre-obesity (25-29.9)	144 (45)	
Obese (≥ 30)	67 (20.9)	
Previous thrombosis	30 (9.4)	
Previous myocardial infarction or stroke	32 (10)	
Previous CMV infection	36 (11.3)	
Previous BK infection	68 (21.3)	
Previous EBV infection	28 (8.8)	
Allograft rejection	46 (14.4)	
Creatinine value [Median (IQR)]	129 (98-165.8)	45-430
CKD EPI [Median (IQR)]	49 (35-64)	0.23-133
Biuret [Median (IQR)]	0.2 (0.1-0.5)	0-79
Vaccinated against COVID-19	246 (76.9)	
Before COVID-19 infection	149 (46.6)	
After COVID-19 infection	97 (30.3)	
Number of vaccine doses [Median (IQR)]	2 (2-3)	1-4
Number of vaccine doses (*n* = 246)		
One	21 (8.5)	
Two	138 (56.1)	
Three	83 (33.7)	
Four	4 (1.6)	
COVID-19 initial symptoms		
Febrility	245 (76.6)	
Diarrhea	39 (12.2)	
Respiratory	230 (71.9)	

Asymptomatic	21 (6.6)	
COVID-19 initial complications		
Hospitalisation	125 (39.1)	
Pneumonia	141 (44.1)	
Mechanical ventilation	4 (1.3)	
Other	66 (20.6)	
Initial immunosuppression		
Tacrolimus	222 (69.4)	
Cyclosporin A	70 (21.9)	
Mycophenolate	280 (87.5)	
Azathioprine	12 (3.8)	
Everolimus	48 (15)	
Prednisolone (dose) [Median (IQR)]	5 (5-5)	0-30
Acute COVID-19 treatment		
Cessation of MMF/Aza	133 (41.6)	
Decreasing MMF/Aza	102 (31.9)	
Cessation of Tac/CyA	1 (0.3)	
Decreasing Tac/CyA	29 (9.1)	
Hyperimmune anti-CMV globulin	30 (9.4)	
Intravenous immunoglobulin	13 (4.4)	

COVID-19: Coronavirus disease 2019; ADPKD: Autosomal dominant polycystic kidney disease; CMV: Cytomegalovirus; EBV: Epstein-Barr virus; BKV: BK virus; MMF: Mycophenolate mofetil; Aza: Azathioprine; CyA: Cyclosporine; Tac: Tacrolimus; BMI: Body mass index.

compared to 1.4% in patients without COVID-19 but with no significant differences in outcomes, including the need for mechanical ventilation, hospital stay and a 50-d follow-up survival rate[15].

A growing body of evidence reveals the relationship between SARS-CoV-2 infection and acute pancreatitis[12,16]. The virus has been isolated from the pancreatic pseudocyst of a patient with acute pancreatitis[17]. The receptor theory suggests that expression of the angiotensin-converting enzyme-2 receptor and transmembrane serine protease 2, which are receptors for the SARS-CoV-2 are more pronounced within the gastrointestinal tract comparable to the respiratory mucosa, thus enabling the transfer of the virus into the tissue with consequent pancreatic tissue damage[18]. This increased pancreatic SARS-CoV-2 affinity may lead to the elevation of pancreatic enzymes without manifesting as acute pancreatitis. Therefore, it is important to interpret data in the clinical context to prevent overdiagnosis/misdiagnosis and patient harm[19].

Besides potential direct and indirect viral effects, antiviral drugs may induce pancreatic lesions. For example, remdesivir, used in COVID-19 treatment, may increase serum triglycerides, thus increasing the risk for acute pancreatitis[20].

Our immunocompromised patient had two out of three criteria for acute pancreatitis. Typical clinical presentation and laboratory findings without radiological changes indicate serous pancreatitis that may be viral aetiology.

Similar to our experience, Kumar *et al*[21] report that patients with acute pancreatitis on admission had a better clinical outcome when compared to patients who developed acute pancreatitis during hospitalization for acute COVID-19.

Our study has several limitations, mainly due to the retrospective nature of this study. We are missing data for 25 transplant recipients who died in the period during or after the infection outside the hospital and 62 transplant recipients who had not been assessed in our clinic and were therefore excluded from the study population, leading to possible underdiagnosis of pancreatitis. Considering that we described only one case with acute pancreatitis and COVID-19, we cannot analyse the specific characteristics of this group of patients. Furthermore, we did not measure amylase and lipase in our patient's cohort to see whether they had increased values compared to the non-COVID population.

CONCLUSION

The incidence of acute pancreatitis in the COVID-19 setting in the transplant population is low. However, the mechanism of injury to the pancreas and its correlation with the severity of the COVID-19 infection in kidney transplant recipients warrants further research.

ARTICLE HIGHLIGHTS

Research background

Acute pancreatitis, an infrequent extrapulmonary manifestation of coronavirus disease 2019 (COVID-19), raises uncertainties about its association with the viral infection. Existing literature presents conflicting evidence, with some studies indicating elevated mortality in COVID-19 patients with acute pancreatitis while others report no significant impact.

Research motivation

No prior literature explores the occurrence of acute pancreatitis in the kidney transplant population in the context of COVID-19.

Research objectives

To describe the occurrence, clinical presentation and outcomes of acute pancreatitis in a cohort of kidney transplant recipients with acute COVID-19.

Research methods

A retrospective observational single-center cohort study conducted at a single transplant center in Croatia, encompassing all adult renal transplant recipients with a functioning kidney allograft between March 2020 and August 2022. Data, including cases of acute pancreatitis during acute COVID-19, were retrieved from electronic medical records.

Research results

Out of 1432 renal allograft recipients, 28.49% developed COVID-19. Hospitalization was necessary for 39.1% of patients, with 44.1% developing pneumonia and 1.3% requiring mechanical ventilation. Treatment involved immunosuppression modification in 77.1% and remdesivir in 16.6%, alongside other supportive measures. Acute pancreatitis occurred in one transplant recipient (0.3%). The patient recovered without complications, maintaining stable kidney allograft function.

Research conclusions

Although uncommon, acute pancreatitis may complicate the course of acute COVID-19 in kidney transplant recipients.

Research perspectives

Further research is warranted to explore the mechanism of pancreatic injury and its correlation with the severity of COVID-19 infection in kidney transplant recipients.

FOOTNOTES

Author contributions: Basic-Jukic N was involved in conceptualization of the study; Juric I, Katalinic L, Furic-Cunko V were responsible for data curation; Juric I and Katalinic L drafted the original version of the manuscript; Basic-Jukic N, Furic-Cunko V, Mrzljak A and Sesa V reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Ethic Committee of University Hospital Centre Zagreb (Approval No. 8.1-21/252-2).

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at: nina_basic@net.hr. Participants gave informed consent for data sharing.

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S-Editor: Qu XL
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Working Group IAP/APA Acute Pancreatitis Guidelines**. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013; **13**: e1-15 [PMID: 24054878 DOI: 10.1016/j.pan.2013.07.063]

2 **Lankisch PG**, Breuer N, Bruns A, Weber-Dany B, Lowenfels AB, Maisonneuve P. Natural history of acute pancreatitis: a long-term population-based study. *Am J Gastroenterol* 2009; **104**: 2797-805; quiz 2806 [PMID: 19603011 DOI: 10.1038/ajg.2009.405]

3 **Cucinotta D**, Vanelli M. WHO Declares COVID-19 a Pandemic. *Acta Biomed* 2020; **91**: 157-160 [PMID: 32191675 DOI: 10.23750/abm.v91i1.9397]

4 **Mao R**, Qiu Y, He JS, Tan JY, Li XH, Liang J, Shen J, Zhu LR, Chen Y, Iacucci M, Ng SC, Ghosh S, Chen MH. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020; **5**: 667-678 [PMID: 32405603 DOI: 10.1016/S2468-1253(20)30126-6]

5 **Qi F**, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. *Biochem Biophys Res Commun* 2020; **526**: 135-140 [PMID: 32199615 DOI: 10.1016/j.bbrc.2020.03.044]

6 **Butt MA**, Gangu K, Ghosh N, Awan RU, Chourasia P, Bobba A, Sheikh AB, Shekhar R. COVID-19 and acute pancreatitis clinical outcomes among hospitalized patients in the United States: A propensity matched analysis of national inpatient sample. *Pancreatology* 2023; **23**: 935-941 [PMID: 37925334 DOI: 10.1016/j.pan.2023.10.013]

7 **Tadkal P**, Siddini V, Augustine R, Babu K, Sundar S. COVID 19 induced acute pancreatitis in patients with renal impairment: report of five cases. *Clin J Gastroenterol* 2022; **15**: 826-833 [PMID: 35471693 DOI: 10.1007/s12328-022-01633-5]

8 **Ratkovic M**, Basic-Jukic N, Radunovic D. Possible Sirolimus-Induced Acute Pancreatitis in a Renal Transplant Recipient. *Ther Apher Dial* 2016; **20**: 208-209 [PMID: 26752587 DOI: 10.1111/1744-9987.12371]

9 **Graham D**, Ito T, Busuttil R, Kaldas F. Pancreatitis in solid organ transplant patients: a review of the literature. *OBM Hepatol Gastroenterol* 2019; **3**: 1 [DOI: 10.21926/obm.hg.1903029]

10 **Hadi A**, Werge M, Kristiansen KT, Pedersen UG, Karstensen JG, Novovic S, Gluud LL. Coronavirus Disease-19 (COVID-19) associated with severe acute pancreatitis: Case report on three family members. *Pancreatology* 2020; **20**: 665-667 [PMID: 32387082 DOI: 10.1016/j.pan.2020.04.021]

11 **Anand ER**, Major C, Pickering O, Nelson M. Acute pancreatitis in a COVID-19 patient. *Br J Surg* 2020; **107**: e182 [PMID: 32339257 DOI: 10.1002/bjs.11657]

12 **Wang F**, Wang H, Fan J, Zhang Y, Zhao Q. Pancreatic Injury Patterns in Patients With Coronavirus Disease 19 Pneumonia. *Gastroenterology* 2020; **159**: 367-370 [PMID: 32247022 DOI: 10.1053/j.gastro.2020.03.055]

13 **Ding P**, Song B, Liu X, Fang X, Cai H, Zhang D, Zheng X. Elevated Pancreatic Enzymes in ICU Patients With COVID-19 in Wuhan, China: A Retrospective Study. *Front Med (Lausanne)* 2021; **8**: 663646 [PMID: 34485322 DOI: 10.3389/fmed.2021.663646]

14 **Martinot M**, Eyriey M, Gravier S, Bonijoly T, Kayser D, Ion C, Mohseni-Zadeh M, Camara S, Dubois J, Haerrel E, Drouaine J, Kaiser J, Ongagna JC, Schieber-Pachart A, Kempf C; Centre Alsace COVID-19 Study Group. Predictors of mortality, ICU hospitalization, and extrapulmonary complications in COVID-19 patients. *Infect Dis Now* 2021; **51**: 518-525 [PMID: 34242842 DOI: 10.1016/j.idnow.2021.07.002]

15 **Kang D**, Park SH, Oh C, Kim YJ, Kim JB, Lee MS, Park JK. Prevalence and prognosis of acute pancreatitis in critically ill patients with COVID-19. *Hepatobiliary Pancreat Dis Int* 2023; **22**: 399-402 [PMID: 36973110 DOI: 10.1016/j.hbpd.2023.03.004]

16 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

17 **Schepis T**, Larghi A, Papa A, Miele L, Panzuto F, De Biase L, Annibale B, Cattani P, Rapaccini GL. SARS-CoV2 RNA detection in a pancreatic pseudocyst sample. *Pancreatology* 2020; **20**: 1011-1012 [PMID: 32498972 DOI: 10.1016/j.pan.2020.05.016]

18 **Scialo F**, Daniele A, Amato F, Pastore L, Matera MG, Cazzola M, Castaldo G, Bianco A. ACE2: The Major Cell Entry Receptor for SARS-CoV-2. *Lung* 2020; **198**: 867-877 [PMID: 33170317 DOI: 10.1007/s00408-020-00408-4]

19 **Troncone E**, Salvatori S, Sena G, De Cristofaro E, Alfieri N, Marafini I, Paganelli C, Argirò R, Giannarelli D, Monteleone G, Del Vecchio Blanco G. Low Frequency of Acute Pancreatitis in Hospitalized COVID-19 Patients. *Pancreas* 2021; **50**: 393-398 [PMID: 33835971 DOI: 10.1097/MPA.0000000000001770]

20 **Miyazaki K**, Yoshimura Y, Miyata N, Sasaki H, Shiba A, Aga M, Hamakawa Y, Taniguchi Y, Misumi Y, Agemi Y, Shimokawa T, Okamoto H, Tachikawa N. Acute pancreatitis or severe increase in pancreatic enzyme levels following remdesivir administration in COVID-19 patients: an observational study. *Sci Rep* 2022; **12**: 5323 [PMID: 35351942 DOI: 10.1038/s41598-022-09170-4]

21 **Kumar V**, Barkoudah E, Souza DAT, Jin DX, McNabb-Baltar J. Clinical course and outcome among patients with acute pancreatitis and COVID-19. *Eur J Gastroenterol Hepatol* 2021; **33**: 695-700 [PMID: 33787541 DOI: 10.1097/MEG.0000000000002160]

World Journal of Clinical Cases

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World J Clin Cases 2024 February 26; 12(6): 1111-1119

DOI: 10.12998/wjcc.v12.i6.1111

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Observational Study

Clinical analysis of 12 cases of ovarian neuroendocrine carcinoma

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Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Moyana T, Canada

Received: November 27, 2023
Peer-review started: November 27, 2023
First decision: December 19, 2023
Revised: December 28, 2023
Accepted: January 22, 2024
Article in press: January 22, 2024
Published online: February 26, 2024

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Abstract

BACKGROUND

Neuroendocrine neoplasms of the female genital tract are rare.

AIM

To enhance our clinical understanding of neuroendocrine carcinoma (NEC) of the ovary.

METHODS

A retrospective review was conducted on 12 patients diagnosed with NEC of the ovary, analyzing clinicopathological characteristics, treatment modalities, and survival status.

RESULTS

The median age at diagnosis was 34.5 years (range: 20 to 62 years). Among the 12 cases, 9 were small cell carcinoma of the ovary and 3 were large cell NEC. Five cases were stage I tumors, one case was stage IV, and six cases were stage III. Eleven patients underwent surgery as part of their treatment. All patients received adjuvant chemotherapy. Among the 12 patients, one patient received radiotherapy, and one patient with a BRCA2 mutation was administered PARP inhibitor maintenance after chemotherapy. The median progression-free survival was 13 months, and the median overall survival was 19.5 months. Four cases remained disease-free, while eight cases experienced tumor recurrence, including three cases that resulted in death due to disease recurrence.

CONCLUSION

NEC of the ovary is a rare condition that is more common in women of child-bearing age and is associated with aggressive behavior and poor clinical outcomes. Surgical resection remains the mainstay of treatment, with some patients benefiting from adjuvant chemoradiation therapy.

Key Words: Neuroendocrine carcinoma; Ovary; Pathology; Treatment

Core Tip: Through the analysis and summary of 12 cases of ovarian neuroendocrine carcinoma, we found that the incidence of ovarian neuroendocrine carcinoma is low and the prognosis is poor. Surgery is the cornerstone of treatment, and some patients may benefit from comprehensive treatment.

Citation: Xing XY, Zhang W, Liu LY, Han LP. Clinical analysis of 12 cases of ovarian neuroendocrine carcinoma. *World J Clin Cases* 2024; 12(6): 1111-1119
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1111.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1111

INTRODUCTION

Neuroendocrine neoplasms (NENs) of the female genital tract are rare, accounting for only 1%-2% of gynecological malignancies[1]. Among these, primary ovarian NENs are even rarer, as most gynecological NENs are located in the uterine cervix. NENs are a heterogeneous group of diseases. Neuroendocrine carcinoma (NEC) of the ovary represents the highly malignant end of this spectrum, characterized by high-grade tumors that often exhibit aggressive clinical behavior and unfavorable outcomes[2]. NEC of the ovary can be further classified into two subtypes: Large cell neuroendocrine carcinoma (LCNEC) and small cell carcinoma of the ovary (SCCO). Diagnosis of NEC primarily relies on histology, which includes immunohistochemistry. Common markers used for diagnosis include chromogranin A (Cg-A), synaptophysin (Syn), neuron- specific enolase, and CD56. The histologic origin of NEC is believed to be either from the ovarian surface epithelium or associated with the dedifferentiation of a de novo carcinoma, as they have often been associated with epithelial neoplasms[3,4]. Currently, there are no established treatment guidelines for NEC of the ovaries due to limited knowledge about this rare entity. Most patients are treated based on guidelines for ovarian epithelial malignancies, which typically involve debulking surgery followed by adjuvant chemotherapy (carboplatin and paclitaxel). The lack of clinical data and evidence-based protocols may contribute to unsatisfactory outcomes in relation to this condition.

In this study, we presented a series of 12 cases of NEC of the ovary, which is one of the largest series reported from a single institution. We analyzed the clinical, pathological, radiological, and survival data of these cases to provide a reference for future therapeutic approaches.

MATERIALS AND METHODS

Materials

A database search was conducted to identify patients with primary ovarian NEC who were treated in the Department of Gynecology at the First Affiliated Hospital of Zhengzhou University from August 2015 to May 2020. A total of 12 cases were identified with a confirmed diagnosis of NEC through postoperative pathology and the pathological interpretation was conducted by a pathologist specialized in gynecologic malignancies and verified by a second gynecological pathologist. Patients with incomplete clinical data and/or who were lost to follow-up were excluded from the study.

Methods

Clinical data were obtained through a retrospective chart review, which included information such as age, chief symptoms, auxiliary examination results, FIGO stage, pathology, and treatment. The follow-up period was defined as the time between the initial diagnosis of NEC of the ovary and the last date of contact or death, and the follow-up included routine gynecological examination, computed tomography (CT)/ positron emission tomography contrast-enhanced and blood tumor marker detection [antigen (CA)-125, HE4 and CA-199]. The performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) score standard. Tumors were staged according to the 2014 FIGO staging classification for ovarian carcinomas. The follow-up period concluded on May 31, 2023. The collection and analysis of data were approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (2023-KY-0892-002).

RESULTS

Clinical characteristics

From August 2015 to May 2020, we searched 2048 records of patients with ovarian cancer, and the incidence of NEC of the ovary among all ovarian malignancies in this series was 0.59% (12/2048). The median age at diagnosis was 34.5 years

(ranging from 20 to 62 years). None of the patients had a family history of ovarian cancers. The initial presentations included abdominal pain (5/12), pelvic mass (4/12), vaginal bleeding (2/12), and abdominal distention (1/12). None of the patients in the study group presented with paraneoplastic syndrome. Eleven out of twelve cases showed an increase in preoperative cancer CA-125 levels, with a median level of 146.6 U/mL (range: 38.63 to 401.2 U/mL; normal range: 35 U/mL). However, after treatment, all elevated tumor markers returned to normal levels. None of the patients showed an increase in CA-199 or HE4 levels. Based on the FIGO 2014 staging standard, 5 cases were classified as stage IA, 1 case as stage IVB, and 6 cases as stage IIIC disease. The clinical features can be found in Table 1.

Radiological characteristics

Abdominal ultrasound (US) was performed on all 12 patients, and CT was performed on 10 patients. Abdominal ultrasound showed that the masses were typically solid or cystic-solid with abundant blood supply within the lesion, occupying the pelvic cavity. The borders of the masses were clearly defined with irregular contours (Figure 1). The CT scan typically revealed a soft tissue mass with varying density in the pelvic cavity. Contrast-enhanced CT demonstrated slight enhancement or uneven enhancement of the solid components (Figure 2).

Pathologic evaluation and classification

Excluding metastatic ovarian cancer, a total of 12 patients with ovarian NEC were identified. Out of the 12 primary ovarian NEC patients, 9 had SCCO and 3 had LCNEC. Three cases of LCNEC were pure large cell carcinoma. The median greatest dimension of the ovarian tumor was 10.4 cm, ranging from 4 to 20 cm. The tumor was unilateral in 5 cases and bilateral in 7 cases (Figure 3). The neoplastic cells were positive for CD56 in all cases (Figure 3C), Cg-A in 5 out of 10 cases (Figure 3D), and Syn in 9 out of 11 cases (Figure 3E). Additionally, cytokeratin (CK) was positive in 5 out of 6 cases (Figure 3F), with CK7 being positive in 4 out of 6 cases, epithelial memberane antigen being positive in 6 out of 7 cases, and PAX-8 being positive in 4 out of 8 cases.

Therapies

Surgery was performed by gynecological oncologists with the primary goals of achieving a complete tumor resection and adequate staging, following the FIGO guidelines. Primary surgery was conducted in 10 patients, with one patient having received neoadjuvant chemotherapy (TCx3), and one patient (case 12) declining surgery due to extensive metastasis. Out of the 11 patients, 8 underwent bilateral salpingo-oophorectomy (BSO) and hysterectomy. Fertility was preserved in two patients (case 3 and 5), while one patient (case 7) only underwent omentectomy and peritoneal biopsy as their family refused debulking surgery. Systemic pelvic and paraaortic lymphadenectomy was performed in all 9 patients. To achieve optimal tumor debulking, omentectomy was performed in all nine patients, with additional extra-ovarian debulking in five patients. After surgery, 10 out of 11 patients showed no visible tumors. Prior to chemotherapy, all patients were evaluated for their performance status using the ECOG 0-1 scale. The chemotherapy regimens used are listed in Table 2. The time interval between surgery and the start of chemotherapy ranged from 2 to 4 wk. Six patients received etoposide/cisplatin (EP), while the remaining cases were treated with paclitaxel/cisplatin (TP) or carboplatin (TC), as indicated. Among the 6 patients treated with TP or TC, patient 10, who requested genetic testing, was found to have a BRCA2 mutation. After chemotherapy, this patient received PARP inhibitor maintenance. However, the tumor recurred 2 months post-chemotherapy. On the other hand, patient 11 received radiotherapy after chemotherapy and remained disease-free during the 49-month follow-up period.

Survival

The follow-up time for the 12 cases ranged from 9 to 49 months, with a median of 19.5 months. Out of the patients, 3 expired due to tumor recurrence, while 9 patients were still alive during the follow-up period. Among the patients, 8 experienced recurrence and/or disease progression, with recurrences observed in the liver, bones, pelvis, and inguinal lymph nodes. Due to the limited number of cases, we were unable to determine the impact of FIGO stage, tumor pathological type, and different chemotherapies on prognosis (Table 2).

DISCUSSION

Diagnosis of ovarian NEC

Patients with NEC of the ovary tend to be younger than those with other histologic subtypes of ovarian cancer. Some studies have also suggested that NEC of the ovary can occur after menopause[5]. In our study, the main symptoms observed were abdominal pain and pelvic mass. Additionally, a majority of the cases (7 out of 12) were diagnosed at an advanced stage, which aligns with findings in the existing literatures[5]. The rate of lymph node metastasis in NEC of the ovary has rarely been reported in previous studies. In our study, only one case showed lymph node metastasis, indicating a potentially low rate of lymph node metastasis for this type of tumor. This suggests that lymphatic metastasis may not be the primary route of metastasis for NEC of the ovary.

The diagnosis of NEC of the ovary often lacks specific findings on US and CT scans alone[6]. However, CT scans can provide valuable information about the location, size, and presence of distant metastasis of the lesion. Therefore, CT scans are of great significance for preoperative staging and determining surgical methods. In this study, it was observed that serum CA-125 levels increased in most cases (11 out of 12), suggesting a potential link between CA-125 and NEC of the ovary. Previous studies have confirmed that CA-125 levels are closely associated with epithelial ovarian cancers and can

Table 1 Clinical characteristics of 12 cases with neuroendocrine carcinoma of the ovary

Case	Age (yr)	Symptom	CA-125 (U/mL)	Size (cm)	Location	Diagnosis	Stage
1	28	Mass	91.4	12	Right	SCCO	IA
2	62	Pain	38.63	14	Left	LCNEC	IA
3	29	Pain	46.4	8	Right	SCCO	IA
4	37	Mass	42.13	8	Right	SCCO	IA
5	20	Pain	401.2	20	Bilateral	SCCO	IC
6	54	Bloating	170.6	5	Bilateral	LCNEC	IIIB
7	26	Pain	150.7	5	Bilateral	SCCO	IIIC
8	31	Mass	61.25	10	Left	SCCO	IIIC
9	32	Pain	146.6	10	Bilateral	SCCO	IIIC
10	46	Mass	191	13	Bilateral	LCNEC	IIIC
11	58	Bleeding	14.5	4	Bilateral	SCCO	IIIC
12	62	Bleeding	166.5	15	Bilateral	SCCO	IVB

CA-125: Antigen 125; SCCO: Small cell carcinoma of the ovary; LCNEC: Large cell neuroendocrine carcinoma.

Table 2 The follow-up time for the 12 cases

Case	Operation	Chemotherapy	Recurrence	PFS/month	Survival state	Follow-up/month
1	BSO/TAH/OM/LN	EP6	No	34	NED	34
2	BSO/TAH/OM/LN	TC6	No	37	NED	37
3	USO	EP7	Yes, brain	9	DOD	10
4	BSO/TAH/OM/LN	EP6	Yes, liver	13	AWD	13
5	BSO/OM /LN	EP6	Yes, bones	17	AWD	25
6	NACT+BSO/TAH/OM/LN	TC8	Yes, pelvic	13	AWD	15
7	OM/PB	TC3	Yes, pelvic	3	DOD	10
8	BSO/TAH/OM/LN	EP6	No	15	NED	26
9	BSO/TAH/OM/LN	TP6	Yes, lymph	6	AWD	17
10	BSO/TAH/OM/LN	TP6 +PARPi	Yes, liver	9	AWD	22
11	BSO/TAH/OM/LN	TC6+ Radiotherapy	No	49	NED	49
12	-	EP6	Yes, pelvic	6	DOD	9

EP: Etoposide/Cisplatin; TC: Paclitaxel/Carboplatin; TP: Paclitaxel/Cisplatin; DOD: Dead of disease; AWD: Alive with disease; NED: No evidence of disease; Om: Omentectomy; USO: Unilateral salpingo-oophorectomy; BSO: Bilateral salpingo-oophorectomy; LN: Lymph node dissection; PB: Peritoneal biopsy; NACT: Neoadjuvant chemotherapy.

be utilized for monitoring and diagnosing such cancers[7]. The elevation of serum CA-125 in ovarian NEC has been reported in the literature[8]. In our study, CA-125 levels increased in 11 out of 12 cases, with an average of 126.7 U/mL. However, the CA-125 level in ovarian NEC was found to be lower than that in ovarian epithelial carcinoma[9]. Therefore, further studies are needed to analyze the relationship between CA-125 and NEC of the ovary. Ascitic fluid cytology was also performed, and only two cases showed the presence of malignant cells in ascites or peritoneal lavage fluid. This demonstrates that identifying malignant cells derived from NEC of the ovary in ascitic fluid may be challenging.

Histopathological analysis of tissue specimens is crucial for diagnosing NEC of the ovary. Immunohistochemistry is necessary to confirm the diagnosis[4]. The results of immunohistochemistry revealed that tumors expressed at least one neuroendocrine marker (Cg-A, CD56, or Syn). In this study, CD56 was expressed in all cases, suggesting that it was the

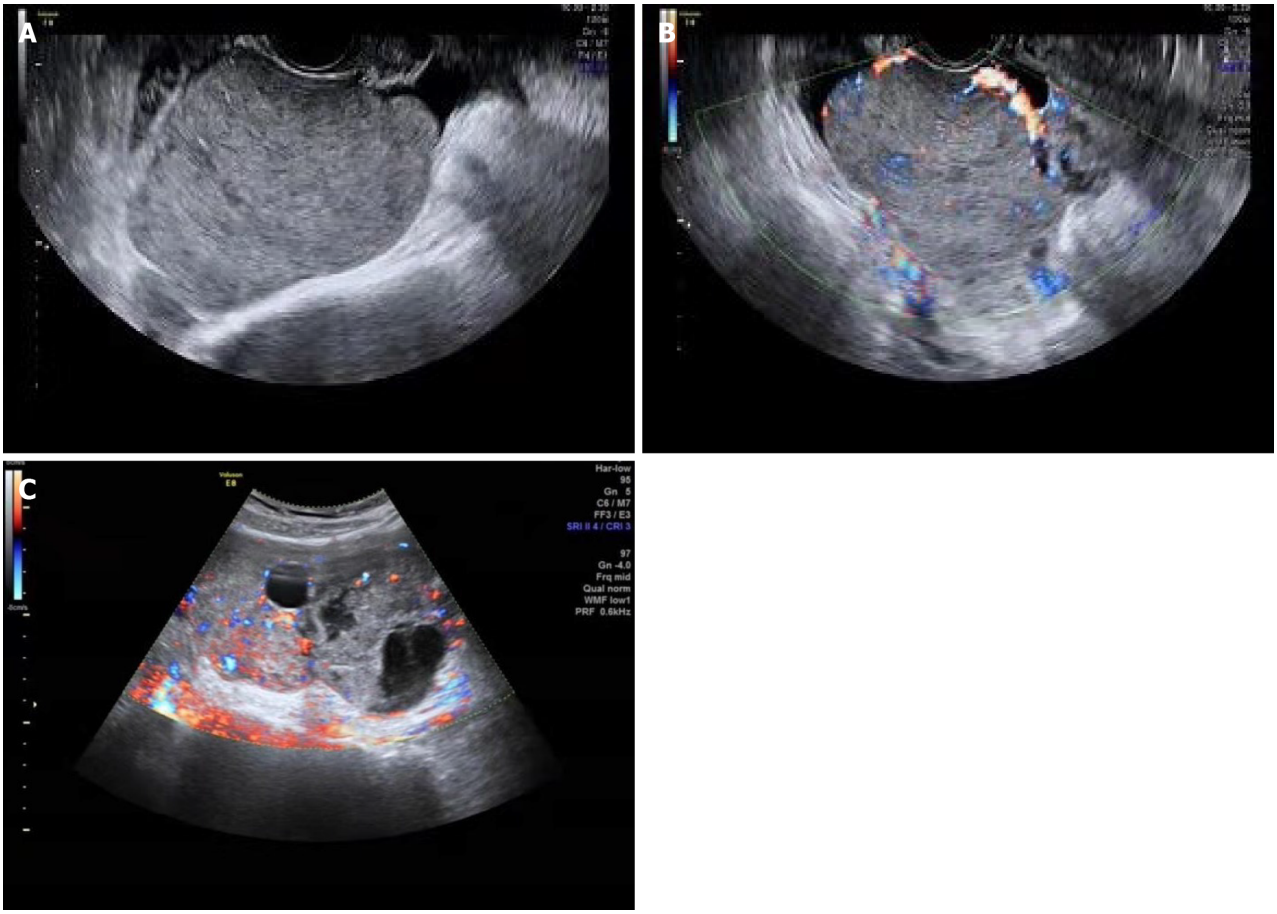

Figure 1 Ultrasound features. A: The tumor was solid with heterogeneous echo in case 4; B and C: Color Doppler flow imaging displayed rich intralesional vascularization in the solid part of the lesion.

most sensitive marker for demonstrating the neuroendocrine nature of these tumors. However, the lack of specificity of CD56 was observed as it was also expressed in nonendocrine tissues such as renal tubules, ovarian sex cord-stromal, and thyroid follicular cells. For this reason, some authors did not recommend relying solely on CD56 to demonstrate neuroendocrine components[10-12]. Therefore, immunohistochemistry plays a crucial role in the diagnosis.

Small cell carcinoma of the ovary is further classified as small cell carcinoma of the ovary-hypercalcemic type (SCCOHT) and small cell ovarian carcinoma of the pulmonary type (SCCOPT)[13]. Due to the differences in age of onset, clinical manifestations, and molecular mechanisms between SCCOPT and SCCOHT, SCCOPT is included in the chapter of neuroendocrine Neoplasms of the Female Reproductive System for the first time in the 2020 edition of World Health Organization[5]. SCCOPT should be differentiated from ovarian metastatic small cell lung cancer by combining medical history and imaging data. When small cell carcinoma is found in the lung and ovary at the same time, the lung tumor is considered to be the primary lesion. When lung small cell carcinoma metastasizes to the ovary, it mostly does not involve the surface of the ovary. The presence or absence of other ovarian epithelial tumors can also be used as a differential direction. In addition, SCCOPT should be distinguished from SCCOHT. The mean age of onset of SCCOHT is 24 years, bilateral ovaries are rarely involved, hypercalcemia occurs in two-thirds of patients, and loss of SMARCA4 protein expression is specific for the diagnosis of SCCOHT[14]. However, only one of the nine patients in our paper with SCCO underwent SMARCA4 detection and was diagnosed as SCCOHT. In the future, we will pay more attention to the detection of SMARCA4 to guide the clinicopathological classification.

Therapy of ovarian NEC

The current main treatment for NEC of the ovary is typically surgical resection followed by adjuvant chemotherapy. However, there is currently no standard guideline in place[15]. The goal of surgical resection is to remove all visible lesions. A recent study has shown that surgeries can significantly improve survival rates, therefore complete surgical resection should be recommended as the primary treatment option. Some young patients may wish to preserve their fertility. However, the use of fertility-sparing surgery is a topic of debate. There have been a few small case series reporting successful pregnancies in patients who underwent unilateral salpingo-oophorectomy (USO) and received adjuvant chemotherapy[16,17]. In another study, 26 patients underwent USO, but none of them resulted in a successful pregnancy[18]. Of these cases, two opted for fertility-sparing surgery. Unfortunately, one patient who had a BSO passed away after 10 months of treatment, and the other patient who had a USO experienced recurrence after 12 months. It is worth noting that postoperative chemotherapy can potentially impact ovarian function[19]. To safeguard the ovary from the harmful effects of chemotherapy, clinical practice has incorporated techniques such as oocyte or embryo cryopreser-

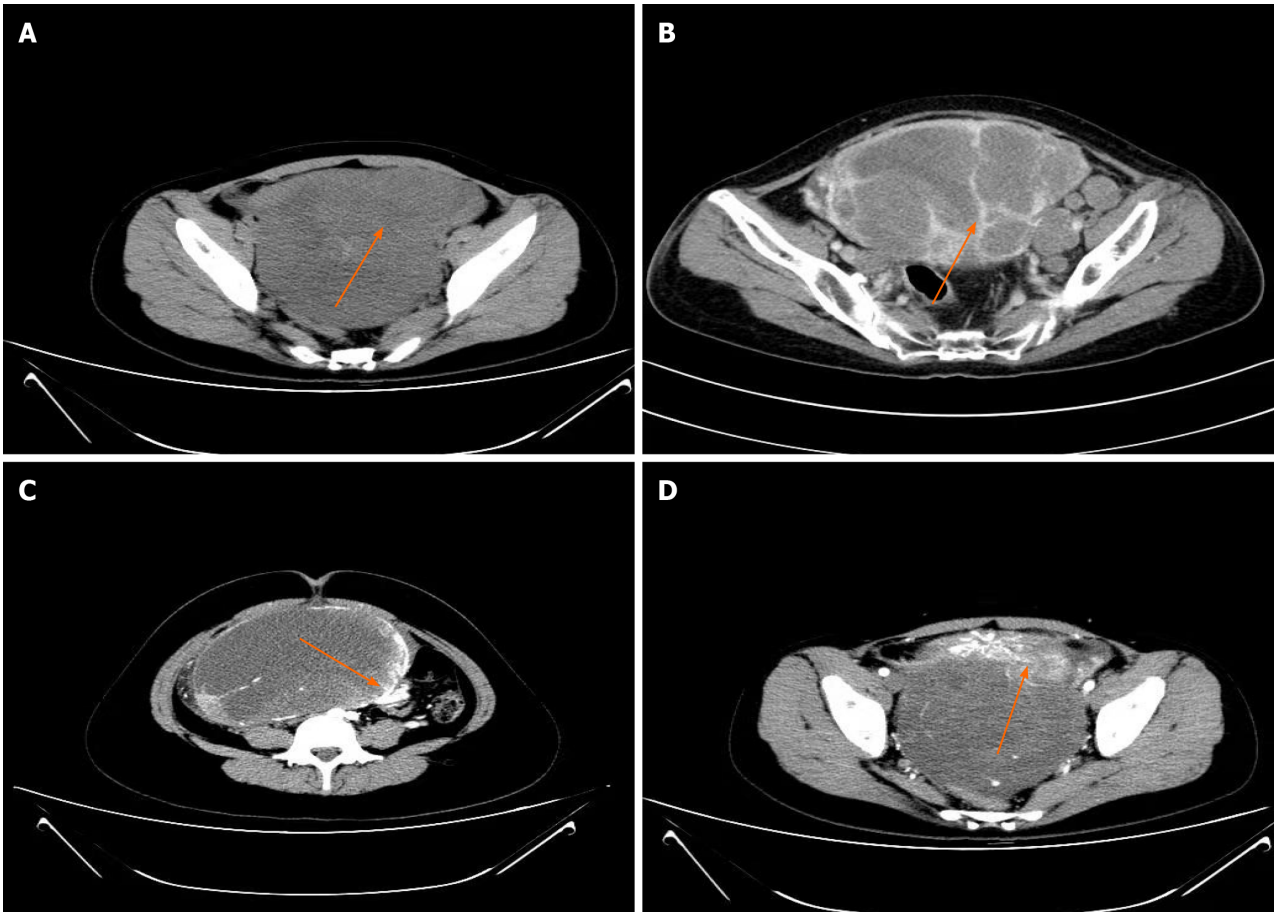

Figure 2 Computed tomography features. A: A soft tissue mass with heterogeneous density occupied the pelvic cavity in case 1; B: Computed tomography (CT) scan revealed a multiseptated mixed solid and cystic mass in case 12; C: Enhanced CT showed marginal enhancement of the tumor in case 5; D: Heterogenous enhancement of the solid part.

vation, as well as cryopreservation of the ovarian cortex. However, performing these methods may be challenging and the future use of cryopreserved germ cells is still uncertain[20]. Therefore, additional studies should be conducted to evaluate the feasibility of fertility-sparing surgery for patients with ovarian NEC.

The present study refers to adjuvant therapies for lung small cell carcinoma, specifically chemotherapy and radiation [2]. The literature suggests that EP and TP are the main chemotherapy regimens[16,21]. Although small sample studies and case reports indicate potential benefits of chemotherapy, the lack of prospective studies hinders the availability of convincing evidence regarding its effect on the prognosis of patients with ovarian NEC. In this study, 6 patients were treated with EP, and 6 patients received PT. Out of the total 8 patients, progression or recurrence was observed. Among these, 3 patients relapsed due to platinum resistance, while 2 patients showed progression during chemotherapy. These findings indicate a poor response of these tumors to the chemotherapy. Hence, further investigation is required to determine the sensitivity of patients to platinum drugs and identify the optimal chemotherapy regimen.

Radiotherapy has been infrequently utilized in the treatment of ovarian cancers[2]. In our study, only one patient received radiation therapy and was followed up for 49 months without any recurrence of the disease. The role of radiotherapy in the management of NEC of the ovary is still not well-established, although some reports have suggested potential benefits[22,23]. Therefore, further investigation is warranted to explore the potential of radiotherapy in NEC of the ovary. Currently, there is limited research on targeted therapy in NEC of the ovary. In this study, a single case with a BRCA2 germline mutation was treated with a PARP inhibitor. However, the patient experienced recurrence after 2 months, suggesting that PARP inhibitors may not be beneficial for patients with NEC of the ovary. Further recruitment of additional cases is necessary to investigate the role of PARP inhibitors in treating NEC of the ovary.

Prognosis of ovarian NEC

The 1-, 3- and 5- year survival rates of ovarian NEC were 58.3%, 33.3% and 27.6%, respectively[5]. Limited studies have been conducted on the prognosis of ovarian neuroendocrine cancer, with tumor staging being considered an important prognostic factor. The median follow-up time of this study was 19.5 months. Three patients died due to disease recurrence, four patients survived without evidence of recurrent disease, and five patients survived with tumor. Among patients with relapse or progression, four patients showed an increase in CA-125 levels. Further data are needed to confirm whether serum CA-125 levels can be used as an indicator for disease monitoring.

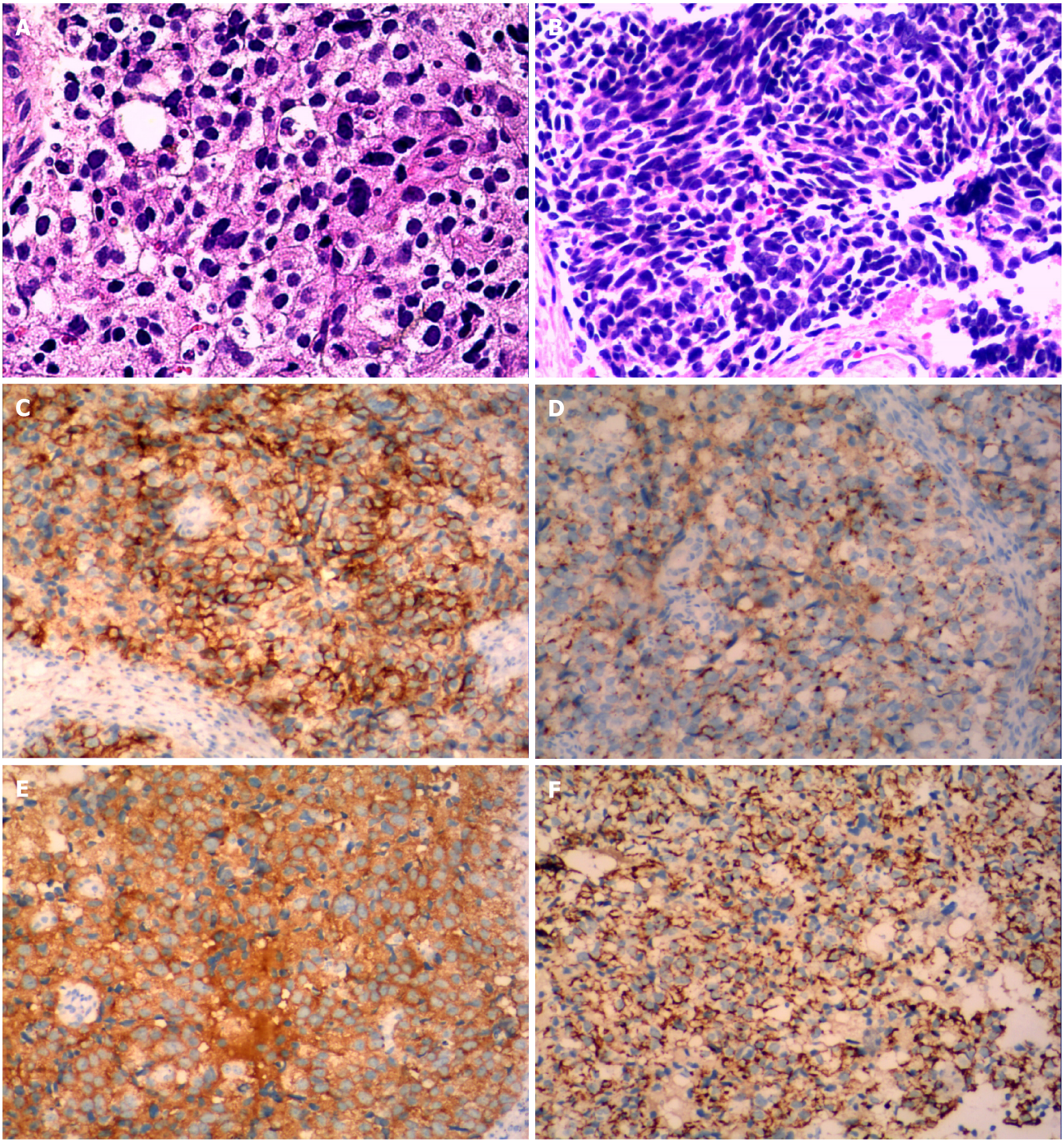

Figure 3 Histological and immunohistochemical large cell neuroendocrine carcinoma. A: Tumor cells are arranged in nests, with relatively abundant basophilic cytoplasm, large round-to-oval nuclei and frequent mitosis in case 10; B: Small cell carcinoma of the ovary: Tumor cells are arranged in an organoid pattern, and some of the cells are spindle-shaped. The nucleus is oat-like, with abundant mitotic and apoptotic activity in case 4; C-E: Neuroendocrine carcinoma positive for CD56 (C), chromogranin A (D) and synaptophysin (E); F: Positive for cytokeratin.

