

World Journal of *Clinical Cases*

World J Clin Cases 2019 June 6; 7(11): 1242-1366



**MINIREVIEWS**

- 1242** Radiation therapy for extrahepatic bile duct cancer: Current evidences and future perspectives
Koo T, Park HJ, Kim K
- 1253** Antibiotics and immunotherapy in gastrointestinal tumors: Friend or foe?
Yan C, Tu XX, Wu W, Tong Z, Liu LL, Zheng Y, Jiang WQ, Zhao P, Fang WJ, Zhang HY

ORIGINAL ARTICLE**Basic Study**

- 1262** Elevated levels of interleukin-1 β , interleukin-6, tumor necrosis factor- α and vascular endothelial growth factor in patients with knee articular cartilage injury
Wang ZW, Chen L, Hao XR, Qu ZA, Huang SB, Ma XJ, Wang JC, Wang WM

Retrospective Cohort Study

- 1270** Anti-hepatitis C virus therapy in chronic kidney disease patients improves long-term renal and patient survivals
Chen YC, Li CY, Tsai SJ, Chen YC

Observational Study

- 1282** Clinical features of syphilitic myelitis with longitudinally extensive myelopathy on spinal magnetic resonance imaging
Yuan JL, Wang WX, Hu WL

Prospective Study

- 1291** Application of pulse index continuous cardiac output system in elderly patients with acute myocardial infarction complicated by cardiogenic shock: A prospective randomized study
Zhang YB, Zhang ZZ, Li JX, Wang YH, Zhang WL, Tian XL, Han YF, Yang M, Liu Y

META-ANALYSIS

- 1302** Efficacy and safety of tranexamic acid in elderly patients with intertrochanteric fracture: An updated meta-analysis
Zhou XD, Li J, Fan GM, Huang Y, Xu NW

CASE REPORT

- 1315** Lupus enteritis as the only active manifestation of systemic lupus erythematosus: A case report
Gonzalez A, Wadhwa V, Salomon F, Kaur J, Castro FJ

- 1323** Development of a biliary multi-hole self-expandable metallic stent for bile tract diseases: A case report
Kobayashi M
- 1330** Paraneoplastic leukemoid reaction in a patient with sarcomatoid hepatocellular carcinoma: A case report
Hu B, Sang XT, Yang XB
- 1337** Multiple synchronous anorectal melanomas with different colors: A case report
Cai YT, Cao LC, Zhu CF, Zhao F, Tian BX, Guo SY
- 1344** Huge primary dedifferentiated pancreatic liposarcoma mimicking carcinosarcoma in a young female: A case report
Liu Z, Fan WF, Li GC, Long J, Xu YH, Ma G
- 1351** A large basal cell adenoma extending to the ipsilateral skull base and mastoid in the right parotid gland: A case report
Du LY, Weng XH, Shen ZY, Cheng B
- 1358** Novel *ATL1* mutation in a Chinese family with hereditary spastic paraplegia: A case report and review of literature
Xiao XW, Du J, Jiao B, Liao XX, Zhou L, Liu XX, Yuan ZH, Guo LN, Wang X, Shen L, Lin ZY

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Kassem A Barada, MD, Professor, Department of Internal Medicine, American University of Beirut Medical Center, Beirut 110 72020, Lebanon

AIMS AND SCOPE

World Journal of Clinical Cases (*World J Clin Cases*, *WJCC*, online ISSN 2307-8960, DOI: 10.12998) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The primary task of *WJCC* is to rapidly publish high-quality Case Report, Clinical Management, Editorial, Field of Vision, Frontier, Medical Ethics, Original Articles, Meta-Analysis, Minireviews, and Review, in the fields of allergy, anesthesiology, cardiac medicine, clinical genetics, clinical neurology, critical care, dentistry, dermatology, emergency medicine, endocrinology, family medicine, gastroenterology and hepatology, etc.

INDEXING/ABSTRACTING

The *WJCC* is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), and Journal Citation Reports/Science Edition. The 2018 Edition of Journal Citation Reports cites the 2017 impact factor for *WJCC* as 1.931 (5-year impact factor: N/A), ranking *WJCC* as 60 among 154 journals in Medicine, General and Internal (quartile in category Q2).

**RESPONSIBLE EDITORS
FOR THIS ISSUE**

Responsible Electronic Editor: Yan-Xia Xing Proofing Editorial Office Director: Jin-Lei Wang

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Semimonthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

EDITORIAL OFFICE

Jin-Lei Wang, Director

PUBLICATION DATE

June 6, 2019

COPYRIGHT

© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Radiation therapy for extrahepatic bile duct cancer: Current evidences and future perspectives

Taeryool Koo, Hae Jin Park, Kyubo Kim

ORCID number: Taeryool Koo (0000-0002-6646-0937); Hae Jin Park (0000-0003-3891-8952); Kyubo Kim (0000-0001-6093-1294).

Author contributions: Kim K conceived and designed the study; Koo T and Park HJ reviewed and analyzed literature, and drafted the manuscript. All authors contributed to critical revision and editing, and approval of the final version.

Conflict-of-interest statement: No potential conflicts of interest. No financial support.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: February 21, 2019

Peer-review started: February 22, 2019

First decision: March 29, 2019

Revised: April 2, 2019

Accepted: April 18, 2019

Article in press: April 19, 2019

Published online: June 6, 2019

Taeryool Koo, Department of Radiation Oncology, Hallym University Sacred Heart Hospital, Anyang 14068, South Korea

Hae Jin Park, Department of Radiation Oncology, Hanyang University College of Medicine, Seoul 04763, South Korea

Kyubo Kim, Department of Radiation Oncology, Ewha Womans University College of Medicine, Seoul 07985, South Korea

Corresponding author: Kyubo Kim, MD, PhD, Associate Professor, Department of Radiation Oncology, Ewha Womans University College of Medicine, 1071 Anyangcheon-ro, Yangcheon-gu, Seoul 07985, South Korea. kyubokim.ro@gmail.com
Telephone: +82-2-2650-5334
Fax: +82-2-2654-0363

Abstract

Extrahepatic bile duct cancer (EBDC) is a rare malignancy that involves neoplastic changes extending from both hepatic ducts to the common bile duct. The treatment of choice is surgical resection, but the predominant pattern of initial treatment failure is locoregional recurrence. Accordingly, adjuvant radiotherapy has been administered after surgical resection based on these rationales. At this time, there is minimal evidence supporting adjuvant radiotherapy, because there have been no phase III trials evaluating its benefit. Relatively small retrospective studies have tried to compare outcomes associated with EBDC treated with or without radiotherapy. We aimed to review studies investigating adjuvant radiotherapy for resected EBDC. Because less than one-third of EBDC cases are amenable to curative resection at diagnosis, other locoregional treatment modalities need to be considered, including radiotherapy. The next aim of this review was to summarize reports of definitive radiotherapy for unresectable EBDC. Patients with advanced EBDC often experience biliary obstruction, which can lead to jaundice and progress to death. Biliary stent insertion is an important palliative procedure, but stents are prone to occlusion after subsequent ingrowth of the EBDC. Radiotherapy can be effective for maintaining the patency of inserted stents. We also reviewed the benefit of palliative radiotherapy combined with the biliary stent insertion. Lastly, we discuss the existing gaps in the evidence supporting radiotherapy in the management of EBDC.

Key words: Extrahepatic bile duct cancer; Patterns of failure; Adjuvant radiotherapy; Definitive radiotherapy; Palliative radiotherapy; Biliary stent

P-Reviewer: Sergi C
S-Editor: Gong ZM
L-Editor: A
E-Editor: Xing YX



©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tips: Radiotherapy has been administered for extrahepatic bile duct cancer patients in adjuvant, definitive, or palliative settings. The evidence in support of radiotherapy is derived from retrospective studies because there is a lack of randomized controlled trials. This review aimed to summarize contemporary series involving radiotherapy treatment for extrahepatic bile duct cancer. These data and findings were then used to propose strategies for generating robust evidence for or against the use of radiotherapy for this disease.

Citation: Koo T, Park HJ, Kim K. Radiation therapy for extrahepatic bile duct cancer: Current evidences and future perspectives. *World J Clin Cases* 2019; 7(11): 1242-1252

URL: <https://www.wjgnet.com/2307-8960/full/v7/i11/1242.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v7.i11.1242>

INTRODUCTION

Extrahepatic bile duct cancer (EBDC) accounts for 3% of all gastrointestinal malignancies^[1]. EBDC is traditionally divided into proximal and distal tumors, and the hallmark feature is a confluence of the cystic duct and common hepatic duct. The treatment of choice is surgical resection: combined hepatic and hilar resection for proximal tumors and pancreaticoduodenectomy for distal tumors. The bile duct system is deeply situated between surrounding critical organs and major vessels, which makes complete resection with pathologically negative margins difficult to achieve^[2]. The 5-year survival rates are up to 50% after complete surgical resection, but survival dramatically decreases to as low as 0% after incomplete resection or without resection^[3-6]. Adjuvant chemotherapy has been applied to increase survival among patients with bile duct malignancies, including cancers involving intrahepatic bile ducts, extrahepatic bile ducts, or the gallbladder. Phase III trials of gemcitabine alone^[7] or gemcitabine plus oxaliplatin^[8] failed to show a survival benefit of adjuvant chemotherapy alone compared with observation. In a palliative setting for unresectable bile duct cancer, cisplatin plus gemcitabine was associated with better survival than gemcitabine alone^[9].

Another potential approach for improving EBDC treatment outcomes is the addition of radiotherapy (RT). Theoretically, adjuvant RT can complement locoregional control (LRC) after incomplete resection. Definitive RT can be applied with curative intent for inoperable patients, or palliative RT can be used for symptom control and for maintaining the patency of biliary stents in advanced cases. Nonetheless—owing to the rareness of the disease—to the best of our knowledge, there is no high-level evidence, including published reports of randomized controlled trials, supporting the use of RT for EBDC. However, there are a few published reports of relatively small retrospective studies demonstrating the efficacy of RT. In this review, we discuss patterns of EBDC treatment failure after curative resection to illustrate the rationale of adjuvant RT. We also discuss the role of RT in definitive treatment and palliative care settings. We searched literatures about RT for EBDC in PubMed, and then reviewed the literatures published between 1995 and 2018.

PATTERNS OF TREATMENT FAILURE

Locoregional failure (LRF) has been reported as the most common type of initial EBDC treatment failure. Two Korean studies^[10,11] reported the patterns of initial treatment failure among EBDC patients who underwent curative resection. Choi *et al*^[10] analyzed the patterns of failure among 93 EBDC patients who underwent gross total resection and no adjuvant RT. Tumor recurrence occurred in 54 patients: isolated LRF in 18 (19%), both LRF and distant metastasis (DM) in 20 (22%), and DM alone in 16 (17%). Another study showed a similar result in 97 EBDC patients after curative resection without adjuvant treatment^[11]. Initial treatment failure was noted in 46 patients (47%): isolated LRF in 24 (25%), both LRF and DM in 13 (13%), and DM alone in 9 (9%). In terms of LRF sites, all of these studies reported similar distributions. The commonly involved LRF sites were tumor beds and lymph nodes (LNs) around the

hepatoduodenal ligament, celiac artery, and superior mesenteric vein. Considering the higher proportion of LRF in initial treatment failures, a potential role for adjuvant RT to prevent LRF had been proposed.

EBDC is more commonly associated with LRF than other biliary malignancies. Jarnagin *et al*^[12] analyzed 80 patients with gallbladder cancer (GBCA) and 76 patients with hilar cholangiocarcinoma (HCCA). All patients underwent potentially curative resection, and 11% of patients (11 with GBCA and 7 with HCCA) received adjuvant therapy. Recurrence occurred in 52 HCCA patients (68%), and the rates of initial LRF and DM were 65% and 36%, respectively. In contrast, 53 GBCA patients (66%) experienced tumor recurrence, and the rates of initial LRF and DM were 28% and 72%, respectively. The authors also noted the resection margin (RM), hilum, and bilioenteric anastomosis as sites of local recurrence. The LRF sites were concordant with those found in the aforementioned studies^[10,11].

EBDC has two patterns of tumor progression: superficial spread and submucosal infiltration^[13]. Consequently, biliary duct extension, liver atrophy, or portal vein involvement frequently occur, especially with proximal EBDC. Because of the natural history of proximal EBDC, hepatectomy is typically required to achieve negative RMs^[14]. Additionally, an adequate radial margin should be obtained for mid-distal EBDC, although the bile duct is surrounded by major vascular structures^[15]. Owing to the surgical complexity, the reported incidence of positive RMs ranges from 10% to 48% after potentially curative resection for EBDC^[2-6,12,14]. Positive RMs are generally associated with poorer survival, and adjuvant RT is a potential solution to this problem.

ADJUVANT RT

The use of adjuvant RT for EBDC has been associated with a change in the patterns of treatment failure. Several studies investigating EBDC patients undergoing adjuvant RT have reported enhanced LRC, with DM identified as a significant pattern of failure. The 5-year locoregional-recurrence-free survival (LRFS) and overall survival (OS) rates are up to 80% and 46%, respectively, in patients with negative RMs^[16-18]. In terms of initial failure sites, DM alone reportedly occurs in 58% to 76% of cases, LRF alone in 12% to 24%, and both LRF plus DM in 19% to 21%^[16-18]. Conflicting results can also be found, for example, LRF reported as the predominant site of failure and the median OS reported as less than 20 mo^[19,20]. Interestingly, the studies reporting lower LRFS used concomitant chemotherapy (20%-54%) less frequently than those reporting improved LRFS (84%-97%). The use of concomitant chemotherapy with adjuvant RT might increase LRC via a radiosensitizing effect. SWOG S0809, a phase II trial^[21] used an intensified adjuvant treatment regimen—four cycles of gemcitabine and capecitabine followed by concurrent capecitabine and RT (54-59.4 Gy)—for EBDC ($n = 54$) and GBCA ($n = 25$) patients after curative resection. With a median follow-up time of 35 mo, the 2-year OS rates were 67% and 60% for R0- and R1-resected patients (not significantly different), respectively, and the 2-year local recurrence rates were 9% and 16% for corresponding patients. Regarding initial failure, distant failure ($n = 24$) was more frequent than local failure ($n = 14$). This was positive evidence, suggesting a high level of local control with the intensified adjuvant chemoradiotherapy (CRT) regimen.

In the absence of randomized controlled trials comparing adjuvant RT *vs* no RT after curative resection, we reviewed retrospective studies investigating potential survival and LRC benefits associated with adjuvant RT for EBDC. In earlier reports, the association between the use of adjuvant RT and improved outcomes was equivocal. Pitt *et al*^[22] compared adjuvant RT *vs* no RT for proximal EBDC ($n = 50$). Adjuvant RT was not associated with improved outcomes, and median OS was not significantly different between the groups. These findings should be interpreted cautiously, however, because curative resection was frequently insufficient. In the resection subgroup ($n = 31$), gross total resection was achieved for only 21 patients, and 10 underwent partial resection. Two studies using the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute^[23,24] also concluded there was no definitive evidence for improved survival with the addition of adjuvant RT for resected EBDC. However, the registries in these studies had no information about the extent of resection, and the study period (1973-2004) was too long to reflect the trend of surgery or RT.

According to recently reported studies based on a multi-institutional database, adjuvant therapy is associated with improved survival for patients with resected EBDC^[25-27]. In particular, adjuvant CRT is more beneficial than adjuvant chemotherapy or RT alone. As detailed methods for these studies were not provided, it is

worthwhile to review retrospective studies. Selected series are summarized in [Table 1](#).

Improved survival or LRC after adjuvant CRT was reported after several studies investigating the treatment of EBDC with resection and adjuvant therapy with curative intent^[28-34]. Kim *et al*^[30] performed survival analyses of EBDC patients who underwent curative resection and compared an adjuvant CRT group *vs* a no-CRT group. The median RT dose was 45 Gy in 25 fractions, and 5-fluorouracil (5-FU)-based chemotherapy was concurrently administered (99.1%). The CRT group had significantly longer 5-year LRFS (58.5% *vs* 44.4%, $P = 0.007$), disease-free survival (DFS; 32.1% *vs* 26.1%, $P = 0.041$), and OS (36.5% *vs* 28.2%, $P = 0.049$) than the no-CRT group. Gwak *et al*^[31] reported the usefulness of adjuvant RT by comparing a surgery-alone group *vs* an adjuvant-RT group; LRF decreased (61.7% *vs* 35.6%, $P = 0.02$) and DFS increased among patients who underwent incomplete resection (4.1% *vs* 13.9%, $P = 0.042$). In contrast, no significant differences were found in the 5-year OS rates (12% *vs* 21%, $P > 0.5$), and less use of chemotherapy (51.6%) for the adjuvant RT group might be one of the reasons ([Table 1](#)).

To determine the patients most likely to benefit, adjuvant RT has been considered in cases with unfavorable disease characteristics. In this context, several studies have suggested that adjuvant RT or CRT yield equivalent even with apparently unfavorable baseline clinical features, such as advanced stage, LN-positive, or RM-positive disease^[35-37]. Borghero *et al*^[35] divided 65 patients who underwent curative resection into surgery-alone (RM-negative, $n = 23$) and adjuvant CRT (RM-positive or pN1, $n = 42$) groups. The median RT dose was 55 Gy (45 Gy to primary field and 10 Gy to boost field), and all patients with adjuvant RT received chemotherapy (5-FU in 52.4% and capecitabine in 47.6%). Even with unfavorable baseline clinical features, the surgery-alone and adjuvant CRT groups showed similar 5-year OS (36% *vs* 42%, $P = 0.6$) and LRFS (38% *vs* 37%, $P = 0.13$) ([Table 1](#)).

DEFINITIVE RT

Although resection is the most important treatment modality for EBDC, less than one-third of patients are amenable to curative resection at the time of diagnosis^[38]. For patients with such advanced disease, an alternative option for LRC must be considered. Definitive CRT has been reported to be feasible and tolerable among patients with unresectable and non-metastatic EBDC^[39,40]. In studies using the SEER database or National Cancer Database, CRT has been associated with improved survival, unlike RT alone^[41] or chemotherapy alone^[42]. Definitive CRT with intensified chemotherapy was a candidate strategy to improve LRC. In a phase I/II trial performed in Germany^[43], 18 EBDC patients (7 resected cases and 11 unresectable cases) underwent CRT up to 49.6 Gy with gemcitabine followed by 66 cycles of gemcitabine and capecitabine. In patients with unresectable tumors, the median OS was 7.9 mo, and four patients experienced grade 3 to 4 cholangitis. Considering high toxicity, the authors did not recommend their protocol to patients with unresectable tumors.

Another option for improving LRC is increasing the RT dose. Because of the anatomic location of EBDCs, a higher RT dose can give rise to frequent and severe adverse events, such as duodenal ulcers, stenosis, and bowel perforation. In this context, a combination of external-beam RT (EBRT) and intraluminal brachytherapy (ILBT) has been tried. ILBT doses are prescribed at 0.5 to 1.5 cm from the center of the source, so the RT dose theoretically can be escalated within a manageable toxicity range. Due to the relative scarcity of studies guiding ILBT, various schemes for ILBT are used in practice, and patients receiving ILBT are frequently analyzed as a subgroup in EBDC studies^[44-46]. In Italy, a phase II trial of definitive CRT with gemcitabine for unresectable EBDC was conducted^[47]. Twenty-seven patients received 50 Gy of EBRT, and six patients were given 15 to 20 Gy of ILBT. After a median follow-up time of 16 mo, the 2-year LRFS and OS rates were 29% and 27%, respectively. Gastrointestinal toxicity was tolerable, and grade 3 and 4 toxicities occurred in four patients and one patient, respectively. Also, patients who received an ILBT boost appeared to have a better LRC than those who did not receive the boost (the 2-year LRFS rates, 53% *vs* 25%).

Several studies reported improved treatment outcomes in patients with unresectable EBDC after combination therapy with EBRT and ILBT^[46,48-50]. Takamura *et al*^[48] prescribed 27 to 50 Gy (mean, 39.2 Gy) of ILBT following 50 Gy of EBRT ($n = 93$). The median OS was 12 mo, and the 1-year and 2-year OS rates were 49.5% and 15.1%, respectively. Grade 3 gastroduodenal complications occurred in 10 patients (10.8%), grade 3 biliary complications in five patients (5.4%), and treatment-related biliary fistulas in eight patients (8.6%). However, results from studies comparing combined

Table 1 Contemporary series of adjuvant radiotherapy for resected extrahepatic bile duct cancer

Ref.	Study period	Study design	No. of pts	RT dose (median)	Concurrent chemo-therapy	Subgroup	5-yr overall survival
Kim <i>et al</i> ^[16]	1995-2002	Retrospective	86	40 Gy	5-FU (96.5%)	R0 (<i>n</i> = 58) R1 (<i>n</i> = 28)	46.3% 41.4%
Park <i>et al</i> ^[17]	1998-2007	Retrospective	101	50 Gy	5-FU (84%)	R0 (<i>n</i> = 52) R1 (<i>n</i> = 37)	44% 33%
Borghero <i>et al</i> ^[35]	1984-2005	Retrospective	65	55 Gy -	5-FU (52.4%), Cap (47.6%)	RT ¹ (<i>n</i> = 42) No RT (<i>n</i> = 23)	36% 42%
Gwak <i>et al</i> ^[31]	1997-2005	Retrospective	78	50.4 Gy -	FP or FL (51.6%) -	RT (<i>n</i> = 31) No RT ² (<i>n</i> = 47)	21.0% 11.6%
Kim <i>et al</i> ^[30] ³	2001-2009	Retrospective	168	45 Gy -	FL (99.1%) -	RT (<i>n</i> = 115) No RT (<i>n</i> = 53)	36.5% 28.2%
Ben-Josef <i>et al</i> ^[21] ⁴	2008-2012	Phase 2	79	54-59.4 Gy	4 cycles of GemCap followed by concurrent Cap	R0 (<i>n</i> = 54) R1 (<i>n</i> = 25)	67% ⁵ 60% ⁵

¹Received adjuvant chemotherapy before chemoradiotherapy in 17% of patients;²Received adjuvant chemotherapy in 17% of patients;³Includes ampullary cancer as well (18.4%);⁴Includes gallbladder cancer as well (31.6%);⁵2-yr overall survival rate. RT: Radiotherapy; 5-FU: 5-fluorouracil; Cap: Capecitabine; FL: 5-FU plus leucovorin; GemCap: Gemcitabine plus capecitabine; NS: Not significant.

EBRT and ILBT *vs* EBRT alone are somewhat conflicting^[49,50]. Shin *et al*^[49] compared treatment outcomes among 17 patients who underwent EBRT alone (median, 50.4 Gy) and 14 patients who underwent EBRT and ILBT (15 Gy). The combination group had a better OS than the EBRT-alone group (at 2 years, 21% *vs* 0%, *P* = 0.015), but LRF rates were similar (36% *vs* 53%, *P* > 0.05). Yoshioka *et al*^[50] performed a propensity-score matched-pair analysis of 209 patients (153 who underwent EBRT alone and 56 who received EBRT and ILBT). OS was similar between the groups (at 2 years, 31% for the ILBT(+) group *vs* 40% for the ILBT(-) group; *P* = 0.862), and there was a trend toward improvement of LRC in the ILBT(+) group (at 2 years, 65% for the ILBT(+) group *vs* 35% for the ILBT(-) group; *P* = 0.094). After sensitivity analysis, it was concluded that ILBT had no significant impact on OS but was associated with enhanced LRC. Selected studies for definitive RT are listed in Table 2.

With the development of new RT techniques, including sophisticated dose delivery and image guidance, intensity-modulated radiation therapy (IMRT) or stereotactic body radiation therapy (SBRT) have been noted as alternatives to ILBT. SBRT can deliver high doses within a narrower safety margin than would be possible with three-dimensional conformal RT. SBRT could be useful in terms of invasiveness and precise dose calculation. Promising results have been reported, especially following studies investigating proximal EBDC^[51-54] (Table 3).

PALLIATIVE RT

Advanced EBDC patients often experience biliary obstruction, which can lead to jaundice, cholangitis, hepatic failure, biliary sepsis, and even death. Biliary stent insertion is commonly used to escape the vicious cycle of malignant biliary obstruction. Traditionally, endoscopic polyethylene stent insertion was preferred due to hemorrhage and bile leaks associated with liver puncture secondary to percutaneous stent insertion^[55]. After stent insertion, recurrent obstruction related to tumor progression is a critical event compromising the quality of life and survival of patients with advanced EBDC. Practically, ILBT can help maintain biliary stent patency, which can significantly prolong stent patency and survival^[56]. However, ILBT is invasive and requires longer hospitalization^[57], and it is uncommonly performed despite positive results^[58], although high-dose ILBT could be an alternative to traditional low-dose ILBT^[59]. As mentioned earlier, advanced EBRT techniques, such as IMRT and SBRT, are expected to meet the need of dose escalation

Table 2 Contemporary series of definitive radiotherapy for unresectable extrahepatic bile duct cancer

Ref.	Study period	Study design	No. of pts	EBRT (median)	Brachytherapy	Chemotherapy	Median OS (mo)
Deodata <i>et al</i> ^[44]	1991-1997	Retrospective	22	50.4 Gy	30-50 Gy (<i>n</i> = 12)	5-FU (95.5%)	23.0 ¹
Brunner <i>et al</i> ^[45]	1994-2001	Retrospective	25	45 Gy	10 Gy (<i>n</i> = 4)	FM (40%), GP (56%)	11.8 ²
Schleicher <i>et al</i> ^[46]	1991-1999	Retrospective	30	30 Gy	24-40 Gy (<i>n</i> = 18)	5-FU (80%)	5.7 ²
Takamura <i>et al</i> ^[48]	1988-1998	Retrospective	93	50 Gy	39.2 Gy ³	-	12 ²
Shin <i>et al</i> ^[49]	1986-1995	Retrospective	31	50.4 Gy	15 Gy (<i>n</i> = 14) - (<i>n</i> = 17)	-	21% ⁴ <i>P</i> = 0.015 0% ⁴
Yoshioka <i>et al</i> ^[50]	2000-2011	Retrospective	209	50 Gy	8-30 Gy (<i>n</i> = 56) - (<i>n</i> = 153)	Various (57%)	31% ⁴ <i>P</i> = 0.862 40% ⁴
Torgeson <i>et al</i> ^[42]	2004-2014	NCBD	1070 1871	54-89 Gy -	- -	Various (100%)	14.5 <i>P</i> < 0.001 12.6
Autorino <i>et al</i> ^[47]	2002-2009	Phase 2	27	50 Gy	15-20 Gy (<i>n</i> = 6)	Gemcitabine (100%)	14

¹From the date of cancer diagnosis;²From the time of radiotherapy initiation;³mean;⁴2-yr overall survival rate. EBRT: External beam radiotherapy; OS: Overall survival; 5-FU: 5-fluorouracil; FM: 5-FU plus mitomycin-C; GP: Gemcitabine plus cisplatin; NCBD: National Cancer Database.

Currently, metallic biliary stent insertion and EBRT are widely used to maintain stent patency and delay fatal biliary obstruction for advanced EBDC patients. Several studies have reported on the safety and effectiveness of EBRT combined with metallic stents in terms of prolonging stent patency (Table 4). Lee *et al*^[60] compared 18 patients who received EBRT (RT group) and 32 patients who did not (no-RT group) after undergoing uncovered metallic stent insertion. Although stent patency (median, 4.7 mo *vs* 4.5 mo, *P* = 0.94) and OS (median, 14 mo *vs* 9 mo, *P* = 0.11) were not significantly different between the RT and no-RT groups, there was no serious adverse reaction in either group.

Meanwhile, Isayama *et al*^[59] reported that RT enhanced OS and stent patency after comparing survival and stent patency among 39 patients with advanced EBDC (RT group, *n* = 28; no-RT group, *n* = 11). The RT group showed improved OS (median, 22.1 mo *vs* 5.7 mo; *P* = 0.0031) and stent patency (at 1 year, 50% *vs* 0%; *P* = 0.0165) relative to the no-RT group. Regarding complications, five patients (18%) in the RT group experienced hemorrhagic gastroduodenal ulcers but recovered after starting on anti-ulcer agents. Shinchi *et al*^[61] also demonstrated that EBRT can provide a definite benefit for advanced EBDC patients (RT group, *n* = 30; no-RT group, *n* = 20) with metallic stents. Chemotherapy was given in 23% of the RT group and 40% of the no-RT group. The RT group had a mean OS of 10.6 mo, which was significantly longer than that of the no-RT group (6.4 mo, *P* < 0.05). RT administration was associated with prolonged stent patency (mean, 9.8 mo *vs* 3.7 mo; *P* < 0.001). Within the RT group, one patient experienced grade 4 hematologic toxicity, one patient experienced grade 3 anorexia and nausea, and one patient presented with grade 3 gastroduodenal bleeding necessitating transfusion.

For most studies, the dose of EBRT for palliation has been 45-50 Gy^[59-61], which is similar to the RT dose used in the definitive treatment setting (Table 2). Five weeks of RT is a relatively long time considering the aim of palliation. Tan *et al*^[62] used a shorter course of palliative RT, with a total dose of 37.0 to 40.7 Gy in 10 to 11 fractions for unresectable EBDC patients (25 patients in the RT group and 13 patients in the no-RT group). Early complications were noted in three patients (12%) and three patients (23%) in the RT and no-RT groups, respectively. There was only one procedure-associated death, which was of a patient who did not undergo RT. RT also prolonged survival (median, 12.2 mo *vs* 8.9 mo; *P* = 0.025) and stent patency (median, 10.9 mo *vs* 6.5 mo; *P* = 0.022).

In summary, biliary stenting offers opportunities to relieve obstruction-related symptoms and delay death for advanced EBDC patients. EBRT could prolong stent patency and survival, and it is less invasive than ILBT. For patient convenience, a shorter course of palliative RT with a larger daily fraction size could be considered.

FUTURE PERSPECTIVES

Although RT may have a positive effect on LRC for EBDC patients, clear evidence

Table 3 Stereotactic body radiotherapy for hilar cholangiocarcinoma

Ref.	Study period	Study design	No. of pts	RT dose	RT modality	Late toxicity ≥ Gr 3	Median OS (mo)
Kopek <i>et al</i> ^[51] ¹	1999-2006	Retrospective	27	45 Gy/3fx	linear accelerator	22.2% (duodenal ulcer)	10.6 ²
Momm <i>et al</i> ^[52]	1998-2008	Retrospective	13	32-56 Gy/8-16fx	linear accelerator	None	33.5 ³
Polistina <i>et al</i> ^[53]	2004-2009	Retrospective	10	30 Gy/3fx	Cyber Knife	None	35.5 ³

¹Includes intrahepatic cholangiocarcinoma as well (3.7%);²from the date of radiotherapy initiation;³From the date of cancer diagnosis.

from phase III trials is required. Limited numbers of phase III clinical trials are being conducted for unresectable or resected EBDC patients. For unresectable EBDC, an important topic is whether CRT is superior to chemotherapy alone. The agents used for single chemotherapy are gemcitabine and cisplatin, and gemcitabine is used for CRT. The doses for definitive RT are 45 Gy in 25 fractions for microscopic disease and a higher dose of 52.5 to 60 Gy in 25 fractions for gross disease (NCT02773485). After resection, adjuvant CRT *vs* chemotherapy alone is also being tested. For adjuvant CRT, induction chemotherapy with gemcitabine plus capecitabine followed by CRT with capecitabine is given; and for adjuvant chemotherapy alone, gemcitabine plus capecitabine is used. The total dose for adjuvant RT is 50.4 Gy in 28 fractions (NCT02798510).

One of the most important barriers to administering RT for EBDC patients is the lack of guidelines for clinical target volume (CTV) delineation. Insufficient CTVs cannot accomplish efficient LRC, while extensive CTVs may lead to unnecessary adverse effects. Recently, visualization of LN recurrence has been used for determining appropriate CTV boundaries^[10,63]; however, discordance among studies is inevitable owing to the rareness of EBDC and its associated complex anatomical classification. To investigate solutions to these limitations, Socha *et al*^[64] comprehensively searched the literature for articles reporting pathological data on the LN involvement patterns and LRF locations of biliary tract cancers. The authors also searched for articles about adjuvant RT and extracted information about CTV. The literature review revealed that the areas of potential geographic misses were the paraaortic LNs (entire EBDC), superior mesenteric artery LNs (middle and distal EBDCs), and anterior pancreaticoduodenal LNs (distal EBDC). Conversely, celiac LNs were considered to be unnecessarily irradiated for middle and distal EBDCs. Based on these results, an atlas was proposed for CTV delineation^[65]. The innovation of RT techniques makes the delivery of higher RT doses within a sub-millimeter scale. To catch up to the technical progress, a sophisticated and standardized guideline for CTV delineation is essential.

CONCLUSION

LRF is the major pattern of initial failure after surgical resection for EBDC patients. The addition of RT has been considered to have the potential to improve LRC. A phase II trial of adjuvant CRT for resected EBDC and GBCA showed a high level of local control even in R1-resected patients. Although there are no phase III trials comparing resection alone *vs* adjuvant treatments, retrospective studies have reported that adjuvant CRT is associated with improved LRC after curative-intent resection of EBDC. For patients with unresectable EBDC, a combination of EBRT and ILBT was traditionally administered. With the progression of modern RT techniques, less invasive and more intensive IMRT or SBRT have been tried as substitutes for ILBT. In patients unamenable to curative treatment, biliary stents are commonly inserted to relieve obstruction-related symptoms and delay death. Additional RT – either ILBT or EBRT – has been reported to be associated with prolonged stent patency and survival. At this time, several phase III clinical trials are being conducted to establish clear evidence. Additionally, a standard guideline for CTV delineation is needed.

Table 4 Palliative radiotherapy for stent patency in hilar cholangiocarcinoma

Ref.	Study period	Study design	No. of pts	EBRT	Brachytherapy	Median OS (mo)	Median stent patency (mo)
Lee <i>et al</i> ^[60] ¹	2005-2008	Retrospective	18	≥ 50 Gy	-	14.0	<i>P</i> = 0.11
			32	-	-	9.0	<i>P</i> = 0.94
Isayama <i>et al</i> ^[59]	1986-2008	Retrospective	28	Median 50 Gy	24 Gy (<i>n</i> = 11)	22.1	<i>P</i> = 0.0031
			11	-	-	5.7	50% ² <i>P</i> = 0.0165
Shinchi <i>et al</i> ^[61]	1992-1998	Retrospective	30	Median 46 Gy ³	-	10.6 ³	<i>P</i> < 0.05
			10	-	-	6.4 ³	9.8 ³ <i>P</i> = 0.0002
Tan <i>et al</i> ^[62]	2007-2013	Retrospective	25	37.0-40.7 Gy	-	12.2	<i>P</i> = 0.025
			13	-	-	8.9	10.9 <i>P</i> = 0.022
							6.5

¹Location not specified;²Crude stent patency rate at 1-yr;³mean. EBRT: External beam radiotherapy; OS: Overall survival.

REFERENCES

- Khan SA, Thomas HC, Davidson BR, Taylor-Robinson SD. Cholangiocarcinoma. *Lancet* 2005; **366**: 1303-1314 [PMID: 16214602 DOI: 10.1016/S0140-6736(05)67530-7]
- Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BS J, Youssef BA M, Klimstra D, Blumgart LH. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg* 2001; **234**: 507-517; discussion 517-519 [PMID: 11573044]
- Kosuge T, Yamamoto J, Shimada K, Yamasaki S, Makuuchi M. Improved surgical results for hilar cholangiocarcinoma with procedures including major hepatic resection. *Ann Surg* 1999; **230**: 663-671 [PMID: 10561090]
- Wakai T, Shirai Y, Moroda T, Yokoyama N, Hatakeyama K. Impact of ductal resection margin status on long-term survival in patients undergoing resection for extrahepatic cholangiocarcinoma. *Cancer* 2005; **103**: 1210-1216 [PMID: 15685618 DOI: 10.1002/cncr.20906]
- Jang JY, Kim SW, Park DJ, Ahn YJ, Yoon YS, Choi MG, Suh KS, Lee KU, Park YH. Actual long-term outcome of extrahepatic bile duct cancer after surgical resection. *Ann Surg* 2005; **241**: 77-84 [PMID: 15621994]
- Hemming AW, Reed AI, Fujita S, Foley DP, Howard RJ. Surgical management of hilar cholangiocarcinoma. *Ann Surg* 2005; **241**: 693-699; discussion 699-702 [PMID: 15849505]
- Ebata T, Hirano S, Konishi M, Uesaka K, Tsuchiya Y, Ohtsuka M, Kaneoka Y, Yamamoto M, Ambo Y, Shimizu Y, Ozawa F, Fukutomi A, Ando M, Nimura Y, Nagino M; Bile Duct Cancer Adjuvant Trial (BCAT) Study Group. Randomized clinical trial of adjuvant gemcitabine chemotherapy versus observation in resected bile duct cancer. *Br J Surg* 2018; **105**: 192-202 [PMID: 29405274 DOI: 10.1002/bjs.10776]
- Edeline J, Benabdelghani M, Bertaut A, Watelet J, Hammel P, Joly JP, Boudjema K, Fartoux L, Bouhier-Leporrier K, Jouve JL, Faroux R, Guerin-Meyer V, Kurtz JE, Assénat E, Seitz JF, Baumgaertner I, Tougeron D, de la Fouchardière C, Lombard-Bohas C, Boucher E, Stanbury T, Louvet C, Malka D, Phelip JM. Gemcitabine and Oxaliplatin Chemotherapy or Surveillance in Resected Biliary Tract Cancer (PRODIGE 12-ACCORD 18-UNICANCER GI): A Randomized Phase III Study. *J Clin Oncol* 2019; **37**: 658-667 [PMID: 30707660 DOI: 10.1200/JCO.18.00050]
- Valle J, Wasan H, Palmer DH, Cunningham D, Anthony A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010; **362**: 1273-1281 [PMID: 20375404 DOI: 10.1056/NEJMoa0908721]
- Choi HS, Kang KM, Jeong BK, Jeong H, Lee YH, Ha IB, Kim TG, Song JH. Patterns of failure after resection of extrahepatic bile duct cancer: implications for adjuvant radiotherapy indication and treatment volumes. *Radiat Oncol* 2018; **13**: 85 [PMID: 29739420 DOI: 10.1186/s13014-018-1024-z]
- Koo TR, Eom KY, Kim IA, Cho JY, Yoon YS, Hwang DW, Han HS, Kim JS. Patterns of failure and prognostic factors in resected extrahepatic bile duct cancer: implication for adjuvant radiotherapy. *Radiat Oncol J* 2014; **32**: 63-69 [PMID: 25061574 DOI: 10.3857/roj.2014.32.2.63]
- Jarnagin WR, Ruo L, Little SA, Klimstra D, D'Angelica M, DeMatteo RP, Wagman R, Blumgart LH, Fong Y. Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. *Cancer* 2003; **98**: 1689-1700 [PMID: 14534886 DOI: 10.1002/cncr.11699]
- Sakamoto E, Nimura Y, Hayakawa N, Kamiya J, Kondo S, Nagino M, Kanai M, Miyachi M, Uesaka K. The pattern of infiltration at the proximal border of hilar bile duct carcinoma: a histologic analysis of 62 resected cases. *Ann Surg* 1998; **227**: 405-411 [PMID: 9527064]
- Burke EC, Jarnagin WR, Hochwald SN, Pisters PW, Fong Y, Blumgart LH. Hilar Cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. *Ann Surg* 1998; **228**: 385-394 [PMID: 9742921]
- Sakamoto Y, Kosuge T, Shimada K, Sano T, Ojima H, Yamamoto J, Yamasaki S, Takayama T, Makuuchi M. Prognostic factors of surgical resection in middle and distal bile duct cancer: an analysis of 55 patients concerning the significance of ductal and radial margins. *Surgery* 2005; **137**: 396-402 [PMID: 15800484 DOI: 10.1016/j.surg.2004.10.008]
- Kim K, Chie EK, Jang JY, Kim SW, Han SW, Oh DY, Im SA, Kim TY, Bang YJ, Ha SW. Adjuvant chemoradiotherapy after curative resection for extrahepatic bile duct cancer: a long-term single center experience. *Am J Clin Oncol* 2012; **35**: 136-140 [PMID: 21325937 DOI: 10.1002/ajco.21325]

- 10.1097/COC.0b013e318209aa29]
- 17 **Park JH**, Choi EK, Ahn SD, Lee SW, Song SY, Yoon SM, Kim YS, Lee YS, Lee SG, Hwang S, Lee YJ, Park KM, Kim TW, Chang HM, Lee JL, Kim JH. Postoperative chemoradiotherapy for extrahepatic bile duct cancer. *Int J Radiat Oncol Biol Phys* 2011; **79**: 696-704 [PMID: [20510541](#) DOI: [10.1016/j.ijrobp.2009.12.031](#)]
- 18 **Nelson JW**, Ghafoori AP, Willett CG, Tyler DS, Pappas TN, Clary BM, Hurwitz HI, Bendell JC, Morse MA, Clough RW, Czito BG. Concurrent chemoradiotherapy in resected extrahepatic cholangiocarcinoma. *Int J Radiat Oncol Biol Phys* 2009; **73**: 148-153 [PMID: [18805651](#) DOI: [10.1016/j.ijrobp.2008.07.008](#)]
- 19 **Ben-David MA**, Griffith KA, Abu-Isa E, Lawrence TS, Knol J, Zalupski M, Ben-Josef E. External-beam radiotherapy for localized extrahepatic cholangiocarcinoma. *Int J Radiat Oncol Biol Phys* 2006; **66**: 772-779 [PMID: [17011452](#) DOI: [10.1016/j.ijrobp.2006.05.061](#)]
- 20 **Oh D**, Lim DH, Heo JS, Choi SH, Choi DW, Ahn YC, Park W, Huh SJ. The role of adjuvant radiotherapy in microscopic tumor control after extrahepatic bile duct cancer surgery. *Am J Clin Oncol* 2007; **30**: 21-25 [PMID: [17278890](#) DOI: [10.1097/01.coc.0000245467.97180.78](#)]
- 21 **Ben-Josef E**, Guthrie KA, El-Khoueiry AB, Corless CL, Zalupski MM, Lowy AM, Thomas CR, Alberts SR, Dawson LA, Micetich KC, Thomas MB, Siegel AB, Blanke CD. SWOG S0809: A Phase II Intergroup Trial of Adjuvant Capecitabine and Gemcitabine Followed by Radiotherapy and Concurrent Capecitabine in Extrahepatic Cholangiocarcinoma and Gallbladder Carcinoma. *J Clin Oncol* 2015; **33**: 2617-2622 [PMID: [25964250](#) DOI: [10.1200/JCO.2014.60.2219](#)]
- 22 **Pitt HA**, Nakeeb A, Abrams RA, Coleman J, Piantadosi S, Yeo CJ, Lillemore KD, Cameron JL. Perihilar cholangiocarcinoma. Postoperative radiotherapy does not improve survival. *Ann Surg* 1995; **221**: 788-97; discussion 797-8 [PMID: [7794082](#)]
- 23 **Vern-Gross TZ**, Shivanli AT, Chen K, Lee CM, Tward JD, MacDonald OK, Crane CH, Talamonti MS, Munoz LL, Small W. Survival outcomes in resected extrahepatic cholangiocarcinoma: effect of adjuvant radiotherapy in a surveillance, epidemiology, and end results analysis. *Int J Radiat Oncol Biol Phys* 2011; **81**: 189-198 [PMID: [20971573](#) DOI: [10.1016/j.ijrobp.2010.05.001](#)]
- 24 **Yu JB**, Decker RH, Knisely JP. The role of postoperative radiation therapy (PORT) in the treatment of extrahepatic bile duct cancer: a surveillance, epidemiology, and end results (SEER) population-based investigation. *J Gastrointest Cancer* 2008; **39**: 11-21 [PMID: [19156542](#) DOI: [10.1007/s12029-008-9045-8](#)]
- 25 **Hoehn RS**, Wima K, Ertel AE, Meier A, Ahmad SA, Shah SA, Abbott DE. Adjuvant Chemotherapy and Radiation Therapy is Associated with Improved Survival for Patients with Extrahepatic Cholangiocarcinoma. *Ann Surg Oncol* 2015; **22** Suppl 3: S1133-S1139 [PMID: [25976862](#) DOI: [10.1245/s10434-015-4599-8](#)]
- 26 **Ecker BL**, Vining CC, Roses RE, Maggino L, Lee MK, Drebin JA, Fraker DL, Vollmer CM, Datta J. Identification of Patients for Adjuvant Therapy After Resection of Carcinoma of the Extrahepatic Bile Ducts: A Propensity Score-Matched Analysis. *Ann Surg Oncol* 2017; **24**: 3926-3933 [PMID: [28952140](#) DOI: [10.1245/s10434-017-6095-9](#)]
- 27 **Krasnick BA**, Jin LX, Davidson JT 4th, Sanford DE, Ethun CG, Pawlik TM, Poultides GA, Tran T, Idrees K, Hawkins WG, Chapman WC, Doyle MBM, Weber SM, Strasberg SM, Salem A, Martin RCG, Isom CA, Scoggins C, Schmidt CR, Shen P, Beal E, Hatzaras I, Shenoy R, Maitheil SK, Fields RC. Adjuvant therapy is associated with improved survival after curative resection for hilar cholangiocarcinoma: A multi-institution analysis from the U.S. extrahepatic biliary malignancy consortium. *J Surg Oncol* 2018; **117**: 363-371 [PMID: [29284072](#) DOI: [10.1002/jso.24836](#)]
- 28 **Todoroki T**, Ohara K, Kawamoto T, Koike N, Yoshida S, Kashiwagi H, Otsuka M, Fukao K. Benefits of adjuvant radiotherapy after radical resection of locally advanced main hepatic duct carcinoma. *Int J Radiat Oncol Biol Phys* 2000; **46**: 581-587 [PMID: [10701737](#)]
- 29 **Heron DE**, Stein DE, Eschelmann DJ, Topham AK, Waterman FM, Rosato EL, Alden M, Anne PR. Cholangiocarcinoma: the impact of tumor location and treatment strategy on outcome. *Am J Clin Oncol* 2003; **26**: 422-428 [PMID: [12902899](#) DOI: [10.1097/01.COC.0000026833.73428.1F](#)]
- 30 **Kim TH**, Han SS, Park SJ, Lee WJ, Woo SM, Moon SH, Yoo T, Kim SS, Kim SH, Hong EK, Kim DY, Park JW. Role of adjuvant chemoradiotherapy for resected extrahepatic biliary tract cancer. *Int J Radiat Oncol Biol Phys* 2011; **81**: e853-e859 [PMID: [21497455](#) DOI: [10.1016/j.ijrobp.2010.12.019](#)]
- 31 **Gwak HK**, Kim WC, Kim HJ, Park JH. Extrahepatic bile duct cancers: surgery alone versus surgery plus postoperative radiation therapy. *Int J Radiat Oncol Biol Phys* 2010; **78**: 194-198 [PMID: [19910130](#) DOI: [10.1016/j.ijrobp.2009.07.003](#)]
- 32 **Im JH**, Seong J, Lee IJ, Park JS, Yoon DS, Kim KS, Lee WJ, Park KR. Surgery Alone Versus Surgery Followed by Chemotherapy and Radiotherapy in Resected Extrahepatic Bile Duct Cancer: Treatment Outcome Analysis of 336 Patients. *Cancer Res Treat* 2016; **48**: 583-595 [PMID: [26323644](#) DOI: [10.4143/crt.2015.091](#)]
- 33 **Kim MY**, Kim JH, Kim Y, Byun SJ. Postoperative radiotherapy appeared to improve the disease free survival rate of patients with extrahepatic bile duct cancer at high risk of loco-regional recurrence. *Radiat Oncol J* 2016; **34**: 297-304 [PMID: [27951624](#) DOI: [10.3857/roj.2016.01879](#)]
- 34 **Kim YJ**, Kim K, Min SK, Nam EM. Role of adjuvant radiotherapy for localized extrahepatic bile duct cancer. *Br J Radiol* 2017; **90**: 20160807 [PMID: [28118028](#) DOI: [10.1259/bjr.20160807](#)]
- 35 **Borghero Y**, Crane CH, Szklaruk J, Oyarzo M, Curley S, Pisters PW, Evans D, Abdalla EK, Thomas MB, Das P, Wistuba II, Krishnan S, Vauthey JN. Extrahepatic bile duct adenocarcinoma: patients at high-risk for local recurrence treated with surgery and adjuvant chemoradiation have an equivalent overall survival to patients with standard-risk treated with surgery alone. *Ann Surg Oncol* 2008; **15**: 3147-3156 [PMID: [18754070](#) DOI: [10.1245/s10434-008-9998-7](#)]
- 36 **Matsuda T**, Fujita H, Harada N, Kunimoto Y, Tanaka T, Kimura T, Kitaoka H, Asano E, Hosono M, Hayashi T, Ogino K. Impact of adjuvant radiation therapy for microscopic residual tumor after resection of extrahepatic bile duct cancer. *Am J Clin Oncol* 2013; **36**: 461-465 [PMID: [22706178](#) DOI: [10.1097/COC.0b013e31825494ab](#)]
- 37 **Lee J**, Kang SH, Noh OK, Chun M, Oh YT, Kim BW, Kim SW. Adjuvant concurrent chemoradiation therapy in patients with microscopic residual tumor after curative resection for extrahepatic cholangiocarcinoma. *Clin Transl Oncol* 2018; **20**: 1011-1017 [PMID: [29256155](#) DOI: [10.1007/s12094-017-1815-y](#)]
- 38 **Khan SA**, Davidson BR, Goldin RD, Heaton N, Karani J, Pereira SP, Rosenberg WM, Tait P, Taylor-Robinson SD, Thillainayagam AV, Thomas HC, Wasan H; British Society of Gastroenterology. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. *Gut* 2012; **61**: 1657-1669

- [PMID: 22895392 DOI: 10.1136/gutjnl-2011-301748]
- 39 **Lee KJ**, Yi SW, Cha J, Seong J, Bang S, Song SY, Kim HM, Park SW. A pilot study of concurrent chemoradiotherapy with gemcitabine and cisplatin in patients with locally advanced biliary tract cancer. *Cancer Chemother Pharmacol* 2016; **78**: 841-846 [PMID: 27586966 DOI: 10.1007/s00280-016-3143-2]
 - 40 **Shinohara ET**, Mitra N, Guo M, Metz JM. Radiotherapy is associated with improved survival in adjuvant and palliative treatment of extrahepatic cholangiocarcinomas. *Int J Radiat Oncol Biol Phys* 2009; **74**: 1191-1198 [PMID: 19201549 DOI: 10.1016/j.ijrobp.2008.09.017]
 - 41 **Pollom EL**, Alagappan M, Park LS, Whitemore AS, Koong AC, Chang DT. Does radiotherapy still have a role in unresected biliary tract cancer? *Cancer Med* 2017; **6**: 129-141 [PMID: 27891822 DOI: 10.1002/cam4.975]
 - 42 **Torgeson A**, Lloyd S, Boothe D, Cannon G, Garrido-Laguna I, Whisenant J, Lewis M, Kim R, Scaife C, Tao R. Chemoradiation Therapy for Unresected Extrahepatic Cholangiocarcinoma: A Propensity Score-Matched Analysis. *Ann Surg Oncol* 2017; **24**: 4001-4008 [PMID: 29043526 DOI: 10.1245/s10434-017-6131-9]
 - 43 **Schoppmeyer K**, Miethe S, Wiedmann M, Liebmann A, Hauss J, Mossner J, Caca K, Witzigmann H, Hildebrandt G. Radiochemotherapy followed by gemcitabine and capecitabine in extrahepatic bile duct cancer: a phase I/II trial. *Am J Clin Oncol* 2006; **29**: 576-582 [PMID: 17148994 DOI: 10.1097/01.coc.0000239167.17922.82]
 - 44 **Deodato F**, Clemente G, Mattiucci GC, Macchia G, Costamagna G, Giuliani F, Smaniotto D, Luzi S, Valentini V, Mutignani M, Nuzzo G, Cellini N, Morganti AG. Chemoradiation and brachytherapy in biliary tract carcinoma: long-term results. *Int J Radiat Oncol Biol Phys* 2006; **64**: 483-488 [PMID: 16242254 DOI: 10.1016/j.ijrobp.2005.07.977]
 - 45 **Brunner TB**, Schwab D, Meyer T, Sauer R. Chemoradiation may prolong survival of patients with non-bulky unresectable extrahepatic biliary carcinoma. A retrospective analysis. *Strahlenther Onkol* 2004; **180**: 751-757 [PMID: 15592694 DOI: 10.1007/s00066-004-1315-1]
 - 46 **Schleicher UM**, Staatz G, Alzen G, Andreopoulos D. Combined external beam and intraluminal radiotherapy for irresectable Klatskin tumors. *Strahlenther Onkol* 2002; **178**: 682-687 [PMID: 12491056 DOI: 10.1007/s00066-002-0947-2]
 - 47 **Autorino R**, Mattiucci GC, Ardito F, Balducci M, Deodato F, Macchia G, Mantini G, Perri V, Tringali A, Gambacorta MA, Tagliaferri L, Giuliani F, Morganti AG, Valentini V. Radiochemotherapy with Gemcitabine in Unresectable Extrahepatic Cholangiocarcinoma: Long-term Results of a Phase II Study. *Anticancer Res* 2016; **36**: 737-740 [PMID: 26851032]
 - 48 **Takamura A**, Saito H, Kamada T, Hiramatsu K, Takeuchi S, Hasegawa M, Miyamoto N. Intraluminal low-dose-rate 192Ir brachytherapy combined with external beam radiotherapy and biliary stenting for unresectable extrahepatic bile duct carcinoma. *Int J Radiat Oncol Biol Phys* 2003; **57**: 1357-1365 [PMID: 14630274]
 - 49 **Shin HS**, Seong J, Kim WC, Lee HS, Moon SR, Lee IJ, Lee KK, Park KR, Suh CO, Kim GE. Combination of external beam irradiation and high-dose-rate intraluminal brachytherapy for inoperable carcinoma of the extrahepatic bile ducts. *Int J Radiat Oncol Biol Phys* 2003; **57**: 105-112 [PMID: 12909222]
 - 50 **Yoshioka Y**, Ogawa K, Oikawa H, Onishi H, Kanesaka N, Tamamoto T, Kosugi T, Hatano K, Kobayashi M, Ito Y, Takayama M, Takemoto M, Karasawa K, Nagakura H, Imai M, Kosaka Y, Yamazaki H, Isohashi F, Nemoto K, Nishimura Y; Japanese Radiation Oncology Study Group (JROSG). Impact of intraluminal brachytherapy on survival outcome for radiation therapy for unresectable biliary tract cancer: a propensity-score matched-pair analysis. *Int J Radiat Oncol Biol Phys* 2014; **89**: 822-829 [PMID: 24969796 DOI: 10.1016/j.ijrobp.2014.04.020]
 - 51 **Kopeck N**, Holt MI, Hansen AT, Høyer M. Stereotactic body radiotherapy for unresectable cholangiocarcinoma. *Radiother Oncol* 2010; **94**: 47-52 [PMID: 19963295 DOI: 10.1016/j.radonc.2009.11.004]
 - 52 **Momm F**, Schubert E, Henne K, Hodapp N, Frommhold H, Harder J, Grosu AL, Becker G. Stereotactic fractionated radiotherapy for Klatskin tumours. *Radiother Oncol* 2010; **95**: 99-102 [PMID: 20347169 DOI: 10.1016/j.radonc.2010.03.013]
 - 53 **Polistina FA**, Guglielmi R, Baiocchi C, Francescon P, Scalchi P, Febbraro A, Costantin G, Ambrosino G. Chemoradiation treatment with gemcitabine plus stereotactic body radiotherapy for unresectable, non-metastatic, locally advanced hilar cholangiocarcinoma. Results of a five year experience. *Radiother Oncol* 2011; **99**: 120-123 [PMID: 21621289 DOI: 10.1016/j.radonc.2011.05.016]
 - 54 **Jung DH**, Kim MS, Cho CK, Yoo HJ, Jang WI, Seo YS, Paik EK, Kim KB, Han CJ, Kim SB. Outcomes of stereotactic body radiotherapy for unresectable primary or recurrent cholangiocarcinoma. *Radiat Oncol J* 2014; **32**: 163-169 [PMID: 25324988 DOI: 10.3857/roj.2014.32.3.163]
 - 55 **Speer AG**, Cotton PB, Russell RC, Mason RR, Hatfield AR, Leung JW, MacRae KD, Houghton J, Lennon CA. Randomised trial of endoscopic versus percutaneous stent insertion in malignant obstructive jaundice. *Lancet* 1987; **2**: 57-62 [PMID: 2439854]
 - 56 **Xu X**, Li J, Wu J, Zhu R, Ji W. A Systematic Review and Meta-analysis of Intraluminal Brachytherapy Versus Stent Alone in the Treatment of Malignant Obstructive Jaundice. *Cardiovasc Intervent Radiol* 2018; **41**: 206-217 [PMID: 29075881 DOI: 10.1007/s00270-017-1827-6]
 - 57 **Bowling TE**, Galbraith SM, Hatfield AR, Solano J, Spittle MF. A retrospective comparison of endoscopic stenting alone with stenting and radiotherapy in non-resectable cholangiocarcinoma. *Gut* 1996; **39**: 852-855 [PMID: 9038668]
 - 58 **Válek V**, Kysela P, Kala Z, Kiss I, Tomásek J, Petera J. Brachytherapy and percutaneous stenting in the treatment of cholangiocarcinoma: a prospective randomised study. *Eur J Radiol* 2007; **62**: 175-179 [PMID: 17344008 DOI: 10.1016/j.ejrad.2007.01.037]
 - 59 **Isayama H**, Tsujino T, Nakai Y, Sasaki T, Nakagawa K, Yamashita H, Aoki T, Koike K. Clinical benefit of radiation therapy and metallic stenting for unresectable hilar cholangiocarcinoma. *World J Gastroenterol* 2012; **18**: 2364-2370 [PMID: 22654427 DOI: 10.3748/wjg.v18.i19.2364]
 - 60 **Lee JK**, Kwack WK, Lee SH, Jung JH, Kwon JH, Han IW, Lee JH. Effect of external beam radiotherapy on patency of uncovered metallic stents in patients with inoperable bile duct cancer. *Hepatobiliary Pancreat Dis Int* 2014; **13**: 423-427 [PMID: 25100128]
 - 61 **Shinchi H**, Takao S, Nishida H, Aikou T. Length and quality of survival following external beam radiotherapy combined with expandable metallic stent for unresectable hilar cholangiocarcinoma. *J Surg Oncol* 2000; **75**: 89-94 [PMID: 11064386]
 - 62 **Tan Y**, Zhu JY, Qiu BA, Xia NX, Wang JH. Percutaneous biliary stenting combined with radiotherapy as

- a treatment for unresectable hilar cholangiocarcinoma. *Oncol Lett* 2015; **10**: 2537-2542 [PMID: [26622885](#) DOI: [10.3892/ol.2015.3589](#)]
- 63 **Ghiassi-Nejad Z**, Tarchi P, Moshier E, Ru M, Tabrizian P, Schwartz M, Buckstein M. Prognostic Factors and Patterns of Locoregional Failure After Surgical Resection in Patients With Cholangiocarcinoma Without Adjuvant Radiation Therapy: Optimal Field Design for Adjuvant Radiation Therapy. *Int J Radiat Oncol Biol Phys* 2017; **99**: 805-811 [PMID: [29063849](#) DOI: [10.1016/j.ijrobp.2017.06.2467](#)]
- 64 **Socha J**, Michalak M, Wołakiewicz G, Kepka L. Nodal areas of potential geographic error in adjuvant radiotherapy for biliary tract cancer. *Radiother Oncol* 2017; **125**: 365-373 [PMID: [29033254](#) DOI: [10.1016/j.radonc.2017.09.025](#)]
- 65 **Bisello S**, Renzulli M, Buwenge M, Calculli L, Sallustio G, Macchia G, Deodato F, Mattiucci G, Cammelli S, Arcelli A, Giaccherini L, Cellini F, Brandi G, Guerri S, Cilla S, Golfieri R, Fuccio L, Morganti AG, Guido A. An atlas for clinical target volume definition, including elective nodal irradiation in definitive radiotherapy of biliary cancer. *Oncol Lett* 2019; **17**: 1784-1790 [PMID: [30675238](#) DOI: [10.3892/ol.2018.9774](#)]

Antibiotics and immunotherapy in gastrointestinal tumors: Friend or foe?