CONCLUSION

NEC of the ovary is a rare and aggressive malignant disease with a poor prognosis. The diagnosis primarily relies on histopathological analysis of tissue specimens, and immunohistochemistry plays a crucial role in both diagnosis and differential diagnosis. Surgical resection is the preferred treatment option, and adjuvant chemotherapy along with potential radiotherapy can potentially extend the survival of certain cases. Considering the rarity of primary ovarian NEC, a future multicenter study is necessary to gain further understanding of this uncommon disease.

ARTICLE HIGHLIGHTS

Research background

Primary ovarian neuroendocrine carcinoma (NEC) are rare and there are no established treatment guidelines for NEC of the ovaries due to limited knowledge about this rare entity.

Research motivation

Primary ovarian NEC are rare, and we want to know more about it.

Research objectives

We retrospectively analyzed the clinicopathological features, treatment and survival of 12 patients with ovarian NEC, and hope to enhance our clinical understanding of NEC of the ovary.

Research methods

The clinical data of 12 patients with ovarian NEC in our hospital were retrospectively analyzed.

Research results

Among more than 2000 patients with ovarian cancer during the same period, we identified 9 cases of small cell ovarian cancer and 3 cases of large cell NEC. Eleven patients underwent surgery, all of whom received adjuvant chemotherapy, and 1 patient with a BRCA2 mutation received PARP inhibitor maintenance therapy after chemotherapy. The median progression-free survival was 13 months, and the median overall survival was 19.5 months. Four patients were alive without tumor recurrence, 8 patients had tumor recurrence, and 3 of them died of tumor recurrence.Abdominal ultrasound showed that the masses were typically solid or cystic-solid with abundant blood supply within the lesion, occupying the pelvic cavity. The borders of the masses were clearly defined with irregular contours. The computed tomography (CT) scan typically revealed a soft tissue mass with varying density in the pelvic cavity. Contrast-enhanced CT demonstrated slight enhancement or uneven enhancement of the solid components. The neoplastic cells were positive for CD56 in all cases, chromogranin A in 5 out of 10 cases, and synaptophysin in 9 out of 11 cases. Additionally, cytokeratin (CK) was positive in 5 out of 6 cases, with CK7 being positive in 4 out of 6 cases, epithelial memberane antigen being positive in 6 out of 7 cases, and PAX-8 being positive in 4 out of 8 cases.

Research conclusions

NEC of the ovary is a rare condition that is more common in women of childbearing age and is associated with aggressive behavior and poor clinical outcomes. Surgical resection remains the mainstay of treatment, with some patients benefiting from adjuvant chemoradiation therapy.

Research perspectives

In my opinion, the future research direction may be pathogenesis and immunotherapy.

FOOTNOTES

Author contributions: Xing XY and Zhang W designed this study and wrote the manuscript; Liu LY participated in collection and analysis of data; Han LP reviewed and revised the manuscript; All authors read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by The First Affiliated Hospital of Zhengzhou University Institutional Review Board (Approval No. 2023-KY-0892-002).

Informed consent statement: Consent was not needed as the study was retrospective without exposure to the patients' data.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Zheng XM

REFERENCES

1 **Rouzbahman M**, Clarke B. Neuroendocrine tumors of the gynecologic tract: select topics. *Semin Diagn Pathol* 2013; **30**: 224-233 [PMID: 24144291 DOI: 10.1053/j.semdp.2013.06.007]
2 **Huang W**, Bao Y, Luo X, Yao L, Yuan L. Neuroendocrine neoplasms of the ovary: an analysis of clinicopathological characteristics and prognosis with a focus on histological grading. *Endocrine* 2022; **77**: 188-198 [PMID: 35538309 DOI: 10.1007/s12020-022-03067-y]
3 **Virarkar M**, Vulasala SS, Morani AC, Waters R, Gopireddy DR, Kumar S, Bhosale P, Lall C. Neuroendocrine Neoplasms of the Gynecologic Tract. *Cancers (Basel)* 2022; **14** [PMID: 35406607 DOI: 10.3390/cancers14071835]
4 **Howitt BE**, Kelly P, McCluggage WG. Pathology of Neuroendocrine Tumours of the Female Genital Tract. *Curr Oncol Rep* 2017; **19**: 59 [PMID: 28735441 DOI: 10.1007/s11912-017-0617-2]
5 **Zhu Y**, Meng F, Fang H, Zhang Z, Wang L, Zheng W. Clinicopathologic characteristics and survival outcomes in neuroendocrine carcinoma of the ovary. *Int J Gynecol Cancer* 2020; **30**: 207-212 [PMID: 31796530 DOI: 10.1136/ijgc-2019-000746]
6 **Choi YD**, Lee JS, Choi C, Park CS, Nam JH. Ovarian neuroendocrine carcinoma, non-small cell type, associated with serous carcinoma. *Gynecol Oncol* 2007; **104**: 747-752 [PMID: 17229461 DOI: 10.1016/j.ygyno.2006.11.008]
7 **Piatek S**, Panek G, Lewandowski Z, Bidzinski M, Piatek D, Kosinski P, Wielgos M. Rising serum CA-125 levels within the normal range is strongly associated recurrence risk and survival of ovarian cancer. *J Ovarian Res* 2020; **13**: 102 [PMID: 32878632 DOI: 10.1186/s13048-020-00681-0]
8 **Hu D**, Ma D, Zhang ZJ, Zhang Y, Huang K, Li X. Prognosis comparison between small cell carcinoma of ovary and high-grade serous ovarian cancer: A retrospective observational cohort study. *Front Endocrinol (Lausanne)* 2023; **14**: 1103429 [PMID: 36742399 DOI: 10.3389/fendo.2023.1103429]
9 **Zhang R**, Siu MKY, Ngan HYS, Chan KKL. Molecular Biomarkers for the Early Detection of Ovarian Cancer. *Int J Mol Sci* 2022; **23** [PMID: 36233339 DOI: 10.3390/ijms231912041]
10 **Gupta P**, Bagga R, Rai B, Srinivasan R. Primary pure large cell neuroendocrine carcinoma of the ovary: histopathologic and immunohistochemical analysis with review of the literature. *Int J Clin Exp Pathol* 2021; **14**: 1000-1009 [PMID: 34646419]
11 **Gupta P**, Kapatia G, Gupta N, Dey P, Rohilla M, Gupta A, Rai B, Suri V, Rajwanshi A, Srinivasan R. Small Cell Carcinoma of the Ovary: Clinicopathologic and Immunohistochemical Analysis of 7 New Cases of a Rare Malignancy. *Int J Surg Pathol* 2021; **29**: 236-245 [PMID: 32772748 DOI: 10.1177/1066896920947788]
12 **McCluggage WG**, McKenna M, McBride HA. CD56 is a sensitive and diagnostically useful immunohistochemical marker of ovarian sex cord-stromal tumors. *Int J Gynecol Pathol* 2007; **26**: 322-327 [PMID: 17581419 DOI: 10.1097/01.pgp.0000236947.59463.87]
13 **Li Y**, Wu Y, Zhang Y, Li X. Case report: Strategies for improving outcomes in patients with primary ovarian small-cell neuroendocrine carcinoma. *Front Oncol* 2022; **12**: 954289 [PMID: 36212497 DOI: 10.3389/fonc.2022.954289]
14 **Tischkowitz M**, Huang S, Banerjee S, Hague J, Hendricks WPD, Huntsman DG, Lang JD, Orlando KA, Oza AM, Pautier P, Ray-Coquard I, Trent JM, Witcher M, Witkowski L, McCluggage WG, Levine DA, Foulkes WD, Weissman BE. Small-Cell Carcinoma of the Ovary, Hypercalcemic Type-Genetics, New Treatment Targets, and Current Management Guidelines. *Clin Cancer Res* 2020; **26**: 3908-3917 [PMID: 32156746 DOI: 10.1158/1078-0432.CCR-19-3797]
15 **Pang L**, Guo Z. Primary neuroendocrine tumors of the ovary: Management and outcomes. *Cancer Med* 2021; **10**: 8558-8569 [PMID: 34773393 DOI: 10.1002/cam4.4368]
16 **Pang L**, Chen J, Chang X. Large-cell neuroendocrine carcinoma of the gynecologic tract: Prevalence, survival outcomes, and associated factors. *Front Oncol* 2022; **12**: 970985 [PMID: 36457506 DOI: 10.3389/fonc.2022.970985]
17 **Dykgraaf RH**, de Jong D, van Veen M, Ewing-Graham PC, Helmerhorst TJ, van der Burg ME. Clinical management of ovarian small-cell carcinoma of the hypercalcemic type: a proposal for conservative surgery in an advanced stage of disease. *Int J Gynecol Cancer* 2009; **19**: 348-353 [PMID: 19407558 DOI: 10.1111/IGC.0b013e3181a1a116]
18 **Callegaro-Filho D**, Gershenson DM, Nick AM, Munsell MF, Ramirez PT, Eifel PJ, Euscher ED, Marques RM, Nicolau SM, Schmeler KM. Small cell carcinoma of the ovary-hypercalcemic type (SCCOHT): A review of 47 cases. *Gynecol Oncol* 2016; **140**: 53-57 [PMID: 26546963 DOI: 10.1016/j.ygyno.2015.11.004]
19 **Cosgrove CM**, Salani R. Ovarian effects of radiation and cytotoxic chemotherapy damage. *Best Pract Res Clin Obstet Gynaecol* 2019; **55**: 37-48 [PMID: 30166215 DOI: 10.1016/j.bpobgyn.2018.07.008]
20 **Sonigo C**, Beau I, Binart N, Grynberg M. The Impact of Chemotherapy on the Ovaries: Molecular Aspects and the Prevention of Ovarian Damage. *Int J Mol Sci* 2019; **20** [PMID: 31717833 DOI: 10.3390/ijms20215342]
21 **He Y**, Zhao H, Li XM, Yin CH, Wu YM. A clinical analysis of small-cell neuroendocrine carcinoma of the gynecologic tract: report of 20 cases. *Arch Gynecol Obstet* 2019; **299**: 543-549 [PMID: 30411160 DOI: 10.1007/s00404-018-4960-9]
22 **Callegaro-Filho D**, Burke TW, Eifel PJ, Ramirez PT, Euscher EE, Schmeler KM. Radiotherapy for recurrent small cell carcinoma of the ovary: A case report and review of the literature. *Gynecol Oncol Rep* 2015; **11**: 23-25 [PMID: 26076089 DOI: 10.1016/j.gore.2014.12.003]
23 **Georgescu TA**, Bohiltea RE, Munteanu O, Furtunescu F, Lisievici AC, Grigoriu C, Gherghiceanu F, Vlădăreanu EM, Berceanu C, Ducu I, Iordache AM. Emerging Therapeutic Concepts and Latest Diagnostic Advancements Regarding Neuroendocrine Tumors of the Gynecologic Tract. *Medicina (Kaunas)* 2021; **57** [PMID: 34946283 DOI: 10.3390/medicina57121338]

World Journal of Clinical Cases

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World J Clin Cases 2024 February 26; 12(6): 1120-1129

DOI: 10.12998/wjcc.v12.i6.1120

ISSN 2307-8960 (online)

META-ANALYSIS

Efficacy and safety of remimazolam in bronchoscopic sedation: A meta-analysis

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Specialty type: Anesthesiology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Rotenberg O, United States

Received: December 12, 2023
Peer-review started: December 12, 2023
First decision: January 2, 2024
Revised: January 14, 2024
Accepted: January 27, 2024
Article in press: January 27, 2024
Published online: February 26, 2024

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Abstract

BACKGROUND

Remimazolam is a new benzodiazepine used for procedural sedation and general anesthesia. Several studies have used remimazolam for bendable bronchoscopy.

AIM

To assess the safety and efficacy of remimazolam for sedation in patients undergoing bendable bronchoscopy by performing a meta-analysis of randomized controlled trials (RCTs).

METHODS

We searched the EMBASE, PubMed, Cochrane Library, and Web of Science databases for RCTs on bendable bronchoscopic procedural sedation with remimazolam *vs* conventional sedatives (CS).

RESULTS

Five studies with 1080 cases were included. Remimazolam had the same sedation success rate compared with CS [relative risk (RR): 1.35, 95%CI: 0.60-3.05, $P = 0.474$, $I^2 = 99.6\%$]. However, remimazolam was associated with a lower incidence of hypotension (RR: 0.61; 95%CI: 0.40-0.95, $P = 0.027$; $I^2 = 65.1\%$) and a lower incidence of respiratory depression (RR: 0.50, 95%CI: 0.33-0.77, $P = 0.002$, $I^2 = 42.3\%$). A subgroup analysis showed a higher success rate of sedation with remimazolam than midazolam (RR: 2.45, 95%CI: 1.76-3.42, $P < 0.001$). Compared with propofol, the incidence of hypotension (RR: 0.45, 95%CI: 0.32-0.64, $P < 0.001$, $I^2 = 0.0\%$), respiratory depression (RR: 0.48, 95%CI: 0.30-0.76, $P = 0.002$, $I^2 = 78.4\%$), hypoxemia (RR: 0.36, 95%CI: 0.15-0.87, $P = 0.023$), and injection pain (RR: 0.04, 95%CI: 0.01-0.28, $P = 0.001$) were lower.

CONCLUSION
Remimazolam is safe and effective during bronchoscopy. The sedation success rate was similar to that in the CS group. However, remimazolam has a higher safety profile, with fewer inhibitory effects on respiration and circulation.

Key Words: Remimazolam; Bronchoscopy; Procedural sedation; Meta-analysis

Core Tip: We searched the databases of EMBASE, PubMed, Cochrane Library, and the Web of Science for randomized controlled trials of bendable bronchoscopic procedural sedation with remimazolam *vs* conventional sedatives (CS) from the time the database was created until August 2023. STATA 15.1 software was applied to data analyses. Five studies with 1080 cases were included. We finally came to the conclusion: Remimazolam is safe and effective for cases with bronchoscopy. Its sedation success rate is similar to CS. However, remimazolam has a higher safety profile with less inhibitory effects on respiration and circulation.

Citation: Zhou Y, Zhao C, Tang YX, Liu JT. Efficacy and safety of remimazolam in bronchoscopic sedation: A meta-analysis. *World J Clin Cases* 2024; 12(6): 1120-1129
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1120.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1120

INTRODUCTION

Bronchoscopy is an endoscopic tool for the diagnosis and treatment of respiratory disease, and plays a key role in the diagnosis and therapy of lung diseases[1]. However, bendable bronchoscopy is an invasive procedure, and patients often experience pain and anxiety as well as serious complications including respiratory depression, cardiac arrhythmias, and cerebrovascular accidents[2]. According to the American Thoracic Society, anesthesia is recommended for all patients undergoing bronchoscopic consultations in the absence of contraindications[3]. Procedural sedation involves the use of sedative drugs and analgesics in addition to routine consultation, which eliminates fear, improves comfort, increases tolerance, and reduces procedural complications while shortening the duration of the procedure[4].

Currently, conventional sedatives (CS) propofol, midazolam, and dexmedetomidine are widely used in painless bendable bronchoscopy practice. Propofol has a rapid onset of action and a short recovery time; however, it causes significant injection site pain, strong respiratory and circulatory depression, and has no antagonist[5]. Midazolam is antagonized by flumazenil. However, the prolonged postoperative sedation affects the time to discharge. Dexmedetomidine is a selective α2-adrenergic receptor agonist with sedative properties[6]. One study reported that dexmedetomidine has a low likelihood of causing respiratory depression but a long recovery time[7].

Remimazolam is a new and effective benzodiazepine whose metabolites are not pharmacologically active, resulting in a faster recovery of cognitive function[8]. Owing to its unique pharmacological properties, remimazolam has been widely used in endoscopy, particularly in gastroenteroscopy[9]. In recent years, with the development of painless diagnostic techniques, the use of remimazolam for bendable bronchoscopy has received much attention. However, there has been no relevant systematic review. Therefore, we conducted a meta-analysis of randomized controlled trials (RCTs) on remimazolam for bronchoscopy to compare its safety with that of CS.

MATERIALS AND METHODS

Search strategy

We searched the EMBASE, PubMed, Cochrane Library, and Web of Science databases from the origin to August 2023. The search terms include "Remimazolam" or "CNS 7056," search scope was "Title and Abstract." The search was limited to human studies in English. Relevant studies were independently obtained by two investigators.

Our inclusion criteria were as follows: (1) RCT study design; (2) patients underwent bendable bronchoscopy; (3) the interventional treatment was either Remimazolam or CS; (4) papers published from establishment to August 1, 2023; and (5) studies that were not in Chinese or English, duplicated, or had incomplete data were excluded.

Data extraction

The data were independently analyzed to extract relevant information: (1) Authors; (2) publication time; (3) country of publication; (4) type of study design; (5) American Society of Anesthesiologists classification (ASA classification); (6) number of participants in each study; (7) age range; (8) sex composition; and (9) specific interventions received by the participants, including the name of the medication, dosage, and dosing program. Disagreements in the extracted data

Table 1 The basic characteristics of included studies

Ref.	Country	Study design	ASA status	Number of patients	Age	Gender (M/F)	Remimazolam	Control
Gao *et al* [13], 2023	China	RCT	I-III	60	18-70	39/21	Initial dose: 6 mg/kg/h; Maintenance dose: 0.6-2 mg/kg/h	Propofol: Initial dose: 2 mg/kg; Maintenance dose: 4-6 mg/kg/h
Zhang *et al* [14], 2023	China	RCT	I-III	192	18-64	92/100	Initial dose: 0.2 mg/kg; Top-up dose: 0.05 mg/kg	Propofol: Initial dose: 1.5 mg/kg; Top-up dose: 0.5-1.0 mg/kg
Zhou *et al* [15], 2022	China	RCT	I-III	310	18-75	154/156	Initial dose: 0.2 mg/kg; Top-up dose: 0.1 mg/kg	Propofol: Initial dose: 2 mg/kg; Top-up dose: 0.75 mg/kg
Pastis *et al* [16], 2019	USA	RCT	I-III	372	50-74	174/198	Initial dose: 5 mg; Top-up dose: 2.5 mg	Midazolam: Initial dose: 1-1.75 mg; Top-up dose: 0.5-1 mg
Chen *et al* [17], 2022	China	RCT	I-III	146	45-65	108/38	Initial dose: 12 mg/kg/h; Maintenance dose: 1-2 mg/kg/h	Dexmedetomidine: Initial dose: 0.5 μg/kg; Maintenance dose: 0.2-0.7 μg/kg/h

ASA: American Society of Anesthesiologists.

Table 2 Number of successful sedation in bronchoscopy

Ref.	Study design	Number of patients in each group		Number of successful sedation	
		Remimazolam	Control	Remimazolam	Control
Zhou *et al*[15], 2022	RCT	155	Propofol: 155	154	Propofol: 154
Pastis *et al*[16], 2019	RCT	310	Midazolam: 73	250	Midazolam: 24
Chen *et al*[17], 2022	RCT	73	Dexmedetomidine: 73	69	Dexmedetomidine: 67

RCT: Randomized controlled trial.

were recorded and discussed with a 3rd researcher until a consensus was reached.

Quality assessment

Two researchers evaluated the quality of the research papers. The Cochrane tool[10] was applied to calculate the risk of bias. Under the study conditions, items related to high or unclear bias risk were regarded as high risk[11]. Disagreements in quality evaluation were documented and discussed with a third researcher until a consensus was reached.

Statistical analysis

All statistical analyses were conducted using STATA15.1 (Stata Statistical Software: Release 18. College Station, TX: StataCorp). I^2 and Q tests were used to test the heterogeneity between studies. If heterogeneity between studies existed ($I^2 \leq 50\%$ and $P > 0.10$), the data was analyzed *via* a fixed-effects model; otherwise, a random-effects model was used[12]. Subgroup analyses were conducted to compare the effects of propofol, midazolam, and dexmedetomidine; $P < 0.05$ was regarded as statistically significant.

RESULTS

Study selection

As shown in Figure 1, 40 studies were identified after a systematic literature search. After removing 20 duplicate studies, the 20 remaining studies were screened. Eight inappropriate studies were eliminated by screening titles and abstracts. Therefore, 12 articles were left for full-text reading. After careful reading of the full text, seven studies were excluded based on the inclusion and exclusion criteria. Finally, five studies were included.

Studies and participants' characteristics

Table 1 shows all the studies included, all five studies[13-17] were RCTs, four[13-15,17] were from China, and one[16] was from the United States. The five studies[13-17] were classified as ASA classes I-III. In studies published between 2018 and 2023, 1080 patients aged from 18 to 75 years, and 52.50% male underwent bendable bronchoscopy; 657 patients were sedated with remimazolam and 423 patients were sedated with CS, of which 281 were sedated with propofol[13-15], 69 with midazolam[16], and 73 with dexmedetomidine[17].

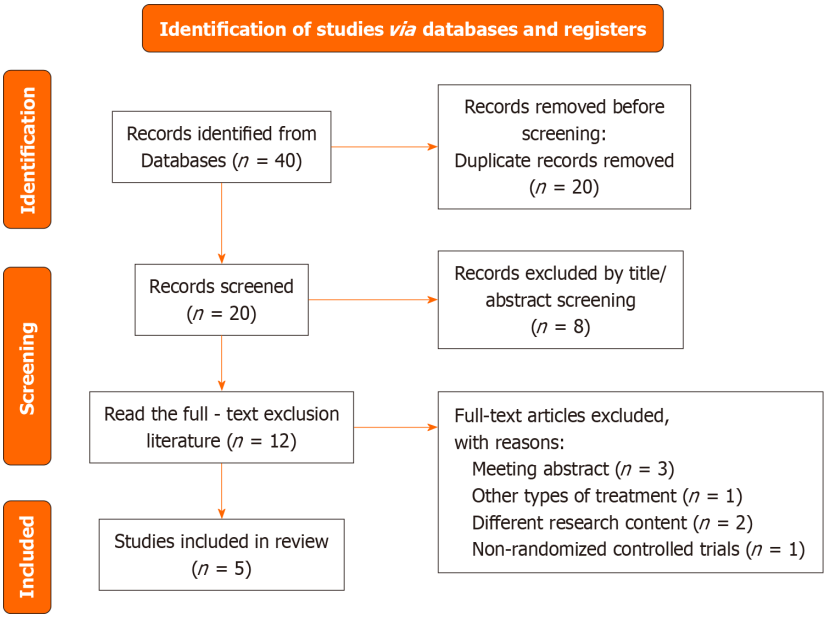

Figure 1 Flow diagram of study searching and selection process.

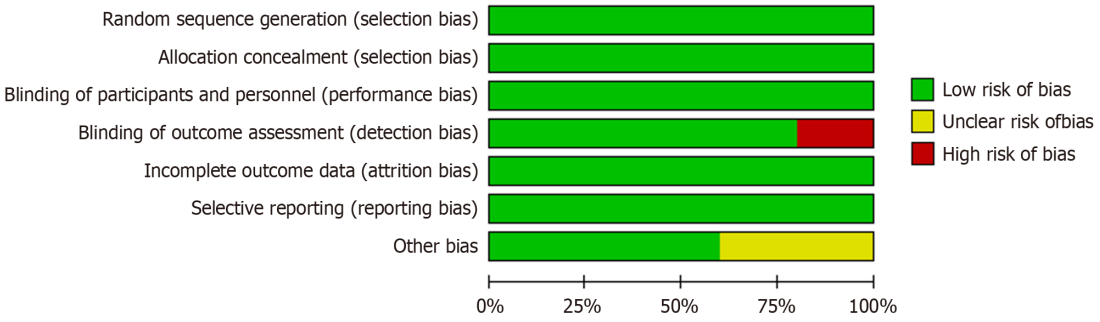

Figure 2 The risk of bias graph of included studies. The five studies showed a low bias risk for they assessed randomized sequence generation (100%), blinding of participants (100%), blinding of outcome (80%), selective reporting (100%), and others (60%).

The same standard was applied to evaluate sedation in 3 studies[15-17]. These studies divided patients into two groups according to the type of sedation used. The percentages of successfully sedated patients were 473/538 using remimazolam and 245/301 in the CS group (propofol 154/155, midazolam 24/73, and dexmedetomidine 67/73) (Table 2). The frequencies of intraoperative adverse events and complications, including hypotension, respiratory depression, and hypoxemia, are shown in Table 3.

Risk of bias assessment

The Cochrane method was used to calculate the risk of bias in the RCTs, as shown in Figures 2 and 3. Five studies showed a low risk of bias for randomized sequence generation (100%), blinding of participants (100%), blinding of outcomes (80%), selective reporting (100%), and others (60%). Three of these exhibited high quality according to the assessment results (Figures 2 and 3).

Results of the meta-analysis

The sedative efficiency: Three studies[15-17] reported the success rates of sedation with remimazolam and CS, involving 1032 cases (research group, n = 538; CS group, n = 301). The heterogeneity test results, I^2 = 99.6% and P < 0.001 in the Q-test, indicate statistically significant heterogeneity among different studies. Therefore, a random-effects model was used for subsequent tests. As shown in Figure 4, the relative risk (RR) value of the 3 studies pooled was 1.35, (95%CI: 0.60-3.05), P = 0.474, suggesting that the success rate of remimazolam for bronchoscopic sedation was similar to that of CS.

As shown in Figure 5, subgroup analysis showed that the success rate of remimazolam sedation was similar to that of propofol (RR: 1, P = 1.000), remimazolam sedation was more successful than midazolam sedation (RR: 2.45, $P \leq 0.001$), and remimazolam and dexmedetomidine had similar sedation success rates (RR: 1.03, P = 0.513).

The incidence of adverse events: As shown in Table 4, there was a significant difference in the incidence of hypotension and respiratory depression between the remimazolam and CS groups (hypotension: RR = 0.61, I^2 = 65.1%, P = 0.027;

Table 3 The number of patients with adverse events during bronchoscopy

Ref.	Patients in each group (*n*)		Hypotension (*n*)		Hypertension (*n*)		Respiratory depression (*n*)		Hypoxemia (*n*)		Bradycardia (*n*)		Tachycardia (*n*)		Injection pain (*n*)	
	Remimazolam	Control	Remimazolam	Control	Remimazolam	Control	Remimazolam	Control	Remimazolam	Control	Remimazolam	Control	Remimazolam	Control	Remimazolam	Control
Gao *et al* [13], 2023	30	Propofol: 30	11	Propofol: 22	1	Propofol: 2	NA	NA	1	Propofol: 2	2	Propofol: 5	6	Propofol: 9	NA	NA
Zhang *et al* [14], 2023	96	Propofol: 96	1	Propofol: 8	NA	NA	13	Propofol: 38	NA	NA	0	Propofol: 22	NA	NA	NA	NA
Zhou *et al* [15], 2022	155	Propofol: 155	22	Propofol: 49	13	Propofol: 5	9	Propofol: 8	13	Propofol: 5	NA	NA	NA	NA	1	Propofol: 26
Pastis *et al* [16], 2019	303	Midazolam: 69	127	Midazolam: 34	186	Midazolam: 41	7	Midazolam: 3	186	Midazolam: 41	13	Midazolam: 3	4	Midazolam: 0	2	Midazolam: 0
Chen *et al* [17], 2022	73	Dexmedetomidine: 73	9	Dexmedetomidine: 8	2	Dexmedetomidine: 3	2	Dexmedetomidine: 2	2	Dexmedetomidine: 3	3	Dexmedetomidine: 2	NA	NA	NA	NA

respiratory depression: RR = 0.50, I^2 = 42.3%, P = 0.002). The incidence of hypertension, hypoxemia, bradycardia, tachycardia, and injection pain was similar between the two groups.

As shown in Table 5, subgroup analyses revealed obvious differences between the two groups in the incidence of hypotension, respiratory depression, hypoxemia, and injection pain (hypotension: RR = 0.42, I^2 = 0.0%, P < 0.001; respiratory depression: RR = 0.48, I^2 = 78.4%, P = 0.002; hypoxemia: RR = 0.4, I^2 = 0.0%, P < 0.001; and injection pain: RR = 0.04, I^2 = 0.0%, P < 0.001). There was no obvious heterogeneity in the incidence of hypertension, bradycardia, or tachycardia among groups. The pooled results suggested that there was no significant difference in the incidence of hypotension, hypertension, respiratory depression, hypoxemia, bradycardia, tachycardia, or injection pain between remimazolam and midazolam. Similarly, there was no heterogeneity in the incidence of hypotension, respiratory depression, hypoxemia, tachycardia, or injection pain between the two groups.

DISCUSSION

This study aimed to explore the efficacy and safety of remimazolam during bronchoscopy. Based on these results, remimazolam had a sedation success rate similar to that of CS. However, remimazolam was associated with a lower risk of hypotension and respiratory depression than was CS. It can be concluded that remimazolam for bronchoscopy provides satisfactory sedation and a favorable safety profile. We compared the efficacy and safety of that with CS (propofol, midazolam, and dexmedetomidine) in bronchoscopic sedation, analyzing a total of 5 studies on the application of remimazolam for bronchoscopy. Of these, three papers compared remimazolam *vs* propofol, one used midazolam, and one used dexmedetomidine. Due to the heterogeneity among the three sedative drugs, this study conducted a meta-analysis and found that remimazolam showed a higher success rate of sedation than midazolam. Compared with

Table 4 Pooled results on the incidence of adverse events for remimazolam versus conventional sedatives

Control	Complications	Relative risk	95%CI	I^2 value (%)	*P* value for effect
Conventional sedatives	Hypotension	0.61	(0.40, 0.95)	65.1	0.027
	Hypertension	1.11	(0.89, 1.38)	23.5	0.359
	Respiratory depression	0.50	(0.33, 0.77)	42.3	0.002
	Hypoxemia	0.74	(0.37, 1.47)	59.7	0.387
	Bradycardia	0.72	(0.33, 1.56)	0.0	0.403
	Tachycardia	0.78	(0.33, 1.85)	0.0	0.576
	Injection pain	0.17	(0.01, 5.30)	72.3	0.316

Table 5 Pooled results of subgroup analyses of adverse event rates for remimazolam *vs* propofol, midazolam, and dexmedetomidine

Control	Complications	Relative risk	95%CI	I^2 value (%)	*P* value for effect
Propofol	Hypotension	0.45	(0.32, 0.64)	0.0	0.000
	Hypertension	2.00	(0.82, 4.85)	37.6	0.125
	Respiratory depression	0.48	(0.30, 0.76)	78.4	0.002
	Hypoxemia	0.36	(0.15, 0.87)	-	0.023
	Bradycardia	0.33	(0.08, 1.33)	0.0	0.119
	Tachycardia	0.67	(0.27, 1.64)	-	0.378
	Injection pain	0.04	(0.01, 0.28)	-	0.001
Midazolam	Hypotension	0.85	(0.65, 1.12)	-	0.247
	Hypertension	1.03	(0.83, 1.28)	-	0.766
	Respiratory depression	0.53	(0.14, 2.00)	-	0.350
	Hypoxemia	1.16	(0.68, 1.97)	-	0.595
	Bradycardia	0.99	(0.29, 3.37)	-	0.983
	Tachycardia	2.07	(0.11, 38.05)	-	0.624
	Injection pain	1.15	(0.06, 23.72)	-	0.927
Dexmedetomidine	Hypotension	0.61	(0.40, 0.95)	-	0.797
	Hypertension	0.67	(0.11, 3.87)	-	0.652
	Respiratory depression	1.00	(0.14, 6.91)	-	1.000
	Hypoxemia	0.80	(0.33, 1.91)	-	0.616
	Bradycardia	1.50	(0.26, 8.71)	-	0.652

propofol, remimazolam has a lower risk of hypotension, respiratory depression, and injection pain.

Remimazolam is a novel benzodiazepine analog[18]. It can be quickly metabolized *in vivo* by esterases independent of renal metabolism, and its metabolites are inactive[19]. The effects of this drug can be reversed by flumazenil, with a rapid onset of action and safe sedation[20]. In addition, the use of remimazolam reduces patient healthcare costs compared with midazolam during bronchoscopy[21]. Therefore, it is a promising drug for bronchoscopic diagnosis and therapy[22]. The number of endoscopic procedures is increasing, and anesthesia is beneficial for endoscopic procedures[9,23]. Anesthetic drug selection for bronchoscopic surgery should improve the safety of the procedure without compromising the success rate[24,25]. This meta-analysis showed that remimazolam reduced intraoperative adverse events and complications while maintaining the sedation success rate.

When writing this article, we identified two similar systematic reviews and meta-analyses[26,27] that compared the reliability and safety of other sedatives in endoscopy, however, we incorporated a wider range of adverse events and complications which included hypotension, hypertension, respiratory depression, hypoxemia, bradycardia, tachycardia, and injection pain, to evaluate the safety of remimazolam more comprehensively. Our study showed that remimazolam exhibited the same success rate as CS for bronchoscopy, which is in contrast to existing studies[27] that stated that remimazolam had a higher procedural success rate than CS. This may be related to the diverse types of endoscopies included in that report, including upper gastrointestinal endoscopy, colonoscopy, hysteroscopy, and bronchoscopy,

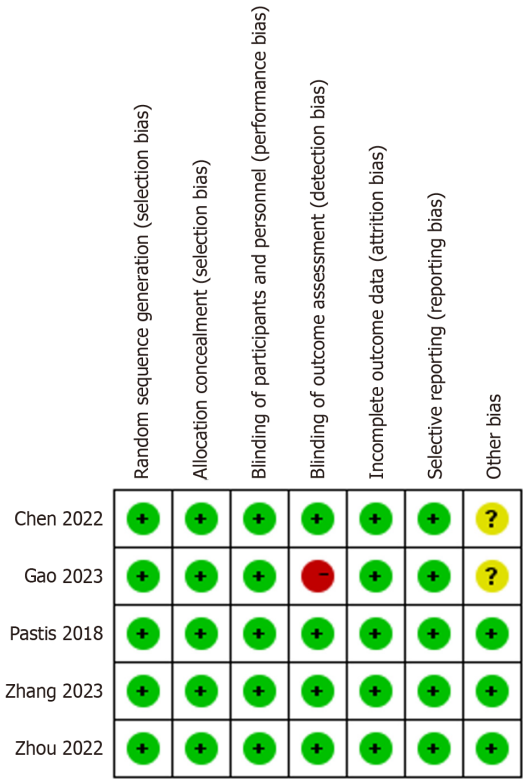

Figure 3 The risk of bias summary of included studies. Three of the five studies exhibit high quality according to the assessment result.

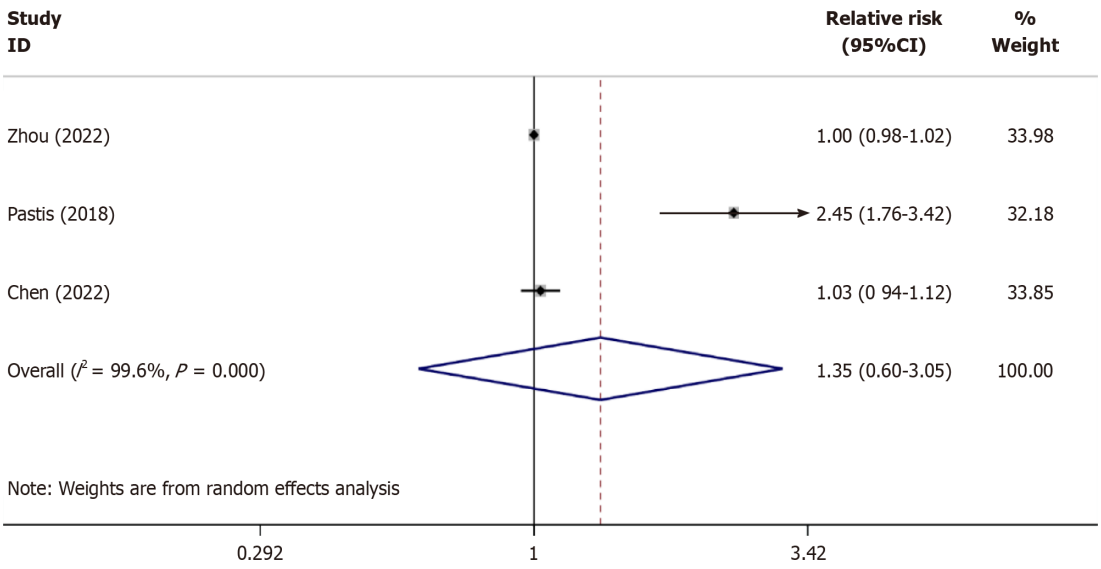

Figure 4 Comparison of the sedation success of remimazolam with conventional sedatives. A total of three studies investigated the sedation success of remimazolam *vs* conventional sedatives, and pooled analyses showed equal sedation success.

whereas only 1 bronchoscopy was included which was clinically heterogeneous. Furthermore, bronchoscopy is generally more stimulating than gastrointestinal endoscopy and hysteroscopy and requires deeper intraoperative sedation[28]. Further studies are warranted to investigate the success of remimazolam *vs* other sedatives at different sedation depths. The occurrence of hypotension and injection pain was lower in patients for whom remimazolam was used for sedation compared with propofol, which is consistent with two previous reports[26,29]. This suggests that remimazolam offers significant advantages in terms of respiration, circulation, and pain during injection.

Our study is the first to explore the efficacy of remimazolam *vs* CS in bronchoscopic procedures using subgroup analysis, providing evidence for the selection of bronchoscopic sedation drugs that remimazolam is safe and effective for bronchoscopic sedation. In clinical practice, patients undergoing bronchoscopy are predominantly elderly and chronically ill[30], and remimazolam facilitates intraoperative safety and postoperative recovery by significantly reducing respiratory and circulatory depression compared to CS. However, our study has some limitations. First, the definitions of different

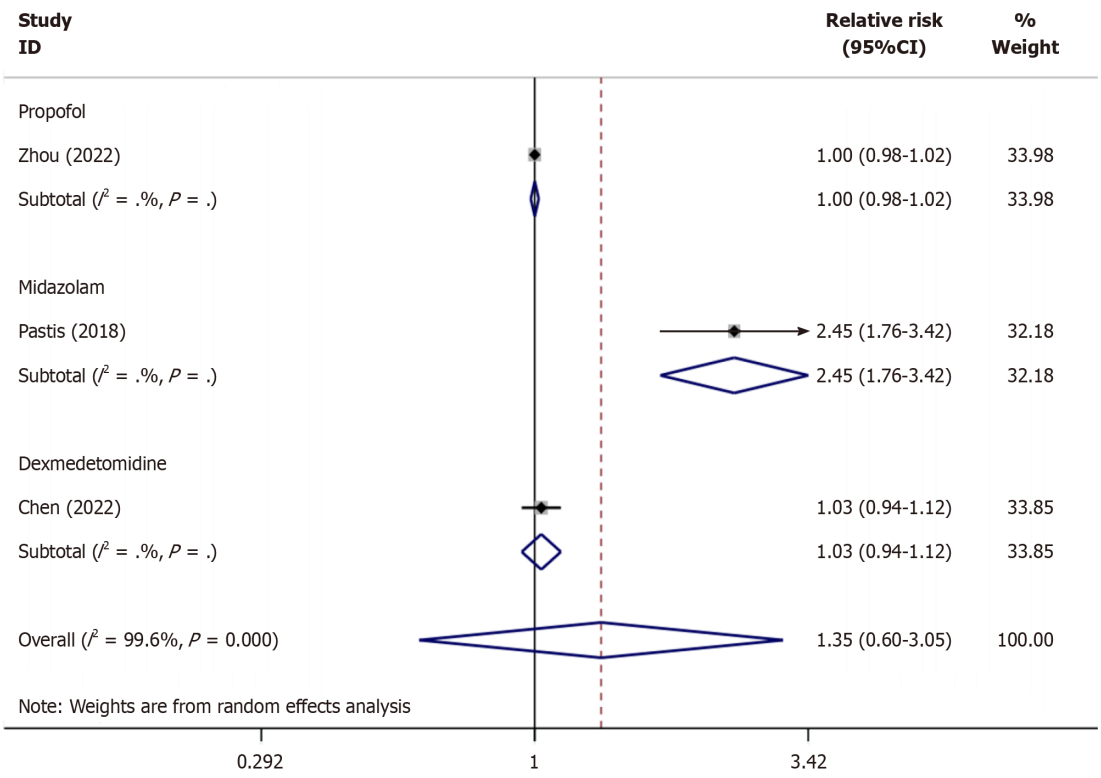

Figure 5 Subgroup analysis of the sedation success of remimazolam compared with propofol, midazolam, and dexmedetomidine. The results showed that there was no significant difference in sedation success between remimazolam and propofol, remimazolam sedation success was higher than midazolam, and there was no significant difference in sedation success between remimazolam and dexmedetomidine.

types of surgical operations, sedation drugs, sedation doses, and outcome metrics varied, which may have influenced the results. Second, most of the patients in the included studies were from China, and there may be racial differences between the populations. Third, different types and uses of opioids in the included studies may have affected the results. Fourth, only a few studies were included because there is limited research on anesthesia during bronchoscopic surgery. There were fewer within-group studies in which we performed subgroup analyses. The reliability of the outcome metrics in a single study was examined, and more studies are needed for future analyses.

CONCLUSION

Remimazolam is safe and effective during bronchoscopy. The sedation success rate was similar to that of the traditional sedatives (propofol, midazolam, and dexmedetomidine). However, it exhibits a weaker inhibitory effect on respiration. Some scholars have reported the sedation efficacy and incidence of adverse events of remimazolam during bronchoscopy, and RCTs with more samples are needed to validate our findings.

ARTICLE HIGHLIGHTS

Research background

Remimazolam is a new ultra-short-acting benzodiazepine sedative that is currently used for procedural sedation and general anesthesia. Several studies have used remimazolam for bendable bronchoscopes.

Research motivation

This is the first systematic review on the safety and efficacy of remimazolam during bronchoscopy.

Research objectives

This study aimed to assess the safety and efficacy of remimazolam for the sedation of patients undergoing bendable bronchoscopy.

Research methods

We searched databases of EMBASE, PubMed, Cochrane Library, and the Web of Science, from the original to August

2023. The search terms include "Remimazolam" or "CNS 7056", search scope was "Title and Abstract". The search was limited to human studies and literature in English.

Research results

This meta-analysis included five studies. The sedation success rate of remimazolam was similar to that of conventional sedatives (CS). However, remimazolam is associated with a lower incidence of hypotension and respiratory depression. The subgroup analysis showed a higher success rate for sedation with remimazolam than with midazolam. The incidences of hypotension, respiratory depression, hypoxemia, and injection pain were lower with remimazolam than with propofol.

Research conclusions

Remimazolam is safe and effective for bronchoscopic sedation. The success rate was similar to that of CS. However, remimazolam has a higher safety profile, with fewer inhibitory effects on respiration and circulation.