Cong Yan, Xiao-Xuan Tu, Wei Wu, Zhou Tong, Lu-Lu Liu, Yi Zheng, Wei-Qin Jiang, Peng Zhao, Wei-Jia Fang, Hang-Yu Zhang

ORCID number: Cong Yan (0000-0002-2550-9095); Xiao-Xuan Tu (0000-0002-5505-0756); Wei Wu (0000-0002-3024-380X); Zhou Tong (0000-0003-0572-9610); Lu-Lu Liu (0000-0002-1762-8529); Yi Zheng (0000-0002-7066-2937); Wei-Qin Jiang (0000-0003-3200-8835); Peng Zhao (0000-0002-5479-899X); Wei-Jia Fang (0000-0001-9849-347X); Hang-Yu Zhang (0000-0003-1325-3915).

Author contributions: Yan C performed the majority of the writing and prepared the tables; Zhang HY designed the outline and coordinated the writing of the paper; other coauthors provided the input in writing the paper.

Supported by the Major Scientific Project of Zhejiang, No. 2017C03028.

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior author or other coauthors who contributed their efforts in this manuscript.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Cong Yan, Xiao-Xuan Tu, Wei Wu, Zhou Tong, Lu-Lu Liu, Yi Zheng, Wei-Qin Jiang, Peng Zhao, Wei-Jia Fang, Hang-Yu Zhang, Department of Medical Oncology, First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310000, Zhejiang Province, China

Corresponding author: Hang-Yu Zhang, MD, Attending Doctor, Department of Medical Oncology, First Affiliated Hospital, School of Medicine, Zhejiang University, No. 79, Qingchun Road, Hangzhou 310000, Zhejiang Province, China. zhanghangyu@zju.edu.cn
Telephone: +86-15757747033
Fax: +86-571-87236858

Abstract

The incidence of gastrointestinal (GI) tumors is increasing year by year, and its pathogenesis is closely related to the intestinal flora. At present, the use of antibiotics is very common in the clinic. And cancer patients with low immunity are vulnerable to all sorts of infections, such as respiratory tract infections and urinary tract infections. Moreover, cancer patients easily run into fever and neutropenia induced by myelosuppression. Therefore, antibiotics are used extensively and even overused in many conditions. However, because of the special anatomical location of the gastrointestinal tract, the antibiotic usage will bring changes to the intestinal flora. Besides, with the expanding popularity of immunotherapy, various factors affecting the efficacy of immune checkpoint inhibitors (ICIs) have been extensively explored, including cancer-associated inflammation and the local and systemic factors that lead to immunosuppression. Some biomarkers for ICIs, including the expression of PD-L1, tumor mutation load, and microbiota, also have been investigated, and many studies have confirmed that gut microbiota can affect the efficacy of immunotherapy. But further studies on the influence of antibiotics directly on immunotherapy are rare. In this review, we discuss the relationship between GI tumors and antibiotics, the current status of immunotherapy in GI tumors, and the influence of antibiotics on immunotherapy.

Key words: Antibiotics; Immunotherapy; Gastrointestinal tumor; Microbiota; Immune checkpoint inhibitors

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: With the widespread use of immunotherapy for almost all types of cancers and the extensive usage of antibiotics in many countries, the association between antibiotics

<http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: March 15, 2019

Peer-review started: March 15, 2019

First decision: March 29, 2019

Revised: April 7, 2019

Accepted: April 18, 2019

Article in press: April 19, 2019

Published online: June 6, 2019

P-Reviewer: Tabll AA, Zhou J

S-Editor: Gong ZM

L-Editor: Wang TQ

E-Editor: Xing YX



and immunotherapy deserves an investigation based on some studies which showed that the gut microbiota plays an important role in immunotherapy. We reviewed the relevant papers and found that antibiotics may attenuate the effect of immunotherapy.

Citation: Yan C, Tu XX, Wu W, Tong Z, Liu LL, Zheng Y, Jiang WQ, Zhao P, Fang WJ, Zhang HY. Antibiotics and immunotherapy in gastrointestinal tumors: Friend or foe? *World J Clin Cases* 2019; 7(11): 1253-1261

URL: <https://www.wjnet.com/2307-8960/full/v7/i11/1253.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v7.i11.1253>

INTRODUCTION

Gastrointestinal (GI) tumors, including colorectal cancer (CRC), gastric cancer, pancreatic cancer, hepatocellular carcinoma (HCC), and cholangiocarcinoma, account for a large proportion of all cancers^[1,2]. Due to the limited effectiveness of traditional chemotherapy, especially for pancreatic cancer and HCC, great efforts have been made in immunotherapy, which has become a potential treatment option for GI tumors in the last decade. In addition, current management strategies and treatments for GI tumors have also been enriched by immune checkpoint inhibitors (ICIs), such as advanced treatment for microsatellite instable CRC and second-line treatment for HCC. However, only a fraction of patients benefited from ICIs and there are some factors affecting their efficacy, such as tumor genomics, PD1 ligand 1 (PD-L1) levels, and gut microbiota^[3].

The correlations between the gut microbiota community and clinical response to ICIs have been confirmed by an increasing number of investigations. Early studies found that the effects of CTLA-4 blockade were associated with T cell responses specific for distinct *Bacteroides* species and tumors in antibiotic-treated or germ-free mice did not respond to CTLA-4 blockade^[4]. Cancer immunotherapy may be modulated by manipulating the microbiota^[5]. Similarly, the anticancer immunity in mouse models induced by anti-PD-L1 is reported to rely on *Bifidobacterium*, which might improve the effectiveness of anticancer immunity through augmenting dendritic cell functions and subsequently enhancing CD8⁺ T cell priming and accumulation in the tumor microenvironment. Furthermore, oral administration of *Bifidobacterium* can generate a similar effect to anti-PD-L1 treatment on tumor elimination, indicating the potentially important role of *Bifidobacterium* in strengthening immune functions^[5]. Subsequently, an increasing number of studies have revealed a correlation between the response to anti-PD-1 and the abundance of diversified bacteria, including *Ruminococcaceae* bacteria, *Bifidobacterium longum*, *Collinsella aerofaciens*, and *Enterococcus faecium*^[6-8].

Since extensively and overused antibiotics can lead to an abnormal intestinal microbiota composition, the effect of antibiotics on immunotherapy has also been explored in several studies. For example, some studies have indicated that antibiotics can weaken the effectiveness of immunotherapy, while others argued that antibiotics have no influence on immunotherapy. In this review, we summarize the relationship between antibiotics, microbiota, and GI tumors, the current status of immunotherapy in GI tumors, and the influence of antibiotics on immunotherapy in a comprehensive manner.

ANTIBIOTICS, MICROBIOTA, AND GI TUMORS

The link between antibiotics and cancers has been around for a long time. Several decades ago, the hypothesis that the use of antibiotics may increase the risk of cancer was first proposed^[9]. Studies have shown the association between increased use of antibiotics and increased incidence and mortality of breast cancer^[10,11]. Antibiotics are also known to influence the development and progression of GI tumors, most notably for colorectal cancer. Cao *et al*^[12] reported a study of 1195 newly diagnosed colorectal adenomas in patients who underwent at least one colonoscopy and reported information on antibiotic use. They found that antibiotic use at ages 20-39 and 40-59 was significantly associated with an increased risk of colorectal adenoma after age 60. Two other case-control studies supported this conclusion: one study found a positive association between the use of anti-anaerobic antibiotics and colorectal cancer, but no

association was found for anti-aerobic agents^[13]; another study found that a high (≥ 8) number of prescriptions of antibiotics was associated with an increased risk of colorectal cancer (CRC), and when antibiotics were used for ≥ 70 d compared to no use of antibiotics, the risk of CRC significantly increased, and both anti-aerobic agents and anti-anaerobic antibiotics were associated with an increased risk of CRC^[14]. Indeed, penicillin can lead to an increased risk of esophageal, gastric, and pancreatic cancers^[15], and antibiotic exposure can promote the development of tumors in the liver^[16].

However, the effect of the microbiota on cancers further complicates the relationship between antibiotics, bacteria, and cancers. The microbiota is reported to be involved in the initiation, progression, and dissemination of cancer both at epithelial barriers and in sterile tissues, and gut microbiota can modulate the response to cancer therapy and susceptibility to toxic side effects^[17]. There are papers showing some microbes associated with GI tumors (Table 1), and common examples of microbes involved in cancer include *Helicobacter pylori*, which is associated with gastric cancer, *Clonorchis sinensis* and *Opisthorchis viverrini*, which are associated with bile duct cancer, and enterotoxigenic *Bacteroides fragilis*, which is associated with colon cancer^[18,19]. In mice receiving broad-spectrum antibiotics, reductions in microbiota, inflammation, and colonic polyposis, which is a precancerous lesion of colon cancer, were observed^[20]. Immune and inflammatory pathways could be regulated by chronic inflammatory conditions, while chronic inflammatory conditions could be affected by microbiota and antibiotics^[20,21]. These observations suggested that a further investigation into the influence of antibiotics on the treatment for GI tumors is necessary.

IMMUNOTHERAPY AND GI TUMORS

Immunotherapy has been a hit in the field of cancer therapy. Unlike melanoma, renal cancer, and non-small cell lung cancer, most GI tumors do not induce effector T-cell responses naturally, which may lead to an unsatisfactory immunotherapy efficacy. Various clinical trials have been conducted to verify the efficacy of ICIs in GI tumors as a single agent or in combination, and tremendous advances have been made (Table 2). For esophageal and gastric cancers, a phase II trial confirmed the safety and activity of nivolumab in 64 patients with treatment-refractory esophageal cancer^[22]. Nivolumab was approved in Japan after the Asian ATTRACTION 02 study^[23], which was a phase III trial performed to compare nivolumab with placebo in patients with unresectable chemorefractory advanced gastric or gastroesophageal junction cancer. Then, the CheckMate-032 phase I/II study evaluated the efficacy and safety of nivolumab and nivolumab plus ipilimumab^[24], and the phase II clinical KEYNOTE-059 trial demonstrated promising activity and manageable safety of pembrolizumab^[25]. All the above studies suggested that immunotherapy may be a potential approach to treating refractory advanced gastric and esophageal cancers. However, the phase III JAVELIN trial^[26] and the KEYNOTE-061 phase III trial^[27] showed negative results.

For HCC, an early phase 1/2 dose escalation and expansion trial to assess the safety and efficacy of nivolumab showed a satisfactory survival end-point and treatment response rate^[28]. Besides, another study evaluated the efficacy and safety of pembrolizumab in patients who had previously experienced sorafenib^[29]. Similarly, small sample clinical trials of camrelizumab (anti-PD-1 antibody)^[30] and tremelimumab (anti-CTLA-4 antibody)^[31] also yielded promising results. For biliary tract cancer, Bang *et al* performed an interim analysis to evaluate the safety and antitumor activity of pembrolizumab in advanced biliary tract cancer and found that pembrolizumab was generally well tolerated and demonstrated promising antitumor activity among 24 enrolled patients. For pancreatic cancer, early studies on BMS-936559 (anti-PD-L1 antibody)^[32] and ipilimumab^[33] showed that they were ineffective when treating advanced pancreatic cancer. Hence, further investigations are suggested to perform.

The immunological benefit in patients with colorectal cancer has been limited to those who had a loss of mismatch repair function and had specific germline mutations in the DNA polymerase gene^[34,35]. A host of current trials are underway in patients with microsatellite stable (MSS) CRC to evaluate the utility of concurrent chemotherapy, VEGF/EGFR inhibitors, radiotherapy, or MEK inhibitors with ICIs; however, more data are still needed to address the efficacy and tolerability of ICIs in MSS CRC patients^[36].

In summary, with respect to advanced gastrointestinal malignancies, ICIs have shown some therapeutic effects. However, for various reasons, such as the stroma

Table 1 Microbes that may cause gastrointestinal tumors

Tumor	Microbes involved
Esophageal cancer	<i>H. pylori</i> , Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, and Fusobacteria phyla.
Gastric cancer	<i>H. pylori</i> , Porphyromonas, Neisseria, Prevotella pallens, Streptococcus sinensis, Lactobacillus coleohominis, Klebsiella pneumoniae, and Acinetobacter baumannii
Colorectal cancer	Faecalibacterium prausnitzii, Eubacterium rectale, Proteobacteria, Bacteroidetes, Fusobacterium
Hepatocellular carcinoma	<i>H. pylori</i> , Escherichia coli
Biliary tract cancer	Pseudomonadaceae, Oxalobacteraceae, Clonorchis sinensis, and Opisthorchis viverrini
Pancreatic cancer	<i>H. pylori</i>

H. pylori: *Helicobacter pylori*.

providing a formidable barrier to effector T-cell infiltration in pancreatic cancer, the therapeutic effect of ICIs needs to be further improved. Therefore, various clinical trials are planned using combinations of ICIs with chemotherapy, molecular targeted therapy, radiation therapy, or other novel immunomodulatory agents in patients with advanced GI tumors. And the factors affecting the immunotherapeutic efficacy for GI tumors are also worthy of further studying, especially the unclarified but important role of antibiotic usage in patients receiving ICIs treatment.

ANTIBIOTICS AND IMMUNOTHERAPY

PD-L1 expression in the tumor tissue has been considered to be a biomarker for pembrolizumab in NSCLC^[37]; however, some PD-L1-positive patients do not benefit from pembrolizumab, while some PD-L1-negative patients could benefit from nivolumab or other ICIs. How to select the appropriate population for ICIs is still a question. A recent study found that tumor mutation burden or tumor infiltrating lymphocytes might be relevant biomarkers for patients treated with ICIs^[38,39], and accumulating evidence supports the hypothesis that the gut microbiota has a great influence on immunotherapy, including ICIs^[19]. Therefore, tumor mutation burden, tumor infiltrating lymphocytes, and the gut microbiota are considered potential immunotherapy biomarkers. The gut microbiota plays a crucial role in balancing inflammation, infection, and commensal antigens, which can modulate the host immune system both locally and systemically^[40]. As interest in the influence of microbiota on immunotherapy has escalated, microbiota and cancer, specific gut microbes, and administration of antibiotics have also attracted extensive attention.

Early studies focusing on the relationship between immunotherapy and antibiotics were all conducted in murine models. For example, cyclophosphamide (CTX) is a well-known chemotherapy that can stimulate antitumor immune responses, including inducing the death of immunogenic cancer cells, destroying immunosuppressive T cells, and promoting Th1 and Th17 cells to control tumor growth. However, mice treated with antibiotics to kill gram-positive bacteria have been found to have a reduction in the number of pathogenic Th17 cells and a worse treatment response^[41]. When pathogenic Th17 cells were transferred to antibiotic-treated mice, the antitumor efficacy of cyclophosphamide was partially restored, which suggests that antibiotics may influence the efficacy of immunotherapy by regulating the gut microbiota. Another study also found that antibiotic-treated mice showed a low response to CpG-oligonucleotides. They found that TNF expression and frequencies of TNF-positive leukocytes induced by CpG-oligonucleotides were significantly impaired^[42]. It is mainly because those antibiotics could affect the microbiota and further affected local and systemic inflammation and the tumor immune microenvironment. Further studies showed that immunotherapy CTLA-4 and/or PD-1/PD-L1 efficacy could be improved by transferring patient fecal samples into germ-free (GF) or antibiotic-treated SPF mice^[7].

In addition to the above animal experimental findings, several independent retrospective analyses in human cohorts of advanced NSCLC, RCC, and urothelial carcinoma have found contradictory results (Table 3). An early study found that antibiotics do not affect the efficacy of nivolumab in NSCLC patients^[43]. A total of 74 locally advanced or metastatic NSCLC patients were treated with nivolumab as a second- or third-line therapy, 15 patients were exposed to antibiotics, and the

Table 2 Completed clinical trials of immune checkpoint inhibitors on gastrointestinal tumors

Trial	Phase	Treatment	ORR% (95%CI)	DCR% (95%CI)	Median PFS months (95%CI)	Median OS months (95%CI)	Adverse events
Esophageal and gastric cancers							
	II	Nivolumab (<i>n</i> = 64)	11 (10-28)	27 (31-54)	1.5 (1.4-2.8)	11 (7.3-13)	G3/4 25%; All-grade 73%
ATTRACTION 02	II	Nivolumab (<i>n</i> = 330)	11 (8-16)	40 (34-46)	1.6 (1.5-2.3)	5.3 (4.6-6.4)	G3/4 27%; All-grade 43%
		Placebo (<i>n</i> = 163)	0(0-3.0)	25 (18-34)	1.5 (1.5-1.5)	4.1 (3.4-4.9)	G3/4 4%; All-grade 27%
CHECKMATE32	I/II	Nivolumab 3 (mg/kg)	12 (5-23)	NR	1.4 (1.2-1.5)	6.2 (3.4-12)	G3/4 17%
		Nivolumab 1 + Ipilimumab 3	24 (13-39)	NR	1.4 (1.2-3.8)	6.9 (3.7-12)	G3/4 47%
		Nivolumab 3 + Ipilimumab 1	8.0 (2.0-19)	NR	1.6 (1.4-2.6)	4.8 (3.0-8.4)	G3/4 27%
KEYNOTE59	II	Pembrolizumab (<i>n</i> = 259)	12 (8-16)	27(21.7-32.9)	2.0 (2.0-2.1)	5.5 (4.2-6.5)	G3/4 18%; All-grade 60%
JAVELIN Gastric 300	III	Avelumab (<i>n</i> = 185)	2.2 (0.6-5.4)	22 (16-29)	1.4 (1.5-2.0)	4.6 (3.6-5.7)	G3/4 9.2%
		Chemotherapy (<i>n</i> = 186)	4.3 (1.9-8.3)	44 (37-52)	2.7 (1.8-2.8)	5.0 (4.5-6.3)	G3/4 32%
KEYNOTE61 PDL CPS ≥ 1	III	Pembrolizumab (<i>n</i> = 196)	16 (11-22)	NR	1.5 (1.4-2.0)	9.1 (6.2-11)	G3/4 25%
		Paclitaxel (<i>n</i> = 199)	14 (9.0-19)	NR	4.1 (3.1-4.2)	8.3 (7.6-9.0)	G3/4 35%
Hepatocellular carcinoma							
CHECKMATE40	I/II	Nivolumab (dose-escalation)	15 (6.0-28)	58 (43-72)	NR	15 (9.6-20)	G3/4 25%
		Nivolumab (dose-expansion)	20 (15-26)	64	5.4 (3.9-8.5)	NR	G3/4 63%
KEYNOTE224	II	Pembrolizumab (<i>n</i> = 169)	18 (11-26)	62 (52-71)	4.9 (3.4-7.2)	13 (10-16)	G3/4 25%; All-grade 73%
Biliary tract cancer							
KEYNOTE28	I	Pembrolizumab (<i>n</i> = 24)	17 (5.0-39)	34	NR	NR	G3/4 17%; All-grade 63%
Pancreatic cancer							
	II	Ipilimumab (<i>n</i> = 27)	0	0	NR	NR	NR
	I	Tremelimumab + gemcitabine (<i>n</i> = 34)	NR	NR	NR	7.4 (5.8-9.4)	All-grade 94%
	Ib/II	Pembrolizumab + gemcitabine + nab-paclitaxel (<i>n</i> = 17)	18	76	9.1 (4.9-15.3)	15 (6.8-23)	G3/4 71%; All-grade 100%
Colorectal cancer (dMMR)							
	II	Pembrolizumab (<i>n</i> = 10)	40 (12-74)	90 (55-100)	NR	NR	G3/4 41%; All-grade 98%
KHECKMATE 142	II	Nivolumab (<i>n</i> = 74)	31 (21-43)	69 (57-79)	NR	NR	G3/4 20%; All-grade 70%

DCR: Disease control rate; ORR: Objective response rate; OS: Overall survival; PFS: Progression free survival; G: Grade; NR: Not reported; dMMR: Mismatch repair deficiency.

remaining 59 patients were not exposed to antibiotics. No significant difference was found in response rates and progression-free survival (PFS) between the two groups of patients. Subsequently, another two independent studies with larger sample sizes drew inconsistent conclusions. Indeed, Kaderbhai *et al*^[43] showed that in RCC patients, antibiotic use compared to no antibiotic use was associated with an increased risk of primary progressive disease (PD), shorter PFS, and shorter overall survival (OS). In NSCLC patients, antibiotic use was associated with similar rates of primary PD but

decreased PFS and OS. In a study by Routy, 69 out of 249 patients were prescribed antibiotics. PFS and OS were significantly shorter in the antibiotics-treated patients when all patients were combined. Furthermore, transplantation of fecal microbiota from patients who responded to ICIs into germ-free non-responders restored or enhanced the ICIs responsiveness. In univariate and multivariate Cox regression analyses, antibiotic use was found to be a predictor of resistance to PD-1 blockade, independent of classical prognostic markers in NSCLC and RCC^[44]. Gut microbiota composition analysis found that *A. muciniphila* was the most significantly associated bacteria with favorable clinical outcome, which increased the recruitment of CCR9+ CXCR3+ CD4+ T lymphocytes into tumor beds in an IL-12-dependent manner.

The different studies come to different conclusions, which may be due to a combination of several reasons. First, the duration time of antibiotic usage is different. Some studies allowed the use of antibiotics for 3 months before immunotherapy, while other studies used antibiotics for only 1 month before immunotherapy, and there is no unified standard. Second, the cancer type is different. RCC, melanoma, and NSCLC are more sensitive to ICIs. Third, all the studies were retrospective studies, which need to be further confirmed by randomized controlled clinical trials.

CONCLUSION

As is well-known, immunotherapy has become an important weapon in the treatment of GI tumors. However, it still lacks effective biomarkers. Besides, microbiota is known to influence the response to anticancer immunotherapy, and antibiotics have been proven to influence the occurrence and development of GI tumors. In this study, we reviewed a reasonable quantity of papers about the relationship between antibiotics and immunotherapy. Although few studies are directly related to GI tumors, the relevant studies suggest that antibiotics can affect the commensal microbiota and further affect the efficacy of immunotherapy. In a word, according to the current research evidence, it remains inconclusive that the relationship between antibiotics and immunotherapy is friend or foe, and we hope that more studies can focus on this area in the future.

ACKNOWLEDGMENTS

The authors thank all patients and researchers for their early works.

Table 3 Studies about antibiotics and immunotherapy

	Research subjects	Tumor type	Patients No.	Research conclusion	Ref.
1	Patients	NSCLC/RCC/urothelia l carcinoma	249	ATB use presents a predictor of resistance to ICI	Routy <i>et al</i> ^[44] , 2018
2	Mice	Sarcoma/melanoma			
2	Patients	NSCLC	74	ATB use does not affect the efficacy of nivolumab	Kaderbhai <i>et al</i> ^[43] , 2017
3	Patients	RCC/NSCLC	360	ATB use reduces clinical benefit from ICI	Derosa <i>et al</i> ^[45] , 2018
4	Mice	Lymphoma/colon cancer/melanoma		ATB treated mice respond poorly to CpG- oligonucleotide	Lida <i>et al</i> ^[42] , 2013
5	Mice			ATB mice are resistant to cyclophosphamide	Viaud <i>et al</i> ^[41] , 2013

ATB: Antibiotics; ICI: Immune checkpoint inhibitor.

REFERENCES

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; **69**: 7-34 [PMID: 30620402 DOI: 10.3322/caac.21551]
- Havel JJ, Chowell D, Chan TA. The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy. *Nat Rev Cancer* 2019; **19**: 133-150 [PMID: 30755690 DOI: 10.1038/s41568-019-0116-x]
- Vétizou M, Pitt JM, Daillère R, Lepage P, Waldschmitt N, Flament C, Rusakiewicz S, Routy B, Roberti MP, Duong CP, Poirier-Colame V, Roux A, Becharef S, Formenti S, Golden E, Cording S, Eberl G, Schlitzer A, Ginhoux F, Mani S, Yamazaki T, Jacquelinot N, Enot DP, Bérard M, Nigou J, Opolon P, Eggermont A, Woerther PL, Chachaty E, Chaput N, Robert C, Mateus C, Kroemer G, Raoult D, Boneca IG, Carbone F, Chamaillard M, Zitvogel L. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science* 2015; **350**: 1079-1084 [PMID: 26541610 DOI: 10.1126/science.aad1329]
- Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, Benyamin FW, Lei YM, Jabri B, Alegre ML, Chang EB, Gajewski TF. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science* 2015; **350**: 1084-1089 [PMID: 26541606 DOI: 10.1126/science.aad4255]
- Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinetz TV, Prieto PA, Vicente D, Hoffman K, Wei SC, Cogdill AP, Zhao L, Hudgens CW, Hutchinson DS, Manzo T, Petaccia de Macedo M, Cotechini T, Kumar T, Chen WS, Reddy SM, Szczepaniak Sloane R, Galloway-Pena J, Jiang H, Chen PL, Shpall EJ, Rezvani K, Alousi AM, Chemaly RF, Shelburne S, Vence LM, Okhuysen PC, Jensen VB, Swennes AG, McAllister F, Marcelo Riquelme Sanchez E, Zhang Y, Le Chatelier E, Zitvogel L, Pons N, Austin-Breneman JL, Haydu LE, Burton EM, Gardner JM, Sirmans E, Hu J, Lazar AJ, Tsujikawa T, Diab A, Tawbi H, Glitza IC, Hwu WJ, Patel SP, Woodman SE, Amaria RN, Davies MA, Gershenwald JE, Hwu P, Lee JE, Zhang J, Coussens LM, Cooper ZA, Futreal PA, Daniel CR, Ajami NJ, Petrosino JF, Tetzlaff MT, Sharma P, Allison JP, Jenq RR, Wargo JA. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science* 2018; **359**: 97-103 [PMID: 29097493 DOI: 10.1126/science.aan4236]
- Matson V, Fessler J, Bao R, Chongsawat T, Zha Y, Alegre ML, Luke JJ, Gajewski TF. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science* 2018; **359**: 104-108 [PMID: 29302014 DOI: 10.1126/science.aao3290]
- Frankel AE, Coughlin LA, Kim J, Froehlich TW, Xie Y, Frenkel EP, Koh AY. Metagenomic Shotgun Sequencing and Unbiased Metabolomic Profiling Identify Specific Human Gut Microbiota and Metabolites Associated with Immune Checkpoint Therapy Efficacy in Melanoma Patients. *Neoplasia* 2017; **19**: 848-855 [PMID: 28923537 DOI: 10.1016/j.neo.2017.08.004]
- Setchell KD, Lawson AM, Borriello SP, Harkness R, Gordon H, Morgan DM, Kirk DN, Adlercreutz H, Anderson LC, Axelson M. Lignan formation in man--microbial involvement and possible roles in relation to cancer. *Lancet* 1981; **2**: 4-7 [PMID: 6113409]
- Tamim HM, Hanley JA, Hajeer AH, Boivin JF, Collet JP. Risk of breast cancer in relation to antibiotic use. *Pharmacoepidemiol Drug Saf* 2008; **17**: 144-150 [PMID: 17943999 DOI: 10.1002/pds.1512]
- Velicer CM, Heckbert SR, Lampe JW, Potter JD, Robertson CA, Taplin SH. Antibiotic use in relation to the risk of breast cancer. *JAMA* 2004; **291**: 827-835 [PMID: 14970061 DOI: 10.1001/jama.291.7.827]
- Cao Y, Wu K, Mehta R, Drew DA, Song M, Lochhead P, Nguyen LH, Izard J, Fuchs CS, Garrett WS, Huttenhower C, Ogino S, Giovannucci EL, Chan AT. Long-term use of antibiotics and risk of colorectal adenoma. *Gut* 2018; **67**: 672-678 [PMID: 28377387 DOI: 10.1136/gutjnl-2016-313413]
- Wang JL, Chang CH, Lin JW, Wu LC, Chuang LM, Lai MS. Infection, antibiotic therapy and risk of colorectal cancer: a nationwide nested case-control study in patients with Type 2 diabetes mellitus. *Int J Cancer* 2014; **135**: 956-967 [PMID: 24470385 DOI: 10.1002/ijc.28738]
- Dik VK, van Oijen MG, Smeets HM, Siersema PD. Frequent Use of Antibiotics Is Associated with Colorectal Cancer Risk: Results of a Nested Case-Control Study. *Dig Dis Sci* 2016; **61**: 255-264 [PMID: 26289256 DOI: 10.1007/s10620-015-3828-0]
- Boursi B, Mamtani R, Haynes K, Yang YX. Recurrent antibiotic exposure may promote cancer formation-

- Another step in understanding the role of the human microbiota? *Eur J Cancer* 2015; **51**: 2655-2664 [PMID: 26338196 DOI: 10.1016/j.ejca.2015.08.015]
- 16 **Itoh T**, Moto M, Takahashi M, Sakai H, Mitsumori K. Liver initiation activity of norfloxacin but not nalidixic acid, pipemidic acid, and ciprofloxacin in in vivo short-term liver initiation assay in rats. *Toxicology* 2006; **222**: 240-246 [PMID: 16580113 DOI: 10.1016/j.tox.2006.02.019]
 - 17 **Roy S**, Trinchieri G. Microbiota: a key orchestrator of cancer therapy. *Nat Rev Cancer* 2017; **17**: 271-285 [PMID: 28303904 DOI: 10.1038/nrc.2017.13]
 - 18 **Schwabe RF**, Jobin C. The microbiome and cancer. *Nat Rev Cancer* 2013; **13**: 800-812 [PMID: 24132111 DOI: 10.1038/nrc3610]
 - 19 **Meng C**, Bai C, Brown TD, Hood LE, Tian Q. Human Gut Microbiota and Gastrointestinal Cancer. *Genomics Proteomics Bioinformatics* 2018; **16**: 33-49 [PMID: 29474889 DOI: 10.1016/j.gpb.2017.06.002]
 - 20 **Dennis KL**, Wang Y, Blatner NR, Wang S, Saadalla A, Trudeau E, Roers A, Weaver CT, Lee JJ, Gilbert JA, Chang EB, Khazaie K. Adenomatous polyps are driven by microbe-instigated focal inflammation and are controlled by IL-10-producing T cells. *Cancer Res* 2013; **73**: 5905-5913 [PMID: 23955389 DOI: 10.1158/0008-5472.CAN-13-1511]
 - 21 **De Almeida CV**, de Camargo MR, Russo E, Amedei A. Role of diet and gut microbiota on colorectal cancer immunomodulation. *World J Gastroenterol* 2019; **25**: 151-162 [PMID: 30670906 DOI: 10.3748/wjg.v25.i2.151]
 - 22 **Kudo T**, Hamamoto Y, Kato K, Ura T, Kojima T, Tsushima T, Hironaka S, Hara H, Satoh T, Iwasa S, Muro K, Yasui H, Minashi K, Yamaguchi K, Ohtsu A, Doki Y, Kitagawa Y. Nivolumab treatment for oesophageal squamous-cell carcinoma: an open-label, multicentre, phase 2 trial. *Lancet Oncol* 2017; **18**: 631-639 [PMID: 28314688 DOI: 10.1016/S1470-2045(17)30181-X]
 - 23 **Kang YK**, Boku N, Satoh T, Ryu MH, Chao Y, Kato K, Chung HC, Chen JS, Muro K, Kang WK, Yeh KH, Yoshikawa T, Oh SC, Bai LY, Tamura T, Lee KW, Hamamoto Y, Kim JG, Chin K, Oh DY, Minashi K, Cho JY, Tsuda M, Chen LT. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; **390**: 2461-2471 [PMID: 28993052 DOI: 10.1016/S0140-6736(17)31827-5]
 - 24 **Janjigian YY**, Bendell J, Calvo E, Kim JW, Ascierto PA, Sharma P, Ott PA, Peltola K, Jaeger D, Evans J, de Braud F, Chau I, Harbison CT, Dorange C, Tschaike M, Le DT. CheckMate-032 Study: Efficacy and Safety of Nivolumab and Nivolumab Plus Ipilimumab in Patients With Metastatic Esophagogastric Cancer. *J Clin Oncol* 2018; **36**: 2836-2844 [PMID: 30110194 DOI: 10.1200/JCO.2017.76.6212]
 - 25 **Fuchs CS**, Doi T, Jang RW, Muro K, Satoh T, Machado M, Sun W, Jalal SI, Shah MA, Metges JP, Garrido M, Golan T, Mandala M, Wainberg ZA, Catenacci DV, Ohtsu A, Shitara K, Geva R, Bleeker J, Ko AH, Ku G, Philip P, Enzinger PC, Bang YJ, Levitan D, Wang J, Rosales M, Dalal RP, Yoon HH. Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer: Phase 2 Clinical KEYNOTE-059 Trial. *JAMA Oncol* 2018; **4**: e180013 [PMID: 29543932 DOI: 10.1001/jamaoncol.2018.0013]
 - 26 **Bang YJ**, Ruiz EY, Van Cutsem E, Lee KW, Wyrwicz L, Schenker M, Alsina M, Ryu MH, Chung HC, Evesque L, Al-Batran SE, Park SH, Lichinitser M, Boku N, Moehler MH, Hong J, Xiong H, Hallwachs R, Conti I, Taieb J. Phase III, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment of patients with advanced gastric or gastro-oesophageal junction cancer: primary analysis of JAVELIN Gastric 300. *Ann Oncol* 2018; **29**: 2052-2060 [PMID: 30052729 DOI: 10.1093/annonc/mdy264]
 - 27 **Shitara K**, Özgüroğlu M, Bang YJ, Di Bartolomeo M, Mandalà M, Ryu MH, Fornaro L, Olesiński T, Caglevic C, Chung HC, Muro K, Goekkurt E, Mansoor W, McDermott RS, Shacham-Shmueli E, Chen X, Mayo C, Kang SP, Ohtsu A, Fuchs CS; KEYNOTE-061 investigators. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. *Lancet* 2018; **392**: 123-133 [PMID: 29880231 DOI: 10.1016/S0140-6736(18)31257-1]
 - 28 **El-Khoueiry AB**, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, Kim TY, Choo SP, Trojan J, Welling TH Rd, Meyer T, Kang YK, Yeo W, Chopra A, Anderson J, Dela Cruz C, Lang L, Neely J, Tang H, Dastani HB, Melero I. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017; **389**: 2492-2502 [PMID: 28434648 DOI: 10.1016/S0140-6736(17)31046-2]
 - 29 **Zhu AX**, Finn RS, Edeline J, Cattani S, Ogasawara S, Palmer D, Verslype C, Zagonel V, Fartoux L, Vogel A, Sarker D, Verset G, Chan SL, Knox J, Daniele B, Webber AL, Ebbinghaus SW, Ma J, Siegel AB, Cheng AL, Kudo M; KEYNOTE-224 investigators. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol* 2018; **19**: 940-952 [PMID: 29875066 DOI: 10.1016/S1470-2045(18)30351-6]
 - 30 **Mo H**, Huang J, Xu J, Chen X, Wu D, Qu D, Wang X, Lan B, Wang X, Xu J, Zhang H, Chi Y, Yang Q, Xu B. Safety, anti-tumour activity, and pharmacokinetics of fixed-dose SHR-1210, an anti-PD-1 antibody in advanced solid tumours: a dose-escalation, phase 1 study. *Br J Cancer* 2018; **119**: 538-545 [PMID: 29755117 DOI: 10.1038/s41416-018-0100-3]
 - 31 **Sangro B**, Gomez-Martin C, de la Mata M, Iñarrairaegui M, Garralda E, Barrera P, Riezu-Boj JI, Larrea E, Alfaro C, Sarobe P, Lasarte JJ, Pérez-Gracia JL, Melero I, Prieto J. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. *J Hepatol* 2013; **59**: 81-88 [PMID: 23466307 DOI: 10.1016/j.jhep.2013.02.022]
 - 32 **Brahmer JR**, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, Pitot HC, Hamid O, Bhatia S, Martins R, Eaton K, Chen S, Salay TM, Alaparthi S, Grosso JF, Korman AJ, Parker SM, Agrawal S, Goldberg SM, Pardoll DM, Gupta A, Wigginton JM. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012; **366**: 2455-2465 [PMID: 22658128 DOI: 10.1056/NEJMoa1200694]
 - 33 **Royal RE**, Levy C, Turner K, Mathur A, Hughes M, Kammula US, Sherry RM, Topalian SL, Yang JC, Lowy I, Rosenberg SA. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J Immunother* 2010; **33**: 828-833 [PMID: 20842054 DOI: 10.1097/CJI.0b013e3181eeec14c]
 - 34 **Le DT**, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Duffy SM, Goldberg RM, de la Chapelle A, Koshiji M, Bhajee F, Huebner T, Hruban RH, Wood LD, Cuka N, Pardoll DM,

- Papadopoulos N, Kinzler KW, Zhou S, Cornish TC, Taube JM, Anders RA, Eshleman JR, Vogelstein B, Diaz LA. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med* 2015; **372**: 2509-2520 [PMID: [26028255](#) DOI: [10.1056/NEJMoa1500596](#)]
- 35 **Le DT**, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; **357**: 409-413 [PMID: [28596308](#) DOI: [10.1126/science.aan6733](#)]
- 36 **Hermel DJ**, Sigal D. The Emerging Role of Checkpoint Inhibition in Microsatellite Stable Colorectal Cancer. *J Pers Med* 2019; **9** [PMID: [30654522](#) DOI: [10.3390/jpm9010005](#)]
- 37 **Reck M**, Rodriguez-Abreu D, Robinson AG, Hui R, Csösz T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR; KEYNOTE-024 Investigators. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* 2016; **375**: 1823-1833 [PMID: [27718847](#) DOI: [10.1056/NEJMoa1606774](#)]
- 38 **Biton J**, Ouakrim H, Dechartres A, Alifano M, Mansuet-Lupo A, Si H, Halpin R, Creasy T, Bantsimba-Malanda C, Arrondeau J, Goldwasser F, Boudou-Rouquette P, Fournel L, Roche N, Burgel PR, Goc J, Devi-Marulkar P, Germain C, Dieu-Nosjean MC, Cremer I, Herbst R, Damotte D. Impaired Tumor-Infiltrating T Cells in Patients with Chronic Obstructive Pulmonary Disease Impact Lung Cancer Response to PD-1 Blockade. *Am J Respir Crit Care Med* 2018; **198**: 928-940 [PMID: [29518341](#) DOI: [10.1164/rccm.201706-1110OC](#)]
- 39 **Sacher AG**, Gandhi L. Biomarkers for the Clinical Use of PD-1/PD-L1 Inhibitors in Non-Small-Cell Lung Cancer: A Review. *JAMA Oncol* 2016; **2**: 1217-1222 [PMID: [27310809](#) DOI: [10.1001/jamaoncol.2016.0639](#)]
- 40 **Belkaid Y**, Naik S. Compartmentalized and systemic control of tissue immunity by commensals. *Nat Immunol* 2013; **14**: 646-653 [PMID: [23778791](#) DOI: [10.1038/ni.2604](#)]
- 41 **Viaud S**, Saccheri F, Mignot G, Yamazaki T, Daillère R, Hannani D, Enot DP, Pfirschke C, Engblom C, Pittet MJ, Schlitzer A, Ginhoux F, Apetoh L, Chachaty E, Woerther PL, Eberl G, Bérard M, Ecobichon C, Clermont D, Bizet C, Gaboriau-Routhiau V, Cerf-Bensussan N, Opolon P, Yessaad N, Vivier E, Ryffel B, Elson CO, Doré J, Kroemer G, Lepage P, Boneca IG, Ghiringhelli F, Zitvogel L. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. *Science* 2013; **342**: 971-976 [PMID: [24264990](#) DOI: [10.1126/science.1240537](#)]
- 42 **Iida N**, Dzutsev A, Stewart CA, Smith L, Bouladoux N, Weingarten RA, Molina DA, Salcedo R, Back T, Cramer S, Dai RM, Kiu H, Cardone M, Naik S, Patri AK, Wang E, Marincola FM, Frank KM, Belkaid Y, Trinchieri G, Goldszmid RS. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. *Science* 2013; **342**: 967-970 [PMID: [24264989](#) DOI: [10.1126/science.1240527](#)]
- 43 **Kaderbhai C**, Richard C, Fumet JD, Aarnink A, Foucher P, Coudert B, Favier L, Lagrange A, Limagne E, Boidot R, Ghiringhelli F. Antibiotic Use Does Not Appear to Influence Response to Nivolumab. *Anticancer Res* 2017; **37**: 3195-3200 [PMID: [28551664](#) DOI: [10.21873/anticancer.11680](#)]
- 44 **Routy B**, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, Fluckiger A, Messaoudene M, Rauber C, Roberti MP, Fidelle M, Flament C, Poirier-Colame V, Opolon P, Klein C, Iribarren K, Mondragón L, Jacquilot N, Qu B, Ferrere G, Clémenson C, Mezquita L, Masip JR, Naltet C, Brosseau S, Kaderbhai C, Richard C, Rizvi H, Levenez F, Galleron N, Quinquis B, Pons N, Ryffel B, Minard-Colin V, Gonin P, Soria JC, Deutsch E, Lortet Y, Ghiringhelli F, Zalcman G, Goldwasser F, Escudier B, Hellmann MD, Eggermont A, Raoult D, Albiges L, Kroemer G, Zitvogel L. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science* 2018; **359**: 91-97 [PMID: [29097494](#) DOI: [10.1126/science.aan3706](#)]
- 45 **Derosa L**, Hellmann MD, Spaziano M, Halpenny D, Fidelle M, Rizvi H, Long N, Plodkowski AJ, Arbour KC, Chaft JE, Rouche JA, Zitvogel L, Zalcman G, Albiges L, Escudier B, Routy B. Negative association of antibiotics on clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non-small-cell lung cancer. *Ann Oncol* 2018; **29**: 1437-1444 [PMID: [29617710](#) DOI: [10.1093/annonc/mdy103](#)]

Basic Study

Elevated levels of interleukin-1 β , interleukin-6, tumor necrosis factor- α and vascular endothelial growth factor in patients with knee articular cartilage injury

Zhen-Wei Wang, Le Chen, Xiao-Rui Hao, Zhen-An Qu, Shi-Bo Huang, Xiao-Jun Ma, Jian-Chuan Wang, Wei-Ming Wang

ORCID number: Zhen-Wei Wang (0000-0001-5766-130X); Le Chen (0000-0002-8505-5603); Xiao-Rui Hao (0000-0002-9532-597X); Zhen-An Qu (0000-0003-2210-6044); Shi-Bo Huang (0000-0001-6812-8914); Xiao-Jun Ma (0000-0001-9349-6655); Jian-Chuan Wang (0000-0002-3091-1572); Wei-Ming Wang (0000-0002-4535-8191).

Author contributions: Wang ZW performed the majority of experiments and analyzed the data; Chen L, Hao XR, Ou ZA, Huang SB, Ma XJ and Wang JC performed the experiments; Wang WM designed the research and wrote the paper.

Institutional review board

statement: This study has been approved by the ethnic committee of Affiliated Zhongshan Hospital of Dalian University.

Conflict-of-interest statement: All authors have no conflict-of-interest to state.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and

Zhen-Wei Wang, Le Chen, Xiao-Rui Hao, Zhen-An Qu, Shi-Bo Huang, Xiao-Jun Ma, Jian-Chuan Wang, Wei-Ming Wang, Department of Sports Medicine, Affiliated Zhongshan Hospital of Dalian University, Dalian 16000, Liaoning Province, China

Corresponding author: Wei-Ming Wang, BSc, MD, PhD, Professor, Department of Sports Medicine, Affiliated Zhongshan Hospital of Dalian University, 6 Jiefang Jie, Zhongshan District, Dalian 116001, Liaoning Province, China. wangwm_01@126.com

Telephone: +86-411-62893145

Fax: +86-411-62893145

Abstract

BACKGROUND

Inflammatory cytokines play a vital role in the occurrence of osteoarticular injury and inflammation. Whether inflammation-associated factors interleukin-1 β (IL-1 β), IL-6, tumor necrosis factor- α (TNF- α) and vascular endothelial growth factor (VEGF) are involved in the pathogenesis of knee articular cartilage injury remains poorly understood.

AIM

To measure the levels of inflammatory factors [IL-1 β , IL-6, TNF- α and VEGF] in patients with knee articular cartilage injury.

METHODS

Fifty-five patients with knee articular cartilage injury were selected as patient groups, who were divided into three grades [mild ($n = 20$), moderate ($n = 19$) and severe ($n = 16$)] according to disease severity and X-ray examinations. Meanwhile, 30 healthy individuals who underwent physical examination were selected as the control group. The levels of IL-1 β , IL-6, TNF- α and VEGF were measured by ELISA and immunohistochemical staining.

RESULTS

Compared with the control group, patient groups displayed significantly higher levels of IL-1 β , IL-6, TNF- α and VEGF, and the extent of increase was directly proportional to the severity of injury ($P < 0.05$). In addition, the number of cells with positive staining of IL-1 β , IL-6, TNF- α and VEGF in the synovial membrane were significantly increased, along with increased disease severity ($P < 0.05$). After treatment, the scores of visual analogue scale and the Western Ontario and

the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Received: February 22, 2019

Peer-review started: February 24, 2019

First decision: March 10, 2019

Revised: March 20, 2019

Accepted: April 8, 2019

Article in press: April 9, 2019

Published online: June 6, 2019

P-Reviewer: Exbrayat JM, Wang Y

S-Editor: Ji FF

L-Editor: Filipodia

E-Editor: Xing YX



McMaster University of Orthopaedic Index in patient groups were 2.26 ± 1.13 and 15.56 ± 7.12 points, respectively, which were significantly lower than those before treatment (6.98 ± 1.32 and 49.48 ± 8.96). Correlation analysis suggested that IL-1 β and TNF- α were positively correlated with VEGF.

CONCLUSION

IL-1 β , IL-6, TNF- α and VEGF levels are increased in patients with knee articular cartilage injury, and are associated with the disease severity, indicating they might play an important role in the occurrence and development of knee articular cartilage injury. Furthermore, therapeutically targeting them might be a novel approach for the treatment of knee articular cartilage injury.

Key words: Knee articular cartilage injury; Interleukin-1 β ; Interleukin-6; Tumor necrosis factor- α ; Vascular endothelial growth factor

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Increased levels of interleukin-1 β (IL-1 β), IL-6, tumor necrosis factor- α and vascular endothelial growth factor are found in patients with knee articular cartilage injury, and are associated with the disease severity, suggesting that they might be involved in the pathogenesis of knee articular cartilage injury. Furthermore, therapeutically targeting them might be beneficial for the treatment of knee articular cartilage injury.

Citation: Wang ZW, Chen L, Hao XR, Qu ZA, Huang SB, Ma XJ, Wang JC, Wang WM. Elevated levels of interleukin-1 β , interleukin-6, tumor necrosis factor- α and vascular endothelial growth factor in patients with knee articular cartilage injury. *World J Clin Cases* 2019; 7(11): 1262-1269

URL: <https://www.wjgnet.com/2307-8960/full/v7/i11/1262.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v7.i11.1262>

INTRODUCTION

Knee articular cartilage injury is a type of joint disease with a high incidence, and is characterized by degenerative changes, such as disintegration and reduction of articular cartilage matrix. This leads to the formation of osteophytes, accompanied by aseptic inflammation of the synovial membrane^[1-3]. It has been proven that inflammatory cytokines play a vital role in the occurrence of osteoarticular injury and inflammation^[4-6]. Tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β) can trigger the production of matrix metalloproteinases, causing degradation of articular cartilage matrix, and eventually leading to osteochondral injury^[7]. IL-6 is a multifunctional cytokine that induces the proliferation and differentiation of immune cells, and plays a central role in the regulation of the complicated immune network in the body. This can lead to long-lasting chronic inflammation by inducing and activating various immune cells *in vivo*^[8-10]. Vascular endothelial growth factor (VEGF) is a platelet-derived growth factor, which is mainly expressed in articular osteoblasts and synovial fibroblasts^[11]. Elevated VEGF promotes neovascularization, and is considered to be one of the strongest angiogenic factors in the body^[12]. Considering the role of inflammatory cytokines in the pathogenesis of osteoarticular injury, whether IL-1 β , IL-6, TNF- α and VEGF are involved in the pathogenesis of knee articular cartilage injury remains poorly understood. The purpose of this study is to explore the expression profiles of IL-1 β , IL-6, TNF- α and VEGF in patients with knee articular cartilage injury, with an attempt to evaluate the clinical significance of the occurrence and development of the disease.

MATERIALS AND METHODS

Patients

A total of 55 patients consisting of 26 males and 29 females with knee osteoarthritis

caused by knee articular cartilage injury who were treated in our hospital from January 2017 to July 2017 were selected. All patients were diagnosed according to the diagnostic criteria of knee osteoarthritis formulated by the American College of Rheumatology^[13]. Patients who had been treated with hormone therapy within 3 mo, or patients with severe organ diseases or surgical contraindications, were excluded. Patients with knee articular cartilage injury were further divided into three grades [mild ($n = 20$), moderate ($n = 19$) and severe ($n = 16$)] according to clinical symptoms, disease severity and X-ray examinations. Another 30 healthy individuals who underwent physical examinations during the same period were selected as the control group. No significant differences were observed in these two groups regarding age, sex and other aspects ($P > 0.05$). This study was approved by the ethics committee of our hospital, and informed consents were received from all participants prior to this study.

Measurement of IL-1 β , IL-6, TNF- α and VEGF levels by ELISA

The fasting venous blood was drawn in the morning and centrifuged at $\times 2000$ g for 20 min to obtain serum, which was used to measure the levels of IL-1 β ; IL-6; TNF- α and VEGF by ELISA according to the manufacturer's instructions.

Immunohistochemical staining

Synovial specimens were collected during the replacement surgery and were fixed, dehydrated and immersed in wax. After embedding in paraffin, synovial specimens were sliced and processed by heating antigen retrieval. After blocking the endogenous peroxidase activity with freshly made 0.3% H2O2 in methanol for 20 min, primary antibodies against IL-1 β , IL-6, TNF- α or VEGF (Cell Signaling Technology) were added and incubated for 1 h, followed by washing and addition of a biotinylated secondary antibody (Cell Signaling Technology) for a 10 min incubation. Then, DAB substrate was added for development, followed by counter-staining and differentiation, and subsequently mounted with mounting medium (Simpomount). Mounted slides were observed and recorded under a light-field microscope. The number of positive cells with IL-1 β , IL-6, TNF- α and VEGF in synovial tissues was counted.

Evaluation indexes

Changes in clinical indicators [visual analog scale (VAS) and Western Ontario and McMaster University of Orthopaedic Index (WOMAC)] before and after treatment were observed, and the overall scores before and after treatment (i.e. the fourth week) were taken as the main evaluating indicators. VAS is an evaluating indicator that can accurately express the subjective pain of the patients. WOMAC scores are on physical function, stiffness and the degree of pain. It was divided into five grades: 0 points (no), 1 (mild), 2 (moderate), 3 (severe) and 4 (extremely severe).