Research perspectives

Endoscopic surgery outside the operating room is currently increasing, and anesthesia provides strong support for the development of endoscopic surgery. The use of remimazolam can fulfill sedation requirements during bronchoscopic procedures while reducing the incidence of intraoperative adverse events and complications.

FOOTNOTES

Author contributions: Zhou Y and Liu JT conducted the systematic review and data collection and proposed an explanation that played an important role in the writing of the paper; Zhao C and Tang YX evaluated and verified the manuscript; Tang YX analyzed the data and reviewed the article; Liu JT developed the concept of reviewing papers and supervised, critically evaluated, and confirmed the manuscript; This article was written and approved by all authors.

Supported by the Fund of the Hunan Provincial Health Commission, No. D20230416797.

Conflict-of-interest statement: The authors claim that the survey did not involve any business or financial links that could be interpreted as potential conflicts of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised in accordance with this checklist.

Country/Territory of origin: China

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S-Editor: Gong ZM
L-Editor: A
P-Editor: Zheng XM

REFERENCES

1 **Criner GJ**, Eberhardt R, Fernandez-Bussy S, Gompelmann D, Maldonado F, Patel N, Shah PL, Slebos DJ, Valipour A, Wahidi MM, Weir M, Herth FJ. Interventional Bronchoscopy. *Am J Respir Crit Care Med* 2020; **202**: 29-50 [PMID: 32023078 DOI: 10.1164/rccm.201907-1292SO]

2 **Kamel T**, Helms J, Janssen-Langenstein R, Kouatchet A, Guillon A, Bourenne J, Contou D, Guervilly C, Coudroy R, Hoppe MA, Lascarrou JB, Quenot JP, Colin G, Meng P, Roustan J, Cracco C, Nay MA, Boulain T; Clinical Research in Intensive Care Sepsis Group (CRICS-TRIGGERSEP). Benefit-to-risk balance of bronchoalveolar lavage in the critically ill. A prospective, multicenter cohort study. *Intensive Care Med* 2020; **46**: 463-474 [PMID: 31912201 DOI: 10.1007/s00134-019-05896-4]

3 **Wahidi MM**, Jain P, Jantz M, Lee P, Mackensen GB, Barbour SY, Lamb C, Silvestri GA. American College of Chest Physicians consensus statement on the use of topical anesthesia, analgesia, and sedation during flexible bronchoscopy in adult patients. *Chest* 2011; **140**: 1342-1350 [PMID: 22045879 DOI: 10.1378/chest.10-3361]

4 **Hong KS**, Choi EY, Park DA, Park J. Safety and Efficacy of the Moderate Sedation During Flexible Bronchoscopic Procedure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Medicine (Baltimore)* 2015; **94**: e1459 [PMID: 26447999 DOI: 10.1097/MD.0000000000001459]

5 **Pertzov B**, Krasulya B, Azem K, Shostak Y, Izhakian S, Rosengarten D, Kharchenko S, Kramer MR. Dexmedetomidine versus propofol sedation in flexible bronchoscopy: a randomized controlled trial. *BMC Pulm Med* 2022; **22**: 87 [PMID: 35291989 DOI: 10.1186/s12890-022-01880-9]

6 **Keating GM**. Dexmedetomidine: A Review of Its Use for Sedation in the Intensive Care Setting. *Drugs* 2015; **75**: 1119-1130 [PMID: 26063213 DOI: 10.1007/s40265-015-0419-5]

7 **McCambridge AJ**, Boesch RP, Mullon JJ. Sedation in Bronchoscopy: A Review. *Clin Chest Med* 2018; **39**: 65-77 [PMID: 29433726 DOI: 10.1016/j.ccm.2017.09.004]

8 **Hu Q**, Liu X, Wen C, Li D, Lei X. Remimazolam: An Updated Review of a New Sedative and Anaesthetic. *Drug Des Devel Ther* 2022; **16**: 3957-3974 [PMID: 36411859 DOI: 10.2147/DDDT.S384155]

9 **Zhao MJ**, Hu HF, Li XL, Li XM, Wang DC, Kuang MJ. The safety and efficacy between remimazolam and propofol in intravenous anesthesia of endoscopy operation: a systematic review and meta-analysis. *Int J Surg* 2023; **109**: 3566-3577 [PMID: 37534687 DOI: 10.1097/JS9.0000000000000638]

10 **Higgins JP**, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928 [PMID: 22008217 DOI: 10.1136/bmj.d5928]

11 **Koster G**, Wetterslev J, Gluud C, Zijlstra JG, Scheeren TW, van der Horst IC, Keus F. Effects of levosimendan for low cardiac output syndrome in critically ill patients: systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med* 2015; **41**: 203-221 [PMID: 25518953 DOI: 10.1007/s00134-014-3604-1]

12 **Wang H**, Luo Q, Li Y, Zhang L, Wu X, Yan F. Effect of Prophylactic Levosimendan on All-Cause Mortality in Pediatric Patients Undergoing Cardiac Surgery-An Updated Systematic Review and Meta-Analysis. *Front Pediatr* 2020; **8**: 456 [PMID: 32923414 DOI: 10.3389/fped.2020.00456]

13 **Gao S**, Wang T, Cao L, Li L, Yang S. Clinical effects of remimazolam alone or in combination with dexmedetomidine in patients receiving bronchoscopy and influences on postoperative cognitive function: a randomized-controlled trial. *Int J Clin Pharm* 2023; **45**: 137-145 [PMID: 36346544 DOI: 10.1007/s11096-022-01487-4]

14 **Zhang L**, Yu L, Xu L, Wang JF, Li JY, Chen ZJ. Effectiveness of remimazolam besylate combined with alfentanil for fiberoptic bronchoscopy with preserved spontaneous breathing: a prospective, randomized, controlled clinical trial. *Eur Rev Med Pharmacol Sci* 2023; **27**: 6071-6080 [PMID: 37458656 DOI: 10.26355/eurrev_202307_32961]

15 **Zhou YY**, Yang ST, Duan KM, Bai ZH, Feng YF, Guo QL, Cheng ZG, Wu H, Shangguan WN, Wu XM, Wang CH, Chai XQ, Xu GH, Liu CM, Zhao GF, Chen C, Gao BA, Li LE, Zhang M, Ouyang W, Wang SY. Efficacy and safety of remimazolam besylate in bronchoscopy for adults: A multicenter, randomized, double-blind, positive-controlled clinical study. *Front Pharmacol* 2022; **13**: 1005367 [PMID: 36313321 DOI: 10.3389/fphar.2022.1005367]

16 **Pastis NJ**, Yarmus LB, Schippers F, Ostroff R, Chen A, Akulian J, Wahidi M, Shojaee S, Tanner NT, Callahan SP, Feldman G, Lorch DG Jr, Ndukwu I, Pritchett MA, Silvestri GA; PAION Investigators. Safety and Efficacy of Remimazolam Compared With Placebo and Midazolam for Moderate Sedation During Bronchoscopy. *Chest* 2019; **155**: 137-146 [PMID: 30292760 DOI: 10.1016/j.chest.2018.09.015]

17 **Chen X**, Xin D, Xu G, Zhao J, Lv Q. The Efficacy and Safety of Remimazolam Tosilate Versus Dexmedetomidine in Outpatients Undergoing Flexible Bronchoscopy: A Prospective, Randomized, Blind, Non-Inferiority Trial. *Front Pharmacol* 2022; **13**: 902065 [PMID: 35721180 DOI: 10.3389/fphar.2022.902065]

18 **Kilpatrick GJ**. Remimazolam: Non-Clinical and Clinical Profile of a New Sedative/Anesthetic Agent. *Front Pharmacol* 2021; **12**: 690875 [PMID: 34354587 DOI: 10.3389/fphar.2021.690875]

19 **Choi JY**, Lee HS, Kim JY, Han DW, Yang JY, Kim MJ, Song Y. Comparison of remimazolam-based and propofol-based total intravenous anesthesia on postoperative quality of recovery: A randomized non-inferiority trial. *J Clin Anesth* 2022; **82**: 110955 [PMID: 36029704 DOI: 10.1016/j.jclinane.2022.110955]

20 **Lee A**, Shirley M. Remimazolam: A Review in Procedural Sedation. *Drugs* 2021; **81**: 1193-1201 [PMID: 34196946 DOI: 10.1007/s40265-021-01544-8]

21 **Pedersen MH**, Danø A, Englev E, Kattenhøj L, Munk E. Economic benefits of remimazolam compared to midazolam and propofol for procedural sedation in colonoscopies and bronchoscopies. *Curr Med Res Opin* 2023; **39**: 691-699 [PMID: 36999319 DOI: 10.1080/03007995.2023.2196198]

22 **Wesolowski AM**, Zaccagnino MP, Malapero RJ, Kaye AD, Urman RD. Remimazolam: Pharmacologic Considerations and Clinical Role in Anesthesiology. *Pharmacotherapy* 2016; **36**: 1021-1027 [PMID: 27496519 DOI: 10.1002/phar.1806]

23 **Rex DK**, Bhandari R, Desta T, DeMicco MP, Schaeffer C, Etzkorn K, Barish CF, Pruitt R, Cash BD, Quirk D, Tiongco F, Sullivan S, Bernstein D. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc* 2018; **88**: 427-437.e6 [PMID: 29723512 DOI: 10.1016/j.gie.2018.04.2351]

24 **Pastis NJ**, Hill NT, Yarmus LB, Schippers F, Imre M, Sohngen W, Randall O, Callahan SP, Silvestri GA. Correlation of Vital Signs and Depth of Sedation by Modified Observer's Assessment of Alertness and Sedation (MOAA/S) Scale in Bronchoscopy. *J Bronchology Interv Pulmonol* 2022; **29**: 54-61 [PMID: 34238838 DOI: 10.1097/LBR.0000000000000784]

25 **José RJ**, Shaefi S, Navani N. Sedation for flexible bronchoscopy: current and emerging evidence. *Eur Respir Rev* 2013; **22**: 106-116 [PMID: 23728864 DOI: 10.1183/09059180.00006412]

26 **Zhu X**, Wang H, Yuan S, Li Y, Jia Y, Zhang Z, Yan F, Wang Z. Efficacy and Safety of Remimazolam in Endoscopic Sedation-A Systematic Review and Meta-Analysis. *Front Med (Lausanne)* 2021; **8**: 655042 [PMID: 34381792 DOI: 10.3389/fmed.2021.655042]

27 **Tang Y**, Yang X, Yu Y, Shu H, Xu J, Li R, Zou X, Yuan S, Shang Y. Remimazolam versus traditional sedatives for procedural sedation: a systematic review and meta-analysis of efficacy and safety outcomes. *Minerva Anestesiol* 2022; **88**: 939-949 [PMID: 35785930 DOI: 10.23736/S0375-9393.22.16631-9]

28 **Nelson ME**. Moderate Sedation Changes for Bronchoscopy in 2017. *Chest* 2017; **152**: 893-897 [PMID: 28687379 DOI: 10.1016/j.chest.2017.06.027]

29 **Zhang J**, Cairen Z, Shi L, Pang S, Shao Y, Wang Y, Lu Z. Remimazolam versus propofol for procedural sedation and anesthesia: a systemic review and meta-analysis. *Minerva Anestesiol* 2022; **88**: 1035-1042 [PMID: 36326772 DOI: 10.23736/S0375-9393.22.16817-3]

30 **Mondoni M**, Radovanovic D, Sotgiu G, Di Marco F, Carlucci P, Centanni S, Santus P. Interventional pulmonology techniques in elderly patients with comorbidities. *Eur J Intern Med* 2019; **59**: 14-20 [PMID: 30279034 DOI: 10.1016/j.ejim.2018.09.015]

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World J Clin Cases 2024 February 26; 12(6): 1130-1137

DOI: 10.12998/wjcc.v12.i6.1130

ISSN 2307-8960 (online)

CASE REPORT

Simple bone cysts of the proximal humerus presented with limb length discrepancy: A case report

Cing Syue Lin, Shang Ming Lin, Syang-Peng Rwei, Chin-Wen Chen, Tsung-Yu Lan

Specialty type: Orthopedics

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Liu TF, China

Received: October 1, 2023
Peer-review started: October 1, 2023
First decision: January 2, 2024
Revised: January 10, 2024
Accepted: January 30, 2024
Article in press: January 30, 2024
Published online: February 26, 2024

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Abstract

BACKGROUND

Simple bone cysts (SBC) are benign tumor-like bone lesions typically identified in children. While SBC may lead to growth disturbances or growth arrest, such cases are uncommon. The mechanisms behind these observations remain unclear. Additionally, research on the etiology of SBC remains inconclusive, and there has been no consensus on the appropriate timing and methodology for treatment.

CASE SUMMARY

Here, we present our experience in the successful surgical management of a 10-year-old girl with SBC, who presented with a pathological fracture complicated by malunion of the displaced fracture, varus deformity, and limb length discrepancy. We hypothesized two possible etiologies for the patient's growth arrest and subsequent humerus varus deformity: (1) Direct disruption of the physis by fluid from the cyst itself; and (2) damage to the epiphysis due to repetitive pathological fractures associated with SBC. In addressing this case, surgical intervention was undertaken to correct the proximal humerus varus deformity. This approach offered the advantages of simultaneously correcting angular abnormalities, achieving mild limb lengthening, providing definitive SBC treatment, and reducing the overall treatment duration.

CONCLUSION

As per current literature, acute correction of acute angular deformity in proximal humeral SBC is not well comprehended. However, in this specific case, acute correction was considered an optimal solution.

Key Words: Bone cyst; Solitary cysts; Benign; Humerus; Growth arrest; Limb length discrepancy; Case report

Core Tip: We successfully operated on a 10-year-old girl with simple bone cysts (SBC), who presented with varus deformity, limb length discrepancy, and malunion resulting from a neglected pathological fracture. We proposed two potential causes for the humeral growth arrest and varus deformity in this patient: (1) Direct disruption of the physis by fluid from the cyst itself; and (2) damage to the epiphysis due to recurrent pathological fractures associated with SBC. Presently, the literature lacks a comprehensive understanding of the acute correction of angular deformity in proximal humeral SBC. However, in this specific case, acute correction was considered an ideal option.

Citation: Lin CS, Lin SM, Rwei SP, Chen CW, Lan TY. Simple bone cysts of the proximal humerus presented with limb length discrepancy: A case report. *World J Clin Cases* 2024; 12(6): 1130-1137
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1130.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1130

INTRODUCTION

Simple bone cysts (SBC), also known as solitary bone cysts are benign, fluid-filled tumor-like bone lesions commonly found in the proximal humerus (70%) or femur (25%) of children and adolescents[1,2]. While SBC may occasionally result in growth disturbances or growth arrest, such cases are uncommon. The underlying mechanisms behind this remain unclear[3]. This article presents a case involving a 10-year-old girl who initially complained of left arm pain attributed to an angulated old fracture, accompanied by limb length discrepancy. Additionally, a review of the current literature on SBC is included in this discussion.

CASE PRESENTATION

Chief complaints

A 10-year-old Chinese girl presented at our orthopedics clinic with a history of restricted left shoulder elevation and left upper limb length discrepancy spanning six months.

History of present illness

The patient experienced difficulty lifting her left arm during undressing, leading her mother to observe a noticeable length difference in the left arm. Concerned about these issues, the mother brought her to our clinic for evaluation.

History of past illness

The patient had no pre-existing medical conditions. No history of trauma, fever, local infection, or other precipitating factors in the left shoulder were noted.

Personal and family history

The patient's mother denied any family history of tumors.

Physical examination

During physical examination, it was observed that the patient's left arm was approximately 4-5 cm shorter than the right. The active range of motion (ROM) for the left shoulder was limited due to pain (Table 1). However, the distal circulation was found to be intact, and no focal neurological signs or symptoms were observed.

Laboratory examinations

Serum C-reactive protein levels were within the normal range, and routine blood and urine analyses showed no abnormalities. A tumor marker workup, which included alpha-fetoprotein, cancer antigen 125, carbohydrate antigen 19-9, prostate-specific antigen, and carcinoembryonic antigen, all revealed values within normal limits.

Imaging examinations

Initial imaging studies indicated an angulated old fracture at the proximal left humeral neck (Figure 1). Subsequent examination with magnetic resonance imaging (MRI) revealed marked deformity of the left humeral head and possible malunion of the displaced fracture in the left humeral neck. No evidence of cortical discontinuity, intraosseous patho-logies, or periosteal reaction was noted (Figure 2).

Table 1 The preoperative and postoperative active range of motion of left shoulder

	Preoperative active ROM	Postoperative-1 month active ROM	Postoperative-1 year active ROM
Flexion	70	176	180
Abduction	80	175	180
External rotation	45	90	95
Internal rotation	10	65	75

ROM: Range of motion.

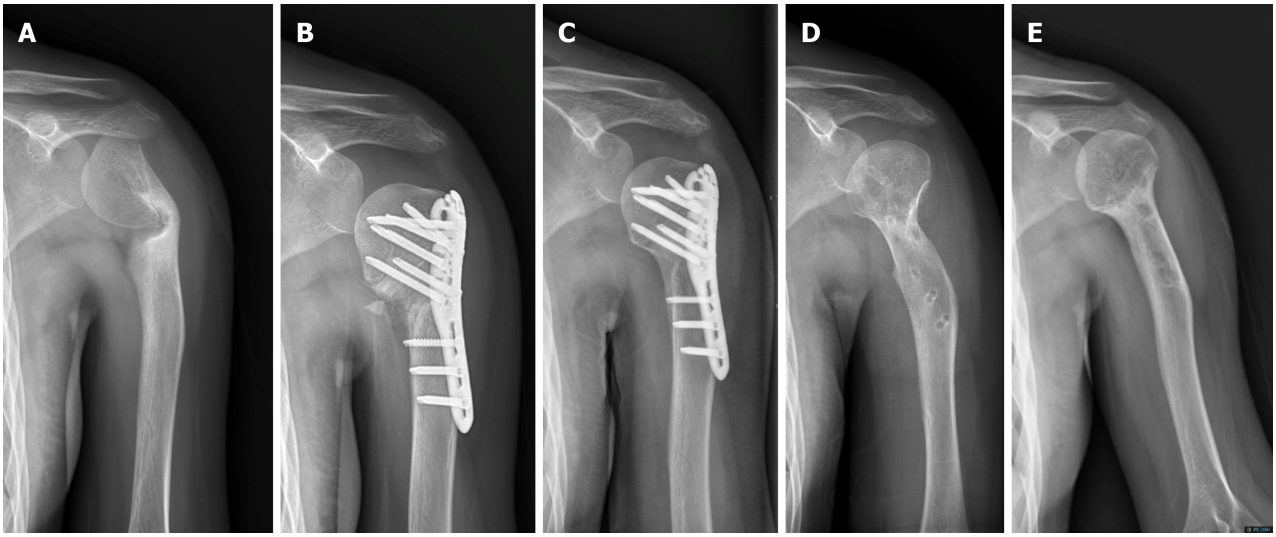

Figure 1 Series anteroposterior plain radiographs of the left humerus. A: Preoperative anteroposterior plain radiographs of the left humerus at initial presentation; B: 1-month postoperative anteroposterior plain radiographs of the left humerus; C: 1-year post-operative anteroposterior plain radiographs of the left humerus; D: Anteroposterior plain radiographs of the left humerus at 1-year post-removal of internal fixator; E: 1-year post-removal of internal fixator surgery.

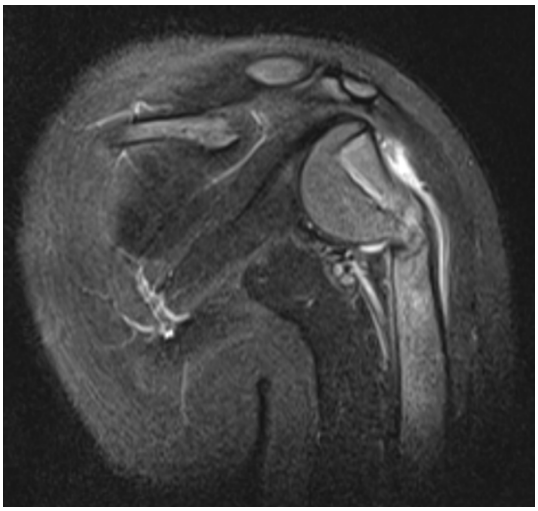

Figure 2 Preoperative magnetic resonance images and pathological results of the patient. Preoperative T2-weighted magnetic resonance images of the left humerus showed a marked deformity of the humeral head and a potential malunion of the displaced fracture in the left humeral neck.

FINAL DIAGNOSIS

Considering the patient's medical history, the final diagnosis indicated a case of left humerus SBC with varus malunion or suspected postinfection sequelae of osteomyelitis.

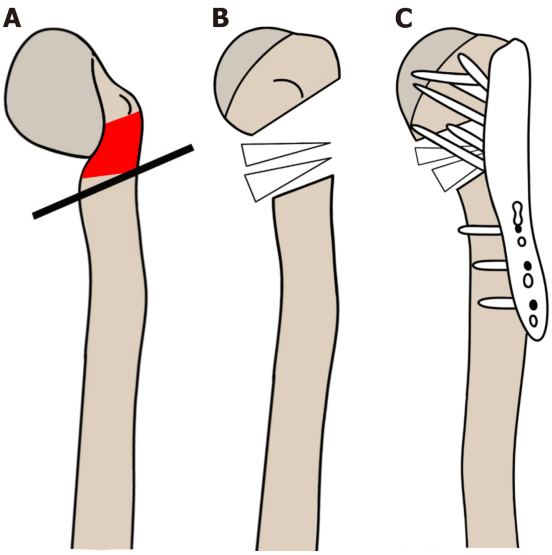

Figure 3 Surgical procedure for acute correction of the proximal humerus for the varus deformity. The red area indicates the location of the simple bone cyst (SBC). A: Osteotomy was performed in the most angulated area, removing the deformity site of the SBC; B: The gap was filled with allograft (donor femoral head); C: The proximal humerus was fixed with an anatomical locking plate (Depuy-Synthesis®, Raynham, MA, United States) in a valgus position.

TREATMENT

Surgical intervention was recommended for this case of left humerus SBC with varus malunion or suspected postinfection sequela of osteomyelitis. The procedure involved placing the patient under general anesthesia in a semi-sitting position. The anterior approach was utilized to expose the proximal metaphysis and diaphysis of the left humerus. Osteotomy was performed at the most angulated area, and curettage over the lesion site was performed, with the specimens sent for pathological study. The proximal humerus was then fixed with an anatomical locking plate (Depuy-Synthes, Raynham, MA, United States) in a valgus position and the gap was filled with an allograft (donor femoral head) (Figure 3). The patient has not received any additional medication therapy beyond the surgical intervention.

OUTCOME AND FOLLOW-UP

Postoperatively, the patient was immobilized in a sling for 2 wk. The left shoulder length discrepancy was reduced by 2 cm. After 1 month, she exhibited full active ROM in the left shoulder, with no reported wound complications or infection (Table 1 and Figure 4). Follow-up radiographs indicated no progression of the lesion; the osteotomy site showed solid union at 1 month and 1 year postoperatively (Figure 1). The histological report revealed degenerated cortical bone and cartilage tissue, with fibrous cystic wall with fibrin-like materials, cholesterol clefts and surrounding some new bone formation (Figure 5), leading to the diagnosis of SBC. While no pain or discomfort was reported, the implant was removed one year later based on the parents' preference. Subsequent radiographs showed that the left proximal humerus had healed with union and was well-aligned (Figure 1). One year following implant removal surgery, radiographic assessment revealed favorable remodeling and alignment of the left proximal humerus. Physical examination showed full active ROM and normal muscle power in the left shoulder (Table 1 and Figure 1). She exhibits the ability to execute motor milestone tasks in accordance with her chronological age. Furthermore, the length discrepancy between both hands was maintained at a 2 cm difference.

DISCUSSION

SBC are benign metaphyseal lytic lesions predominantly occurring in males[3]. Despite research, the etiology of SBC remains inconclusive[4,5]. Most cases of SBC are asymptomatic and are discovered incidentally. Spontaneous resolution of SBC occurs in only about 5% to 10% of cases[6,7]. Symptomatic cases are often associated with pathological fractures (63%-87%)[1,8] and less than 15% of cysts resolve spontaneously after a fracture occurs[5,9]. Presently, there is no consensus or established guidelines on the optimal timing and method of treating SBC[2,6,7,10]. To the best of our knowledge, the acute correction of angular deformity in proximal humeral SBC is not yet fully understood.

The primary differential diagnoses for pathological fractures in children aged 5–10 years include SBC, aneurysmal bone cysts (ABC), non-ossifying fibroma, and osteomyelitis[11]. In our patient, the lesion was located in the proximal humerus, consistent with the predisposing location of SBC. As our patient exhibited no signs of inflammation, bruises, or swelling, and had not received antibiotic treatment, chronic osteomyelitis was ruled out. Given the similar clinical symptoms of SBC, ABC, and non-ossifying fibroma, imaging and pathology played a crucial role in differentiating these

Figure 4 Two-week postoperative photos of the patient. A: Full active range of motion of the left shoulder; B: About 2-3 cm length discrepancy on the affected side.

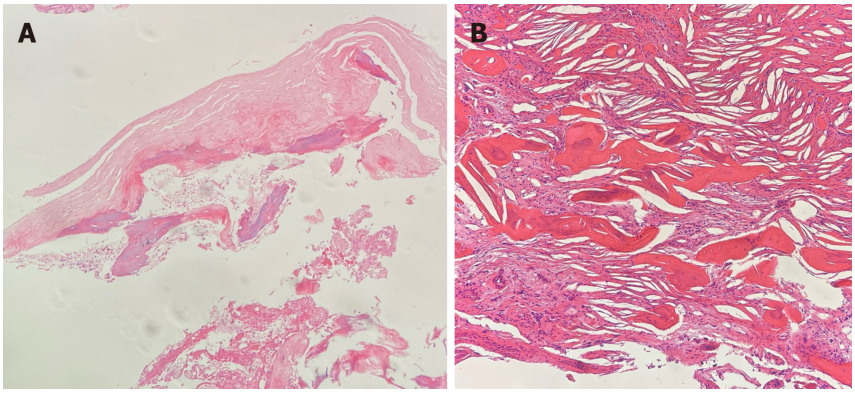

Figure 5 Pathological results of the patient. A: Histological results showed fibrous cyst wall with fibrin-like material and calcification; B: Histological results showed cystic wall with cholesterol clefts and surrounding some new bone formation, all of which may be indicative of a diagnosis of a simple bone cyst.

diseases.

Radiographic findings in our case revealed an old, angulated fracture at the proximal left humeral neck (Figure 1). Although the characteristic cystic lesions of SBC were not visibly evident on radiography and MRI, the possibility of SBC could not be ruled out. Furthermore, MRI showed a smoother sclerotic junction with the absence of fat stranding or inflammation in the surrounding soft tissue (Figure 2), suggesting fluid reabsorption and healing. These findings, combined with the histological report, were indicative of a benign cause.

A pathological fracture occurred in association with the benign lesion, leading to the subsequent displacement of the fracture and resulting in a malunion at the left humeral neck. The histological report showed fibrous cystic wall with fibrin-like materials, cholesterol clefts and surrounding some new bone formation, consistent with SBC. Considering the patient's history, the results suggest fibrosis with chronic inflammation, supporting a diagnosis of SBC. Pathologic fractures can often remain asymptomatic until the moment of fracture or may occur after lesions that cause prodromal pain. However, they typically do not present with accompanying symptoms.

As such, we posit that this patient experienced an initially asymptomatic pathologic fracture due to low-energy trauma, resulting in a delayed diagnosis and treatment. The lack of a proper diagnosis and timely intervention contributed to the development of malunion in the old, displaced pathological fracture at the left humeral neck, along with subsequent issues of limb length discrepancy and angular deformity.

On rare occasions, SBC may lead to growth disturbances, and, the underlying mechanism remains a subject of debate. Some evidence suggests that the cyst fluid itself may directly disrupt the physis, causing growth disturbances[12-14]. Other potential processes include: (1) Fractures through the cyst, damaging the physis and resulting in growth arrest; (2) direct extension of the cyst through the physis; and (3) iatrogenic damage to a developing physis due to surgical removal

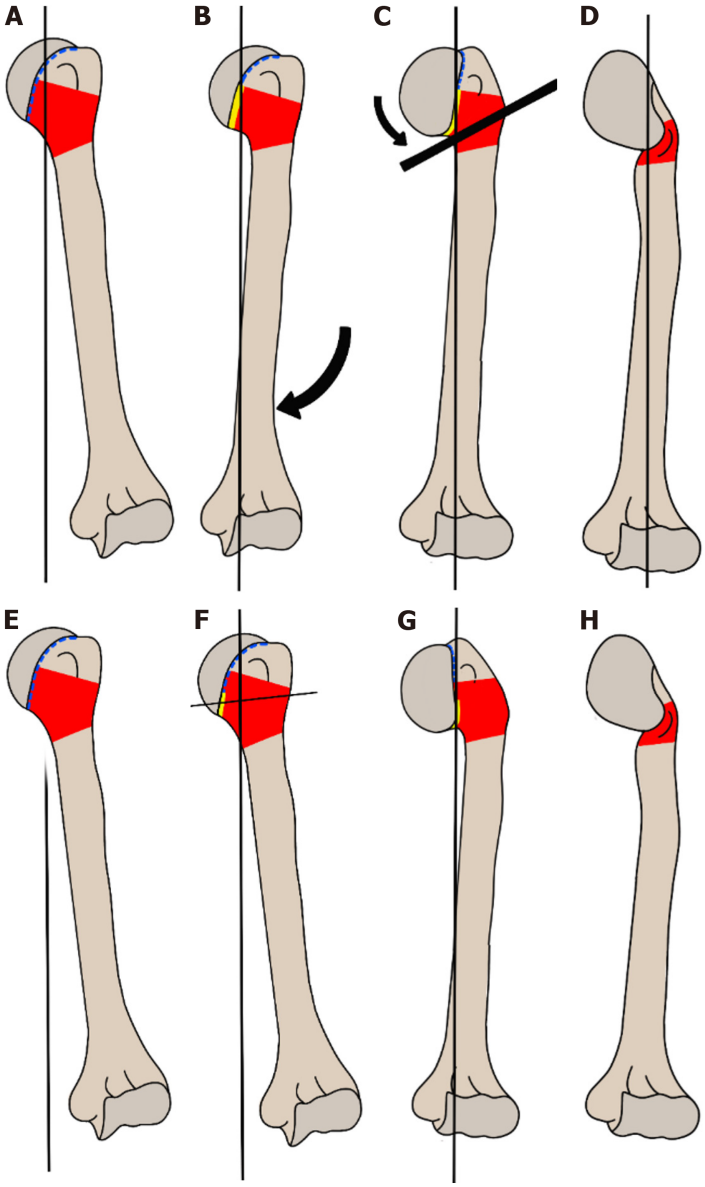

Figure 6 Two hypotheses for the etiology of our patient with simple bone cyst who presented with a pathological fracture, angular deformity, and limb length discrepancy. The red area represents the location of simple bone cyst (SBC); the blue dotted line represents the epiphysis; and the yellow line indicates the affected epiphysis. A–D: The first hypothesis. A: The proximal humeral simple bone cyst extends through the physis on the medial side; B: The SBC subsequently caused growth arrest and varus deformity of the humerus; C: Due to a proximal humerus fracture, additional varus angulation of the humeral head occurs; D: SBC presenting with a pathological fracture, complicated with malunion of the displaced fracture, varus deformity and limb length discrepancy. E–H: The second hypothesis. E: A proximal humeral simple bone cyst develops; F: Repetitive pathological fractures due to SBC damaged the medial epiphysis of the proximal humerus and varus humeral head angulation was established as a consequence; G: The humerus develops varus deformity and a length discrepancy due to a damaged epiphysis; H: SBC presenting with a pathological fracture, complicated with malunion of the displaced fracture, varus deformity and limb length discrepancy.

of a cyst in proximity[6,12-18]. Regardless of the etiology, growth disturbances ultimately result in angular deformity and/or limb length discrepancy in the affected limb. In the case of our patient, limb length discrepancy was evident before surgical treatment, making it less likely that her injury was related to iatrogenic damage.

We proposed two hypotheses to explain the etiology of our patient's condition. First, we considered the possibility of direct extension of the SBC through the epiphysis on the medial side, or the direct disruption of the physis by the cyst fluid itself, leading to growth arrest and subsequent varus deformity of the humerus. Given that the proximal physis contributes to approximately 80% of the humerus' development, any disturbance in this region can result in significant upper limb length discrepancy[6]. The additional varus angulation of the humeral head occurred as a sequela of the proximal humerus fracture (Figure 6).

The second hypothesis proposed was that the epiphysis was damaged by repetitive pathological fractures due to SBC. The bone affected by SBC is weakened and prone to pathological fractures, which can, in turn, damage the epiphysis. As a consequence of these pathological fractures, varus humeral head angulation developed. The muscles pulling on the proximal humerus allowed pathological fractures to heal with an increasing varus deformity, giving rise to the typical complaint of severe shoulder ROM limitations in abduction and flexion. Furthermore, due to a defective medial epi-

physis, the humerus developed further varus deformity and a length discrepancy (Figure 6).

We presented two surgical intervention options for the patient. The first option involved acute correction of the proximal humerus varus deformity. The alternative was distraction osteogenesis with external fixation, such as Ilizarov or Taylor spatial frame, combined with internal lengthening nails for limb lengthening and angle correction. Following careful consideration, the parents opted for the first treatment due to its shorter course, while recognizing the inherent limitation in correcting limb length discrepancy. Considering the nearly closed proximal humeral physis in the patient, the likelihood of developing subsequent length disparities was deemed low. Minor discrepancies in arm length, up to 5 or 6 cm, are generally well-tolerated without causing significant functional constraints, given the primary role of the upper extremity, which is non-weight-bearing[18,19].

Thus, the surgical treatment of acute correction for the proximal humerus varus deformity was performed. This approach offers the advantage of simultaneously correcting angular abnormalities, providing mild limb lengthening, definitive cyst therapy, and a shortened course of treatment. Consequently, we believe that the acute correction of the varus deformity was the optimal option in this case.

CONCLUSION

In conclusion, we presented a case of SBC presenting with a pathological fracture, complicated with malunion of the displaced fracture, varus deformity, and limb length discrepancy. The discussion included differential diagnoses of SBC, alongside a comprehensive review of the current literature. In our case, the patient's limb length discrepancy and varus deformity emerged as complications of the SBC and pathological fracture. It underscores the importance of close follow-up in patients with SBC to monitor the potential occurence of growth arrest.

FOOTNOTES

Author contributions: Lan TY, Lin SM, Rwei SP, and Chen CW contributed to conceptualization and supervision; Lin CS contributed to data collection, software, paper review, manuscript writing and editing; Lan TY contributed to clinical examination, surgery, original draft preparation and editing; All authors have read and agreed to the published version of the final manuscript.

Informed consent statement: Informed consent was obtained from the subject involved in the study. Written informed consent has been obtained from the patient to publish this paper.

Conflict-of-interest statement: All authors declare that they have no conflict of interest to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Taiwan

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S-Editor: Liu JH
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Zhang K**, Wang Z, Zhang Z. Comparison of curettage and bone grafting combined with elastic intramedullary nailing *vs* curettage and bone grafting in the treatment of long bone cysts in children. *Medicine (Baltimore)* 2019; **98**: e16152 [PMID: 31232970 DOI: 10.1097/MD.0000000000016152]

2 **Donaldson S**, Chundamala J, Yandow S, Wright JG. Treatment for unicameral bone cysts in long bones: an evidence based review. *Orthop Rev (Pavia)* 2010; **2**: e13 [PMID: 21808696 DOI: 10.4081/or.2010.e13]

3 **Deventer N**, Deventer N, Gosheger G, de Vaal M, Vogt B, Budny T. Current strategies for the treatment of solitary and aneurysmal bone cysts: A review of the literature. *J Bone Oncol* 2021; **30**: 100384 [PMID: 34367902 DOI: 10.1016/j.jbo.2021.100384]

4 **Zhang P**, Zhu N, Du L, Zheng J, Hu S, Xu B. Treatment of simple bone cysts of the humerus by intramedullary nailing and steroid injection. *BMC Musculoskelet Disord* 2020; **21**: 70 [PMID: 32019514 DOI: 10.1186/s12891-020-3054-6]

5 **Sung AD**, Anderson ME, Zurakowski D, Hornicek FJ, Gebhardt MC. Unicameral bone cyst: a retrospective study of three surgical treatments.

Clin Orthop Relat Res 2008; **466**: 2519-2526 [PMID: 18679761 DOI: 10.1007/s11999-008-0407-0]

6 **Ahn JI**, Park JS. Pathological fractures secondary to unicameral bone cysts. *Int Orthop* 1994; **18**: 20-22 [PMID: 8021063 DOI: 10.1007/BF00180173]

7 **Chuo CY**, Fu YC, Chien SH, Lin GT, Wang GJ. Management strategy for unicameral bone cyst. *Kaohsiung J Med Sci* 2003; **19**: 289-295 [PMID: 12873037 DOI: 10.1016/S1607-551X(09)70475-9]

8 **Erol B**, Onay T, Topkar OM, Tokyay A, Aydemir AN, Okay E. A comparative study for the treatment of simple bone cysts of the humerus: open curettage and bone grafting either without instrumentation or with intramedullary nailing. *J Pediatr Orthop B* 2017; **26**: 5-13 [PMID: 27341120 DOI: 10.1097/BPB.0000000000000353]

9 **Neer CS 2nd**, Francis KC, Marcove RC, Terz J, Carbonara PN. Treatment of unicameral bone cyst. A follow-up study of one hundred seventy-five cases. *J Bone Joint Surg Am* 1966; **48**: 731-745 [PMID: 15580740]

10 **Hou HY**, Wu K, Wang CT, Chang SM, Lin WH, Yang RS. Treatment of unicameral bone cyst: a comparative study of selected techniques. *J Bone Joint Surg Am* 2010; **92**: 855-862 [PMID: 20360508 DOI: 10.2106/JBJS.I.00607]

11 **Canavese F**, Samba A, Rousset M. Pathological fractures in children: Diagnosis and treatment options. *Orthop Traumatol Surg Res* 2016; **102**: S149-S159 [PMID: 26774903 DOI: 10.1016/j.otsr.2015.05.010]

12 **Stanton RP**, Abdel-Mota'al MM. Growth arrest resulting from unicameral bone cyst. *J Pediatr Orthop* 1998; **18**: 198-201 [PMID: 9531401]

13 **Gupta AK**, Crawford AH. Solitary bone cyst with epiphyseal involvement: confirmation with magnetic resonance imaging. A case report and review of the literature. *J Bone Joint Surg Am* 1996; **78**: 911-915 [PMID: 8666611]

14 **Ovadia D**, Ezra E, Segev E, Hayek S, Keret D, Wientroub S, Lokiec F. Epiphyseal involvement of simple bone cysts. *J Pediatr Orthop* 2003; **23**: 222-229 [PMID: 12604955]

15 **Cohen J**. Unicameral bone cysts. a current synthesis of reported cases. *Orthop Clin North Am* 1977; **8**: 715-736 [PMID: 335313]

16 **Violas P**, Salmeron F, Chapuis M, Sales de Gauzy J, Bracq H, Cahuzac JP. Simple bone cysts of the proximal humerus complicated with growth arrest. *Acta Orthop Belg* 2004; **70**: 166-170 [PMID: 15165020]

17 **Haims AH**, Desai P, Present D, Beltran J. Epiphyseal extension of a unicameral bone cyst. *Skeletal Radiol* 1997; **26**: 51-54 [PMID: 9040144 DOI: 10.1007/s002560050191]

18 **Reif TJ**, Matthias J, Fragomen AT, Rozbruch SR. Limb Length Discrepancy and Angular Deformity due to Benign Bone Tumors and Tumor-like Lesions. *J Am Acad Orthop Surg Glob Res Rev* 2021; **5** [PMID: 33720060 DOI: 10.5435/JAAOSGlobal-D-20-00214]

19 **Lee FY**, Schoeb JS, Yu J, Christiansen BD, Dick HM. Operative lengthening of the humerus: indications, benefits, and complications. *J Pediatr Orthop* 2005; **25**: 613-616 [PMID: 16199941 DOI: 10.1097/01.bpo.0000164868.97060.bb]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2024 February 26; 12(6): 1138-1143

DOI: 10.12998/wjcc.v12.i6.1138

ISSN 2307-8960 (online)

CASE REPORT

Postoperative abdominal herpes zoster complicated by intestinal obstruction: A case report

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bortolotti M, Italy; Valek V, Czech Republic

Received: October 7, 2023
Peer-review started: October 7, 2023
First decision: December 8, 2023
Revised: January 6, 2024
Accepted: January 29, 2024
Article in press: January 29, 2024
Published online: February 26, 2024

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Abstract

BACKGROUND

Intestinal obstruction is a common occurrence in clinical practice. However, the occurrence of herpes zoster complicated by intestinal obstruction after abdominal surgery is exceedingly rare. In the diagnostic and treatment process, clinicians consider it crucial to identify the primary causes of its occurrence to ensure effective treatment and avoiding misdiagnosis.

CASE SUMMARY

Herein, we present the case of a 40-year-old female patient with intestinal obstruction who underwent laparoscopic appendectomy and developed herpes zoster after surgery. Combining the patient's clinical manifestations and relevant laboratory tests, it was suggested that the varicella zoster virus reactivated during the latent period after abdominal surgery, causing herpes zoster. Subsequently, the herpes virus invaded the visceral nerve fibers, causing gastrointestinal dysfunction and loss of intestinal peristalsis, which eventually led to intestinal obstruction. The patient was successfully treated through conservative treatment and antiviral therapy and subsequently discharged from the hospital.

CONCLUSION

Pseudo-intestinal obstruction secondary to herpes zoster infection is difficult to distinguish from mechanical intestinal obstruction owing to various causes. In cases of inexplicable intestinal obstructions, considering the possibility of a viral

infection is essential to minimize misdiagnosis and missed diagnoses.

Key Words: Herpes zoster; Pseudo-intestinal obstruction; Ogilvie syndrome; Peripheral motor neuropathy; Case report

Core Tip: Herpes zoster may induce a rare pseudo-obstruction of the small intestine in addition to pseudo-obstruction of the colon. We highlight an extremely rare case of a patient with small bowel pseudo-obstruction caused by herpes zoster after abdominal surgery. More unusual, this patient presented with intestinal symptoms after the onset of rash. In cases of inexplicable intestinal obstructions, considering the possibility of a viral infection is essential to minimize misdiagnosis and missed diagnosis.

Citation: Dong ZY, Shi RX, Song XB, Du MY, Wang JJ. Postoperative abdominal herpes zoster complicated by intestinal obstruction: A case report. *World J Clin Cases* 2024; 12(6): 1138-1143
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1138.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1138

INTRODUCTION

The occurrence of herpes zoster in the abdomen causing gastrointestinal symptoms is extremely rare. Herpes zoster complicated by pseudo-intestinal obstruction, primarily manifests as acute colonic obstruction (known as the Ogilvie syndrome). In addition to pseudo-obstruction of the colon, herpes zoster can induce a rare pseudo-obstruction of the small intestine[1-3]. Previous reports have suggested that herpes zoster induces acute pseudocolonic obstruction in patients who had undergone abdominal surgery, presenting bowel obstruction as the initial manifestation[4]. In most cases, pseudo-intestinal obstruction develops days to weeks before a rash appears[1]. In this case report, we highlight an extremely rare case of a patient with small bowel pseudo-obstruction, induced by herpes zoster after abdominal surgery. Remarkably, this patient presented with intestinal symptoms later than the onset of rash.

CASE PRESENTATION

Chief complaints

Skin rash on the right lower abdomen for 3 d and, abdominal pain with bloating for 1 d.

History of present illness

A 40-year-old female patient underwent a laparoscopic appendectomy at Baotou Central Hospital in April 2022. By day 2 after abdominal surgery, the patient transitioned to her regular diet and was successfully discharged from the hospital. On day 4, the patient developed clusters of erythematous rashes in the right lower abdomen, causing itching and pain at the site of the rash, along with intermittent radiating pain in the bilateral iliolumbar region. On the day 7, the patient experienced abdominal pain localized to the center of the abdomen, accompanied by nausea, vomiting, abdominal distension, and cessation of exhaust, with passage of only a small amount of stools. The abdominal pain later increased paroxysmally and persisted without relief, leading the patient to seek further treatment at Baotou Central Hospital.

History of past illness

The patient had been vaccinated against varicella in early childhood and experienced a varicella infection for the first time in 2017. The patient underwent laparoscopic appendectomy at Baotou Central Hospital in April 2022 and was in close contact with a patient who developed herpes zoster after abdominal surgery.

Personal and family history

The patient denied any family history of malignant tumors.

Physical examination

After admission to the hospital, the patient's temperature was 37.1 ºC. Physical examination revealed clusters of red rashes in the right lower abdomen (Figure 1), tenderness in the middle and lower abdomen, and active bowel sounds.

Laboratory examination

Laboratory examination revealed an elevated white blood cell count (11.28 × 10^9 cells /L), neutrophil ratio (86.40%), and erythrocyte sedimentation rate (50 mm/h).

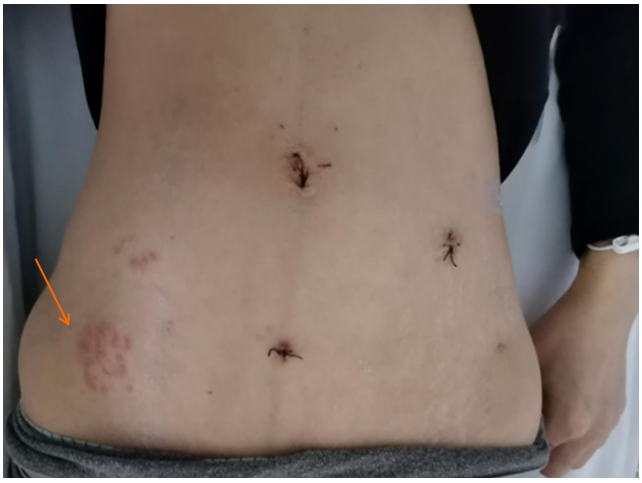

Figure 1 Clusters of red rashes. Clusters of red rashes can be seen on the patient's right lower abdomen (as shown by the arrow).

Imaging examination

Abdominal ultrasonography revealed the presence of fluid inside the abdominal cavity. An upright abdominal plain radiograph indicated gas accumulation and scattered fluid levels in the abdominal intestine, suggesting intestinal obstruction (Figure 2). Whole-abdominal computed tomography confirmed considerable dilation and fluid accumulation in the abdominal and pelvic bowel, supporting the diagnosis (Figure 3A). Furthermore, it revealed fluid accumulation in the abdominal and pelvic cavities (Figures 3B-D). Additionally, at the coronal level, we could observe the position of the hem-lock clamp used during the patient's previous laparoscopic appendectomy (Figure 4).

FINAL DIAGNOSIS

Herpes zoster complicated by small bowel pseudo-obstruction was diagnosed.

TREATMENT

The patient was treated with conservative management, including fasting on water, gastrointestinal decompression, enema and defecation, and fluid replenishment, along with antiviral therapy.

OUTCOME AND FOLLOW-UP

Over the next 5 d, the patient's abdominal pain and distension gradually subsided, with a concurrent reduction in the extent of the herpes zoster. At the follow-up visit after 15 d, the abdominal herpes zoster had completely disappeared and the patient recovered successfully. The patient remained symptom-free throughout the 1-year follow-up period.

DISCUSSION

Primary varicella zoster virus (VZV) infection results in varicella, which usually occurs in early childhood and causes a diffuse rash and viremia. The virus then establishes lifelong latency in the neurons of the dorsal-root, cranial-nerve, and enteric nervous system (ENS) ganglia[5]. Reactivation of VZV reactivates from latency is observed in approximately 30% of individuals, leading to a secondary cutaneous herpes zoster. Predisposing factors for VZV reactivation from latency include old age, stress, malnutrition, menstruation, and immunosuppression associated with malignancy, post-transplantation, and chemotherapy[6]. Herpes zoster is characterized by clustered blisters distributed along the peripheral nerves on one side of the body, accompanied by significant neuralgia[7]. Infection with herpes zoster virus causes a series of complications, including acute pain syndrome and postherpetic neuralgia. Peripheral motor neuropathy is an uncommon complication (2.5%–9.4%), affecting approximately 15% of the general population[8]. They can be somatic or visceral[9]. Depending on the level of the lesion, peripheral neuropathy may manifest as segmental motor paralysis of the upper and lower limb muscles, trunk, bladder, intestine, or diaphragm, whereas visceral neuropathy may involve the bladder and cause cystitis and/or urinary retention[1].

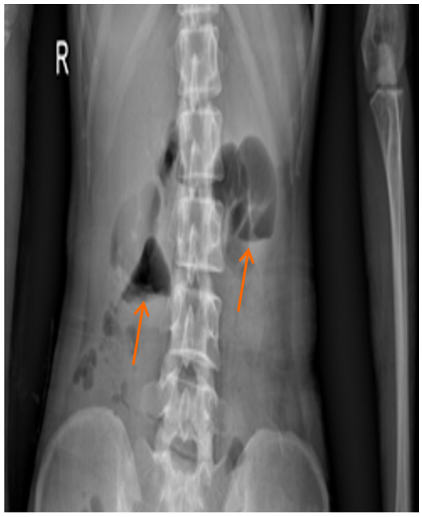

Figure 2 Abdominal upright plain film. Gas accumulation in the abdominal intestine, and scattered fluid levels are seen, indicating intestinal obstruction.

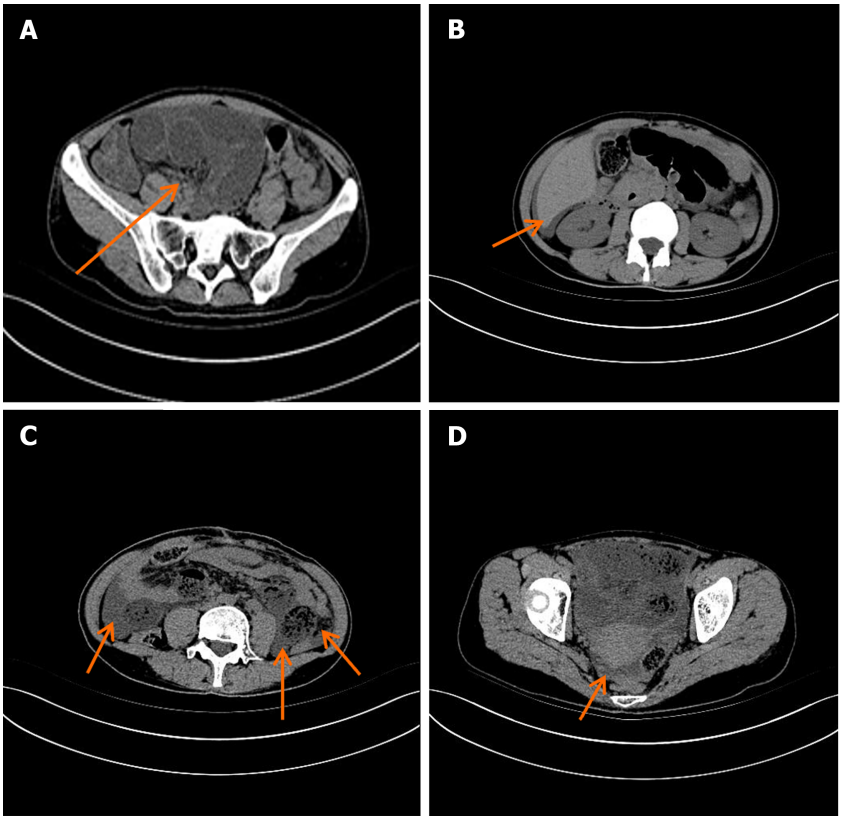

Figure 3 Representative whole-abdominal computed tomography images. A: Significant dilation and fluid accumulation of the bowel; B: An arc-shaped hypodense shadow under the capsule of the liver at the point indicated by the arrow; C: Fluid accumulation in abdominal cavity by the arrow; D: Fluid accumulation in pelvic cavity by the arrow.

Cases of herpes zoster causing gastrointestinal symptoms in the abdomen are extremely rare, with colonic pseudo-obstruction considered the most common gastrointestinal complication[1]. In Ogilvie syndrome, the typical radiographic findings include marked dilatation of the cecum, ascending colon, and transverse colon[10]. Ogilvie syndrome, a special type of visceral herpes zoster, is a motor dysfunction caused by intestinal muscle neuropathy and is believed to occur when, owing to low immunity, VZV invades the visceral nerve fibers of the sympathetic and parasympathetic nerves, resulting in edema and inflammation of the motor nerve fibers[11]. Although it can occur at any age, it generally affects adults over 60 years of age. Common ganglion distribution is mainly concentrated at T10–T12 and L1-L4[12]. Small bowel pseudo-obstruction caused by herpes zoster is thought to share a similar mechanism with colonic pseudo-obstruction[2]. The herpes zoster virus stimulates sympathetic nerves, inhibits small intestinal peristalsis, and damages the myenteric plexus and muscularis propria[1,3].

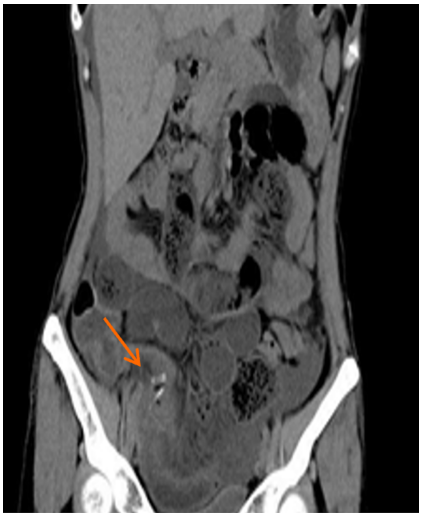

Figure 4 Representative coronal plane whole-abdominal computed tomography image. The position of the Hem-Lock clamp during the patient's previous laparoscopic appendectomy.

VZV reaches the ENS through two potential mechanisms: transportation by peripheral T-lymphocytes and retrograde axonal transport from dorsal-root ganglion neurons infected through their epidermal projections[13]. Regardless of the triggering factors, VZV reactivation is likely to have the same effect on the ENS neurons[11]. Various theories on the pathogenesis of zoster-related gut obstruction are: (1) Parietal and visceral peritoneal inflammation; (2) extrinsic autonomic nervous system viral involvement; (3) direct VZV injury of both the enteric submucosal and myenteric plexus, as well as the muscularis propria; (4) possible hemorrhagic infarction of the abdominal sympathetic ganglia; (5) viral interruption of afferent C-fibers that cause intestinal hypomotility and subsequent pseudo-obstruction; and (6) viral injury of the thoracolumbar or sacral lateral columns resulting in disruption of parasympathetic nerves and subsequent intestinal hypomotility[1,2,11,12].

The best initial treatment for Ogilvie syndrome caused by herpes zoster is conservative management, which is successful in approximately 75% of patients. In cases where conservative treatment fails or the caecum is considerably dilated (> 12 cm), alternative treatments, including medical therapy, endoscopic decompression, or surgery, are considered[14]. For small bowel pseudo-obstruction, given the sympathetic innervation of the small bowel occurring through the T9 and T10 branches, epidural catheter insertion from the T9–T10 branches and local anesthetics administration can effectively block the sympathetic nerves, thereby shortening the treatment course and preventing severe complications requiring surgical intervention (*i.e.* intestinal necrosis and perforation)[2,15].

This reported case of pseudo small bowel obstruction due to herpes zoster after laparoscopic appendectomy is exceptionally rare. In particular, the onset of intestinal symptoms occurring later than the appearance of rash is an extremely rare pattern. However, current reports on pseudo-intestinal obstruction secondary to herpes zoster infection, both nationally and internationally, show that cutaneous herpes zoster occurs within a few days or weeks after intestinal involvement[6]. In this case, we considered that the patient had just undergone abdominal surgery and had close contact with herpes zoster virus-infected patients after the surgery, which had led to the reactivation of the VZV in the latent period. In our patient, herpes zoster was detected in the right lower abdomen. The virus is thought to invade the visceral nerve fibers and caused gastrointestinal dysfunction, resulting in intestinal obstruction due to the loss of intestinal motility. In addition, the patient in this case was a middle-aged woman, younger than the typical patient with pseudo-obstruction, who had an atypical location of the small bowel; therefore, several underlying causes for the intestinal obstruction is possible. Postoperative small bowel obstruction is a common complication of appendectomy. Women, in particular, have a higher risk of small bowel obstruction after appendectomy[16]. Additionally, occult etiologies causing small bowel obstruction, such as subclinical pelvic inflammatory pelvic disease, endometriosis, or inflammation of the adnexa, may also be misdiagnosed as adhesive small bowel obstruction.

CONCLUSION

In conclusion, herpes zoster complicated by pseudointestinal obstruction after abdominal surgery is rare. The clinical presentation of pseudo-intestinal obstruction secondary to herpes zoster infection is difficult to distinguish from that of mechanical intestinal obstruction due to other causes. For some inexplicable intestinal obstructions, considering the possibility of a viral infection is essential to minimize misdiagnosis and missed diagnoses.

FOOTNOTES

Co-first authors: Zhen-Yu Dong and Rui-Xian Shi.

Author contributions: Dong ZY and Shi RX analyzed the data and wrote the manuscript; Dong ZY, Shi RX and Wang JJ designed the research study; Dong ZY, Shi RX and Du MY performed the research; Song XB contributed new reagents and analytic tools; Dong ZY and Shi RX contributed equally to this work as co-first authors; All authors have read and approve the final manuscript.

Informed consent statement: All study participants or their legal guardian provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors have no conflicting interests to report.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Ji-Jun Wang 0009-0007-1089-0448.

S-Editor: Zhang H
L-Editor: Filipodia
P-Editor: Cai YX

REFERENCES

1 **Anaya-Prado R**, Pérez-Navarro JV, Corona-Nakamura A, Anaya-Fernández MM, Anaya-Fernández R, Izaguirre-Pérez ME. Intestinal pseudo-obstruction caused by herpes zoster: Case report and pathophysiology. *World J Clin Cases* 2018; **6**: 132-138 [PMID: 29988868 DOI: 10.12998/wjcc.v6.i6.132]
2 **Lin YC**, Cui XG, Wu LZ, Zhou DQ, Zhou Q. Resolution of herpes zoster-induced small bowel pseudo-obstruction by epidural nerve block: A case report. *World J Clin Cases* 2022; **10**: 9873-9878 [PMID: 36186216 DOI: 10.12998/wjcc.v10.i27.9873]
3 **Pui JC**, Furth EE, Minda J, Montone KT. Demonstration of varicella zoster virus infection in the muscularis propria and myenteric plexi of the colon in an HIV-positive patient with herpes zoster and small bowel pseudo-obstruction (Ogilvie's syndrome). *Am J Gastroenterol* 2001; **96**: 1627-1630 [PMID: 11374712 DOI: 10.1111/j.1572-0241.2001.03808.x]
4 **Ma C**, Lv XP, Xia H and Song T. A case of acute colonic obstruction complicated by herpes zoster after abdominal surgery. *Zhonghua Putong Waike Xue Wenxian (Electron Ed)* 2015; **9**: 232-233 [DOI: 10.3877/cma.j.issn.1674-0793.2015.03.014]
5 **Alpay K**, Yandt M. Herpes zoster and Ogilvie's syndrome. *Dermatology* 1994; **189**: 312 [PMID: 7949493 DOI: 10.1159/000246870]
6 **Edelman DA**, Antaki F, Basson MD, Salwen WA, Gruber SA, Losanoff JE. Ogilvie syndrome and herpes zoster: case report and review of the literature. *J Emerg Med* 2010; **39**: 696-700 [PMID: 19327938 DOI: 10.1016/j.jemermed.2009.02.010]
7 **Schmader K**. Herpes Zoster. *Ann Intern Med* 2018; **169**: ITC19-ITC31 [PMID: 30083718 DOI: 10.7326/AITC201808070]
8 **Thomas JE**, Howard FM Jr. Segmental zoster paresis--a disease profile. *Neurology* 1972; **22**: 459-466 [PMID: 4673442 DOI: 10.1212/wnl.22.5.459]
9 **Maeda K**, Furukawa K, Sanada M, Kawai H, Yasuda H. Constipation and segmental abdominal paresis followed by herpes zoster. *Intern Med* 2007; **46**: 1487-1488 [PMID: 17827858 DOI: 10.2169/internalmedicine.46.0328]
10 **Haran C**, Kyngdon RJ. Herpes zoster: a rare cause of Ogilvie syndrome. *ANZ J Surg* 2021; **91**: E637-E639 [PMID: 33590666 DOI: 10.1111/ans.16667]
11 **Carrascosa MF**, Salcines-Caviedes JR, Román JG, Cano-Hoz M, Fernández-Ayala M, Casuso-Sáenz E, Abascal-Carrera I, Campo-Ruiz A, Martín MC, Díaz-Pérez A, González-Gutiérrez P, Aguado JM. Varicella-zoster virus (VZV) infection as a possible cause of Ogilvie's syndrome in an immunocompromised host. *J Clin Microbiol* 2014; **52**: 2718-2721 [PMID: 24808241 DOI: 10.1128/JCM.00379-14]
12 **Masood I**, Majid Z, Rind W, Zia A, Riaz H, Raza S. Herpes Zoster-Induced Ogilvie's Syndrome. *Case Rep Surg* 2015; **2015**: 563659 [PMID: 26664758 DOI: 10.1155/2015/563659]
13 **Chen JJ**, Gershon AA, Li Z, Cowles RA, Gershon MD. Varicella zoster virus (VZV) infects and establishes latency in enteric neurons. *J Neurovirol* 2011; **17**: 578-589 [PMID: 22190254 DOI: 10.1007/s13365-011-0070-1]
14 **Ben Ameur H**, Boujelbene S, Beyrouti MI. [Treatment of acute colonic pseudo-obstruction (Ogilvie's Syndrome). Systematic review]. *Tunis Med* 2013; **91**: 565-572 [PMID: 24281995]
15 **Ponec RJ**, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med* 1999; **341**: 137-141 [PMID: 10403850 DOI: 10.1056/NEJM199907153410301]
16 **Tseng CJ**, Sun DP, Lee IC, Weng SF, Chou CL. Factors Associated With Small Bowel Obstruction Following Appendectomy: A Population-Based Study. *Medicine (Baltimore)* 2016; **95**: e3541 [PMID: 27149462 DOI: 10.1097/MD.0000000000003541]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2024 February 26; 12(6): 1144-1149

DOI: 10.12998/wjcc.v12.i6.1144

ISSN 2307-8960 (online)

CASE REPORT

Clinical evolution of antisynthetase syndrome-associated interstitial lung disease after COVID-19 in a man with Klinefelter syndrome: A case report

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Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Freund O, Israel

Received: October 11, 2023
Peer-review started: October 11, 2023
First decision: December 5, 2023
Revised: December 13, 2023
Accepted: January 12, 2024
Article in press: January 12, 2024
Published online: February 26, 2024

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Abstract

BACKGROUND

This study presents a case of rapidly developing respiratory failure due to anti-synthetase syndrome (AS) following coronavirus disease 2019 (COVID-19) in a 33-year-old man diagnosed with Klinefelter syndrome (KS).

CASE SUMMARY

A 33-year-old man with a diagnosis of KS was admitted to the Department of Pulmonary and Critical Care Medicine of a tertiary hospital in China for fever and shortness of breath 2 wk after the onset of COVID-19. Computed tomography of both lungs revealed diffuse multiple patchy heightened shadows in both lungs, accompanied by signs of partial bronchial inflation. Metagenomic next-generation sequencing of the bronchoalveolar lavage fluid suggested absence of pathogen. A biopsy specimen revealed organizing pneumonia with alveolar septal thickening. Additionally, extensive auto-antibody tests showed strong positivity for anti-SSA, anti-SSB, anti-Jo-1, and anti-Ro-52. Following multidisciplinary discussions, the patient received a final diagnosis of AS, leading to rapidly progressing respiratory failure.

CONCLUSION

This study underscores the clinical progression of AS-associated interstitial lung disease subsequent to viral infections such as COVID-19 in patients diagnosed with KS.

Key Words: Antisynthetase syndrome; COVID-19; Klinefelter syndrome; Interstitial lung disease; Anti-Jo-1; Case report

Core Tip: Antisynthetase syndrome (AS) presents as an idiopathic inflammatory muscle disease typified by the presence of anti-Jo1 antibodies. Mainstream treatments encompass corticosteroids and immunosuppressants. Occasionally, certain rheumatic immune diseases can be precipitated by infectious diseases. Herein, we present a case detailing the rapid onset of respiratory failure due to AS subsequent to coronavirus disease 2019 (COVID-19) in an individual diagnosed with Klinefelter syndrome (KS). Following a multidisciplinary discussion, the conclusive diagnosis for the patient's rapid respiratory decline was AS. This investigation accentuates the clinical progression of AS-associated interstitial lung disease following viral infections such as COVID-19 in individuals with KS.

Citation: Wu XX, Cui J, Wang SY, Zhao TT, Yuan YF, Yang L, Zuo W, Liao WJ. Clinical evolution of antisynthetase syndrome-associated interstitial lung disease after COVID-19 in a man with Klinefelter syndrome: A case report. *World J Clin Cases* 2024; 12(6): 1144-1149

URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1144.htm

DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1144

INTRODUCTION

Since January 2023, reported cases of coronavirus disease 2019 (COVID-19) have notably surged in China. A large study revealed that more than 30% of patients with severe COVID-19 concurrently exhibit a second active clinical condition[1]. Although the impact of COVID-19 on individuals with rheumatic disorders has been partially evaluated, its influence on the progression of these diseases remains incompletely understood[2-4]. Antisynthetase syndrome (AS) is an idiopathic inflammatory muscle disease characterized by anti-Jo1 antibodies, showcasing diverse clinical presentations and a female-to-male sex bias[5]. Evidence from a review suggests a relatively robust association between Klinefelter syndrome (KS) and various rheumatic and autoimmune diseases, including AS and systemic lupus erythematosus[6]. To the best of our knowledge, this is the first reported clinical case of AS subsequent to COVID-19 in a male patient with KS.

CASE PRESENTATION

Chief complaints

A 33-year-old man was admitted to the Department of Pulmonary and Critical Care Medicine at a tertiary hospital located in China with a complaint of fever and shortness of breath for 2 d on June 30, 2023.

History of present illness

His symptoms commenced 2 d before admission, marked by fever and difficulty breathing. Upon arrival, the patient's condition required high-flow nasal cannula oxygen (HFNC) to maintain normal transcutaneous oxygen saturation.

History of past illness

His past medical history included KS and novel coronavirus pneumonia diagnosis. At the age of approximately 10-years-old, the patient had a confirmed diagnosis of KS in a tertiary children's hospital because of small external genitalia. Two weeks before the current hospitalization, the patient had fever and tested positive for COVID-19 by nucleic acid assay at a local county hospital. A chest computed tomography (CT) scan revealed a few patchy ground glass shadows outside the upper lungs. Following a 5-d oral paxlovid treatment and subsequent chest CT confirming lesion absorption, he was discharged, as detailed in the discharge record.

Personal and family history

The patient denied any family history related to malignant tumors, rheumatoid diseases, or immune conditions.

Physical examination

Upon admission, his initial vital signs were as follows: blood pressure, 100/80 mmHg; pulse rate, 130 beats per minute; respiratory rate, 40 breaths per minute; and body temperature, 38°C. He exhibited flushed cheeks, agitated nostrils, and shallow, rapid breathing, along with significant wet rales heard in both lungs. No other abnormalities were observed during physical examination.

Laboratory examinations

His laboratory findings indicated a red blood cell count of 3.94 × 10^{12}/L, white blood cell count of 2.95 × 10^{9}/L, lymphocyte count of 0.59 × 10^{9}/L, platelet count of 272 × 10^{9}/L, C-reactive protein level of 20.75 mg/L, albumin level of 29 g/L, creatine kinase level of 1150 U/L, and creatine kinase isoenzyme level of 36.8 U/L. These results revealed reduced white blood cell and lymphocyte counts, mildly elevated C-reactive protein, hypoproteinemia, and significantly increased muscle enzymes. Arterial blood gas analysis indicated type I respiratory failure with an oxygenation index of approximately 138. Procalcitonin, coagulation function, 1,3-β-D-glucan detection, and galactomannan antigen detection assays yielded normal results.

Imaging examinations

Lung CT examination revealed diffuse multiple patchy areas of increased shadows in both lungs, displaying a partial bronchial inflation sign (Figure 1).

Further diagnostic work-up

On the 2nd day, a bronchoscopy was conducted on suspicion of infectious pneumonia. The cells in the bronchoalveolar lavage fluid (BALF) were counted, showing a notably elevated ratio of neutrophils at 53%, lymphocytes at 15%, and eosinophils at 9%. Subsequently, microbial next-generation sequencing of BALF showed no detectable pathogens. On the 5th day, additional testing for autoimmune disease-related antibodies indicated strong positive results for anti-SSA, anti-SSB, anti-Jo-1, and anti-Ro-52. To prevent infection, the patient received cefoperazone and sulbactam. Moreover, a dosage of methylprednisolone (40 mg once daily) was initiated 6 d after hospitalization. Remarkably, the diffuse multiple patches of increased density in both upper lungs significantly diminished (Figure 2). To ascertain the nature of the diffuse multiple lesions in both lungs, a color ultrasound-guided percutaneous lung biopsy was performed on day 10 while the patient received HFNC oxygen from a mobile oxygen cylinder. The biopsy specimen obtained on day 14 revealed organizing pneumonia with alveolar septal thickening (Figure 3).

FINAL DIAGNOSIS

Following a comprehensive multidisciplinary team meeting (MDT) discussion, the patient had a final diagnosis of AS-associated interstitial lung disease (ILD).

TREATMENT

Subsequently, the patient underwent treatment with methylprednisolone at 500 mg paxlovid for 3 d, followed by a regimen of methylprednisolone at 80 mg paxlovid in conjunction with tacrolimus at 1 mg bid.

OUTCOME AND FOLLOW-UP

By day 30, the patient regained the ability to walk without requiring oxygen inhalation. A follow-up chest CT examination indicated substantial absorption of diffuse multiple consolidations in both lower lungs (Figure 4).

DISCUSSION

In this case study, we report a case of rapidly developing respiratory failure 2 wk after COVID-19 onset in a man with KS. A previous study revealed that all KS patients with COVID-19 experienced mild symptoms, suggesting that the presence of an extra X chromosome might contribute to a more favorable clinical outcome[7]. However, the patient with KS in this study encountered respiratory failure shortly after contracting COVID-19. To address this, we performed a color ultrasound-guided percutaneous lung puncture on the patient and conducted relevant autoimmune tests. Following multidisciplinary team (MDT) discussion, we made a diagnosis of AS alongside KS. Treatment with glucocorticoids and tacrolimus rapidly alleviated the respiratory failure. A 6-mo follow-up analysis indicated that following recovery, COVID-19 could trigger AS flares, leading to previously absent clinical manifestations[8].

AS is a rare autoimmune disease characterized by the presence of aminoacyl-transfer RNA synthetase antibodies, often accompanied by clinical manifestations such as ILD, myopathy, and nonerosive arthritis. AS occurs distinct from other inflammatory myopathies owing to its significant lung involvement and rapidly progressive ILD (AS-ILD). Hence, managing AS-ILD necessitates thorough clinical, serologic, and radiologic assessments[9]. While several scientific models aid in diagnosing AS, an MDT discussion is frequently valuable in confirming AS-ILD. Lung biopsies should be sparingly performed, as diagnosis primarily relies on high-resolution CT findings, patient symptoms, physical examination, serologic data, and pulmonary function testing[10]. Radiological examination results commonly include an interstitial pattern or ground glass lesions, with patients exhibiting organizing pneumonia generally experiencing a better prognosis[11].

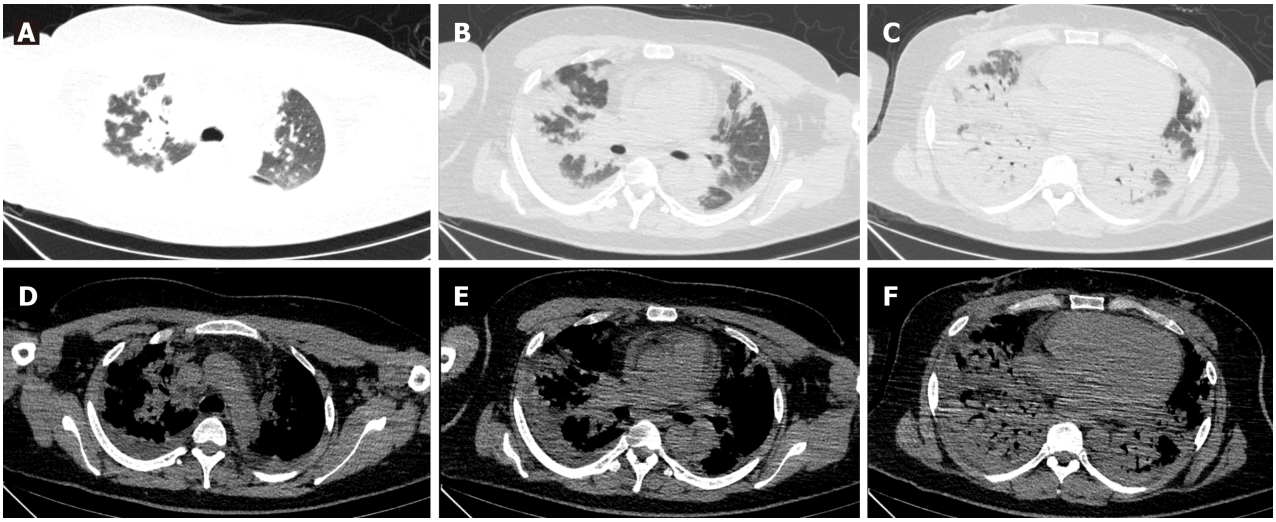

Figure 1 Lung computed tomography examination in admission. There were diffuse multiple patchy heightening shadows in both lungs, with a partial bronchial inflation sign. A: Both upper lungs in the lung window; B: Middle lobe and tongue lobe in the lung window; C: Both lower lungs in the lung window; D: Both upper lungs in the mediastinal window; E: Middle lobe and tongue lobe in the mediastinal window; F: Both lower lungs in the mediastinal window.

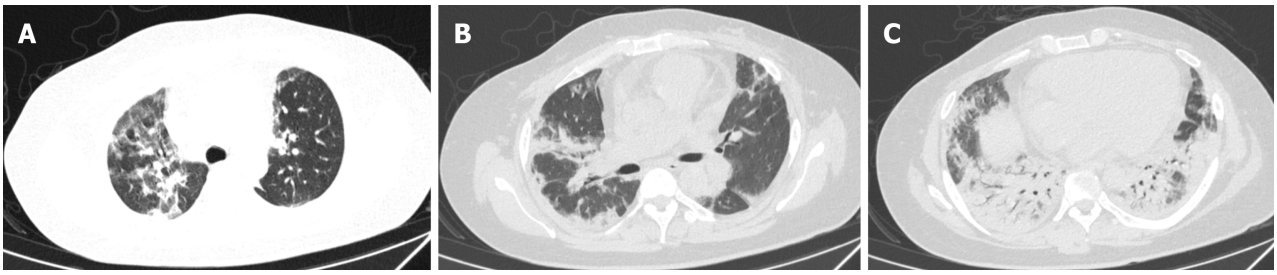

Figure 2 Lung computed tomography examination after methylprednisolone 40 mg paxlovid 6 d. Diffuse multiple patches of increased density in both upper lungs were significantly absorbed. A: Both upper lungs in the lung window; B: Middle lobe and tongue lobe in the lung window; C: Both lower lungs in the lung window.

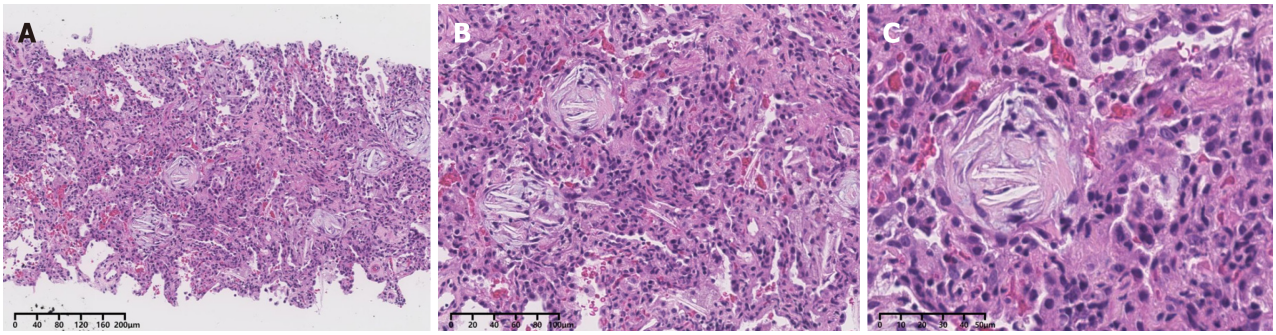

Figure 3 Color ultrasound-guided percutaneous lung puncture. Organizing pneumonia with alveolar septal thickening was found under the microscope (hematoxylin-eosin). A: Original magnification × 10; B: Original magnification × 20; C: Original magnification × 40.

Currently, there is no standardized treatment for AS-ILD because of the absence of randomized controlled trials. The selection of immunosuppression is usually consistent with treatment strategies adopted for ILD secondary to inflammatory myopathies. Treatment options encompass corticosteroids and immunosuppressants, with rituximab often reserved as salvage therapy for refractory cases[12]. Similarly, due to a lack of randomized controlled trials, there are no evidence-based medicine guidelines outlining a recommended corticosteroid treatment strategy. Based on our past clinical practice, we suggest initiating corticosteroid therapy by starting oral prednisone at 1 mg/kg/d. In patients with acute respiratory failure, higher doses of methylprednisolone (approximately 7.5 mg/kg for 3 d) may be required[10]. Although there is no specific method to reduce steroid dosages, we choose to gradually reduce the dosage within 6-8 wk to achieve a maintenance dose in our clinical practice.

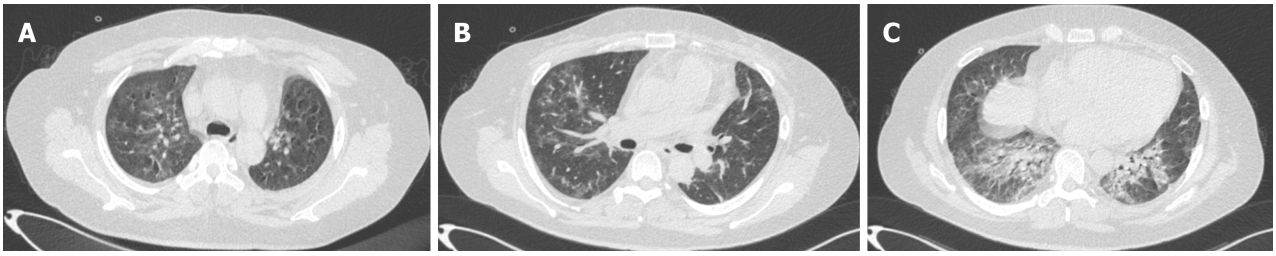

Figure 4 Lung computed tomography examination at 1 mo follow-up. Diffuse multiple consolidations in both lower lungs were significantly absorbed. A: Both upper lungs in the lung window; B: Middle lobe and tongue lobe in the lung window; C: Both lower lungs in the lung window.

While the prevalence of autoimmune diseases in KS remains unknown, it is believed that the estimated frequency is higher in men, nearly reaching the levels observed in women. This could be elucidated by several genes on the X chromosome that regulate immune system function and are associated with the escape of X inactivation during embryogenesis in the early development of KS[13]. To the best of our knowledge, this is the first reported clinical case of AS-associated ILD after COVID-19 in a male patient with KS.

CONCLUSION

In summary, we have described a rare clinical case of AS-associated ILD following COVID-19 in a male patient with KS in China. Clinicians should be cognizant of this rare clinical entity, and timely MDT discussions can significantly contribute to the diagnosis of AS in patients with KS, especially those facing potentially severe respiratory failure.

FOOTNOTES

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Co-corresponding authors: Wei Zuo and Wen-Jian Liao.

Author contributions: Wu XX and Cui J contributed equally to this manuscript; Wu XX and Cui J made substantial contributions to clinical data collection; Wang SY and Zhao TT contributed to the disease analysis; Yuan YF and Yang L drafted the manuscript; Zuo W and Liao WJ are the co-corresponding authors of this manuscript; Zuo W and Liao WJ critically revised the manuscript for literature review and edited it for clarity.

Supported by the Natural Science Foundation of Jiangxi Province, No. 20202BAB206002 and No. 20224BAB216084.

Informed consent statement: All study participants or their legal guardian provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

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S-Editor: Wang JJ
L-Editor: Filipodia
P-Editor: Xu ZH

REFERENCES

1 **Freund O**, Azolai L, Sror N, Zeeman I, Kozlovsky T, Greenberg SA, Epstein Weiss T, Bornstein G, Tchebiner JZ, Frydman S. Diagnostic delays among COVID-19 patients with a second concurrent diagnosis. *J Hosp Med* 2023; **18**: 321-328 [PMID: 36779316 DOI:

10.1002/jhm.13063]

2 **Bozzalla Cassione E**, Zanframundo G, Biglia A, Codullo V, Montecucco C, Cavagna L. COVID-19 infection in a northern-Italian cohort of systemic lupus erythematosus assessed by telemedicine. *Ann Rheum Dis* 2020; **79**: 1382-1383 [PMID: 32398281 DOI: 10.1136/annrheumdis-2020-217717]

3 **Monti S**, Balduzzi S, Delvino P, Bellis E, Quadrelli VS, Montecucco C. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. *Ann Rheum Dis* 2020; **79**: 667-668 [PMID: 32241793 DOI: 10.1136/annrheumdis-2020-217424]

4 **Ferri C**, Giuggioli D, Raimondo V, Dagna L, Riccieri V, Zanatta E, Guiducci S, Tavoni A, Foti R, Cuomo G, De Angelis R, Cozzi F, Murdaca G, Cavazzana I, Romeo N, Codullo V, Ingegnoli F, Pellegrini R, Varcasia G, Rossa AD, De Santis M, Abignano G, Colaci M, Caminiti M, L'Andolina M, Lubrano E, Spinella A, Lumetti F, De Luca G, Bellando-Randone S, Visalli E, Bilia S, Giannini D, Masini F, Pellegrino G, Pigatto E, Generali E, Dall'Ara F, Mariano GP, Barsotti S, Pettiti G, Zanframundo G, Brittelli R, Aiello V, Scorpiniti D, Ferrari T, Caminiti R, Campochiaro C, D'Angelo S, Iannone F, Matucci-Cerinic M, Doria A, Miccoli M, Fallahi P, Antonelli A; COVID-19 & Autoimmune Systemic Diseases Italian Study Group. COVID-19 and systemic sclerosis: clinicopathological implications from Italian nationwide survey study. *Lancet Rheumatol* 2021; **3**: e166-e168 [PMID: 33521657 DOI: 10.1016/S2665-9913(21)00007-2]

5 **Rovenský J**, Kovalancík M, Payer J, Kohler K. Klinefelter syndrome with antisynthetase syndrome: why might they be associated? *J Clin Rheumatol* 2003; **9**: 62-63 [PMID: 17041429 DOI: 10.1097/01.RHU.0000049718.58846.22]

6 **Rovenský J**, Imrich R, Lazúrová I, Payer J. Rheumatic diseases and Klinefelter's syndrome. *Ann N Y Acad Sci* 2010; **1193**: 1-9 [PMID: 20398000 DOI: 10.1111/j.1749-6632.2009.05292.x]

7 **Aliberti L**, Gagliardi I, Lupo S, Verrienti M, Bondanelli M, Zatelli MC, Ambrosio MR. Investigation of COVID-19 infection in subjects with Klinefelter syndrome. *J Endocrinol Invest* 2022; **45**: 1065-1069 [PMID: 35064538 DOI: 10.1007/s40618-021-01727-w]

8 **Vertui V**, Zanframundo G, Castañeda S, Biglia A, Palermo BL, Cavazzana I, Meloni F, Cavagna L. Clinical evolution of antisynthetase syndrome after SARS-CoV2 infection: a 6-month follow-up analysis. *Clin Rheumatol* 2022; **41**: 2601-2604 [PMID: 35612768 DOI: 10.1007/s10067-022-06216-w]

9 **Fu H**, Zheng Z, Zhang Z, Yang Y, Cui J, Wang Z, Xue J, Chi S, Cao M, Chen J. Prediction of progressive pulmonary fibrosis in patients with anti-synthetase syndrome-associated interstitial lung disease. *Clin Rheumatol* 2023; **42**: 1917-1929 [PMID: 36929316 DOI: 10.1007/s10067-023-06570-3]

10 **Sawal N**, Mukhopadhyay S, Rayancha S, Moore A, Garcha P, Kumar A, Kaul V. A narrative review of interstitial lung disease in anti-synthetase syndrome: a clinical approach. *J Thorac Dis* 2021; **13**: 5556-5571 [PMID: 34659821 DOI: 10.21037/jtd-20-3328]

11 **Zanframundo G**, Faghihi-Kashani S, Scirè CA, Bonella F, Corte TJ, Doyle TJ, Fiorentino D, Gonzalez-Gay MA, Hudson M, Kuwana M, Lundberg IE, Mammen A, McHugh N, Miller FW, Monteccucco C, Oddis CV, Rojas-Serrano J, Schmidt J, Selva-O'Callaghan A, Werth VP, Sakellariou G, Aggarwal R, Cavagna L. Defining anti-synthetase syndrome: a systematic literature review. *Clin Exp Rheumatol* 2022; **40**: 309-319 [PMID: 35225224 DOI: 10.55563/clinexprheumatol/8xj0b9]

12 **Witt LJ**, Curran JJ, Strek ME. The Diagnosis and Treatment of Antisynthetase Syndrome. *Clin Pulm Med* 2016; **23**: 218-226 [PMID: 27594777 DOI: 10.1097/CPM.0000000000000171]

13 **Kalayci Yigin A**, Alay MT, Uğurlu S, Seven M. The First Case Report of 47,XXY/46,XX/46,XY Mosaic Klinefelter Syndrome Patient With Mixed Connective Tissue Disorder. *Am J Mens Health* 2023; **17**: 15579883231165173 [PMID: 37131295 DOI: 10.1177/15579883231165173]

World Journal of Clinical Cases

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World J Clin Cases 2024 February 26; 12(6): 1150-1156

DOI: 10.12998/wjcc.v12.i6.1150

ISSN 2307-8960 (online)

CASE REPORT

Giant bile duct dilatation in newborn: A case report

Dong-Wen Quan, Peng-Gang Li, Xiang-Hua Xu, Shi-Qi Liu

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Varma V, India

Received: October 15, 2023
Peer-review started: October 15, 2023
First decision: December 15, 2023
Revised: December 26, 2023
Accepted: January 22, 2024
Article in press: January 22, 2024
Published online: February 26, 2024

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Abstract

BACKGROUND

Giant congenital biliary dilation (CBD) is a rare condition observed in clinical practice. Infants born with this condition often experience a poor overall health status, and the disease progresses rapidly, leading to severe biliary obstruction, infections, pressure exerted by the enlarged CBD on abdominal organs, disturbances in the internal environment, and multiple organ dysfunction. The treatment of giant CBD using laparoscopy is challenging due to the high degree of variation in the shape of the bile duct and other organs, making it difficult to separate the bile duct wall from adjacent tissues or to control bleeding.