Statistical analysis

The data were processed by Statistical Product and Service Solutions (SPSS) 19.0 software [International Business Machines Corporation] and displayed as mean \pm SD. Student *t*-tests were performed to compare the differences between the two groups, and one-way ANOVA was conducted to compare the difference among multiple groups. The correlation between two variables was analyzed by Pearson correlation analysis. $P < 0.05$ indicated a statistical difference.

RESULTS

Elevated levels of IL-1 β , IL-6, TNF- α and VEGF in patients

The levels of IL-1 β , IL-6, TNF- α and VEGF in the serum of patients group were 74.91 ± 3.48 , 40.35 ± 27.18 , 67.12 ± 3.15 and 224.42 ± 31.06 ng/L, respectively, which were significantly higher than those of the control group (13.41 ± 1.50 , 12.25 ± 2.58 , 6.91 ± 4.20 and 135.48 ± 20.41 ng/L) ($P < 0.05$) (Figure 1).

Levels of IL-1 β , IL-6, TNF- α and VEGF in patients with different degrees of knee articular cartilage injury

The levels of IL-1 β , IL-6, TNF- α and VEGF showed an increased trend from patients with mild, moderate or severe knee articular cartilage injury, with statistically significant differences ($P < 0.05$) (Figure 2).

Immunohistochemical staining analysis of the levels of IL-1 β , IL-6, TNF- α and VEGF in synovial membrane

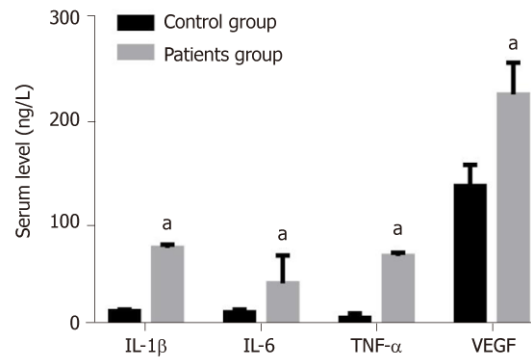


Figure 1 Levels of interleukin-1 β , interleukin-6, tumor necrosis factor- α and vascular endothelial growth factor in patient and control groups.^a $P < 0.05$, vs control group. IL-1 β : Interleukin-1 β ; TNF- α : Tumor necrosis factor- α ; VEGF: Vascular endothelial growth factor.

As seen in Figure 3, the number of positive cells of IL-1 β , IL-6, TNF- α and VEGF in synovial membrane in patients with severe knee articular cartilage injury were significantly higher than those in patients with moderate knee articular cartilage injury. These were also higher than those in the group of patients with mild knee articular cartilage injury ($P < 0.05$).

Changes of clinical indices in patients before and after treatment

After the treatment, the scores of VAS and WOMAC in patients were 2.26 ± 1.13 and 15.56 ± 7.12 points, respectively, which were significantly lower than those before treatment (6.98 ± 1.32 vs 49.48 ± 8.96 points) ($P < 0.05$) (Figure 4).

Correlation analysis of inflammatory factors with VEGF

Pearson correlation analysis results showed that serum inflammatory factors (IL-1 β and TNF- α) in patients were positively correlated with VEGF ($r = 0.6763$, $r = 0.4856$, $P < 0.01$) (Figure 5). However, there was no significant correlation between IL-6 and VEGF.

DISCUSSION

In recent years, many studies have found that osteoarthritis patients have immune abnormalities, and abnormal secretions of cytokines might damage cartilage function and metabolism^[14,15]. In addition, aggravated gradual decomposition of cartilage matrix can bring irreversible injury to the joint structure of patients, which is manifested as the corresponding clinical symptoms, thus accelerating the progress of articular cartilage injury^[16,17]. IL-1 β , IL-6 and TNF- α are secreted from macrophages and immune cells, which mainly come from the lining cells of the synovial membrane. These participate in the occurrence and development of osteoarthritis^[18,19]. VEGF is an important factor in promoting neovascularization, and abnormal cell proliferation and differentiation may lead to the persistence of synovial inflammation^[20]. The mechanism of VEGF in promoting the progress of osteoarthritis is believed to promote the proliferation of vascular endothelial cells and the growth of tumor lymphatic vessels, as well as upregulate the expression of anti-apoptotic proteins^[21]. This thereby accelerates the formation of neovascularization in synovial pannus, and the subsequent division of endothelium cells, which is an important factor leading to increased vascular permeability^[22].

Consistent with the role of inflammatory cytokines in the pathogenesis of osteoarthritis, we showed in this study that levels of IL-1 β , IL-6 and TNF- α in the serum of patients with knee articular cartilage injury group were significantly higher than those in the control group ($P < 0.05$). In addition, immunohistochemical staining showed that the numbers of cells with positive staining of IL-1 β , TNF- α and VEGF were statistically increased with disease progression. This suggests that an imbalance of cellular and humoral immunity *in vivo* might be involved in the pathophysiological process of the damage and progress of synovial membrane in knee osteoarthritis^[23]. Patients with osteoarthritis are characterized by articular cartilage degeneration and changes of cartilage matrix composition, and the decrease of anti-angiogenic factors indirectly enhances the functions of pro-angiogenic factors, such as VEGF, in the pathogenesis of osteoarthritis. It was reported that different levels of VEGF are

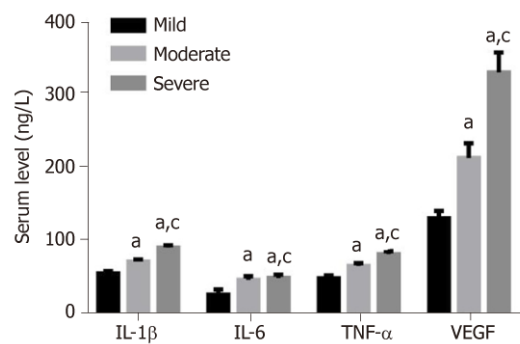


Figure 2 Serum levels of interleukin-1 β , interleukin-6 and tumor necrosis factor- α in patients with different degrees of knee articular cartilage injury.^a $P < 0.05$, vs mild; ^c $P < 0.05$, vs moderate group. IL-1 β : Interleukin-1 β ; TNF- α : Tumor necrosis factor- α ; VEGF: Vascular endothelial growth factor.

detected in patients with osteoarthritis^[24]. In accordance with this, our study showed that, along with osteoarthritis progression, the serum level of VEGF in patients was significantly increased, further supporting the role of VEGF in the pathogenesis and development of osteoarthritis.

VAS is an evaluating indicator that can accurately reflect the subjective pain of patients. Through assessment of physical function, stiffness and the degree of pain, WOMAC scores are currently widely used in the treatment of osteoarthritis to evaluate the therapeutic effect of drugs. In this study, we showed that VAS and WOMAC in patients with knee articular cartilage injury after treatment were significantly lower than those before treatment, indicating that the clinical symptoms were greatly improved. Furthermore, Pearson correlation analysis showed that serum inflammatory factors (IL-1 β and TNF- α) in patients was positively correlated with VEGF, indicating that the imbalance of the immune state *in vivo*, and the increase of factors related to neovascularization, might contribute to the development of osteoarthritis^[25].

In conclusion, IL-1 β , IL-6, TNF- α and VEGF levels are significantly increased in patients with knee articular cartilage injury, and are associated with the severity of disease. This suggests they might play an important role in the occurrence and development of knee articular cartilage injury. Thus, targeting them might be a novel approach for the treatment of knee articular cartilage injury.

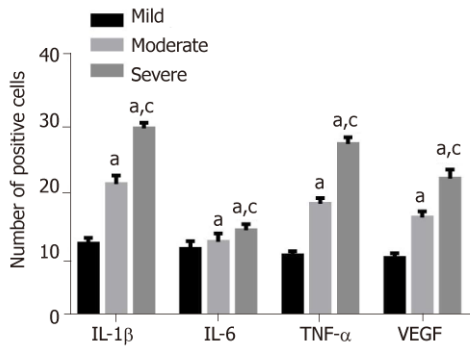


Figure 3 Immunohistochemical staining analysis of the number of positive cells of interleukin-1 β , interleukin-6, tumor necrosis factor- α and vascular endothelial growth factor in synovial membrane (%).^a $P < 0.05$, vs mild; ^c $P < 0.05$, vs moderate group. IL-1 β : Interleukin-1 β ; TNF- α : Tumor necrosis factor- α ; VEGF: Vascular endothelial growth factor.

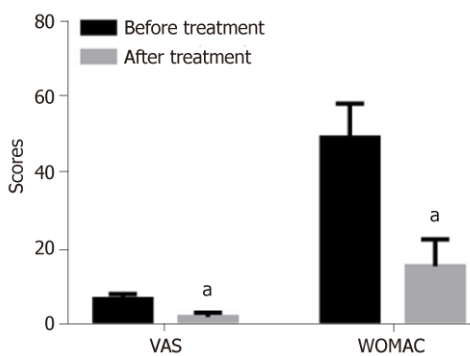


Figure 4 Comparisons of changes in clinical indices before and after treatment.^a $P < 0.05$, vs before treatment. VAS: Visual analogue scale; WOMAC: Western Ontario and McMaster University of Orthopaedic Index.

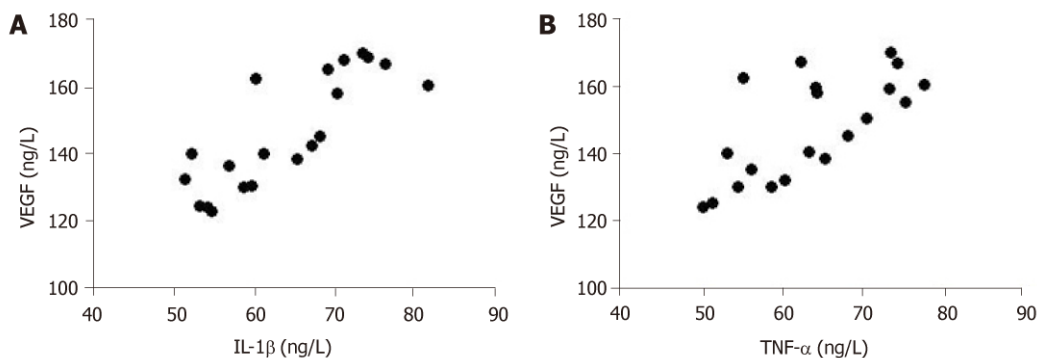


Figure 5 Correlation analysis of interleukin-1 β (A) or tumor necrosis factor- α (B) with vascular endothelial growth factor. IL-1 β : Interleukin-1 β ; TNF- α : Tumor necrosis factor- α ; VEGF: Vascular endothelial growth factor.

ARTICLE HIGHLIGHTS

Research background

Inflammatory cytokines play a vital role in the occurrence of osteoarticular injury and inflammation. Whether inflammation-associated factors interleukin-1 β (IL-1 β), IL-6, tumor necrosis factor- α (TNF- α) and vascular endothelial growth factor (VEGF) are involved in the pathogenesis of knee articular cartilage injury remains poorly understood.

Research motivation

The main topic is the inflammatory cytokines in knee articular cartilage injury.

Research objectives

To measure the levels of inflammatory factors [IL-1 β , IL-6, TNF- α and VEGF] in patients with knee articular cartilage injury.

Research methods

Fifty-five patients with knee articular cartilage injury were selected as the patients groups, and were divided into three grades [mild ($n = 20$), moderate ($n = 19$) and severe ($n = 16$)] according to disease severity and X-ray examinations. Meanwhile, 30 healthy individuals who underwent physical examination were selected as the control group. The levels of IL-1 β , IL-6, TNF- α and VEGF were measured by ELISA and immunohistochemical staining.

Research results

Compared with the control group, the patients group displayed significantly higher levels of IL-1 β , IL-6, TNF- α and VEGF, and the extent of increase was directly proportional to the severity of injury ($P < 0.05$). In addition, the number of cells with positive staining of IL-1 β , IL-6, TNF- α and VEGF in the synovial membrane was significantly increased, along with an increase in disease severity ($P < 0.05$). After treatment, the scores of visual analogue scale (VAS) and the Western Ontario and McMaster University of Orthopaedic Index in the patient group were 2.26 ± 1.13 and 15.56 ± 7.12 points, respectively, which were significantly lower than those before treatment (6.98 ± 1.32 and 49.48 ± 8.96). The correlation analysis suggested that IL-1 β and TNF- α were positively correlated with VEGF.

Research conclusions

IL-1 β , IL-6, TNF- α and VEGF levels are increased in patients with knee articular cartilage injury, and are associated with disease severity. This indicates that they might play an important role in the occurrence and development of knee articular cartilage injury. In addition, therapeutically targeting them might be a novel approach for the treatment of knee articular cartilage injury.

Research perspectives

Abnormal levels of IL-1 β , IL-6, TNF- α and VEGF were found in patients with knee articular cartilage injury, indicating that they might be novel therapeutic targets for the treatment of knee articular cartilage injury.

REFERENCES

- 1 **Ma J**, Niu DS, Wan NJ, Qin Y, Guo CJ. Elevated chemerin levels in synovial fluid and synovial membrane from patients with knee osteoarthritis. *Int J Clin Exp Pathol* 2015; **8**: 13393-13398 [PMID: 26722546]
- 2 **Abdelnaby R**, El Deeb S, Khachab A, Bläsius K, Tingart M, Rath B. Plasma level of Osteopontin does not respond to total replacement Surgery in patients with severe Primary knee/Hip Osteoarthritis. *J Orthop* 2017; **14**: 354-357 [PMID: 28706379 DOI: 10.1016/j.jor.2017.06.008]
- 3 **Yokogawa N**, Toribatake Y, Murakami H, Hayashi H, Yoneyama T, Watanabe T, Tsuchiya H. Differences in Gait Characteristics of Patients with Lumbar Spinal Canal Stenosis (L4 Radiculopathy) and Those with Osteoarthritis of the Hip. *PLoS One* 2015; **10**: e0124745 [PMID: 25893667 DOI: 10.1371/journal.pone.0124745]
- 4 **Kapoor M**, Martel-Pelletier J, Lajeunesse D, Pelletier JP, Fahmi H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat Rev Rheumatol* 2011; **7**: 33-42 [PMID: 21119608 DOI: 10.1038/nrrheum.2010.196]
- 5 **Wojdasiewicz P**, Poniatowski LA, Szukiewicz D. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. *Mediators Inflamm* 2014; **2014**: 561459 [PMID: 24876674 DOI: 10.1155/2014/561459]
- 6 **Miller RE**, Miller RJ, Malfait AM. Osteoarthritis joint pain: the cytokine connection. *Cytokine* 2014; **70**: 185-193 [PMID: 25066335 DOI: 10.1016/j.cyto.2014.06.019]
- 7 **Yuan PW**, Liu DY, Chu XD, Hao YQ, Zhu C, Qu Q. Effects of preventive administration of juanbi capsules on TNF- α , IL-1 and IL-6 contents of joint fluid in the rabbit with knee osteoarthritis. *J Tradit Chin Med* 2010; **30**: 254-258 [PMID: 21287781 DOI: 10.1016/S0254-6272(10)60052-0]
- 8 **Funck-Brentano T**, Cohen-Solal M. Subchondral bone and osteoarthritis. *Curr Opin Rheumatol* 2015; **27**: 420-426 [PMID: 26002035 DOI: 10.1097/BOR.0000000000000181]
- 9 **Tanaka T**, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol* 2014; **6**: a016295 [PMID: 25190079 DOI: 10.1101/cshperspect.a016295]
- 10 **Gabay C**. Interleukin-6 and chronic inflammation. *Arthritis Res Ther* 2006; **8** Suppl 2: S3 [PMID: 16899107 DOI: 10.1186/ar1917]
- 11 **Nagao M**, Hamilton JL, Kc R, Berendsen AD, Duan X, Cheong CW, Li X, Im HJ, Olsen BR. Vascular Endothelial Growth Factor in Cartilage Development and Osteoarthritis. *Sci Rep* 2017; **7**: 13027 [PMID: 29026147 DOI: 10.1038/s41598-017-13417-w]
- 12 **Liu M**, Yang S, Zhang D, Shui P, Song S, Yao J, Dai Y, Sun Q. Fructopyranose-(1 \rightarrow 4)-glucopyranose inhibits the proliferation of liver cancer cells and angiogenesis in a VEGF/VEGFR dependent manner. *Int J Clin Exp Med* 2014; **7**: 3859-3869 [PMID: 25550894]
- 13 **Cojocaru IM**, Ștefănescu V, Trașcă D, Șerban-Perețeanu A, Chicoș B, Cojocaru M. Multiple Intracerebral Hemorrhages in an Old Patient with Rheumatoid Arthritis. *Rom J Intern Med* 2015; **53**: 365-373 [PMID: 26939215 DOI: 10.1515/rjim-2015-0048]
- 14 **Steinhaus ME**, Christ AB, Cross MB. Total Knee Arthroplasty for Knee Osteoarthritis: Support for a Foregone Conclusion? *HSS J* 2017; **13**: 207-210 [PMID: 28690473 DOI: 10.1007/s11420-017-9558-4]
- 15 **Kong R**, Gao J, Si Y, Zhao D. Combination of circulating miR-19b-3p, miR-122-5p and miR-486-5p expressions correlates with risk and disease severity of knee osteoarthritis. *Am J Transl Res* 2017; **9**: 2852-2864 [PMID: 28670374]
- 16 **Loures FB**, Carrara RJ, Góes RFA, Albuquerque RSPE, Barretto JM, Kinder A, Gameiro VS, Marchiori

- E. Anthropometric study of the knee in patients with osteoarthritis: intraoperative measurement versus magnetic resonance imaging. *Radiol Bras* 2017; **50**: 170-175 [PMID: [28670028](#) DOI: [10.1590/0100-3984.2016.0007](#)]
- 17 **Willett M**, Duda J, Gautrey C, Fenton S, Greig C, Rushton A. Effectiveness of behavioural change techniques in physiotherapy interventions to promote physical activity adherence in patients with hip and knee osteoarthritis: a systematic review protocol. *BMJ Open* 2017; **7**: e015833 [PMID: [28667221](#) DOI: [10.1136/bmjopen-2017-015833](#)]
 - 18 **Lim SH**, Hong BY, Oh JH, Lee JI. Relationship between knee alignment and the electromyographic activity of quadriceps muscles in patients with knee osteoarthritis. *J Phys Ther Sci* 2015; **27**: 1261-1265 [PMID: [25995602](#) DOI: [10.1589/jpts.27.1261](#)]
 - 19 **Bar-Or D**, Rael LT, Thomas GW, Brody EN. Inflammatory Pathways in Knee Osteoarthritis: Potential Targets for Treatment. *Curr Rheumatol Rev* 2015; **11**: 50-58 [PMID: [26002457](#) DOI: [10.2174/1573397111666150522094131](#)]
 - 20 **Bai J**, Li G, Shen M, Sui D, Lin S. Primary central nervous system histiocytic sarcoma mimicking glioma. *Neurol India* 2014; **62**: 684-685 [PMID: [25591690](#) DOI: [10.4103/0028-3886.149409](#)]
 - 21 **Minchenko OH**, Garmash IA, Kovalevska OV, Tsybal DO, Minchenko DO. Expression of phosphoribosyl pyrophosphate synthetase genes in U87 glioma cells with ERN1 knockdown: effect of hypoxia and endoplasmic reticulum stress. *Ukr Biochem J* 2014; **86**: 74-83 [PMID: [25816608](#) DOI: [10.15407/ubj86.06.074](#)]
 - 22 **Ozawa A**, Kadowaki E, Haga Y, Sekiguchi H, Hemmi N, Kaneko T, Maki T, Sakabe K, Hara S, Yamamoto M, Arishima K, Sakaue M. Acetylcholine esterase is a regulator of GFAP expression and a target of dichlorvos in astrocytic differentiation of rat glioma C6 cells. *Brain Res* 2013; **1537**: 37-45 [PMID: [24001591](#) DOI: [10.1016/j.brainres.2013.08.031](#)]
 - 23 **Wang XP**, Deng XL, Li LY. MicroRNA-584 functions as a tumor suppressor and targets PTTG1IP in glioma. *Int J Clin Exp Pathol* 2014; **7**: 8573-8582 [PMID: [25674221](#)]
 - 24 **Lee SS**, Joo YS, Kim WU, Min DJ, Min JK, Park SH, Cho CS, Kim HY. Vascular endothelial growth factor levels in the serum and synovial fluid of patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2001; **19**: 321-324 [PMID: [11407088](#) DOI: [10.1002/1529-0131\(200105\)44:5<1229::AID-ANR209>3.0.CO;2-E](#)]
 - 25 **Sun XP**, Dong X, Lin L, Jiang X, Wei Z, Zhai B, Sun B, Zhang Q, Wang X, Jiang H, Krissansen GW, Qiao H, Sun X. Up-regulation of survivin by AKT and hypoxia-inducible factor 1 α contributes to cisplatin resistance in gastric cancer. *FEBS J* 2014; **281**: 115-128 [PMID: [24165223](#) DOI: [10.1111/febs.12577](#)]

Retrospective Cohort Study

Anti-hepatitis C virus therapy in chronic kidney disease patients improves long-term renal and patient survivals

Yi-Chun Chen, Chung-Yi Li, Shiang-Jiun Tsai, Yen-Chun Chen

ORCID number: Yi-Chun Chen (0000-0003-2153-272X); Chung-Yi Li (0000-0002-0321-8908); Shiang-Jiun Tsai (0000-0002-0644-8223); Yen-Chun Chen (0000-0002-9739-9905).

Author contributions: Chen YC designed the research; Chen YC, Li CY, and Tsai SJ performed the research; Chen YC, Li CY, Tsai SJ, and Chen YC analyzed the data; Chen YC wrote the paper; Li CY, Tsai SJ, and Chen YC critically revised the manuscript for important intellectual content.

Supported by Dalin Tzu Chi Hospital, No. DTCRD 104-I-16.

Institutional review board

statement: This study was approved by the institutional review board of the Dalin Tzu Chi Hospital (B10302011).

Informed consent statement: All patient information was de-identified in the database (LHID2005) and no informed consent was required. This study was exempt from a full ethical review by the institutional review board of the Dalin Tzu Chi Hospital (B10302011).

Conflict-of-interest statement: All authors have no conflict of interests.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to

Yi-Chun Chen, Division of Nephrology, Department of Internal Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi County 622, Taiwan

Yi-Chun Chen, School of Medicine, Tzu Chi University, Hualien 970, Taiwan

Chung-Yi Li, Department and Graduate Institute of Public Health, College of Medicine, National Cheng Kung University, Tainan 701, Taiwan

Chung-Yi Li, Department of Public Health, College of Public Health, China Medical University, Taichung 404, Taiwan

Shiang-Jiun Tsai, Department of Medical Research, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi County 622, Taiwan

Yen-Chun Chen, Division of Hepato-Gastroenterology, Department of Internal Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi County 622, Taiwan

Corresponding author: Yi-Chun Chen, MD, Assistant Professor, Doctor, Division of Nephrology, Department of Internal Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, No. 2, Minsheng Rd., Dalin Township, Chiayi County 622, Taiwan. chenyichun0320@yahoo.com.tw

Telephone: +886-5-2648000-5665

Fax: +886-5-2648128

Abstract

BACKGROUND

Hepatitis C virus (HCV) infection is a documented risk factor for chronic kidney disease (CKD) and progression to end-stage renal disease (ESRD). However, to date there are no reports on the long-term hard endpoints (ESRD and death) of anti-HCV therapy [interferon-based therapy (IBT) or new direct-acting antivirals] in CKD patients. Direct-acting antivirals are not available in Taiwan's single-payer national health insurance database currently released for research. Therefore, we hypothesized that a retrospective analysis of the long-term outcomes of IBT in CKD patients will serve as a proxy for direct-acting antivirals to increase our understanding of progression to ESRD following HCV infection.

AIM

To evaluate the long-term outcomes (ESRD and death) of anti-HCV therapy, especially IBT, in HCV-infected patients with stage 1-5 CKD.

METHODS

We analyzed 93894 Taiwanese adults diagnosed with CKD and without HBV

distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Received: March 4, 2019

Peer-review started: March 4, 2019

First decision: March 27, 2019

Revised: April 14, 2019

Accepted: April 18, 2019

Article in press: April 19, 2019

Published online: June 6, 2019

P-Reviewer: Ohsawa M, Shimizu Y

S-Editor: Ji FF

L-Editor: Filipodia

E-Editor: Xing YX



infection. Of these, 4.9% were infected with HCV. Of the 4582 HCV-infected CKD patients, 482 (10.5%) received IBT (treated cohort). They were matched 1:4 with 1928 untreated HCV-infected CKD patients (untreated cohort) by propensity scores and year, which further matched 1:2 by propensity scores with 3856 CKD patients without HCV infection (uninfected cohort). All participants were followed until the occurrence of ESRD, death, or the end of 2012. The association between HCV infection, IBT use, and risks of ESRD and death was analyzed using competing risk analysis.

RESULTS

Taking the uninfected cohort as a reference, the adjusted hazard ratios for ESRD, after adjusting for competing mortality, were 0.34 (0.14-0.84, $P = 0.019$) and 1.28 (1.03-1.60, $P = 0.029$) in the treated and untreated cohorts, respectively. The treated cohort had a 29% (0.54-0.92, $P = 0.011$) decrease in mortality compared to the untreated cohort, in which the mortality was 31% (1.18-1.45, $P < 0.001$) higher than in the uninfected cohort. The reduced risks of ESRD (0.14, 0.03-0.58, $P = 0.007$) and death (0.57, 0.41-0.79, $P = 0.001$) were greatest in HCV-infected CKD patients who received at least 4 mo of IBT, which accounted for 74% of the treated cohort.

CONCLUSION

Adequate anti-HCV therapy in CKD patients improves long-term renal and patient survival.

Key words: Hepatitis C virus; Chronic kidney disease; End-stage renal disease; Anti-hepatitis C virus therapy; Cohort study

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This large nationwide retrospective cohort study used propensity score-matched and competing risk analyses to evaluate the long-term hard endpoints of hepatitis C virus (HCV) infection and anti-HCV therapy, especially interferon-based therapy, in chronic kidney disease patients. We found that untreated HCV infection in chronic kidney disease was associated with increased risks of end-stage renal disease and mortality. On the contrary, adequate anti-HCV therapy in chronic kidney disease patients improves long-term renal and patient survival.

Citation: Chen YC, Li CY, Tsai SJ, Chen YC. Anti-hepatitis C virus therapy in chronic kidney disease patients improves long-term renal and patient survivals. *World J Clin Cases* 2019; 7(11): 1270-1281

URL: <https://www.wjgnet.com/2307-8960/full/v7/i11/1270.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v7.i11.1270>

INTRODUCTION

Hepatitis C virus (HCV) infection and chronic kidney disease (CKD) are recognized public health concerns with global implications that affect 3%^[1] and 10%^[2], respectively, of people worldwide. Furthermore, the two remain economic threats due to their high morbidity and mortality^[3]. HCV mainly targets the liver but can also induce at least one extrahepatic manifestation in 40% of the infected patients, including renal injury, insulin resistance (IR), accelerated atherosclerosis, and cardiovascular event risk^[2]. Accumulating evidence has implicated HCV infection as an important cause and consequence of CKD^[1-4]. HCV is an initiating factor for CKD in the general population^[5,6], regardless of the presence of conventional risk factors for CKD^[6,7], including aging, diabetes, and hypertension. It is also a progression factor of CKD to end-stage renal disease (ESRD) in the general population^[8,9], CKD population of any etiology^[10], and patients with diabetes^[11] and glomerulonephritis^[12]. The immunosuppression caused by CKD^[13], especially stages 3-5^[1,13-15], also makes CKD patients more vulnerable to the cytopathic effects of the HCV infection^[3] and to HCV infection with high viremic potential^[13,14,16], independent of a history of blood transfusions^[13,17]. This further decreases renal^[10,18] and patient survivals^[10]. In the past

decades, interferon-based therapy (IBT) was shown to be beneficial for eradicating HCV in some populations^[19-24]. However, there are no large-scale studies that document the long-term outcomes (renal and patient survivals) of HCV therapy in patients with CKD stages 1-5.

Although direct-acting antivirals (DAAs), the new paradigm of HCV therapy, are effective in eradicating HCV and are well tolerated in the general population, their short-term efficacy and tolerability seem promising but not representative to all patients with advanced CKD, as shown in a recent meta-analysis^[25] that was small-sized and only included 16.3% Asian individuals among the 264 patients. Moreover, their long-term outcomes and safety in CKD patients have not been elucidated. The exorbitant costs of DAAs remain the biggest barrier to their universal adoption in developed countries^[26]. In Taiwan, DAAs could be reimbursed by single-payer national health insurance (NHI) for a minority of HCV-infected patients since 2018 and for all those since 2019. However, DAAs were not available for research in the Taiwan's National Health Insurance Research Database (NHIRD), which was just released for academic research in 2016. The significant risk of drug-drug interactions^[26,27] is another concern in CKD patients mostly suffering from multiple comorbidities.

Even though IBT is less well-tolerated in patients with kidney disease, it has a low dropout rate (0.18)^[28], it is easy to access for studies in the NHIRD, it could be offered with much less chance of sustained virological response (SVR) but at a lesser cost^[27], and it has been widely used for decades with excellent therapeutic responses in Asian countries where the favorable interleukin-28B is prevalent^[20]. Given the reported higher percentage of viremia in HCV-infected CKD patients^[13,14,16] and the clinical benefits that are derived from HCV eradication, we hypothesized that treating HCV infection in CKD patients might improve long-term hard endpoints. In order to fill this knowledge gap and in light of the easy access to IBT in the NHIRD, we analyzed data between 1997 and 2012 to examine the long-term impact of treating HCV infection with IBT on renal and survival outcomes among CKD patients.

MATERIALS AND METHODS

Data source

This retrospective nationwide cohort study used data from Taiwan's NHIRD. The NHIRD has been prospectively recording comprehensive nationwide healthcare data of all beneficiaries since 1995, the year when the Taiwan NHI was implemented. The NHIRD adopts ICD-9 codes and drug codes to define diseases and drugs and was released by the National Health Research Institute for academic research after all personal information was de-identified. Thus, no informed consent was required and this study was exempt from a full ethical review by the institutional review board of the Dalin Tzu Chi Hospital (B10302011). Because of the single-payer and compulsory policy, the NHI program reached coverage of more than 99% by the end of 2012. The details of the NHIRD have been described in our previous work^[5,21,29-32].

Study (CKD) population

We enrolled CKD patients who had a diagnosis of ≥ 1 inpatient or ≥ 2 outpatient CKD ICD-9 codes (250.4*, 274.1*, 283.11, 403.*1, 404.*2, 404.*3, 440.1, 442.1, 447.3, 572.4, 580-588, 642.1*, 646.2*)^[5,21,32] between January 1, 1997 and December 31, 2012. We excluded CKD patients < 18 years, those who had claim-based diagnoses of HBV (ICD-9 codes 070.22, 070.23, 070.32, 070.33, V02.61) during this period, or those who developed ESRD (indicating the need for long-term renal replacement therapy) before the identification of CKD. A total of 93894 CKD adults without HBV infection were eligible for analysis (Figure 1). However, the exact stage of CKD cannot be assessed from the NHIRD.

Study cohorts

Eligible CKD enrollees were grouped into three cohorts according to a claim-based diagnosis of HCV infection (ICD-9 codes 070.41, 070.44, 070.51, 070.54, V02.62)^[5,21] and the use of IBT (namely, interferon alpha, pegylated interferon alpha-2a, or pegylated interferon alpha-2b alone or in combination with ribavirin)^[19,21]. There were 4582 (4.9%) CKD patients who were infected with HCV. Of the 4582 HCV-infected CKD patients, 482 (10.5%) were treated with IBT during this period (treated cohort) and the date of IBT initiation was considered the index date of the treated cohort. There were no treated HCV-infected CKD patients receiving ribavirin. Each treated patient was matched with four untreated patients who never received IBT throughout the study period by propensity score (to avoid confounding by indication bias) and during the

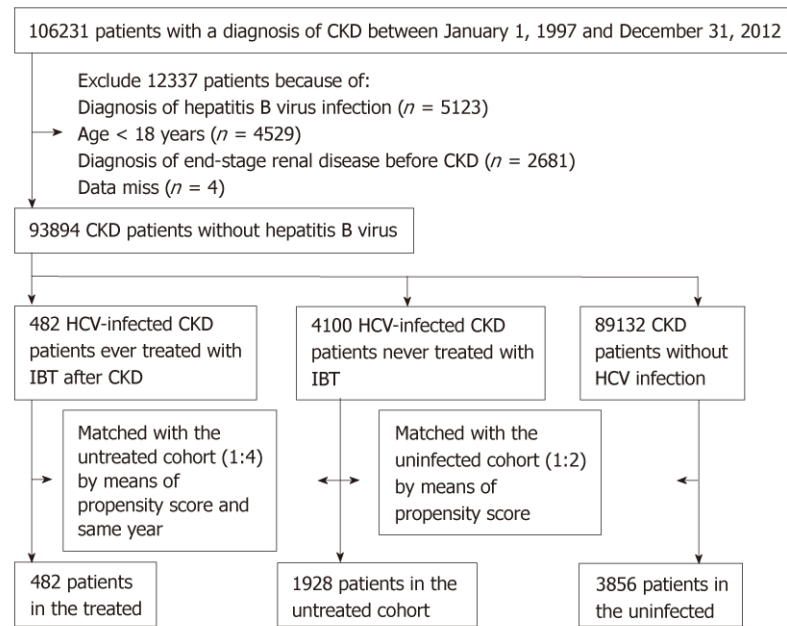


Figure 1 Flow diagram of the enrollment process. CKD: Chronic kidney disease; HCV: Hepatitis C virus; IBT: Interferon-based therapy.

same year of the index date (to avoid immortal time bias)^[33,34]. The propensity score was estimated by the logistic regression built on age, sex, and comorbidity. The propensity score model was reliable (Hosmer–Lemeshow test $P > 0.05$) and provided fair discrimination between the treated and untreated cohorts (c-index > 0.6)^[35] every year. Next, each untreated patient was propensity score-matched with two uninfected patients who never coded for HCV infection throughout the study period. The index dates of the untreated and uninfected cohorts were their corresponding matched dates. The propensity score model was reliable (Hosmer–Lemeshow test $P = 0.999$) and provided fair discrimination between the untreated and uninfected cohorts (c-index, 0.686). A total of 482 CKD patients were in the treated cohort, 1,928 patients were in the untreated cohort, and 3,856 patients were in the uninfected cohort for the final analysis.

Definition of hard endpoints

Follow-up started in the treated cohort after IBT was initiated, and in the untreated and uninfected cohorts after their matched dates. All patients were followed until ESRD occurrence, death, or December 31, 2012, whichever came first. Death before reaching ESRD was considered a competing risk event^[29] in estimating the incidence of ESRD. In Taiwan, ESRD is a statutory major disease, and patients who develop ESRD and require long-term dialysis are issued a catastrophic illness certificate that is validated by at least two experienced nephrologists after a rigorous review of the clinical data. This grants exemption from copayment for healthcare. Thus, the diagnostic accuracy of ESRD is reliable. In the present study, all ESRD cases were identified from the Registry of Catastrophic Illness Patient Database, a part of the NHIRD.

Covariate assessment

We included the enrollee category [1 (highest status) to 4 (lowest status)] as a proxy for socioeconomic status and major comorbidity, including diabetes (ICD-9 code 250), hypertension (ICD-9 codes 401-405), coronary heart disease (ICD-9 codes 410-414), hyperlipidemia (ICD-9 codes 272-272.4), and cirrhosis (ICD-9 codes 571.2, 571.5, 571.6), which were associated with ESRD^[29]. Additional confounding factors used in administrative medical databases included the number of medical visits and the Charlson comorbidity index (CCI) score^[5,29]. Angiotensin-converting-enzyme inhibitor/angiotensin II receptor blocker (ACEI/ARB) was also identified because it is used as a mainstream drug against CKD progression and because of the strong correlations with ESRD and mortality^[36]. Usage was defined as having used the drug for over 5% of the follow-up period.

Statistical analysis

The statistical methods of this study were reviewed by our coauthor Chung-Yi Li. The modified Kaplan-Meier method and Gray's method^[37] were used to calculate and compare the cumulative incidence of ESRD in data with competing risk. After confirming the assumption of proportional hazards (Supplementary Figure 1), we applied the modified Cox proportional hazard model to evaluate the relationship between IBT and the ESRD risk after adjusting all covariates (age per year, sex, major comorbidity, the use of ACEI/ARB, enrollee category, number of medical visits, and CCI score) and competing mortality. A sensitivity analysis was performed to evaluate the individual risk of ESRD and death between the treated and untreated cohorts as well as between the untreated and uninfected cohorts. Two stratified analyses were performed to investigate the individual impact of IBT and lack of IBT on the ESRD risk according to age, sex, comorbidity, and the use of ACEI/ARB. The impact of IBT duration, classified as < 4 mo *versus* ≥ 4 mo^[20], on the ESRD risk was also examined. Data were managed with SAS (version 9.4; SAS Institute, Inc., Cary, NC, United States), SPSS (version 20.0; IBM Corp., New York, NY, United States), and Stata software, version 12 (StataCorp, College Station, TX, United States). A 2-sided *P*-value less than 0.05 was considered significant.

RESULTS

Baseline characteristics of the propensity score-matched CKD patients

Table 1 summarizes the baseline profiles of the three study cohorts. The distribution by age, sex, comorbidity, and use of ACEI/ARB, except for enrollee category, CCI score, and the number of medical visits, was balanced among the three cohorts.

Cumulative incidences of ESRD and death in the three study cohorts

During the total mean follow-up of 6.0 ± 4.4 years, 327 patients (5.2%) developed ESRD, with 5 (1.0%), 134 (7.0%), and 188 (4.9%) in the treated, untreated, and uninfected cohorts, respectively ($P < 0.0001$), and 1570 patients (25.1%) died, with 61 (12.7%), 648 (33.6%), and 861 (22.3%) in the treated, untreated, and uninfected cohorts, respectively ($P < 0.0001$) (Table 2). The 16-year cumulative incidence of ESRD was significantly higher in the untreated cohort [11.7%, 95% confidence interval (CI): 8.0%-16.1%] as compared to the treated (2.4%, 95%CI: 0.9%-5.2%) and uninfected cohorts (8.2%, 95%CI: 6.2%-10.5%), respectively ($P = 0.0032$). The 16-year cumulative incidence of death was significantly higher in the untreated cohort (58.0%, 95%CI: 51.5%-63.9%) as compared to the treated (41.4%, 95%CI: 37.8%-44.9%) and uninfected cohorts (37.8%, 95%CI: 34.4%-41.3%), respectively ($P < 0.0001$).

IBT in association with ESRD risk after multivariate and competing mortality adjustment

Taking the uninfected cohort as a reference, the adjusted hazard ratios for ESRD were 1.28 (1.03-1.60, $P = 0.029$) and 0.34 (0.14-0.84, $P = 0.019$) in the untreated and treated cohorts, respectively (Table 3). In addition, diabetes (3.06, 2.37-3.95, $P < 0.001$), hypertension (3.51, 2.57-4.79, $P < 0.001$), and enrollee category 4 (1.4, 1.03-1.92, $P = 0.03$) were also associated with an increased risk of ESRD. Advanced aging (0.99, 0.98-0.99, $P = 0.006$), cirrhosis (0.61, 0.44-0.84, $P = 0.003$), and CCI score (0.93, 0.89-0.98, $P = 0.008$) were associated with a lower risk of ESRD.

Sensitivity analysis

We compared individual ESRD and death risks between the treated *versus* untreated cohorts as well as between the untreated *versus* uninfected cohorts (Table 4). The treated cohort had 29% (0.54-0.92, $P = 0.011$) and 72% (0.11-0.71, $P = 0.007$) decreases in death and ESRD, respectively, as compared with the untreated cohort, which had 31% (1.18-1.45, $P < 0.001$) and 28% (1.03-1.1, $P = 0.028$) increases in death and ESRD, respectively, as compared with the uninfected cohort.

Impact of IBT duration on the risk of ESRD

Of those in the treated cohort, 356 (74%) participants received 4 or more mo of IBT (Table 5). These individuals had 86% (0.03-0.58, $P = 0.007$) and 43% (0.41-0.79, $P = 0.001$) decreases in ESRD and mortality, respectively.

Stratified analyses according to patient subgroups

The associations between treatment and risk reduction of ESRD were consistent across most strata, except for patients without hypertension (Supplementary Figure 2A). The associations between lack of treatment and risk increment of ESRD were consistent across all strata (Supplementary Figure 2B).

Table 1 Baseline characteristics of the three study cohorts, 1997-2012, *n* = 6266

Variables	Propensity score-matched CKD patients			<i>P</i> value
	Treated(<i>n</i> = 482)	Untreated(<i>n</i> = 1928)	Uninfected(<i>n</i> = 3856)	
Sex				0.38
Men	253 (52.5)	979 (50.8)	2032 (52.7)	
Women	229 (47.5)	949 (49.2)	1824 (47.3)	
Age in yr	58.5 ± 10.5	58.5 ± 13.7	58.4 ± 14.1	0.96
Interferon-based therapy duration in yr	0.5 ± 0.8	-	-	
Comorbidity				
Diabetes	228 (47.3)	878 (45.5)	1727 (44.8)	0.55
Hypertension	290 (60.2)	1150 (59.6)	2315 (60.0)	0.95
Coronary heart disease	182 (37.8)	746 (38.7)	1519 (39.4)	0.73
Hyperlipidemia	239 (49.6)	961 (49.8)	1938 (50.3)	0.93
Cirrhosis	120 (24.9)	446 (23.1)	892 (23.1)	0.68
ACEI/ARB use	14 (2.9)	37 (1.9)	66 (1.7)	0.19
Enrollee category				< 0.0001
1	152 (31.5)	546 (28.3)	1332 (34.5)	
2	10 (2.1)	30 (1.6)	61 (1.6)	
3	255 (52.9)	968 (50.2)	1622 (42.1)	
4	65 (13.5)	384 (19.9)	841 (21.8)	
Number of medical visits	38.6 ± 25.6	34.4 ± 26.7	30.0 ± 25.0	< 0.0001
Charlson comorbidity index score	4.2 ± 2.7	3.5 ± 2.6	3.2 ± 2.7	< 0.0001

Data are presented as *n* (%).

¹For comparison among three cohorts. Categorical variables given as number (percentage); continuous variable, as mean ± SD. CKD: Chronic kidney disease; ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

DISCUSSION

The present study is the first large national cohort to investigate the long-term effects of treating HCV infection in patients with CKD stages 1-5 of any etiology on hard endpoints after taking propensity score matching and competing risk analysis into consideration. Our most encouraging finding is a significant 66% decrease and a 28% increase in the ESRD risk in treated and untreated HCV-infected CKD patients, respectively, compared with uninfected CKD patients, during a total mean follow-up of six years. Of note, a greater risk reduction of ESRD and death occurred in those receiving ≥ 4 mo of IBT, and these risks were not attenuated when IBT was incomplete, and its duration was shorter than 4 mo. In addition to improved renal survival, the treated cohort had a significant 29% decrease in mortality compared with the untreated cohort.

Our results have three clinical implications. First, our results support the practice of routine HCV testing in all CKD patients for early detection and treatment^[3,38] to ameliorate CKD progression and mortality regardless of the severity of the kidney disease. Second, our results fill the knowledge gap in the long-term impact of HCV therapy in CKD patients and serve as a reference to accelerate the study of long-term outcomes and safety of DAAs in CKD patients, given the better tolerance and efficacy of DAAs in CKD patients. Third, the renal benefits from eliminating HCV after adequate IBT suggest the pathogenic role of HCV in renal injuries.

The goal of anti-HCV treatment is to achieve SVR by viral clearance^[2,26]. Anti-HCV treatment with IBT, particularly the successful attainment of SVR^[24,39], has been shown to improve renal^[20-22,24] and non-renal^[19,20,22,39] prognosis in the general population^[19-21] and patients with cirrhosis^[39], diabetes^[22], and glomerulonephritis^[24]. Three studies that examined the association between SVR based on IBT and renal and survival benefits have been documented in patients with cirrhosis and glomerulonephritis. A hospital-based retrospective study^[23] of 650 cirrhotic Japanese patients showed that failure to achieve SVR was a predictor of CKD during a mean follow-up of 6.5 yr. Recently, a multicenter prospective study^[39] of 1323 cirrhotic French patients showed that the success to achieve SVR decreased the overall mortality in a median follow-up of 4.8 yr. A meta-analysis^[24] involving 11 short follow-up small-scale clinical trials (one controlled and ten uncontrolled) of 225 patients with HCV-infected glomerulone-

Table 2 Outcomes between treated, untreated, and uninfected cohorts, *n* = 6266

	Treated cohort (<i>n</i> = 482)	Untreated cohort (<i>n</i> = 1928)	Uninfected cohort (<i>n</i> = 3856)	<i>P</i> value
End-stage renal disease				
Events number (%)	5 (1.0)	134 (7.0)	188 (4.9)	< 0.0001
Competing mortality (%)	58 (12.0)	573 (29.7)	775 (20.1)	< 0.0001
Cumulative incidence (%)	2.4 (95%CI: 0.9-5.2)	11.7 (95%CI: 8.0-16.1)	8.2 (95%CI: 6.2-10.5)	0.0032
Overall mortality				
Events number (%)	61 (12.7)	648 (33.6)	861 (22.3)	< 0.0001
Cumulative incidence (%)	41.4 (95%CI: 8.1-54.1)	58.0 (95%CI: 51.5-63.9)	37.8 (95%CI: 34.4-41.3)	< 0.0001

phritis indicated that IBT alleviated greater proteinuria when SVR was achieved and stabilized serum creatinine (both were used as soft renal endpoints). Regrettably, the impact on hard endpoints of ESRD and patient survival remained unknown.

The present study, despite its retrospective design, is the first large-scale analysis with a long follow-up to address the hard endpoints in HCV-treated CKD patients. Although a randomized placebo-controlled trial is the ideal design to appraise the effectiveness of an intervention, it seems impractical because of the greater expense, longer observation time, and violation of research ethics while performing randomization to placebo^[20]. Despite the paucity of SVR to directly measure the therapeutic response, four Taiwanese retrospective interventional cohorts that enrolled individuals from the general population^[19-21] and diabetic^[22] patients used the NHIRD to address the amelioration of CKD^[21], ESRD^[20,22], overall mortality^[20], and non-renal^[19,20,22] complications conferred by IBT.

The efficacy of IBT appears convincing: In the treated cohort, IBT generally achieved an eradication rate of over 70% in Taiwan due to the prevalent and favorable genetic variation in interleukin-28B^[20,22]. Another hospital-based American retrospective analysis^[40] of 159 HCV-infected patients treated with IBT indicated that a history of IBT was a significant negative predictor of CKD. Similarly to the aforementioned studies, our results demonstrated renal and survival benefits in HCV-infected patients with CKD stages 1-5 who received IBT. In agreement with one American retrospective study^[18] of 1603 untreated HCV-infected patients with CKD stages 3-5 during a mean follow-up of 3.8 yr, our results also found a 28% increase in the ESRD risk in untreated compared with uninfected CKD patients. We further demonstrated that treated compared with untreated CKD patients had significant 72% and 29% decreases in ESRD and mortality risks, respectively. Of note, the treated cohort receiving IBT for ≥ 4 mo experienced greater clinical benefits, but the risk of ESRD and mortality failed to decline if the duration of IBT was shorter than 4 mo, a result comparable with a prior Taiwanese study^[20].

However, the impact of the degree of HCV viremia on the risk of progression to ESRD in CKD patients remains uncertain, although prior research^[14,16] found a higher percentage of viremia in CKD patients with positive anti-HCV antibodies. Three studies examined the association between the degree of viremia and worsening renal outcomes in the general population^[40,41] and HIV/HCV-coinfected patients^[42]. A prospective cohort of 8235 HIV/HCV-coinfected patients demonstrated that patients with HCV-RNA titers over 615 IU/mL were at an increased risk for CKD during 36123 person-years of follow-up^[42]. A community-based prospective cohort^[41] of 19984 Taiwanese individuals, with over 15 years of follow-up, revealed that HCV-RNA levels increased the risk of ESRD in a dose-dependent manner, with the highest risk in patients with HCV-RNA over 167000 IU/mL. A hospital-based retrospective analysis^[40] that compared 552 HCV-infected American patients with matched controls indicated that a high baseline HCV-RNA viral load (> 700000 cps/mL) was a significant positive predictor for CKD at 74 mo.

Taken collectively, published evidence supports the clinical benefits of IBT, suggesting that eliminating the virus underlie this association. Given the higher prevalence of HCV infection^[43] and the higher potential of viremia in CKD patients^[13,14,16], the renal and survival benefits from HCV therapy in CKD patients seem promising. Further research is warranted to clarify how the influence of viremia and SVR correlate with clinical outcomes in CKD patients.

The exact mechanisms through which HCV therapy improves clinical outcomes have not been fully elucidated, but based on the existing clinical evidence they are most likely mediated by viral clearance^[23,24,40]. HCV can trigger local and systemic oxidative stress and promote IR, endothelial dysfunction, and accelerated atherosclerosis, all of which contribute to renal injury and mortality^[7]. The su-

Table 3 Crude and adjusted hazard ratios for end-stage renal disease

Variable	Crude			Adjusted ¹		
	HR	95%CI	P value	HR	95%CI	P value
CKD patients						
Uninfected	1.00	Reference		1.00	Reference	
Treated	0.31	0.13-0.77	0.011	0.34	0.14-0.84	0.019
Untreated	1.25	1.00-1.56	0.046	1.28	1.03-1.60	0.029
Sex, men/women	1.11	0.89-1.38	0.35	1.23	0.99-1.55	0.07
Age, per year	1.01	1.00-1.01	0.15	0.99	0.98-0.99	0.006
Comorbidity, yes/no						
Diabetes	2.87	2.28-3.61	< 0.001	3.06	2.37-3.95	< 0.001
Hypertension	3.08	2.37-4.01	< 0.001	3.51	2.57-4.79	< 0.001
Coronary heart disease	1.28	1.02-1.59	0.031	0.92	0.72-1.16	0.46
Hyperlipidemia	1.29	1.04-1.60	0.023	0.85	0.68-1.07	0.16
Cirrhosis	0.62	0.46-0.83	0.001	0.61	0.44-0.84	0.003
ACEI/ARB, yes/no	1.38	0.65-2.92	0.40	0.96	0.46-2.04	0.92
Enrollee category						
1	1.00	Reference		1.00	Reference	
2	0.68	0.21-2.14)	0.50	0.56	0.17-1.80	0.33
3	1.26	0.97-1.64	0.08	1.24	0.95-1.63	0.11
4	1.47	1.09-1.99	0.012	1.40	1.03-1.92	0.03
Number of medical visits	1.00	1.00-1.01	0.36	1.00	0.99-1.00	0.41
Charlson comorbidity index score	1.01	0.98-1.04	0.46	0.93	0.89-0.98	0.008

¹Adjusted for all covariates (age per year, sex, comorbidity, ACEI/ARB, enrollee category, number of medical visits, and Charlson comorbidity index score) and competing mortality. CKD: Chronic kidney disease; ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CI: Confidence interval.

ppression of HCV replication by IBT seems to alleviate these injuries. Treating HCV infection by either IBT or DAAs in CKD patients is challenging. The former is cheaper and universal but not tolerated as well, and this might account for 10.5% of the 4582 HCV-infected CKD patients in the present study. The latter is well tolerated but very costly, which limits patient access and has a significant risk of drug-drug interactions^[26,27] with concomitant polypharmacy in CKD patients that have multiple comorbidities. DAAs can be used in patients with kidney disease depending on their hepatic metabolism, but this does not guarantee the lack of adverse renal effects in cirrhotic patients, who are at a high risk of renal pharmacokinetic changes^[27]. Another growing concern is the reactivation of hepatitis B^[44], which is also a risk factor for CKD progression^[32]. Further cost-effectiveness analyses comparing the costs of IBT with DAAs in HCV-infected CKD patients are warranted in the future.

In line with a Taiwanese study by Wu *et al*^[22] that examined the use of IBT in a large diabetic cohort, the 16-year cumulative incidence of ESRD was greater in our untreated CKD cohort, followed by the uninfected and treated CKD cohorts. However, the 16-year cumulative incidence of ESRD was strikingly lower in the treated than in the uninfected CKD cohorts. This might be because the sample size was smaller in the treated than in the uninfected CKD cohorts. In accordance with the aforementioned study^[22], the 16-year cumulative mortality was higher in our untreated CKD cohort, followed by the treated and uninfected CKD cohorts. Compared with the uninfected CKD cohort, our treated CKD cohort still had a higher cumulative mortality, which may be attributable to their higher CCI scores. Furthermore, we found that CKD patients with HCV who underwent HCV treatment had lower risk of ESRD compared to the risk in CKD patients without HCV infection. Wu *et al*^[22] similarly observed that diabetic patients with HCV who underwent HCV treatment had a lower risk of ESRD compared to the risk in diabetic patients without HCV infection. The efficacy of anti-HCV therapy in alleviating IR, which has been convincingly demonstrated in previous research^[45], may account for the abovementioned finding. IR is a prevalent feature in CKD^[46] and diabetes^[47]. The clinical impacts of IR include endothelial dysfunction and initiation and progression of CKD^[46]. This is why IR may be a therapeutic target in the attempt to improve clinical outcomes of CKD^[46] and diabetic vascular complications^[48]. The mechanism

Table 4 Sensitivity analysis of adjusted hazard ratios for end-stage renal disease and death between the untreated and uninfected chronic kidney disease patients as well as between the treated and untreated chronic kidney disease patients

	Adjusted HR for ESRD ¹			Adjusted HR for death ²		
	HR	95%CI	P value	HR	95%CI	P value
Propensity score-matched CKD patients						
Uninfected cohort (n = 3856)	1.00	Reference		1.00	Reference	
Untreated HCV-infected cohort (n = 1928)	1.28	1.03-1.61	0.028	1.31	1.18-1.45	< 0.001
Propensity score-matched CKD patients						
Untreated HCV-infected cohort (n = 1928)	1.00	Reference		1.00	Reference	
Treated HCV-infected cohort (n = 482)	0.28	0.11-0.71	0.007	0.71	0.54-0.92	0.011

¹Adjusted for all covariates (age per year, sex, comorbidity, ACEI/ARB, enrollee category, number of medical visits, and Charlson comorbidity index score) and competing mortality;

²Adjusted for all covariates (age per year, sex, comorbidity, ACEI/ARB, enrollee category, number of medical visits, and Charlson comorbidity index score). CKD: Chronic kidney disease; CI: Confidence interval; ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker; ESRD: End-stage renal disease; HCV: Hepatitis C virus.

through which antiviral therapy ameliorates IR was most likely mediated *via* viral clearance, instead of direct pharmacological effects of IBT^[22]. Conjeevaram *et al*^[45] reported that successful viral eradication was central to sustain the beneficial effects in IR. We believe that our finding should result from viral elimination in the treated patients, although this study could not directly measure SVR because of the absence of laboratory information in the NHIRD. Future research is warranted to better understand the pathological mechanism underlying this association. Our results after competing risk analysis showed that aging was associated with a lower risk of ESRD, a result consistent with prior research^[6,32] showing that younger rather than older age predicted ESRD.