CASE SUMMARY

Herein, we present the details of an 11-d-old male newborn who was diagnosed with giant CBD. The patient was admitted to the neonatal surgery department of our hospital due to a history of common bile duct cyst that was detected more than 3 mo ago, and also because the patient had been experiencing yellowish skin for the past 9 d. The abnormal echo in the fetal abdomen was first noticed by the patient's mother during a routine ultrasound examination at a local hospital, when the patient was at 24 wk + 6 d of pregnancy. This finding raised concerns about the possibility of congenital biliary dilatation (22 mm × 21 mm). Subsequent ultrasound examinations at different hospitals consistently confirmed the presence of a congenital biliary dilatation. No specific treatment was administered for biliary dilatation during this period. A computed tomography scan conducted during the hospitalization revealed a large cystic mass in the right upper quadrant and pelvis, measuring approximately 9.2 cm × 7.4 cm × 11.3 cm. Based on the

scan, it was classified as a type I biliary dilatation.

CONCLUSION
The analysis reveals that prenatal imaging techniques, such as ultrasound and magnetic resonance imaging, play a crucial role in the early diagnosis, fetal prognosis, and treatment plan for giant CBD. Laparoscopic surgery for giant CBD presents certain challenges, including difficulties in separating the cyst wall, anastomosis, and hemostasis, as well as severe biliary system infection and ulceration. Consequently, there is a high likelihood of converting to laparotomy. The choice between surgical methods like hepaticojejunostomy (HJ) or hepaticoduodenostomy has not been standardized yet. However, we have achieved favorable outcomes using HJ. Preoperative management of inflammation, biliary drainage, liver function protection, and supportive treatment are particularly vital in improving children's prognosis. After discharge, it is essential to conduct timely reexamination and close follow-up to identify potential complications.

Key Words: Acute cholangitis; Congenital biliary dilation; Laparoscopic surgery *vs* Open hepatic duct-jejunostomy; Case report

Core Tip: Clinically, giant congenital biliary dilation (CBD) is a rare condition compared to ordinary CBD. There are numerous research articles discussing surgical treatment options for common CBD. The choice of specific surgical method should be based on the individual circumstances of the hospital, the child, and the family members. In our case report, we present the experience of treating a very young child (11 d old) with a significantly dilated biliary tract. The overall condition of the child before the operation was critical. During laparoscopic biliary reconstruction, we encountered a thin and ulcerated cyst wall, making separation and bleeding control challenging. Therefore, we opted for an open laparotomy and performed a Roux-en-Y anastomosis between the common hepatic duct and jejunum. Taking into consideration the analysis of similar cases indexed in PubMed, we suggest that open surgery is more advantageous than laparoscopic treatment for children with giant CBD who are in critical condition and have severe biliary tract distortion.

Citation: Quan DW, Li PG, Xu XH, Liu SQ. Giant bile duct dilatation in newborn: A case report. *World J Clin Cases* 2024; 12(6): 1150-1156
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1150.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1150

INTRODUCTION

Congenital biliary dilation (CBD) is a common developmental malformation of the biliary system in newborns. It predominantly occurs in childhood, with a higher incidence in females and Asians compared to males and Caucasians[1, 2]. Advancements in prenatal diagnostic technologies, such as B-ultrasound and magnetic resonance imaging (MRI), have enabled the diagnosis of CBD in some children during the fetal period[3-6]. CBD is associated with numerous serious complications, necessitating early surgical intervention following a clear diagnosis[7]. In this report, we present a case of a newborn with giant CBD, characterized by a young age, a large cyst, and significant anatomical variations in abdominal organs. The surgical treatment of this case posed significant challenges. We provide a summary of the diagnosis and treatment experience with this baby and conduct a review of relevant literature.

CASE PRESENTATION

Chief complaints

An 11-d-old Chinese male infant with a weight of 2.84 kg was admitted to the neonatal surgery department of our hospital due to obvious abdominal distension, vomiting and jaundice for 9 d.

History of present illness

Abnormal abdominal echo was found for the first time during the routine ultrasound examination of the mother at the local hospital during pregnancy (24 wk + 6 d), suggesting that the possibility of congenital biliary dilatation (22 mm × 21 mm) is high, and it is recommended to refer to a higher-level hospital. During the period, ultrasound examinations in different hospitals revealed congenital dilation of the biliary tract, and no special treatment was performed. Cesarean section was performed at 37 wk + 5 d of pregnancy, with a birth weight of 3.05 kg. Nine days ago, the child's skin and sclera were found to be yellow-stained and he vomited yellow-white stomach contents 7 to 8 times a day which was accompanied by crying, no fever, and the defecation of yellow stool. Parents were referred to our hospital for further

treatment.

History of past illness
No other medical conditions have been identified in the past.

Personal and family history
The patient denied any family history of similar diseases and had no other special medical history.

Physical examination
On physical examination, the vital signs were as follows: Body temperature, 36.5 °C; blood pressure, 85/50 mmHg; heart rate, 108 beats per min; respiratory rate, 28 breaths per min. Furthermore, the skin and sclera exhibited jaundice throughout the body, accompanied by a palpable soft mass in the right upper quadrant.

Laboratory examinations
The abnormal laboratory test indicators observed after admission suggest that the child's overall condition is poor: Liver function: Total bilirubin: 300.0 μmol/L, direct bilirubin: 174.90 μmol/L, total protein: 62.3 g/L, aspartate aminotransferase: 77 U/L, serum alkaline phosphatase: 163 U/L, glutamyl transpeptidase: 473 U/L; electrolyte: Carbon dioxide (CO_2): 30.5 mmol/L, K^+: 6.08 mmol/L, Na^+: 110.2 mmol/L, Cl^-: 59.7 mmol/L, Ca^{2+}: 2.32 mmol/L; renal function: Urea: 16.69 mmol/L, Cr: 67 μmol/L, uric acid: 408 μmol/L, CO_2: 20.7 mmol/L; blood routine: White blood cells 26.70 × 10^9, neutrophils (NEUT): 15.58 × 10^9, percentage of NEUT: 58.3%; high-sensitivity C-reactive protein: 8.06 mg/L; blood ammonia: 90.00 μmol/L; routine urine and stool analysis showed no abnormalities.

Imaging examinations
Abdominal computed tomography (CT) examination conducted after admission revealed a large cystic mass located in the right upper quadrant and pelvis (Figure 1). The mass was identified as a type I biliary dilatation, with dimensions measuring approximately 9.2 cm × 7.4 cm × 11.3 cm. Prior to the surgery, contrast agent was injected through the choledochal cyst drainage tube and an X-ray was taken, which confirmed the presence of a significant cystic dilatation in the common bile duct, with visualization of a portion of the common hepatic duct (Figure 2).

FINAL DIAGNOSIS
Combined with the child's medical history, clinical manifestations, imaging and pathological examination results (Figure 3), the final diagnosis was CBD.

TREATMENT
Considering the child's initial poor general condition upon admission, immediate surgical treatment was not possible. Therefore, the child was initially provided with symptomatic and supportive treatment, including anti-infection measures, biliary drainage, electrolyte supplementation, coagulation factor supplementation, and albumin infusion. This treatment was continued for a duration of 15 d, and surgical treatment was subsequently performed once the child's basic condition had stabilized.

Surgical procedure: In the initial laparoscopic exploration, it was observed that the common bile duct was dilated and cystic, exhibiting severe edema and congestion in the cyst wall. Subsequently, the cyst was incised and decompressed, revealing multiple green ulcers tightly adhering to the cyst wall, which posed challenges in their separation. Notably, when attempting to separate the middle part of the posterior wall of the cyst, significant bleeding occurred, making the separation process difficult. As a result, the decision was made to convert the operation to open surgery.

We used Roux-en-Y anastomosis technique, the common bile duct and jejunum were connected. The jejunum was then cut off, with a 20 cm gap from the ligament of Treitz. The distal port was closed, while ensuring that there was no tension on the mesentery. The hepatic branch was lifted through the colon and joined end-to-side with the common bile duct. The anastomotic stoma had a width of 1.5 cm. The proximal port of the jejunum was anastomosed end-to-side with the biliary branch, 15 cm away from the anastomosis stoma of the common bile duct.

Following the placement of an abdominal drainage tube and confirming the absence of active bleeding and leakage, a small tissue sample was taken from the edge of the liver for biopsy. Electrocoagulation was performed to stop any bleeding, the abdominal cavity was closed, and the wound was bandaged. The operation was successfully completed.

OUTCOME AND FOLLOW-UP
The patient recovered well after surgery, and there were no recent complications such as wound infection, incisional hernia, massive bleeding, biliary fistula, pancreatic fistula, intestinal fistula, peritonitis, *etc*. After 6 mo of follow-up, no long-term complications such as adhesive intestinal obstruction, anastomotic stricture, cholangitis, pancreatitis, biliary

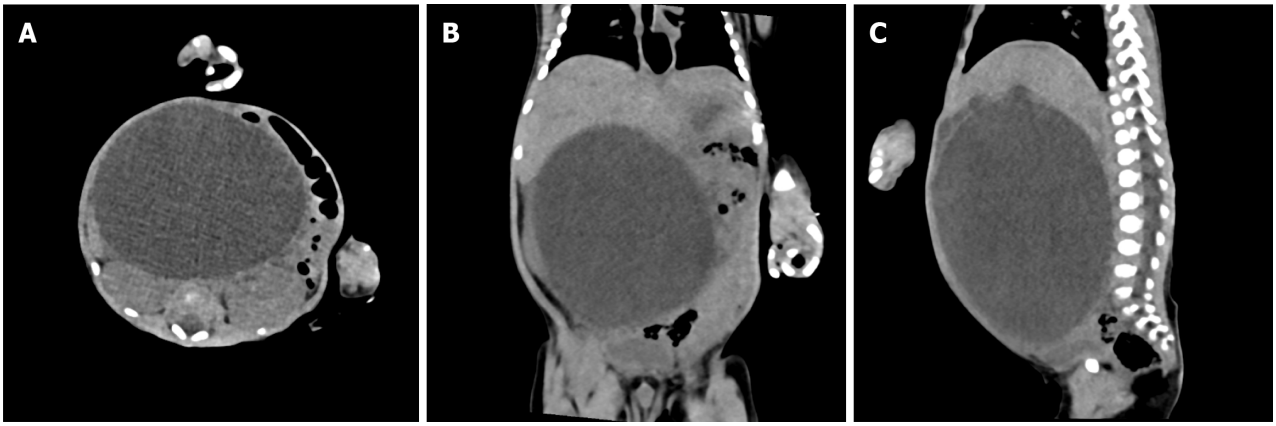

Figure 1 Preoperative computed tomography imaging of giant biliary dilation. A: Horizontal view; B: Coronal view; C: Sagittal view.

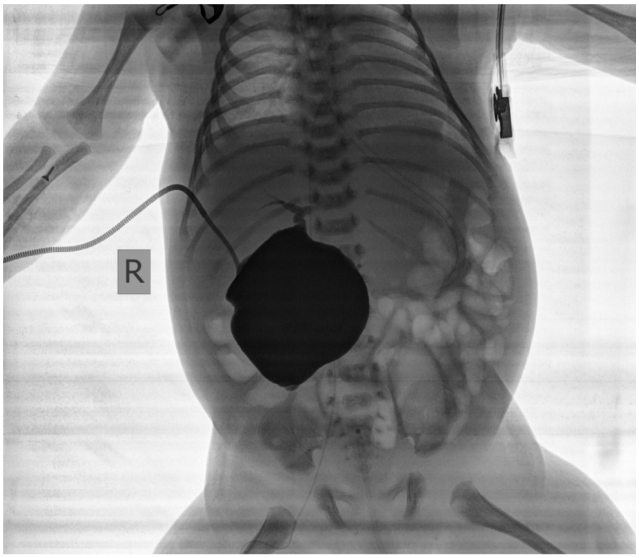

Figure 2 X-ray showed huge cystic dilation of the common bile duct and partial visualization of the common hepatic duct.

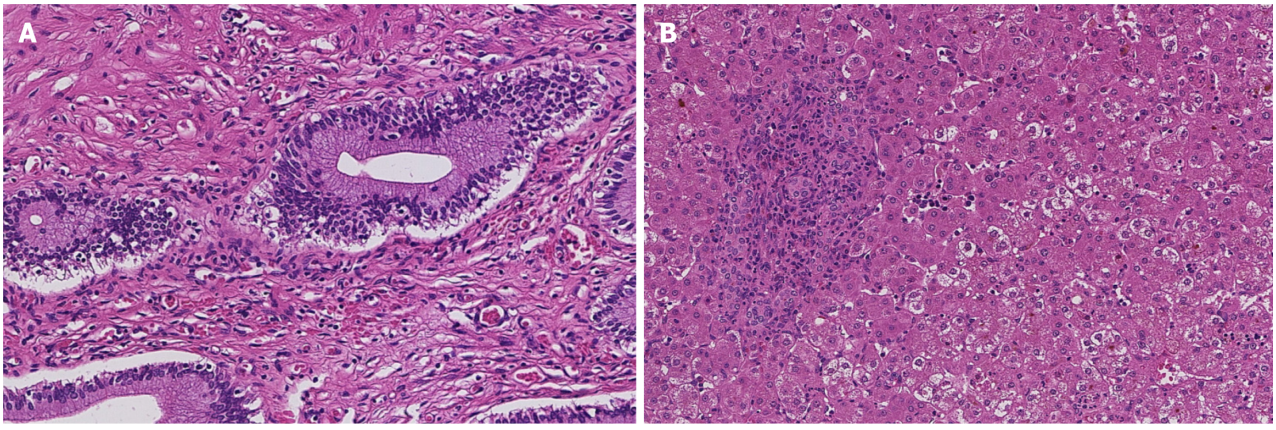

Figure 3 Pathological results of biliary tract tissue and liver tissue. A: Hematoxylin and eosin (HE) staining of bile duct (× 10), it is consistent with a choledochal cyst, with congestion in the cyst wall and scattered chronic inflammatory cell infiltration; B: HE staining of liver tissue (× 10), liver tissue pathology shows loose and light staining of the cytoplasm, mild to moderate inflammation in the lobules, moderate inflammation in the portal area, more acute and chronic inflammatory cell infiltration, and some sinks. Hyperplasia of small bile ducts and fibrous tissue in duct area.

stones, or reflux esophagitis were found.

DISCUSSION

The causes and mechanisms of CBD-related pathogenesis have not yet been fully elucidated. The prevailing view suggests that an abnormal pancreaticobiliary junction leads to reflux of pancreatic juice, resulting in damage to the bile duct, destruction of the bile duct intima, and fibrosis. These factors contribute to fetal biliary dilatation. Some scholars also propose that congenital biliary dysplasia caused by certain genetic factors is an important cause of CBD[8]. CBD is predominantly observed in infants and young children and may manifest as abdominal distension, jaundice, high fever, vomiting, pale stools, and impaired liver function. According to the Todani classification, CBD can be divided into types I to V, with type I being the most common clinically. At present, the surgical treatment methods with the largest number of reports in domestic and foreign literature are mainly laparoscopic hepaticojejunostomy and hepaticoduodenostomy. A few qualified centers have been able to complete the corresponding surgery with the assistance of robots. For some special cases, whether using laparoscopy or robot-assisted surgery, it is necessary to convert to laparotomy for treatment.

Prenatal imaging technologies such as ultrasound and MRI play an important role in the early diagnosis of fetal congenital malformations, fetal prognosis and treatment options. With the continuous development and application of ultrasound technology in routine prenatal examinations of pregnant women, the detection rate of CBD has gradually increased. The first suspicion of common bile duct dilatation in this child was discovered during a routine physical examination by his mother. When performing prenatal ultrasound examination, it is necessary to make a reasonable judgment based on the characteristics of ultrasound imaging, and pay attention to the differentiation from other congenital diseases of the fetal abdomen, such as liver cysts, biliary atresia, ovarian cysts, *etc*.

The prenatal imaging characteristics of CBD under ultrasound are mainly oval in shape, with a cystic ductal-like structure. They have a thin cyst wall and clear cyst fluid. The size of the cyst ranges from 1.4 to 3.0 cm and gradually increases with gestational age. There is no presence of blood, but there is an abundant blood flow around the cyst. Biliary atresia and CBD can be distinguished based on the presence of echo, the size of the echo, and whether the size of the echo increases over time. Small, anechoic cysts indicate biliary atresia, while if the cyst enlarges as the pregnancy progresses, it suggests dilation of the bile ducts[3-5]. According to Wu *et al*[6] the MRI imaging characteristics of CBD during the fetal period include the cyst being located above the lower edge of the liver and connected with the intrahepatic bile duct. The researchers also evaluated the daily growth rate of choledochal cysts from the fetal to preoperative time and observed that the length, width, and size of the cyst may increase over time. They argue that prenatal MRI has a higher diagnostic accuracy for CBD compared to ultrasound because MRI is superior in depicting the cyst's location and its relationship with the biliary tract[6].

After being diagnosed with CBD, it is recommended to perform surgery promptly in order to mitigate the negative impacts of the abnormal biliary tract in children. In the process of researching domestic and foreign literature on the diagnosis and treatment of CBD, it was found that the majority of articles are retrospective studies that investigate the effectiveness of conventional volume CBD reconstruction using various surgical techniques. These studies also examine the short-term and long-term complications associated with this approach. However, there is a limited number of case reports that specifically concentrate on neonatal giant CBD.

Yurttutan *et al*[9] reported a case study involving a child with a giant CBD, which bears some resemblance to the present case. The child in question was just 4 mo and 15 d of age, and the cyst height was measured to be over 16 cm, making it the largest volume recorded thus far. Prior to the surgery, ultrasound and CT scans were conducted as imaging examinations. The surgical approach employed was an abdominal common hepatic duct-jejunostomy Roux-en-Y anastomosis. The patient was discharged from the hospital 10 d after the operation. However, the article did not provide information regarding the incidence of postoperative complications or the mid- and long-term follow-up results in children[9]. The special features of our case reported in this article are as follows: (1) The child underwent surgery at the age of 28 d, which is younger than any other child with CBD reported so far; (2) In newborns who are only 11 d old, there is a huge bile duct with a height of 11 cm; and (3) The disease progressed rapidly within a short period after birth, causing significant compression of the intestines, spleen, and kidneys in the abdominal cavity. The child has the characteristics of young age, large cyst volume, acute onset, and critical condition. Based on the actual situation of the child, the reasons for conversion to laparotomy in this case were analyzed as follows: (1) The child had severe bile duct infection in the early stage, and the highest value of high-sensitivity C-reactive protein exceeded the normal range by more than 100 times, resulting in serious adhesion between the enlarged cystic wall and surrounding tissues which is not easy to separate under laparoscopy; (2) The cyst wall ulcer is seriously damaged, the cyst wall is thin, and it is difficult to anastomose under laparoscopy; (3) During the separation process under laparoscopy, bleeding cannot be effectively controlled; (4) The coagulation function is caused by hepatic insufficiency in children; (5) The volume of the cyst is giant (> 11 cm) occupying most of the abdominal cavity of the child; and (6) The child is young and the space in the abdominal cavity is limited, making the laparoscopic operation difficult. We consider that larger cysts in children may result in more significant distortion of the biliary system, thinner cyst walls, and increased compression of surrounding tissues and organs. Additionally, severe cholangitis can lead to adhesions, further complicating the laparoscopic biliary reconstruction procedure for giant choledochal cysts in children. Consequently, this operation becomes challenging and may require conversion to open surgery. Delayed surgery can further exacerbate the risk of liver fibrosis. Therefore, when cholangitis is resolved, early surgery should be performed as much as possible to avoid further fibrosis changes in the liver. In a retrospective analysis, Guzman *et al*[10] discovered a potential correlation between the size of bile duct dilatation and the likelihood of laparotomy. Their findings suggest that as the cyst size increases, there is a higher proportion

of cases requiring laparotomy. The largest reported cyst diameter in their study was 9 cm, which is smaller than the cyst diameter observed in our current case.

The key to successful surgical reconstruction of the biliary system in children with giant CBD lies in providing comprehensive supportive treatment for the children prior to surgery. It is particularly crucial to address inflammation, correct internal environment disorders, improve coagulation function, and ensure proper nutrition. The selection of the specific reconstruction method should be based on the patient's individual conditions and the expertise of different medical centers.

CONCLUSION

The disease progresses rapidly in children with giant CBD shortly after birth, and their overall condition is critical. Therefore, timely surgical treatment is necessary to improve the situation. Based on this case and the literature retrieved from PubMed, we recommend laparotomy as a treatment option due to its reliable efficacy and it being a relatively simple operation. Imaging examinations during the fetal period are also crucial for diagnosing and identifying CBD, enabling timely assessment and formulation of treatment plans.

ACKNOWLEDGEMENTS

Thanks to Professor Liu for his guidance and support in writing this article.

FOOTNOTES

Author contributions: Quan DW contributed to manuscript writing, editing and data collection; Xu XH and Liu SQ contributed to data analysis, conceptualization and supervision; Li PG contributed to translating and reviewing; All authors have read and approved the final manuscript.

Supported by National Natural Science Foundation of China, No. 82170676; Natural Science Foundation of Shaanxi Provincial Key Industries Innovation Chain (Cluster)-Social Development Project, No. 2020ZDLSF02-03; and Xi'an Talents Plan Project: Clinical Application of Minimally Invasive Treatment of Alimentary Tract Malformation in Children by Combining Medical and Industrial Innovative Technology of Magnetic Surgery, No. XAYC210064.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: All the authors report having no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

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S-Editor: Wang JJ
L-Editor: Filipodia
P-Editor: Zhao S

REFERENCES

1 **Urushihara N**, Fukumoto K, Yamoto M, Miyake H, Takahashi T, Nomura A, Sekioka A, Yamada Y, Nakaya K. Characteristics, management, and outcomes of congenital biliary dilatation in neonates and early infants: a 20-year, single-institution study. *J Hepatobiliary Pancreat Sci* 2018; **25**: 544-549 [PMID: 30328288 DOI: 10.1002/jhbp.590]

2 **Aly MYF**, Mori Y, Miyasaka Y, Ohtsuka T, Sadakari Y, Nakata K, Oda Y, Shimizu S, Nakamura M. Laparoscopic surgery for congenital biliary dilatation: a single-institution experience. *Surg Today* 2018; **48**: 44-50 [PMID: 28555266 DOI: 10.1007/s00595-017-1545-3]

3 **Shin HJ**, Yoon H, Han SJ, Ihn K, Koh H, Kwon JY, Lee MJ. Key imaging features for differentiating cystic biliary atresia from choledochal

cyst: prenatal ultrasonography and postnatal ultrasonography and MRI. *Ultrasonography* 2021; **40**: 301-311 [PMID: 33050687 DOI: 10.14366/usg.20061]

4 **Koukoura O**, Kelesidou V, Delianidou M, Athanasiadis A, Dagklis T. Prenatal sonographic diagnosis of biliary tract malformations. *J Clin Ultrasound* 2019; **47**: 292-297 [PMID: 30729537 DOI: 10.1002/jcu.22705]

5 **Weng R**, Hu W, Cai S, Guo X, Luo Q. Prenatal diagnosis and prognosis assessment of congenital choledochal cyst in 21 cases. *J Obstet Gynaecol* 2016; **36**: 324-327 [PMID: 26467207 DOI: 10.3109/01443615.2015.1050648]

6 **Wu H**, Tian J, Li H, Liu H, Liu Y, Lu L, Chen X, Zhang X, Xu W. Accuracy of Magnetic Resonance Imaging in Prenatal Diagnosis of Choledochal Cysts: A Single-Center Retrospective Analysis. *Int J Clin Pract* 2022; **2022**: 3268797 [PMID: 36238902 DOI: 10.1155/2022/3268797]

7 **Ai C**, Wu Y, Xie X, Wang Q, Xiang B. Roux-en-Y hepaticojejunostomy or hepaticoduodenostomy for biliary reconstruction after resection of congenital biliary dilatation: a systematic review and meta-analysis. *Surg Today* 2023; **53**: 1-11 [PMID: 35059844 DOI: 10.1007/s00595-021-02425-z]

8 **Liem NT**, Agrawal V, Aison DS. Laparoscopic management of choledochal cyst in children: Lessons learnt from low-middle income countries. *J Minim Access Surg* 2021; **17**: 279-286 [PMID: 32964871 DOI: 10.4103/jmas.JMAS_114_20]

9 **Yurttutan N**, Karakus SC, Koku N, Demirci M, Ucak R. A giant choledochal cyst in infancy: a case report. *Korean J Pediatr* 2016; **59**: 239-241 [PMID: 27279889 DOI: 10.3345/kjp.2016.59.5.239]

10 **Guzman JPS**, III LLR, Suntay MLR, Bernaldez RG. Comparison between hepaticojejunostomy and hepaticoduodenostomy after excision of choledochal cyst in children: a cohort study. *World J Pediatric Surg* 2019; **2**: e000029 [DOI: 10.1136/wjps-2018-000029]

World Journal of Clinical Cases

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World J Clin Cases 2024 February 26; 12(6): 1157-1162

DOI: 10.12998/wjcc.v12.i6.1157

ISSN 2307-8960 (online)

CASE REPORT

Left atrial appendage occluder detachment treated with transthoracic ultrasound combined with digital subtraction angiography guided catcher: A case report

Kai Yu, Yun-Hua Mei

Specialty type: Radiology, nuclear medicine and medical imaging

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Boffano P, Italy

Received: November 3, 2023
Peer-review started: November 3, 2023
First decision: January 5, 2024
Revised: January 11, 2024
Accepted: February 3, 2024
Article in press: February 3, 2024
Published online: February 26, 2024

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Abstract

BACKGROUND

There are very few cases of cardiac occluder detachment, and it is rare to completely remove the occluder using interventional methods without undergoing thoracotomy surgery after detachment. This case innovatively used ultrasound guidance combined with digital subtraction angiography (DSA) to completely remove the occluder, accumulating some experience.

CASE SUMMARY

The patient underwent left atrial appendage occlusion surgery in our hospital due to atrial fibrillation. After the surgery, the occluder fell off and became free in the left ventricle, which is very dangerous. We innovatively used ultrasound guidance, combined with DSA, and interventional surgery to successfully capture the free occluder using a catcher, completely remove it, and then re implant a new left atrial appendage occluder. After the surgery, the patient recovered very well.

CONCLUSION

The size selection of the occluder is slightly conservative, and the shape of the left atrial appendage opening is irregular.

Key Words: Left atrial appendage occluder; Detachment; Ultrasound combined with digital subtraction angiography; Interventional operation; Successfully captured; Case report

Core Tip: A case of successfully removing the detached left atrial appendage occluder using a catcher under the combined guidance of transthoracic ultrasound and digital subtraction angiography.

Citation: Yu K, Mei YH. Left atrial appendage occluder detachment treated with transthoracic ultrasound combined with digital subtraction angiography guided catcher: A case report. *World J Clin Cases* 2024; 12(6): 1157-1162
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1157.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1157

INTRODUCTION

Left atrial appendage occluder detachment is one of the most serious complications of left atrial appendage occlusion, but the incidence is low, and most treatment measures are removal after thoracotomy. In this case, we innovatively used ultrasound combined with digital subtraction angiography (DSA) guided percutaneous intervention surgery to successfully remove the detached occluder.

CASE PRESENTATION

Chief complaints

An 80-year-old man was admitted on September 1, 2023, two days after a sudden syncope.

History of present illness

The patient suddenly fainted and fell to the ground while standing up from the chair 9 days ago, with a facial landing and bleeding from a torn lip, accompanied by temporary loss of consciousness. After self relief, there was no obvious discomfort, no limb convulsions, no urinary and fecal incontinence, no foaming at the mouth, no headache or nausea and vomiting, and no palpitations or chest tightness before onset. Come to the emergency department of our hospital for treatment. The emergency blood pressure was measured at 98/56 mmHg, and the head computed tomography (CT) showed no bleeding and the electrocardiogram showed atrial fibrillation. Go home after being hospitalized in the neurology department for treatment. Now, in order to further treat heart disease, the patient has been readmitted to the cardiovascular department and diagnosed with coronary heart disease and atrial fibrillation.

History of past illness

Has a history of atrial fibrillation and medication is unknown. Have a history of gastric bleeding. Have a history of appendectomy.

Personal and family history

Long term alcohol consumption, approximately 100 mL/d. Deny any history of infectious diseases such as hepatitis and tuberculosis, no history of trauma, no history of food or drug allergies, and no family history of hereditary diseases.

Physical examination

T 36.4 ℃, P 72 bpm, R 18 bpm, BP 145/72 mmHg. Clear consciousness, cooperative physical examination, clear respiratory sounds in both lungs, no dry or wet rales heard, heart rate 76 beats per minute, arrhythmia, atrial fibrillation rhythm. The abdomen is flat and soft, without tenderness or rebound pain, the liver and spleen are not large. There is no edema in both lower limbs. The muscle strength and tension of the limbs are normal, and the pathological signs are negative. Bilateral tendon reflexes exist symmetrically, without obvious sensory impairment, with a soft neck without resistance, and negative Kniger and Brucella signs on both sides.

Laboratory examinations

Cardiac troponin I < 0.03 ng/mL; NT-proBNP: 4391.7 pg/mL.

Imaging examinations

After admission, a dynamic electrocardiogram showed: (1) Atrial fibrillation; (2) two hundred and thirty-seven premature ventricular contractions; and (3) four hundred and seventy-one long R-R intervals > 2.0 s, with a maximum of 3273 ms during the entire process.

Transthoracic echocardiography suggested: (1) Enlargement of the ascending aorta; (2) left atrial enlargement and right ventricular enlargement; (3) mild mitral regurgitation and moderate tricuspid regurgitation; and (4) arrhythmias.

FINAL DIAGNOSIS

(1) Cardiogenic syncope; and (2) persistent atrial fibrillation.

TREATMENT

Considering that the patient had a history of gastrointestinal bleeding and a high risk of stroke and bleeding, left atrial appendage closure surgery was planned after the team was able to communicate with the patient and his family members.

At 08:00 am on September 12, 2023, the surgery was performed under the guidance of DSA and transthoracic echocardiography. After a successful atrial septal puncture, the pigtail catheter was sent along the outer sheath to the left atrial appendage for an imaging examination (Figure 1A). The inner diameter and opening diameter of the left atrial appendage were measured, and LACbes 22 mm were configured *in vitro* according to the size of the patient's left atrial appendage × 32 mm of the occluded left atrial appendage. Under radiographic guidance, the occlusion was adjusted to the left atrial appendage, and with the assistance of RAOSO+CAU20 imaging, the occlusion umbrella was released. Radiography revealed that the occlusion umbrella was stable at the left atrial appendage opening, and the imaging showed that the left atrial appendage had been isolated from the left atrial blood flow (Figure 1B). A traction test was performed for another minute. RAOS0+CAU20 confirmed that the occlusion umbrella was firmly fixed, and there was no obvious leakage of contrast agent around the umbrella. The occlusion was, accordingly, considered satisfactory. Cardiac ultrasound examination showed that the occlusion umbrella was stably fixed at the opening of the left atrial appendage, and no blood flow signal was observed from the left atrial appendage or left atrium around the umbrella (Figure 1C), indicating successful occlusion of the left atrial appendage. Under radiographic guidance, the separation and delivery system, and the sealing umbrella were separated. Postoperatively, the patient's vital signs were stable, and the puncture point was ligated with sheath removal and pressure. The patient returned to the ward safely.

OUTCOME AND FOLLOW-UP

At 9:37 am on September 13, 2023, the patient visited the ultrasound imaging department for a follow-up cardiac ultrasound examination, which showed that the occluder had fallen off and was free in the left ventricle (Figure 2). CT confirmed this finding. After consultation with the superior hospital staff, the left atrial appendage occluder was removed and a left atrial appendage occlusion was performed at 18:35 on the same day. After a successful atrial septal puncture, a Medtronic 4FC12 adjustable sheath was inserted, followed by a 7F AL1 guide tube to the left ventricle along the adjustable bent sheath. The occluder grasping device was inserted along the guide tube, and the occluder was grasped under ultrasound guidance and X-ray fluoroscopy (Figure 3A). After successfully capturing the occluder, ice saline was injected along the adjustable curved sheath to soften the occluder (Figure 3B), and it was grabbed successfully by the sheath (Figure 3C and D). The occluder was successfully removed (Figure 3E), and the patient's vital signs were stable without any special discomfort reported. In this way, an in vitro configuration LACbes 26 mm × 32 mm left atrial appendage occlusion was performed. Under radiographic guidance, the occlusion umbrella was adjusted to the left atrial appendage, and with the assistance of RAOS0+CAU20 imaging, the occlusion was released. Radiography revealed that the occlusion was stable at the left atrial appendage opening, and the imaging showed that the left atrial appendage was isolated from the left atrial blood flow. A traction test was performed for another minute. RAOS0+CAU20 confirmed that the occlusion was fixed and there was no obvious leakage of contrast agent around the umbrella, indicating the satisfactory completion of the surgery.

After a cardiac ultrasound examination conducted immediately postoperatively, it was evident that the closure umbrella was stably fixed at the left atrial appendage opening. No blood flow signal was observed from the left atrial appendage or left atrium around the umbrella. There was a small amount of mitral regurgitation, a small amount of septal blood flow was observed in the middle of the atrial septum, and no fluid accumulation was obvious in the pericardial cavity, indicating successful closure of the left atrial appendage. Under radiographic guidance, the conveying system and sealing umbrella had been separated. Postoperatively, the patient's vital signs were stable, and the puncture point of the pressure package was removed. The patient returned to the ward safely.

The next morning, a follow-up cardiac ultrasound was performed, and the closure umbrella was stably fixed at the left atrial appendage opening (Figure 4A). Mild mitral regurgitation was observed, and a shunt signal with a width of approximately 4mm was observed at the atrial septal puncture site (Figure 4B).

DISCUSSION

The left atrial appendage is the most prone site for atrial thrombus formation during atrial fibrillation, and stroke is among the most common complications of atrial fibrillation[1]. This patient with atrial fibrillation had a history of gastric bleeding and was unwilling to receive long-term oral anticoagulant therapy. After a multidisciplinary consultation, and after hearing the opinions of the patient and his family, left atrial appendage closure surgery was performed. An unpredictable occluder detachment occurred postoperatively.

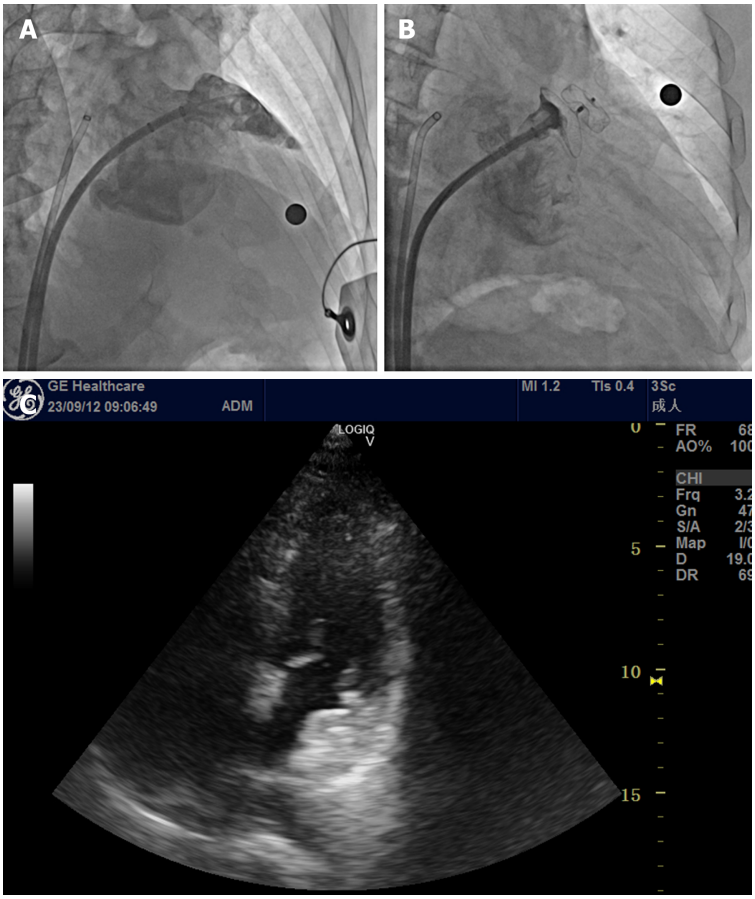

Figure 1 First surgery: Left atrial appendage occlusion. A: Left atrial appendage angiography before occlusion; B: Before the release of LACbes 22 mm × 32 mm occluder, no leakage of contrast agent was obvious around the umbrella during the imaging examination; C: Transthoracic echocardiography shows that the occluder is fixed to the opening of the left atrial appendage, and no blood flow signal is observed from the left atrial appendage or left atrium around the umbrella.

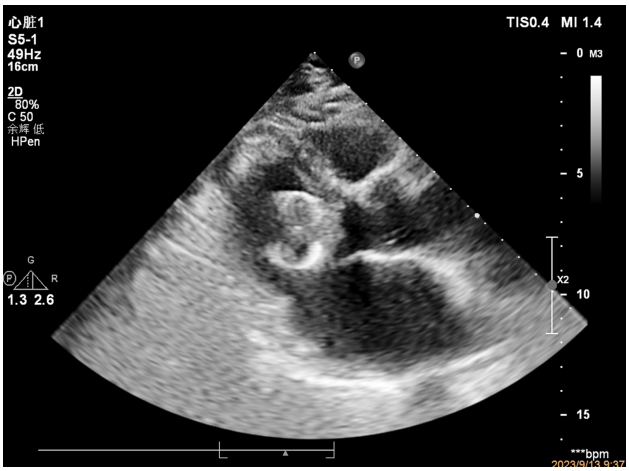

Figure 2 Occluder detachment and detachment into the left ventricle.

CONCLUSION

The detachment of occluders is among the most serious complications of left atrial appendage closure surgery, but the incidence is low. Not many cases have been reported at home and abroad[2], and most remedial measures are thoracotomy and removal. In this case, ultrasound combined with DSA-guided percutaneous intervention was used to successfully remove the detached occluder[3].

The method used is as follows: under ultrasound guidance, the occluder was clamped and fixed in the left ventricle using toothed forceps in the occluder, and ice saline was injected into the sheath to fully soften the occluder. After fully softening the occluder, it was pulled into the sheath as much as possible, and withdrawn through the mitral valve, left

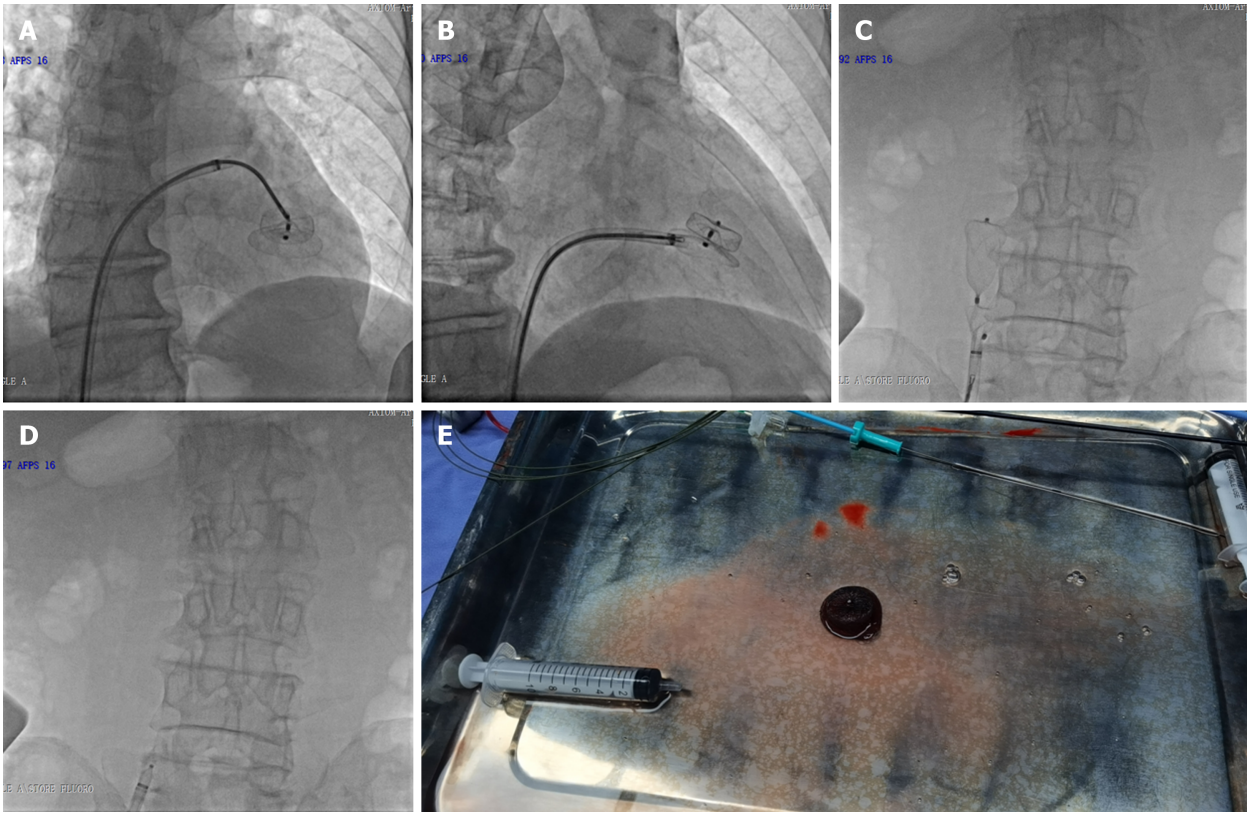

Figure 3 Second surgery. A: Catcher capture blocker; B: Successful capture of the occluder and injected ice salt water along the sheath to soften the occluder; C: Partial recovery of the occluder into the sheath and withdrawal from the sheath; D: Complete recovery of the occluder into the sheath; E: Successful removal of the occluder.

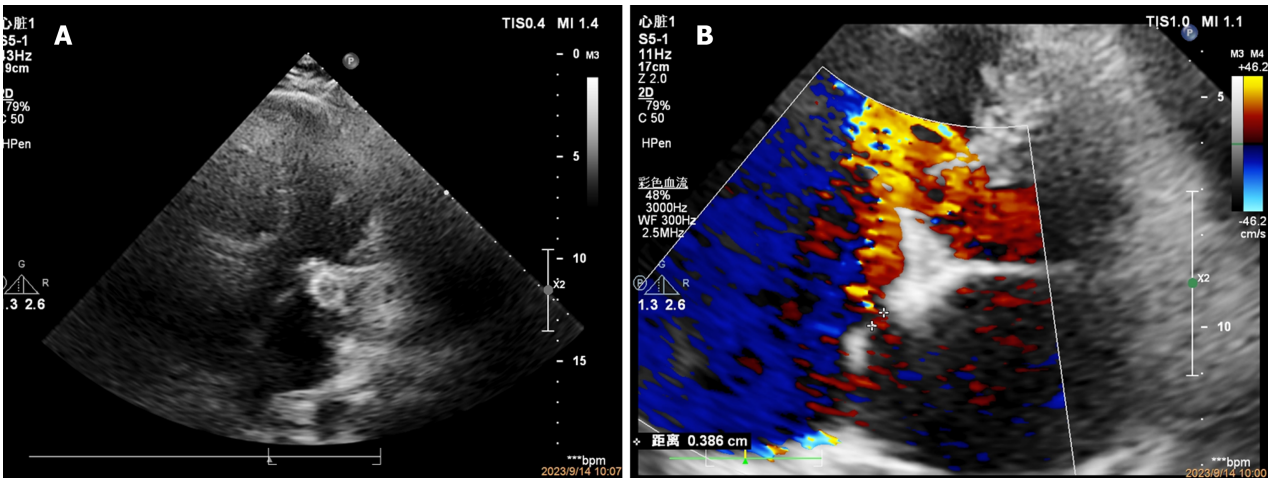

Figure 4 Transthoracic echocardiography. A: Transthoracic echocardiography shows the occluder located at the left atrial appendage opening; B: Transseptal blood flow at the puncture site of the atrial septum.

atrium, atrial septum, right atrium, and inferior vena cava.

The surgical approach is summarized as follows: (1) Fully softening the occluder with ice saline is the key step of the entire surgery; (2) transthoracic ultrasound combined with DSA guidance is an important means of quickly capturing the occlude; (3) during the process of grasping and capturing the occluder, toothed forceps should be selected, but physical damage to structures such as the valves, tendons, or myocardium, must be avoided; (4) it is necessary to immediately evaluate the mechanical damage to structures such as the mitral valve and atrial septum using ultrasound after removing the original sealing device; and (5) finally, the detachment of the occluder may be caused by the irregular shape of the left atrial appendage opening and the slightly conservative size selection of the occluder.

FOOTNOTES

Author contributions: Yu K designed this article; Yu K collected case data and images; Mei YH has played a significant role in literature retrieval work; Mei YH drafted the initial draft; Mei YH revised the manuscript based on the editor's comments; Yu K reviewed the manuscript and kept track of the progress.

Informed consent statement: The patient and their family have signed an informed consent form for treatment.

Conflict-of-interest statement: All authors have declared no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Liu JH
L-Editor: A
P-Editor: Cai YX

REFERENCES

1 **Chinese Society of Cardiology of Chinese Medical Association**; Editorial Board of Chinese Journal of Cardiology. [2019 Chinese Society of Cardiology (CSC) expert consensus statement on left atrial appendage closure in the prevention of stroke in patients with atrial fibrillation]. *Zhonghua Xin Xue Guan Bing Za Zhi* 2019; **47**: 937-955 [PMID: 31877589 DOI: 10.3760/cma.j.issn.0253-3758.2019.12.002]

2 **Fastner C**, Lehmann R, Behnes M, Sartorius B, Borggrefe M, Akin I. Veno-venous double lasso pull-and-push technique for transseptal retrieval of an embolized Watchman occluder. *Cardiovasc Revasc Med* 2016; **17**: 206-208 [PMID: 26916569 DOI: 10.1016/j.carrev.2016.01.006]

3 **Meng W**, Zheng Y, Ren Z, Yang H, Li S, Zhao D, Chen W, Zhu M, Liu W, Zhang Y, Xu Y. A case of left atrial appendage occluder detachment treated with double sheath tube combined with double foreign body forceps. *Zhonghua Xin Xue Guan Bing Za Zhi* 2022; **50**: 817-818 [DOI: 10.3760/cma.j.cn112148-20211007-00856]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2024 February 26; 12(6): 1163-1168

DOI: 10.12998/wjcc.v12.i6.1163

ISSN 2307-8960 (online)

CASE REPORT

Adult sigmoid intussusception resembling rectal prolapse: A case report

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Specialty type: Surgery

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Jackson T, United States; Mehrvarz S, Iran

Received: November 5, 2023
Peer-review started: November 5, 2023
First decision: December 15, 2023
Revised: December 25, 2023
Accepted: January 22, 2024
Article in press: January 22, 2024
Published online: February 26, 2024

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Abstract

BACKGROUND

Rectal prolapse arises from benign etiology. When symptoms of internal intussusception mirror those of rectal prolapse, a misdiagnosis is possible, especially under limited clinical presentation. It is crucial to recognize and differentiate rectal prolapse from internal intussusception because the two diagnoses have different prognoses. Here, we describe a case of adult sigmoid intussusception presenting as rectal prolapse.

CASE SUMMARY

A 64-year-old woman with no known medical history visited a gastrointestinal outpatient department due to hard bloody stool defecation for 1 wk followed by constipation for 3 d. Colonoscopy revealed a huge polypoid ulcerated tumor at the sigmoid colon with lumen stenosis. The patient was admitted due to post-procedural dull abdominal pain. Due to failed colonoscopy reduction and stent insertion, the patient underwent sigmoid colon resection with primary end-to-end anastomosis, with the transverse colostomy pathological report showing adenocarcinoma, pT3N0M0. She recovered well from the operation and was discharged with regular outpatient clinic follow-up.

CONCLUSION

Presentation and manifestation of sigmoid intussusception may resemble that of rectal prolapse, necessitating careful observation due to distinct prognostic implications.

Key Words: Sigmoid intussusception; Rectal prolapse; Endoscopic reduction; Adenocarcinoma; Case report

Core Tip: This case underscores the potential for sigmoid intussusception to bear a resemblance to rectal prolapse. These two diagnoses have distinct etiologies and treatment. Adults and children have different etiological factors. Sigmoid intussusception related to malignancy leads to an unfavorable outcome, whereas rectal prolapse has a better prognosis. A comprehensive literature review was conducted to elucidate the advantages and disadvantages of preoperative reduction.

Citation: Tsai TJ, Liu YS. Adult sigmoid intussusception resembling rectal prolapse: A case report. *World J Clin Cases* 2024; 12(6): 1163-1168
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1163.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1163

INTRODUCTION

Rectal prolapse occurs more frequently in elderly females, and a large rectal mass may not undergo spontaneous reduction. Symptoms of internal intussusception may bear a resemblance to rectal prolapse. In acute clinical scenarios, a paucity of the medical history may result in misdiagnosis. The prognosis of the two is different; so, recognition and differentiation are of the utmost importance. In this article, we describe a case of adult sigmoid intussusception presenting as rectal prolapse.

CASE PRESENTATION

Chief complaints

Hard bloody stool defecation for 1 wk followed by constipation for 3 d.

History of present illness

A 64-year-old woman visited a gastrointestinal outpatient department due to hard bloody stool defecation for 1 wk followed by constipation for 3 d. A digital examination diagnosed the patient with a second-degree hemorrhoid. Laxative medication was prescribed to aid constipation. However, constipation persisted, and she visited the outpatient department again 2 d later. Abdominal X-ray, abdominal computed tomography, and colonoscopy were arranged on the same day. Sigmoid cancer was suspected. One day after the examinations, she visited the emergency department for dull lower abdominal pain, bloody mucus, and obstipation.

History of past illness

There was no remarkable history of past illness.

Personal and family history

There was no personal or familial history of any specific disease.

Physical examination

The physical examination revealed tenderness in the lower quadrant of the abdomen. A digital rectal examination revealed rectal prolapse.

Laboratory examinations

Laboratory tests revealed a normal white blood cell count of 4100/μL (normal range: 4000-91000/μL), normal neutrophil level of 58.1% (normal range: 39.4%-72.6%), and normal hemoglobin of 11.4 g/dL (12-15 g/dL).

Imaging examinations

An abdominal X-ray showed fecal impaction in the colon. However, the colonoscope could not be advanced beyond about 15 cm from the anal verge. A huge polypoid ulcerated tumor with lumen stenosis was seen at the sigmoid colon, estimated to be 4 cm from the rectum (Figure 1). Abdominal computed tomography demonstrated sigmoid intussusception with inner irregular soft tissue (Figure 2).

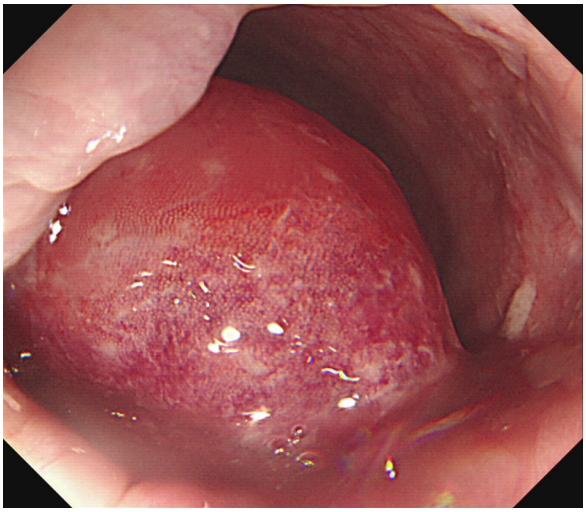

Figure 1 Colonoscopic images. A polypoid ulcerated tumor causing intestinal stenosis.

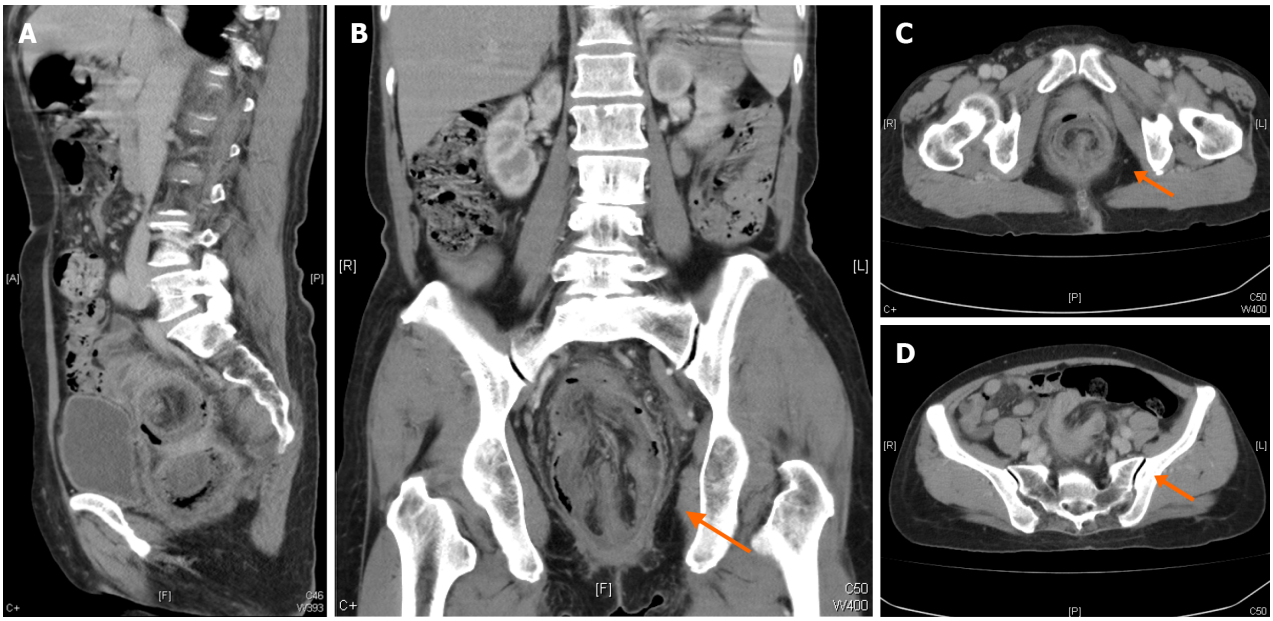

Figure 2 Computed tomography images. A and B: Coronal and sagittal abdominal computed tomography (CT) revealed sigmoid intussusception (arrow); C and D: Axial abdominal CT demonstrated target sign (arrow).

FINAL DIAGNOSIS

Sigmoid intussusception resembling rectal prolapse.

TREATMENT

After discussion with the patient and her family, we established their expressed preference for nonsurgical treatment. Hence, we attempted colonoscopic reduction with stent insertion 2 d after admission. Colonoscopy treatment failed; so, a surgical approach was taken. Laparotomy for sigmoid colectomy with primary anastomosis was carried out. Intraoperative reduction of the prolapsed intussusception was not achieved by either the manual method or rectum dilator (Courtesy of Covidien, Inc., Norwalk, CT, United States) due to tense sigmoid intussusception with sigmoid cancer (Figure 3A). Distal resection under manual check *via* digital examination followed by primary end-to-end anastomosis with a transverse colostomy was performed (Figure 3B).

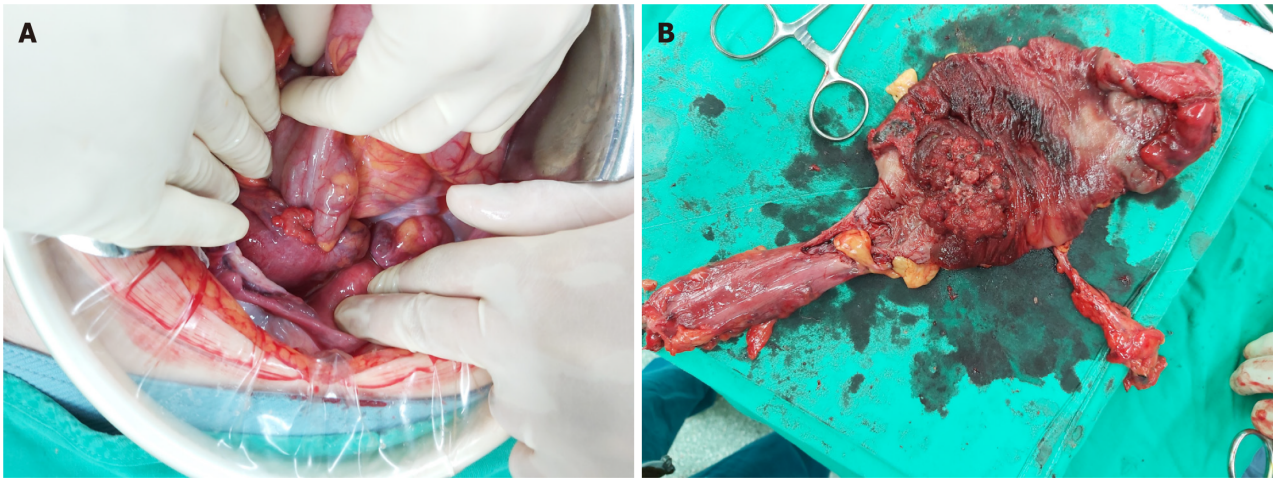

Figure 3 Perioperative images. A: Sigmoid intussusception; B: Ulcerated and ischemic change of sigmoid colon.

OUTCOME AND FOLLOW-UP

The patient recovered well post operation and was discharged on the 9th post-operative day. The pathology report confirmed a 5.1 cm adenocarcinoma, pT3NOMO, with KRAS Wild Type. The patient recovered and has returned to the outpatient clinic for close follow-up.

DISCUSSION

In comparison to its occurrence in children, adult intussusception is a rare condition. Pediatric intussusception is predominantly located in the small intestine, with 80%-90% of cases being idiopathic. By contrast, about half of adult intussusceptions occur in the large bowel, particularly in the right colon (70% of cases)[1]. Sigmoido-rectal intussusception is distinctly rare in the adult population.

Table 1[2-14] summarizes similar case reports that were published within the last 30 years. All cases involve sigmoid intussusception presenting as rectal prolapse. It is evident that sigmoido-rectal or sigmoido-anal intussusception are often misdiagnosed as rectal prolapse, especially when a detailed digital examination is not performed. Intussusception should be suspected after a tumor is observed. The classic triad of pediatric intussusception is paroxysmal abdominal pain, rectal bleeding, and abdominal palpable mass[15]. The symptoms of the classic triad are only observed in 9.8% of cases of adult intussusception. The clinical presentation of adult intussusception is nonspecific and chronic or subacute, presenting as intestinal obstruction (70.7%), abdominal pain (95.1%), bloody stool (26.8%), and a palpable abdominal mass (34.1%)[16, 17].

Diagnosis is crucial, and a colonoscopy or sigmoidoscopy can provide insight into the potential underlying causes and obtain a specimen for histology. Computed tomography is considered superior because it can pinpoint the location and reveal the cause of the obstruction. In malignancy cases, computed tomography images provide more details of lymph nodes and metastasis status.

Treatment for adult colo-colonic or sigmoido-rectal intussusception is controversial. Sarr *et al*[18] investigated preoperative reduction due to malignant seeding risk. However, preoperative reduction can mean avoidance of emergent surgery or lesion survey and reduce the extent of intestinal resection and radical surgery for cancer. Though most cases of intussusception are related to lesions, few are idiopathic. In a recent study, preoperative endoscopy reduction was found to be more advantageous than emergent surgery because of the simultaneous diagnosis and treatment[17]. Moreover, endoscopy can provide a direct evaluation of the mucosal surface to determine the severity, such as ischemia or total obstruction or special intussusception. Laparoscopic reduction is feasible in idiopathic intussusception in adults. Radical resection is a priority for malignant cause. Rectal prolapse usually has a benign etiology, whereas sigmoido-rectal intussusception is mostly related to tumors.

CONCLUSION

Sigmoid intussusception in adults is mostly related to malignancy. Clinicians should be more cautious in differentiating between sigmoid intussusception and rectal prolapse based on limited presentation and medical history.

Table 1 Cases about sigmoid intussusception presenting as rectal prolapse

Ref.	Sex	Site of intussusception	Histopathology	Symptom	Reduction	Surgery
Younes *et al*[2], 1998	F	Sigmoid	Lipoma	Rectal prolapse	Yes	Sigmoid colon resection, and rectopexy
Tony *et al*[3], 2007	F	Colo-colonic	Lipoma	Rectal prolapse	No	External surgical resection
Chen *et al*[4], 2008	M	Ileocolic	Lipoma	Abdominal pain, rectal prolapse	Yes	Subtotal colectomy
Ochiai *et al*[5], 2010	F	Sigmoid	Adenocarcinoma	Abdominal pain, rectal prolapse	Yes	Intraoperative reduction and low anterior resection
Teyha *et al*[6], 2011	M	Sigmoid	Idiopathic	Rectal prolapse	No	Sigmoid colon resection
Roy *et at*[7], 2011	F	Sigmoid	Idiopathic	Rectal prolapse	Yes	Partial resection of the sigmoid colon
Elliott *et al*[8], 2014	M	Sigmoid	Lipoma	Obstruction, rectal bleeding, rectal prolapse	Yes	Sigmoid colon resection
Mahmood *et al*[9], 2014	M	Colo-colonic	Villous adenoma	Rectal prolapse, obstruction	Yes	Intraoperative reduction and sigmoid colon resection
Du *et al*[10], 2015	F	Sigmoid-rectum	Tubulovillous adenoma	Obstruction, rectal bleeding, rectal prolapse	Yes	Total colectomy
West *et al*[11], 2019	F	Sigmoid	Polyp	Rectal prolapse, hematochezia	No	Enterotomy and polypectomy
Mazumdar *et al* [12], 2021	M	Sigmoid–rectum	Adenocarcinoma	Abdominal pain, rectal prolapse	No	Hartmann's procedure
West *et al*[13], 2022	F	Sigmoid	Lipoma	Rectal bleeding, rectal prolapse	No	Hartmann's procedure
Penton *et al*[14], 2023	M	Sigmoid	Adenocarcinoma	Rectal prolapse	Yes	Sigmoid colon resection

F: Female; M: Male.

FOOTNOTES

Author contributions: Liu YS contributed to the conceptualization, investigation and supervision; Tsai TJ contributed to the data curation, investigation, preparation of the manuscript, and editing; Both authors have read and approved the final manuscript.

Informed consent statement: Informed written consent was obtained from the patient for the publication of this report and all accompanying images.

Conflict-of-interest statement: The authors declare having no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised accordingly.

Country/Territory of origin: Taiwan

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S-Editor: Gong ZM
L-Editor: Filipodia
P-Editor: Zhao S

REFERENCES

1 **Lambrou NA**, Dunn WK, Robinson MH. Perineal resection of a sigmoid tumour presenting as colorectoanal intussusception: report of a case and review of the literature. *Int J Colorectal Dis* 2006; **21**: 286-287 [PMID: 15700152 DOI: 10.1007/s00384-004-0700-7]

2 **Younes ZH**, Johnson DA, Dimick L. Sigmoido-anal intussusception presenting as rectal prolapse: role of endoscopic diagnosis. *Gastrointest Endosc* 1998; **47**: 561-563 [PMID: 9647396 DOI: 10.1016/s0016-5107(98)70267-6]

3 **Tony J**, Saji S, Sandesh K, Sunilkumar K, Ramachandran TM, Thomas V. External resection of a giant sigmoid lipoma causing colonic intussusception and prolapse through the anal canal. *Trop Gastroenterol* 2007; **28**: 127-128 [PMID: 18384003]

4 **Chen R**, Zhao H, Sang X, Mao Y, Lu X, Yang Y. Severe adult ileosigmoid intussusception prolapsing from the rectum: A case report. *Cases J* 2008; **1**: 198 [PMID: 18826634 DOI: 10.1186/1757-1626-1-198]

5 **Ochiai H**, Ohishi T, Seki S, Tokuyama J, Osumi K, Urakami H, Shimada A, Matsui A, Isobe Y, Murata Y, Endo T, Ishii Y, Hasegawa H, Matsumoto S, Kitagawa Y. Prolapse of Intussusception through the Anus as a Result of Sigmoid Colon Cancer. *Case Rep Gastroenterol* 2010; **4**: 346-350 [PMID: 21060698 DOI: 10.1159/000320770]

6 **Teyha PS**, Chandika A, Kotecha VR. Prolapsed sigmoid intussusception per anus in an elderly man: a case report. *J Med Case Rep* 2011; **5**: 389 [PMID: 21849068 DOI: 10.1186/1752-1947-5-389]

7 **Roy J**, Gouda M, Reddy BS, Baker RP. Sigmoid intussusception presenting as rectal prolapse in an adult. *Colorectal Dis* 2011; **13**: e385 [PMID: 21689366 DOI: 10.1111/j.1463-1318.2011.02699.x]

8 **Elliott M**, Martin J, Mullan F. Prolapsed giant sigmoid lipoma: a rare cause of adult ischaemic intussusception. *BMJ Case Rep* 2014; **2014** [PMID: 24855078 DOI: 10.1136/bcr-2014-204036]

9 **Mahmood A**, Ruan QZ, O'Hara R, Canna K. Adult intussusception presenting as rectal prolapse. *BMJ Case Rep* 2014; **2014**: bcr2013203281 [PMID: 24777082 DOI: 10.1136/bcr-2013-203281]

10 **Du JZ**, Teo LT, Chiu MT. Adult rectosigmoid junction intussusception presenting with rectal prolapse. *Singapore Med J* 2015; **56**: e78-e81 [PMID: 26034324 DOI: 10.11622/smedj.2015078]

11 **West CT**, Pilarski A, White D, Ricketts D. An intussuscepting colonic lipoma causing prolapse of the sigmoid colon in an adult. *Br J Hosp Med (Lond)* 2019; **80**: ii [PMID: 30860916 DOI: 10.12968/hmed.2019.80.3.ii]

12 **Mazumdar P**, Kumar P, Katiyar G, Mulla M, Sardessai S. Sigmoid carcinoma with sigmoid-rectal intussusception presenting as rectal prolapse and large bowel obstruction in the ED. *Egypt J Radiol Nucl Med* 2021; **52**: 34 [DOI: 10.1186/s43055-021-00414-3]

13 **West J**, Bellamy F, Smith B. Submucosal lipoma causing recto-sigmoid intussusception associated with an incidental gastrointestinal tumour. *ANZ J Surg* 2022; **92**: 1570-1572 [PMID: 34730868 DOI: 10.1111/ans.17348]

14 **Penton AA**, Jochum SB, Eberhardt JM. Unusual presentation of colon cancer as rectal prolapse in middle-aged male. *Clin Case Rep* 2023; **11**: e6908 [PMID: 36873063 DOI: 10.1002/ccr3.6908]

15 **Erkan N**, Haciyanli M, Yildirim M, Sayhan H, Vardar E, Polat AF. Intussusception in adults: an unusual and challenging condition for surgeons. *Int J Colorectal Dis* 2005; **20**: 452-456 [PMID: 15759123 DOI: 10.1007/s00384-004-0713-2]

16 **Tarchouli M**, Ait Ali A. Adult Intussusception: An Uncommon Condition and Challenging Management. *Visc Med* 2021; **37**: 120-127 [PMID: 33981752 DOI: 10.1159/000507380]

17 **Wang N**, Cui XY, Liu Y, Long J, Xu YH, Guo RX, Guo KJ. Adult intussusception: a retrospective review of 41 cases. *World J Gastroenterol* 2009; **15**: 3303-3308 [PMID: 19598308 DOI: 10.3748/wjg.15.3303]

18 **Sarr MG**, Nagorney DM, McIlrath DC. Postoperative intussusception in the adult: a previously unrecognized entity? *Arch Surg* 1981; **116**: 144-148 [PMID: 7469741 DOI: 10.1001/archsurg.1981.01380140010002]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2024 February 26; 12(6): 1169-1173

DOI: 10.12998/wjcc.v12.i6.1169

ISSN 2307-8960 (online)

CASE REPORT

Gigantic occipital epidermal cyst in a 56-year-old female: A case report

Yao Wei, Peng Chen, Hao Wu

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Yarmahmoodi F, Iran

Received: November 13, 2023
Peer-review started: November 13, 2023
First decision: January 9, 2024
Revised: January 12, 2024
Accepted: February 2, 2024
Article in press: February 2, 2024
Published online: February 26, 2024

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Abstract

BACKGROUND

Gigantic epidermal cysts (GECs) are rare benign skin appendicular tumours also known as keratinocysts. GECs have a high incidence and their wall is made up of epidermis. Epidermal cysts can occur in any part of the skin; clinical manifestations include skin colour hemispherical swelling; cystic; mobile; 0.5 cm to several centimetres in diameter; and slow growth.

CASE SUMMARY

Herein, we report a case involving a 56-year-old female with a GEC in the occipitalia. On July 25, 2023, a patient with a GEC was admitted to the neurosurgery Department of the Second Affiliated Hospital of Xi'an Medical University. The phyma was shown to be a solid mass during the operation and was confirmed to be a GEC based on pathological examination.

CONCLUSION

Epidermal cysts are common cystic nodules on the surface of the body, the aetiology is unclear, the clinical manifestations can vary, and the misdiagnosis rate is high. However, giant epidermal cysts are rare. In most cases, however, the prognosis is satisfactory. This paper analyses and summarizes the population, location, clinical and pathological characteristics and pathogenesis of the disease to strengthen the understanding of this disease and improve the accuracy of clinical diagnosis.

Key Words: Epidermal cyst; Occipital; Brain; Cyst; Case report

Core Tip: The clinical manifestations of epidermal cysts are varied and the misdiagnosis rate is high. The disease occurs mostly in the head, face and upper torso of young men. Most patients usually have no symptoms, but epidermal cysts that are gigantic or located in important organs can press on the surrounding tissue structure and produce corresponding symptoms. However, gigantic epidermal cysts occurring in the occipital part of the brain in female patients are relatively rare. This report aims to strengthen the understanding of the disease and improve the accuracy of clinical diagnosis.

Citation: Wei Y, Chen P, Wu H. Gigantic occipital epidermal cyst in a 56-year-old female: A case report. *World J Clin Cases* 2024; 12(6): 1169-1173
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1169.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1169

INTRODUCTION

Epidermal cysts are among the most common benign skin tumours, but very few epidermal cysts can be secondary to malignant tumours, such as basal cell carcinoma and squamous cell carcinoma[1,2]. Epidermal cysts can occur in any part of the body, mainly under the skin, mostly in the head, face and upper torso of young men, and a small number of cysts can occur in the injured region or in deep tissues and organs, such as the cranium, abdominal cavity, mammary gland, *etc.* Epidermal cysts occur more than a single time; are multiple rare, usually asymptomatic, have a large volume or are located in important organs and can compress the surrounding tissue structure and produce corresponding symptoms. Most patients are treated because of secondary infection resulting in a rapid increase in volume, severe pain, and rupture.

CASE PRESENTATION

Chief complaints

Occipital phyma for 20 years.

History of present illness

The patient was found to have developed occipital phyma more than 20 years ago, without redness, swelling, or rupture, and no diagnosis or treatment was given. Recently, the patient self-reported that the scalp mass was larger than before without rupture; therefore, she came to the Department of Neurosurgery, the Second Affiliated Hospital of Xi'an Medical University for treatment.

History of past illness

The patient had a history of diabetes, heart disease, hypertension, hepatitis, tuberculosis and other infectious diseases; a history of trauma and surgery; and a history of drug allergy.

Personal and family history

There was no family history of genetic disease.

Physical examination

The vital signs were as follows: Body temperature, 36.2 °C; blood pressure, 120/82 mmHg; heart rate, 79 beats per min; and respiratory rate, 17 breaths per min.

The physical examination revealed a 77 mm × 44 mm mass on the occipitalia with a clear border, tough texture, good mobility, and tenderness. The transillumination test was negative. There was no red or swollen skin or ulceration (Figure 1A-C).

Laboratory examinations

There were no abnormalities in routine blood test results, blood biochemistry results, blood coagulation function, or routine stool or urine test results.

Imaging examinations

Craniocerebral computed tomography revealed a subcutaneous space-occupying lesion in the left occipital head, possibly a benign lesion (Figure 2A and B). Body surface colour ultrasound revealed a subcutaneous hypoechoic solid mass in the occipital region (Figure 2C-E).

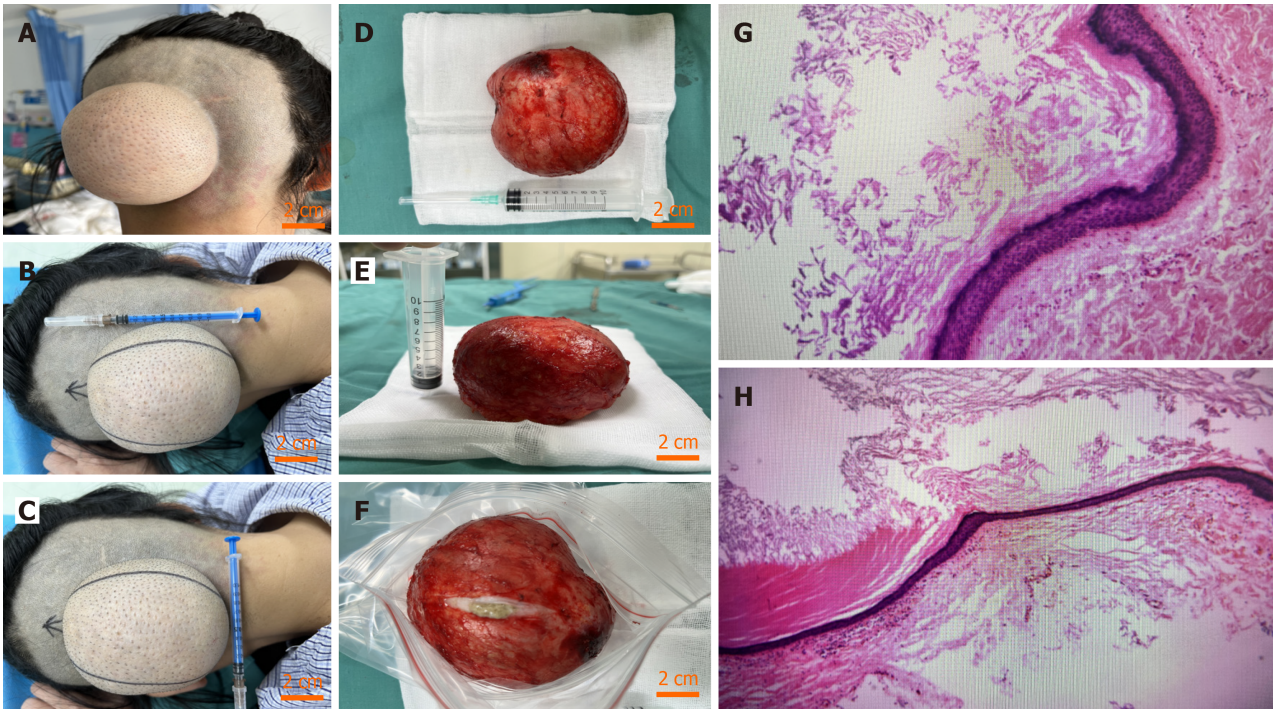

Figure 1 Preoperative manifestation, intraoperative presentation and pathology results. A: A general view of epidermal cyst; B: The long diameter of epidermal cyst; C: The wide diameter of epidermal cyst; D: Height of epidermal cyst; E and F: Image of the cyst after incision; G: Layered cutinise (the pathological results indicated epidermal cyst); H: Squamous epithelium (the pathological results indicated epidermal cyst).

FINAL DIAGNOSIS

Combined with the intraoperative findings (Figure 1D-F) and pathological examination, these findings revealed a large epidermal cyst (Figure 1G and H).

TREATMENT

Resection of the tumour was performed under local anaesthesia.

OUTCOME AND FOLLOW-UP

After 3 months of follow-up, the wound had healed well, and there was no recurrence, no rupture, or fever.

DISCUSSION

However, the pathogenesis of epidermal cysts is still unclear. It is generally believed that epidermal cysts originate from the infundibular region of the hair follicle and are caused by progressive cystic dilation and destruction of the infundibular region of the hair follicle. However, this hypothesis does not explain the rare occurrence of hairless skin, such as epidermal cysts on the palm or plantar, so other ideas have been proposed. Some scholars have found that patients with palmar and plantar epidermal cysts have a history of local trauma before disease onset, and further believe that epidermal cysts are formed by the implantation of epidermal fragments into the dermis due to penetrating injury[3]. This view is also supported by the formation of epidermal cysts in the operative area of some patients who underwent surgery for other diseases[4]. Several other studies have shown evidence of human papilloma virus (HPV) infection in epidermal cysts in the palm and plantar parts and limbs, especially in patients infected with HPV type 57, which further suggests that HPV infection may be related to the pathogenesis of epidermal cysts[5]. In addition, some scholars have found that plantar epidermal cysts are attached to or located near exocrine ducts, suggesting that epidermal cysts may originate from exocrine ducts. Studies have shown the structural relationship between plantar epidermal cysts and surrounding exocrine ducts. It has been shown that epidermal cysts are compressed by a large number of sweat glands and have structural features connected to them on the epidermal side, indicating that plantar epidermal cysts may be connected to exocrine dermal ducts, which supports the hypothesis that plantar epidermal cysts develop from epidermoid metaplasia of exocrine ducts[6]. Moreover, an HPV 60-associated epidermoid cyst with immunoreactivities for carcinoembryonic

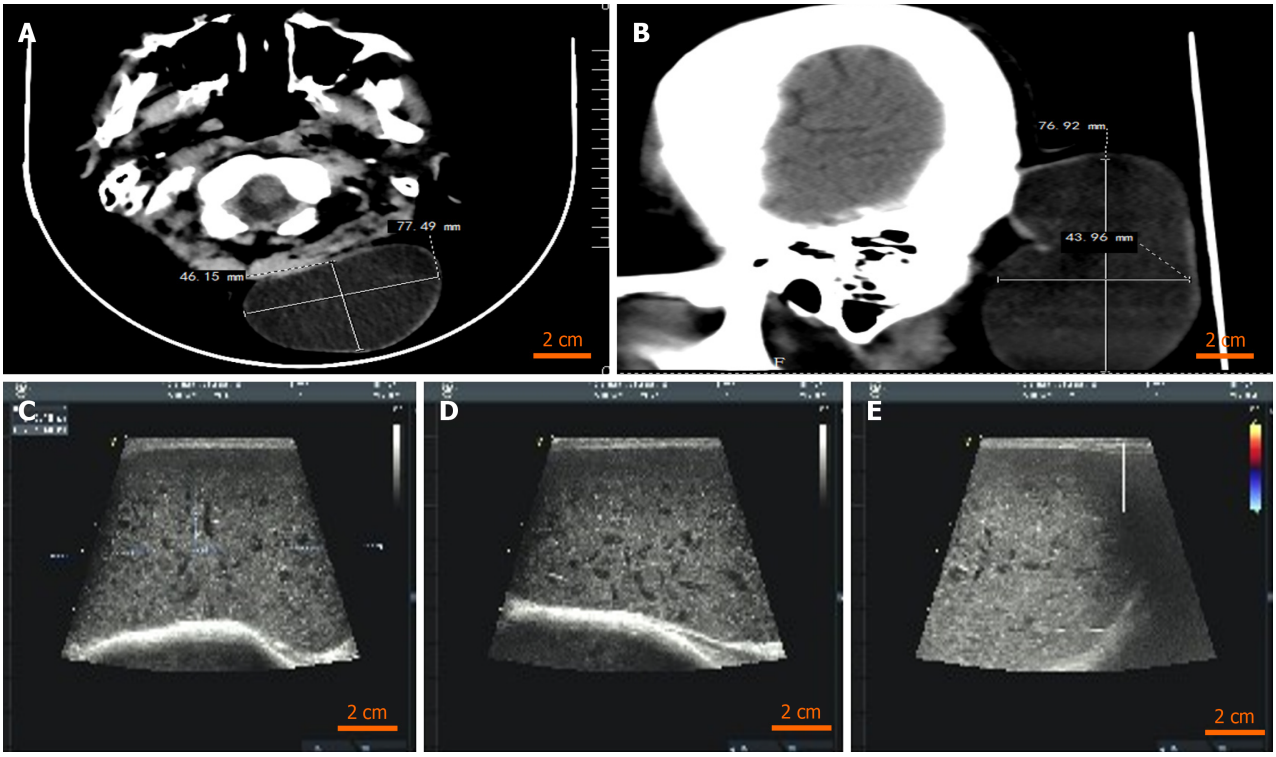

Figure 2 The computed tomography and ultrasonic image. A: The length and width of cyst of axial computed tomography (CT); B: The length and width of cyst of sagittal CT; C: A mass can be found at the subcutaneous distance of 2.3 mm from the body surface (ultrasonic image); D: The volume of the mass is 38 mm × 87 mm × 90 mm (ultrasonic image); E: The occipital mass is a solid mass with low echo, regular shape, clear boundary, complete envelope and less uniform internal echo (ultrasonic image).

antigen, involucrin and CKs identical to those of the epidermis connected with the eccrine dermal duct was found, suggesting that certain palmoplantar epidermoid cysts may develop following the epidermoid metaplasia of eccrine ducts with HPV 60 infection[7]. In conclusion, the pathogenesis of epidermal cysts is still unclear and controversial.

Currently, histopathology is still the gold standard for diagnosing epidermal cysts. Some cysts have no epithelial wall structure. Skin cysts are divided into three main types according to the conditions of the cyst wall: (1) Skin cysts with lamellar squamous epithelium mainly consist of epidermal cysts, hair sheath cysts, lipocysts, vellus hair cysts, *etc.*, which are common on the scalp, face, trunk and so on; (2) Nonlaminated squamous epithelial skin cysts, which mainly include apocrine sweat gland cysts, eccrine sweat gland cysts, branchial cleft cysts, and thyrohyoid cysts; these cysts are more common in the head and face; and (3) Skin cysts lacking epithelium mainly include mucous cysts, auricle pseudocysts, and tendon sheath cysts, which are mostly found in the oral mucosa, auricle, distal extension side of fingers, and near wrist joints. The pathological manifestations of epidermal cysts include the formation of intradermal cysts, a cyst wall composed of several layers of squamous epithelium, an upper cortex facing the cyst cavity, and keratinocytes constantly shed to form the contents of the cyst, which cause the tumour to grow continuously; additionally, the cyst is full of keratin, and rupture may occur when the size of the cyst increases to a certain extent[8,9].

Some studies have also shown that patients with unruptured epidermal cysts have larger diameters and thinner walls than those with ruptured epidermal cysts, which is consistent with most of the research findings: The larger the diameter is, the thinner the wall is, and the more likely the cyst is to rupture. Some scholars speculate that rupture may lead to an overall reduction in the size of the cyst, possibly caused by the body's foreign body reaction to the contents of the cyst and the release of various inflammatory factors, including growth factors. These factors promote the proliferation of cyst wall cells and subsequently thicken the cyst wall[10]. Several scholars have also shown that there is a positive correlation between cyst wall thickness and epidermal thickness and that cysts are thicker in patients with a history of infection than in those without a history of infection. There was no significant difference between epidermal thickness and skin lesion site [11].

CONCLUSION

Epidermal cysts are common cystic nodules on the surface of the body. The aetiology of these cysts is unclear, the clinical manifestations can vary, and the misdiagnosis rate is high. However, gigantic epidermal cysts are rare. In most cases, however, the prognosis is satisfactory. This paper analyses and summarizes the population, location, clinical and pathological characteristics and pathogenesis of the disease to strengthen the understanding of this disease and improve the accuracy of clinical diagnosis.

FOOTNOTES

Co-first authors: Yao Wei and Hao Wu.

Author contributions: Wei Y and Wu H contributed to manuscript writing and editing, and data collection; Chen P contributed to data analysis; Wu H contributed to conceptualization and supervision; All authors have read and approved the final manuscript.

Informed consent statement: Written informed consent was obtained from the patient for publication of this report and any accompanying images. We guarantee patient anonymity.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read CARE Checklist (2016), and the manuscript was prepared and revised according to CARE Checklist (2016).