In addition to the universal coverage of a nationwide population to reduce selection bias, the study has several methodological strengths. First, maximum cardinality matching of treated and untreated patients was performed according to the propensity score to optimize comparability^[21], which is an effective method of pseudorandomization when the effects of treatment and interventions are compared. Second, to avoid immortal time bias, we used the same year of IBT prescription time distribution^[33,34]. Third, taking competing mortality into consideration to avoid overestimating the results in the untreated cohort^[20] is another merit. Fourth, the well-known renoprotective ACEI/ARB was also included in the final analysis. On the whole, despite its retrospective nature, the present study provides the most persuasive data to date in addressing the long-term renal and survival benefits of treating HCV infection in CKD patients.

Some limitations of our study should be mentioned. First, the adverse reactions and actual compliance related to IBT were not assessed in the NHIRD. However, 74% of the treated CKD patients in our study used IBT for more than 4 mo. Excessive prescription of IBT is impossible under the strict regulations in Taiwan's NHI. Second, due to the lack of laboratory data in the NHIRD, the association between the HCV genotype, viral load, SVR, CKD stages (severity), and survival failed to be clarified. Third, lifestyle and family history were not available in the NHIRD either. Fourth, some patients who spontaneously cleared the virus were enrolled as untreated cohort. Nonetheless, this might lead to the underestimation of the adverse events in the untreated cohort^[20]. Finally, caution is advised before applying our results to the West because of higher antiviral efficacy of IBT in Taiwan than in most Western countries^[22].

In conclusion, this nationwide cohort study shows that treating HCV infection with IBT in CKD patients is associated with improved long-term renal and patient survivals. Further large-scale research on the long-term clinical outcomes of DAAs in CKD patients seems to deserve attention.

Table 5 The effect of the duration of interferon-based therapy for hepatitis C virus infection on the risk of end-stage renal disease and death

	IBT duration	ESRD events (%)	Adjusted HR ¹ (95%CI)	P value	Death events (%)	Adjusted HR ² (95%CI)	P value
Propensity score-matched HCV-infected CKD patients (n = 2410)	No (n = 1928)	134 (7.0)	1.00 (reference)		648 (33.6)	1.00 (reference)	
	< 4 mo (n = 126)	3 (2.4)	0.79 (0.24-2.63)	0.70	23 (18.3)	1.18 (0.78-1.81)	0.44
	≥ 4 mo (n = 356)	2 (0.6)	0.14 (0.03-0.58)	0.007	38 (10.7)	0.57 (0.41-0.79)	0.001

¹Adjusted for all covariates (age per year, sex, comorbidity, ACEI/ARB, enrollee category, number of medical visits, and Charlson comorbidity index score) and competing mortality; ²Adjusted for all covariates (age per year, sex, comorbidity, ACEI/ARB, enrollee category, number of medical visits, and Charlson comorbidity index score). CKD: Chronic kidney disease; CI: Confidence interval; ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker; ESRD: End-stage renal disease; HCV: Hepatitis C virus.

ARTICLE HIGHLIGHTS

Research background

It is unknown whether adequate hepatitis C virus (HCV) treatment [interferon-based therapy (IBT) or new direct-acting antivirals (DAAs)] improves long-term renal and patient survivals in chronic kidney disease (CKD) patients with HCV infection. Yet, there is a significant value to explore this critical issue.

Research motivation

There is a significant and increasing burden of CKD, end-stage renal disease (ESRD), and HCV infection in Taiwan and worldwide. Taiwan provides an ideal setting for studying this relationship because it has a high prevalence of these three conditions. Because information on DAAs was not available in Taiwan's single-payer national health insurance database currently released for research, we performed a retrospective analysis of IBT, in CKD patients with HCV infection to increase our understanding of their long-term outcomes following HCV infection and HCV treatment.

Research objectives

To evaluate the long-term outcomes (ESRD and death) of HCV treatment, especially IBT, in HCV-infected patients with stage 1-5 CKD.

Research methods

By analyzing the Taiwan Longitudinal Health Insurance Database 2005, the authors used propensity score-matched and competing risk analyses to evaluate the long-term effect of HCV infection with and without IBT on the risks of ESRD and death in CKD patients. All participants were followed until the occurrence of ESRD, death, or the end of 2012.

Research results

Taking the uninfected cohort as a reference, the adjusted hazard ratios for ESRD, after adjusting for competing mortality, were 0.34 (0.14-0.84, $P = 0.019$) and 1.28 (1.03-1.60, $P = 0.029$) in the treated and untreated cohorts, respectively. The treated cohort had a 29% (0.54-0.92, $P = 0.011$) decrease in mortality compared to the untreated cohort, in which the mortality was 31% (1.18-1.45, $P < 0.001$) higher than in the uninfected cohort. The reduced risks of ESRD (0.14, 0.03-0.58, $P = 0.007$) and death (0.57, 0.41-0.79, $P = 0.001$) were greatest in HCV-infected CKD patients who received at least 4 mo of IBT, which accounted for 74% of the treated cohort.

Research conclusions

To the best of our knowledge, this is the first study to investigate the long-term renal and patient outcomes in CKD patients with HCV infection and HCV treatment. Adequate HCV treatment in CKD patients improves long-term renal and patient survivals.

Research perspectives

Future prospective study is warranted to confirm our findings with new DAAs and better understand the pathological mechanism underlying this association.

REFERENCES

- 1 **Kidney Disease: Improving Global Outcomes (KDIGO).** KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int Suppl* 2008; **109**: S1-99 [PMID: 18382440 DOI: 10.1038/ki.2008.81]
- 2 **Azmi AN, Tan SS, Mohamed R.** Hepatitis C and kidney disease: An overview and approach to management. *World J Hepatol* 2015; **7**: 78-92 [PMID: 25624999 DOI: 10.4254/wjh.v7.i1.78]
- 3 **Chacko EC, Surrin SK, Mubarak Sani TP, Pappachan JM.** Chronic viral hepatitis and chronic kidney

- disease. *Postgrad Med J* 2010; **86**: 486-492 [PMID: 20709771 DOI: 10.1136/pgmj.2009.092775]
- 4 **Perico N**, Cattaneo D, Bikbov B, Remuzzi G. Hepatitis C infection and chronic renal diseases. *Clin J Am Soc Nephrol* 2009; **4**: 207-220 [PMID: 19129320 DOI: 10.2215/CJN.03710708]
- 5 **Chen YC**, Lin HY, Li CY, Lee MS, Su YC. A nationwide cohort study suggests that hepatitis C virus infection is associated with increased risk of chronic kidney disease. *Kidney Int* 2014; **85**: 1200-1207 [PMID: 24257691 DOI: 10.1038/ki.2013.455]
- 6 **Chen YC**, Chiou WY, Hung SK, Su YC, Hwang SJ. Hepatitis C virus itself is a causal risk factor for chronic kidney disease beyond traditional risk factors: a 6-year nationwide cohort study across Taiwan. *BMC Nephrol* 2013; **14**: 187 [PMID: 24011024 DOI: 10.1186/1471-2369-14-187]
- 7 **Gordon CE**, Balk EM, Becker BN, Crooks PA, Jaber BL, Johnson CA, Michael MA, Pereira BJ, Uhlig K, Levin A. KDOQI US commentary on the KDIGO clinical practice guideline for the prevention, diagnosis, evaluation, and treatment of hepatitis C in CKD. *Am J Kidney Dis* 2008; **52**: 811-825 [PMID: 18971009 DOI: 10.1053/j.ajkd.2008.08.005]
- 8 **Tsui JI**, Vittinghoff E, Shlipak MG, Bertenthal D, Inadomi J, Rodriguez RA, O'Hare AM. Association of hepatitis C seropositivity with increased risk for developing end-stage renal disease. *Arch Intern Med* 2007; **167**: 1271-1276 [PMID: 17592100 DOI: 10.1001/archinte.167.12.1271]
- 9 **Molnar MZ**, Alhourani HM, Wall BM, Lu JL, Streja E, Kalantar-Zadeh K, Kovesdy CP. Association of hepatitis C viral infection with incidence and progression of chronic kidney disease in a large cohort of US veterans. *Hepatology* 2015; **61**: 1495-1502 [PMID: 25529816 DOI: 10.1002/hep.27664]
- 10 **Lee JJ**, Lin MY, Chang JS, Hung CC, Chang JM, Chen HC, Yu ML, Hwang SJ. Hepatitis C virus infection increases risk of developing end-stage renal disease using competing risk analysis. *PLoS One* 2014; **9**: e100790 [PMID: 24971499 DOI: 10.1371/journal.pone.0100790]
- 11 **Crook ED**, Penumalee S, Gavini B, Filippova K. Hepatitis C is a predictor of poorer renal survival in diabetic patients. *Diabetes Care* 2005; **28**: 2187-2191 [PMID: 16123488 DOI: 10.2337/diacare.28.9.2187]
- 12 **Nouredine LA**, Usman SA, Yu Z, Moorthi RN, Moe SM. Hepatitis C increases the risk of progression of chronic kidney disease in patients with glomerulonephritis. *Am J Nephrol* 2010; **32**: 311-316 [PMID: 20714136 DOI: 10.1159/000319456]
- 13 **Li Cavoli G**, Ferrantelli A, Bono L, Tortorici C, Giammarresi C, Zagarrigo C, Schillaci O, Tralongo A, Soresi M, Rotolo U. Incidence of hepatitis C virus infection in patients with chronic kidney disease on conservative therapy. *Int J Infect Dis* 2011; **15**: e514-e516 [PMID: 21680217 DOI: 10.1016/j.ijid.2011.04.001]
- 14 **Garcia-Valdecasas J**, Bernal C, Garcia F, Cerezo S, Umana WO, von Albertini B, Kimmel PL. Epidemiology of hepatitis C virus infection in patients with renal disease. *J Am Soc Nephrol* 1994; **5**: 186-192 [PMID: 7527663 DOI: 10.1080/20786204.2005.10873195]
- 15 **Sit D**, Kadiroglu AK, Kayabasi H, Yilmaz ME, Goral V. Seroprevalence of hepatitis B and C viruses in patients with chronic kidney disease in the predialysis stage at a university hospital in Turkey. *Intervirology* 2007; **50**: 133-137 [PMID: 17191015 DOI: 10.1159/000098239]
- 16 **Lemos LB**, Perez RM, Lemos MM, Draibe SA, Silva IS, Silva AE, Ferraz ML. Hepatitis C among predialysis patients: prevalence and characteristics in a large cohort of patients. *Nephron Clin Pract* 2008; **108**: c135-c140 [PMID: 18230916 DOI: 10.1159/000114452]
- 17 **Fabrizi F**, Marcelli D, Bacchini G, Guarnori I, Erba G, Locatelli F. Antibodies to hepatitis C virus (HCV) in chronic renal failure (CRF) patients on conservative therapy: prevalence, risk factors and relationship to liver disease. *Nephrol Dial Transplant* 1994; **9**: 780-784 [PMID: 7526275 DOI: 10.1590/S0102-311X2010000100018]
- 18 **Tartof SY**, Hsu JW, Wei R, Rubenstein KB, Hu H, Arduino JM, Horberg M, Derose SF, Qian L, Rodriguez CV. Kidney Function Decline in Patients with CKD and Untreated Hepatitis C Infection. *Clin J Am Soc Nephrol* 2018; **13**: 1471-1478 [PMID: 30242027 DOI: 10.2215/CJN.01530218]
- 19 **Hsu CS**, Huang CJ, Kao JH, Lin HH, Chao YC, Fan YC, Tsai PS. Interferon-based therapy decreases risks of hepatocellular carcinoma and complications of cirrhosis in chronic hepatitis C patients. *PLoS One* 2013; **8**: e70458 [PMID: 23894660 DOI: 10.1371/journal.pone.0070458]
- 20 **Hsu YC**, Ho HJ, Huang YT, Wang HH, Wu MS, Lin JT, Wu CY. Association between antiviral treatment and extrahepatic outcomes in patients with hepatitis C virus infection. *Gut* 2015; **64**: 495-503 [PMID: 25398770 DOI: 10.1136/gutjnl-2014-308163]
- 21 **Chen YC**, Hwang SJ, Li CY, Wu CP, Lin LC. A Taiwanese Nationwide Cohort Study Shows Interferon-Based Therapy for Chronic Hepatitis C Reduces the Risk of Chronic Kidney Disease. *Medicine (Baltimore)* 2015; **94**: e1334 [PMID: 26266379 DOI: 10.1097/MD.0000000000001334]
- 22 **Hsu YC**, Lin JT, Ho HJ, Kao YH, Huang YT, Hsiao NW, Wu MS, Liu YY, Wu CY. Antiviral treatment for hepatitis C virus infection is associated with improved renal and cardiovascular outcomes in diabetic patients. *Hepatology* 2014; **59**: 1293-1302 [PMID: 24122848 DOI: 10.1002/hep.26892]
- 23 **Arase Y**, Suzuki F, Kawamura Y, Suzuki Y, Kobayashi M, Matsumoto N, Akuta N, Sezaki H, Hosaka T, Ogawa K, Imai N, Seko Y, Saito S, Ikeda K, Kobayashi M, Kumada H. Development rate of chronic kidney disease in hepatitis C virus patients with advanced fibrosis after interferon therapy. *Hepatol Res* 2011; **41**: 946-954 [PMID: 21883737 DOI: 10.1111/j.1872-034X.2011.00845.x]
- 24 **Feng B**, Eknoyan G, Guo ZS, Jadoul M, Rao HY, Zhang W, Wei L. Effect of interferon-alpha-based antiviral therapy on hepatitis C virus-associated glomerulonephritis: a meta-analysis. *Nephrol Dial Transplant* 2012; **27**: 640-646 [PMID: 21558431 DOI: 10.1093/ndt/gfr236]
- 25 **Li T**, Qu Y, Guo Y, Wang Y, Wang L. Efficacy and safety of direct-acting antivirals-based antiviral therapies for hepatitis C virus patients with stage 4-5 chronic kidney disease: a meta-analysis. *Liver Int* 2017; **37**: 974-981 [PMID: 27943605 DOI: 10.1111/liv.13336]
- 26 **Fabrizi F**, Martin P, Messa P. New treatment for hepatitis C in chronic kidney disease, dialysis, and transplant. *Kidney Int* 2016; **89**: 988-994 [PMID: 27083277 DOI: 10.1016/j.kint.2016.01.011]
- 27 **Isnard Bagnis C**, Cacoub P. Hepatitis C Therapy in Renal Patients: Who, How, When? *Infect Dis Ther* 2016; **5**: 313-327 [PMID: 27388502 DOI: 10.1007/s40121-016-0116-z]
- 28 **Carvalho-Filho RJ**, Feldner AC, Silva AE, Ferraz ML. Management of hepatitis C in patients with chronic kidney disease. *World J Gastroenterol* 2015; **21**: 408-422 [PMID: 25593456 DOI: 10.3748/wjg.v21.i2.408]
- 29 **Chen YC**, Su YC, Li CY, Wu CP, Lee MS. A nationwide cohort study suggests chronic hepatitis B virus infection increases the risk of end-stage renal disease among patients in Taiwan. *Kidney Int* 2015; **87**: 1030-1038 [PMID: 25426815 DOI: 10.1038/ki.2014.363]
- 30 **Tung CH**, Lai NS, Li CY, Tsai SJ, Chen YC, Chen YC. Risk of rheumatoid arthritis in patients with hepatitis C virus infection receiving interferon-based therapy: a retrospective cohort study using the

- Taiwanese national claims database. *BMJ Open* 2018; **8**: e021747 [PMID: 30037875 DOI: 10.1136/bmjopen-2018-021747]
- 31 **Hwang JH**, Tsai SJ, Liu TC, Chen YC, Lai JT. Association of Tinnitus and Other Cochlear Disorders With a History of Migraines. *JAMA Otolaryngol Head Neck Surg* 2018; **144**: 712-717 [PMID: 30003226 DOI: 10.1001/jamaoto.2018.0939]
 - 32 **Chen YC**, Li CY, Tsai SJ, Chen YC. Nationwide cohort study suggests that nucleos(t)ide analogue therapy decreases dialysis risk in Taiwanese chronic kidney disease patients acquiring hepatitis B virus infection. *World J Gastroenterol* 2018; **24**: 917-928 [PMID: 29491685 DOI: 10.3748/wjg.v24.i8.917]
 - 33 **Zhou Z**, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. *Am J Epidemiol* 2005; **162**: 1016-1023 [PMID: 16192344 DOI: 10.1093/aje/kwi307]
 - 34 **Ramos R**, Garcia-Gil M, Comas-Cufi M, Quesada M, Marrugat J, Elosua R, Sala J, Grau M, Martí R, Ponjoan A, Alves-Cabreros L, Blanch J, Bolibar B. Statins for Prevention of Cardiovascular Events in a Low-Risk Population With Low Ankle Brachial Index. *J Am Coll Cardiol* 2016; **67**: 630-640 [PMID: 26868687 DOI: 10.1016/j.jacc.2015.11.052]
 - 35 **Gershon A**, Croxford R, To T, Stanbrook MB, Upshur R, Sanchez-Romeu P, Stukel T. Comparison of inhaled long-acting β -agonist and anticholinergic effectiveness in older patients with chronic obstructive pulmonary disease: a cohort study. *Ann Intern Med* 2011; **154**: 583-592 [PMID: 21536937 DOI: 10.7326/0003-4819-154-9-201105030-00003]
 - 36 KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; **3**: 1-150
 - 37 **Gray RJ**. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988; **16**: 1141-1154 [DOI: 10.1214/aos/1176350951]
 - 38 **Ghany MG**, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009; **49**: 1335-1374 [PMID: 19330875 DOI: 10.1002/hep.22759]
 - 39 **Nahon P**, Bourcier V, Layese R, Audureau E, Cagnot C, Marcellin P, Guyader D, Fontaine H, Larrey D, De Ledinghen V, Ouzan D, Zoulim F, Roulot D, Tran A, Bronowicki JP, Zarski JP, Leroy V, Riachi G, Calès P, Péron JM, Alric L, Bourlière M, Mathurin P, Dharancy S, Blanc JF, Abergel A, Serfaty L, Mallat A, Grangé JD, Attali P, Bacq Y, Wartelle C, Dao T, Benhamou Y, Pilette C, Silvain C, Christidis C, Capron D, Bernard-Chabert B, Zucman D, Di Martino V, Thibaut V, Salmon D, Zioli M, Sutton A, Pol S, Roudot-Thoraval F; ANRS CO12 CirVir Group. Eradication of Hepatitis C Virus Infection in Patients With Cirrhosis Reduces Risk of Liver and Non-Liver Complications. *Gastroenterology* 2017; **152**: 142-156.e2 [PMID: 27641509 DOI: 10.1053/j.gastro.2016.09.009]
 - 40 **Satapathy SK**, Lingisetty CS, Williams S. Higher prevalence of chronic kidney disease and shorter renal survival in patients with chronic hepatitis C virus infection. *Hepatol Int* 2012; **6**: 369-378 [PMID: 21698519 DOI: 10.1007/s12072-011-9284-9]
 - 41 **Lai TS**, Lee MH, Yang HL, You SL, Lu SN, Wang LY, Yuan Y, L'Italien G, Chien KL, Chen CJ; REVEAL-HCV Study Group. Hepatitis C viral load, genotype, and increased risk of developing end-stage renal disease: REVEAL-HCV study. *Hepatology* 2017; **66**: 784-793 [PMID: 28370058 DOI: 10.1002/hep.29192]
 - 42 **Peters L**, Grint D, Lundgren JD, Rockstroh JK, Soriano V, Reiss P, Grzeszczuk A, Sambatakou H, Mocroft A, Kirk O; EuroSIDA in EuroCoord. Hepatitis C virus viremia increases the incidence of chronic kidney disease in HIV-infected patients. *AIDS* 2012; **26**: 1917-1926 [PMID: 22781222 DOI: 10.1097/QAD.0b013e3283574e71]
 - 43 **Ladino M**, Pedraza F, Roth D. Opportunities for treatment of the hepatitis C virus-infected patient with chronic kidney disease. *World J Hepatol* 2017; **9**: 833-839 [PMID: 28740594 DOI: 10.4254/wjh.v9.i19.833]
 - 44 **Bersoff-Matcha SJ**, Cao K, Jason M, Ajao A, Jones SC, Meyer T, Brinker A. Hepatitis B Virus Reactivation Associated With Direct-Acting Antiviral Therapy for Chronic Hepatitis C Virus: A Review of Cases Reported to the U.S. Food and Drug Administration Adverse Event Reporting System. *Ann Intern Med* 2017; **166**: 792-798 [PMID: 28437794 DOI: 10.7326/M17-0377]
 - 45 **Conjeevaram HS**, Wahed AS, Afdhal N, Howell CD, Everhart JE, Hoofnagle JH; Virahep-C Study Group. Changes in insulin sensitivity and body weight during and after peginterferon and ribavirin therapy for hepatitis C. *Gastroenterology* 2011; **140**: 469-477 [PMID: 21070775 DOI: 10.1053/j.gastro.2010.11.002]
 - 46 **Teta D**. Insulin resistance as a therapeutic target for chronic kidney disease. *J Ren Nutr* 2015; **25**: 226-229 [PMID: 25511524 DOI: 10.1053/j.jrn.2014.10.019]
 - 47 **DeFronzo RA**, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. *Diabetes Care* 2009; **32** Suppl 2: S157-S163 [PMID: 19875544 DOI: 10.2337/dc09-S302]
 - 48 **Kang YS**, Lee MH, Song HK, Hyun YY, Cha JJ, Ko GJ, Kim SH, Lee JE, Han JY, Cha DR. Aliskiren improves insulin resistance and ameliorates diabetic vascular complications in db/db mice. *Nephrol Dial Transplant* 2011; **26**: 1194-1204 [PMID: 20921292 DOI: 10.1093/ndt/gfq579]

Observational Study

Clinical features of syphilitic myelitis with longitudinally extensive myelopathy on spinal magnetic resonance imaging

Jun-Liang Yuan, Wei-Xue Wang, Wen-Li Hu

ORCID number: Jun-Liang Yuan (0000-0002-9443-9203); Wei-Xue Wang (0000-0002-3043-8439); Wen-Li Hu (0000-0003-4971-9035).

Author contributions: Yuan JL and Wang WX are co-first authors; Yuan JL, Wang WX, and Hu WL designed and performed the research; Yuan JL and Wang WX collected and analyzed the data; Yuan JL and Wang WX wrote the paper.

Supported by the National Natural Science Foundation of China, No. 81301016; and the Beijing Municipal Administration of Hospitals Incubating Program, No. PX2019009.

Institutional review board

statement: Our work was approved by the Ethics Committee of Beijing Chaoyang Hospital, Capital Medical University.

Informed consent statement: The patient gave informed consent.

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

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.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external

Jun-Liang Yuan, Wen-Li Hu, Department of Neurology, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, China

Wei-Xue Wang, Department of Oncology, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, China

Corresponding author: Wen-Li Hu, MD, Director, Doctor, Department of Neurology, Beijing Chaoyang Hospital, Capital Medical University, 8 Gongti South, Chaoyang District, Beijing 100020, China. wenlihu3366@126.com

Telephone: +86-10-85231376

Fax: +86-10-85231376

Abstract

BACKGROUND

Syphilitic myelitis caused by *Treponema pallidum* is an extremely rare disease. However, symptomatic neurosyphilis, especially syphilitic myelitis, and its clinical features have been infrequently reported. Only a few cases of syphilitic myelitis have been documented. To the best of our knowledge, there are only 19 reported cases of syphilitic myelitis. However, the clinical features of syphilitic myelitis with longitudinally extensive myelopathy have been still not clear.

AIM

To explore the clinical features of syphilitic myelitis with longitudinally extensive myelopathy on spinal magnetic resonance imaging (MRI).

METHODS

First, we report a patient who suffered from syphilitic myelitis with symptoms of sensory disturbance, with longitudinally extensive myelopathy with "flip-flop sign" on spinal MRI. Second, we performed a literature search to identify other reports (reviews, case reports, or case series) from January 1987 to December 2018, using the PubMed and Web of Science databases with the terms including "syphilis", "neurosyphilis", "syphilitic myelitis", "meningomyelitis", "central nervous system", and "spine". We also summarized the clinical features of syphilitic myelitis with longitudinally extensive myelopathy.

RESULTS

A total of 16 articles of 20 cases were identified. Sixteen patients presented with the onset of sensory disturbance (80%), 15 with paraparesis (75%), and 9 with urinary retention (45%). Eleven patients had a high risk behavior (55%). Five patients had concomitant human immunodeficiency virus infection (25%).

reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Received: January 23, 2019

Peer-review started: January 23, 2019

First decision: March 14, 2019

Revised: April 16, 2019

Accepted: May 2, 2019

Article in press: May 2, 2019

Published online: June 6, 2019

P-Reviewer: El-Razek AA

S-Editor: Gong ZM

L-Editor: Wang TQ

E-Editor: Wu YXJ



Serological data showed that 15 patients had positive venereal disease research laboratory test (VDRL)/treponema pallidum particle agglutination (TPHA), and 17 had positive VDRL/TPHA in cerebrospinal fluid (CSF). Seventeen patients were found to have elevated leukocytosis and protein in CSF. On MRI, 16 patients showed abnormal hyperintensities involved the thoracic spine, 6 involved the cervical spine, and 3 involved both the cervical and thoracic spine. There were 3 patients with the "flip-flop sign". All the patients were treated with penicillin, and 15 patients had a good prognosis.

CONCLUSION

Our case further raises awareness of syphilitic myelitis as an important complication of neurosyphilis due to homosexuality, especially in developing countries such as China.

Key words: Neurosyphilis; Syphilitic myelitis; Syphilitic meningomyelitis; Human immunodeficiency virus

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Syphilitic myelitis is a very rare manifestation of neurosyphilis. Early diagnosis and treatment are crucial because it represents a treatable and potentially reversible cause of myelopathy if treated with penicillin. Herein, we report a 25-year-old young man presenting with symptoms of sensory disturbance, due to syphilitic myelitis with longitudinally extensive myelopathy with "flip-flop sign" on spinal magnetic resonance imaging. Furthermore, we summarized the clinical features of syphilitic myelitis with longitudinally extensive myelopathy by reviewing the relevant literature. Our study also raises awareness of an important complication of neurosyphilis due to homosexuality. Attention is drawn upon the importance of doing serological tests for syphilis when any atypical neurological disorders are presented.

Citation: Yuan JL, Wang WX, Hu WL. Clinical features of syphilitic myelitis with longitudinally extensive myelopathy on spinal magnetic resonance imaging. *World J Clin Cases* 2019; 7(11): 1282-1290

URL: <https://www.wjnet.com/2307-8960/full/v7/i11/1282.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v7.i11.1282>

INTRODUCTION

Syphilis is a sexually-transmitted disease caused by *Treponema pallidum* infection. About 2.1 million pregnant women have active syphilis every year^[1]. It is both individual and public health issues due to its direct morbidity, increased risk of human immunodeficiency virus (HIV) infection, and lifelong morbidity especially in low-income countries^[2]. It could progress over years through a series of clinical stages and result in irreversible neurological complications without treatment. Syphilis continues to be a major public health problem all over the world.

One-third of patients with early syphilis have the manifestations of the central nervous system, and the recent resurgence in syphilis has seen an accompanying increase in cases of neurosyphilis. It can also affect the brain, brainstem, spinal cord, meninges, nerve roots, and cerebral/spinal vessels^[3]. The clinical presentations of neurosyphilis include acute lymphocytic meningitis (acute syphilitic meningitis), stroke (meningovascular syphilis), dementia (general paresis), and/or myelopathy (tabes dorsalis, meningomyelitis, and syringomyelia)^[4]. The clinical symptoms of syphilitic meningomyelitis usually develop at between 1 and 30 years after the initial infection^[5]. The treatment with penicillin and corticosteroids can diminish the affected lesions with partially reversible changes. However, symptomatic neurosyphilis, especially syphilitic myelitis, and its clinical features have been infrequently reported^[6].

Only quite a few cases of syphilitic myelitis have been documented in the reported literature. To the best of our knowledge, there are only 19 reported cases of syphilitic myelitis in the literature^[4,7-21]. We herein report a case of syphilitic myelitis with longitudinally extensive myelopathy presenting with the characteristic of "flip-flop

sign" on spinal magnetic resonance imaging (MRI). We also summarized the clinical features of syphilitic myelitis with longitudinally extensive myelopathy based on the prior reported literature.

MATERIALS AND METHODS

Case presentation

A 25-year-old man was admitted to the Department of Neurology with the symptoms of acute onset of sensory disturbance and numbness for 7 d. He was homosexual and exposed to unprotected intercourse. A neurological examination revealed hypalgesia below the T6 level. The other physical examinations were normal. Laboratory tests revealed the treponema pallidum particle agglutination (TPPA) and toluidine red unheated serum test (TRUST) were positive, and the serum rapid plasma reagin (RPR) was 1:16. The antibody against HIV was negative. The levels of homocysteine, folic acid, and vitamin B12 were 26 $\mu\text{mol/L}$ (0-15 $\mu\text{mol/L}$), 2.59 ng/mL (>5.4 ng/mL), and 325 pg/mL (211-911 pg/mL), respectively. The results of cerebrospinal fluid test (CSF) showed a higher level of cells (110/ μL) and protein (148 mg/dL). The immunological tests of aquaporin 4 (AQP4)-IgG were negative both in serum and CSF. The other inflammatory, immune, and infectious biomarkers both in CSF and serum were also unremarkable. The cranial MRI yielded normal findings. However, the spinal cord MRI showed abnormal longitudinally extensive T2 weighted hyperintensities involving the posterior columns from C7 through T6, with characteristic "flip-flop sign" on cervical spinal MRI (Figure 1B and C, Figure 2B and C). Focal contrast enhancement was observed in the dorsal aspect of the thoracic cord on T1 weighted gadolinium-enhanced images at T3-T4 level (Figures 1C and 2C).

With the treatment of penicillin (24-million IU/d) for 2 weeks, the symptoms of sensation almost disappeared 3 months later. The abnormal hyperintensities of spinal MRI also resolved at the 3-month follow-up (Figure 3). Moreover, the laboratory data of CSF showed reduced cells (24/ μL) and protein (65 mg/dL). The findings of TPPA and TRUST (1:8) in serum were still positive. The examination of CSF showed that TPPA was positive and TRUST was 1:1. The diagnosis of syphilitic myelitis was established according to the history of homosexuality, clinical manifestations, MRI findings with typical "flip-flop sign", also with the favorable prognosis after the penicillin treatment.

Our study was approved by the Ethics Committee of Beijing Chaoyang Hospital, Capital Medical University. Written informed consent was obtained from the patient to publish this case.

Literature search and selection

To better understand the clinical characteristics of syphilitic myelitis, we performed a literature search to identify other reports (reviews, case reports, or case series) from January 1987 to February 2019, using the PubMed and web of science databases with the terms including "syphilis", "neurosyphilis", "syphilitic myelitis", "meningomyelitis", "central nervous system", and "spine". All pertinent English-language articles were retrieved. A manual search by reviewing the reference sections of the retrieved articles was also performed.

Data extraction

Two investigators collected data from the selected articles. The following data were extracted: the author, country, age, gender, symptoms, neurological examination, etiology, auxiliary examinations, therapy, and outcome. We also summarized the clinical characteristics of this rare disorder.

RESULTS

A total of 16 articles of 20 cases between January 1987 and February 2019 were identified by preliminary literature search. The clinical characteristics of the involved cases are presented in Table 1. Of the 20 patients with syphilitic myelitis, the age of onset varied between 17 and 63 years. Sixteen patients were male (80%). The duration of symptoms was variable from 3 days to 9 months. Sixteen patients presented with the onset of sensory disturbance (80%), 15 with paraparesis (75%), 9 with urinary retention (45%), and 2 with gait disorder (10%). Eleven patients had a high risk behavior such as homosexuality or bisexuality (55%). Two patients presented with non-pruritic rash or erythema with the diagnosis of secondary syphilis (10%). One patient was diagnosed with syphilis and had been treated previously (5%). Five

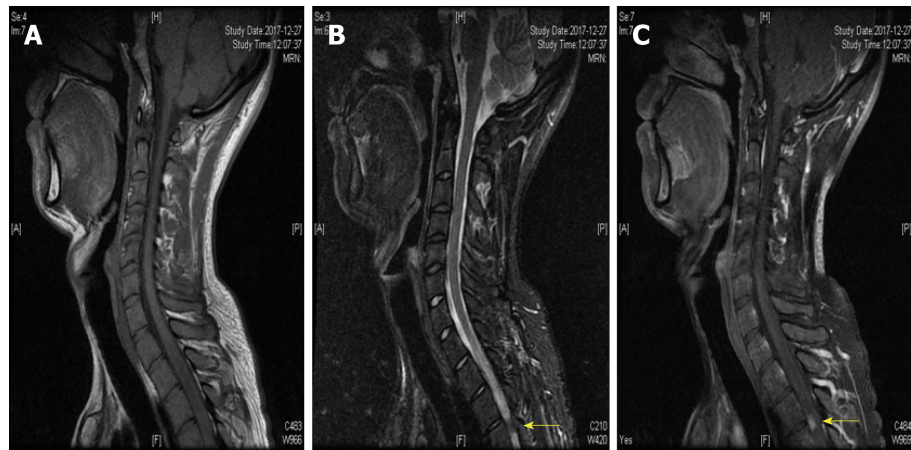


Figure 1 Spinal cord magnetic resonance imaging showed abnormal longitudinally extensive T2 weighted hyperintensities involving the posterior columns from C7 through T6, with "flip-flop sign" on cervical spinal magnetic resonance imaging.

patients had concomitant HIV infection (25%). Serological data showed that 15 patients had positive venereal disease research laboratory test (VDRL) and/or high Treponema pallidum hemagglutination (TPHA), and 17 patients had positive VDRL/TPHA in CSF. We also found that the raised protein was seen in 15 patients and pleocytosis was seen in 17 patients in CSF. On MRI, 16 patients showed abnormal signal intensities involving the thoracic spine, 6 involved the cervical spine, and 3 involved both the cervical and thoracic spine. There were 3 patients with the "flip-flop sign". All the patients were treated with penicillin, and 15 patients had a good prognosis.

DISCUSSION

Syphilitic myelitis caused by *Treponema pallidum* is an extremely rare disease. Herein, we report a rare case in a 25-year-old young man presenting with symptoms of sensory disturbance, due to syphilitic myelitis with longitudinally extensive myelopathy with typical "flip-flop sign" on spinal MRI. Furthermore, we also summarized the clinical features of syphilitic myelitis with longitudinally extensive myelopathy.

In the pre-antibiotic era, syphilis was one of the most frequent causes of myelopathy^[22]. Syphilitic meningomyelitis represents less than 3% of neurosyphilitic cases. The diagnosis is based on a high CSF white blood cell count (≥ 20 mL) with either a reactive CSF VDRL test or a positive CSF antibody^[15]. Syphilitic myelitis is a very rare but not well-recognized manifestation of neurosyphilis. It is a form of meningo-vascular syphilis with abnormalities confined to the spinal cord. The patients can present with sensory disturbance, lower extremity weakness, pyramidal signs, and variable degrees of bladder and bowel dysfunction. Diagnosis is difficult as it may mimic idiopathic transverse myelitis, spinal cord infarction, and acute disseminated encephalomyelitis, or neuromyelitis optica spectrum disorders (NMOSD). On spinal MRI, longitudinally extensive myelopathy is common, especially the feature of "flip-flop sign". Our case further suggested that the presence of "flip-flop sign" may indicate syphilitic myelitis.

Syphilis is a sexually transmitted and systemic disease, and the most common mechanism of transmission is sexual intercourse. HIV and syphilis affect similar patient groups and co-infection is common. The neurological complications of both infections occasionally occur during a clinical course. In the United States, 16% of all syphilis patients, and 28% of male syphilis patients were co-infected with HIV^[23]. If syphilis is detected in a patient with an elevated CSF TPHA-albumin index, it is crucial to check for serum HIV antibodies. As for our finding, 11 (55%) patients had a high risk behavior, such as homosexual and/or bisexual individuals. Five patients had concomitant HIV infection (25%). Determining which of the infections, syphilis or HIV, is crucial for allowing for a prompt diagnosis and the initiation of appropriate treatment. Our case further raised the importance of the serious consequences of homosexuality or high risk of unprotected sexual intercourse.

Although there are several hypotheses, the exact origin of the disease remains unknown^[24], which may be due to reversible edema from infection or ischemia^[13]. In

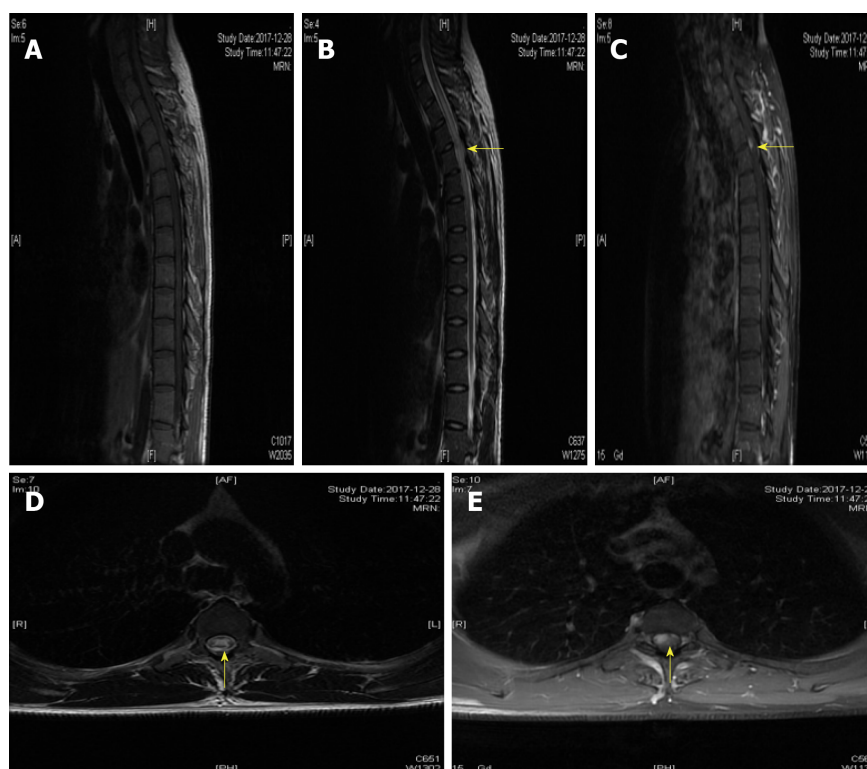


Figure 2 Spinal cord magnetic resonance imaging showed abnormal longitudinally extensive T2 weighted hyperintensities involving the posterior columns from C7 through T6, with "flip-flop sign" on cervical spinal magnetic resonance imaging. Focal enhancement was observed in the dorsal aspect of the thoracic cord on T1-weighted gadolinium-enhanced images at T3-T4 level.

syphilitic myelitis, there is primary involvement of the meninges and vessels. It is pathologically characterized by meningeal inflammation and spinal cord ischemia and edema due to syphilitic vasculopathy. The MRI abnormalities of the spinal cord probably result from meningeal inflammation and spinal cord ischemia. Spinal cord lesions which have resolved completely following treatment have been reported, and the disappearance of high-signal lesion may indicate that ischemic or inflammatory changes are reversible^[13]. As for our case, the high intensity areas on T2-weighted imaging may indicate reversible ischemic change or inflammation^[7].

The strengths of our case are listed as follows. First, our case revealed extensive T2-weighted abnormal signals in the spinal cord with "flip-flop sign". To the best of our knowledge, only two cases have been previously described of such longitudinally extensive T2-weighted hyperintensities with "flip-flop sign"^[9,14]. Thus, the technique of MRI could be of great importance to explore such disorders^[25]. Second, the medical history of homosexuality, clinical presentations, physical examination, laboratory examinations of serum and CSF, imaging findings of "flip-flop sign", good effect of penicillin, and favorable prognosis all contributed to our diagnosis of syphilitic myelitis. Moreover, in view of the longitudinally extensive myelopathy on MRI, we also tested AQP4 both in CSF and serum timely. The results were negative, and the misdiagnosis of NMOSD was avoided. Third, to date, our study is the largest study to explore the clinical features of syphilitic myelitis with longitudinally extensive myelopathy on spinal MRI.

In summary, syphilitic myelitis is a very rare manifestation of neurosyphilis. Early diagnosis and treatment are crucial because it represents a treatable and potentially reversible cause of myelopathy with penicillin. Our study also raises awareness of an important complication of neurosyphilis due to homosexuality. Attention is drawn upon the importance of doing serological tests for syphilis when any atypical neurological situation is presented.

Table 1 Clinical features of syphilitic myelitis with longitudinally extensive myelopathy

Case series	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Ref.	[7]	[8]	[9]	[9]	[10]	[11]	[12]	[13]	[14]	[15]	[16]	[17]	[4]	[18]	[18]	[19]	[20]	[21]	[21]	Our case
Age	46	31	17	29	17	28	63	57	36	46	63	38	32	35	30	49	41	36	49	25
Gender	M	M	F	F	M	M	M	F	M	M	M	M	M	M	F	M	M	M	M	M
Clinical features	Gait sensory disturbance, paraparesis, dysuria	Sensory disturbance, paraparesis, urinary retention	Paraparesis, sensory disturbance, paraparesis	Numbness, sensory disturbance, paraparesis	Paraparesis, sensory disturbance, paraparesis	Chorea, sensory deficit, paraparesis, urinary retention	Sensory deficit, paraparesis, urinary retention	Paraparesis, sensory deficit, paraparesis, urinary retention	Pain, paraparesis	Numbness, pain	Pain, weakness	Pain, weakness, numbness, retained urine	Tingling, numbness	Acute transverse myelitis	Acute transverse myelitis	Gait, paraparesis, loss of pain and temperature, urinary retention	Unconsciousness, numbness	Paresthesia, ascending paresis in lower limbs	Loss of bilateral strength, sensory impairment	Sensory disturbance, numbness
Duration	2 wk	10 d	8 d	9 mo	NA	180 d	60 d	3 d	4 mo	7 d	12 d	4 mo	4 mo	2 wk	1 mo	2 wk	NA	NA	NA	7 d
High risk behavior	NA	+	+	+	NA	+	NA	NA	NA	+	NA	+	+	+	NA	+	+	NA	NA	+
HIV infection	NA	NA	NA	NA	+	-	-	-	-	-	-	-	-	-	-	+	+	+	+	-
Blood VDR L	NA	1:640	1:4	1:4	1:16	NA	NA	1:8	Reactive	1:64	1:16	RPR (1:128)	1:16	Reactive	Non-reactive	Reactive	RPR+	NA	NA	TRUST+ RPR (1:16)
Blood TPHA	NA	>1:20480	Reactive	Reactive	FTA-ABS (1:6400)	NA	NA	FTA (3+) TPHA (2+)	1:5120	1:81920	Reactive	4+	1:160	1:5120	1:1280	1:2560	+	NA	NA	+
CSF protein (mg/dL)	High	94	52	54	106	94	200	Normal	243	72	91.70	88	40	123	57	79	NA	NA	NA	148
CSF cells (/μL)	Pleocytosis	120	75	20	180	120	498	Pleocytosis	346	113	303	18	40	115	170	202	NA	NA	NA	110
CSF VDR L	Reactive	1:80	Non-reactive	Non-reactive	NA	+	+	1:2	NA	NA	Reactive	1:16	+	Reactive	Reactive	NA	+	NA	NA	NA
CSF TPHA A	Reactive	1:5120	Non-reactive	Reactive	FTA-ABS (1:100)	TPHA+	NA	NA	FTA-ABS (1:320), TPHA (1:640)	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA

Spin -al MRI	High T2 inten- sity, abnor- mal Gd- DTP A enhan- ced	T3/4 wedge - shaped Gd- DTP A enhan- ced high intens- ity, swoll- en spinal cord	Below the C4 diffu- se high signal flip- flop cand- le gutter -ing appea- rance	T1- T11 abnor- mal signal flip- flop sign	NA	T6-T8	LET M, Gadol- in- ium -enhan- ced -ent	Exten- sive central high T2 signal flip- flop sign enhan- ced -nt of the dorsal T8- T9	Diffu- se high T2 signal flip- flop sign	T2-T6 high signal focal Gd- DTP A enhan- ced -nt	T6- T11 high signal focal Gd- DTP A enhan- ced -nt	Ventr- al part on the level of T6-T7	T5- T12 hyper- intense signals	Spine -cord edema from cervic- al up to T6 conus medu- llaris	Spine -cord edema from cervic- al up to T6 conus	High- inten- sity lesion s C4 to T6	Spinal cord edema from C3-T1	Signal impai- ment in the spinal cord (T2- T12)	Diffu- se hyper- signal at sever- al levels	Longi- tudinal exten- sive T2 hyper- intens- ities invol- ving C7 to T6
Trea- tment	Antib- iotic thera- py	Penici- llin, predn- isolone	Penici- llin, ceph- alospo- rins	Penici- llin, ceph- alospo- rins	Penici- llin, ceph- alospo- rins	Penici- llin, dexameth- asone	Antib- iotic thera- py	Penici- llin, meth- ylpre- dnisolone	Penici- llin, meth- ylpre- dnisolone	Ceftri- axone, meth- ylpre- dnisolone	Penici- llin, predn- isolone	Penici- llin, predn- isolone	Proca- ine penici- llin, Meth- ylpre- dnisolone	Proca- ine penici- llin, Meth- ylpre- dnisolone	Penici- llin, potas- sium, meth- ylpre- dnisolone	Penici- llin, potas- sium, meth- ylpre- dnisolone	Penici- llin, potas- sium, meth- ylpre- dnisolone	Penici- llin, potas- sium, meth- ylpre- dnisolone	Penici- llin, potas- sium, meth- ylpre- dnisolone	Penici- llin, potas- sium, meth- ylpre- dnisolone
Foll- ow- up dura- tion	NA	16 d	14 d	1 mo	NA	NA	2 yr	4 wk	28 d	21 d	30 d	NA	14 d	6 mo	Lost	2 wk	1 wk	NA	NA	3 mo
Stat- us	Impr- oved	Impr- oved	Com- plete remis- sion	Impr- oved	Spasti- city	NA	Impr- oved	Non- impro- ved	Impr- oved	Impr- oved	Impr- oved	Posi- tive effect	NA	Same	NA	Impr- oved	Impr- oved	Com- plete impro- vement	Parti- al impro- vement	Impr- oved
Rep- eat CSF find- ing	NA	TPH A (1:256 0), VDRL mg/dL (1:40)	Cells 9/ μ L, protein 38 mg/dL	NA	Non- reac- tive	NA	NA	NA	Redu- ced	NA	Cells 34/ μ L, protein 45.4mg/ dL	NA	NA	NA	NA	NA	MA	NA	NA	Cells 24/ μ L, prote- in 65 mg/dL, TPPA +, TRUST 1:1.
Rep- eat blood find- ing	NA	TPH A (1:102 40), VDR L (1:160)	NA	NA	NA	NA	NA	NA	NA	VDR L (1:16)	RPR (1:4)	RPR (1:64)	NA	NA	NA	NA	NA	NA	NA	TPPA (+), TRUST T (1:8)
Rep- eat MRI find- ing	Disap- pearance of intra- medu- llary high intens- ity areas	Redu- ction in the intensity of lesions	Redu- ction in the intensity of lesions	Redu- ction in the intensity of lesions	NA	NA	NA	Disap- pearance of high signal lesion on T2- weig- hted images dimin- ished	Gadol- in- ium -enhan- ced disap- peared on the high signal intensity dimin- ished	NA	Redu- ction in the intensity of lesions	NA	NA	NA	NA	Redu- ction in the size of the cervic- al and thora- cic cord lesions	NA	NA	NA	Disso- lved with three month follow up

M: Male; F: Female; NA: Not applicable; VDRL: Venereal disease research laboratory; TPHA: Treponema pallidum hemagglutination assay; LETM: Longitudinally extensive transverse myelitis; RPR: Rapid plasma regain; TRUST: Toluene red unheated serum test; T: Thoracic; C: Cervical; CSF: Cerebrospinal fluid; HIV: Human immunodeficiency virus; NA: Not applicable; FTA-Abs: Fluorescent treponemal antibody-absorption; +: Positive.

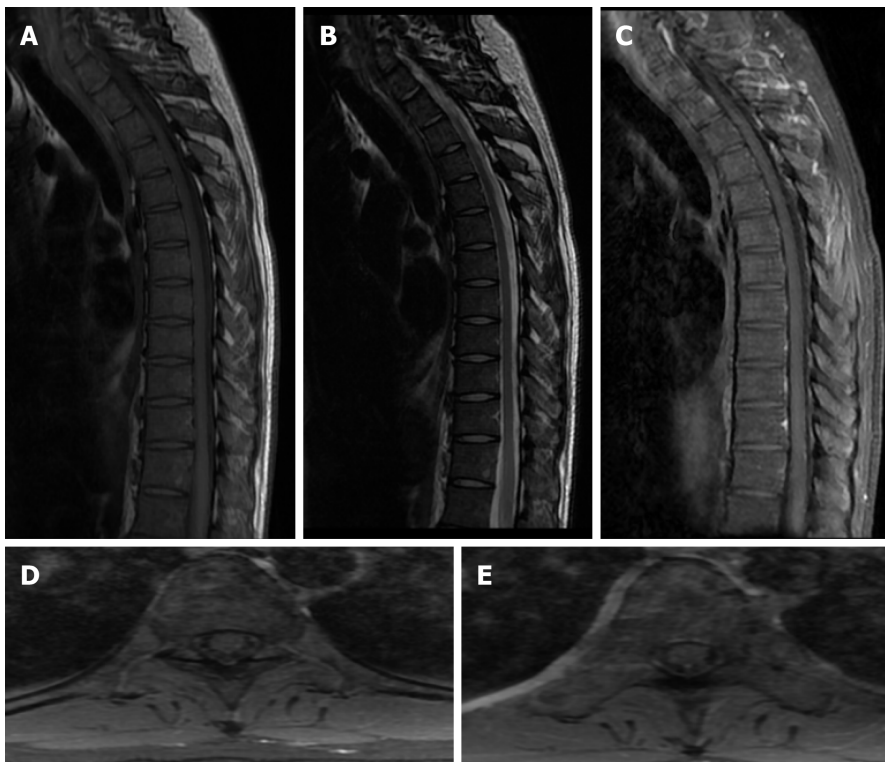


Figure 3 Abnormal hyperintensities on spinal magnetic resonance imaging also resolved at three-month follow-up.

ARTICLE HIGHLIGHTS

Research background

Syphilitic myelitis caused by *Treponema pallidum* is an extremely rare disease. However, symptomatic neurosyphilis, especially syphilitic myelitis, and its clinical features have been infrequently reported.

Research motivation

Only a few cases of syphilitic myelitis have been documented in the international literature. To the best of our knowledge, there are only 19 reported cases of syphilitic myelitis in the literature.

Research objectives

Our study was aimed to summarize the clinical features of syphilitic myelitis with longitudinally extensive myelopathy.

Research methods

First, we report a patient who suffered from syphilitic myelitis with symptoms of sensory disturbance, with longitudinally extensive myelopathy with "flip-flop sign" on spinal magnetic resonance imaging (MRI). This patient experienced complete clinical and radiologic recovery after treatment. Second, we summarized the clinical features of syphilitic myelitis with longitudinally extensive myelopathy.

Research results

A total of 16 articles of 20 cases were identified. Sixteen patients presented with the onset of sensory disturbance (80%), 15 with paraparesis (75%), and 9 with urinary retention (45%). Eleven patients had a high risk behavior (55%). Five patients had concomitant HIV infection (25%). Serological data showed that 15 patients had positive venereal disease research laboratory test (VDRL)/treponema pallidum particle agglutination (TPHA), and 17 patients had positive VDRL/TPHA in cerebrospinal fluid (CSF). Seventeen patients had elevated cells and protein in CSF. On MRI, 16 patients showed abnormal signal intensities involving the thoracic spine, 6 involved the cervical spine, and 3 involved both cervical and thoracic spine. There were 3 patients with the "flip-flop sign". All the patients were treated with penicillin, and 15 patients had a good prognosis.

Research conclusions

Our case raises awareness of syphilitic myelitis as an important complication of neurosyphilis due to homosexuality, especially in developing countries.

Research perspectives

Attention is drawn upon the importance of doing serological tests for syphilis when any atypical neurological situation is presented. A high index of suspicion is necessary so that this potentially treatable disease would not be overlooked.

REFERENCES

- 1 **Hawkes S**, Matin N, Broutet N, Low N. Effectiveness of interventions to improve screening for syphilis in pregnancy: a systematic review and meta-analysis. *Lancet Infect Dis* 2011; **11**: 684-691 [PMID: [21683653](#) DOI: [10.1016/S1473-3099\(11\)70104-9](#)]
- 2 **Hook EW**. Syphilis. *Lancet* 2017; **389**: 1550-1557 [PMID: [27993382](#) DOI: [10.1016/S0140-6736\(16\)32411-4](#)]
- 3 **Berger JR**, Dean D. Neurosyphilis. *Handb Clin Neurol* 2014; **121**: 1461-1472 [PMID: [24365430](#) DOI: [10.1016/B978-0-7020-4088-7.00098-5](#)]
- 4 **Srivastava T**, Thussu A. MRI in syphilitic meningomyelitis. *Neurol India* 2000; **48**: 196-197 [PMID: [10878799](#)]
- 5 **Bhai S**, Lyons JL. Neurosyphilis Update: Atypical is the New Typical. *Curr Infect Dis Rep* 2015; **17**: 481 [PMID: [25896752](#) DOI: [10.1007/s11908-015-0481-x](#)]
- 6 **O'donnell JA**, Emery CL. Neurosyphilis: A Current Review. *Curr Infect Dis Rep* 2005; **7**: 277-284 [PMID: [15963329](#)]
- 7 **Nabatame H**, Nakamura K, Matuda M, Fujimoto N, Dodo Y, Imura T. MRI of syphilitic myelitis. *Neuroradiology* 1992; **34**: 105-106 [PMID: [1603304](#) DOI: [10.1007/BF00588152](#)]
- 8 **Tashiro K**, Moriwaka F, Sudo K, Akino M, Abe H. Syphilitic myelitis with its magnetic resonance imaging (MRI) verification and successful treatment. *Jpn J Psychiatry Neurol* 1987; **41**: 269-271 [PMID: [3437614](#)]
- 9 **Lu H**, Jiao L, Liu Z, Wang B. The syphilitic myelitis with longitudinally extensive myelopathy: two cases report and literature review. *Zhonghua Shenjingke Zazhi* 2016; **49**: 967-969
- 10 **Janier M**. Acute syphilitic myelitis in a young man. *Genitourin Med* 1988; **64**: 206 [PMID: [3410471](#) DOI: [10.1136/sti.64.3.206](#)]
- 11 **Strom T**, Schneck SA. Syphilitic meningomyelitis. *Neurology* 1991; **41**: 325-326 [PMID: [1812840](#) DOI: [10.1212/WNL.41.2_Part_1.325](#)]
- 12 **Jacquemin GL**, Proulx P, Gilbert DA, Albert G, Morcos R. Functional recovery from paraplegia caused by syphilitic meningomyelitis. *J Spinal Cord Med* 2002; **25**: 133-137 [PMID: [12137218](#) DOI: [10.1080/10790268.2002.11753614](#)]
- 13 **Tsui EY**, Ng SH, Chow L, Lai KF, Fong D, Chan JH. Syphilitic myelitis with diffuse spinal cord abnormality on MR imaging. *Eur Radiol* 2002; **12**: 2973-2976 [PMID: [12439578](#) DOI: [10.1007/s00330-001-1244-7](#)]
- 14 **Kikuchi S**, Shinpo K, Niino M, Tashiro K. Subacute syphilitic meningomyelitis with characteristic spinal MRI findings. *J Neurol* 2003; **250**: 106-107 [PMID: [12528004](#) DOI: [10.1007/s00415-003-0921-7](#)]
- 15 **Chilver-Stainer L**, Fischer U, Hauf M, Fux CA, Sturzenegger M. Syphilitic myelitis: rare, nonspecific, but treatable. *Neurology* 2009; **72**: 673-675 [PMID: [19221304](#) DOI: [10.1212/01.wnl.0000342460.07764.5c](#)]
- 16 **He D**, Jiang B. Syphilitic myelitis: magnetic resonance imaging features. *Neurol India* 2014; **62**: 89-91 [PMID: [24608474](#) DOI: [10.4103/0028-3886.128347](#)]
- 17 **Matijosaitis V**, Vaitkus A, Pauza V, Valiukeviciene S, Gleizniene R. Neurosyphilis manifesting as spinal transverse myelitis. *Medicina (Kaunas)* 2006; **42**: 401-405 [PMID: [16778468](#)]
- 18 **Kayal AK**, Goswami M, Das M, Paul B. Clinical spectrum of neurosyphilis in North East India. *Neurol India* 2011; **59**: 344-350 [PMID: [21743160](#) DOI: [10.4103/0028-3886.82719](#)]
- 19 **Tohge R**, Shinoto Y, Takahashi M. Longitudinally Extensive Transverse Myelitis and Optic Neuropathy Associated with Syphilitic Meningomyelitis and Human Immunodeficiency Virus Infection: A Case Report and Review of the Literature. *Intern Med* 2017; **56**: 2067-2072 [PMID: [28768983](#) DOI: [10.2169/internalmedicine.56.8236](#)]
- 20 **Siu G**. Syphilitic Meningomyelitis. *J Am Osteopath Assoc* 2017; **117**: 671 [PMID: [28973189](#) DOI: [10.7556/jaoa.2017.130](#)]
- 21 **Borges CR**, Almeida SM, Sue K, Koslyk JLA, Sato MT, Shiokawa N, Teive HAG. Neurosyphilis and ocular syphilis clinical and cerebrospinal fluid characteristics: a case series. *Arq Neuropsiquiatr* 2018; **76**: 373-380 [PMID: [29972419](#) DOI: [10.1590/0004-282X20180054](#)]
- 22 **Berger JR**, Sabet A. Infectious myelopathies. *Semin Neurol* 2002; **22**: 133-142 [PMID: [12524558](#) DOI: [10.1055/s-2002-36536](#)]
- 23 **Zetola NM**, Engelman J, Jensen TP, Klausner JD. Syphilis in the United States: an update for clinicians with an emphasis on HIV coinfection. *Mayo Clin Proc* 2007; **82**: 1091-1102 [PMID: [17803877](#) DOI: [10.4065/82.9.1091](#)]
- 24 **Breitenfeld D**, Kust D, Breitenfeld T, Prpić M, Lucijanić M, Zibar D, Hostić V, Franceschi M, Bolanča A. Neurosyphilis in Anglo-American Composers and Jazz Musicians. *Acta Clin Croat* 2017; **56**: 505-511 [PMID: [29479917](#) DOI: [10.20471/acc.2017.56.03.18](#)]
- 25 **Razek AAKA**, Ashmalla GA. Assessment of paraspinal neurogenic tumors with diffusion-weighted MR imaging. *Eur Spine J* 2018; **27**: 841-846 [PMID: [28821978](#) DOI: [10.1007/s00586-017-5265-6](#)]

Prospective Study

Application of pulse index continuous cardiac output system in elderly patients with acute myocardial infarction complicated by cardiogenic shock: A prospective randomized study

Yuan-Bo Zhang, Zhi-Zhong Zhang, Jun-Xia Li, Yu-Hong Wang, Wei-Lin Zhang, Xin-Li Tian, Yun-Feng Han, Meng Yang, Yu Liu

ORCID number: Yuan-Bo Zhang (0000-0002-4272-2314); Zhi-Zhong Zhang (0000-0001-6015-5774); Jun-Xia Li (0000-0002-1810-9333); Yu-Hong Wang (0000-0002-4091-3440); Wei-Lin Zhang (0000-0002-9821-3690); Xin-Li Tian (0000-0002-0076-3943); Yun-feng Han (0000-0003-2751-7045); Meng Yang (0000-0003-2495-7694); Yu Liu (0000-0001-9354-9649).

Author contributions: Zhang YB and Zhang ZZ contributed equally to this work; Zhang YB and Li JX obtained and analyzed the study; Zhang YB and Zhang ZZ wrote the paper; Wang YH, Zhang WL, Tian XL and Yang M interpreted the patient data; Zhang YB, Liu Y and Han YF revised the manuscript; All authors read and approved the final manuscript.

Institutional review board

statement: The study was reviewed and approved by the General Hospital of Chinese PLA Institutional Review Board.

Clinical trial registration statement:

This study is registered at Chinese Trial Registry (<http://www.chictr.org.cn/index.aspx>). The registration identification number is ChiCTR1000022691.

Informed consent statement:

Written informed consent form was provided by family members of the patients.

Conflict-of-interest statement: The authors of this manuscript have no

Yuan-Bo Zhang, Jun-Xia Li, Xin-Li Tian, Yun-Feng Han, Meng Yang, Department of Cardiovascular Medicine, The Seventh Medical Center, General Hospital of the Chinese PLA, Beijing 100700, China

Zhi-Zhong Zhang, Department of Emergency Medicine, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China

Yu-Hong Wang, Department of Emergency Medicine, The Seventh Medical Center, General Hospital of Chinese PLA, Beijing 100700, China

Wei-Lin Zhang, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China

Yu Liu, Department of Emergency Medicine, Dongzhimen Hospital, The First Affiliated Hospital of Beijing University of Chinese Medicine, Beijing 100700, China

Corresponding author: Yu Liu, MD, Associate Professor, Department of Emergency Medicine, Dongzhimen Hospital, The First Affiliated Hospital of Beijing University of Chinese Medicine, No.5, Haiyuncang, Dongcheng District, Beijing 100700, China.

davidliuyu@126.com

Telephone: +86-10-84011792

Fax: +86-10-84011792

Abstract

BACKGROUND

Cardiogenic shock (CS) secondary to acute myocardial infarction (AMI) complicates management of the condition, and often leads to poor prognosis. Prompt and accurate monitoring of cardiovascular and accompanying hemodynamic changes is crucial in achieving adequate management of the condition. Advances in technology has availed procedures such as pulse index continuous cardiac output (PiCCO), which can offer precise monitoring of cardiovascular functions and hemodynamic parameters. In this study, PiCCO is evaluated for its potential utility in improving management and clinical outcomes among elderly patients with AMI complicated by CS.

AIM

To assess whether use of the PiCCO system can improve clinical outcomes in elderly patients with AMI complicated by CS.

conflicts of interest to disclose.

Data sharing statement: There is no additional data available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Received: February 28, 2019

Peer-review started: March 4, 2019

First decision: April 18, 2019

Revised: April 26, 2019

Accepted: May 1, 2019

Article in press: May 2, 2019

Published online: June 6, 2019

P-Reviewer: Wong KL

S-Editor: Dou Y

L-Editor: Filipodia

E-Editor: Xing YX



METHODS

Patients from emergency intensive care units (EICU) or coronary care units (CCU) were randomized to receive PiCCO monitoring or not. The APACHE II score, SOFA score, hs-TnI, NT-proBNP, PaO₂/FiO₂ ratio and lactate levels on day 1, 3 and 7 after treatment were compared. The infusion and urine volume at 0-24 h, 24-48 h and 48-72 h were recorded, as were the cardiac index (CI), extravascular lung water index (EVLWI), intrathoracic blood volume index (ITBVI) and global end diastolic volume index (GEDVI) at similar time intervals.

RESULTS

Sixty patients with AMI complicated by CS were included in the study. The PiCCO group had a significantly lower APACHE II score, SOFA score, hs-TnI and NT-proBNP levels on day 1, 3 and 7 after treatment. The infusion and urine volume during 0-24 h in the PiCCO group were significantly greater, and this group also showed significantly higher ADL scores. Furthermore, the PiCCO group spent lesser days on vasoactive agents, mechanical ventilation, and had a reduced length of stay in EICU/CCU. Additionally, the CI was significantly higher at 48 h and 72 h in the PiCCO group compared with that at 24 h, and the EVLWI, ITBVI and GEDVI were significantly decreased at 48 h and 72 h.

CONCLUSION

Applying the PiCCO system could improve the clinical outcomes of elderly patients with AMI complicated by CS.

Key words: Pulse index continuous cardiac output; Elderly patients; Cardiogenic shock; Acute myocardial infarction

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Previous studies investigating the usefulness of the pulse index continuous cardiac output (PiCCO) system have mainly focused on patients with septic shock, acute respiratory distress syndrome and necrotizing pancreatitis. There are few reported studies conducted in elderly patients with acute myocardial infarction (AMI) complicated by cardiogenic shock (CS). Therefore, the aim of the present randomized controlled trial was to assess whether the application of PiCCO could improve clinical outcomes for elderly patients with AMI complicated by CS.

Citation: Zhang YB, Zhang ZZ, Li JX, Wang YH, Zhang WL, Tian XL, Han YF, Yang M, Liu Y. Application of pulse index continuous cardiac output system in elderly patients with acute myocardial infarction complicated by cardiogenic shock: A prospective randomized study. *World J Clin Cases* 2019; 7(11): 1291-1301

URL: <https://www.wjgnet.com/2307-8960/full/v7/i11/1291.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v7.i11.1291>

INTRODUCTION

Acute myocardial infarction (AMI) is a leading cause of hospitalizations and mortality worldwide. The incidence of AMI increases progressively with age, and a larger proportion of patients presenting with AMI in the future is predicted to be older than 65 years. Classic symptoms of AMI include chest pain but, in the elderly, atypical presentations without chest pain are more common; this may lead to missed or delayed diagnosis^[1]. Cardiogenic shock (CS) is a primary complication following AMI, and is the main cause of early death^[2]. Therefore, AMI complicated by CS remains one of the most serious and challenging conditions to manage, with mortality rates approaching 50-80% according to data from the SHOCK registry^[3,4]. Additionally, elderly patients, with a variety of disorders and multiple organ dysfunction have significantly higher mortality risks^[5,6]. When it occurs, CS is an emergency requiring rapid diagnosis and effective clinical management. Hemodynamic monitoring and the associated fluid therapy are of critical importance in the management of these conditions. Prognosis of CS depends on the degree of hemodynamic abnormalities. In critical care settings, the management and optimization of fluid status remains a

considerable challenge because inadequate circulatory volume can lead to insufficient tissue perfusion and oxygen delivery, whereas fluid overload can cause heart failure and pulmonary edema. Thus, inadequate fluid balance can increase the mortality associated with these conditions. For this reason, a monitoring method capable of reflecting the real status of the entire circulatory system is paramount for sufficient CS management.

Pulse index continuous cardiac output (PiCCO) is an efficient advanced procedure of continuously monitoring the hemodynamic status in clinical practice. The procedure is based on the use of a specific thermodilution arterial (femoral, brachial, or axillary) catheter and a central venous line^[7]. The technique is minimally invasive, and can quantify different hemodynamic parameters reflecting the vascular tone, preload, and cardiac function. Cardiac function profiles that can be discerned from PiCCO include cardiac output, intrathoracic blood volume (ITBV), global end-diastolic volume (GEDV), extra vascular lung water (EVLW) and peripheral vascular resistance. Monitoring these parameters can enable a clinician to optimize volume status, myocardial contractility, and tissue perfusion^[8]. Previous studies investigating the usefulness of the PiCCO system have mainly focused on patients with septic shock^[9,10], acute respiratory distress syndrome^[10,11] and necrotizing pancreatitis^[12], while there are few available studies conducted in elderly patients with AMI complicated by CS. Therefore, the aim of the present randomized controlled trial was to assess whether the application of PiCCO can improve clinical outcomes for elderly patients with AMI complicated by CS.

MATERIALS AND METHODS

Patient selection

This prospective study was conducted from January 2015 to January 2017 in the Department of Emergency Medicine, PLA Army General Hospital, Beijing, China. The study was approved and monitored by the Institutional Review Board of the PLA General Hospital, Beijing, China. The registration identification number for the study is ChiCTR-IOC-16009923. Patients admitted to the emergency intensive care unit (EICU) or coronary care unit (CCU) were recruited if they were over 65 years of age and had CS consequent to AMI. The diagnosis of AMI was confirmed as follows: (1) An increase in cardiac troponin I (cTnI) or creatine kinase-MB (CK-MB) levels above the 99th percentile of a healthy; (2) Characteristic electrocardiogram (ECG) changes—either ST segment elevation, new ST segment depression or T wave flattening, inversion; and (3) At least one of the following signs or symptoms: (a) Persistent ischemic chest pain; (b) Echocardiographic findings/segmental wall motion abnormalities; and (c) Abnormal coronary angiography findings. CS was diagnosed on the basis of the following criteria: (1) Objective evidence of cardiac dysfunction; (2) Systolic blood pressure < 90 mmHg for at least 30 min, or vasopressors required to maintain the systolic blood pressure \geq 90 mmHg; (3) A reduced cardiac index (CI) (< 2.2 L/min/m²); and (4) Clinical signs of tissue hypoperfusion (cold, clammy skin, altered mental status, oliguria or peripheral vasoconstriction). Exclusion criteria included the following: viral myocarditis, pericardial tamponade, CS due to chronic heart failure and congenital heart disease, malignant tumor, septic shock and multiple organ dysfunction syndrome, moribund, or informed consent cannot be obtained; contraindications to catheter insertion, including overlying infection and arterial grafting; conditions likely to render PiCCO measurements inaccurate, including intracardiac shunts, significant tricuspid regurgitation, and cooling or rewarming. A written informed consent form was provided by family members of the patients, and the study was approved by the Ethics Committee of PLA Army General Hospital.

This study aimed to explore the clinical efficacy of PiCCO *versus* control group in the treatment of elderly patients with AMI complicated by CS. The patients were randomized into the two groups. The APACHE II score was used as the main measuring index. Considering the outcomes based on the work by Zhang and colleagues^[13], a minimum sample size of 20 patients in each group (control and PiCCO) was determined to be enough to provide statistical differences with $\alpha = 0.05$ and 80% power, assuming a 20% failure rate.

Treatment methods

Patients that met the inclusion criteria were randomly assigned to either PiCCO or control groups based on the random number table method. The control group received conventional treatment, such as ECG monitoring, oxygen inhalation, establishing intravenous access and inserting a central venous catheter for the measurement of central venous pressure (CVP). Anticoagulants, antiplatelet agents

and antiarrhythmic therapy were offered. Emergency revascularization with direct percutaneous coronary intervention (PCI) or emergency coronary artery bypass graft (CABG) was required. If patients were not suitable for receiving revascularization therapy, intravenous thrombolysis was given. In the control group, blood pressure, heart rate and CVP were used to guide fluid resuscitation therapy, including the administration of intravenous fluid, vasoactive agents, diuretics or inotropic drugs to maintain appropriate cardiac output.

For the patients enrolled in the PiCCO group, either they themselves or their legal representatives signed the consent forms for arterial catheterization. The PiCCO procedure was conducted within 2 h of patient enrollment. A central venous catheter was placed into a central vein (right subclavian or jugular vein), and a thermistor-tipped arterial catheter was inserted into the femoral artery; both were then connected to the PiCCO system for detecting hemodynamics^[14]. An infusion *via* central venous catheter was stopped for at least 30 s before the infusion of saline. Then, 10–15 mL of normal saline at a temperature of 0–8 °C was injected into the central vein, and various hemodynamic parameters were obtained *via* the analysis of variations in blood temperature taken by the temperature sensor of the arterial catheter^[15]. At least three cold boluses were considered necessary for each calibration to obtain readings with acceptable precision. The measurements of hemodynamic parameters representing an average of three readings were recorded at least every 8 h^[16]. These hemodynamic parameters were used to guide the application of vasoactive drugs, fluids and diuretics according to the protocol of our institution on the basis of conventional treatment. If $CI < 3 \text{ L/min/m}^2$, global end-diastolic volume index (GEDVI) $< 680 \text{ mL/m}^2$ and extravascular lung water index (EVLWI) $< 3 \text{ mL/kg}$, intravenous fluid was applied. Vasoactive drugs (inotropes and vasopressors) were used to improve cardiac contractility when $CI < 3 \text{ L/min/m}^2$, $800 \text{ mL/m}^2 > GEDVI > 680 \text{ mL/m}^2$ and $EVLWI < 3 \text{ mL/kg}$. If $CI < 3 \text{ L/min/m}^2$, $GEDVI > 800 \text{ mL/m}^2$ and $EVLWI > 3 \text{ mL/kg}$, both vasoactive drugs and diuretics were applied. If $CI > 3 \text{ L/min/m}^2$, $GEDVI < 680 \text{ mL/m}^2$ and $EVLWI < 3 \text{ mL/kg}$, intravenous fluid was administered. If $CI > 3 \text{ L/min/m}^2$, $800 \text{ mL/m}^2 > GEDVI > 680 \text{ mL/m}^2$ and $EVLWI < 3 \text{ mL/kg}$, there was no need to give intravenous fluid, and real-time monitoring was performed based on the changes of patient conditions. Diuretics were used to reduce fluid overload when $CI > 3 \text{ L/min/m}^2$, $GEDVI > 800 \text{ mL/m}^2$ and $EVLWI > 3 \text{ mL/kg}$. The target was to maintain $5 \text{ L/min/m}^2 > CI > 3 \text{ L/min/m}^2$, $800 \text{ mL/m}^2 > GEDVI > 680 \text{ mL/m}^2$ and $EVLWI < 3 \text{ mL/kg}$. The PiCCO procedure was discontinued and removed if the patient was clinically stable for 48 h, as determined by the attending physicians. The system was maintained for a maximum of 10 d. If catheter-related bloodstream infection was suspected, the central venous catheter was removed and sent for microbiological study, and the catheter was exchanged for a new one.

Data collection

The following data were recorded: Age, sex, body mass index, comorbidities, acute physiology and chronic health evaluation II (APACHE II) score, sequential organ failure assessment (SOFA) score, high-sensitive Troponin I (hs-TnI), N-terminal pro-brain natriuretic peptide (NT-proBNP), PaO_2/FiO_2 ratio, lactate levels, urine output, infusion volume, activities of daily living (ADL) scale, days on vasoactive agents, days on mechanical ventilation, duration of mechanical ventilation, EICU/CCU length of stay and incidence of pulmonary edema. The CI, EVLWI, ITBVI, and GEDVI were recorded at various time points: 0–24 h, 24–48 h and 48–72 h of the PiCCO group.

Statistical analysis

Statistical analyses were completed using SPSS 17.0 software. Data are reported as the mean (standard deviation) or number (%). Outcomes were compared between two groups with two-sided *t*-tests for continuous variables and chi-square tests for categorical variables; ANOVA was used to calculate multi-parametric significance. All tests were two-sided, and $P < 0.05$ was considered to be statistically significant.

RESULTS

Comparison of baseline characteristics in patients

The patient screening process is as outlined in **Figure 1**. A total of 92 patients were assessed for eligibility to participate in the study. Out of this, 21 patients were excluded for: not meeting inclusion criteria ($n = 13$), declined to participate ($n = 5$), and other reasons ($n = 3$). The remaining 71 patients were randomized to control group ($n = 35$) and PiCCO group ($n = 36$). However, in the control group, 5 patients in the control group were lost to follow-up, leaving 30 patients who completed the

study. On the other hand, in the PiCCO group, 34 patients received the procedure, 2 patients did not receive the procedure due to relative's refusal, and 4 patients were lost to follow-up. Therefore 30 patients from this group were analyzed at the end of the study. Consequently, a total of 60 patients, comprising 34 men and 26 women, with AMI complicated by CS were included in the present study. The age range was 66-87 years. Baseline characteristics of patients in the two groups are presented in [Table 1](#). No statistically significant differences regarding baseline characteristics of patients between the two groups were observed (all $P > 0.05$).

Comparison of clinical outcome variables in patients

A comparison was made of the APACHE II score, SOFA score, hs-TnI, NT-proBNP, lactate levels and oxygenation index on day 1, 3 and 7 after treatment between the groups ([Table 2](#)). In the PiCCO group, APACHE II score, SOFA score, hs-TnI and NT-proBNP levels gradually decreased after treatment, and these indicators were significantly lower ($P < 0.05$ or $P < 0.01$) in comparison to the control group. When comparing oxygenation index and lactate levels, no significant difference on day 1 and 3 after treatment was seen between two groups ($P > 0.05$). However, on day 7 after treatment, the PiCCO group showed greater oxygenation indices and lower lactate levels ($P < 0.05$).

The infusion and urine volume at various time frames are presented in [Table 3](#). The infusion ($P < 0.05$) and urine volume ($P < 0.01$) during 0-24 h in the PiCCO group was significantly greater than the control group. Notably, there were no differences between the two groups in the infusion and urine volume between 24-48 h and 48-72 h.

A comparison was made of the primary outcomes of ADL score, and secondary outcomes such as the days on vasoactive agents, days on mechanical ventilation, duration of mechanical ventilation, EICU/CCU length of stay and occurrence of pulmonary edema between the two groups ([Table 4](#)). The PiCCO group showed significantly higher ADL scores ($P = 0.000$) compared to control group. Days on vasoactive agents ($P = 0.013$), duration of mechanical ventilation ($P = 0.000$), days on mechanical ventilation ($P = 0.011$) and EICU/CCU length of stay ($P = 0.005$) were significantly lower in the PiCCO group than in the control group. However, no significant difference was observed in the incidence of pulmonary edema between the two groups ($P = 0.589$).

The parameters CI, EVLWI, ITBVI and GEDVI were assessed at various time points, and the results are summarized in [Table 5](#). The results show that the levels of EVLWI ($P = 0.000$), ITBVI ($P = 0.000$) and GEDVI ($P = 0.000$) were significantly lower at 48 h and 72 h than those at 24 h. On the other hand, the value of CI ($P = 0.001$) was significantly higher at 48 h and 72 h than that at 24 h.

DISCUSSION

AMI is a serious cardiovascular emergency, and CS, characterized by inadequate tissue perfusion resulting from cardiac dysfunction, is a dreadful complication of AMI, occurring in around 10% of patients with AMI^[17]. Elderly patients with AMI are more likely to have severe coronary artery disease and large MI size, and most of them often suffer from diabetes mellitus, hypertension and other chronic diseases. The clinical features and prognosis associated with AMI in the elderly warrant special consideration. The elderly are considered to be at high risk for AMI complicated by CS^[18]. Abnormal distribution of systemic blood flow upon CS leads to absolute or relative lack of effective circulating blood volume, which also makes CS refractory. To improve prognosis, in addition to the need for an early and accurate diagnosis, fast coronary artery revascularization including PCI and CABG is performed to improve perfusion. Then, medications such as vasoactive drugs, diuretics and positive inotropic agents are a key component of treatment strategies for hemodynamic stabilization and shock reversal. For these critically ill patients, effective mechanical circulatory support is also required.

Presently, there are several different monitoring systems available for patients with circulatory failure to evaluate cardiac output, cardiac function and preload. However, none of these methods are ideal, as they do not meet *all* the criteria in being non-invasive, continuous, safe, reproducible and having a fast response time. Pulmonary artery catheterization, also known as Swan-Ganz catheter, has been accepted as a gold standard for the clinical measurement of cardiac output for more than 20 years, and it is an important hemodynamic monitoring tool for critically ill patients to guide diagnosis and treatment. However, its use has progressively declined due to difficulties in data interpretation and the potential development of serious com-

Table 1 Baseline characteristics of patients in PiCCO and control groups

	PiCCO group, <i>n</i> = 30	Control group, <i>n</i> = 30	<i>P</i> value
Age in yr	76.37 ± 6.67	75.93 ± 6.55	0.801
Male	18 (60.0%)	16 (53.3%)	0.602
BMI	24.89 ± 2.90	24.50 ± 3.52	0.752
Comorbidities			
Hypertension	18 (60.0%)	15 (50.0%)	0.436
Hyperlipidemia	8 (26.7%)	7 (23.3%)	0.766
Diabetes	8 (26.7%)	7 (23.3%)	0.766
Pneumonia	8 (26.7%)	6 (20.0%)	0.542
Respiratory failure	3 (10.0%)	4 (13.3%)	0.688
APACHE II score	24.07 ± 6.54	26.03 ± 7.00	0.266
SOFA score	10.07 ± 3.34	10.09 ± 3.23	0.330
Hs-TnI in ng/mL	0.39 ± 0.32	0.48 ± 0.32	0.304
NT-proBNP in pg/mL	10459.47 ± 4784.84	12871.13 ± 8681.39	0.189
PaO ₂ /FiO ₂ in mmHg	239.18 ± 96.67	252.50 ± 109.64	0.619
Lac in mmol/L	2.32 ± 1.13	2.40 ± 1.35	0.820

Continuous data are expressed as mean ± SD. Categorical variables are expressed as *n* (%). PiCCO: Pulse index continuous cardiac output; BMI: Body mass index; APACHE II: Acute physiology and chronic health evaluation II; SOFA: Sequential organ failure assessment; Hs-TnI: High-sensitive Troponin I; NT-proBNP: N-terminal pro-brain natriuretic peptide; PaO₂/FiO₂: Oxygenation index; Lac: Lactate.

plications^[19,20]. Doppler echocardiography has become a standard imaging modality for the assessment of cardiac pumping function, and can provides a number of non-invasive hemodynamic measurements. Unfortunately, its clinical utility for hemodynamic monitoring is limited by the fact that echocardiography cannot be used as a continuous monitoring procedure at the patient's bedside^[21,22]. Intra-aortic balloon pump counter-pulsation (IABP) is a widely used mechanical assist device for hemodynamic support in the clinical treatment for patients with CS due to AMI^[23]. Unfortunately, in the largest randomized controlled clinical trial (IABP-SHOCK II) where 600 patients with CS in 37 centers in Germany were enrolled, results showed that IABP support was not associated with reduced 30-d mortality compared with control^[24]. As a result, there are an increasing number of alternative methods for hemodynamic monitoring. The PiCCO system is one such alternative in clinical practice, integrating a wide array of both static and dynamic hemodynamic data through a combination of the lung heat dilution method and pulse contour analysis technique. Readings obtained from PiCCO procedures such as CVP, GEDVI and ITBVI provide more precise estimations of the cardiac preload, and are able to more accurately predict a patient's response to fluid administration^[25,26]. In addition, for the elderly with CS, the elasticity of peripheral vessels decreases and central venous access is often required in the care of critically ill patients. During PiCCO, only a small arterial thermodilution catheter is inserted into the femoral artery, then an accurate assessment and monitoring of cardiac function can be performed. For this reason, use of PiCCO is very suitable among these elderly patients.

Severity assessment is necessary for the management of patients, including decision-making for treatment choices and patient disposition. The results of the present study showed that in comparison to the control group, the PiCCO group had a significantly lower APACHE II score and SOFA score on day 1, 3 and 7 after treatment ($P < 0.05$ or $P < 0.01$). APACHE II, a severity-of-disease classification system, has been widely used to measure the illness severity among critically ill patients admitted to the intensive care unit (ICU). It has been demonstrated that the APACHE II is a very useful tool to prognosticate hospital mortality of ICU patients^[27]. On the other hand, the SOFA score is commonly used to quantify the degree of organ dysfunction/failure and the prognosis of severely ill patients^[28]. A previous study showed that the SOFA score can provide potentially valuable prognostic information for predicting long-term mortality in AMI patients^[29]. Lower APACHE II and SOFA scores indicate a decrease in disease severity. Cardiac troponin I (cTnI) is a highly sensitive, specific marker for myocardial cell injury, and is recommended for the management of patients presenting with AMI. However, Hs-TnI has been shown to be more sensitive in detecting AMI than cTnI^[30]. On the other hand, NT-proBNP is synthesized by myocytes and fibroblasts principally in the ventricles in response to

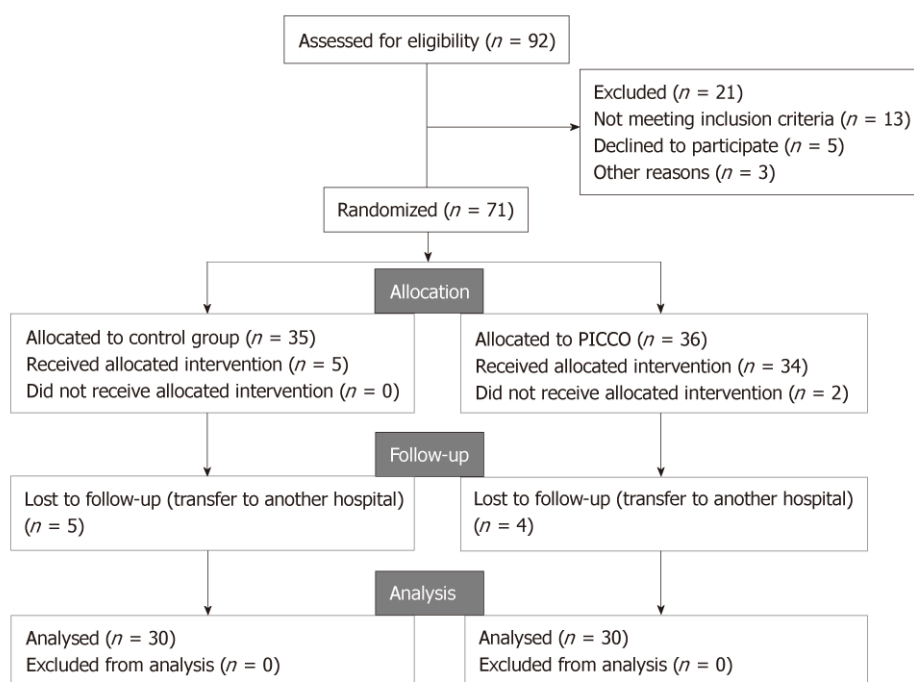


Figure 1 Flowchart of patient screening process in the study.

left ventricular filling pressure and wall stress^[31]. In a study, blood NT-proBNP levels showed a positive correlation with GEDVI and CI, suggesting that it can be used as a good indicator of cardiac preload in hemodynamically unstable patients^[32]. Lower levels of both hs-TnT and NT-proBNP in the PiCCO group were associated with sufficient coronary perfusion and improved heart function. The $\text{PaO}_2/\text{FiO}_2$ ratio is often used as an indicator of lung function in critically ill patients. Our study found that there were significant differences in the $\text{PaO}_2/\text{FiO}_2$ ratio and lactate levels on day 7 after treatment between the two groups ($P < 0.05$). This reveals that tissue oxygen supply and metabolic status of patients in the PiCCO group improved over the course of treatment. In terms of fluid management, although the infusion ($P < 0.05$) and urine volume ($P < 0.01$) during 0-24 h in the PiCCO group was significantly greater than the control group, there was no significant difference in the incidence of pulmonary edema ($P > 0.05$). Adequate fluid resuscitation is one of the most important components of early management following CS, which can effectively maintain tissue perfusion and increase aerobic metabolism.

This randomized trial showed that days on vasoactive agents, days on mechanical ventilation and EICU/CCU length of stay (all $P < 0.05$) in the PiCCO group were significantly lower than in the control group. This indicates that for the elderly patients with AMI complicated by CS, the use of PiCCO technology with the conventional treatment can guide accurate adjustments in the use of vasoactive drugs and optimize mechanical ventilation therapy, thereby improving rehabilitation and survival of patients. The patients in the PiCCO group had higher ADL scores reflective of improved functional status. ADL scoring is an instrument widely used for functional status assessment, and has been effective as a significant predictor of prognosis in elderly patients with AMI^[33].

Guided by the results of the study, we thus conclude that the clinical outcomes of elderly patients with AMI complicated by CS are improved under the monitoring and guidance of the PiCCO system. This randomized controlled trial, therefore, provides support for the use of the PiCCO technique in fluid management in critical care settings.

Table 2 Comparison of APACHE II score, SOFA score, Hs-TnI, NT-proBNP, PaO₂/FiO₂ and Lac on day 1, 3 and 7 after treatment between PiCCO and control groups

Group	No.	Treatment time	APACHE II score	SOFA score	Hs-TnI (ng/mL)	NT-proBNP (pg/ml)	PaO ₂ /FiO ₂ (mmHg)	Lac (mmol/L)
Control group	30	1 d	25.03 ± 7.35	11.31 ± 3.57	0.54 ± 0.33	13781.31 ± 9508.70	260.32 ± 111.50	2.41 ± 1.17
		3 d	22.00 ± 5.61	9.00 ± 3.39	0.40 ± 0.35	11537.69 ± 9701.62	294.94 ± 102.80	2.30 ± 1.03
		7 d	17.57 ± 4.89	7.09 ± 3.34	0.33 ± 0.28	9083.04 ± 7702.01	341.10 ± 98.05	1.99 ± 0.70
PiCCO Group	30	1 d	21.10 ± 5.95 ^a	8.37 ± 3.44 ^b	0.34 ± 0.25 ^a	8947.00 ± 5739.86 ^a	284.05 ± 127.06	2.15 ± 1.13
		3 d	17.52 ± 4.88 ^b	6.38 ± 3.05 ^b	0.17 ± 0.24 ^b	7294.83 ± 3638.23 ^a	346.96 ± 108.39	1.80 ± 0.95
		7 d	11.89 ± 3.38 ^b	4.07 ± 2.02 ^b	0.11 ± 0.14 ^b	5939.14 ± 2396.84 ^a	395.36 ± 88.20 ^a	1.52 ± 0.74 ^a

Data are present as mean ± SD. Compared with control group,

^a*P* < 0.05 and

^b*P* < 0.01. PiCCO: Pulse index continuous cardiac output; APACHE II: Acute physiology and chronic health evaluation II; SOFA: Sequential organ failure assessment; Hs-TnI: High-sensitivity cardiac troponin I; NT-proBNP: N-terminal pro-brain natriuretic peptide; PaO₂/FiO₂: Oxygenation index; Lac: Lactate.

Table 3 Infusion and urine volume in patients in PiCCO and control groups

Group	No.	Time frame	Infusion volume in mL	Urine volume in mL
Control group	30	0-1 d	2673.52 ± 945.22	1895.28 ± 717.58
		1-2 d	2806.61 ± 724.07	2111.75 ± 684.02
		2-3 d	2643.42 ± 674.59	2199.85 ± 666.83
PiCCO group	30	0-24 h	3201.07 ± 967.64 ^a	2492.67 ± 868.05 ^b
		24-48 h	3162.48 ± 770.95	2363.10 ± 755.36
		48-72 h	2842.76 ± 765.30	2502.76 ± 728.34

Data are present as mean ± SD.

^a*P* < 0.05,

^b*P* < 0.01, *vs* control group. PiCCO: Pulse index continuous cardiac output.

Table 4 Comparison of primary and secondary outcomes between PiCCO and control groups

	PiCCO group, <i>n</i> = 30	Control group, <i>n</i> = 30	<i>P</i> value
Primary outcome			
ADL score	66.83 ± 14.65	11.33 ± 5.71	0.000
Secondary outcomes			
Days on vasoactive agents	10.04 ± 2.52	12.09 ± 3.16	0.013
Duration of mechanical ventilation in d	8.13 ± 1.51	10.81 ± 2.10	0.000
Days on MV	9.21 ± 4.40	12.39 ± 4.14	0.011
EICU/CCU length of stay	12.57 ± 2.78	14.83 ± 2.59	0.005
Pulmonary edema	18 (60%)	21 (70%)	0.589

Continuous data are expressed as mean ± SD. Categorical variables are expressed as *n* (%). PiCCO: Pulse index continuous cardiac output; ADL: Activities of daily living scale; MV: Mechanical ventilation; EICU: Emergency intensive care unit; CCU: Coronary care unit.

Table 5 The monitoring indexes of PiCCO group at three point-in-times

Index	24 h	48 h	72 h	Integral analysis			Multiple comparison		
				Adjustment coefficients	F	P	P1	P2	P3
CI in L/min/m ²	2.16 ± 0.43	2.62 ± 0.39	2.88 ± 0.91	0.835	13.723	0.001	0.000	0.000	0.104
EVLWI in mL/kg	8.95 ± 1.85	7.59 ± 1.45	6.84 ± 0.82	1.024	21.669	0.000	0.001	0.000	0.018
ITBVI in mL/m ²	972.49 ± 104.28	753.91 ± 85.28	583.18 ± 65.61	0.799	199.825	0.000	0.000	0.000	0.000
GEDVI in mL/m ²	783.85 ± 88.36	604.28 ± 94.11	452.29 ± 67.89	0.948	133.476	0.000	0.000	0.000	0.000

P1 is 48 h vs 24 h, P2 is 72 h vs 24 h, and P3 is 72 h vs 48 h. CI: Cardiac index; EVLWI: Extravascular lung water index; ITBVI: Intrathoracic blood volume index; GEDVI: Global end diastolic volume index.

ARTICLE HIGHLIGHTS

Research background

Acute myocardial infarction (AMI) continues to cause morbidity and mortality, with the outcomes worsened by the development of cardiogenic shock (CS). Classical management of AMI in the setting of CS is based on hemodynamic monitoring and the use of vasopressor, as well as inotropic agents. To effectively monitor and control hemodynamic changes, techniques such as Pulse index Continuous Cardiac output (PiCCO) can be applied. In PiCCO, a central venous pressure (CVP) catheter and a thermodilution arterial line are used to monitor pressure changes thereby enabling precise evaluation of cardiovascular functions. The technique has been applied in hemodynamic assessments of conditions such as septic shock and acute respiratory syndrome. However, there is scanty utilization of the technique reported in the management of AMI complicated by CS, more so among elderly patients.

Research motivation

During AMI, compromised cardiovascular functions leading to CS often occur, and this can be fatal in the absence of timely intervention. Hemodynamic changes that manifest in the setting of CS can cause heart failure and inadequate tissue perfusion. Accurate and precise measurement of hemodynamic parameters that reflect the changes experienced during CS is critical for adequate management of the condition. There is clinical need to adopt methods and techniques that can provide the clinician with accurate hemodynamic changes for appropriate measures to be instituted to correct the condition. When this is achieved, better prognosis following CS after AMI can be attained.

Research objectives

The main objective of the study was to explore the usefulness of PiCCO in the management of elderly patients who have suffered from AMI and developed CS. Accordingly, the study aimed to evaluate and compare various hemodynamic parameters reflective of vascular tone and myocardial contractility among patients who received the PiCCO services and the control group, which was not assigned to receive PiCCO. A further objective was to compare the clinical outcomes and functional status, as described by daily activity life scores, in addition to the duration of hospitalization between the two groups.

Research methods

This was a prospective clinical trial study involving patients who satisfied predetermined inclusion criteria, which included being over 65-years-old and having suffered from AMI, together with encountering CS. All participants or their legal representatives provided written informed consent to participate in the study, which received ethical approval from the Review Board of the PLA General Hospital, Beijing, China. Diagnosis of AMI was confirmed using classic clinical techniques such as ECG readings, echocardiogram findings and determination of cardiac troponin I and creatine kinase-MB levels. On the other hand, CS was established by clinical observation of features consistent with hypoperfusion, and measurements of blood pressure changes during the cardiac cycle. The PiCCO procedure was conducted by insertion of a CVP catheter and a thermodilution arterial line. These allowed for the measurement of cardiac output functions and hemodynamic parameters. Other information gathered during the study included patients' biodata and history of prevailing comorbidities, as well as biomarkers of AMI. Additionally, details regarding the use of vasoactive agents, mechanical ventilation and length of hospitalization in the emergency and critical care units were gathered. Differences between the groups were analyzed using the SPSS 17.0 software with two-sided t-tests and chi-square tests used for continuous and categorical variables, respectively. Multiparametric analysis was performed using ANOVA and, in all cases, a $P < 0.05$ was considered statistically significant.

Research results

This study provides promising outcomes in the use of PiCCO among elderly patients being managed for AMI with accompanying CS. Compared to the control group, patients who received PiCCO services displayed statistically significant lower APACHE II and SOFA scores, as well as lower levels of hs-TnI and NT-proBNP. Similarly, there were generally lower lactate

levels, and a diminished oxygenation index among patients in the PiCCO group on day 7 after treatment. Infusion and urine volumes were evidently higher ($P < 0.01$) in the PiCCO group in the first day after treatment; thereafter, no differences in these parameters were discernible on subsequent days between the two groups. There was an appreciable increase in the functional health status of patients in the PiCCO, as demonstrated by the greater ADL scores ($P < 0.001$). Moreover, patients in this group needed less critical care support, use of mechanical ventilation, and blood pressure modifying drugs compared to the control group (all $P < 0.05$). The difference in the incidence of pulmonary edema, although significantly higher among the control group, did not reach the threshold for statistical significance ($P = 0.589$). Considering indicators of cardiac function and vascular competence, the levels of EVLWI, ITBVI and GEDVI were all significantly lower at 48 h and 72 h as compared to 24 h after initiation of the PiCCO procedure ($P < 0.001$).

Research conclusions

Our study provides clinical data that supports the need to consider applying PiCCO in managing elderly patients who have AMI that has been further confounded by CS. Improved precision in the monitoring of cardiovascular and hemodynamic changes empowers the clinician to implement appropriate and timely interventions to maintain systemic functions. Importantly, there is undisputable benefits with regards to reduced length and, by inference, cost of hospitalizations when the PiCCO technique is used. Additional positive outcomes of using PiCCO concerns the improved prognosis as manifested in better ADL scores. Based on the study findings and resources permitting, we argue for the consideration to employ the PiCCO procedure when attending to elderly patients with AMI who have also developed CS. More studies involving this technique and incorporating more, and diverse patient groups are needed to provide threshold clinical evidence that can influence future practice in managing these conditions.

Research perspectives

Arising from the present study, it is evident that the application of PiCCO can go beyond its traditional use in septic shock and respiratory distress syndrome. Improved clinical outcomes observed among patients who received the PiCCO procedure call for conscious efforts to explore this technique more routinely among related groups of patients. For greater application, more robust data involving clinical trials in other population segments and geographical settings need to be generated to contribute to the pool of evidence in support of the utility of this method in managing AMI confounded by CS.

REFERENCES

- 1 **Chien DK**, Huang MY, Huang CH, Shih SC, Chang WH. Do elderly females have a higher risk of acute myocardial infarction? A retrospective analysis of 329 cases at an emergency department. *Taiwan J Obstet Gynecol* 2016; **55**: 563-567 [PMID: 27590383 DOI: 10.1016/j.tjog.2016.06.015]
- 2 **Khalid L**, Dhakam SH. A review of cardiogenic shock in acute myocardial infarction. *Curr Cardiol Rev* 2008; **4**: 34-40 [PMID: 19924275 DOI: 10.2174/157340308783565456]
- 3 **Hochman JS**, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med* 1999; **341**: 625-634 [PMID: 10460813 DOI: 10.1056/NEJM199908263410901]
- 4 **Hochman JS**, Sleeper LA, White HD, Dzavik V, Wong SC, Menon V, Webb JG, Steingart R, Picard MH, Menegus MA, Boland J, Sanborn T, Buller CE, Modur S, Forman R, Desvigne-Nickens P, Jacobs AK, Slater JN, LeJemtel TH; SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. One-year survival following early revascularization for cardiogenic shock. *JAMA* 2001; **285**: 190-192 [PMID: 11176812 DOI: 10.1001/jama.285.2.190]
- 5 **Batchelor WB**, Anstrom KJ, Muhlbaier LH, Grosswald R, Weintraub WS, O'Neill WW, Peterson ED. Contemporary outcome trends in the elderly undergoing percutaneous coronary interventions: results in 7,472 octogenarians. National Cardiovascular Network Collaboration. *J Am Coll Cardiol* 2000; **36**: 723-730 [PMID: 10987591 DOI: 10.1016/s0735-1097(00)00777-4]
- 6 **DeGeare VS**, Stone GW, Grines L, Brodie BR, Cox DA, Garcia E, Wharton TP, Boura JA, O'Neill WW, Grines CL. Angiographic and clinical characteristics associated with increased in-hospital mortality in elderly patients with acute myocardial infarction undergoing percutaneous intervention (a pooled analysis of the primary angioplasty in myocardial infarction trials). *Am J Cardiol* 2000; **86**: 30-34 [PMID: 10867088 DOI: 10.1016/s0002-9149(00)00824-9]
- 7 **Perny J**, Kimmoun A, Perez P, Levy B. Evaluation of cardiac function index as measured by transpulmonary thermodilution as an indicator of left ventricular ejection fraction in cardiogenic shock. *Biomed Res Int* 2014; **2014**: 598029 [PMID: 25013790 DOI: 10.1155/2014/598029]
- 8 **Cottis R**, Magee N, Higgins DJ. Haemodynamic monitoring with pulse-induced contour cardiac output (PiCCO) in critical care. *Intensive Crit Care Nurs* 2003; **19**: 301-307 [PMID: 14516759 DOI: 10.1016/s0964-3397(03)00063-6]
- 9 **Liu X**, Ji W, Wang J, Pan T. Application strategy of PiCCO in septic shock patients. *Exp Ther Med* 2016; **11**: 1335-1339 [PMID: 27073445 DOI: 10.3892/etm.2016.3040]
- 10 **Zhang Z**, Xu X, Yao M, Chen H, Ni H, Fan H. Use of the PiCCO system in critically ill patients with septic shock and acute respiratory distress syndrome: a study protocol for a randomized controlled trial. *Trials* 2013; **14**: 32 [PMID: 23374652 DOI: 10.1186/1745-6215-14-32]
- 11 **Muller L**, Candela D, Nyonyama L, Mattatia L, Suehs C, Fabbro-Peray P, Louart G, de La Coussaye JE, Jaber S, Leone M, Lefrant JY; AzuRéa group. Disagreement between pulse contour analysis and transpulmonary thermodilution for cardiac output monitoring after routine therapeutic interventions in ICU

- patients with acute circulatory failure. *Eur J Anaesthesiol* 2011; **28**: 664-669 [PMID: [21562424](#) DOI: [10.1097/EJA.0b013e328346adda](#)]
- 12 **Huber W**, Umgelter A, Reindl W, Franzen M, Schmidt C, von Delius S, Geisler F, Eckel F, Fritsch R, Siveke J, Henschel B, Schmid RM. Volume assessment in patients with necrotizing pancreatitis: a comparison of intrathoracic blood volume index, central venous pressure, and hematocrit, and their correlation to cardiac index and extravascular lung water index. *Crit Care Med* 2008; **36**: 2348-2354 [PMID: [18596637](#) DOI: [10.1097/CCM.0b013e3181809928](#)]
 - 13 **Zhang YB**, Han JQ, Guo K, Yang M, Jin JR, Chang H, Chen DM, Wang YH, Zhou RB, He YB. Role of PiCCO in monitoring elderly acute myocardial infarction patients with cardiac shock. *Zhonghua Laonian Xinnaoxueguanbing Zazhi* 2017; **19**: 708-711 [DOI: [10.3969/j.issn.1009-0126.2017.07.009](#)]
 - 14 **Segal E**, Katzenelson R, Berkenstadt H, Perel A. Transpulmonary thermodilution cardiac output measurement using the axillary artery in critically ill patients. *J Clin Anesth* 2002; **14**: 210-213 [PMID: [12031755](#) DOI: [10.1016/S0952-8180\(02\)00345-8](#)]
 - 15 **Monnet X**, Persichini R, Ktari M, Jozwiak M, Richard C, Teboul JL. Precision of the transpulmonary thermodilution measurements. *Crit Care* 2011; **15**: R204 [PMID: [21871112](#) DOI: [10.1186/cc10421](#)]
 - 16 **Bendjelid K**. When to recalibrate the PiCCO? From a physiological point of view, the answer is simple. *Acta Anaesthesiol Scand* 2009; **53**: 689-690 [PMID: [19419373](#) DOI: [10.1111/j.1399-6576.2009.01919.x](#)]
 - 17 **Kolte D**, Khera S, Aronow WS, Mujib M, Palaniswamy C, Sule S, Jain D, Gotsis W, Ahmed A, Frishman WH, Fonarow GC. Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. *J Am Heart Assoc* 2014; **3**: e000590 [PMID: [24419737](#) DOI: [10.1161/JAHA.113.000590](#)]
 - 18 **Yoo YP**, Kang KW, Yoon HS, Myung JC, Choi YJ, Kim WH, Park SH, Jung KT, Jeong MH; Korean Acute Myocardial Infarction Registry Investigators. One-year clinical outcomes in invasive treatment strategies for acute ST-elevation myocardial infarction complicated by cardiogenic shock in elderly patients. *J Geriatr Cardiol* 2013; **10**: 235-241 [PMID: [24133510](#) DOI: [10.3969/j.issn.1671-5411.2013.03.008](#)]
 - 19 **Chatterjee K**. The Swan-Ganz catheters: past, present, and future. A viewpoint. *Circulation* 2009; **119**: 147-152 [PMID: [19124674](#) DOI: [10.1161/CIRCULATIONAHA.108.811141](#)]
 - 20 **Rossello X**, Vila M, Rivas-Lasarte M, Ferrero-Gregori A, Sans-Roselló J, Duran-Cambra A, Sionis A. Impact of Pulmonary Artery Catheter Use on Short- and Long-Term Mortality in Patients with Cardiogenic Shock. *Cardiology* 2017; **136**: 61-69 [PMID: [27553044](#) DOI: [10.1159/000448110](#)]
 - 21 **Steiner HA**, Hasin Y. Echo is the preferred modality for hemodynamic monitoring in the cardiac intensive care unit. *World J Cardiovasc Dis* 2012; **2**: 165-167 [DOI: [10.4236/wjcd.2012.23028](#)]
 - 22 **Khan SS**, Rich JD. Novel technologies and devices for monitoring and treating pulmonary arterial hypertension. *Can J Cardiol* 2015; **31**: 478-488 [PMID: [25840097](#) DOI: [10.1016/j.cjca.2015.01.040](#)]
 - 23 **Prondzinsky R**, Lemm H, Swyter M, Wegener N, Unverzagt S, Carter JM, Russ M, Schlitt A, Buerke U, Christoph A, Schmidt H, Winkler M, Thiery J, Werdan K, Buerke M. Intra-aortic balloon counterpulsation in patients with acute myocardial infarction complicated by cardiogenic shock: the prospective, randomized IABP SHOCK Trial for attenuation of multiorgan dysfunction syndrome. *Crit Care Med* 2010; **38**: 152-160 [PMID: [19770739](#) DOI: [10.1097/CCM.0b013e3181b78671](#)]
 - 24 **Thiele H**, Schuler G, Neumann FJ, Hausleiter J, Olbrich HG, Schwarz B, Hennersdorf M, Empen K, Fuernau G, Desch S, de Waha S, Eitel I, Hambrecht R, Böhm M, Kurovski V, Lauer B, Minden HH, Figulla HR, Braun-Dullaues RC, Strasser RH, Rochor K, Maier SK, Möllmann H, Schneider S, Ebelst H, Werdan K, Zeymer U. Intraaortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock: design and rationale of the Intraaortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial. *Am Heart J* 2012; **163**: 938-945 [PMID: [22709745](#) DOI: [10.1016/j.ahj.2012.03.012](#)]
 - 25 **Marik PE**, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. *Annals of Intensive Care* 2011; **11**: 1 [DOI: [10.1186/2110-5820-1-1](#)]
 - 26 **Saugel B**, Huber W, Nierhaus A, Kluge S, Reuter DA, Wagner JY. Advanced Hemodynamic Management in Patients with Septic Shock. *Biomed Res Int* 2016; **2016**: 8268569 [PMID: [27703980](#) DOI: [10.1155/2016/8268569](#)]
 - 27 **Zhou XY**, Ben SQ, Chen HL, Ni SS. A comparison of APACHE II and CPIS scores for the prediction of 30-day mortality in patients with ventilator-associated pneumonia. *Int J Infect Dis* 2015; **30**: 144-147 [PMID: [25461659](#) DOI: [10.1016/j.ijid.2014.11.005](#)]
 - 28 **Arts DG**, de Keizer NF, Vroom MB, de Jonge E. Reliability and accuracy of Sequential Organ Failure Assessment (SOFA) scoring. *Crit Care Med* 2005; **33**: 1988-1993 [PMID: [16148470](#) DOI: [10.1097/01.ccm.0000178178.02574.ab](#)]
 - 29 **Huang SS**, Chen YH, Lu TM, Chen LC, Chen JW, Lin SJ. Application of the Sequential Organ Failure Assessment score for predicting mortality in patients with acute myocardial infarction. *Resuscitation* 2012; **83**: 591-595 [PMID: [22198421](#) DOI: [10.1016/j.resuscitation.2011.12.014](#)]
 - 30 **Lim SH**, Lin ZW. Update on the use of cardiac markers in the diagnosis of acute coronary syndrome. *J Acute Med* 2013; **3**: 125-131 [DOI: [10.1016/j.jacme.2013.08.001](#)]
 - 31 **Möllmann H**, Weber M, Elsässer A, Nef H, Dill T, Rixe J, Schmitt J, Sperzel J, Hamm CW. NT-ProBNP predicts rhythm stability after cardioversion of lone atrial fibrillation. *Circ J* 2008; **72**: 921-925 [PMID: [18503217](#) DOI: [10.1253/circj.72.921](#)]
 - 32 **Yamanouchi S**, Kudo D, Endo T, Kitano Y, Shinozawa Y. Blood N-terminal proBNP as a potential indicator of cardiac preload in patients with high volume load. *Tohoku J Exp Med* 2010; **221**: 175-180 [PMID: [20505308](#) DOI: [10.1620/tjem.221.175](#)]
 - 33 **Nakajima H**, Yoshioka J, Totsuka N, Miyazawa I, Usui T, Urasawa N, Kobayashi T, Mochidome T. Activities of daily living as an additional predictor of complications and outcomes in elderly patients with acute myocardial infarction. *Clin Interv Aging* 2016; **11**: 1141-1147 [PMID: [27601890](#) DOI: [10.2147/CIA.S107136](#)]

Efficacy and safety of tranexamic acid in elderly patients with intertrochanteric fracture: An updated meta-analysis

Xin-Die Zhou, Jin Li, Guo-Ming Fan, Yong Huang, Nan-Wei Xu

ORCID number: Xin-Die Zhou (0000-0003-4948-0191); Jin Li (0000-0003-1284-529X); Guo-Ming Fan (0000-0003-4422-3663); Yong Huang (0000-0003-1944-3656); Nan-Wei Xu (0000-0001-6927-3312).

Author contributions: Zhou XD and Li J contributed equally to this work; Zhou XD, Huang Y, and Xu NW designed the research; Zhou XD, Li J, and Fan GM performed the research; Zhou XD and Li J contributed new reagents/analytic tools; Zhou XD, Li J, and Xu NW analyzed the data; and Zhou XD, Li J, and Huang Y wrote the paper.

Supported by (in part) National Natural Science Foundation of China, No. 81702179; and Major Scientific and Technological Project of Changzhou Municipal Commission of Health and Family Planning, No. ZD201809.