Country/Territory of origin: China

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S-Editor: Li L
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Park BS**, Shin DH, Kim SH, Jung HJ, Son GM, Kim HS. Perineal squamous cell carcinoma arising from an epidermal cyst: a case report. *World J Surg Oncol* 2018; **16**: 155 [PMID: 30055637 DOI: 10.1186/s12957-018-1442-2]
2 **Frank E**, Macias D, Hondorp B, Kerstetter J, Inman JC. Incidental Squamous Cell Carcinoma in an Epidermal Inclusion Cyst: A Case Report and Review of the Literature. *Case Rep Dermatol* 2018; **10**: 61-68 [PMID: 29681810 DOI: 10.1159/000487794]
3 **Choi JE**, Kwon IH, Seo SH, Kye YC, Ahn HH. Pathogenesis of Plantar Epidermal Cyst: Three-Dimensional Reconstruction Analysis. *Ann Dermatol* 2016; **28**: 133-135 [PMID: 26848239 DOI: 10.5021/ad.2016.28.1.133]
4 **Posthuma JJ**, de Ruiter KJ, de Jong VM, Schepers T. Traumatic Epidermal Inclusion Cyst After Minimally Invasive Surgery of a Displaced Intra-Articular Calcaneal Fracture: A Case Report. *J Foot Ankle Surg* 2018; **57**: 1253-1255 [PMID: 30146338 DOI: 10.1053/j.jfas.2018.03.042]
5 **Doorbar J**, Egawa N, Griffin H, Kranjec C, Murakami I. Human papillomavirus molecular biology and disease association. *Rev Med Virol* 2015; **25**: 2-23 [PMID: 25752814 DOI: 10.1002/rmv.1822]
6 **Itoh Y**, Ninomiya Y, Chishiki M, Ishibashi A. A gigantic epidermal cyst. *Ann Plast Surg* 1999; **42**: 572 [PMID: 10340873 DOI: 10.1097/00000637-199905000-00023]
7 **Egawa K**, Egawa N, Honda Y. Human papillomavirus-associated plantar epidermoid cyst related to epidermoid metaplasia of the eccrine duct epithelium: a combined histological, immunohistochemical, DNA-DNA in situ hybridization and three-dimensional reconstruction analysis. *Br J Dermatol* 2005; **152**: 961-967 [PMID: 15888153 DOI: 10.1111/j.1365-2133.2005.06562.x]
8 **Lee KI**, Namgoong S, You HJ, Jeon TS. Epidemiological characteristics and importance of lobulation of giant epidermal cysts: An 18-year retrospective review of 19 cases. *Medicine (Baltimore)* 2022; **101**: e29978 [PMID: 35945748 DOI: 10.1097/MD.0000000000029978]
9 **Ito R**, Fujiwara M, Kaneko S, Takagaki K, Nagasako R. Multilocular giant epidermal cysts. *J Am Acad Dermatol* 2008; **58**: S120-S122 [PMID: 18489045 DOI: 10.1016/j.jaad.2007.05.028]
10 **Park JS**, Ko DK. A histopathologic study of epidermoid cysts in Korea: comparison between ruptured and unruptured epidermal cyst. *Int J Clin Exp Pathol* 2013; **6**: 242-248 [PMID: 23330009]
11 **Min HJ**, Lee JM, Han JK, Kim YJ. Influence Factor in Thickness of Cyst Wall of Epidermal Cysts. *J Craniofac Surg* 2017; **28**: e369-e372 [PMID: 28328606 DOI: 10.1097/SCS.0000000000003687]

World Journal of Clinical Cases

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World J Clin Cases 2024 February 26; 12(6): 1174-1181

DOI: 10.12998/wjcc.v12.i6.1174

ISSN 2307-8960 (online)

CASE REPORT

Autoimmune hepatitis-primary biliary cholangitis overlap syndrome complicated by various autoimmune diseases: A case report

Yu-Jie Qin, Ting Gao, Xing-Nian Zhou, Ming-Liang Cheng, Hong Li

Specialty type: Infectious diseases

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Montasser IF, Egypt

Received: November 25, 2023
Peer-review started: November 25, 2023
First decision: December 27, 2023
Revised: January 28, 2024
Accepted: February 2, 2024
Article in press: February 2, 2024
Published online: February 26, 2024

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Abstract

BACKGROUND

Autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) are two common clinical autoimmune liver diseases, and some patients have both diseases; this feature is called AIH-PBC overlap syndrome. Autoimmune thyroid disease (AITD) is the most frequently overlapping extrahepatic autoimmune disease. Immunoglobulin (IgG) 4-related disease is an autoimmune disease recognized in recent years, characterized by elevated serum IgG4 levels and infiltration of IgG4-positive plasma cells in tissues.

CASE SUMMARY

A 68-year-old female patient was admitted with a history of right upper quadrant pain, anorexia, and jaundice on physical examination. Laboratory examination revealed elevated liver enzymes, multiple positive autoantibodies associated with liver and thyroid disease, and imaging and biopsy suggestive of pancreatitis, hepatitis, and PBC. A diagnosis was made of a rare and complex overlap syndrome of AIH, PBC, AITD, and IgG4-related disease. Laboratory features improved on treatment with ursodeoxycholic acid, methylprednisolone, and azathioprine.

CONCLUSION

This case highlights the importance of screening patients with autoimmune diseases for related conditions.

Key Words: Overlap syndrome; Autoimmune hepatitis; Primary biliary cholangitis; Primary sclerosing cholangitis; Autoimmune thyroid disease; Case report

Core Tip: Autoimmune hepatitis-primary biliary cholangitis overlap syndrome is relatively rare in clinical practice. In this report, we describe the case of a patient presenting with autoimmune hepatitis, primary biliary cholangitis, thyroid disease, and autoimmune pancreatitis overlap syndrome. The report underscores the significance of vigilance and routine screening for related autoimmune diseases to prevent missed diagnoses and treatment opportunities, which can significantly impact the disease course and the patient's quality of life. Additionally, it highlights the importance of tailoring treatment to individual patients to optimize effectiveness and enhance patient adherence.

Citation: Qin YJ, Gao T, Zhou XN, Cheng ML, Li H. Autoimmune hepatitis-primary biliary cholangitis overlap syndrome complicated by various autoimmune diseases: A case report. *World J Clin Cases* 2024; 12(6): 1174-1181
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1174.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1174

INTRODUCTION

Autoimmune liver diseases include autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). Rarely, patients present with clinical features of multiple autoimmune liver diseases, known as overlap syndromes (OS)[1,2]. Among the overlap syndromes, AIH-PBC OS is the most common[3,4]. IgG4-related disease is a chronic, progressive inflammatory disease resulting in fibrosis affecting the lymph nodes, salivary glands, pancreas, bile ducts, and central nervous system[5-7]. Here, we introduce a complex case of AIH-PBC OS combined with autoimmune thyroid disease (AITD) and IgG4-associated autoimmune pancreatitis (IgG4 AIP).

CASE PRESENTATION

Chief complaints

A 68-year-old female patient was admitted to the Affiliated Hospital of Guizhou Medical University in Guiyang, China, March 21, 2021, with complaints of "right upper quadrant pain for the past year" and "nausea when consuming greasy food for the past week".

History of present illness

The patient's symptoms began a year before her presentation, characterized by right upper quadrant pain. In the week leading up to the visit, she also experienced fatigue, a decreased appetite, and accompanying nausea.

History of past illness

The patient has no history of alcohol consumption. She had well-controlled hypertension for the past 3 years, managed with irbesartan. In 2020, she reported experiencing upper right abdominal pain and mild scleral yellowing, although there were no systemic jaundice or itching symptoms.

Personal and family history

The patient's daughter has been diagnosed with PBC.

Physical examination

On physical examination, the vital signs were as follows: Body temperature, 36.3 °C; blood pressure, 128/78 mmHg; heart rate, 72 beats per min; respiratory rate, 18 breaths per min. Mild jaundice and scleral icterus were noted, and there was tenderness to percussion in the right upper abdominal quadrant.

Laboratory examinations

Laboratory examination revealed an alanine aminotransferase level of 1073.5 U/L (Figure 1A), an aspartate aminotransferase level of 1172.10 U/L (Figure 1B), an alkaline phosphatase level of 165.00 U/L, a gamma-glutamyl transpeptidase level of 210.42 U/L (Figure 1C), a total bilirubin level of 55.70 μmol/L with a direct bilirubin level of 39.6 μmol/L (Figure 1D) and an indirect bilirubin level of 17.65 μmol/L, a total bile acid level of 86.0 μmol/L, an albumin level of 37.00 g/L, and an albumin to globulin ratio of 0.940.

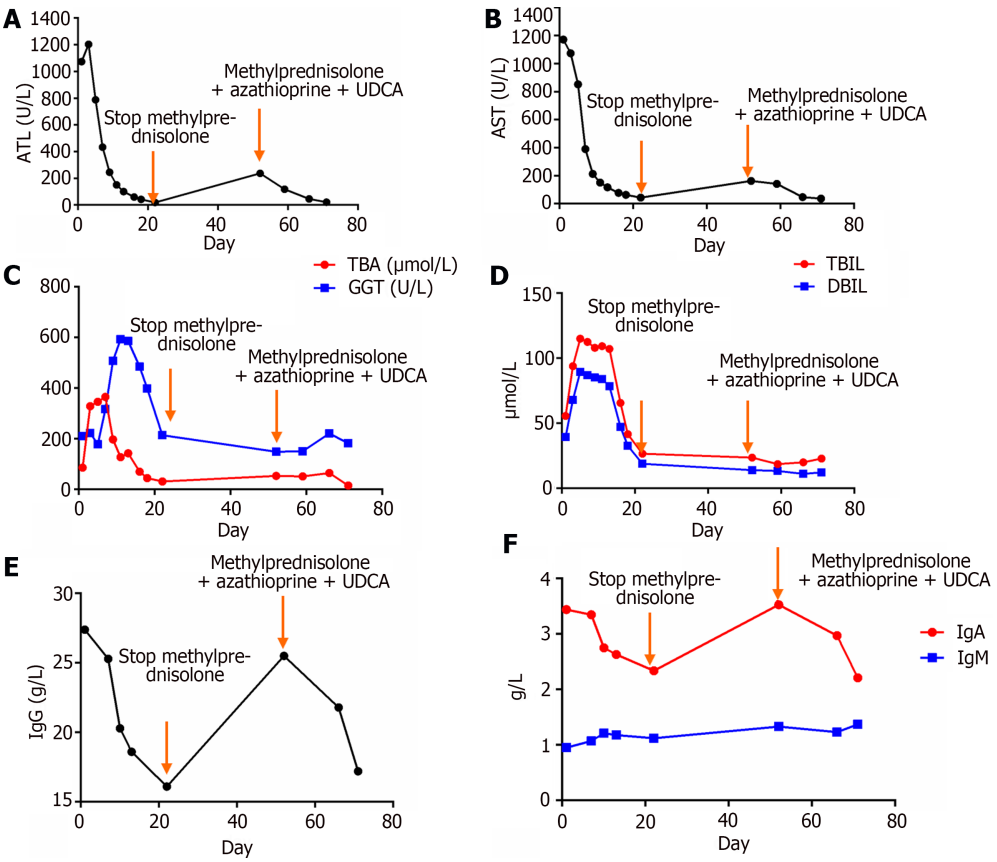

Figure 1 Biochemical indicators of patients. A: Dynamic changes in ALT; B: Dynamic changes in AST; C: Dynamic changes in TBA and GGT; D: Dynamic changes in TBIL and DBIL; E: Dynamic changes in serum IgG; F: Dynamic changes in serum IgA and IgM. ALT: Alanine aminotransferase; UDCA: Ursodeoxycholic acid; AST: Aspartate aminotransferase; TBA: Total bile acid; GGT: Glutamyl transpeptidase; TBIL: Total bilirubin; DBIL: Direct bilirubin; IgG: Immunoglobulin G; IgA: Immunoglobulin A; IgM: Immunoglobulin M.

Liver disease-related autoantibodies were investigated. The patient tested positive for antinuclear antibodies (titers of 1:1000) using indirect immunofluorescence (FC 1510-1010-1, EUROIMMUN reagent, Germany), positive for anti-mitochondrial antibodies (AMA), and strongly positive for anti-mitochondrial M2 antibodies using indirect immunofluorescence. IgG levels were 27.4 g/L (Figure 1E), IgA levels were 3.44 g/L, IgM levels were 0.95 g/L (Figure 1F), and IgG4 Levels were 1620.9 mg/L. Thyroid function tests were normal, with an anti-thyroglobulin antibody level of 222 U/mL and an antithyroid peroxidase autoantibody level of 45.2 U/mL. The patient tested negative for hepatitis A, B, C, D, and E, Epstein-Barr virus, and cytomegalovirus, and ceruloplasmin was normal. Whole-exome sequencing was negative.

Imaging examinations

Magnetic resonance cholangiopancreatography was sought and demonstrated multiple enlarged lymph nodes surrounding the hepatic hilum and pancreatic head, slightly dilated pancreatic ducts, and nodules in the pancreatic duct and pancreatic head (Figure 2). Thyroid ultrasonography revealed diffuse thyroid enlargement with non-uniform echogenicity. Enhanced computerized tomography imaging of the upper abdomen showed multiple enlarged hilar and pancreatic head lymph nodes, and dilated pancreatic ducts. Bone densitometry demonstrated severe osteoporosis.

Further diagnostic work-up

The patient underwent liver and pancreatic needle biopsies. An abundance of lymphocytes and plasma cells were observed in a lymph node of the porta hepatis (Figure 3A). HE staining of the liver revealed scattered liver necrosis and a large number of inflammatory cell infiltration (Figure 3B). Masson staining of the liver tissue revealed fibrosis in the portal area and the formation of fibrous septa (Figure 3C). The infiltration of inflammatory cells in the portal area of the liver tissue was negative for IgG4 staining (Figure 3D) but positive for IgG staining (Figure 3E). HE staining of the pancreatic tissue revealed a small amount of inflammatory cell infiltration that could be seen in the pancreatic glands (Figure 3F). IHC staining of the pancreatic tissue was negative for IgG4 (Figure 3G) and was considered to be the result of insufficient sampling. Endoscopic ultrasonography revealed a dilated main pancreatic duct and multiple enlarged lymph nodes in the hepatic hilum, pancreatic head, and pancreatic lymph nodes (Figure 4A, C and D); Figure 4B shows the uncinate process of the pancreas.

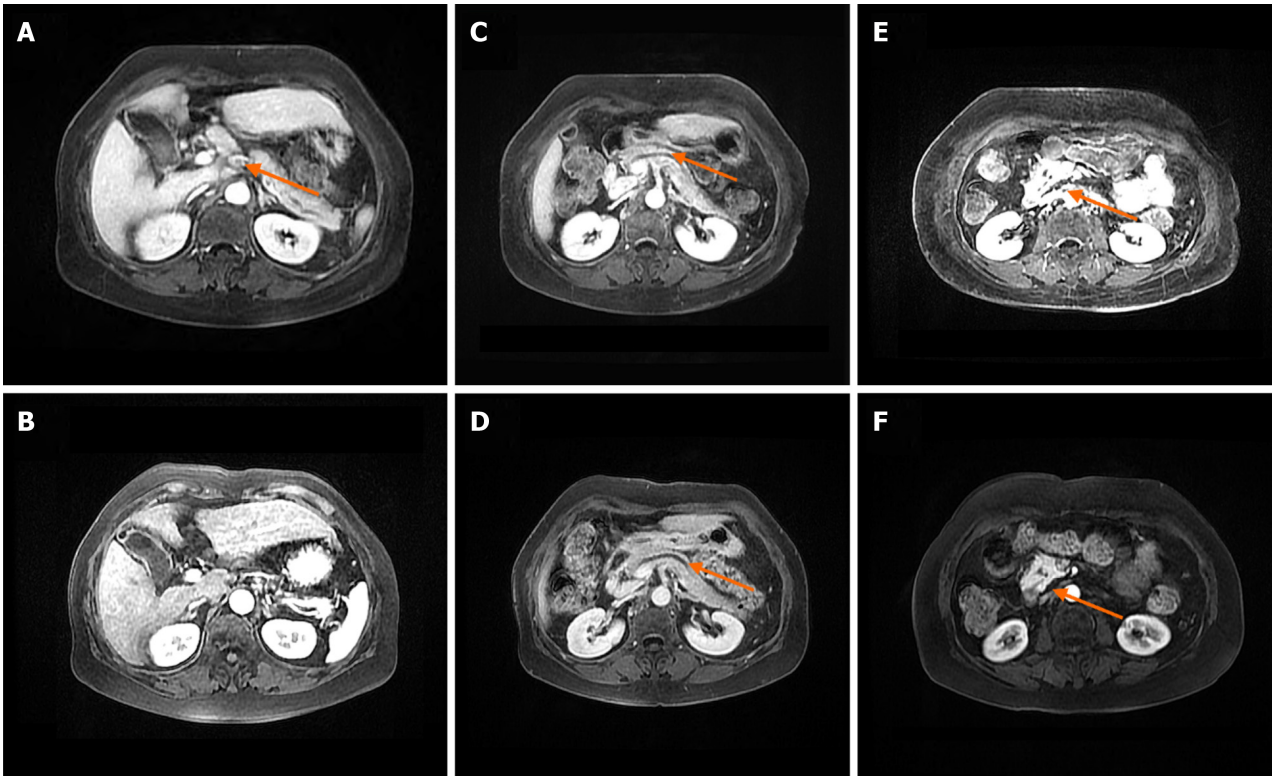

Figure 2 Patient magnetic resonance imaging findings. A: Multiple enlarged lymph nodes in the hepatic hilum at admission; B: The hilar lymphadenopathy resolved after 8 wk of treatment; C: Pancreatic duct dilatation at admission; D: Pancreatic duct dilatation persists after 8 wk of treatment; E: Enlargement of the head of the pancreas at admission; F: Pancreatic head enlargement has been significantly reduced after 8 wk of treatment.

FINAL DIAGNOSIS

Based on the physical examination, laboratory features, and imaging findings, a final diagnosis of AIH-PBC OS, AIP, and AITD was made.

TREATMENT

The patient, with a weight of 61 kg, initially received treatment with ursodeoxycholic acid at a dose of 15 mg/kg/d and orally administered methylprednisolone at 60 mg/d, gradually reduced to 20 mg/d for maintenance. Symptomatic management of the patient's osteoporosis involved the use of chewable vitamin D calcium tablets. Subsequently, the patient's liver function showed significant improvement, and serum levels of IgG4, IgG, IgA, and IgM decreased. This improvement led to the patient's discharge from the hospital (Figure 1). After discharge, the patient discontinued methylprednisolone due to experiencing tremors and increased blood pressure. Consequently, the patient's liver function deteriorated. Prior to initiating azathioprine, genetic testing was performed for the patient's TPMT and NUDT15 genes, both of which showed normal results. As a result, the patient's medication regimen was adjusted to include ursodeoxycholic acid at 15 mg/kg/d, methylprednisolone at 8 mg/d, and azathioprine at 50 mg/d, resulting in another improvement in liver function.

OUTCOME AND FOLLOW-UP

The patient responded well to the standard clinical treatment, with her liver function and overall physical condition returning to a satisfactory level. All indicators for the patient are now within the normal range. She continues to be under continuous follow-up.

DISCUSSION

Both AIH and PBC are immune-mediated liver diseases with different clinical and biochemical manifestations, with 2%-19% of AIH patients being diagnosed with overlapping PBC and 7%-14% of AIH patients developing overlapping PSC. AIH mainly causes hepatocellular damage, while PBC mainly targets the bile ducts[8,9]. The diagnosis of AIH-PBC OS is

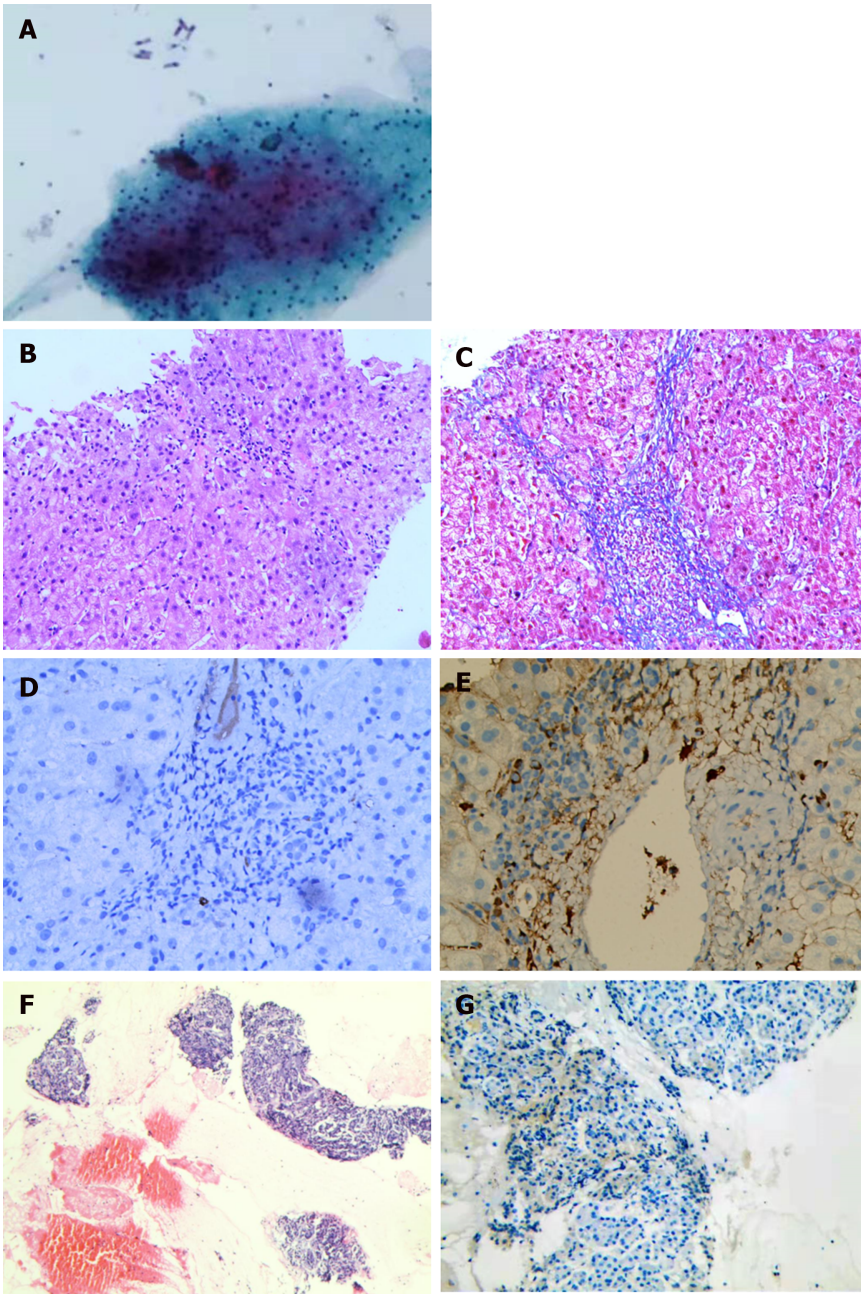

Figure 3 Patient pathological manifestations. A: Plentiful lymphocytes and plasma cells can be seen in a lymph node of the porta hepatis; B: Liver tissue HE staining; scattered punctate necrosis of the liver and infiltration of a large number of inflammatory cells can be seen (HE × 100); C: Liver tissue Masson staining; visible portal fibrosis with fibrous septa formation can be seen (IHC × 100); D: Inflammatory cell infiltration in the portal area of the liver tissue; liver tissue immunoglobulin (IgG) 4-negative (IHC × 200); E: Inflammatory cell infiltration in the portal area of the liver tissue; liver tissue IgG-positive (IHC × 200); F:Pancreatic HE staining; small amount of inflammatory cell infiltration can be seen in the glands of the pancreas (HE × 100); G: Pancreatic IgG4-negative (IHC × 200).

made using the Paris criteria: interface hepatitis on liver histopathology in conjunction with laboratory and biopsy results meeting the diagnostic criteria of PBC. The diagnostic criteria for AIH are as follows: (1) ALT ≥ 5 times the upper limit of normal (ULN); (2) IgG ≥ 2 ULN or anti-smooth muscle antibody ≥ 1:80; and (3) at least 2 of periportal or interlobular lymphocytic infiltration and borderline hepatitis on liver biopsy. The diagnostic criteria for PBC are as follows: (1) ALT ≥ 2 ULN or GGT ≥ 5 ULN; (2) AMA ≥ 1:40; and (3) at least two bile duct lesions in liver biopsy. When both these sets of criteria are met, AIH-PBC OS can be diagnosed[10,11]. The biochemical indicators, immunological indicators, and liver histopathological characteristics of this patient were consistent with AIH-PBC OS.

The recommended treatment regimen for patients with AIH-PBC is long-term or lifelong administration of ursodeoxycholic acid combined with glucocorticoids[12]. In this case, the biochemical indexes improved rapidly after treatment with ursodeoxycholic acid and glucocorticoids, and the indexes rebounded after discontinuing the drug due to side effects.

IgG4-related diseases are immune-mediated diseases that have been gradually recognized and valued in recent years. They can affect almost all organs and tissues in the body, such as the pancreas, biliary tract, breast, kidney, and so on. The clinical manifestations vary depending on the involved organs. IgG4 hepatobiliary disease includes IgG4-related

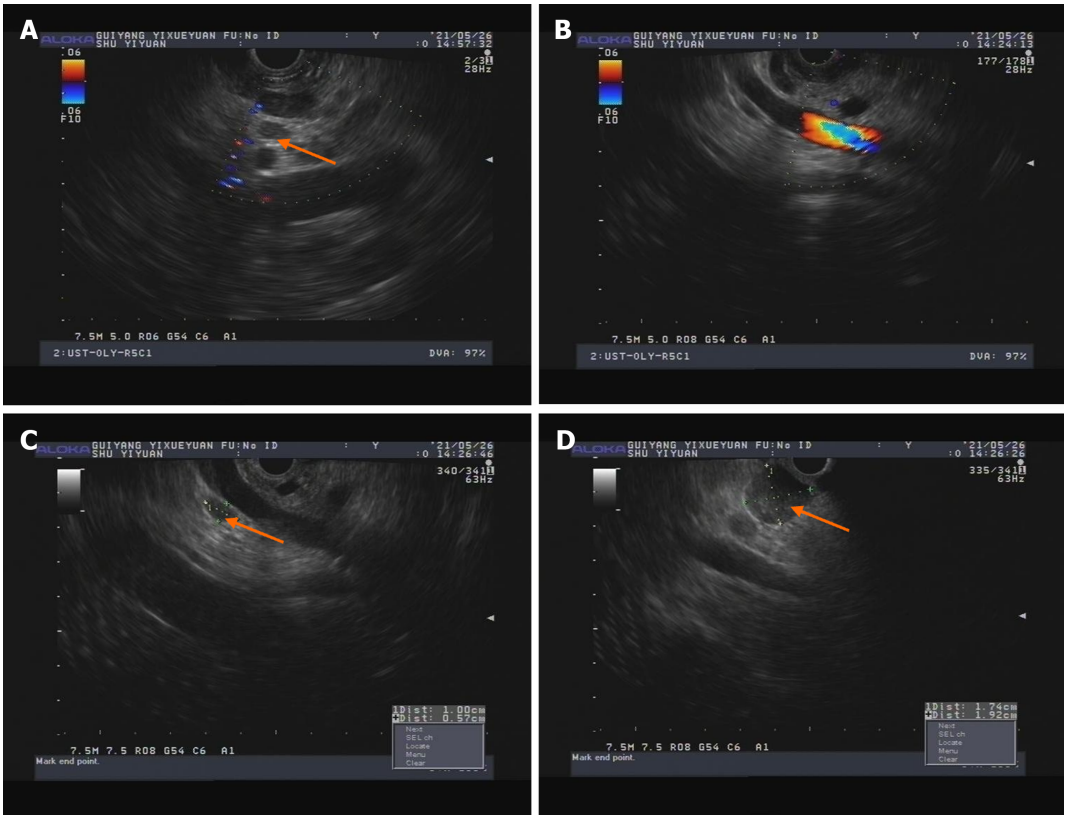

Figure 4 Endoscopic ultrasound findings of patients. A: Endoscopic ultrasonography of hepatic lymph node; B: Uncinate process of the pancreas; C: Pancreatic lymph node; D: Pancreatic lymph node.

sclerosing cholangitis and IgG4-related liver disease[13]. The diagnostic criteria for IgG4-related diseases were published by the Japanese scientific research group in 2011: (1) Diffuse or characteristic nodules, masses, and swellings in single or multiple organs; (2) serum IgG4 level ≥1.35 g/L; and (3) histopathology: (a) obvious lymphocyte and plasma cell infiltration and fibrotic or sclerotic changes; (b) IgG4-positive plasma cell infiltration with an IgG4/IgG ratio > 0.4 and IgG4-positive plasma cells > 10/high power field. The gold standard for the diagnosis of IgG4-related disease relies on histopathology and immunohistochemical staining of IgG4-positive plasma cells. In this case, IgG4 was significantly elevated at the initial diagnosis, but no typical IgG4 sclerosing cholangitis manifestations, such as bile duct stenosis and deformation, were found on imaging. IgG4-related autoimmune hepatitis was excluded on the basis of negative IgG4 staining on liver biopsy.

IgG4-AIP has the highest incidence among IgG4-related disease, and the early misdiagnosis rate is high[14]. This patient's magnetic resonance cholangiopancreatography revealed an enlarged pancreatic head and mild dilatation of the pancreatic duct. The patient's serum IgG4 Levels were 1620.9 mg/L, over 1350 mg/L. Imaging examination showed focal enlargement of the pancreatic head, and the pancreatic duct was dilated, although the degree of dilatation was less than 0.5 cm. Negative IgG4 immunohistochemistry in the pancreatic tissue was considered to be the result of insufficient sampling; therefore, insufficient sampling is a limitation of our study. Although autoimmune thyroiditis was diagnosed based on elevated autoantibodies and ultrasonographic abnormalities, no thyroid biopsy was performed, and IgG4-related thyroid disease could not be confirmed or excluded.

Autoimmune liver disease is sometimes associated with AITD and connective tissue disorders such as systemic sclerosis or Sjögren's syndrome[15]. The most common extrahepatic diseases associated with AIH type 1 are thyroiditis, ulcerative colitis, and rheumatoid arthritis. There are case reports of PBC-AIH OS with diabetes, autoimmune thyroiditis, and antiphospholipid syndrome. Pamfil *et al*[16] reported that 61.2% of patients with PBC have extrahepatic autoimmune disease, and up to 46.6% have one or more connective tissue diseases. AITD is observed in 23% of PBC patients and 18.3% of PBC-AIH OS patients. As a result of active screening, our awareness of extrahepatic diseases such as AITD has increased. Being aware of related autoimmune diseases enables clinicians to avoid missing a diagnosis of AIH-PBC combined with other autoimmune diseases. Autoimmune diseases are multisystemic, and missed diagnoses can affect treatment and disease monitoring. Therefore, for patients with autoimmune liver diseases, clinicians should be vigilant for the coexistence of related autoimmune diseases.

Studies have shown that genetic factors are closely related to the occurrence and development of autoimmune liver diseases (AILD). Each subtype of AILD demonstrates familial aggregation[17]. WES detection technology is a powerful tool for finding genetic mutations in genetic diseases. It is mainly used for the related research of complex diseases and Mendelian genetic diseases caused by mutations in coding regions, especially for the search for pathogenic mutation genes in rare familial genetic diseases. It can play a key role in clinical decision-making and can obtain single nucleotide polymorphism maps of 90% of the genome coding regions, including rare variants and new variants[18]. In this case, the

WES test was negative, and genetic factors were not considered for the time being.

This patient presented a complex case with multiple diseases. Since autoimmune hepatitis is characterized by liver damage caused by autoimmune dysfunction, when it is combined with other immune diseases such as rheumatoid arthritis, Sjögren's syndrome, *etc*., patients will have corresponding extrahepatic manifestations, such as joint pain, dry eyes, dry mouth, itchy skin, and other symptoms. Fortunately, the patient reported here did not have the above-mentioned extrahepatic manifestations, but the diagnosis of such diseases still needs to be carefully screened. Similarly, missing the diagnosis of AIH should be avoided in patients with extrahepatic manifestations, and in this regard, a liver biopsy should be performed if necessary.

Patient rescue therapy and follow-up are crucial. It is necessary to explain to the patient that after discharge, they should focus on rest, avoid fatigue, consume a light and easily digestible diet, enhance their nutritional intake, and strictly avoid medications that could harm the liver. After discharge, the patient must continue following the doctor's instructions, which include taking methylprednisolone (2 tablets of 8 mg each) and one tablet of azathioprine (50 mg) daily. The patient should also schedule a follow-up appointment at the liver disease clinic 1 wk after discharge. For patients with hypertension, irbesartan should be continued to control blood pressure and monitor any fluctuations. In cases of inadequate blood pressure control, seeking medical attention at a hypertensive clinic is advised. Throughout the medication process, patients are required to visit the liver disease clinic every 3 months for follow-up to monitor their physical condition. Currently, the patient remains under follow-up, and the treatment effect remains favorable.

CONCLUSION

This case report underscores that autoimmune diseases are multisystemic, and it highlights the intricate and severe clinical course of this disease. As demonstrated, patients with autoimmune diseases have an elevated risk of developing other immune-mediated diseases. Therefore, it is essential to conduct tests for additional autoantibodies and perform necessary histopathological examinations to screen for additional diagnoses. This patient responded positively following the timely initiation of treatment, and the biochemical response remained favorable after transitioning to a low-dose triple-drug regimen due to side effects. This emphasizes the importance of customizing treatment plans based on factors such as the patient's age, underlying disease, and drug tolerance.

ACKNOWLEDGEMENTS

We thank the patient for her contribution to this case report.

FOOTNOTES

Co-first authors: Yu-Jie Qin and Ting Gao.

Author contributions: Qin YJ and Gao T contributed to manuscript writing and editing, and data collection; Zhou XN and Cheng ML contributed to data analysis; Li H contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

Supported by National Natural Science Foundation of China, No. 82060123; and National Health Commission of Guizhou Province, No. gzwjk2019-1-082.

Informed consent statement: Informed consent was obtained from the patient before the publication of this case report.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read CARE Checklist (2016), and the manuscript was prepared and revised according to CARE Checklist (2016).

Country/Territory of origin: China

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S-Editor: Gong ZM
L-Editor: A

P-Editor: Cai YX

REFERENCES

1 **Bunchorntavakul C**, Reddy KR. Diagnosis and management of overlap syndromes. *Clin Liver Dis* 2015; **19**: 81-97 [PMID: 25454298 DOI: 10.1016/j.cld.2014.09.005]

2 **Chazouillères O**. Overlap Syndromes. *Dig Dis* 2015; **33** Suppl 2: 181-187 [PMID: 26641819 DOI: 10.1159/000440831]

3 **Freedman BL**, Danford CJ, Patwardhan V, Bonder A. Treatment of Overlap Syndromes in Autoimmune Liver Disease: A Systematic Review and Meta-Analysis. *J Clin Med* 2020; **9** [PMID: 32414025 DOI: 10.3390/jcm9051449]

4 **Jiang Y**, Xu BH, Rodgers B, Pyrsopoulos N. Characteristics and Inpatient Outcomes of Primary Biliary Cholangitis and Autoimmune Hepatitis Overlap Syndrome. *J Clin Transl Hepatol* 2021; **9**: 392-398 [PMID: 34221925 DOI: 10.14218/JCTH.2021.00008]

5 **Chen LYC**, Mattman A, Seidman MA, Carruthers MN. IgG4-related disease: what a hematologist needs to know. *Haematologica* 2019; **104**: 444-455 [PMID: 30705099 DOI: 10.3324/haematol.2018.205526]

6 **Minaga K**, Watanabe T, Chung H, Kudo M. Autoimmune hepatitis and IgG4-related disease. *World J Gastroenterol* 2019; **25**: 2308-2314 [PMID: 31148902 DOI: 10.3748/wjg.v25.i19.2308]

7 **Wallace ZS**, Perugino C, Matza M, Deshpande V, Sharma A, Stone JH. Immunoglobulin G4-related Disease. *Clin Chest Med* 2019; **40**: 583-597 [PMID: 31376893 DOI: 10.1016/j.ccm.2019.05.005]

8 **van Gerven NM**, de Boer YS, Mulder CJ, van Nieuwkerk CM, Bouma G. Auto immune hepatitis. *World J Gastroenterol* 2016; **22**: 4651-4661 [PMID: 27217697 DOI: 10.3748/wjg.v22.i19.4651]

9 **Tanaka A**. Current understanding of primary biliary cholangitis. *Clin Mol Hepatol* 2021; **27**: 1-21 [PMID: 33264835 DOI: 10.3350/cmh.2020.0028]

10 **Bairy I**, Berwal A, Seshadri S. Autoimmune Hepatitis - Primary Biliary Cirrhosis Overlap Syndrome. *J Clin Diagn Res* 2017; **11**: OD07-OD09 [PMID: 28892963 DOI: 10.7860/JCDR/2017/25193.10242]

11 **Gilchrist AA**. Potency in psychotherapy. *Aust N Z J Psychiatry* 1976; **10**: 191-200 [PMID: 1067838 DOI: 10.1016/j.jhep.2010.09.002]

12 **Castro Limo JD**, Romero-Gutiérrez M, Ruiz Martín J. Effective treatment of autoimmune hepatitis-primary biliary cholangitis overlap syndrome with obeticholic acid. *Rev Esp Enferm Dig* 2020; **112**: 737 [PMID: 32496125 DOI: 10.17235/reed.2020.6883/2020]

13 **Iaccarino L**, Talarico R, Scirè CA, Amoura Z, Burmester G, Doria A, Faiz K, Frank C, Hachulla E, Hie M, Launay D, Montecucco C, Monti S, Mouthon L, Tincani A, Toniati P, Van Hagen PM, Van Vollenhoven RF, Bombardieri S, Mueller-Ladner U, Schneider M, Smith V, Cutolo M, Mosca M, Alexander T. IgG4-related diseases: state of the art on clinical practice guidelines. *RMD Open* 2018; **4**: e000787 [PMID: 30729031 DOI: 10.1136/rmdopen-2018-000787]

14 **Okamoto A**, Watanabe T, Kamata K, Minaga K, Kudo M. Recent Updates on the Relationship between Cancer and Autoimmune Pancreatitis. *Intern Med* 2019; **58**: 1533-1539 [PMID: 30713326 DOI: 10.2169/internalmedicine.2210-18]

15 **Khoury T**, Kadah A, Mari A, Sbeit W, Drori A, Mahamid M. Thyroid Dysfunction is Prevalent in Autoimmune Hepatitis: A Case Control Study. *Isr Med Assoc J* 2020; **22**: 100-103 [PMID: 32043327]

16 **Pamfil C**, Candrea E, Berki E, Popov HI, Radu PI, Rednic S. Primary biliary cirrhosis--autoimmune hepatitis overlap syndrome associated with dermatomyositis, autoimmune thyroiditis and antiphospholipid syndrome. *J Gastrointestin Liver Dis* 2015; **24**: 101-104 [PMID: 25822440 DOI: 10.15403/jgld.2014.1121.cpa]

17 **Zachou K**, Arvaniti P, Lyberopoulou A, Dalekos GN. Impact of genetic and environmental factors on autoimmune hepatitis. *J Transl Autoimmun* 2021; **4**: 100125 [PMID: 34622188 DOI: 10.1016/j.jtauto.2021.100125]

18 **Rakela J**, Rule J, Ganger D, Lau J, Cunningham J, Dehankar M, Baheti S, Lee WM; Acute Liver Failure Study Group. Whole Exome Sequencing Among 26 Patients With Indeterminate Acute Liver Failure: A Pilot Study. *Clin Transl Gastroenterol* 2019; **10**: e00087 [PMID: 31609742 DOI: 10.14309/ctg.0000000000000087]

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2024 February 26; 12(6): 1182-1189

DOI: 10.12998/wjcc.v12.i6.1182

ISSN 2307-8960 (online)

CASE REPORT

Parotid metastasis of rare lung adenocarcinoma: A case report

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Specialty type: Dentistry, oral surgery and medicine

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ekine-Afolabi B, United Kingdom

Received: December 8, 2023
Peer-review started: December 8, 2023
First decision: December 29, 2023
Revised: January 5, 2024
Accepted: January 29, 2024
Article in press: January 29, 2024
Published online: February 26, 2024

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Abstract

BACKGROUND

Lung cancer (LC) is the leading cause of malignancy-related deaths worldwide. The most common sites of metastasis include the nervous system, bone, liver, respiratory system, and adrenal glands. LC metastasis in the parotid gland is very rare, and its diagnosis presents a challenge. Here, we report a case of parotid metastasis in primary LC.

CASE SUMMARY

The patient was a 74-year-old male who was discovered to have bilateral facial asymmetry inadvertently two years ago. The right earlobe was slightly swollen and without pain or numbness. Computed tomography (CT) examination showed bilateral lung space-occupying lesions. Pulmonary biopsy was performed and revealed adenocarcinoma (right-upper-lung nodule tissue). Positron emission tomography-CT examination showed: (1) Two hypermetabolic nodules in the right upper lobe of the lung, enlarged hy-permetabolic lymph nodes in the right hilar and mediastinum, and malignant space-occupying lesion in the right upper lobe of the lung and possible metastasis to the right hilar and mediastinal lymph nodes; and (2) multiple hypermetabolic nodules in bilateral parotid glands. Parotid puncture biopsy was performed considering lung adenocarcinoma metastasis. Gene detection of lung biopsy specimens revealed an *EGFR* gene 21 exon L858R mutation.

CONCLUSION

This case report highlights the challenging diagnosis of parotid metastasis in LC given its rare nature. Such lesions should be differentiated from primary tumors of the parotid gland. Simple radiological imaging is unreliable, and puncture biopsy is needed for final diagnosis of this condition.

Key Words: Lung cancer; Metastasis; Parotid gland; Pathology; Positron emission tomography/computed tomography; Case report

Core Tip: A 74-year-old male presented with a bilateral facial asymmetry. Computed tomography examination revealed bilateral lung space-occupying lesions. Pulmonary biopsy was performed on the right-upper-lung nodule tissue and revealed the presence of adenocarcinoma. Parotid puncture biopsy was performed considering lung adenocarcinoma metastasis. This work highlights the challenging diagnosis of parotid metastasis in lung cancer and the need for biopsy in the final diagnosis.

Citation: Yan RX, Dou LB, Wang ZJ, Qiao X, Ji HH, Zhang YC. Parotid metastasis of rare lung adenocarcinoma: A case report. *World J Clin Cases* 2024; 12(6): 1182-1189
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1182.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1182

INTRODUCTION

Lung cancer (LC) refers to the second most common malignant tumor in the world, next to breast cancer, and is a serious threat to human life and health[1]. LC can be classified as small-cell or non-small-cell carcinoma (*e.g.*, adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma). Non-small-cell LC (NSCLC) accounts for nearly 85% of all LCs[2]. The most common metastatic sites of LC comprise the nervous system, bone, liver, respiratory system, and adrenal glands[3]. Reports on the metastasis of LC in the parotid gland are extremely rare. In this study, we report a case of parotid metastasis from lung adenocarcinoma and review the published literature.

CASE PRESENTATION

Chief complaints

A 74-year-old male presented with a bilateral facial asymmetry for 2 years.

History of present illness

The patient was a 74-year-old male who was discovered to have bilateral facial asymmetry inadvertently two years ago. The right earlobe was slightly swollen and without pain or numbness.

History of past illness

He used to be healthy, denied diabetes, heart disease, hypertension for 15 years, and denied trauma surgery.

Personal and family history

He denied any history of exposure to special chemicals and radiation. He had a smoking history of 50 years and had quit smoking for 7 years. He denied drinking alcohol. There were no infectious diseases, metabolic diseases, diabetes, hemophilia, hereditary diseases, tumors and similar diseases in the family.

Physical examination

The patient's vitals were stable upon examination. The following conditions were noted: asymmetric left and right sides of his face, swollen posterior inferior pole of the bilateral parotid glands, intact surface skin without ulceration, low local skin temperature, the left tumor measuring approximately 5.0 cm × 4.0 cm, right tumor with a size of around 3.0 cm × 3.0 cm, smooth surface, clear boundary with the surrounding tissues, good mobility, no evident spontaneous pain or tenderness, and the facial nerve showing no sign of involvement. In addition, the patient showed normal mouth opening degree, good oral hygiene condition, minimal swelling of the corresponding parotid duct opening, and normal saliva secretion.

Laboratory examinations

Parotid puncture biopsy: Considering lung adenocarcinoma metastasis. Pulmonary biopsy was performed: (right upper lung nodule tissue) adenocarcinoma; Gene detection of lung biopsy specimens showed *EGFR* gene 21 exon L858R mutation.

Imaging examinations

Computed tomography (CT) examination revealed bilateral lung space-occupying lesions. Pulmonary biopsy was performed and revealed adenocarcinoma in the right-upper-lung nodule tissue. Positron emission tomography (PET)-CT examination showed the following: (1) Two hypermetabolic nodules in the right upper lobe of the lung, enlarged hypermetabolic lymph nodes in the right hilar and mediastinum; malignant space-occupying lesion in the right upper lobe of the lung and possible metastasis to the right hilar and mediastinal lymph nodes; and (2) multiple hypermetabolic nodules in bilateral parotid glands.