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

PRISMA 2009 Checklist statement: The guidelines of the PRISMA 2009 Statement have been adopted.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and

Xin-Die Zhou, Yong Huang, Nan-Wei Xu, Department of Orthopedics, The Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, Changzhou 213003, Jiangsu Province, China

Jin Li, Guo-Ming Fan, Department of Orthopedic Surgery, the Second Affiliated Hospital of Jiaxing University, Jiaxing 314000, Zhejiang Province, China

Corresponding author: Yong Huang, MD, Doctor, Full Professor, Department of Orthopedics, The Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, Changzhou 213003, Jiangsu Province, China. huangyong@njmu.edu.cn

Telephone: +86-519-88123506

Fax: +86-519-88123506

Abstract

BACKGROUND

Intertrochanteric fracture (ITF) is a common type of injury, and nearly 30% of ITF patients die in the first 12 mo, especially the elderly with limited activity. Tranexamic acid (TXA) has been widely used in reducing traumatic and surgical bleeding, however, the paucity of studies regarding its use in orthopedic trauma surgery has limited its integration into this field, which may benefit most from TXA. The safety of TXA in this group has not achieved a consensus.

AIM

This meta-analysis was designed to investigate the efficacy and safety of TXA in elderly ITF patients undergoing surgery.

METHODS

Databases, including Medline and PubMed, were searched for randomized controlled trials (RCTs) that were published before October 2018 and that addressed the efficacy and safety of TXA in patients who underwent ITF surgery. The Consolidated Standards of Reporting Trials 2010 Statement Checklist was used to assess the methodological quality of each study. Trials without and with heterogeneity were compared by fixed-effects analysis and random-effects analysis, respectively. For each study, odds ratio (OR) and 95%CI and mean differences and 95%CI were calculated for dichotomous and continuous outcomes, respectively. The Power and Sample Size Program software was used to calculate power and sample size. Stability of the results was assessed via sensitivity analysis.

RESULTS

A total of 836 patients from eight RCTs were subjected to meta-analysis. TXA

the use is non-commercial. See:
<http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: January 22, 2019

Peer-review started: January 23, 2019

First decision: January 27, 2019

Revised: February 15, 2019

Accepted: March 16, 2019

Article in press: March 16, 2019

Published online: June 6, 2019

P-Reviewer: Anand A, Emara KM, Tangtrakulwanich B

S-Editor: Gong ZM

L-Editor: Wang TQ

E-Editor: Wang J



treatment compared with the control group significantly reduced postoperative blood loss (95%CI, -20.83 to -7.93 mL, $P < 0.0001$), hidden blood loss (95%CI, -213.67 to -64.43 mL, $P = 0.0003$), and total blood loss (95%CI, -332.49 to -23.18 mL, $P = 0.02$) by weighted mean differences of -14.38, -139.05, and -177.83 mL, respectively. However, no significant difference was observed between groups for analysis of intraoperative blood loss. The meta-analysis also proved that the usage of TXA in ITFs may not significantly increase the incidence of deep venous thrombosis. Allogeneic blood transfusion data showed that significantly fewer patients in the TXA group (42%) required transfusion than the control group (95%CI, 0.36 to 0.69; $P < 0.0001$).

CONCLUSION

In ITF surgery, intravenous administration of TXA reduces the risk of hidden blood loss and the need for allogeneic transfusion, without increasing thrombotic risk.

Key words: Tranexamic acid; Intertrochanteric fracture; Blood loss; Randomized controlled trial; Meta-analysis

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Intertrochanteric fracture (ITF) is a common type of injury in the elderly population. Although minimally invasive surgical therapy has been routinely performed, the overall blood loss volume may still be much larger than that observed. Tranexamic acid (TXA) has been widely used in reducing surgical bleeding, however, the paucity of studies regarding its use in ITF surgery has limited its integration into this field. Thus, in order to investigate the efficacy and safety of TXA administration in elderly ITF patients, we meta-analyzed the relevant literature regarding the potential risks and benefits of TXA in ITF surgery.

Citation: Zhou XD, Li J, Fan GM, Huang Y, Xu NW. Efficacy and safety of tranexamic acid in elderly patients with intertrochanteric fracture: An updated meta-analysis. *World J Clin Cases* 2019; 7(11): 1302-1314

URL: <https://www.wjgnet.com/2307-8960/full/v7/i11/1302.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v7.i11.1302>

INTRODUCTION

Hip fractures are a common type of injuries, but the incidence increases rapidly and will surpass 6.3 million by 2050^[1,2]. In the United States, more than 250000 hip fractures occur annually and mostly in the elderly, and the 1-year mortality rates range from 14% to 36%, because of the frequently associated osteoporosis^[3,4]. As one of the two subgroups of hip fractures (the other subgroup is femoral neck fractures), nearly 30% of intertrochanteric fracture (ITF) patients die in the first 12 mo, especially the elderly with limited activity^[5]. The major problems for the high mortality are the return to the preoperative level of activity and the dependence in daily routines^[6]. Consequently, nearly half of these patients require assistance in daily living activities, and 25% need long-term care after treatments^[7]. The functional outcomes and mortality are associated with several factors, especially perioperative anemia and operative blood loss^[8,9]. With the improvement of surgical methods, minimally invasive surgical therapy has significantly reduced trauma with reliable efficacy. However, the overall blood loss volume may be much larger than that observed. As reported, the median total blood loss in patients with extra-capsular fracture of the hip is 2100 mL^[10]. To prevent and reduce the blood loss during the perioperative period, researchers have proposed various methods, such as permissive hypotension, topical freezing saline, thromboplastic agent, auto-transfusion devices, erythropoietin administration, autologous blood transfusion, and anti-fibrinolytic agents^[11-13]. Despite the effectiveness, these methods are still faced by many defects.

Tranexamic acid (TXA), a synthetic derivative of amino acid lysine, competitively inhibits the activation of plasminogen to plasmin, the serine protease, via binding to Kringle domains. TXA is also a competitive inhibitor of tissue plasminogen activator

via blocking the lysine-binding sites of plasminogen^[14]. Nowadays, TXA has been widely used in reducing traumatic and surgical bleeding^[15]. A large trial involving 20,211 adult trauma patients reported that early administration of TXA safely and effectively reduced the risk of death in bleeding trauma patients^[16]. If TXA was given to all patients with, or at risk of, traumatic bleeding, this would reduce the number of deaths by 120,000 per annum worldwide^[16]. However, the optimum time may be within three hours, and otherwise, the treatment would be ineffective. Because of its benefit demonstrated in several clinical trials^[17,18], TXA has gained interest in orthopedic and trauma surgery recently. Since significant investigations of its use in joint replacement and spine surgery were reported^[15,19], wide incorporation of TXA into the everyday practice of these surgeons has been promoted. Large prospective studies and meta-analyses demonstrate the effectiveness and safety of TXA in total knee and hip arthroplasty^[15,20]. Clinical trials prove that TXA is effective in reducing blood loss in spine surgery without incremental risk or complications^[21,22]. Although the use of TXA in arthroplasty and spine surgery has been verified and extensively studied, the paucity of studies regarding its use in orthopedic trauma has limited its integration into this field, which may benefit most from TXA.

Recently, more studies focus on the use of TXA in hip fractures^[10,23]. Lei *et al*^[23] reported that TXA significantly reduced postoperative hidden blood loss in ITF patients undergoing proximal femoral nail antirotation (PFNA). Tengberg *et al*^[10] found that TXA significantly reduced total blood loss in patients with extracapsular hip fractures. However, the safety of TXA in this group has not achieved a consensus. Thus, in order to investigate and help determine the efficacy and safety of TXA administration in reducing bleeding and transfusion in elderly ITF patients, we meta-analyzed the relevant literature regarding the potential risks and benefits of TXA in ITF surgery.

MATERIALS AND METHODS

This meta-analysis was performed according to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses'^[24].

Inclusion criteria and search strategy for meta-analysis

This meta-analysis evaluated randomized controlled trials (RCTs) that were published in English and investigated the efficacy and safety of TXA both in and after operation. Studies involving any type of fracture fixation were involved, while other types of surgery including arthroscopy and hemiarthroplasty were excluded. Articles with the diagnosis not being ITF were excluded. Studies providing only abstracts or protocols were excluded. The participants were adults who had undergone ITF fixation, regardless of the type or size of internal fixation material, anesthesia, postoperative care, or different methods or doses of TXA administration. We searched Medline and PubMed for the publications in English (up to October 2018), using the words of "hip fracture", "intertrochanteric fracture", and "tranexamic acid", as well as their extended words, without other limits. Full-texts were obtained if the titles and abstracts did not allow us to include or exclude the studies.

Intervention and data extraction for outcomes

In the meta-analysis, different authors used the search strategy to independently scan the titles and abstracts for appropriate articles. Duplicates were firstly removed on Endnote X6. When any of the above vital information was uncertain, we retrieved the full article for further scrutiny, or directly contacted the authors of individual trials to acquire further information if necessary. The following data were extracted: (1) Name of first author and publication time; (2) Demographics, gender, and age of participants; (3) Methods and doses of TXA administration; (4) Anesthesia; (5) Operative methods and related information; (6) Follow-up time; (7) Blood loss; (8) Postoperative hemoglobin (Hb) and hematocrit (Hct) changes; (9) Transfusion-related information; and (10) All kinds of complications. The extracted data were then entered independently by two reviewers. Any disagreement was solved by a consensus through discussion with a review team. Primary outcomes including blood loss, transfusion, and complications were estimated.

Validity assessment

Two of the authors independently assessed the methodological quality of each article according to the Consolidated Standards of Reporting Trials 2010 Statement Checklist (2010 CONSORT statement) for RCTs^[25], and the scores ranged from 0 to 25. Disagreements were resolved by discussion. The quality of evidence of outcomes was judged according to the Grading of Recommendations Assessment, Development and

Evaluation (GRADE) criteria, with five factors (risk of bias, inconsistency, indirectness, imprecision, and publication bias) which may downgrade the quality level of evidence. The recommendation level of evidence was classified into four categories: High, moderate, low, or very low. High quality meant that further research was very unlikely to change the confidence in the estimate of the effect; moderate quality indicated that further research was likely to have an important impact on our confidence in the estimate of the effect and could change the estimate; low quality implied that further research was very likely to have an important impact on our confidence in the estimate of the effect and was likely to change the estimate; and very low quality indicated that we were very uncertain about the estimate^[26].

Trial sequential analysis (TSA)

If the data is sparse, or if the test significance is repeated after adding a new trial, a meta-analysis may lead to type I and type II errors^[27,28]. TSA is analogous to the interim analysis in a single trial in which the monitoring boundaries are performed to determinate whether it is sufficient for the small value of *P* to demonstrate the desired results and whether the study should be terminated in advance. Therefore, TSA relies on quantification of the required information size, which can be calculated according to the diversity-adjusted (D^2) between trials: 5% risk of type I error, 20% risk of type II error (a power of 80%), and relative risk reduction of 20% with low risk bias (using the data of allele model).

As such, if the Z-curve crosses the TSA monitoring boundary before the required information size is reached, a sufficient level of evidence may have been established and further trials are not needed. Otherwise, continuous trials are necessary to identify the issue.

Statistical analysis

To perform this meta-analysis, two reviewers independently pooled data from each study for analysis using Review manager 5.0 (Cochrane Collaboration, Oxford, England). Dichotomous and continuous data were entered as number of events and mean \pm SD, respectively. Numerical data and measured data were compared by the *t*-test and chi-squared test, respectively. Before the data were pooled, statistical heterogeneity for each study was assessed by the chi-squared test with significance level at $P < 0.1$, and quantified by I^2 ^[29]. The origin of heterogeneity, if present, was analyzed according to differences in methodological quality, characteristics of participants, and intervention. Trials without and with heterogeneity were compared by fixed-effects analysis and random-effects analysis, respectively. For each study, odds ratio (OR) and 95%CI and mean differences and 95%CI were calculated for dichotomous and continuous outcomes, respectively. The Power and Sample Size Program software was used to calculate power and sample size. The following parameters were used: α , the type I error probability for a two-sided test; P_0 , the probability of exposure in controls; N , the number of case patients; m , the ratio of control to experimental subjects; Ψ , odd ratio of exposure in cases relative to controls. Stability of the results was assessed via sensitivity analysis. If the data was enough, subgroup analysis was conducted to explore possible heterogeneity. $P < 0.05$ was considered as significance.

RESULTS

After a detailed evaluation, eight independent RCTs^[10,23,30-35] with cumulatively 836 patients were included in the overall meta-analysis (Figure 1). Most of the RCTs were relatively well-designed and their CONSORT adherence scores ranged from 19 to 24, with a maximum score of 25. These eight trials were all focused on ITF patients, most of who underwent intramedullary nail. The characteristics of the included studies are summarized in Table 1, and the methodological quality is illustrated in Figure 2. Judgments about each risk of bias item are presented as percentages across all included studies (Figure 3). Six outcomes in this meta-analysis were evaluated utilizing the GRADE system, and all of them were important or critical, and the quality of the evidence was high for all of the six outcomes (Table 2).

Blood loss was one of the main outcomes and reported in six included studies^[10,23,30-33]. TXA treatment compared with the control group significantly reduced postoperative blood loss (95%CI, -20.83 to -7.93 mL, $P < 0.0001$, Figure 4A), hidden blood loss (95%CI, -213.67 to -64.43 mL, $P = 0.0003$, Figure 4B), and total blood loss (95%CI, -332.49 to -23.18 mL, $P = 0.02$, Figure 4C) by weighted mean differences of -14.38, -139.05 and -177.83 mL, respectively. Four studies^[10,23,30,32] including 309 patients were eligible for analysis of intraoperative blood loss, but no significant difference was observed between groups (Figure 4D). Analysis of deep venous thrombosis (DVT) from five studies^[10,23,30,33,35] showed that the incidence rates of postoperative

Table 1 Characteristic of included studies in meta-analysis

Study and year	Country	Design	TXA group	Control group	DVT PPX	Sample size (cases/controls)	No. of females (cases/controls, %)	Surgical procedure	Anesthesia method	Drainage	Transfusion trigger	Follow-up	QAS
Mohib_2015	Pakistan	DB-RCT	15 mg/kg, IV, twice	Normal saline	Enoxaparin	50/50	58/52	Not mentioned	Not mentioned	Not mentioned	< 7g/dL	Discharge	21
Baruah_2016	India	RCT	15 mg/kg, IV	Normal saline	Not mentioned	30/30	20/16.7	DHS	Spinal anaesthesia	Yes	< 8.5 g/dL	Discharge	19
Drakos_2016	Creece	DB-RCT	3 g, local administration, at the end of surgery	None	LMWH	100/100	73/79	Short Cephalo medullary Nail (GAMMA A3)	Spinal anaesthesia	None	< 8 g/dL	12 mo	21
Tengberg_2016	Denmark	DB-RCT	1 g, IV, pre-operation; 3 g, IV, post-operation	Placebo	LMWH	33/39	78.7/64.1	Short Intramedullary Nail (IMH)	Epidural analgesia	Not mentioned	< 9.96 g/dL	4 mo	24
Virani_2016	India	RCT	2 g, intramuscular and subfascial infiltration	None	Not mentioned	67/70	62/61	DHS	Spinal anaesthesia	Yes	Not mentioned	Discharge	20
Lei_2017	China	RCT	1 g, IV, pre-operation	Normal saline	Not mentioned	37/40	82.1/80.4	PFNA	Not mentioned	Yes	< 9 g/dL	1 mo	20
Tian_2018	China	RCT	10 mg/kg IV, pre-operation and post-operation	None	LMWH	50/50	62/72	Intramedullary nail	Not mentioned	Yes	< 9 g/dL	4 mo	21
Schiavone_2018	Italy	RCT	15 mg/kg, IV, start with surgery	Saline	Not mentioned	47/43	35/28	Gamma nail	Loco-regional anaesthesia, or general anaesthesia	Not mentioned	< 8.5 g/dL	3 mo	20

DB: Double blind; RCT: Randomized controlled trial; IV: Intravenous administration; DHS: Dynamic hip screw; LMWH: Low molecular weight heparin; QAS: Quality assessment score; PFNA: Proximal femoral nail antirotation.

DVT in the TXA and control groups were 2.99% and 2.20%, respectively. The meta-analysis also proved that the usage of TXA in ITFs may not significantly increase the incidence of DVT (Figure 5). Due to thromboprophylaxis, only two other studies^[10,23] reported four cases of pulmonary embolism (PE) during follow-up, and the incidence of PE decreased markedly, but without significant difference. Allogeneic blood transfusion data were provided by eight studies^[10,23,30-35], which showed that significantly fewer patients in the TXA group (42%) required transfusion than the control group (95% CI, 0.36 to 0.69; $P < 0.0001$; Figure 6).

Sensitivity analysis was conducted by deleting one study from overall pooled analysis each time so as to check the influence of the removed data on the overall data set, and no significant changes were found for the outcomes of hidden blood loss, allogeneic blood transfusion data, and thrombotic events. However, with regard to intraoperative blood loss, sensitivity analysis excluding the study of Lei *et al.*^[23] resulted in statistical significance (WMD = -50.25, 95% CI, -84.02 to -16.48, $P = 0.004$). Moreover, concerning postoperative blood loss, sensitivity analysis excluding the study of Tian *et al.*^[30] resulted in no statistical significance (WMD = -5.1, 95% CI, -19.36 to 9.15, $P = 0.48$). Regarding total blood loss, sensitivity analysis excluding the study of Baruah *et al.*^[32], Tengberg *et al.*^[10], or Lei *et al.*^[23] all led to no statistical significance.

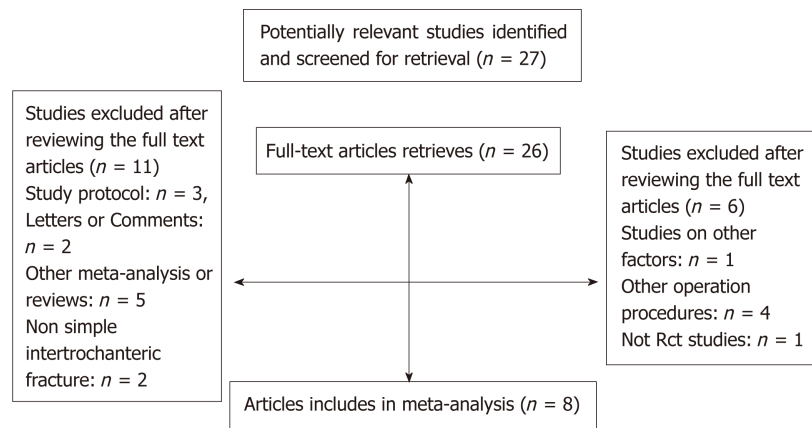


Figure 1 Flow chart of included and excluded studies.

The sample size required to identify the issue using TSA is 499 subjects. Until now, the cumulative Z-curve crossed the trial sequential monitoring boundary, indicating that TXA is associated with decreased risk of ITF and further relevant trials are unnecessary (Figure 7). The TSA-adjusted 95%CI was 0.60 to 0.83. The power analysis indicated that this study had a power of 99.9% to detect the effect of TXA on the risk of transfusion of ITF patients, assuming an OR of 0.71.

DISCUSSION

TXA has been widely used to reduce traumatic and surgical bleeding, and its safety and effectiveness in total hip and knee arthroplasty^[15,36] have also been proved recently. However, there are few studies about its safety and effectiveness in ITF surgery. Thus, in this meta-analysis, it was found the use of TXA could significantly reduce hidden blood losses as well as the number of patients who needed allogeneic transfusions, without increasing the risk of thromboembolism.

TXA is an antifibrinolytic agent that acts by binding to plasminogen and blocking the interaction of plasmin (ogen) with fibrin, thereby preventing the fibrin clot dissolution^[37]. On this account, its significant effects of reducing perioperative blood loss have been proved in various surgical procedures, including cardiac surgery with or without cardiopulmonary bypass^[38], total hip and knee replacement^[15], and prostatectomy^[39]. Moreover, TXA can significantly reduce all-cause mortality and death due to bleeding in trauma patients with significant bleeding, particularly when administered early after injury^[40]. It is predicted that TXA use in surgery and trauma would be very cost-effective and potentially life-saving^[41]. Because of the effectiveness, TXA has been increasingly used in surgical procedures. The secondary research focus is the security, especially the thromboembolism and ischemia event. In this regard, three issues that must be addressed are whether TXA influences the fibrinolytic system postoperatively, whether it also affects prothrombin time, activated partial thromboplastin time, international normalized ratio, and platelets, and whether TXA interacts with thromboprophylaxis agents. So far, the use of TXA in orthopedic surgery focuses on arthroplasties and spinal operation. Also, the outcomes are partially positive: TXA can significantly reduce blood loss and blood transfusion requirements, without intensifying the risk of thromboprophylaxis^[15,36,42]. However, studies about the use of TXA in fracture surgery are still few.

Femoral ITFs are clinically one group of common fractures and especially attack the elderly. The global number of hip fractures will increase from 1.66 million in 1990 to 6.26 million in 2050^[43]. Surgery is used for almost all femoral ITFs. Blood loss occurs as a consequence of both the fracture and surgery and thus RBC transfusion is frequently used. However, blood transfusions are correlated with an increased risk of bacterial infections, possibly increased mortality, and the substantial costs involved in the blood collection, preparation, transport, and administration^[44,45]. The incidence of DVT is as high as 80% in femoral ITF patients^[46]. Therefore, investigating the efficacy and safety of TXA in femoral ITF surgery is of great significance. As reported, TXA reduces erythrocyte transfusion but may promote a hypercoagulable state^[47]. Moreover, its efficacy is lower than observed in hip or knee arthroplasty. Three studies^[10,33,34] similarly confirm the safety and effectiveness of TXA administration in elderly patients undergoing ITF surgery. Blood loss, transfused blood units, and

Table 2 Tranexamic acid for intertrochanteric fracture

Outcomes	Illustrative comparative risks ¹ (95%CI)			No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk	Relative effect (95%CI)			
	Control	TXA				
Intraoperative blood loss. Measurement. Scale: 0 to 5; follow-up: 0.25 to 12 mo.	See comments	See comments		309 (4 studies)	++++ high	
Postoperative blood loss Drainage. Scale: 0 to 4; follow-up: 0.25 to 12 mo.	See comments	See comments		214 (3 studies)	++++ high	
Hidden blood loss. Calculation. Scale: 0 to 4; follow-up: 0.25 to 12 mo.	See comments	See comments		177 (2 studies)	++++ high	
Total blood loss. Measurement. Scale: 0 to 5; follow-up: 0.25 to 12 mo.	See comments	See comments		309 (4 studies)	++++ high	
DVT. Imageological examination; follow-up: 0.25 to 12 mo.	Study population 22 per 1000 Moderate	29 per 1000 (11 to 77)	OR = 1.34 (0.49 to 3.69)	539 (5 studies)	++++ high	
No. of transfusion. Follow-up; follow-up: 0.25 to 12 mo.	Study population 505 per 1000 Moderate	338 per 1000 (268 to 413)	OR = 0.50 (0.36 to 0.69)	836 (8 studies)	++++ high	

¹The basis for the assumed risk (*e.g.*, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI). Patient or population: Patients with intertrochanteric fracture; Settings: Inpatients; Intervention: Tranexamic acid Grading of Recommendations Assessment, Development and Evaluation. Working Group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. TXA: Tranexamic acid.

health care cost can be significantly reduced. Two other studies^[23,30] and our trial verify the effectiveness of TXA in reducing hidden blood loss. Our outcomes are consistent with previous studies, although some complications, including DVT, PE, myocardial infarction, ischemic cerebral infarction, hematoma, and infection, were observed. However, we were unable to ascertain a reliable cause of these complications, especially when there were no significant differences between groups, and only small dosage was used during the operation. The conclusions also were notarized by our meta-analysis. Our meta-analysis involving 836 participants from eight RCTs is an update of another meta-analysis^[48] involving only four studies and 514 participants, but the findings are similar.

Despite the effectiveness of TXA in femoral ITF, there are still some problems to be solved. In our meta-analysis involving eight RCTs, heterogeneity or confounding factors still exist. Five studies^[10,23,30,33,35] and two studies^[31,32] reported the use of intramedullary nail and dynamic hip screw (DHS), respectively, but one study^[34] referred to nothing. Subgroup analyses showed no significant difference between groups in the number of patients who needed transfusion with DHS (data not supplied). Moreover, the methods and dosages used in different studies are both inconsistent. Intravenous use was reported in six studies^[10,23,30,32,34,35], and the dosages ranged from 1 to 4 g in total. We found the maximal WMD of 570.8 mL compared with the largest dosage of 4 g (Figure 4C), implying that the better effectiveness accords with the larger dose on the premise of safety. Two other studies^[31,33] reported the local or intramuscular administration around the wound, and only one study^[33] found the effectiveness in reducing the blood loss and need of transfusion. It was concluded that TXA did not play a significant role in reducing postoperative blood

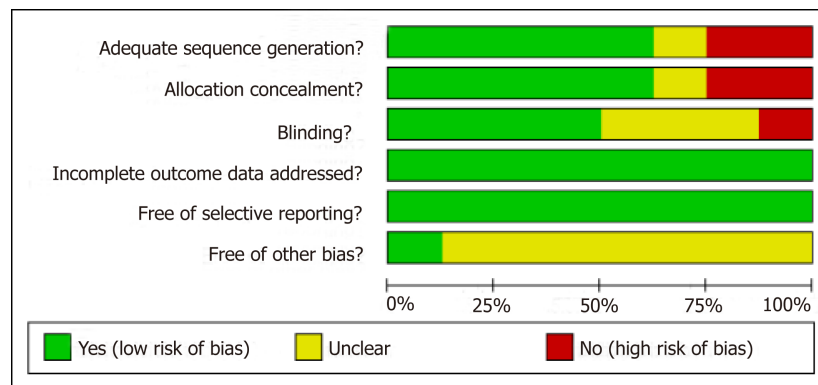


Figure 2 Risk of bias graph: Review authors' judgements about each risk of bias item presented as percentages across all included studies.

loss or blood transfusion when used locally in femoral ITF surgery^[31]. At last, the outcomes of sensitivity analyses showed the heterogeneity and instability of the outcomes of blood loss, except the hidden blood loss, which might be caused by different intervention conditions, including drainage, surgical procedures, time of operation and so on. Generally, our study verifies the effectiveness of intravenous TXA in femoral ITF, but the safety still needs more experimental verification. The use of method and dosage should also be investigated in future.

This study has some limitations. First, our meta-analysis included only eight RCTs published in English, with no unpublished data, which may lead to publication bias. Second, the differences in autotransfusion protocol, surgical techniques, drainage, low-molecular-weight heparin, operative time, dosage, and mode of administration may all contribute to between-study differences in the outcomes. Third, in most of the included studies, the follow-up time only lasted to discharge, which made long-term evaluation indices (*e.g.*, DVT and PE) unavailable.

In conclusion, our study suggests the use of TXA in ITF surgery significantly reduced the risk of hidden blood losses as well as the need for allogeneic transfusion, without increasing other complications, especially DVT, particularly for intravenous use. However, larger high-quality prospective trials are required to strengthen our conclusions, define the optimal regimen, and assess the safety and cost-effectiveness of TXA before its use is recommended in ITF surgery.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Baruah_2016	+	+	+	+	+	?
Drakos_2016	+	+	+	+	+	?
Lei_2017	+	+	+	+	+	?
Mohib_2015	+	+	+	+	+	?
Schiavone_2018	?	?	?	+	+	+
Tengberg_2016	+	+	+	+	+	?
Tian_2018	+	+	?	+	+	?
Virani_2016	+	+	?	+	+	?

Figure 3 Risk of bias summary: Review authors' judgements about each risk of bias item for each included study.

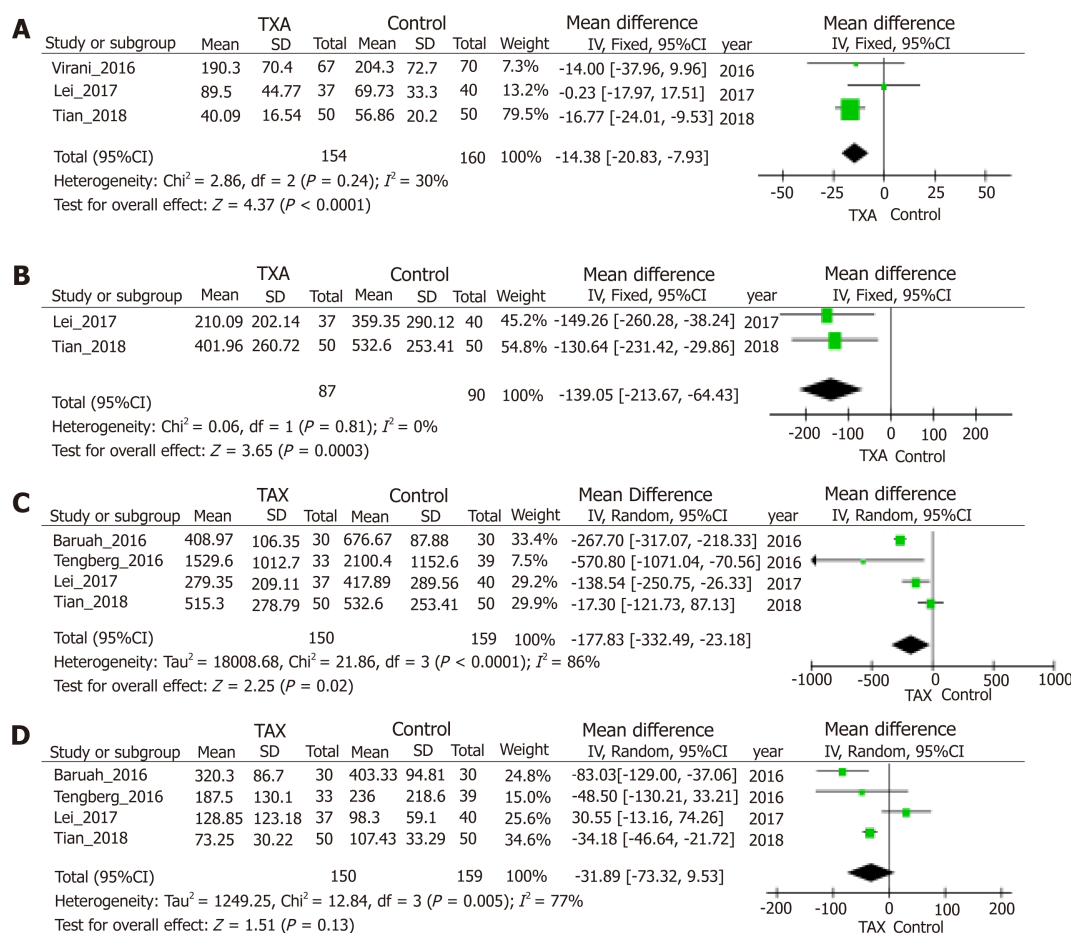


Figure 4 Forest plot diagram showing the effect of tranexamic acid on postoperative blood loss (A), hidden blood loss (B), total blood loss (C), and intraoperative blood loss (D). TXA: Tranexamic acid; CI: Confidence interval; SD: Standard deviation; IV: Inverse variance; df: Degree of freedom.

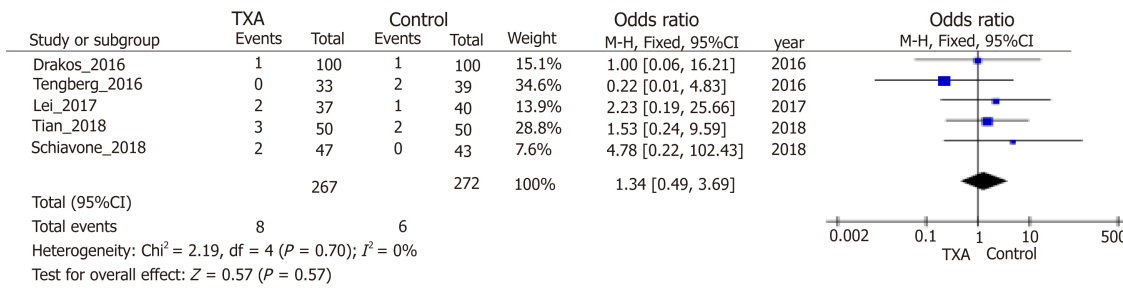


Figure 5 Forest plot diagram showing the effect of tranexamic acid on deep venous thrombosis. TXA: Tranexamic acid; CI: Confidence interval; df: Degree of freedom.

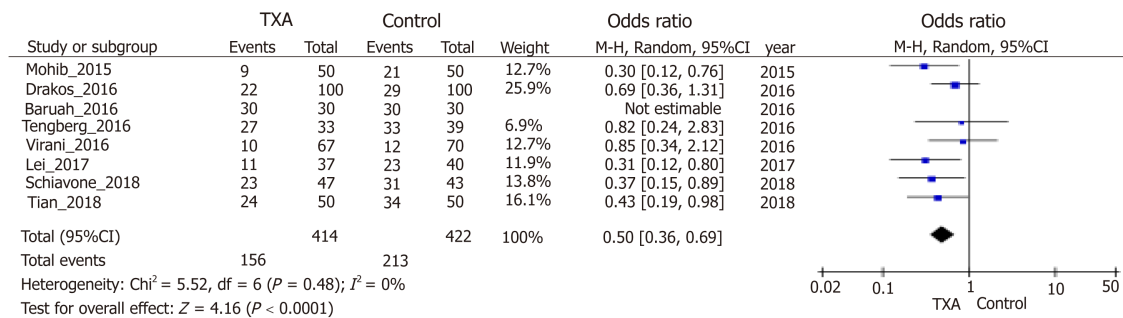


Figure 6 Forest plot diagram showing the effect of tranexamic acid on the number of patients who needed homologous transfusion. TXA: Tranexamic acid; CI: Confidence interval; df: Degree of freedom.

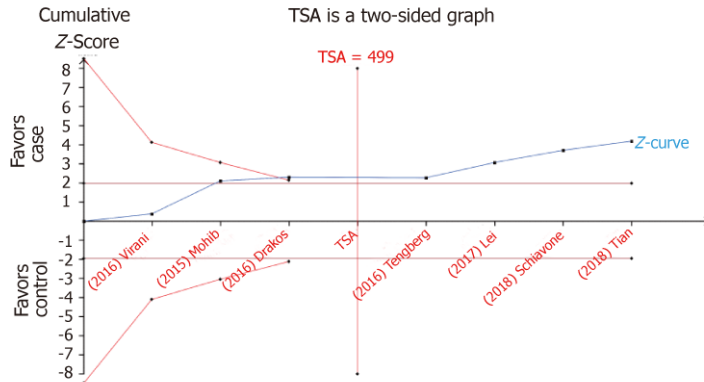


Figure 7 Trial sequential analysis of tranexamic acid on risk of intertrochanteric fractures. The diversity-adjusted required information size was calculated using $\alpha = 0.05$ (two sided), $\beta = 0.20$ (power 80%), and a relative risk reduction of 20%; the blue cumulative Z-curve was carried out using a random-effects model.

ARTICLE HIGHLIGHTS

Research background

Intertrochanteric fracture is a common type of injury, and nearly 30% of intertrochanteric fracture patients die in the first 12 mo, especially the elderly with limited activity. With the improvement of surgical methods, minimal invasive surgical therapy has significantly reduced trauma with reliable efficacy. Anyway, the overall blood loss volume may be much larger than that observed. Tranexamic acid has been widely used in reducing traumatic and surgical bleeding, however, the paucity of studies regarding its use in orthopedic trauma has limited its integration into this field, which may benefit most from tranexamic acid. The safety of tranexamic acid in this group has not achieved a consensus.

Research motivation

Recently, the impact of tranexamic acid on intertrochanteric fracture surgery has been controversial due to several studies. For instance, some studies reported that the association

between tranexamic acid and intertrochanteric fracture was significant, while others reported the opposite conclusion.

Research objectives

To date, although several studies focus on the use of tranexamic acid in hip fractures, the results have been controversial and limited. Thus, in order to investigate and help determine the efficacy and safety of tranexamic acid administration in reducing bleeding and transfusion in elderly intertrochanteric fracture patients, we meta-analyzed the relevant literature regarding the potential risks and benefits of tranexamic acid in intertrochanteric fracture surgery.

Research methods

We searched Medline and PubMed for the publications in English (up to October 2018), that focused on the effectiveness and safety of tranexamic acid on the intertrochanteric fracture. The Consolidated Standards of Reporting Trials 2010 Statement Checklist was used to assess the methodological quality of each study. Trials without and with heterogeneity were compared by fixed-effects analysis and random-effects analysis, respectively. For each study, odds ratio (OR) and 95%CI and mean differences and 95%CI were calculated for dichotomous and continuous outcomes, respectively. The Power and Sample Size Program software was used to calculate power and sample size. Stability of the results was assessed via sensitivity analysis.

Research results

After a detailed evaluation, eight independent randomized controlled trials with cumulatively 836 patients were included in the overall meta-analysis. Tranexamic acid treatment compared with the control group significantly reduced postoperative blood loss (95%CI, -20.83 to -7.93 mL, $P < 0.0001$), hidden blood loss (95%CI, -213.67 to -64.43 mL, $P = 0.0003$), and total blood loss (95%CI, -332.49 to -23.18 mL, $P = 0.02$) by weighted mean differences of -14.38, -139.05, and -177.83 mL, respectively. But no significant difference was observed between groups for analysis of intraoperative blood loss. The meta-analysis also proved that the usage of tranexamic acid in intertrochanteric fractures may not significantly increase the incidence of deep vein thrombosis. Allogeneic blood transfusion data showed that significantly fewer patients in the tranexamic acid group (42%) required transfusion than the control group (95%CI, 0.36 to 0.69; $P < 0.0001$).

Research conclusions

Our study suggests the use of tranexamic acid in intertrochanteric fracture surgery significantly reduced the risk of hidden blood losses as well as the need for allogeneic transfusion, without increasing other complications, especially deep vein thrombosis, particularly for intravenous use. However, larger high-quality prospective trials are required to strengthen our conclusions, define the optimal regimen, and assess the safety and cost-effectiveness of tranexamic acid before its use is recommended in intertrochanteric fracture surgery.

REFERENCES

- Gullberg B, Johnell O, Kanis JA. World-wide projections for hip fracture. *Osteoporos Int* 1997; **7**: 407-413 [PMID: 9425497]
- 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]
- Zuckerman JD. Hip fracture. *N Engl J Med* 1996; **334**: 1519-1525 [PMID: 8618608 DOI: 10.1056/NEJM199606063342307]
- Sheehan SE, Shyu JY, Weaver MJ, Sodickson AD, Khurana B. Proximal Femoral Fractures: What the Orthopedic Surgeon Wants to Know. *Radiographics* 2015; **35**: 1563-1584 [PMID: 26186669 DOI: 10.1148/rg.2015140301]
- Panula J, Pihlajamäki H, Mattila VM, Jaatinen P, Vahlberg T, Aarnio P, Kivelä SL. Mortality and cause of death in hip fracture patients aged 65 or older: a population-based study. *BMC Musculoskelet Disord* 2011; **12**: 105 [PMID: 21599967 DOI: 10.1186/1471-2474-12-105]
- Blomfeldt R, Törnkvist H, Eriksson K, Söderqvist A, Ponzer S, Tidermark J. A randomised controlled trial comparing bipolar hemiarthroplasty with total hip replacement for displaced intracapsular fractures of the femoral neck in elderly patients. *J Bone Joint Surg Br* 2007; **89**: 160-165 [PMID: 17322427 DOI: 10.1302/0301-620X.89B2.18576]
- Lu-Yao GL, Keller RB, Littenberg B, Wennberg JE. Outcomes after displaced fractures of the femoral neck. A meta-analysis of one hundred and six published reports. *J Bone Joint Surg Am* 1994; **76**: 15-25 [PMID: 8288658]
- Gregersen M, Borris LC, Damsgaard EM. Postoperative blood transfusion strategy in frail, anemic elderly patients with hip fracture: the TRIFE randomized controlled trial. *Acta Orthop* 2015; **86**: 363-372 [PMID: 25586270 DOI: 10.3109/17453674.2015.1006980]
- Zhang L, Yin P, Lv H, Long A, Gao Y, Zhang L, Tang P. Anemia on Admission Is an Independent Predictor of Long-Term Mortality in Hip Fracture Population: A Prospective Study With 2-Year Follow-Up. *Medicine (Baltimore)* 2016; **95**: e2469 [PMID: 26844456 DOI: 10.1097/MD.0000000000002469]
- Tengberg PT, Foss NB, Palm H, Kallemose T, Troelsen A. Tranexamic acid reduces blood loss in patients with extracapsular fractures of the hip: results of a randomised controlled trial. *Bone Joint J* 2016; **98-B**: 747-753 [PMID: 27235515 DOI: 10.1302/0301-620X.98B6.36645]
- Hughes NT, Burd RS, Teach SJ. Damage control resuscitation: permissive hypotension and massive transfusion protocols. *Pediatr Emerg Care* 2014; **30**: 651-6; quiz 657-8 [PMID: 25186511 DOI: 10.1097/PEC.0000000000000217]
- Rüegger CM, Hagmann CF, Bühner C, Held L, Bucher HU, Wellmann S; EpoRepair Investigators. Erythropoietin for the Repair of Cerebral Injury in Very Preterm Infants (EpoRepair). *Neonatology* 2015;

- 108: 198-204 [PMID: 26278911 DOI: 10.1159/000437248]
- 13 Scully C, Robinson NA. Anti-thrombotic agents. *Br Dent J* 2015; **219**: 515 [PMID: 26657425 DOI: 10.1038/sj.bdj.2015.904]
- 14 Astedt B. Clinical pharmacology of tranexamic acid. *Scand J Gastroenterol Suppl* 1987; **137**: 22-25 [PMID: 3321402]
- 15 Zhou XD, Tao LJ, Li J, Wu LD. Do we really need tranexamic acid in total hip arthroplasty? A meta-analysis of nineteen randomized controlled trials. *Arch Orthop Trauma Surg* 2013; **133**: 1017-1027 [PMID: 23615973 DOI: 10.1007/s00402-013-1761-2]
- 16 Roberts I, Shakur H, Coats T, Hunt B, Balogun E, Barnetson L, Cook L, Kawahara T, Perel P, Prieto-Merino D, Ramos M, Cairns J, Guerriero C. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health Technol Assess* 2013; **17**: 1-79 [PMID: 23477634 DOI: 10.3310/hta17100]
- 17 Chen TT, Jiandong-Liu, Wang G, Jiang SL, Li LB, Gao CQ. Combined treatment of ulinastatin and tranexamic acid provides beneficial effects by inhibiting inflammatory and fibrinolytic response in patients undergoing heart valve replacement surgery. *Heart Surg Forum* 2013; **16**: E38-E47 [PMID: 23439357 DOI: 10.1532/HSF98.20121072]
- 18 Hasegawa T, Oshima Y, Maruo A, Matsuhisa H, Tanaka A, Noda R, Yokoyama S, Iwasaki K. Intraoperative tranexamic acid in pediatric bloodless cardiac surgery. *Asian Cardiovasc Thorac Ann* 2014; **22**: 1039-1045 [PMID: 24637029 DOI: 10.1177/0218492314527991]
- 19 Wang W, Duan K, Ma M, Jiang Y, Liu T, Liu J, Hao D. Tranexamic Acid Decreases Visible and Hidden Blood Loss Without Affecting Prethrombotic State Molecular Markers in Transforaminal Thoracic Interbody Fusion for Treatment of Thoracolumbar Fracture-Dislocation. *Spine (Phila Pa 1976)* 2018; **43**: E734-E739 [PMID: 29189568 DOI: 10.1097/BRS.0000000000002491]
- 20 Poeran J, Rasul R, Suzuki S, Danninger T, Mazumdar M, Opperer M, Boettner F, Memtsoudis SG. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. *BMJ* 2014; **349**: g4829 [PMID: 25116268 DOI: 10.1136/bmj.g4829]
- 21 Cheriyan T, Maier SP 2nd, Bianco K, Slobodyanyuk K, Rattenni RN, Lafage V, Schwab FJ, Lonner BS, Errico TJ. Efficacy of tranexamic acid on surgical bleeding in spine surgery: a meta-analysis. *Spine J* 2015; **15**: 752-761 [PMID: 25617507 DOI: 10.1016/j.spinee.2015.01.013]
- 22 Raksakietisak M, Sathitkammanee B, Srisaen P, Duangrat T, Chinachoti T, Rushatamukayanunt P, Sakulpacharoen N. Two Doses of Tranexamic Acid Reduce Blood Transfusion in Complex Spine Surgery: A Prospective Randomized Study. *Spine (Phila Pa 1976)* 2015; **40**: E1257-E1263 [PMID: 26208230 DOI: 10.1097/BRS.0000000000001063]
- 23 Lei J, Zhang B, Cong Y, Zhuang Y, Wei X, Fu Y, Wei W, Wang P, Wen S, Huang H, Wang H, Han S, Liu S, Zhang K. Tranexamic acid reduces hidden blood loss in the treatment of intertrochanteric fractures with PFNA: a single-center randomized controlled trial. *J Orthop Surg Res* 2017; **12**: 124 [PMID: 28810918 DOI: 10.1186/s13018-017-0625-9]
- 24 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700 [PMID: 19622552 DOI: 10.1136/bmj.b2700]
- 25 Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; **340**: c332 [PMID: 20332509 DOI: 10.1136/bmj.c332]
- 26 Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer T, Varonen H, Vist GE, Williams JW, Zaza S; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004; **328**: 1490 [PMID: 15205295 DOI: 10.1136/bmj.328.7454.1490]
- 27 Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* 2008; **61**: 64-75 [PMID: 18083463 DOI: 10.1016/j.jclinepi.2007.03.013]
- 28 Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive--Trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *Int J Epidemiol* 2009; **38**: 287-298 [PMID: 18824466 DOI: 10.1093/ije/dyn188]
- 29 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539-1558 [PMID: 12111919 DOI: 10.1002/sim.1186]
- 30 Tian S, Shen Z, Liu Y, Zhang Y, Peng A. The effect of tranexamic acid on hidden bleeding in older intertrochanteric fracture patients treated with PFNA. *Injury* 2018; **49**: 680-684 [PMID: 29426608 DOI: 10.1016/j.injury.2018.01.026]
- 31 Virani SR, Dahapute AA, Panda I, Bava SS. Role of Local Infiltration of Tranexamic Acid in Reducing Blood Loss in Peritrochanteric Fracture Surgery in the Elderly Population. *Malays Orthop J* 2016; **10**: 26-30 [PMID: 28553444 DOI: 10.5704/MOJ.1611.013]
- 32 Baruah RK, Borah PJ, Haque R. Use of tranexamic acid in dynamic hip screw plate fixation for trochanteric fractures. *J Orthop Surg (Hong Kong)* 2016; **24**: 379-382 [PMID: 28031511 DOI: 10.1177/1602400322]
- 33 Drakos A, Raoulis V, Karatzios K, Doxariotis N, Kontogeorgakos V, Malizos K, Varitimidis SE. Efficacy of Local Administration of Tranexamic Acid for Blood Salvage in Patients Undergoing Intertrochanteric Fracture Surgery. *J Orthop Trauma* 2016; **30**: 409-414 [PMID: 26978136 DOI: 10.1097/BOT.0000000000000577]
- 34 Mohib Y, Rashid RH, Ali M, Zubairi AJ, Umer M. Does tranexamic acid reduce blood transfusion following surgery for inter-trochanteric fracture? A randomized control trial. *J Pak Med Assoc* 2015; **65**: S17-S20 [PMID: 26878513]
- 35 Schiavone A, Bisaccia M, Inkov I, Rinonapoli G, Manni M, Rollo G, Meccariello L, Vicente CI, Ceccarini P, Ruggiero C, Caraffa A. Tranexamic Acid in Pertrochanteric Femoral Fracture: Is it a Safe Drug or Not? *Folia Med (Plovdiv)* 2018; **60**: 67-78 [PMID: 29668448 DOI: 10.1515/folmed-2017-0070]
- 36 Yang ZG, Chen WP, Wu LD. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. *J Bone Joint Surg Am* 2012; **94**: 1153-1159 [PMID: 22623147 DOI: 10.1007/s00402-013-1761-2]

- 10.2106/JBJS.K.00873]
- 37 **McCormack PL.** Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis. *Drugs* 2012; **72**: 585-617 [PMID: [22397329](#) DOI: [10.2165/11209070-000000000-00000](#)]
- 38 **Fiechtner BK,** Nuttall GA, Johnson ME, Dong Y, Sujirattanawimol N, Oliver WC, Sarpal RS, Oyen LJ, Ereth MH. Plasma tranexamic acid concentrations during cardiopulmonary bypass. *Anesth Analg* 2001; **92**: 1131-1136 [PMID: [11323334](#)]
- 39 **Crescenti A,** Borghi G, Bignami E, Bertarelli G, Landoni G, Casiraghi GM, Briganti A, Montorsi F, Rigatti P, Zangrillo A. Intraoperative use of tranexamic acid to reduce transfusion rate in patients undergoing radical retropubic prostatectomy: double blind, randomised, placebo controlled trial. *BMJ* 2011; **343**: d5701 [PMID: [22012809](#) DOI: [10.1136/bmj.d5701](#)]
- 40 **Williams-Johnson JA,** McDonald AH, Strachan GG, Williams EW. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2) A randomised, placebo-controlled trial. *West Indian Med J* 2010; **59**: 612-624 [PMID: [21702233](#)]
- 41 **Guerriero C,** Cairns J, Perel P, Shakur H, Roberts I; CRASH 2 trial collaborators. Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. *PLoS One* 2011; **6**: e18987 [PMID: [21559279](#) DOI: [10.1371/journal.pone.0018987](#)]
- 42 **Elwatidy S,** Jamjoom Z, Elgamal E, Zakaria A, Turkistani A, El-Dawlatly A. Efficacy and safety of prophylactic large dose of tranexamic acid in spine surgery: a prospective, randomized, double-blind, placebo-controlled study. *Spine (Phila Pa 1976)* 2008; **33**: 2577-2580 [PMID: [19011538](#) DOI: [10.1097/BRS.0b013e318188b9c5](#)]
- 43 **Dennison E,** Mohamed MA, Cooper C. Epidemiology of osteoporosis. *Rheum Dis Clin North Am* 2006; **32**: 617-629 [PMID: [17288968](#) DOI: [10.1016/j.rdc.2006.08.003](#)]
- 44 **Carson JL,** Altman DG, Duff A, Noveck H, Weinstein MP, Sonnenberg FA, Hudson JI, Provenzano G. Risk of bacterial infection associated with allogeneic blood transfusion among patients undergoing hip fracture repair. *Transfusion* 1999; **39**: 694-700 [PMID: [10413276](#)]
- 45 **Vincent JL,** Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, Meier-Hellmann A, Nollet G, Peres-Bota D; ABC (Anemia and Blood Transfusion in Critical Care) Investigators. Anemia and blood transfusion in critically ill patients. *JAMA* 2002; **288**: 1499-1507 [PMID: [12243637](#)]
- 46 **Geerts WH,** Code KI, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after major trauma. *N Engl J Med* 1994; **331**: 1601-1606 [PMID: [7969340](#) DOI: [10.1056/NEJM199412153312401](#)]
- 47 **Zufferey PJ,** Miquet M, Quenet S, Martin P, Adam P, Albaladejo P, Mismetti P, Molliex S; tranexamic acid in hip-fracture surgery (THIF) study. Tranexamic acid in hip fracture surgery: a randomized controlled trial. *Br J Anaesth* 2010; **104**: 23-30 [PMID: [19926634](#) DOI: [10.1093/bja/aep314](#)]
- 48 **Wang W,** Yu J. Tranexamic acid reduces blood loss in intertrochanteric fractures: A meta-analysis from randomized controlled trials. *Medicine (Baltimore)* 2017; **96**: e9396 [PMID: [29384916](#) DOI: [10.1097/MD.0000000000009396](#)]



Lupus enteritis as the only active manifestation of systemic lupus erythematosus: A case report

Adalberto Gonzalez, Vaibhav Wadhwa, Fayssa Salomon, Jeevna Kaur, Fernando J Castro

ORCID number: Adalberto Jose Gonzalez (0000-0001-8108-5402); Vaibhav Wadhwa (orcid.org/0000-0002-4019-2110); Fayssa Salomon (0000-0003-0336-1824); Jeevna Kaur (0000-0003-1105-4955); Fernando J Castro (0000-0001-9968-6118).

Author contributions: Gonzalez A and Salomon F were the patient's Internal Medicine physicians and contributed to manuscript drafting. Wadhwa V was one of the patient's gastroenterologists, reviewed the literature, and contributed to manuscript writing. Kaur J reviewed the literature and contributed to manuscript writing. Castro FJ was the patient's gastroenterologist and is responsible for the revision of the manuscript. All authors issued final approval for the version to be submitted.

Informed consent statement:

Informed written consent was obtained from the patient for publication of this report and any accompanying images.

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).

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in

Adalberto Gonzalez, Fayssa Salomon, Jeevna Kaur, Department of Internal Medicine, Cleveland Clinic Florida, Weston, FL 33331, United States

Vaibhav Wadhwa, Fernando J Castro, Department of Gastroenterology and Hepatology, Cleveland Clinic Florida, Weston, FL 33331, United States

Corresponding author: Fernando Castro, MD, AGAF, Staff Physician, Department of Gastroenterology and Hepatology, Cleveland Clinic Florida, 2950 Cleveland Clinic Boulevard, Weston, FL 33331, United States. castrof@ccf.org

Telephone: +1-954-6895646

Abstract

BACKGROUND

Lupus enteritis is a rare manifestation of systemic lupus erythematosus (SLE). Diagnosis of this condition is difficult, especially in the absence of other symptoms related to active SLE. We present the case of a 25-year-old female with lupus enteritis as the sole initial manifestation of active SLE.

CASE SUMMARY

A 25-year-old African American female presented to the Emergency Department complaining of diffuse abdominal pain, diarrhea, nausea, and vomiting for 2 days. Her past medical history was significant for seasonal allergies and family history was pertinent for discoid lupus in her father and SLE in a cousin. The patient's vital signs on presentation were normal. Her physical exam was remarkable for significant lower abdominal tenderness without guarding or rigidity. A computed tomography of the abdomen and pelvis revealed marked circumferential wall thickening and edema of the proximal and mid small bowel predominantly involving the submucosa. Our main differential diagnoses were intestinal angioedema and mesenteric vein thrombosis. However, mesenteric vessels were patent, and laboratory testing for hereditary angioedema showed a normal C1 Esterase Inhibitor level and low C3 and C4 levels. Infectious work-up was negative. Autoimmune tests showed elevated anti-nuclear antibodies (ANA) (13.6), anti-Smith antibody, and anti-ribonucleoprotein (anti-RNP) antibody. The patient was diagnosed with SLE enteritis. She was maintained on bowel rest, given intravenous hydration, and started on methylprednisolone 60 mg IV daily. She had significant improvement in her abdominal pain, diarrhea, and emesis after 2 days of treatment. Steroids were tapered and maintained on Hydroxychloroquine with no relapses one year after presentation.

CONCLUSION

accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: February 12, 2019

Peer-review started: February 15, 2019

First decision: March 14, 2019

Revised: March 27, 2019

Accepted: April 18, 2019

Article in press: April 19, 2019

Published online: June 6, 2019

P-Reviewer: Rothschild BM, Tanaka H

S-Editor: Gong ZM

L-Editor: A

E-Editor: Xing YX



This case of lupus enteritis represents a rare manifestation of SLE. Diagnosis requires clinical suspicion, characteristic imaging and laboratory tests. Endoscopic appearance and biopsies usually yield non-specific findings. High dose steroids are the preferred treatment modality for moderate and severe cases.

Key words: Lupus enteritis; Systemic lupus erythematosus; Abdominal pain; Hereditary angioedema; Case report

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Lupus enteritis is a rare manifestation of systemic lupus erythematosus (SLE). It is a difficult diagnosis, especially in the absence of other symptoms related to active SLE. We present the case of a 25-year-old female with lupus enteritis as the sole initial manifestation of active SLE. The diagnosis can be made with history, physical exam, laboratory testing, and imaging. Endoscopy is not required nor recommended to make the diagnosis. Treatment depends on the severity. In this patient with moderate severity lupus enteritis, high dose steroids were an efficient initial treatment. Hydroxychloroquine was used to maintain remission.

Citation: Gonzalez A, Wadhwa V, Salomon F, Kaur J, Castro FJ. Lupus enteritis as the only active manifestation of systemic lupus erythematosus: A case report. *World J Clin Cases* 2019; 7(11): 1315-1322

URL: <https://www.wjgnet.com/2307-8960/full/v7/i11/1315.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v7.i11.1315>

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disorder affecting about 161000 to 322000 people in the United States^[1]. It typically affects multiple organ systems, including the gastrointestinal system. Lupus enteritis, defined as a vasculitis or inflammation of the small bowel, is a rare manifestation of SLE that affects 0.2% to 5.8%^[2,3] of these patients. Its diagnosis can be difficult, especially in the absence of other SLE symptoms. To our knowledge, there are only a few case reports mentioning lupus enteritis as the only and initial presentation of active SLE^[4-11]. We present the case of a 25-year-old female who presented with non-specific gastrointestinal symptoms that led to the diagnosis of lupus enteritis as the only presenting manifestation of active SLE.

CASE PRESENTATION

Chief complaints

A 25-year-old African American female presented to the Emergency Department (ED) complaining of diffuse abdominal pain, non-bloody diarrhea, nausea, and non-bloody emesis.

History of present illness

The patient's symptoms started the day prior to arrival to the ED. She described the abdominal pain as sudden onset, sharp and stabbing in quality, 10 out of 10 in intensity, and located in the suprapubic region with radiation to the right and left flanks. She denied any rash (including malar erythema), aphthous ulcers, hematuria, pleuritic chest pain, shortness of breath, or fever. Of note, several months prior, the patient had developed left eyelid swelling non-specific arthralgias (without swelling) of her wrists, fingers, and ankles. Her workup, including autoimmune laboratory tests, was inconclusive at the time. No diagnosis was made. Her arthralgias resolved spontaneously after a few days. She denied any arthralgias at the time of examination. The rest of her review of systems was non-contributory.

History of past illness

Her past medical history was significant for seasonal allergies. Her family history was significant for discoid lupus in her father, rheumatoid arthritis (RA) in one of her

paternal cousins, and SLE in another paternal cousin.

Physical examination

On presentation, the patient's vital signs were normal: 36.7 °C, heart rate of 92 bpm, blood pressure of 110/70 mmHg, respiratory rate of 18, and oxygen saturation of 100% on room air. Her abdominal exam revealed normal bowel sounds, mild abdominal distention but no lesions, scars, or hernias. There was significant lower abdominal tenderness without guarding or rigidity.

Laboratory examinations

Initial laboratory testing included a complete blood count (CBC) and comprehensive metabolic panel (CMP) (Table 1). The patient had leukopenia with a WBC count of 3.25 k/uL, lymphopenia with an absolute lymphocyte count of 740, and anemia with a hemoglobin level of 11.7 g/dL. The CMP revealed a low albumin of 3.1 but was otherwise normal.

Imaging examinations

A contrast computed tomography of the abdomen and pelvis done in the emergency room revealed marked circumferential wall thickening and edema of the proximal and mid small bowel loops predominantly involving the submucosa (Figures 1 and 2).

Further diagnostic work-up

At this point, the main differential diagnoses were intestinal angioedema and mesenteric vein thrombosis given the radiographic findings. However, the mesenteric vessels were patent, and there was no evidence of thrombosis. Laboratory testing for hereditary angioedema showed a normal C1 Esterase inhibitor level, low C3 (48 mg/dL), and low C4 (4 mg/dL) (Table 2). Autoimmune work-up revealed elevated ANA of 13.6, normal double stranded DNA antibody of 25 IU/mL (anti-dsDNA ab), high anti-Smith antibody (>8 AI), and high anti-ribonucleic protein of 6.9 AI (anti-RNP) antibody (Table 3). A urinalysis to screen for concomitant lupus nephritis did not show hematuria or red blood cell casts, and a urine protein to creatinine ratio was negative (0.1).

FINAL DIAGNOSIS

The patient was diagnosed with lupus enteritis.

TREATMENT

She was maintained on bowel rest, given intravenous (IV) hydration, and started on methylprednisolone 60 mg IV once daily.

OUTCOME AND FOLLOW-UP

She had significant improvement in her abdominal pain, diarrhea, and emesis after 2 days of treatment. She continued to have some symptoms during evening hours. Her dosing regimen was switched to methylprednisolone 20 mg IV three times daily with improvement of her nighttime symptoms as well. She was discharged on prednisone 75 mg by mouth daily and was tapered off over two weeks. She was transitioned to Hydroxychloroquine (HCQ) 200 mg by mouth twice daily. After 12 mo of treatment with HCQ, the patient did not have recurrence of symptoms.

DISCUSSION

We have presented a rare case of lupus enteritis as the sole initial manifestation of active SLE. Lupus enteritis is seen in only 13% of patients without a previous diagnosis of SLE^[12]. To our knowledge, there are only ten previously reported cases in which lupus enteritis was the only initial presentation of active SLE^[4-12].

Lupus enteritis presents with very non-specific signs and symptoms, such as abdominal pain (97%), ascites (78%), nausea (49%), vomiting (42%), diarrhea (32%), and fever (20%)^[13]. In fact, gastrointestinal activity is not one of the 17 SLICC (Systemic Lupus International Collaborating Clinics) criteria for SLE^[14]. SLE patients with gastrointestinal manifestations commonly have a high SLE Disease Activity

Table 1 Initial laboratory values

Value	Result	Reference range
White blood cells	4.26	3.70-11.0 k/uL
Hemoglobin	11.4	11.5-15.5 g/dL
Hematocrit	33.2	36.0%-46.0%
Platelet Count	182	15-400 k/uL
Sodium	141	136-144 mmol/L
Potassium	4.0	3.7-5.1 mmol/L
Bicarbonate	21	22-30 mmol/L
BUN	20	8-21 mg/dL
Creatinine	0.70	0.58-0.96 mg/dL
Glucose	95	65-100 mg/dL
Total Bilirubin	0.5	0.0-1.5 mg/dL
Alkaline Phosphatase	52	32-117 U/L
ALT	14	7-38 U/L
AST	36	13-35 U/L

Index (SLEDAI), but our patient denied symptoms of other organ involvement (Table 4). This certainly created diagnostic difficulty, and SLE was initially low on our initial list of differential diagnoses.

Laboratory testing may aid in the diagnosis of lupus enteritis. Our patient had several hematologic (leukopenia, lymphopenia, and anemia) and autoimmune (positive ANA, elevated anti-Smith antibodies, and decreased complement levels) laboratory markers that were consistent with SLE (Tables 2 and 3). Double stranded DNA was negative in her despite being seropositive in 74% of lupus enteritis cases^[13]. In comparison, laboratory studies from similar case reports yielded a positive ANA in 100%, a positive ds-DNA in 80%, low complement levels in 70%, and positive anti-Smith antibodies in 20% of cases. Lymphopenia and hypocomplementemia have been shown to correlate with the occurrence of lupus enteritis^[4,15]. Interestingly, C-reactive protein is usually not elevated in lupus enteritis^[4,13] and was not increased in our case. It is also important to rule out concomitant lupus nephritis, which is present in 65% of all lupus enteritis cases^[3] and appears to co-exist in the majority of SLE cases presenting initially with lupus enteritis^[16-18]. Screening for lupus nephritis was negative in our patient.

Imaging typically helps establish the diagnosis of lupus enteritis. Computed tomography (CT) scan of the abdomen with contrast is considered the gold standard^[3,13]. Lupus enteritis primarily causes submucosal edema of the jejunum and ileum, leading to classic findings of circumferential bowel wall thickening (known as the “target sign”), dilation of intestinal segments, and engorgement of mesenteric vessels (known as the “comb sign”) (Image 1, 2)^[19]. The “target sign”, seen on our patient’s CT scan, is not pathognomonic and may be seen in other conditions such as intestinal angioedema, mesenteric vein thrombosis, inflammatory bowel disease, and intestinal infections^[13,19]. In similar case reports, 8 of 10 patients received an abdominal CT scan and all mentioned findings of bowel wall edema, thickening, or the “target sign”. However, most authors^[4-8,10] still had difficulty making the correct diagnosis even after obtaining the CT, given its lack of specificity.

Hereditary angioedema was our initial diagnostic impression given her history of allergies and the “target sign” on CT scan, but laboratory values revealed a normal C1 esterase inhibitor (Table 2). Thrombosis was ruled out as the mesenteric vessels were found to be patent. The patient’s negative work-up for mesenteric vein thrombosis and intestinal angioedema, her remote history of nonspecific joint pain, and her family history of lupus prompted us to send autoimmune laboratory testing for SLE. Overall, our patient met five of the 17 criteria needed for SLE diagnosis according to the SLICC criteria (Table 4)^[14]. In most other similar case reports, lupus enteritis was not the initial diagnosis, with initial impressions ranging from infectious gastroenteritis^[5,8] to acute appendicitis^[6].

Endoscopy is usually not helpful nor necessary in making the diagnosis of lupus enteritis since only superficial tissue is analyzed^[19,20]. The yield of biopsy is only about 6%^[17]. Endoscopy with biopsy should be reserved to confirm or rule out alternative etiologies in cases of diagnostic uncertainty^[13]. 56% of patients reported in the literature underwent an endoscopic procedure with biopsy; 1 patient had a co-



Figure 1 Computed tomography scan of the abdomen and pelvis with contrast, transverse view. Marked circumferential wall thickening consistent with “target sign” involving small loops of proximal small bowel.

lonoscopy^[5], 2 patients had an upper endoscopy^[7,10], 1 patient had both endoscopy and colonoscopy^[4], and 1 patient had a small balloon enteroscopy (SBE). Only the small balloon enteroscopy by Chowichian *et al*^[9] yielded a definitive diagnosis of vasculitis, which re-iterates the fact that endoscopy is of low yield in lupus enteritis. In our case, we did not perform endoscopy and were able to establish a diagnosis and management plan quickly.

There are no prospective controlled studies on the treatment of lupus enteritis, but steroids seem to be the consensus first line treatment^[2-18]. According to a 2013 review by Janssens *et al*^[13], the route and dose depends on the severity of abdominal pain and the response to symptoms. Patients with mild abdominal pain tolerating oral intake should receive oral prednisone at 1 mg/kg per day; patients with severe abdominal pain or not tolerating oral intake may receive as high as methylprednisolone 250 mg to 1 g IV daily^[13]. Patients who do not respond to pulse dose steroids or have other severe SLE features, such as lupus nephritis, should be treated with IV cyclophosphamide or mycophenolate. No published guidelines or recommendations exist for the management of lupus enteritis patients who have moderately severe abdominal pain and are unable to tolerate oral intake, which was the scenario in our case. We were able to control her symptoms with methylprednisolone 60 mg IV daily.

Prognosis is generally excellent for patients with lupus enteritis given its good response to steroids. Nevertheless, it is still imperative to identify and adequately treat this disease manifestation in a timely manner as it can have a mortality of 2.7%^[13]. In addition, diagnostic uncertainty can lead to unnecessary invasive and costly procedures, such as appendectomy^[6], exploratory laparoscopy^[7,12], laparotomy, and SBE^[9]. Lupus enteritis is estimated to recur in up to 23% of cases^[13], which correlates with a lower cumulative dosage of prednisone and a shorter duration of treatment^[21]. It has not been established whether the use of hydroxychloroquine, mycophenolate, or azathioprine would prevent recurrences^[13]. The patient^[7] that was mentioned to have a follow up period of one year without remission did not mention if he was on long-term immunosuppression. Our patient did not have recurrence of lupus enteritis after 12 mo on Hydroxychloroquine (HCQ). Thus, HCQ may indeed be effective in the long-term prevention of lupus enteritis occurrence.

CONCLUSION

Lupus enteritis as the sole presenting manifestation of active SLE is very rare. Diagnosis of lupus enteritis requires a combination of high clinical suspicion from symptoms, laboratory testing, and imaging. Diagnosis does not require endoscopy. Treatment depends on the severity. In this patient with moderately severe lupus enteritis, high dose steroids were an efficient initial treatment. Our patient has remained in remission on Hydroxychloroquine.

Table 2 Hereditary angioedema evaluation

Laboratory test	Result	Reference range
Complement Deficiency Assay	75	> 60 Units
C1 Esterase Inhibitor Function	102	> 40%
C1q Complement	10	12-22 mg/dL
C1 Esterase Inhibitor	32	21-39 mg/dL
C4	4.0	13-46 mg/dL
C3	48	86-166 mg/dL

Table 3 Autoimmune evaluation

Laboratory test	Result	Reference range
ANA	13	None detected
Ds-DNA antibody	25	< 30 IU/mL
Anti-RNP antibody	6.9	< 1.0 AI
Anti-Smith antibody	> 8.0	< 1.0 AI
C4	4.0	13-46 mg/dL
C3	48	86-166 mg/dL

Table 4 Systemic Lupus International Collaboration Clinics Criteria

Criteria	Result
Acute Rash	No
Chronic Rash	No
Oral/nasal Ulcers	No
Non-scarring Alopecia	No
Arthritis	No
Serositis	No
Abnormal Urine	No
Renal	No
Neurologic	No
Hemolytic Anemia	Yes
Leukopenia/Lymphopenia	Yes
Thrombocytopenia	No
ANA	Yes
Anti-dsDNA	No
Anti-Sm	Yes
Antiphospholipid antibody	No
Low Complement	Yes



Figure 2 Computed tomography scan of the abdomen and pelvis with contrast, coronal view. There is predominantly submucosal thickening/edema in the mid abdomen, thickened small bowel loops that are minimally dilated, no transition point, and moderate ascites.

REFERENCES

- 1 **Helmick CG**, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, Liang MH, Kremers HM, Mayes MD, Merkel PA, Pillemer SR, Reveille JD, Stone JH; National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum* 2008; **58**: 15-25 [PMID: [18163481](#) DOI: [10.1002/art.23177](#)]
- 2 **Koo BS**, Hong S, Kim YJ, Kim YG, Lee CK, Yoo B. Lupus enteritis: clinical characteristics and predictive factors for recurrence. *Lupus* 2015; **24**: 628-632 [PMID: [25391541](#) DOI: [10.1177/0961203314558858](#)]
- 3 **Brewer BN**, Kamen DL. Gastrointestinal and Hepatic Disease in Systemic Lupus Erythematosus. *Rheum Dis Clin North Am* 2018; **44**: 165-175 [PMID: [29149925](#) DOI: [10.1016/j.rdc.2017.09.011](#)]
- 4 **Lin HP**, Wang YM, Huo AP. Severe, recurrent lupus enteritis as the initial and only presentation of systemic lupus erythematosus in a middle-aged woman. *J Microbiol Immunol Infect* 2011; **44**: 152-155 [PMID: [21439520](#) DOI: [10.1016/j.jmii.2009.12.001](#)]
- 5 **Mushtaq H**, Razzaque S, Ahmed K. Lupus Enteritis: An Atypical Initial Presentation of Systemic Lupus Erythematosus. *J Coll Physicians Surg Pak* 2018; **28**: 160-161 [PMID: [29394979](#) DOI: [10.29271/jcpsp.2018.02.160](#)]
- 6 **Anoosh F**, Shariff R, Ambujakshan D, Nandipati KC, Turner JW, Mandava N. Acute abdomen as initial presentation in a patient with Systemic Lupus Erythematosus. *Am J Case Rep* 2009; **10**: 55-58
- 7 **Seyyedmajidi M**, Vafaieimaneh J. Severe, Recurrent Mesenteric Vasculitis as the Initial Presentation of Systemic Lupus Erythematosus. *Zahedan J Res Med Sci* 2014; **16**: 55-56
- 8 **Shwarzbaum D**, Rubinov J, Oikonomou I. P2472 - On target: A rare case of Lupus Enteritis as the initial presentation of Systemic Lupus Erythematosus. World Congress of Gastroenterology at ACG2017 Meeting Abstracts. Orlando, FL: American College of Gastroenterology. Available from: URL: <https://eventscribe.com/2017/wcogacg2017/ajaxcalls/PosterInfo.asp?efp=S11VTUxLQVozODMy&PosterID=116114&rnd=0.3164736>
- 9 **Chowichian M**, Aanpreung P, Pongpaibul A, Charuvanij S. Lupus enteritis as the sole presenting feature of systemic lupus erythematosus: case report and review of the literature. *Paediatr Int Child Health* 2018; **1-5** [PMID: [30191770](#) DOI: [10.1080/20469047.2018.1504430](#)]
- 10 **Chung HV**, Ramji A, Davis JE, Chang S, Reid GD, Salh B, Freeman HJ, Yoshida EM. Abdominal pain as the initial and sole clinical presenting feature of systemic lupus erythematosus. *Can J Gastroenterol* 2003; **17**: 111-113 [PMID: [12605248](#) DOI: [10.1155/2003/768184](#)]
- 11 **Tu YL**, Chen LC, Ou LH, Huang JL. Mesenteric vasculitis as the initial presentation in children with systemic lupus erythematosus. *J Pediatr Gastroenterol Nutr* 2009; **49**: 251-253 [PMID: [19543109](#) DOI: [10.1097/MPG.0b013e31819f1df4](#)]
- 12 **Stoddard CJ**, Kay PH, Simms JM, Kennedy A, Hughes P. Acute abdominal complications of systemic lupus erythematosus. *Br J Surg* 1978; **65**: 625-628 [PMID: [698534](#)]
- 13 **Janssens P**, Arnaud L, Galicier L, Mathian A, Hie M, Sene D, Haroche J, Veyssier-Belot C, Huynh-Charlier I, Grenier PA, Piette JC, Amoura Z. Lupus enteritis: from clinical findings to therapeutic management. *Orphanet J Rare Dis* 2013; **8**: 67 [PMID: [23642042](#) DOI: [10.1186/1750-1172-8-67](#)]
- 14 **Petri M**, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, Bruce IN, Isenberg D, Wallace DJ, Nived O, Sturfelt G, Ramsey-Goldman R, Bae SC, Hanly JG, Sánchez-Guerrero J, Clarke A, Aranow C, Manzi S, Urowitz M, Gladman D, Kalunian K, Costner M, Werth VP, Zoma A, Bernatsky S, Ruiz-Irastorza G, Khamashta MA, Jacobsen S, Buyon JP, Maddison P, Dooley MA, van Vollenhoven RF, Ginzler E, Stoll T, Peschken C, Jorizzo JL, Callen JP, Lim SS, Fessler BJ, Inanc M, Kamen DL, Rahman A, Steinsson K, Franks AG, Sigler L, Hameed S, Fang H, Pham N, Brey R, Weisman MH, McGwin G, Magder LS. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012; **64**: 2677-2686 [PMID: [22553077](#) DOI: [10.1002/art.34473](#)]
- 15 **Lee CK**, Ahn MS, Lee EY, Shin JH, Cho YS, Ha HK, Yoo B, Moon HB. Acute abdominal pain in systemic lupus erythematosus: focus on lupus enteritis (gastrointestinal vasculitis). *Ann Rheum Dis* 2002; **61**: 547-550 [PMID: [12006332](#) DOI: [10.1136/ard.61.6.547](#)]
- 16 **Lee HA**, Shim HG, Seo YH, Choi SJ, Lee BJ, Lee YH, Ji JD, Kim JH, Song GG. Panenteritis as an Initial Presentation of Systemic Lupus Erythematosus. *Korean J Gastroenterol* 2016; **67**: 107-111 [PMID: [26907488](#) DOI: [10.4166/kjg.2016.67.2.107](#)]
- 17 **Bodh V**, Kalwar R, Sharma R, Sharma B, Mahajan S, Raina R, Jarial A. Lupus enteritis: An uncommon manifestation of systemic lupus erythematosus as an initial presentation. *J Dig Endosc* 2017; **8**: 134-136

- [DOI: [10.4103/jde.JDE_36_16](https://doi.org/10.4103/jde.JDE_36_16)]
- 18 **Patro PS**, Phatak S, Zanwar A, Lawrence A. Presumptive Lupus Enteritis. *Am J Med* 2016; **129**: e277-e278 [PMID: [27235005](https://pubmed.ncbi.nlm.nih.gov/27235005/) DOI: [10.1016/j.amjmed.2016.04.032](https://doi.org/10.1016/j.amjmed.2016.04.032)]
- 19 **Demiselle J**, Sayegh J, Cousin M, Olivier A, Augusto JF. An Unusual Cause of Abdominal Pain: Lupus Enteritis. *Am J Med* 2016; **129**: e11-e12 [PMID: [26841297](https://pubmed.ncbi.nlm.nih.gov/26841297/) DOI: [10.1016/j.amjmed.2016.01.011](https://doi.org/10.1016/j.amjmed.2016.01.011)]
- 20 **Tian XP**, Zhang X. Gastrointestinal involvement in systemic lupus erythematosus: insight into pathogenesis, diagnosis and treatment. *World J Gastroenterol* 2010; **16**: 2971-2977 [PMID: [20572299](https://pubmed.ncbi.nlm.nih.gov/20572299/) DOI: [10.3748/wjg.v16.i24.2971](https://doi.org/10.3748/wjg.v16.i24.2971)]
- 21 **Kim YG**, Ha HK, Nah SS, Lee CK, Moon HB, Yoo B. Acute abdominal pain in systemic lupus erythematosus: factors contributing to recurrence of lupus enteritis. *Ann Rheum Dis* 2006; **65**: 1537-1538 [PMID: [17038460](https://pubmed.ncbi.nlm.nih.gov/17038460/) DOI: [10.1136/ard.2006.053264](https://doi.org/10.1136/ard.2006.053264)]

Development of a biliary multi-hole self-expandable metallic stent for bile tract diseases: A case report

Makoto Kobayashi

ORCID number: Makoto Kobayashi (0000-0001-5075-268X).

Author contributions: Kobayashi M designed and performed the research, analyzed the data and wrote the paper.

Informed consent statement: Written informed consent was obtained from all patients.

Conflict-of-interest statement: Kobayashi M has a patent on the multi-hole self-expandable metallic stent with royalties paid by M.I.Tech Co., Ltd.

CARE Checklist (2016) statement: The authors have read the CARE 2016 Checklist, and the manuscript was prepared and revised according to the CARE 2016 Checklist.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: October 31, 2018

Peer-review started: October 31,

Makoto Kobayashi, Division of Gastroenterology, Yokkaichi Municipal Hospital, Yokkaichi, Mie 5108657, Japan

Corresponding author: Makoto Kobayashi, MD, PhD, Doctor, Division of Gastroenterology, Yokkaichi Municipal Hospital, 2-2-37 Shibata, Yokkaichi, Mie 5108657, Japan.

makoto-kobayashi@aroma.ocn.ne.jp

Telephone: +81-593-541111

Fax: +81-59-3521565

Abstract

BACKGROUND

Uncovered stents used for malignant obstructions in the biliary tree, especially in the hilar area, are prone to obstruction by tumor ingrowths. In comparison, however, covered stents may block bile duct branches and are at risk of migration. We have developed a multi-hole self-expandable metallic stent (MHSEMS), with a hole in each cell, to prevent the obstruction of bile duct branches. In addition, the holes may prevent migration due to small ingrowths by reducing the tension of the membrane.

CASE SUMMARY

MHSEMS were placed in five patients with a malignant obstruction and one with post-endoscopic sphincterotomy bleeding. Each MHSEMS was successfully deployed in all cases. Patients showed no complications. Two cases were reviewed. Case 1: A 74-year-old male presented with jaundice and was diagnosed with a sigmoid colon cancer and giant liver metastases in the right liver lobe. A MHSEMS was placed in the left bile duct. The jaundice improved and peroral cholangioscopy was performed. Case 2: A 90-year-old female was admitted to hospital for jaundice and diagnosed with cholangiocarcinoma. A MHSEMS was placed in the left bile duct but after 8 months the stent became obstructed by tumor ingrowth. We treated the patient by ablation therapy. A silicone cover separated the internal bile duct from the surrounding tissue, protecting the latter from thermal injury during treatment by endobiliary ablation of the re-obstruction.

CONCLUSION

A MHSEMS is a new choice of stent for biliary tract diseases.

Key words: Multi-hole self-expandable metallic stent; Malignant biliary stricture; Benign biliary stricture; Hilar biliary obstruction; Distal biliary obstruction; Endobiliary radiofrequency ablation; Case report

2018

First decision: December 5, 2018**Revised:** April 20, 2019**Accepted:** May 11, 2019**Article in press:** May 11, 2019**Published online:** June 6, 2019**P-Reviewer:** Kwon CI, Yan SL**S-Editor:** Ma RY**L-Editor:** A**E-Editor:** Wang J

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: We have developed a multi-hole self-expandable metallic stent (MHSEMS), with a hole in each cell, to prevent the obstruction of bile duct branches. In addition, the holes prevent migration due to small ingrowths by reducing the tension of the membrane. MHSEMS were placed in six patients. Each MHSEMS was successfully deployed with no complications in all cases. An ingrowth case was treated by electrical ablation therapy. Two cases were reviewed. We concluded that a MHSEMS is a new choice of stent for biliary tract diseases.

Citation: Kobayashi M. Development of a biliary multi-hole self-expandable metallic stent for bile tract diseases: A case report. *World J Clin Cases* 2019; 7(11): 1323-1329

URL: <https://www.wjgnet.com/2307-8960/full/v7/i11/1323.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v7.i11.1323>

INTRODUCTION

In biliary stenting, an uncovered self-expandable metallic stent (UCSEMS) is prone to occlusion due to tumor ingrowth^[1-4]. In comparison, when using a covered self-expandable metallic stent (CSEMS) the side branches of hepatic ducts may become blocked, preventing bile juice flow and making it difficult for a stent to be placed in the hilar area. A specific CSEMS, known as a fully CSEMS (FCSEMS), also has a risk of migration^[1-4]. Another type of stent, known as a partially covered SEMS (PCSEMS), was developed with the aim of lowering migration rates compared to CSEMS; however, this is also difficult to place in the hilar area.

In order to resolve these problems, we, together with M.I.Tech Co., Ltd (Pyeongtaek, South Korea), have developed a multi-hole self-expandable metallic stent (MHSEMS; [Figure 1](#)) with numerous holes in its cover.

A MHSEMS has a hole in each stent cell on its covering membrane. When the stent is positioned in a junction connected by side branches, bile flows inside the stent through the holes in its covering membrane. Tumors may grow through these holes but may become suppressed due to the size of the ingrowth. As a result of low membrane tension caused by the holes, the placed stent becomes fixed to surrounding tissues and is prevented from migrating. Presently, the MHSEMS is available with two types of hole sizes: small ([Figure 1A](#)) and large ([Figure 1B](#)).

In addition, a lasso attached to the distal end of the MHSEMS ([Figure 1A](#)) is helpful for stent removal. Even if an obstruction by a tumor ingrowth does occur, the silicone cover will protect the surrounding tissue and enhance any ablation effect, such as during endobiliary radiofrequency ablation (RFA), allowing the patient to be a candidate for such treatment. We treated patients with malignant biliary obstruction using MHSEMS.

CASE PRESENTATION

Case 1

Chief complaints: A 74-year-old male presented to our hospital with jaundice and liver function failure.

History of present illness: The patient had attended the outpatient department of another hospital, and liver dysfunction was identified in a regular check-up.

History of past illness: The patient had a medical history of diabetes and benign prostatic hypertrophy.

Personal and family history: A personal or family history of malignant tumors did not exist.

Physical examination upon admission: On physical examination, icterus of the patient's conjunctiva was observed. An enlarged liver was palpable in the upper right quadrant. The skin and bulbar conjunctiva were icteric.

Laboratory examinations: The laboratory findings on admission were as follows:

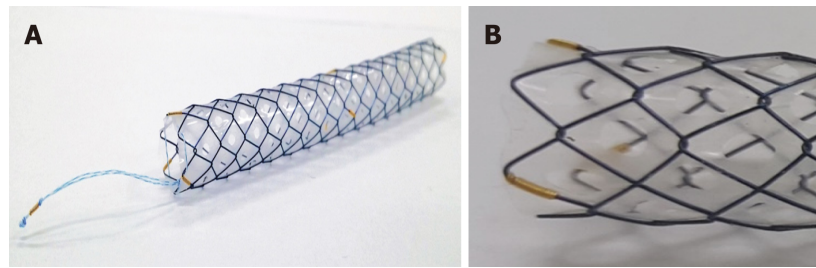


Figure 1 Multi-hole self-expandable metallic stent. A: With lasso (small-hole type); B: Large-hole type.

Aspartate trans-aminase (AST) 73 IU/L, alanine aminotransferase (ALT) 61 IU/L, alkaline phosphatase (ALP) 1962 IU/L, gamma-glutamyl transpeptidase (γ -GTP) 704 IU/L, total bilirubin (T-bil) 8.8 mg/dL, direct bilirubin (D-bil) 5.1 mg/dL, carcinoembryonic antigen (CEA) 1117.1 ng/mL and carbohydrate antigen 19-9 (CA19-9) 32 U/mL.

Imaging examinations: Computed tomography (CT) of the abdomen revealed a sigmoid colon tumor and multiple liver metastases, including a right liver lobe that was almost totally occupied by tumors; the left intrahepatic bile duct was remarkably dilated (Figure 2A).

Case 2

Chief complaints: A 90-year-old female was referred to our hospital by the family doctor because of jaundice.

History of present illness: The patient did not have a history of jaundice.

History of past illness: The patient had a past history of hypertension.

Personal and family history: But she had no personal or family history of malignant tumors.

Physical examination upon admission: On physical examination, the patient's skin was icteric. A large gall bladder was palpable in the upper right quadrant.

Laboratory examinations: AST 371 IU/L, ALT 418 IU/L, ALP 4273 IU/L, γ -GTP 1367 IU/L, T-bil 9.6 mg/dL, D-bil 6.3 mg/dL, CEA 1.5 ng/mL and CA19-9 39 U/mL.

Imaging examinations: An intrahepatic biliary dilation was detected by computerized tomography (Figure 2B).

FINAL DIAGNOSIS

Case 1

The patient was diagnosed with obstructive jaundice caused by a sigmoid colon cancer and multiple liver metastases.

Case 2

The patient was diagnosed with obstructive jaundice caused by hilar cholangiocarcinoma.

TREATMENT

Case 1

We selected MHSEMS to keep the left bile duct free from invasion by the right lobe tumor, the presence of the latter meaning the right liver lobe was not functioning (Figure 2A). A MHSEMS was placed from the left bile duct to the common bile duct (CBD; Figure 3A and B).

Case 2

We selected a MHSEMS because of an expectation of reduced tumor ingrowth. The patient had a MHSEMS placed from the right hepatic duct to the common bile duct to protect the duct from ingrowth and to keep the bile duct patent from left and

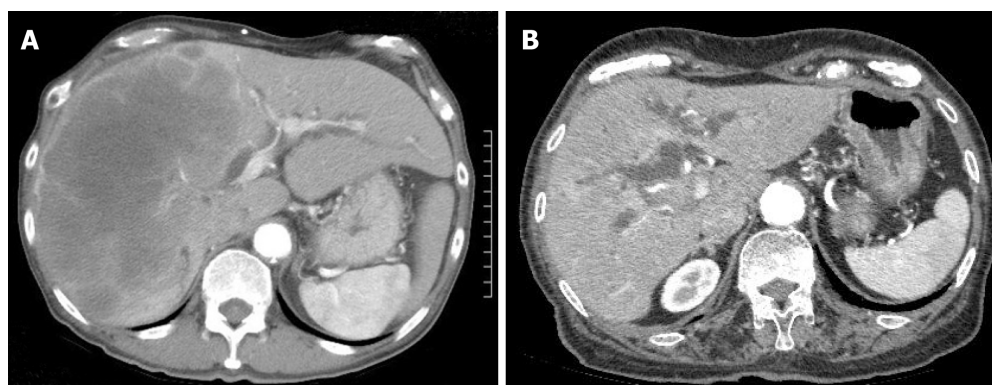


Figure 2 Computerized tomography images. A: A large metastasis in the right liver lobe; B: Intrahepatic biliary dilation.

posterior branches (Figure 4A).

OUTCOME AND FOLLOW-UP

Case 1

After MHSEMS placement, T-bil decreased from 11.9 mg/dL to 1.3 mg/dL. Nine days after stent placement, cholangiography was undertaken using a direct peroral cholangioscope with a slim endoscope. An intrahepatic bile duct branch was successfully filled with contrast material from a slim endoscope through the stent's holes. The metallic mesh was found not to be buried in tissue but was fixed to the wall because of the low tension of the covering membrane (Figure 3C). Thirty-six days after MHSEMS placement, the patient died due to cancer. However, the total bilirubin level had been kept almost within normal range after stent placement.

Case 2

After MHSEMS placement, T-bil decreased from 9.6 mg/dL to 1.1 mg/dL. However, after 8 mo, the stent became obstructed by tumor ingrowth. We treated the patient by ablation therapy and a monopolar catheter (Figure 4B). After ablation therapy, a tube stent was placed and liver function improved. The patient was transferred to another hospital in order to receive palliative medicine.

DISCUSSION

Most biliary stents may be broadly classified into two types: UCSEMS and CSEMS. An UCSEMS can be placed in a hilar lesion, but has a risk of ingrowth. In contrast, the use of a CSEMS has the disadvantage of the chance of branch obstruction occurring. Another type of stent, a PCSEMS, may reduce the risk of migration; however, it is also unusable in the hilar region. To date, these have been the main types of stents available for the treatment of biliary strictures.

In various meta-analyses undertaken, little difference was observed between the use of UCSEMS and CSEMS in terms of stent failure and patient mortality. However, stent ingrowth and migration rates differed for these two types of biliary stents. The rate of tumor ingrowth for UCSEMS was significantly higher than the rate for CSEMS. In contrast, the stent migration rate was higher for CSEMS compared with UCSEMS. In addition, meta-analyses revealed a lack of difference in the overall complication rate^[1-4]. Overall estimates by meta-analyses also revealed a lack of substantial difference between FCSEMS and PCSEMS^[1]. Compared to UCSEMS, PCSEMS did not prolong stent patency in unresectable malignant distal biliary obstructions^[5]. Identifying a need for a new type of stent, we therefore collaborated with M.I.Tech to develop a MHSEMS. This stent has many holes in its cover designed to prevent not only blockage of bile duct branches, but also stent migration.

We treated six cases showing bile duct obstructions with MHSEMS, and had a 100% success rate for stent deployment (Table 1). Stent patency was also 100% successful (Table 1). In addition, jaundice improved in all patients with a malignant stricture, while complications such as pancreatitis, bleeding and cholangitis did not occur. The mean patency duration was found to be 274 d.

The MHSEMS has been designed with a lasso at its distal end for removability. In

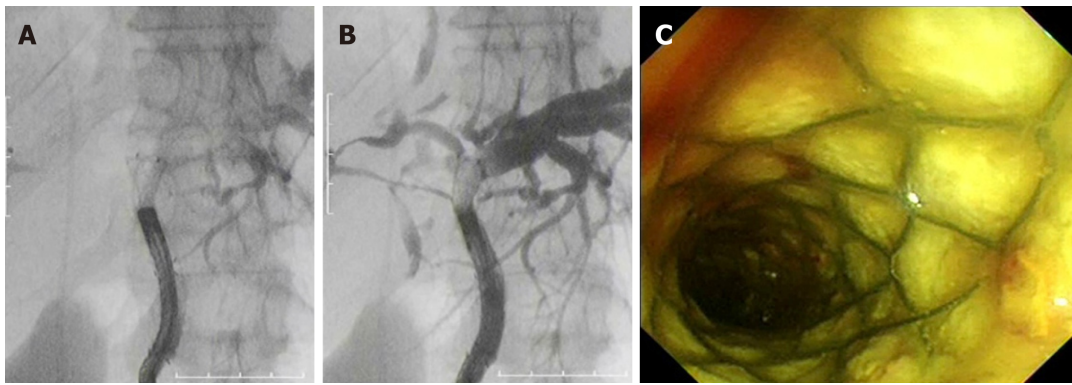


Figure 3 Cholangiography via a direct peroral cholangioscope. A, B: The right bile duct was visualized by contrast material through the stent openings; C: After cholangiography, the metallic mesh was not found buried in tissue but fixed to the bile duct wall.

the event of the stent obstructing a bile duct branch and causing cholangitis, it can be removed very early after placement because the cover prevents the stent from becoming buried in tumor tissue.

In cases of benign strictures, the MHSEMS can also be easily removed. For example, MHSEMS were inserted in six mini pigs with artificial hilar biliary strictures; after 4 wk, all stents were easily and safely taken out^[6]. For one of our studied cases, a MHSEMS was used for uncontrolled post-endoscopic sphincterotomy bleeding and was safely removed after 2 wk.

It is thought that endobiliary RFA is safe and has efficacy for unresectable malignant bile duct obstructions^[7,8]. Pertinently, the successful and safe use of UCSEMS for occlusive endobiliary RFA has been reported^[9,10]. With the use of MHSEMS, endobiliary RFA may become an even more effective and secure treatment since the insulated silicone cover can protect surrounding tissue from thermal injury.

The larger hole size of the MHSEMS is characteristic of an UCSEMS, but the smaller hole size and number is more typical of a CSEMS. With regard to preventing migration and ingrowth in a distal bile duct malignant stricture, it may be that the hole size and number need to be reduced. It would be ideal if hole size and number are adapted to the condition of each stricture.

CONCLUSION

In summary, MHSEMS may be considered a hybrid-type stent, with characteristics that fall between those of UCSEMS and CSEMS. Thus, MHSEMS may be regarded as a promising new treatment option for benign and malignant bile duct strictures.

Table 1 Characteristics and outcomes of six cases treated with multi-hole self-expandable metallic stents

Case No.	Age (yr)/sex	Diagnosis	Obstruction region	Migration	Occlusion	Ingrowth	Removal	Pancreatitis
1	74/M	Liver metastasis of colon carcinoma	Hilar bile duct	No	No	Not clear	N/A	No
2	89/F	Cholangiocarcinoma	Hilar bile duct	No	249 d	Yes	N/A	No
3	86/M	Cholangiocarcinoma	Hilar bile duct	No	329 d	Yes	N/A	No
4	48/M	Gall bladder carcinoma	Hilar bile duct	No	295 d	Yes	N/A	No
5	82/M	Pancreas head carcinoma	Distal bile duct	No	223 d	Slight	Successful	No
6	74/M	Post-endoscopic sphincterotomy bleeding	Distal bile duct	No	No	Slight	Successful (2 wk later)	No

M: Male; F: Female; N/A: Not applied.

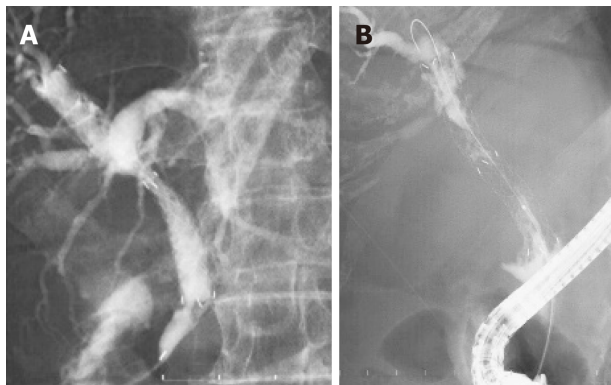


Figure 4 Cholangiography of a multi-hole self-expandable metallic stent and ablation therapy. A: The left bile duct was visualized by contrast material through the stent openings; B: Ablation therapy by monopolar catheter and endoscopic retrograde cholangiography.

REFERENCES

- 1 **Tringali A**, Hassan C, Rota M, Rossi M, Mutignani M, Aabakken L. Covered vs. uncovered self-expandable metal stents for malignant distal biliary strictures: a systematic review and meta-analysis. *Endoscopy* 2018; **50**: 631-641 [PMID: 29342491 DOI: 10.1055/s-0043-125062]
- 2 **Moole H**, Bechtold ML, Cashman M, Volmar FH, Dhillon S, Forcione D, Taneja D, Puli SR. Covered versus uncovered self-expandable metal stents for malignant biliary strictures: A meta-analysis and systematic review. *Indian J Gastroenterol* 2016; **35**: 323-330 [PMID: 27566620 DOI: 10.1007/s12664-016-0682-8]
- 3 **Almadi MA**, Barkun AN, Martel M. No benefit of covered vs uncovered self-expandable metal stents in patients with malignant distal biliary obstruction: a meta-analysis. *Clin Gastroenterol Hepatol* 2013; **11**: 27-37.e1 [PMID: 23103324 DOI: 10.1016/j.cgh.2012.10.019]
- 4 **Saleem A**, Leggett CL, Murad MH, Baron TH. Meta-analysis of randomized trials comparing the patency of covered and uncovered self-expandable metal stents for palliation of distal malignant bile duct obstruction. *Gastrointest Endosc* 2011; **74**: 321-327.e1-3 [PMID: 21683354 DOI: 10.1016/j.gie.2011.03.1249]
- 5 **Kim JY**, Ko GB, Lee TH, Park SH, Lee YN, Cho YS, Jung Y, Chung IK, Choi HJ, Cha SW, Moon JH, Cho YD, Kim SJ. Partially Covered Metal Stents May Not Prolong Stent Patency Compared to Uncovered Stents in Unresectable Malignant Distal Biliary Obstruction. *Gut Liver* 2017; **11**: 440-446 [PMID: 28208003 DOI: 10.5009/gnl16245]
- 6 **Park JS**, Jeong S, Kobayashi M, Sung W, Don HL. Efficacy, and removability of a fully covered multi-hole metal stent in a swine model of hilar biliary stricture: A feasibility study. *Endosc Int Open* 2019; **7**: e498-e503 [DOI: 10.1055/a-0846-0775]
- 7 **Steel AW**, Postgate AJ, Khorsandi S, Nicholls J, Jiao L, Vlavianos P, Habib N, Westaby D. Endoscopically applied radiofrequency ablation appears to be safe in the treatment of malignant biliary obstruction. *Gastrointest Endosc* 2011; **73**: 149-153 [PMID: 21184881 DOI: 10.1016/j.gie.2010.09.031]
- 8 **Alvarez-Sánchez MV**, Napoléon B. Review of endoscopic radiofrequency in biliopancreatic tumours with

- emphasis on clinical benefits, controversies and safety. *World J Gastroenterol* 2016; **22**: 8257-8270 [PMID: 27729733 DOI: 10.3748/wjg.v22.i37.8257]
- 9 **Yoon WJ**, Kim YT, Daglilar ES, Mino-Kenudson M, Brugge WR. Evaluation of bipolar radiofrequency ablation for occluded self-expandable metal stents in the bile duct: in vivo and in vitro study. *Endoscopy* 2015; **47**: 1167-1170 [PMID: 26111360 DOI: 10.1055/s-0034-1392252]
- 10 **Betgeri S**, Rajesh S, Arora A, Panda D, Bhadoria AS, Mukund A. Percutaneous endobiliary RFA combined with balloon-sweep for re-opening occluded metallic biliary stents. *Minim Invasive Ther Allied Technol* 2017; **26**: 124-127 [PMID: 27611763 DOI: 10.1080/13645706.2016.1235052]

Paraneoplastic leukemoid reaction in a patient with sarcomatoid hepatocellular carcinoma: A case report

Bo Hu, Xin-Ting Sang, Xiao-Bo Yang

ORCID number: Bo Hu (0000-0002-7918-2235); Xin-Ting Sang (0000-0003-1952-0527); Xiao-Bo Yang (0000-0003-1929-8866).

Author contributions: Hu B collected the patient's clinical data and wrote the paper; Sang XT and Yang XB analyzed the data and designed the report.

Informed consent statement: Consent was obtained from the patient at the time of investigations, but not at the time of writing this case report.

Conflict-of-interest statement: The authors declare that they have 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).

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Bo Hu, Xin-Ting Sang, Xiao-Bo Yang, Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

Corresponding author: Xin-Ting Sang, MD, Director, Professor, Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 1 Shuaifuyuan, Wangfujing, Beijing 100730, China.

sangxt@pumch.cn

Telephone: +86-010-69152836

Fax: +86-010-69156043

Abstract

BACKGROUND

Sarcomatoid hepatocellular carcinoma (SHC) combined with paraneoplastic leukemoid reaction (PLR), which is associated with a poor prognosis, is rarely seen in the clinic. Here, we report the case of a patient in the above situation.

CASE SUMMARY

A 75-year-old female patient with a past medical history of hypertension and cerebral infarction paid a hospital visit as a result of right upper quadrant abdominal pain and anorexia for two months. Laboratory examination revealed a white blood cell (WBC) count of 43790/ μ L, which was then increased up to 77050/ μ L. In addition, the results of bone marrow examination suggested a leukemoid reaction. Computed tomography (CT) revealed a focal hepatic mass, which was confirmed through pathological examination to be an SHC postoperatively. In addition, the WBC count had fallen to a normal level before she left the hospital. However, the patient died two and a half months after the second hospital admission.

CONCLUSION

This is a rare case of SHC combined with PLR, both of which have an extremely poor prognosis.

Key words: Paraneoplastic leukemoid reaction; White blood cells; Bone marrow examination; Sarcomatoid hepatocellular carcinoma; Poor prognosis; Case report

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Sarcomatoid hepatocellular carcinoma (SHC) is a rare histological subtype of hepatocellular carcinoma (HCC), with largely incompletely described clinical

Received: January 21, 2019**Peer-review started:** January 22, 2019**First decision:** March 9, 2019**Revised:** April 2, 2019**Accepted:** April 18, 2019**Article in press:** April 19, 2019**Published online:** June 6, 2019**P-Reviewer:** Kozarek R, Labusca L, Xavier-Elsas P**S-Editor:** Dou Y**L-Editor:** Wang TQ**E-Editor:** Xing YX

manifestations and outcomes. SHC combined with paraneoplastic leukemoid reaction (PLR), which is defined as reactive leukocytosis exceeding 50000/ μ L, is associated with a poor prognosis and is rarely seen in the clinic. A surgery or surgery-centered multidisciplinary team may benefit patients in this situation.

Citation: Hu B, Sang XT, Yang XB. Paraneoplastic leukemoid reaction in a patient with sarcomatoid hepatocellular carcinoma: A case report. *World J Clin Cases* 2019; 7(11): 1330-1336

URL: <https://www.wjgnet.com/2307-8960/full/v7/i11/1330.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v7.i11.1330>

INTRODUCTION

Leukemoid reaction is referred to as the condition in which reactive leukocytosis has exceeded 50000/ μ L, accompanied by a significant increase in the early neutrophil precursors. Typically, leukemoid reaction can serve as a paraneoplastic manifestation of various malignant tumors, including lung, gastrointestinal, genitourinary, ovarian, and head and neck cancers, as well as hepatocellular carcinoma (HCC)^[1]. Generally, the most common presentation of the paraneoplastic leukemoid reaction (PLR) is less severe and lacks an increase in the levels of inflammatory markers. It shows no response to antibiotic therapy^[2-5]. Moreover, the PLR-induced complications mainly result from increased blood viscosity, and gangrene in the foot has been described in one report^[6]. As a result, to manage PLR is indeed to treat the underlying tumor.

Sarcomatoid hepatocellular carcinoma (SHC) is characterized by the proliferation of spindle cells or bizarre giant cells^[7] and is usually associated with a dismal prognosis and high risks of recurrence and metastasis. Typically, the hepatocellular markers were negative in the malignant spindle cell component, whereas creatine kinase (CK) and vimentin were positive in most SCC patients^[8]. SHC is distinct from nonsarcomatoid liver cancer. However, it can be misdiagnosed as intrahepatic cholangiocarcinoma, making differential diagnosis necessary. PLR is even more rarely seen in SHC patients, which was fatal in our case.

CASE PRESENTATION

Chief complaints

A 75-year-old female patient presented to the hospital as a result of right upper quadrant abdominal pain. Meanwhile, she also complained of anorexia and progressive generalized weakness.

History of present illness

Patient's symptoms started two months ago with recurrent episodes of bloating.

History of past illness

The patient had a past history of hypertension and cerebral infarction that caused mild instability in walking.

Physical examination

On the first admission, her temperature was 36.4 °C, blood pressure was 100/63 mmHg, pulse rate was 82 beats/min, and respiratory rate was 16 breaths/min. Physical examination revealed tenderness in her right upper abdomen, with no evidence of any abdominal mass.

Laboratory examination

Laboratory examination showed a white blood cell (WBC) count of 43790/ μ L, with 87.1% of neutrophils, hemoglobin of 12.7 g/dL, platelets of 36200/ mm^3 , total bilirubin of 0.12 mg/dL, direct bilirubin of 0.05 mg/dL, albumin of 3.7 g/dL, aspartate aminotransferase of 18 U/L, and alanine aminotransferase of 22 U/L. In addition, tests for serum tumor markers revealed no abnormalities in the levels of α -fetoprotein (AFP; 3.4 ng/mL) and carcinoembryonic antigen (1.80 ng/mL) but elevated levels of carbohydrate antigenic determinant (CA19-9; 72.6 U/mL). In addition, the coagulation profile was within normal limits, and the results of the hepatitis panel

and human immunodeficiency virus antibody tests were negative. In view of the elevated WBC levels, the patient was discharged to the Hematology Clinic for bone marrow biopsy and other tests to rule out the possibility of blood diseases. Two weeks later, the patient was admitted again, and routine blood examination showed a WBC count of $77050/\mu\text{L}$. Subsequently, the patient developed a fever of 38.6°C , which did not subside after antibiotic infusion, and her blood WBC levels were not significantly lowered. The results of the bone marrow examination showed that the proportion of granulocyte-neutrophil nucleated cells was increased by 40%, and toxic granules could be observed (Figure 1). In addition, a peripheral smear revealed neutrophilia with band forms but no blasts. Subsequently, procalcitonin test was performed, and the result was 0.31 ng/mL , indicating a lower risk of infection. Moreover, repeat blood cultures were negative, but the WBC count was elevated continuously.

Imaging examination

Computed tomography (CT) revealed a 9.3-cm focal hepatic mass in the left lobe of the liver, along with dilatation of the intrahepatic bile duct (Figure 2). A chest radiograph suggested no abnormality.

FINAL DIAGNOSIS

Hence, symptoms, signs, and laboratory studies were negative for an infectious etiology. In summary, the elevation in WBC count was believed to be caused by a PLR, which was not a surgical contraindication.

TREATMENT

Hepatectomy for the liver mass was performed 5 d after the second hospitalization. Immediately after tumor removal, her presenting symptoms and laboratory values were improved remarkably. Typically, her WBC count had dropped to the normal level 5 d after surgery (Figure 3). Postoperative pathology examination revealed that the poorly differentiated malignant cells were positive for CD34, Vimentin, human epithelial membrane antigen, and cytokeratin 7 (CK7), while negative for CK19 (Figure 4), which was suggestive of SHC.

OUTCOME AND FOLLOW-UP

Unfortunately, the patient died two and a half months after the second discharge. Since the patient's family did not cooperate with our follow-up work, we are unable to know the specific circumstances of the patient's death.

DISCUSSION

Generally, leukemoid reaction is conventionally defined as the condition in which the peripheral WBC count has exceeded $50000/\mu\text{L}$, with a dominance of mature neutrophils, and it is related to the reactive causes outside the bone marrow, such as severe infection, poisoning, allergic reaction, drugs, or malignant tumors^[3,9,10]. After the causes of the leukemoid reaction are removed, the abnormal changes in WBC counts in blood and bone marrow can return to normal levels within a short period of time.

Specifically, a PLR is a cancer-associated leukemoid reaction. Some scholars believe that PLR is more likely to occur in malignant tumor patients at middle-age^[11]. At the same time, tumor stage is also related to the occurrence of PLR, which is particularly true for stage III-IV tumors. Notably, the underlying mechanism appears to be the production of growth factors by the tumor cells, such as granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte CSF (G-CSF), and interleukins (IL-3 and IL-6)^[11].

PLR is rarely reported in SHC, and both have dismal prognoses. SHC is a rare histological subtype of HCC, which is discovered in 3.9%-9.4% of HCC autopsy cases and 1.8% of patients with surgically resected HCC^[12-14]. However, the pathogenesis of SHC has not been fully elucidated yet, which may be associated with chronic hepatitis B, chronic hepatitis C, liver cirrhosis, preoperative radiotherapy or chemotherapy, and interventional therapy. Kim *et al.*^[15] believed that mutations in the *p53* gene might be related to the occurrence of SHC. In our case, the patient showed no abovementioned

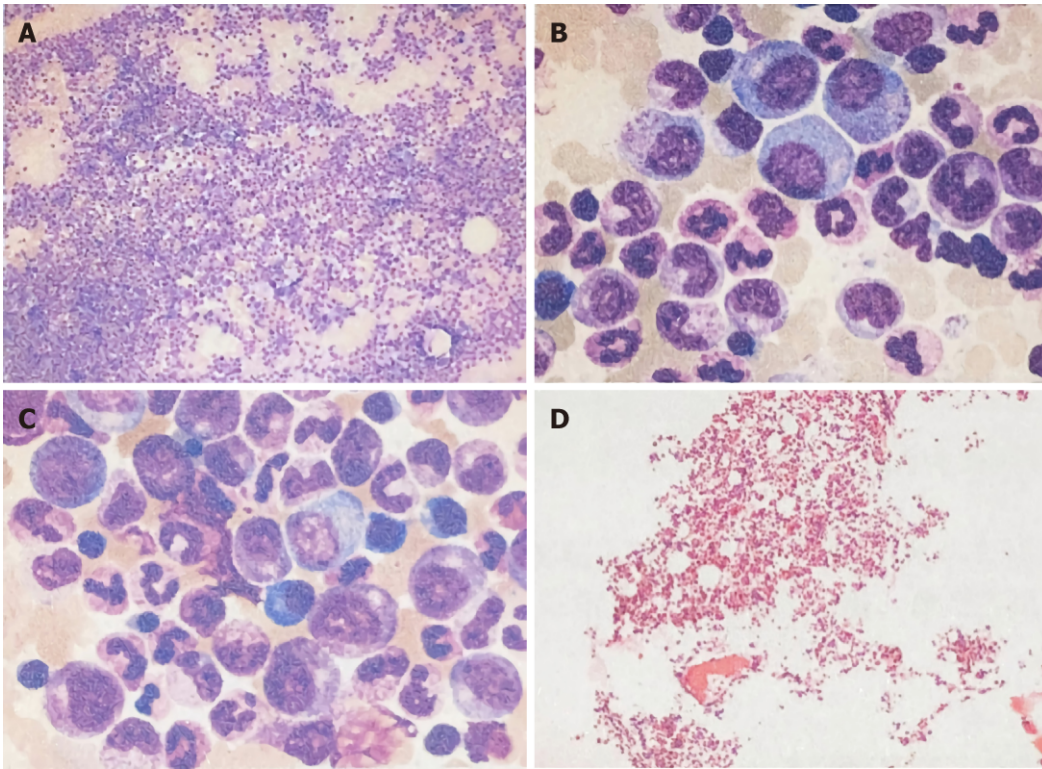


Figure 1 Bone marrow smear and bone marrow biopsy results. A-C: Bone marrow smears showed that hyperplasia was extremely active, the proportion of granulocyte-neutrophil nucleated cells increased, and most of the granules were coarse and numerous; D: Bone marrow biopsy examination showed that the hematopoietic tissue was obviously increased, the adipose tissue was reduced, the ratio of granulocytes to red blood cells was increased, and the megakaryocytes were visible.

predisposing factors and had not received any nonsurgical treatment. Some scholars call it “pure” SHC^[16,17]. Typically, SHC is characterized by high malignancy grade, rapid progression, and poor prognosis. Compared with nonsarcomatoid HCC, SHC is characterized by lower levels of bilirubin, liver enzymes, and AFP, as well as a lower FIB-4 score. In addition, central necrosis and hemorrhage can be more frequently seen in SHC than in the ordinary type of HCC^[14,18-20]. Our results are in accordance with previous studies reporting that more than 50% patients were negative for both HBsAg and hepatitis C virus antibody and had negative or low serum AFP levels. According to literature reports, some patients may have fever, but the WBC count is generally not high or is slightly elevated, suggesting the presence of noninfectious fever, which may be related to the sarcomatoid components or tumor parenchymal ischemia and necrosis. In our case, the patient developed fever after admission, with a significant increase in WBC count and neutrophil percentage, and her blood culture results were negative, which was suggestive of PLR. The WBC count in our case had dropped rapidly after surgery, which had confirmed our diagnosis.