Diagnostic assessment and interventions

The patient's was assessed further. Color ultrasound examination indicated multiple heterogeneous hypoechoic nodules in bilateral parotid glands. The patient had smoked for 50 years and had no crucial medical history. CT of the chest revealed density shadows of solid nodules at the posterior and anterior ends of the right upper lobe (2.5 and 1.3 cm in diameter, respectively), with burrs at the edges and pulling adjacent to the pleura. Given the possibility of metastatic lymphatic lesions in the neck, systemic PET/CT showed 18F fluorodeoxyglucose (FDG) in hilum and mediastinum [maximum standardized uptake value (SUV_{max}): 12.1], bilateral cervical lymph nodes (SUV_{max}: 10.2), and bilateral parotid glands (SUV_{max}: 27.3), which indicate the possibility of LC metastasis (Figure 1). The disseminated tumor was characterized by multifocal FDG accumulation, and thus, we decided to conduct further study of the parotid gland mass. The left upper pulmonary nodule was subjected to transthoracic puncture biopsy. The histopathology of the puncture biopsy revealed LC (primary adenocarcinoma of the lung). Subsequently, fine-needle aspiration cytology of the left mandibular angle lymph node confirmed the parotid mass as metastatic lung adenocarcinoma (Figure 2) and ruled it out as a LC coexisting tumor. After consultation with the patient's family, chemotherapy was refused, and the targeted drug Ectinib was administered to the patient.

FINAL DIAGNOSIS

Right lung adenocarcinoma stage 4; Bilateral parotid gland lung metastatic cancer.

TREATMENT

The patient is currently receiving immunotherapy.

OUTCOME AND FOLLOW-UP

The patient's condition was stable upon reexamination in May 2023 but showed slight progression during another assessment in August 2023.

DISCUSSION

Clinically, the metastasis of LC to the parotid gland rarely occurs. The metastatic routes of LC include direct diffusion, lymphatic metastasis, and hematogenous metastasis. In this case, metastatic signs of lymph node enlargement were observed on the neck of the patient, and parotid gland metastasis of LC was considered lymphatic. LC usually shows no distinct sequence of metastatic sites. The most common sites of metastasis comprise the nervous system, bone, liver, respiratory system, and adrenal gland[3].

Gupta *et al*[4] retrospectively reviewed published literature over the past 44 years (August 1977 to December 2021) and discovered 122 documented cases of oral soft tissue metastasis (OSTM) from LC as the sole primary source (Table 1). In Sonia Gupta's study, no difference was observed in the age of onset of OSTM, which occurred in 5-6 years, between sexes. The male majority showed a clear gender advantage. A total of 35 patients (28.7%) had a history of LC. This number is more than the average patients who present with oral soft tissue as the only metastatic site. LC is the most common primary source of OSTM, and attached gums are the most common site[5,6]. A total of 80% of the 122 patients had a history of smoking, and the study suggested that nicotine and its derivatives, which are found in tobacco smoke, may contribute to tumor cell growth and metastasis[7]. The clinical features of the patient reported in this case are consistent with the findings of Gupta *et al*[4].

Of the 122 cases of LC metastasis, 14 involved the parotid gland. The submandibular and sublingual glands lack lymph nodes, and the route of metastasis is primarily blood derived. Thus, metastasis to these salivary glands is very rare. Gupta *et al*[4] reported five cases of LC-induced submandibular gland metastasis but found no cases involving sublingual gland metastasis.

The detection of distant metastases in the diagnosis of malignant tumors plays a crucial role in the accurate prognosis and guidance of treatment strategies[8,9]. In the case of LC, FDG-PET/CT sensitively identifies extrathoracic metastases, especially bone and adrenal lesions. However, several benign diseases (infection or inflammation) or malignant lesions

Table 1 Summary of results documented from literature describing the characteristics of oral soft tissue metastasis from lung cancer (August 1, 1977 to December 31, 2021)

Feature	
Total number of papers published	120
CR	111
SC	3
LTE	3
Co	2
RA	1
Total number of patients	122
World-wide distribution of cases, *n* (%)	
Japan	31 (25.8)
India	14 (11.7)
United States	13 (10.8)
China	10 (8.3)
Turkey	9 (7.5)
Italy	7 (5.8)
Korea = United Kingdom	5 (4.2)
Brazil	4 (3.3)
Morocco = Taiwan = France = Greece = Tunisia = Germany = Switzerland = Australia = Spain	2 (1.7)
Israel = Beirut = Bangladesh = Victoria	1 (0.8)
Gender, *n* (%)	
M	100 (82)
F	22 (18)
Average age of patients (range), yr	60.8 (25-87)
Average age of male patients (range), yr	61.4 (25-87)
Average age of female patients (range), yr	58.3 (36-87)
Chief complaint, *n* (%)	
Related to oral health	97 (79.5)
Not related to oral health	22 (18)
Routine check-up	3 (2.5)
Previous history of LC, *n* (%)	35 (28.7)
No previous history LC, *n* (%)	78 (63.9)
NA data on previous history of LC, *n* (%)	9 (7.4)
Associated risk factors, *n* (%)	66 (54.1)
S	53 (80.3)
A	9 (13.6)
HT	7 (10.7)
As	6 (9.1)
TB	3 (4.5)
Others	15 (27.2)
No risk factors, *n* (%)	38 (31.1)

NA data on associated risk factors, *n* (%)	18 (14.8)
Site of metastasis, *n* (%)	
G	51 (41.8)
Max (Ant-6, Post-12, Both-1, SNA-5/R-10, L-5, Both-4, SNA-5)	24 (47)
Mand (Ant-6, Post-9, Both-2, SNA-8/R-8, L-12, Both-2, SNA-3)	25 (49)
SNA-2	2 (4)
T (Ant-6, Base-4, DL-6, SNA-3, Tip-2)	21 (17.2)
To [Palatine-19 (R-10, L-9), Lingual-2]	21 (17.2)
P (R-8, L-4, BL-2)	14 (11.5)
SMG (L-3, R-1, BL-1)	5 (4.1)
Pa	3 (2.5)
Lip (U-1, L-1)	2 (1.6)
BM	1 (0.8)
RMT	1 (0.8)
MS	3 (2.5)
Oral soft tissues as the initial site of metastasis, *n* (%)	
Y	74 (60.6)
N	44 (36.1)
NA	4 (3.3)
Oral soft tissues as the only site of metastasis, *n* (%)	
Y	63 (51.6)
N	54 (44.2)
NA	5 (4.2)
Average time of detection of metastasis from diagnosis of LC	Few days to 10 yr
Most common clinical features, *n* (%)	
Swelling	100 (81.9)
Ulceration	13 (10.6)
Exophytic	12 (9.8)
Pedunculated	10 (8.2)
Nodules	6 (4.9)
Edema	5 (4.2)
Erosive	2 (1.6)
BOP	10 (8.2)
ST = LP = FNP	1 (0.8)
Type of LC, *n* (%)	
AD	46 (37.7)
SCLC	19 (15.6)
MT	17 (13.9)
SCC	10 (8.2)
NSCLC	8 (6.5)
LCC	6 (4.9)
NEC	5 (4.1)
Sa	3 (2.4)

Ha	2 (1.6)
AC	2 (1.6)
AS	2 (1.6)
PI	2 (1.6)
LC Metastasis, *n* (%)	
IL	55 (45.1)
CL	33 (27)
BL	2 (1.6)
NA	32 (26.2)
Treatment aids, *n* (%)	
RT + CH	31 (25.4)
CH	27 (22.1)
RT = SU	12 (9.8)
CH + RT + SU	8 (6.5)
CH + SU	2 (1.6)
SU + Ta = SU = Sy	1 (0.8)
NG	11 (9)
NA	5 (4.1)
RBP	4 (3.3)
STO	2 (1.6)
Death, *n* (%)	66 (54.1%)
Reasons of death, *n* (%)	
MM	18 (27.2)
DC	18 (27.2)
RF	4 (6.1)
Others	13 (19.7)
NA	13 (19.7)
Average time of death from diagnosis of metastasis	1 wk to 2.5 yr
Partial relief of symptoms, *n* (%)	1 (0.8)
Favorable prognosis, *n* (%)	13 (10.6)
TGO, *n* (%)	5 (4.1)
LFU, *n* (%)	6 (4.9)

A: Alcohol; AC: Acinar cell carcinoma; AD: Adenocarcinoma; AFP: Anterior faucial pillar; Ant: Anterior; AS: Adenosquamous carcinoma; As: Arsenic; BL: Bilateral; BM: Buccal mucosa; BOP: Bleeding on probing; CH: Chemotherapy; CL: Contralateral; Co: Correspondence; CR: Case report; DL: Dorsolateral left; LC: Lung cancer; LCC: Large cell carcinoma; LFU: Lost to follow up; M: Male; MS: Multiple sites; MM: Multiple metastasis; MT: Mesothelioma; N: No; NA: Not available; NEC: Neuroendocrine carcinoma; NG: Not given; NSCLC: Non-small-cell lung carcinoma; P: Parotid; Pa: Palate; Pl: Pleomorphic; Post: Posterior; R: Right; RA: Retrospective analysis; RBP: Refused by patient; RF: Respiratory failure; RMT: Retromolar triagone; S: Smoking; Sa: Sarcomatous; SC: Short communication; SCC: Squamous cell carcinoma; SCLC: Small-cell lung carcinoma; SMG: Submandibular gland; SNA: Site not available; ST: Sore throat; STO: Sent to oncologist; SU: Surgery; Sy: Symptomatic; T: Tongue; TB: Tuberculosis; To: Tonsil; TGO: Treatment going on; Y: Yes. Citation: Gupta S, Jawanda MK, Kedia NB, Deb AR, Ganganna A, Saurabh K, Yadav SK, Yadav AB. Lung cancer metastasis to oral soft tissues; Systematic review of 122 cases. *J Clin Exp Dent* 2022; 14: e854-e874. Copyright ©2022 Medicina Oral SL[4].

that are unrelated to primary NSCLC may show strong FDG uptake, similar to distant metastases such as adenomas[10]. Studies have reported cases of misdiagnosis of Warthin tumor (WT) as a metastatic disease based solely on radiological imaging of LC patients[11]. High FDG-PET/CT uptake cannot be used to distinguish metastatic disease from WTs. WT is the second most common benign tumor in salivary glands after pleomorphic adenoma, and most of related cases occur in the parotid gland. Most of the WTs are benign, and the incidence of malignancy reaches 0.3%[11]. Differential diagnosis relies on a detailed medical history and imaging studies. Clinically, benign tumors of the parotid gland have a long cour-

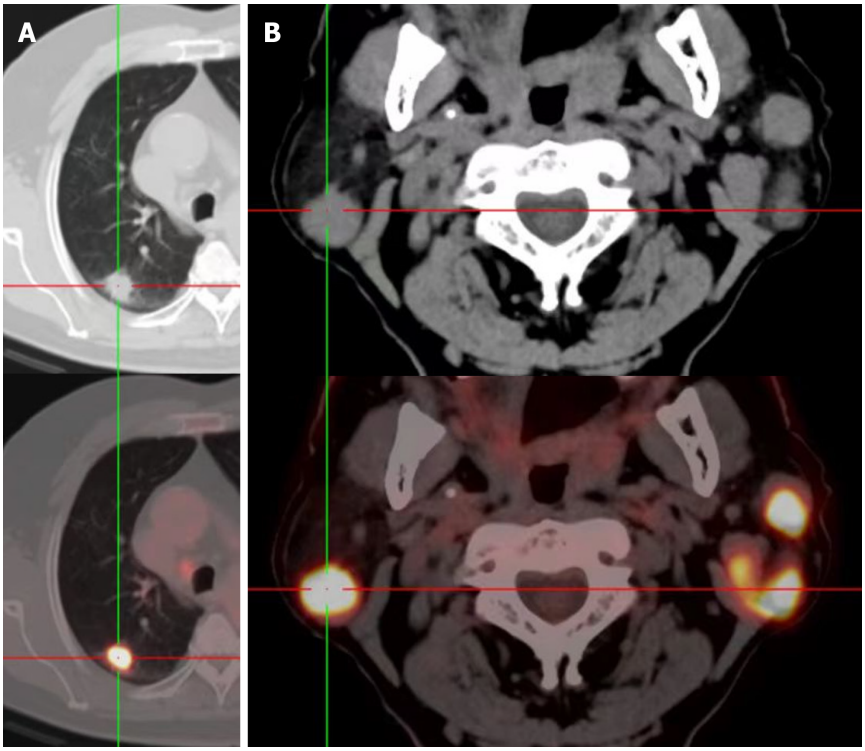

Figure 1 18F fluorodeoxyglucose values shown by positron emission tomography. A: Superior lobe of right lung (18.2); B: Bilateral parotid gland (27.3).

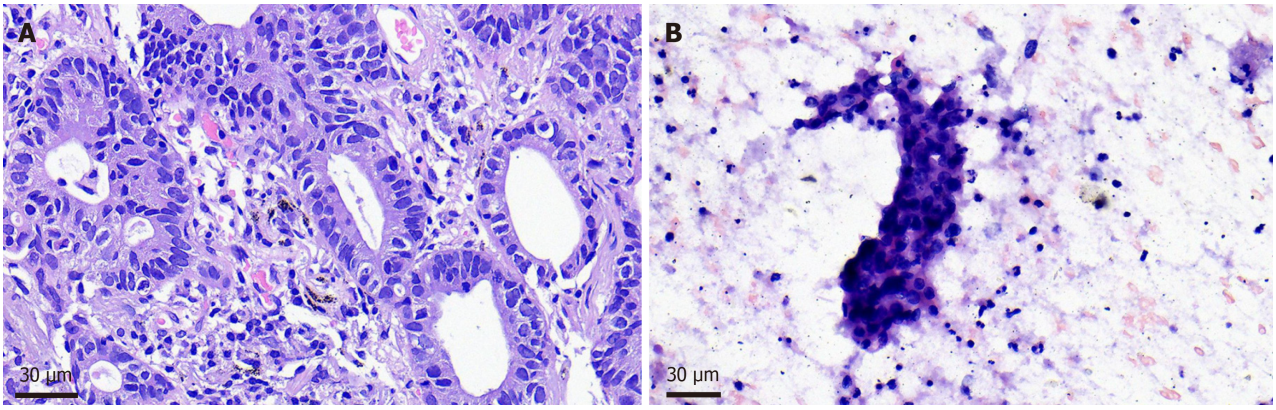

Figure 2 Histopathological examination. A: Lung (× 400); B: Parotid gland (× 400).

se and develop slowly; they are usually located in the superficial lobe of the parotid gland, with no surrounding tissue infiltration and distinct borders. By contrast, parotid malignancies usually exhibited rapid grow, are usually found in deep or superficial and deep lobes, invade the facial nerve or surrounding tissue, and have ambiguous borders[13]. Emerging imaging techniques, such as the use of apparent diffusion coefficient, diffusion-weighted imaging, and dynamic contrast-enhanced magnetic resonance imaging, can effectively aid in distinguishing malignancies. However, although pathological biopsy can be used for the above features, it still cannot accurately distinguish LC parotid metastasis and LC coexisting with WT[12]. The coexistence of LC and WT is rarely reported in the literature. A retrospective study by White *et al*[13] revealed that nearly one-fifth of patients diagnosed with WT were associated with LC. Patients with WTs have a high risk of lung malignancy, and thus, the early detection of WT may contribute to the early diagnosis of LC. However, the association between LC and WT has not been confirmed in published literature and requires further exploration.

CONCLUSION

The diagnosis of LC parotid metastases presents a challenge because of rare nature. Lesions should be differentiated from primary parotid tumors. Radiological imaging alone is unreliable, and puncture biopsy is needed for final diagnosis.

FOOTNOTES

Co-corresponding authors: Hong-Hai Ji and Yan-Cong Zhang.

Author contributions: Yan RX and Dou LB were involved in management of case and preparation of manuscript; Wang ZJ and Qiao X were responsible for the revision of the manuscript for important intellectual content and collecting references; Ji HH and Zhang YC were involved in workup of the case and also helped in preparing the manuscript. Ji HH and Zhang YC contributed equally to this work as co-corresponding authors, they contributed efforts of equal substance throughout the research process, the designation of co-corresponding authorship accurately reflects our team's collaborative spirit and equal contributions.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: the authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

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S-Editor: Zhang H
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **World Health Organization**, International Agency for Research on Cancer. Geneva: 2020. Lung Cancer. International Agency for Research on Cancer. [cited 2023 Nov 8]. Available from: https://www.who.int/zh/news-room/fact-sheets/detail/cancer
2 **American Cancer Society**. Key statistics for lung cancer. 2018. [cited 2023 Nov 8]. Available from: https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/key-statistics.html
3 **Riihimäki M**, Hemminki A, Fallah M, Thomsen H, Sundquist K, Sundquist J, Hemminki K. Metastatic sites and survival in lung cancer. *Lung Cancer* 2014; **86**: 78-84 [PMID: 25130083 DOI: 10.1016/j.lungcan.2014.07.020]
4 **Gupta S**, Jawanda MK, Kedia NB, Deb AR, Ganganna A, Saurabh K, Yadav SK, Yadav AB. Lung cancer metastasis to oral soft tissues; Systematic review of 122 cases. *J Clin Exp Dent* 2022; **14**: e854-e874 [PMID: 36320671 DOI: 10.4317/jced.59773]
5 **Irani S**. Metastasis to the oral soft tissues: A review of 412 cases. *J Int Soc Prev Community Dent* 2016; **6**: 393-401 [PMID: 27891304 DOI: 10.4103/2231-0762.192935]
6 **Hirshberg A**, Shnaiderman-Shapiro A, Kaplan I, Berger R. Metastatic tumours to the oral cavity - pathogenesis and analysis of 673 cases. *Oral Oncol* 2008; **44**: 743-752 [PMID: 18061527 DOI: 10.1016/j.oraloncology.2007.09.012]
7 **Schaal C**, Chellappan SP. Nicotine-mediated cell proliferation and tumor progression in smoking-related cancers. *Mol Cancer Res* 2014; **12**: 14-23 [PMID: 24398389 DOI: 10.1158/1541-7786.MCR-13-0541]
8 **Kwee RM**, Kwee TC. Modern imaging techniques for preoperative detection of distant metastases in gastric cancer. *World J Gastroenterol* 2015; **21**: 10502-10509 [PMID: 26457011 DOI: 10.3748/wjg.v21.i37.10502]
9 **Lin A**, Ma S, Dehdashti F, Markovina S, Schwarz J, Siegel B, Powell M, Grigsby P. Detection of distant metastatic disease by positron emission tomography with (18)F-fluorodeoxyglucose (FDG-PET) at initial staging of cervical carcinoma. *Int J Gynecol Cancer* 2019; **29**: 487-491 [PMID: 30739082 DOI: 10.1136/ijgc-2018-000108]
10 **Farsad M**. FDG PET/CT in the Staging of Lung Cancer. *Curr Radiopharm* 2020; **13**: 195-203 [PMID: 31868151 DOI: 10.2174/1874471013666191223153755]
11 **Yaranal PJ**, T U. Squamous Cell Carcinoma Arising in Warthin's Tumour: A Case Report. *J Clin Diagn Res* 2013; **7**: 163-165 [PMID: 23449505 DOI: 10.7860/JCDR/2012/4683.2697]
12 **Wang R**, Wang T, Zhou Q. Parotid metastases from primary lung cancer: Case series and systematic review of the features. *Front Oncol* 2022; **12**: 963094 [PMID: 36091176 DOI: 10.3389/fonc.2022.963094]
13 **White CK**, Williams KA, Rodriguez-Figueroa J, Langer CJ. Warthin's tumors and their relationship to lung cancer. *Cancer Invest* 2015; **33**: 1-5 [PMID: 25472027 DOI: 10.3109/07357907.2014.979365]

World Journal of Clinical Cases

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World J Clin Cases 2024 February 26; 12(6): 1190-1195

DOI: 10.12998/wjcc.v12.i6.1190

ISSN 2307-8960 (online)

CASE REPORT

Management of retroperitoneal high-grade serous carcinoma of unknown origin: A case report

Wen-Lin Hsieh, Dah-Ching Ding

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Mahmoud MZ, Saudi Arabia; Zhang G, China

Received: December 18, 2023
Peer-review started: December 18, 2023
First decision: January 10, 2024
Revised: January 15, 2024
Accepted: January 23, 2024
Article in press: January 23, 2024
Published online: February 26, 2024

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Abstract

BACKGROUND

Retroperitoneal high-grade serous carcinoma (HGSC) of unknown origin is a sporadic tumor that can originate from ovarian cancer. Herein, we report the case of a woman with retroperitoneal HGSC of unknown origin and describe how she was diagnosed and treated.

CASE SUMMARY

A 71-year-old female presented with the tumor marker CA125 elevated to 1041.9 U/mL upon a regular health examination. Computed tomography revealed retroperitoneal lymph node enlargement. Subsequently, positron emission tomography scanning revealed lesions with increased F-18 fluorodeoxyglucose uptake at the nodes. As a result, she underwent laparoscopic lymph node resection, and pathology revealed metastatic adenocarcinoma with CK7(+), PAX8(+), WT1(+), PR(-), and p53 mutational loss of expression, indicating that the origin may be from the adnexa. The patient was admitted to our ward and underwent laparoscopic staging; however, the pathological results were negative. Under the suspicion of retroperitoneal HGSC of unknown origin, chemotherapy and targeted therapy were initiated. Tumor marker levels decreased after treatment.

CONCLUSION

We present a case of HGSC of unknown origin managed using retroperitoneal lymphadenectomy, staging surgery, chemotherapy, and targeted therapy.

Key Words: High-grade serous carcinoma; Retroperitoneum; Origin; Chemotherapy; Lymph node; Case report

Core Tip: We report a case of high-grade serous carcinoma (HGSC) of unknown origin in a postmenopausal woman treated with lymphadenectomy and chemotherapy. We provide updated information regarding the symptoms, signs, diagnosis, treatment, and prognosis of HGSCs of unknown origin. Based on our experience, we report our strategy to diagnose and treat this condition.

Citation: Hsieh WL, Ding DC. Management of retroperitoneal high-grade serous carcinoma of unknown origin: A case report. *World J Clin Cases* 2024; 12(6): 1190-1195
URL: https://www.wjgnet.com/2307-8960/full/v12/i6/1190.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i6.1190

INTRODUCTION

Primary retroperitoneal carcinoma is sporadic. To date, only 16 cases of retroperitoneal serous carcinoma and 10 cases of high-grade serous carcinoma (HGSC) have been reported[1]. Retroperitoneal carcinoma shows a similar histological subtype and sex preference to ovarian carcinoma and, therefore, may share a similar pathogenesis[2]. Serous carcinomas are classified as HGSC or low-grade serous carcinoma[2]. A notable percentage of HGSCs develop within the secretory epithelial cells of the tubal fimbria[3].

The pathogenesis of retroperitoneal serous carcinoma appears to be associated with endosalpingiosis and a remnant Müllerian tract[4,5]. Several gene mutations have been associated with retroperitoneal serous carcinoma; *KRAS, NRAS,* and *TP53* play a crucial role in high-grade transformation, and *BRCA* gene mutations have been reported to be relevant to endosalpingiosis[6]. Retroperitoneal carcinoma presents with nonspecific signs and symptoms, making its diagnosis difficult[7]. Evaluating tumor markers, such as CA125, which has high sensitivity in retroperitoneal serous carcinoma, can reveal the disease[7]. Imaging studies, such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), can be used for diagnosis[8].

Complete tumor resection in patients without ruptured capsules improves outcomes[9]. Furthermore, surgery may be done for better results, including exploration of the abdominal cavity and bilateral salpingo-oophorectomy with hysterectomy[1]. HGSC is sensitive to chemotherapy consisting of paclitaxel and carboplatin[10,11]. The role of targeted therapy for retroperitoneal HGSC of unknown origin has not yet been revealed; however, it is worth investigating further. Targeted therapies, including vascular endothelial growth factor (VEGF) and poly ADP-ribose polymerase (PARP) inhibitors, have been proven to be efficient with carboplatin-placitaxel treatment in ovarian HGSC[12].

Herein, we report the case of a woman with retroperitoneal HGSC of unknown origin and describe how she was diagnosed and treated.

CASE PRESENTATION

Chief complaints

Increased tumor marker CA125 level.

History of present illness

A 71-year-old female underwent a regular health examination at Da-Lin Tzu Chi Hospital, which revealed an elevation in the tumor marker CA125 (1041.9 U/mL) at 4 months before admission. No other discomfort was reported. Pelvic ultrasound did not reveal any abnormalities, and a subsequent CT scan (2 months before admission) revealed two enlarged retroperitoneal lymph nodes. A PET scan was performed and reported increased F-18 fluorodeoxyglucose (FDG) uptake in lesions located in the bilateral abdominal para-aortic region, which was probably the primary malignant or metastatic nodule.

Consequently, the patient visited our general surgery department for further evaluation. Laparoscopic lymph node biopsy (two lymph nodes in the suprapancreatic region and one lymph node in the right pleural area) was performed 1 month before admission, which revealed metastatic adenocarcinoma, with CK7(+), CDX2(-), GATA(-), TTF-1(-), PAX8(+), WT1(+), PR(-), and p53 mutational loss of expression (Figure 1). Next-generation sequencing did not detect any clinically significant variants or biomarkers. The metastatic lesions were suspected to have originated from a gynecological organ, and the patient was referred to our outpatient department for further evaluation.

History of past illness

Gastric ulcers were diagnosed using panendoscopy performed 4 months before admission. The patient was under medical treatment and was regularly followed up. Sicca syndrome and interstitial cystitis were regularly followed up at the Da-Lin Tzu Chi Hospital. She also underwent tympanic membrane perforation/tympanoplasty 10 years previously,

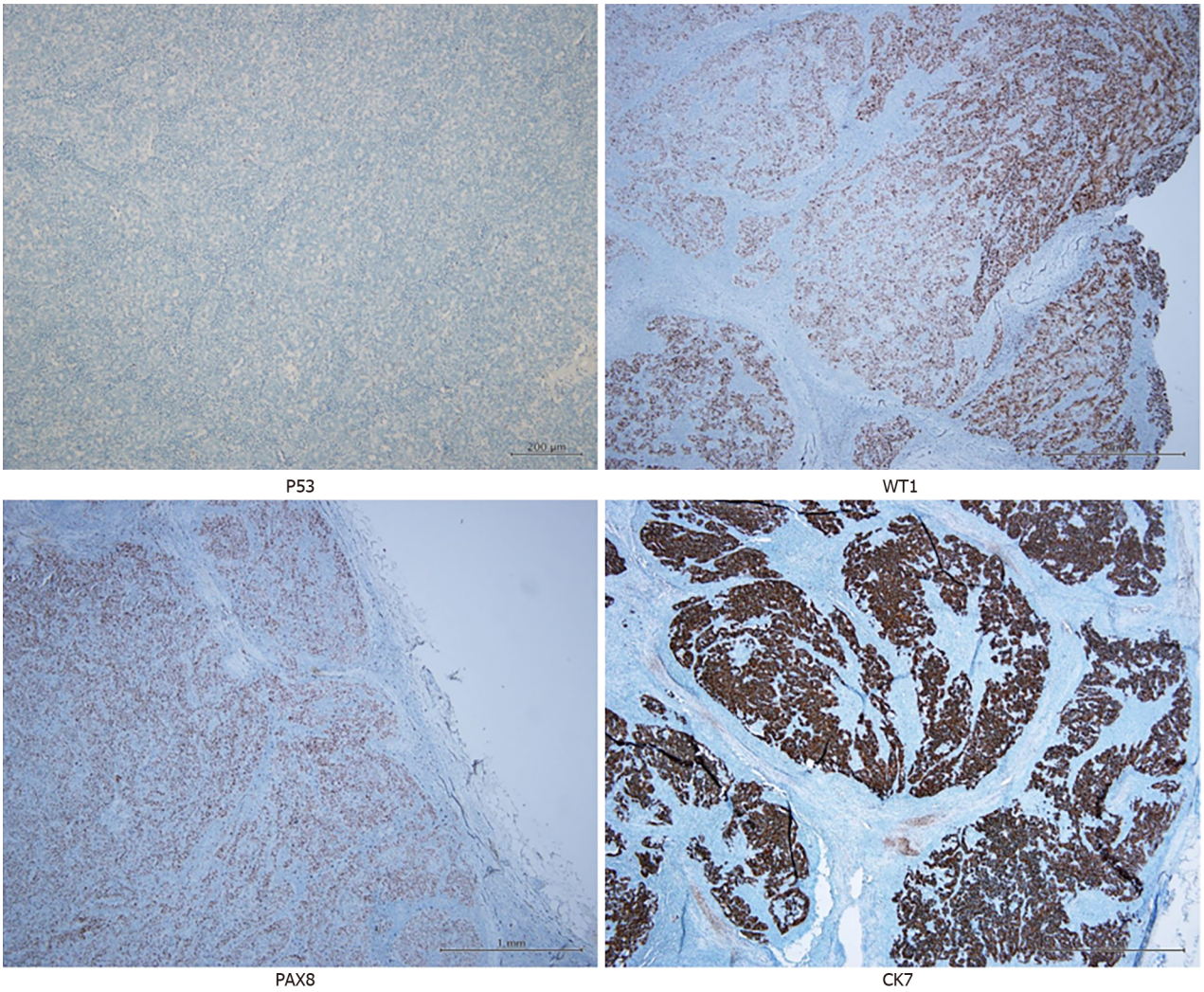

Figure 1 Immunohistochemistry of the retroperitoneal high-grade serous carcinoma. The carcinoma was negative for p53 (scale bar = 200 μm), and positive for WT1, PAX8, and CK7 (scale bar = 1 mm).

and had undergone cholecystectomy 3 years prior to presentation for cholelithiasis.

Personal and family history

The patient experienced menarche at the age of 13 years and menopause at the age of 54 years, without receiving menopausal hormonal therapy. She delivered one child and had a spontaneous abortion. The patient had no history of oral contraceptive use. No previous hysterectomy, salpingectomy, or tubectomy was performed. Her mother had diabetes mellitus and there was no gynecological family history.

Physical examination

Pelvic examination revealed no abnormalities. Physical examinations of the abdomen, chest, heart, and musculoskeletal system did not reveal any significant findings. The neurological examination results were normal. Pelvic examination revealed atrophy of the vagina and cervix. No palpable masses are observed.

Laboratory examinations

Four and one month before admission, her CA125 levels were 1041.9 and 1742.0 U/mL, respectively, showing a remarkable elevation of the tumor marker. After retroperitoneal lymphadenectomy, the value decreased to 17.8 U/mL. On the other hand, her creatinine ranged from 0.53 to 0.6 mg/dL, and her estimated glomerular filtration rate was 111.13–120.86 mL/min.

Imaging examinations

Two months prior to admission, pelvic ultrasonography did not reveal any abnormalities. CT performed on the same day revealed two lymph nodes of up to 26 mm in the para-aortic retroperitoneum, some lung nodules, a liver mass, and a calcified uterine myoma. Subsequently, a PET scan was arranged, and two enlarged lymph nodes in the bilateral abdominal para-aortic region were reported with intense uptake (maximum standardized uptake value: 9.3 and 10.0, right and left, respectively). One month before admission, the ultrasound showed an anteverted uterus sized 3.7 cm × 2.1

cm, with calcified myoma sited at the right lateral wall; the bilateral adnexa was invisible without discovering ascites.

FINAL DIAGNOSIS

HGSC of unknown origin with suprapancreatic and right pleural region lymph node metastasis was the final diagnosis.

TREATMENT

After discussion with the patient, the possible origin of HGSC was suggested to have been the adnexa. Therefore, the patient was admitted to our ward and laparoscopic staging surgery was performed.

Laparoscopic staging surgery including total hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic lymph node dissection. We did not find any abnormalities in the pelvic or retroperitoneal cavity. Histopathological examination did not reveal carcinoma in the specimen.

OUTCOME AND FOLLOW-UP

Chemotherapy with paclitaxel and carboplatin has been suggested for HGSCs of unknown origin. Three weeks after the surgery, paclitaxel was administered for the first time; however, chemotherapy was discontinued immediately after the development of tachycardia, dyspnea, and desaturation. As no chemotherapy was administered, a PARP inhibitor (Lynparza) was prescribed. After 3 wk, she was admitted and received the first course of Lipodox and Avastin; no side effects were noted.

The value of CA125 after this admission and the first course of failed chemotherapy was 69.7 and 58.7 U/mL, respectively. CA125 levels increased slightly after staging surgery and in the first month after lymphadenopathy. The patient is undergoing follow-up to determine the outcomes of subsequent chemotherapy and targeted therapy.

DISCUSSION

Primary retroperitoneal carcinoma, a rare tumor, represents 0.1%-0.2% of all malignancies, which is in contrast to the more prevalent ovarian cancer in females[1]. While its pathogenesis remains unknown, there is a potential association with ovarian carcinoma, evidenced by similarities in histological subtype and sex preference, although differences in histological subtypes may exist[13]. Carcinomas with an unidentified primary source, particularly when confined to the retroperitoneal space, may be classified as primary retroperitoneal carcinomas, as illustrated in situations where the carcinoma is exclusively found in the lymph nodes, resembling a carcinoma of unknown origin[1]. To date, only 16 cases of retroperitoneal serous carcinoma and 10 cases of HGSC have been reported[1].

The development of retroperitoneal serous carcinoma is believed to be linked to endosalpingiosis and a remnant Müllerian tract, with two main theories explaining the mechanism of endosalpingiosis: The tubal escape theory and Müllerian metaplasia theory[4,5]. According to the tubal escape theory, shed tubal epithelium may either be implanted on the peritoneal surface or spread through the lymphatic system to reach a lymph node[5]. According to the Müllerian metaplasia theory, dormant cells located outside the Müllerian tract, which includes the fallopian tube, endometrium, and endocervix, retain the ability to develop benign glands resembling those of the fallopian tube[4]. Additionally, endosalpingiosis can result from displacement of the primitive tubal tissue outside the fallopian tube[14].

Various gene mutations, including *KRAS*, *NRAS*, *TP53*, and *BRCA*, are associated with retroperitoneal serous carcinoma; *TP53* mutation (loss of expression) was identified in our case to be relevant to the disease[15]. Among 10 patients with retroperitoneal HGSC, *TP53* mutations have been noted in seven patients[1].

The diagnosis of retroperitoneal carcinoma is difficult because of its nonspecific symptoms and signs. Common symptoms of retroperitoneal carcinoma include abdominal discomfort and a palpable mass[7]. Of those patients with asymptomatic retroperitoneal carcinoma, imaging studies and evaluation of tumor markers may incidentally detect the disease. CA125 has a high sensitivity in retroperitoneal serous carcinoma, with 90% of cases showing an elevation[7]. CT and MRI revealed the location, size, shape, and thickness of the wall rather than the histological subtype of the tumor. Furthermore, PET scans can be helpful in discriminating between benign and malignant masses[16]. Therefore, surgery is the only way to provide a definitive diagnosis[17]. Our case is the first to report tumor marker elevation during a regular health examination without other noted symptoms. Subsequently, a CT scan revealed two enlarged lymph nodes and PET revealed that the lymph nodes had increased FDG uptake.

Surgery is necessary to diagnose retroperitoneal carcinoma. Furthermore, complete tumor resection in patients without ruptured capsules improves outcomes[9]. In patients with retroperitoneal serous carcinoma, it is crucial to explore the abdominal cavity using diaphragmatic implants and detect peritoneal recurrence after tumor resection[1]. Patients with retroperitoneal serous carcinoma may undergo bilateral salpingo-oophorectomy with hysterectomy because of the potential presence of concurrent adnexal serous carcinomas, including intraepithelial carcinoma[1]. Previous studies have revealed that 9 of 10 patients with retroperitoneal HGSC underwent surgical treatment[1]. Our patient was also treated

with surgical resection of the lymph nodes followed by staging surgery.

The drug selection for chemotherapy after surgery depends on the histological subtype. HGSC is sensitive to chemotherapy consisting of paclitaxel and carboplatin[10,11]. The role of targeted therapy for retroperitoneal HGSC of unknown origin remains unknown; however, considering its histological type and pathogenic similarity to high-grade ovarian serous carcinoma, it is worth investigating further. Targeted therapies include VEGF and PARP inhibitors, which have been proven to be efficient in combination with carboplatin-paclitaxel treatment[12]. Ten retroperitoneal HGSC patients were treated with chemotherapy (eight with carboplatin and paclitaxel, one with docetaxel and carboplatin) and one with combined chemotherapy with nivolumab or avastin[1]. Our patient was also treated with Lynparza (a PARP inhibitor), Lipodox, and Avastin (a VEGF inhibitor).

Patients diagnosed with retroperitoneal serous carcinoma exhibit low survival rates, with 53% and 18% disease-free survival at 2 and 5 years, respectively[1]. Notably, patients with nodal-type retroperitoneal serous carcinoma may experience more favorable survival outcomes[11], similar to patients with serous carcinoma of the ovary, fallopian tube, or peritoneum who present with lymph node metastasis and minimal peritoneal disease[13]. The patient's prognosis is to follow.

Our case report involved only a single case of retroperitoneal HGSC, limiting the generalizability of the clinical manifestations, diagnosis, and treatment of our findings. We anticipate that future research with a larger sample size or more extensive trials will provide a better understanding of the disease.

CONCLUSION

In conclusion, we present a case of HGSC of unknown origin that was managed using retroperitoneal lymphadenectomy, staging surgery, chemotherapy, and targeted therapy. Ongoing monitoring is essential to evaluate patient prognosis.

FOOTNOTES

Author contributions: Ding DC contributed to conceptualization, methodology, formal analysis, writing-original draft preparation, and writing, review, and editing; Hsieh WL contributed to data curation and wrote the original draft. All the authors have read and agreed to the published version of the manuscript.

Informed consent statement: Written informed consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Fan JR
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 **Otsuka I**. Primary Retroperitoneal Carcinomas: New Insights into Pathogenesis and Clinical Management in Comparison with Ovarian Carcinomas and Carcinoma of Unknown Primary. *Cancers (Basel)* 2023; **15** [PMID: 37760583 DOI: 10.3390/cancers15184614]

2 **Matulonis UA**, Sood AK, Fallowfield L, Howitt BE, Sehouli J, Karlan BY. Ovarian cancer. *Nat Rev Dis Primers* 2016; **2**: 16061 [PMID: 27558151 DOI: 10.1038/nrdp.2016.61]

3 **Otsuka I**. Mechanisms of High-Grade Serous Carcinogenesis in the Fallopian Tube and Ovary: Current Hypotheses, Etiologic Factors, and Molecular Alterations. *Int J Mol Sci* 2021; **22** [PMID: 33922503 DOI: 10.3390/ijms22094409]

4 **Wang Y**, Sessine MS, Zhai Y, Tipton C, McCool K, Kuick R, Connolly DC, Fearon ER, Cho KR. Lineage tracing suggests that ovarian endosalpingiosis does not result from escape of oviductal epithelium. *J Pathol* 2019; **249**: 206-214 [PMID: 31131879 DOI: 10.1002/path.5308]

5 **Gallan AJ**, Antic T. Benign müllerian glandular inclusions in men undergoing pelvic lymph node dissection. *Hum Pathol* 2016; **57**: 136-139 [PMID: 27438608 DOI: 10.1016/j.humpath.2016.07.003]

6 **Zhang Y**, Cao L, Nguyen D, Lu H. TP53 mutations in epithelial ovarian cancer. *Transl Cancer Res* 2016; **5**: 650-663 [PMID: 30613473 DOI: 10.21037/tcr.2016.08.40]

7 **Myriokefalitaki E**, Luqman I, Potdar N, Brown L, Steward W, Moss EL. Primary retroperitoneal mucinous cystadenocarcinoma (PRMCa): a systematic review of the literature and meta-analysis. *Arch Gynecol Obstet* 2016; **293**: 709-720 [PMID: 26681306 DOI: 10.1007/s00404-015-3975-8]

8 **Engbersen MP**, Van Driel W, Lambregts D, Lahaye M. The role of CT, PET-CT, and MRI in ovarian cancer. *Br J Radiol* 2021; **94**: 20210117 [PMID: 34415198 DOI: 10.1259/bjr.20210117]

9 **Tokai H**, Nagata Y, Taniguchi K, Matsumura N, Kitasato A, Tokunaga T, Takeshita H, Kuroki T, Maeda S, Ito M, Fujioka H. The long-term survival in primary retroperitoneal mucinous cystadenocarcinoma: a case report. *Surg Case Rep* 2017; **3**: 117 [PMID: 29177806 DOI: 10.1186/s40792-017-0394-z]

10 **Chae YK**, Saleem N, Roh Y, Bilal H, Viveiros P, Sukhadia B, Lin X, Sheikh MM, Park LC. Exceptional response to chemotherapy followed by concurrent radiotherapy and immunotherapy in a male with primary retroperitoneal serous Adenocarcinoma: a case report and literature review. *BMC Cancer* 2019; **19**: 748 [PMID: 31362708 DOI: 10.1186/s12885-019-5934-4]

11 **Otsuka I**, Honma K. FDG PET/CT in Primary Retroperitoneal Serous Carcinoma. *Clin Nucl Med* 2023; **48**: 625-626 [PMID: 37167336 DOI: 10.1097/RLU.0000000000004692]

12 **Gadducci A**, Guarneri V, Peccatori FA, Ronzino G, Scandurra G, Zamagni C, Zola P, Salutari V. Current strategies for the targeted treatment of high-grade serous epithelial ovarian cancer and relevance of BRCA mutational status. *J Ovarian Res* 2019; **12**: 9 [PMID: 30691488 DOI: 10.1186/s13048-019-0484-6]

13 **Berek JS**, Renz M, Kehoe S, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum: 2021 update. *Int J Gynaecol Obstet* 2021; **155** Suppl 1: 61-85 [PMID: 34669199 DOI: 10.1002/ijgo.13878]

14 **Homsi MJ**, Dadlani A, Khazai B, Anendaga CM, Bakhru S, Flaherty F. Diffuse abdominal and pelvic endosalpingiosis: A case report. *Radiol Case Rep* 2022; **17**: 3515-3518 [PMID: 35936880 DOI: 10.1016/j.radcr.2022.06.075]

15 **Boyarskikh UA**, Gulyaeva LF, Avdalyan AM, Kechin AA, Khrapov EA, Lazareva DG, Kushlinskii NE, Melkonyan A, Arakelyan A, Filipenko ML. Spectrum of TP53 Mutations in BRCA1/2 Associated High-Grade Serous Ovarian Cancer. *Front Oncol* 2020; **10**: 1103 [PMID: 32766142 DOI: 10.3389/fonc.2020.01103]

16 **Narayanan P**, Sahdev A. The role of (18)F-FDG PET CT in common gynaecological malignancies. *Br J Radiol* 2017; **90**: 20170283 [PMID: 28830238 DOI: 10.1259/bjr.20170283]

17 **Kohada Y**, Teishima J, Hattori Y, Kurimura Y, Fujii S, Sadahide K, Fukuoka K, Ueno T, Kitano H, Goto K, Hieda K, Shinmei S, Sentani K, Inoue S, Hayashi T, Yasui W, Matsubara A. Serous adenocarcinoma of retroperitoneum: a case report. *Int Cancer Conf J* 2017; **6**: 154-157 [PMID: 31149492 DOI: 10.1007/s13691-017-0296-8]

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