In our case, SHC combined with a PLR was fatal, reflecting that such condition was aggressive. Shin *et al* reported a 71-year-old patient diagnosed with SHC, whose leukocyte count increased to 147800/ μ L and died on the 10th day of hospitalization, which also suggested the danger of this state. Unlike our case, the patient did not undergo surgery, and the pathological results were obtained by fine needle aspiration biopsy. We hypothesized that timely surgical treatment may be beneficial to such patient to some extent, but overall the prognosis is still poor. For malignant tumor patients with persistently unexplained elevated WBC count, PLR should be considered once infection is excluded. With regard to the relationship between PLR and sarcomatoid carcinoma, some scholars have reported cases of renal cell carcinoma and lung cancer with sarcomatous changes, accompanying PLR; however, it has not been specifically reported whether PLR is more common in sarcomatoid cancer^[21,22]. It is likely that the progression and necrosis of SHC may be associated with an increase in inflammatory cytokine response, which may thereby result in leukemoid reaction. In an article examining the relationship between PLR and solid tumors, Chakraborty *et al*^[10] reported a case of SHC with PLR who died 10 d after admission, which is earlier than most other types of tumors (such as cervical cancer, HCC, and gastric cancer). In terms of treatment, liver resection or liver transplantation is the therapeutic gold standard for such patients^[23], but the effect is still unclear. On the other hand,

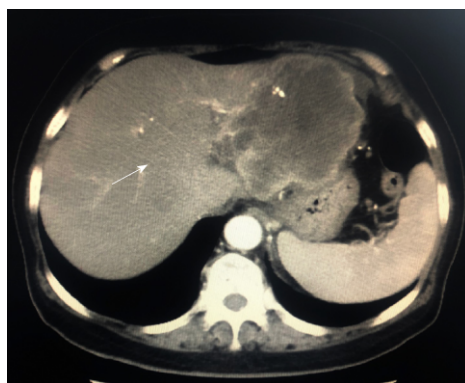


Figure 2 Computerized tomography image showing a 9.3-cm focal hepatic mass in the left lobe of the liver and dilatation of intrahepatic bile duct, as indicated by the arrow.

with actively evolving tumor treatment modalities and concepts, and knowing that optimal efficacy can rarely be achieved by a single treatment regimen, surgery-centered multidisciplinary team as a collaborative health care model has been increasingly recognized^[24], which may also benefit patients in this situation. In short, different factors that influence leukocyte elevation and tumor progression should be considered to understand their pathogenesis and to devise effective strategies for their clinical management.

As evidenced by our case, patients with malignant tumors should consider the possibility of PLR in the presence of persistently unexplained elevated levels of WBC. Nonetheless, the association of SHC with leukemoid reaction could not be concluded due to the limited data and care reports, but a prompt diagnostic approach to identify the underlying cause and early application of the most effective treatment might result in a better prognosis for such patients.

CONCLUSION

This is a rare case of SHC combined with PLR, both of which had carried an extremely poor prognosis and had been associated with shorter postoperative survival periods.

ACKNOWLEDGMENTS

We would like to express our gratitude to the participants of the study, and to Dr. Hai-Tao Zhao for his contributions in preparing the manuscript.

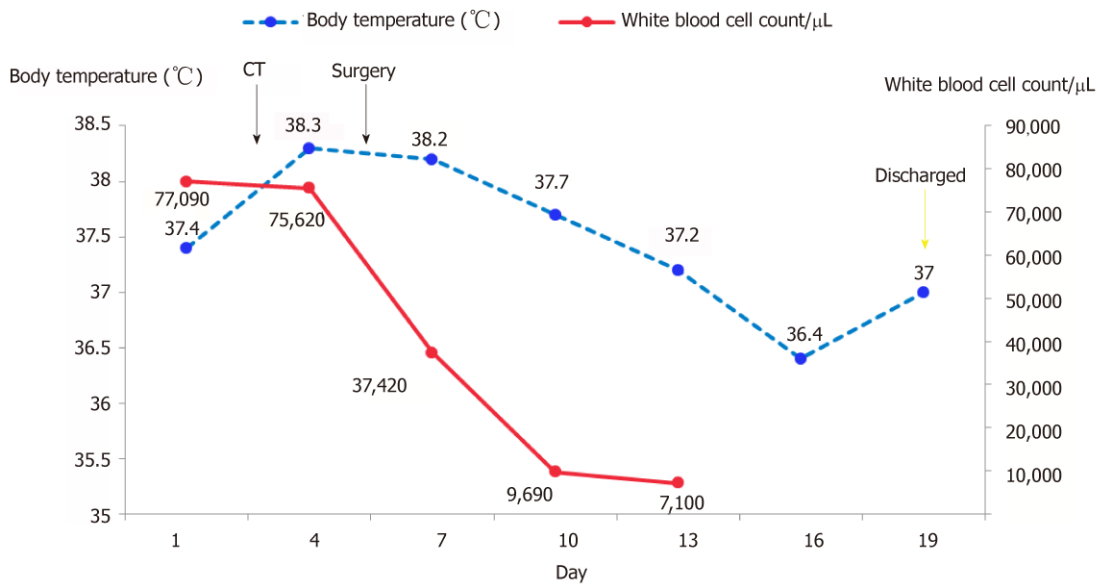


Figure 3 Illustration of the clinical course of body temperature and white blood cell counts during the second hospitalization.

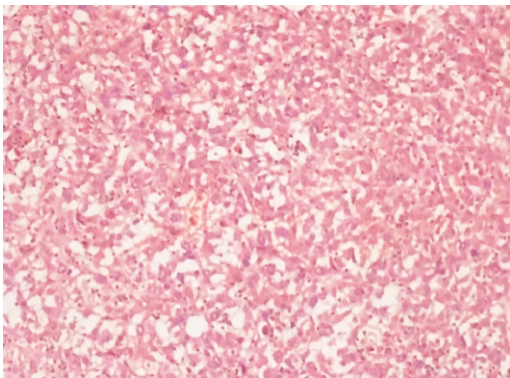


Figure 4 Microscopic image of the tumor showing poorly differentiated malignant cells suggestive of SHC.

REFERENCES

- 1 **Shin HP**, Jeon JW, Park JJ, Cha JM, Joo KR, Lee JI, Kim GY, Kang SY. A case of leukemoid reaction in a patient with sarcomatous hepatocellular carcinoma. *Korean J Hepatol* 2011; **17**: 226-228 [PMID: 22102390 DOI: 10.3350/kjhep.2011.17.3.226]
- 2 **Schniewind B**, Christgen M, Hauschild A, Kurdow R, Kalthoff H, Klomp HJ. Paraneoplastic leukemoid reaction and rapid progression in a patient with malignant melanoma: establishment of KT293, a novel G-CSF-secreting melanoma cell line. *Cancer Biol Ther* 2005; **4**: 23-27 [PMID: 15662134 DOI: 10.4161/cbt.4.1.1447]
- 3 **Sakka V**, Tsioudas S, Giamarellos-Bourboulis EJ, Giamarellou H. An update on the etiology and diagnostic evaluation of a leukemoid reaction. *Eur J Intern Med* 2006; **17**: 394-398 [PMID: 16962944 DOI: 10.1016/j.ejim.2006.04.004]
- 4 **Wilcox RA**. Cancer-associated myeloproliferation: old association, new therapeutic target. *Mayo Clin Proc* 2010; **85**: 656-663 [PMID: 20592171 DOI: 10.4065/mcp.2010.0077]
- 5 **Schmidt H**, Bastholt L, Geertsen P, Christensen IJ, Larsen S, Gehl J, von der Maase H. Elevated neutrophil and monocyte counts in peripheral blood are associated with poor survival in patients with metastatic melanoma: a prognostic model. *Br J Cancer* 2005; **93**: 273-278 [PMID: 16052222 DOI: 10.1038/sj.bjc.6602702]
- 6 **Lammel V**, Stoeckle C, Padberg B, Zweifel R, Kienle DL, Reinhart WH, Simon HU. Hypereosinophilia driven by GM-CSF in large-cell carcinoma of the lung. *Lung Cancer* 2012; **76**: 493-495 [PMID: 22420949 DOI: 10.1016/j.lungcan.2012.02.014]
- 7 **Hung Y**, Hsieh TY, Gao HW, Chang WC, Chang WK. Unusual computed tomography features of ruptured sarcomatous hepatocellular carcinoma. *J Chin Med Assoc* 2014; **77**: 265-268 [PMID: 24726675 DOI: 10.1016/j.jcma.2014.02.006]
- 8 **Shafizadeh N**, Kakar S. Hepatocellular Carcinoma: Histologic Subtypes. *Surg Pathol Clin* 2013; **6**: 367-384 [PMID: 26838979 DOI: 10.1016/j.path.2013.03.007]
- 9 **Mandal SK**, Ganguly J, Sil K, Mondal SS, Sardar D, Sarkar P. Renal cell carcinoma with paraneoplastic leucocytosis. *J Cancer Res Ther* 2015; **11**: 660 [PMID: 26458671 DOI: 10.4103/0973-1482.139388]

- 10 **Chakraborty S**, Keenportz B, Woodward S, Anderson J, Colan D. Paraneoplastic leukemoid reaction in solid tumors. *Am J Clin Oncol* 2015; **38**: 326-330 [PMID: [24145395](#) DOI: [10.1097/COC.0b013e3182a530dd](#)]
- 11 **McCoach CE**, Rogers JG, Dwyre DM, Jonas BA. Paraneoplastic Leukemoid Reaction as a Marker of Tumor Progression in Non-Small Cell Lung Cancer. *Cancer Treat Commun* 2015; **4**: 15-18 [PMID: [25932381](#) DOI: [10.1016/j.ctrc.2015.03.003](#)]
- 12 **Da Ines D**, Bailly A, Lannareix V, Petitcolin V, Boldor L, Charpy C, Abergel A, Pezet D, Garcier JM. Hepatocellular carcinoma with sarcomatous change: prompt and fatal intraabdominal recurrence after liver transplantation. *Gastroenterol Clin Biol* 2009; **33**: 590-593 [PMID: [19481391](#) DOI: [10.1016/j.gcb.2009.04.008](#)]
- 13 **Liao SH**, Su TH, Jeng YM, Liang PC, Chen DS, Chen CH, Kao JH. Clinical Manifestations and Outcomes of Patients with Sarcomatoid Hepatocellular Carcinoma. *Hepatology* 2019; **69**: 209-221 [PMID: [30014620](#) DOI: [10.1002/hep.30162](#)]
- 14 **Koo HR**, Park MS, Kim MJ, Lim JS, Yu JS, Jin H, Kim KW. Radiological and clinical features of sarcomatoid hepatocellular carcinoma in 11 cases. *J Comput Assist Tomogr* 2008; **32**: 745-749 [PMID: [18830104](#) DOI: [10.1097/RCT.0b013e3181591ccd](#)]
- 15 **Kim DG**, Park SY, Kim H, Chun YH, Moon WS, Park SH. A comprehensive karyotypic analysis on a newly established sarcomatoid hepatocellular carcinoma cell line SH-J1 by comparative genomic hybridization and chromosome painting. *Cancer Genet Cytogenet* 2002; **132**: 120-124 [PMID: [11850072](#) DOI: [10.1016/s0165-4608\(01\)00543-x](#)]
- 16 **Seok JY**, Kim YB. [Sarcomatoid hepatocellular carcinoma]. *Korean J Hepatol* 2010; **16**: 89-94 [PMID: [20375648](#) DOI: [10.3350/kjhep.2010.16.1.89](#)]
- 17 **Wang QB**, Cui BK, Weng JM, Wu QL, Qiu JL, Lin XJ. Clinicopathological characteristics and outcome of primary sarcomatoid carcinoma and carcinosarcoma of the liver. *J Gastrointest Surg* 2012; **16**: 1715-1726 [PMID: [22767081](#) DOI: [10.1007/s11605-012-1946-y](#)]
- 18 **Llovet JM**, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology* 1999; **30**: 1434-1440 [PMID: [10573522](#) DOI: [10.1002/hep.510300629](#)]
- 19 **Pompili M**, Saviano A, de Matthaeis N, Cucchetti A, Ardito F, Federico B, Brunello F, Pinna AD, Giorgio A, Giulini SM, De Sio I, Torzilli G, Fornari F, Capussotti L, Guglielmi A, Piscaglia F, Aldrighetti L, Caturelli E, Calise F, Nuzzo G, Rapaccini GL, Giulante F. Long-term effectiveness of resection and radiofrequency ablation for single hepatocellular carcinoma ≤ 3 cm. Results of a multicenter Italian survey. *J Hepatol* 2013; **59**: 89-97 [PMID: [23523578](#) DOI: [10.1016/j.jhep.2013.03.009](#)]
- 20 **Liu C**, Xiao GQ, Yan LN, Li B, Jiang L, Wen TF, Wang WT, Xu MQ, Yang JY. Value of α -fetoprotein in association with clinicopathological features of hepatocellular carcinoma. *World J Gastroenterol* 2013; **19**: 1811-1819 [PMID: [23555170](#) DOI: [10.3748/wjg.v19.i11.1811](#)]
- 21 **Huang W**, Wang F, Li Y, Duan F, Yu Z. Leukemoid reaction in sarcomatoid renal cell carcinoma: a two-case report. *World J Surg Oncol* 2014; **12**: 100 [PMID: [24745762](#) DOI: [10.1186/1477-7819-12-100](#)]
- 22 **Wang D**, Zhang H, Yu F, Fang B. Extreme leukocytosis and leukemoid reaction associated with the lung sarcomatoid carcinoma: an unusual case report. *Int J Gen Med* 2016; **10**: 7-9 [PMID: [28096688](#) DOI: [10.2147/IJGM.S102524](#)]
- 23 **Levi Sandri GB**, Ettorre GM, Colasanti M, De Werra E, Mascianà G, Ferraro D, Tortorelli G, Sciuto R, Lucatelli P, Pizzi G, Visco-Comandini U, Vennarecci G. Hepatocellular carcinoma with macrovascular invasion treated with yttrium-90 radioembolization prior to transplantation. *Hepatobiliary Surg Nutr* 2017; **6**: 44-48 [PMID: [28261594](#) DOI: [10.21037/hbsn.2017.01.08](#)]
- 24 **Wang K**, Zhang H, Xia Y, Liu J, Shen F. Surgical options for intrahepatic cholangiocarcinoma. *Hepatobiliary Surg Nutr* 2017; **6**: 79-90 [PMID: [28503555](#) DOI: [10.21037/hbsn.2017.01.06](#)]

Multiple synchronous anorectal melanomas with different colors: A case report

Yan-Tao Cai, Li-Chen Cao, Chen-Fang Zhu, Feng Zhao, Bao-Xing Tian, Shan-Yu Guo

ORCID number: Yan-Tao Cai (0000-0003-4768-5273); Li-Chen Cao (0000-0002-4454-0178); Chen-Fang Zhu (0000-0003-1588-4905); Feng Zhao (0000-0003-2464-0259); Bao-Xing Tian (0000-0003-1464-6817); Shan-Yu Guo (0000-0001-6021-7103).

Author contributions: Cai YT and Cao LC contributed equally to this work; Cai YT and Guo SY designed the study; Zhu CF, Zhao F, Tian BX, and Guo SY performed the surgery; Cao LC and Zhu CF performed postoperative follow-up; Cai YT and Cao LC wrote the manuscript; Guo SY revised the manuscript; all authors read and approved the final manuscript.

Informed consent statement: Written informed consent was obtained from the patient and her relatives.

Conflict-of-interest statement: All the authors have no conflicts of interest to declare.

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).

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works

Yan-Tao Cai, Li-Chen Cao, Chen-Fang Zhu, Feng Zhao, Bao-Xing Tian, Shan-Yu Guo, Department of General Surgery, Shanghai Ninth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China

Corresponding author: Shan-Yu Guo, MD, PhD, Chief Doctor, Department of General Surgery, Shanghai Ninth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, No. 639, Zhizaoju Road, Huangpu District, Shanghai 200011, China.

guoshyu1@163.com

Telephone: +86-21-23271699

Abstract

BACKGROUND

Anorectal melanoma (AM) is an extremely rare malignant tumor originating from anorectal melanocytes with a poor prognosis. AM has been reported to have a much lower incidence than cutaneous or choroid melanoma, accounting for 0.4%-1.6% of all melanomas.

CASE SUMMARY

We report a 76-year-old female patient diagnosed with anorectal malignant melanoma by colonoscopy and biopsy. Intraoperative examination revealed two distinct anorectal tumors, one melanotic and another amelanotic, as well as two pigmented mucosal zones at the dentate line level. Abdominal perineal resection was performed. A pathological report confirmed all four lesions to be melanomas. Postoperatively, we followed an immunotherapy protocol targeting PD-1 (nivolumab). The patient had 24 mo of disease-free follow-up upon completion of nivolumab treatment.

CONCLUSION

This is the first reported case presenting coexistence of pigmented and unpigmented AMs in the same patient.

Key words: Anorectal melanoma; Melanotic; Amelanotic; Synchronous; Case report

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Anorectal melanoma (AM) is an extremely rare malignant tumor. We report a 76-year-old female patient diagnosed with anorectal malignant melanoma by colonoscopy and biopsy. Intraoperative examination revealed two distinct anorectal tumors, one melanotic and another amelanotic. Two satellite melanotic implantations

on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Received: January 24, 2019

Peer-review started: January 25, 2019

First decision: January 30, 2019

Revised: February 19, 2019

Accepted: March 16, 2019

Article in press: March 16, 2019

Published online: June 6, 2019

P-Reviewer: Coskun A, de Moura DTH

S-Editor: Ji FF

L-Editor: Wang TQ

E-Editor: Xing YX



were also found in the near mucosal area. This is the first reported case presenting coexistence of pigmented and unpigmented AMs in the same patient and may contribute to further prognostic factor studies in the future research.

Citation: Cai YT, Cao LC, Zhu CF, Zhao F, Tian BX, Guo SY. Multiple synchronous anorectal melanomas with different colors: A case report. *World J Clin Cases* 2019; 7(11): 1337-1343

URL: <https://www.wjgnet.com/2307-8960/full/v7/i11/1337.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v7.i11.1337>

INTRODUCTION

First reported by Moore in 1857, anorectal melanoma (AM) is an extremely rare malignant tumor originating from anorectal melanocytes. AM accounts for 0.5%-4.6% of anorectal malignant tumors and 0.4%-1.6% of all melanomas^[1,2]. Prognosis of AM is dismal with five-year survival rates estimated to be less than 20%^[3]. About 30% of AMs appear to be amelanotic^[4]. Amelanotic AM is easily misdiagnosed with other anorectal diseases, including anorectal cancer, polyps, and hemorrhoids.

In some studies, amelanotic melanoma in AM was associated with worse prognoses than melanotic melanoma^[5]. To our knowledge, this is the first study to successfully demonstrate a case of multiple synchronous melanomas with different colors.

CASE PRESENTATION

Chief complaints

A 76-year-old female patient experiencing symptoms of hematochezia and tenesmus for one month was admitted in our institution.

History of present illness

After symptom onset, the patient had previously undergone a colonoscopy at the community hospital, which revealed two masses, one located at the anal canal level (unpigmented, diameter 2.5 cm) and another 3 cm above the dentate line (pigmented, diameter 2 cm). A biopsy indicated anorectal malignant melanoma with positive expression of Melan-A and HMB-45.

History of past illness

No specific related past illness was found.

Personal and family history

The patient had no specific personal or family history of cancer related disease.

Physical examination upon admission

When subjected to a digital rectal examination, the patient reported pain, but bleeding was not observed. Digital rectal examination revealed two firm and immobile anorectal masses, locations and size of which matched description in previous colonoscopy.

Laboratory examinations

Tumor markers including CEA and CA19-9 were within normal levels. Other preoperative laboratory tests revealed normal levels.

Imaging examinations

No evidence of distal metastasis or significant inguinal lymphadenopathy was suggested by B-ultrasound and enhanced computed tomography. We confirmed the location of the two anorectal masses by preoperative colonoscopy (Figure 1) and pelvic CT (Figure 2).

FINAL DIAGNOSIS

The final diagnosis of the presented case was anorectal malignant melanoma,

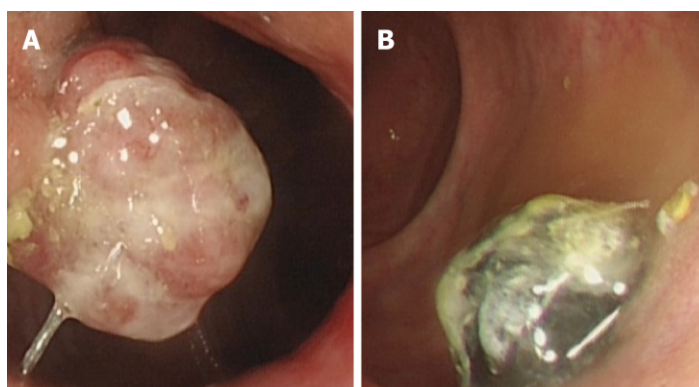


Figure 1 Preoperative colonoscopy images revealing two anorectal masses, one pedunculated mass located at the anal canal level (unpigmented, diameter 2.5 cm) (A), and the other sessile mass 3 cm above the dentate line (pigmented, diameter 2 cm) (B).

according to the biopsy report.

TREATMENT

Surgery was performed under general anesthesia in the lithotomy position. During the procedure, the two anorectal tumors were observed as expected, but two additional mottled mucosal pigmented zones, 1 and 5 mm in diameter, were also observed under an anoscope (Figure 3). Abdominoperineal resection was performed eventually. Intraoperative frozen pathological report suggested a negative resection margin. The deepest invasion of the tumor extended to the muscular layer of the rectum. Histologic illustration of the four lesions were presented in Figure 4. Result of lymph nodes was 0/8. Histopathology showed S100+, HMB45+, MelanA+, CyclinD1+, CK-, EMA-, and VIM+. According to Falch's staging classification (Table 1), the patient was grouped into stage II^[6]. We followed an immunotherapy protocol involving administration of nivolumab, a monoclonal antibody targeting PD-1.

OUTCOME AND FOLLOW-UP

Bowel movement occurred and fluid diet was given in 48 h. Postoperative recovery was well and the patient got discharged two weeks after surgery. Upon completion of nivolumab treatment, the patient had 24 mo of disease-free follow-up. However, due to economic burden, the patient stopped nivolumab treatment 3 mo before being diagnosed with lung metastasis.

DISCUSSION

As an extremely rare malignant disease, AM is known for its poor prognosis^[1,2,7]. Systemic dissemination was recorded to occur in about 67% of patients who were diagnosed early. Misdiagnosis occurs in more than half of the AM patients, mistaken for hemorrhoids, polyps, or rectal cancer^[3]. Late and incorrect diagnoses are common due to atypical symptoms and low incidence^[8]. About 30% of AMs appear to be amelanotic, which also contributes to the difficulty of diagnosis^[4]. But interestingly, misdiagnosis has no significant negative effect on survival time as reported by Zhang *et al*^[9], which suggested that early diagnosis may not mean advantage in survival time because of the extreme malignancy of AM. Larger cohort of AM cases may help confirm or refute this hypothesis.

TNM classification is unsuitable for AM staging. Lymph node metastasis in AM is associated with an increased risk of metastasis and poor prognosis (5-year survival: 45% *vs* 0%, Ballo *et al*^[10]). Tumor infiltration into the muscular layer has been demonstrated as an independent prognosis factor by several studies^[3,11]. Falch created a 4-stage AM classification system according to retrospective analysis of total survival time (Table 1). When depth of muscular infiltration was taken into consideration, local AM was divided into two stages (stage 1 and stage 2)^[6]. Median survival time was significantly worse when the tumor infiltrated into the muscular layer (29 mo in stage



Figure 2 Enhanced pelvic computed tomography image revealing a pedunculated mass from the anterior wall of the rectum, and the other sessile mass from the side wall of the rectum. Both masses invaded into muscular layer and were enhanced at the arterial phase.

1, and 11 mo in stage 2). Cases with lymph node involvement were grouped into stage 3 with a median survival time of less than 1 year. Systemic metastasis was a feature of stage 4, characterized by a very dismal prognosis.

Amelanotic melanoma type in AM was reported to have a worse prognosis than melanotic type in some studies. Reason for this phenomenon remains uncertain. Some authors believe that this is either because amelanotic melanoma is more difficult to diagnose, or it is possibly more invasive in nature^[5]. Satellite lesions may have a relationship with a poor prognosis, which has been proven in cutaneous melanoma studies. Tumor size has also been proposed as another potential prognostic factor, but more subjects are needed to confirm this result^[4]. AM with multiple lesions is rarely reported and currently has no sufficient evidence to be regarded as an independent prognostic factor^[12].

Although therapy for AM has not yet been standardized, surgical resection is recognized as the primary treatment approach^[1]. Patients grouped into stages 1 and 2 may benefit from radical surgery in total survival time^[13]. Abdominal perineal resection (APR) and wild local excision (WLE) are the most commonly used surgical procedures. Controversy still remains regarding choice of operation method. APR showed its superiority in local control as revealed in several studies, but support for WLE is becoming more widespread as well. WLE preserves sphincter function and demonstrates less postoperative morbidity, indicating that WLE may provide superior quality of life compared to APR. Additionally, the resection margin in WLE requires no less than 10 mm to achieve R0 excision^[14]. Several studies showed that WLE had lower morbidity and non-inferior prognosis compared with APR^[15], but the subjects in this study were limited to early stage patients, so further work with additional subjects in later stages is needed to confirm this result. Some clinicians prefer local excision, considering that both procedures lead to very poor postoperative prognoses^[16]. Most studies have indicated no difference between APR and WLE regarding postoperative prognosis^[3]. On the basis of R0 resection, WLE is recommended when it is technically available. APR is more commonly chosen in case of a locally advanced tumor.

Most studies do not recommend prophylactic therapy^[17]. In local lymph node metastasis cases, lymph node dissection remains controversial. No strong evidence exists to demonstrate that ilioinguinal lymph node dissection prolongs total postoperative survival time^[18]. Inguinal sentinel lymph node biopsy may help in assessing status of local lymph node metastasis. Lymph node metastasis usually indicates a poor prognosis and high percentage of distal metastasis. Therapeutic value of this technique remains limited. In this case, existence of the four lesions deprived the possibility for sphincter preserving surgery. APR without ilioinguinal lymph node dissection was eventually performed, because no evidence suggested inguinal lymph node metastasis.

Chemotherapy and radiotherapy might improve survival in cutaneous melanoma according to related studies, but no evidence has been found to prolong total survival time in AM cases^[19]. Radiotherapy may be applied as an adjuvant or palliative intervention and may help contribute to local control. Immunotherapy is extrapolated from its research achievements and incorporated into clinical practice^[20]. Because mutations are observed in most AM cases, C-Kit is regarded as a viable therapeutic target. Various inhibitors of C-kit have been tested in clinical trials. Monoclonal antibodies targeting CTLA-4, PD-1, and BRAF have also demonstrated significant

Table 1 Falch staging classification of anorectal melanoma

Stage	Tumor spread	Median survival time (mo)
I	Local tumor spread + no infiltration of muscular layer	29
II	Local tumor spread + infiltration of the muscular layer	11
III	Regional tumor spread and/or lymph node metastasis	9
IV	Distal metastasis	

impact on controlling AM^[2].

In this case we report, AM was diagnosed definitely before surgery *via* colonoscopy and biopsy. We chose to perform APR instead of WLE, because the four lesions distributed in anorectal zone made sphincter preserving radical surgery unachievable. Pathological report suggested multiple AMs with muscular invasion without lymph node metastasis. This case should be classified as stage II with an 11-mo expected survival time according to Falch staging classification. The patient was diagnosed with lung metastasis but still alive 27 mo after surgery, which was significantly longer than expected. Whether it was nivolumab (PD-1 inhibitor) treatment or just individual difference that contributed to the prolonged survival time remains uncertain. Curative effect of nivolumab treatment and other monoclonal antibody induced targeted therapy requires further evidence from clinical trials.

CONCLUSION

In this article, we report an AM case with multiple synchronous melanomas with different colors, which has never been reported previously. Treatment of AM include R0 surgical resection (APR or WLE), chemotherapy, and immunotherapy. Further clinical research and larger cohort of patients may help to standardize treatment guidelines and improve the prognosis of AM.

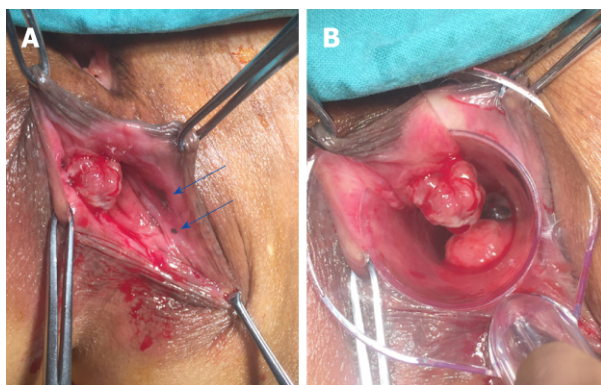


Figure 3 Transanal exploration of anorectal masses. A: Derived from the anterior wall of the rectum, one pedunculated mass appeared at the anal canal level without melanin pigmentation. Two mucosal melanic zones were found at the anal canal level (blue arrows); B: Another pigmented mass was 3 cm above the dentate line under anoscope vision.

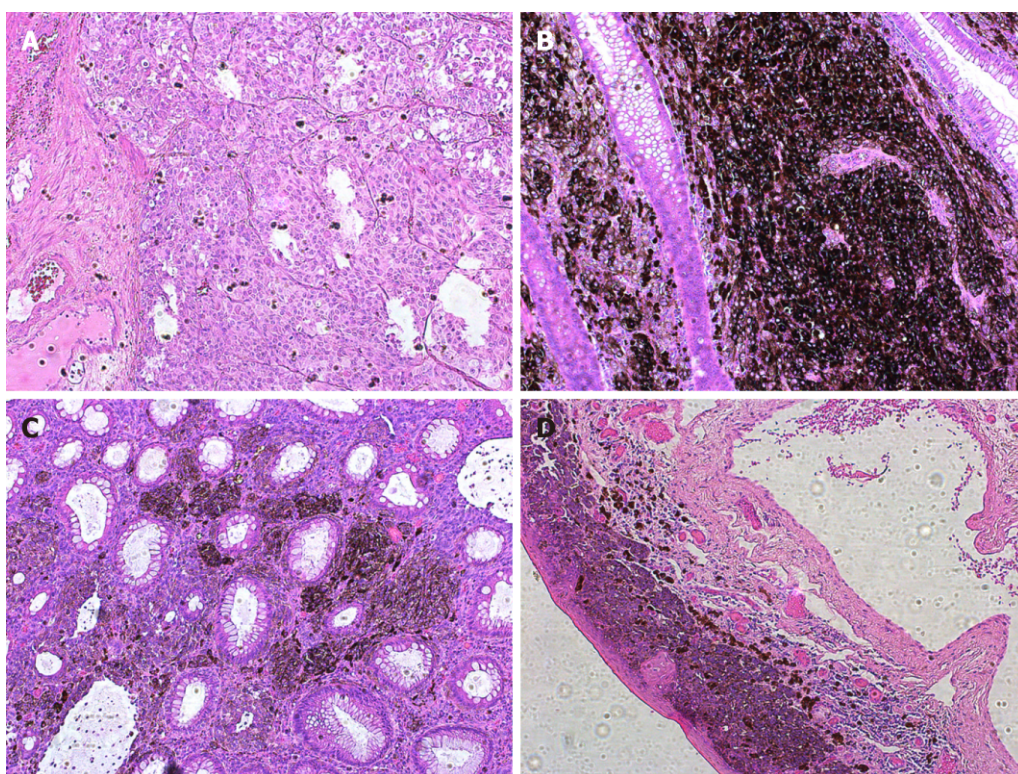


Figure 4 Histologic illustration of the four lesions in this case (HE staining, 10×). A: Pedunculated mass located at the anal canal level. Although this lesion appeared unpigmented via visualization, scattered round atypical pigmented cells were found microscopically; B: The sessile mass 3 cm above the dentate line showed densely distributed pigmented cells; C and D: Two mucosal melanic zones were analyzed. Infiltration of atypical pigmented cells was found distributed in the mucosal and submucosal layers.

REFERENCES

- 1 Meguerditchian AN, Meterissian SH, Dunn KB. Anorectal melanoma: diagnosis and treatment. *Dis Colon Rectum* 2011; **54**: 638-644 [PMID: 21471767 DOI: 10.1007/DCR.0b013e31820c9b1b]
- 2 Bello DM, Smyth E, Perez D, Khan S, Temple LK, Ariyan CE, Weiser MR, Carvajal RD. Anal versus rectal melanoma: does site of origin predict outcome? *Dis Colon Rectum* 2013; **56**: 150-157 [PMID: 23303142 DOI: 10.1097/DCR.0b013e31827901dd]
- 3 Che X, Zhao DB, Wu YK, Wang CF, Cai JQ, Shao YF, Zhao P. Anorectal malignant melanomas: retrospective experience with surgical management. *World J Gastroenterol* 2011; **17**: 534-539 [PMID: 21274385 DOI: 10.3748/wjg.v17.i4.534]
- 4 Hillenbrand A, Barth TF, Henne-Bruns D, Formentini A. Anorectal amelanotic melanoma. *Colorectal Dis* 2008; **10**: 612-615 [PMID: 17944970 DOI: 10.1111/j.1463-1318.2007.01400.x]
- 5 Thomas NE, Krickler A, Waxweiler WT, Dillon PM, Busman KJ, From L, Groben PA, Armstrong BK, Anton-Culver H, Gruber SB, Marrett LD, Gallagher RP, Zanetti R, Rosso S, Dwyer T, Venn A, Kanetsky PA, Orlov I, Paine S, Ollila DW, Reiner AS, Luo L, Hao H, Frank JS, Begg CB, Berwick M; Genes,

- Environment, and Melanoma (GEM) Study Group. Comparison of clinicopathologic features and survival of histopathologically amelanotic and pigmented melanomas: a population-based study. *JAMA Dermatol* 2014; **150**: 1306-1314 [PMID: 25162299 DOI: 10.1001/jamadermatol.2014.1348]
- 6 **Falch C**, Stojadinovic A, Hann-von-Weyhern C, Protic M, Nissan A, Faries MB, Daumer M, Bilchik AJ, Itzhak A, Brucher BL. Anorectal malignant melanoma: extensive 45-year review and proposal for a novel staging classification. *J Am Coll Surg* 2013; **217**: 324-335 [PMID: 23697834 DOI: 10.1016/j.jamcollsurg.2013.02.031]
 - 7 **Belli F**, Gallino GF, Lo Vullo S, Mariani L, Poiasina E, Leo E. Melanoma of the anorectal region: the experience of the National Cancer Institute of Milano. *Eur J Surg Oncol* 2009; **35**: 757-762 [PMID: 18602790 DOI: 10.1016/j.ejso.2008.05.001]
 - 8 **Hicks CW**, Pappou EP, Magruder JT, Gazer B, Fang S, Wick EC, Gearhart SL, Ahuja N, Efron JE. Clinicopathologic Presentation and Natural History of Anorectal Melanoma: A Case Series of 18 Patients. *JAMA Surg* 2014; **149**: 608-611 [PMID: 24848283 DOI: 10.1001/jamasurg.2013.4643]
 - 9 **Zhang S**, Gao F, Wan D. Abdominoperineal resection or local excision? a survival analysis of anorectal malignant melanoma with surgical management. *Melanoma Res* 2010; **20**: 338-341 [PMID: 20414138 DOI: 10.1097/CMR.0b013e328339b159]
 - 10 **Ballo MT**, Gershenwald JE, Zagars GK, Lee JE, Mansfield PF, Strom EA, Bedikian AY, Kim KB, Papadopoulos NE, Prieto VG, Ross MI. Sphincter-sparing local excision and adjuvant radiation for anorectal melanoma. *J Clin Oncol* 2002; **20**: 4555-4558 [PMID: 12454112 DOI: 10.1200/jco.2002.03.002]
 - 11 **Ren M**, Lu Y, Lv J, Shen X, Kong J, Dai B, Kong Y. Prognostic factors in primary anorectal melanoma: a clinicopathological study of 60 cases in China. *Hum Pathol* 2018; **79**: 77-85 [PMID: 29763716 DOI: 10.1016/j.humpath.2018.05.004]
 - 12 **Duarte P**, Ramos R, Vicente C, Casteleiro Alves C. Anal melanoma with satellite implantations on the lower rectum. *Rev Esp Enferm Dig* 2011; **103**: 49-51 [PMID: 21341945 DOI: 10.4321/S1130-01082011000100016]
 - 13 **Chen H**, Cai Y, Liu Y, He J, Hu Y, Xiao Q, Hu W, Ding K. Incidence, Surgical Treatment, and Prognosis of Anorectal Melanoma From 1973 to 2011: A Population-Based SEER Analysis. *Medicine (Baltimore)* 2016; **95**: e2770 [PMID: 26886623 DOI: 10.1097/MD.0000000000002770]
 - 14 **Thibault C**, Sagar P, Nivatvongs S, Ilstrup DM, Wolff BG. Anorectal melanoma--an incurable disease? *Dis Colon Rectum* 1997; **40**: 661-668 [PMID: 9194459 DOI: 10.1007/BF02140894]
 - 15 **Iddings DM**, Fleisig AJ, Chen SL, Faries MB, Morton DL. Practice patterns and outcomes for anorectal melanoma in the USA, reviewing three decades of treatment: is more extensive surgical resection beneficial in all patients? *Ann Surg Oncol* 2010; **17**: 40-44 [PMID: 19774417 DOI: 10.1245/s10434-009-0705-0]
 - 16 **Glowka TR**, Keyver-Paik MD, Thiesler T, Landsberg J, Kalff JC, Pantelis D. [Anorectal malignant melanoma : Treatment recommendations]. *Chirurg* 2016; **87**: 768-774 [PMID: 27392764 DOI: 10.1007/s00104-016-0242-x]
 - 17 **Perez DR**, Trakarnsanga A, Shia J, Nash GM, Temple LK, Paty PB, Guillem JG, Garcia-Aguilar J, Bello D, Ariyan C, Carvajal RD, Weiser MR. Locoregional lymphadenectomy in the surgical management of anorectal melanoma. *Ann Surg Oncol* 2013; **20**: 2339-2344 [PMID: 23328972 DOI: 10.1245/s10434-012-2812-6]
 - 18 **Latteri S**, Teodoro M, Malaguarnera M, Mannino M, Currò G, La Greca G. Abdominal perineal resection or wilde local excision in primary anorectal malignant melanoma. Case report and review. *Ann Med Surg (Lond)* 2017; **19**: 74-77 [PMID: 28702180 DOI: 10.1016/j.amsu.2017.03.039]
 - 19 **Ishizone S**, Koide N, Karasawa F, Akita N, Muranaka F, Uhara H, Miyagawa S. Surgical treatment for anorectal malignant melanoma: report of five cases and review of 79 Japanese cases. *Int J Colorectal Dis* 2008; **23**: 1257-1262 [PMID: 18633625 DOI: 10.1007/s00384-008-0529-6]
 - 20 **Miguel I**, Freire J, Passos MJ, Moreira A. Anorectal malignant melanoma: retrospective analysis of management and outcome in a single Portuguese Institution. *Med Oncol* 2015; **32**: 445 [PMID: 25502089 DOI: 10.1007/s12032-014-0445-2]

Huge primary dedifferentiated pancreatic liposarcoma mimicking carcinosarcoma in a young female: A case report

Zhe Liu, Wu-Feng Fan, Gui-Chen Li, Jin Long, Yuan-Hong Xu, Gang Ma

ORCID number: Zhe Liu (0000-0002-0650-118X); Wu-Feng Fan (0000-0001-9591-0901); Gang Ma (0000-0002-7045-9840); Yuan-hong Xu (0000-0001-9264-8207); Gui-Chen Li (0000-0002-4260-6348); Jin Long (0000-0002-5079-9717).

Author contributions: All authors contributed to the acquisition of data and writing and revision of the manuscript.

Supported by the Liaoning Provincial Department of Education Science Research Project, No. L2014299; NSFC Molecular mechanism of aberrant expression of JDP2 and the regulation by JDP2 of TGF-beta-induced epithelial to mesenchymal transition in human pancreatic carcinoma, No. 81572360 (2016.1-2019.12).

Institutional review board statement: The study was performed retrospectively and was not antecedently reviewed by the Ethics Committee of China Medical University.

Informed consent statement: The patient involved in this study gave her written informed consent authorizing use and disclosure of her protected health information.

Conflict-of-interest statement: The authors declared that they have no conflicts of interest related to this work.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE

Zhe Liu, Wu-Feng Fan, Gui-Chen Li, Jin Long, Yuan-Hong Xu, Gang Ma, Department of Pancreatic-Biliary Surgery, First Hospital of China Medical University, Shenyang 110001, Liaoning Province, China

Corresponding author: Gang Ma, MD, Assistant Professor, Department of Pancreatic-Biliary Surgery, First Hospital of China Medical University, Heping District, Nanjing Road No. 155, Shenyang 110001, Liaoning Province, China. liuzhecmu@126.com

Telephone: +86-024-83283330

Fax: +86-024-83283350

Abstract

BACKGROUND

Pancreatic liposarcoma is a rare tumor. According to a literature review, the patient described in this study is the seventh case of pancreatic liposarcoma reported in the English literature and the third case of dedifferentiated liposarcoma. Furthermore, this case had the largest primary tumor volume, and a primary pancreatic liposarcoma was diagnosed based on sufficient evidence.

CASE SUMMARY

We here report a rare case of a 28-year-old female with a huge dedifferentiated liposarcoma in the pancreatic tail. In June 2015, the patient underwent distal pancreatectomy with splenectomy. During the operation, a huge liposarcoma of approximately 28.0 cm × 19.0 cm × 8.0 cm was found, which had a yellow and white fish-like incised surface. Based on both pathology and *MDM2* gene amplification, the tumor was diagnosed as a dedifferentiated liposarcoma. The patient was treated with surgery but declined postoperative chemotherapy. She was well at the 26-mo follow-up, and no relapse was observed.

CONCLUSION

Pancreatic liposarcoma has a low incidence. Chemotherapy should be included in the treatment regimens. Complete resection is the only effective treatment.

Key words: Pancreatic liposarcoma; Huge tumor; Distal pancreatectomy and splenectomy; Chemotherapy; Case report

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Pancreatic liposarcoma is a rare tumor. We report a case of a 28-year-old female with a huge dedifferentiated liposarcoma in the pancreatic tail, 28.0 cm × 19.0 cm

Checklist (2016).

Open-Access: This article is an open-access article that was selected by an inhouse editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is noncommercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: December 28, 2018

Peer-review started: December 29, 2018

First decision: March 10, 2019

Revised: April 9, 2019

Accepted: May 1, 2019

Article in press: May 2, 2019

Published online: June 6, 2019

P-Reviewer: Dasgupta S, Neri V

S-Editor: Dou Y

L-Editor: Filipodia

E-Editor: Xing YX



× 8.0 cm in size, with a yellow and white fish-like incisal surface. According to a literature review, this is the seventh case of pancreatic liposarcoma reported in the English literature and the third case of dedifferentiated liposarcoma. Furthermore, this case had the largest primary tumor volume, and a primary pancreatic liposarcoma was diagnosed based on sufficient evidence. The patient was treated with surgery but declined postoperative chemotherapy. She was well at the 26-mo follow-up, without relapse.

Citation: Liu Z, Fan WF, Li GC, Long J, Xu YH, Ma G. Huge primary dedifferentiated pancreatic liposarcoma mimicking carcinosarcoma in a young female: A case report. *World J Clin Cases* 2019; 7(11): 1344-1350

URL: <https://www.wjgnet.com/2307-8960/full/v7/i11/1344.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v7.i11.1344>

INTRODUCTION

Based on molecular morphology, liposarcoma can be divided into well-differentiated/dedifferentiated liposarcoma, myxoid/round cell liposarcoma, and pleomorphic liposarcoma^[1-3]. For dedifferentiated liposarcoma, it is thought that a malignant non-fat sarcomatous region exists in the well-differentiated liposarcoma area at the same time. To date, six cases of pancreatic liposarcoma have been reported in the English literature^[4-9]. In the present study, a patient with a huge dedifferentiated liposarcoma in the pancreatic tail is reported. Pathology after operation revealed coexisting areas of well-differentiated liposarcoma, dedifferentiated liposarcoma, and the tissue of pancreatic canal. *MDM2* gene amplification by fluorescence *in situ* hybridization showed a dedifferentiated liposarcoma that did not originate from the retroperitoneum.

CASE PRESENTATION

Chief complaints

A 28-year-old female presented with left upper abdominal discomfort with nausea and vomiting for more than 2 mo and fever for 2 wk.

History of present illness

The patient developed left epigastric discomfort with postprandial nausea and vomiting 2 mo previously without obvious predilection, the vomit consisted of stomach contents and abdominal distension was relieved after vomiting. She attended a local hospital for gastroscopy and was diagnosed with chronic atrophic gastritis, but no significant improvement was achieved after symptomatic treatment including acid inhibition and gastric preservation. She also had fever and chills for 2 wk, and as her temperature reached 39 °C, she was sent to the People's Liberation Army 202 Hospital, where an abdominal mass was found during computed tomography (CT) examination. The patient was then transferred to our hospital for further diagnosis and treatment. She was mentally stable, with a poor diet and poor sleep, with no obvious defecation and urinary abnormalities, and her weight loss was approximately 8 kg.

History of past illness

None.

Personal and family history

None.

Physical examination upon admission

The sclera showed no yellow staining, and no bleeding spots or petechiae were observed in the skin mucosa. No liver palm or spider mole was present, superficial lymph nodes were not palpable, the left epigastrium was slightly distended, gastrointestinal peristaltic wave was not observed, the abdomen was soft without tenderness, Murphy's sign was negative, and the liver and spleen were not palpable under the rib. The mass was palpable in the left epigastric region and was

approximately 15 cm in diameter. There was no muscle tension or rebound pain, no percussion pain in the liver and spleen area, shifting dullness was negative, and bowel sounds were 3-4 times/min, with no smell, air water sound, or high-pitched bowel sounds.

Laboratory examinations

Carcinoembryonic antigen was 0.76 ng/mL, alpha-fetoprotein was 2.14 ng/mL, cancer antigen 12-5 was 45.40 U/mL, carbohydrate antigen 19-9 was 6.13 U/mL, total bilirubin was 8.80 μ mol/L, and direct bilirubin was 4.70 μ mol/L.

Imaging examinations

The enhanced pancreatic 3D-CT images suggested a huge mass in the left upper abdomen with low density and a maximum cross-sectional area of 14.0 cm \times 18.0 cm. The plain CT value was 16-24 HU.

Multiple vascular shadows were observed in the arterial phase, and the enhanced CT value was 60-95 HU in the lag period. Compressed and tortuous superior and inferior mesenteric arteries and veins were observed. A pancreatic tumor was considered, and pancreatic carcinosarcoma was not excluded (Figure 1).

Preoperatively, pancreatic carcinosarcoma was suspected, and the patient underwent surgery. Intra-operatively, the transverse colon, stomach, and jejunum were compressed by the huge tumor, which had an irregular shape, an acceptable boundary, and a clear boundary with the retroperitoneum, suggesting that the tumor was originated from the pancreatic tail. Complete resection of the pancreatic tail was performed. A mass with a proximal margin of 1.0 cm of normal pancreatic tissue was removed (Figure 2A). The inside of the mass was fish-like in texture and yellow-white. The distal pancreatic tissue was normal. Morphology inside the tumor showed no normal tissue (Figure 2B). Thus, a pancreatic source was considered and not retroperitoneal encapsulated pancreas as suggested by visual observation.

Postoperative pathology showed well-differentiated adipose tissue. Various cell sizes and shapes were observed with different trachychromatic atypia nuclei and a coexisting pancreatic canal (Figures 3A, C). Spindle cell hyperplasia was also observed when the coexisting area of undifferentiated liposarcoma and pancreatic canal were examined (Figures 3B, D). The pancreatic source was microscopically verified. Immunohistochemistry results showed the following: CK (-), vimentin (+), CD34 (+), CD117 (\pm), smooth muscle actin (-), S-100 (\pm), Dog-1 (\pm), CD68 (+), Desmin (-), MyoD1 (focus+), Bcl-2 (+), Beta-catenin (-), and Ki-67 (25%+). In order to verify whether the tumor was an undifferentiated liposarcoma, had a pancreatic source, and local infiltration and metastasis were present, *MDM2* gene amplification of the mass and adjacent normal retroperitoneal tissue was performed. *MDM2* gene amplification of the mass was positive (Figure 4A), while that of adjacent retroperitoneal tissue was negative (Figure 4B). This reconfirmed that the mass was pancreatic in origin and was a dedifferentiated liposarcoma.

FINAL DIAGNOSIS

Primary dedifferentiated pancreatic liposarcoma.

TREATMENT

Surgery.

OUTCOME AND FOLLOW-UP

The patient declined chemotherapy, but was well at her 26-mo follow-up, without relapse.

DISCUSSION

Dedifferentiated liposarcoma is a frequent type of liposarcoma that can occur in any part of the body^[10]. It mainly occurs in the head, neck, limbs, and retroperitoneum^[11-14]. Studies have shown that it amplifies to the 12q13-15 area^[15]. Genes such as *MDM2* and *CDK4* are included in this area, with *MDM2* the most constantly expressed gene^[16-19]. Therefore, high expression of *MDM2* plays a vital role in diagnosing dedifferentiated



Figure 1 Preoperative computed tomography. Preoperative computed tomography shows a huge cystic-solid mass in the left upper abdomen, which compressed the superior mesenteric vein (Black arrow); necrosis can be seen in the mass (White arrow).

liposarcoma. Although liposarcoma is a common tumor, pancreatic liposarcoma is rare. To date, there are only six cases of primary pancreatic liposarcoma reported in the English literature^[4-9] (Table 1). According to a review of the existing literature, it is essential to confirm whether the tumor is a differentiated liposarcoma and to assess whether it originates from the pancreas. We suggest that this tumor can be diagnosed according to the following aspects: (1) Preoperative CT revealed pancreatic occupancy with an iconographic “interspace” in the retroperitoneum, stomach, colon, and small intestine; (2) A mass located in the pancreas or a pancreatic source was found during surgery, which could be completely cut out by blunt and sharp dissection; (3) Post-operative microscopic examination detected the co-existing area of the pancreatic canal, a well-differentiated liposarcoma, and undifferentiated liposarcoma; (4) *MDM2* gene amplification by fluorescence *in situ* hybridization examination confirmed that the mass had a positive amplification, and the retroperitoneum or other control tissues had a negative amplification; and (5) There was no evidence of liposarcoma at the other sites.

CONCLUSION

Most cases are diagnosed *via* surgery combined with pathology. One of the cases in the literature was diagnosed by positive amplification of *MDM2*. However, from the comprehensive review, the diagnosis lacked evidence, which is the key in diagnosing this disease. In addition, we did not exclude the pancreatic source according to preoperative CT, and the first histological report revealed a pancreatic liposarcoma. We revised the diagnosis following *MDM2* detection and re-evaluated the microscopic hematoxylin and eosin staining. In all seven cases, it was found that the tumor may be derived from the pancreatic matrix, and evidence of a pancreatic source is not enough. This tumor has a poor prognosis when the onset site is the pancreatic tail. Therefore, post-operative chemotherapy was suggested for the patient in the present study with gemcitabine and cis-platinum, but it was declined. The patient was well at the 26-mo follow-up, without relapse. We conclude that this tumor has a low incidence. When a patient is diagnosed with liposarcoma, chemotherapy should be included in the treatment regimen. Complete resection is the only effective treatment.

Table 1 Previously reported cases of pancreatic liposarcoma

First author	Age/sex	Symptoms	Yr	Liposarcoma subtype	Liposarcoma size	Treatment	Outcome	Evidence of pancreatic origin
Elliott	59/F	Abdominal distension	1980	Pleomorphic	16 cm	DP	6 yr	Surgery
Dodo	76/M	Abdominal pain	2005	Well differentiated with area of de-differentiation	9 cm	DP	26 mo	Surgery
Kuramoto	24/M	Abdominal distension	2013	Myxoid	25 cm	MP	44 mo	Surgery
Machado	42/M	Abdominal pain	2016	Dedifferentiated with high grade components	6.8 cm	DP	5 yr	Intrapancreatic
Matthews	65/F	None	2016	Well differentiated	4 cm	DP	none	Intrapancreatic + adjacent retroperitoneal MDM2 FISH
Han	29/F	None	2017	Dedifferentiated	20 cm	DP	1 yr	Surgery
Present case	28/F	Abdominal pain		Dedifferentiated with high grade components	28 cm	DP	26 mo	Surgery + histology + adjacent retroperitoneal MDM2 FISH

F: Female; M: Male; DP: Distal pancreatectomy; CP: Central pancreatectomy; MP: Middle pancreatectomy; FISH: Fluorescence *in situ* hybridization.

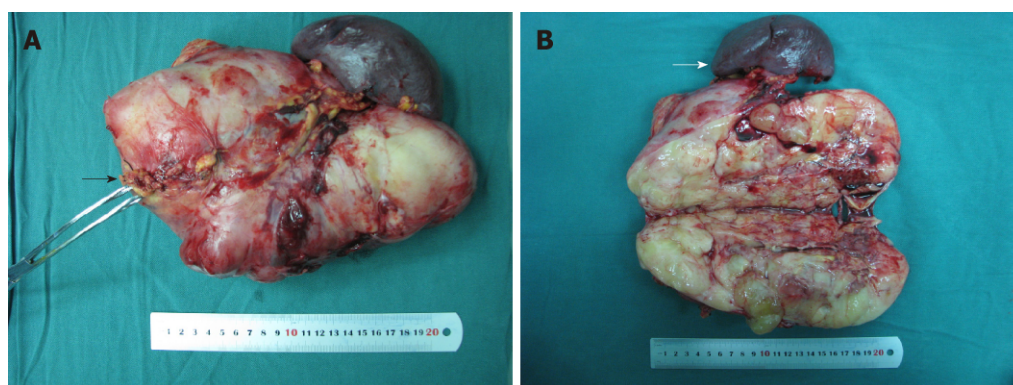


Figure 2 Surgical procedure. The pancreatic tail was removed. A: The giant mass in the pancreatic tail was approximately 28.0 cm × 19.0 cm × 8.0 cm. The black arrow shows the normal pancreatic tissue; B: The mass was longitudinally opened. The gray-white and fish-like incised surface can be seen. The spleen is shown by the white arrow.

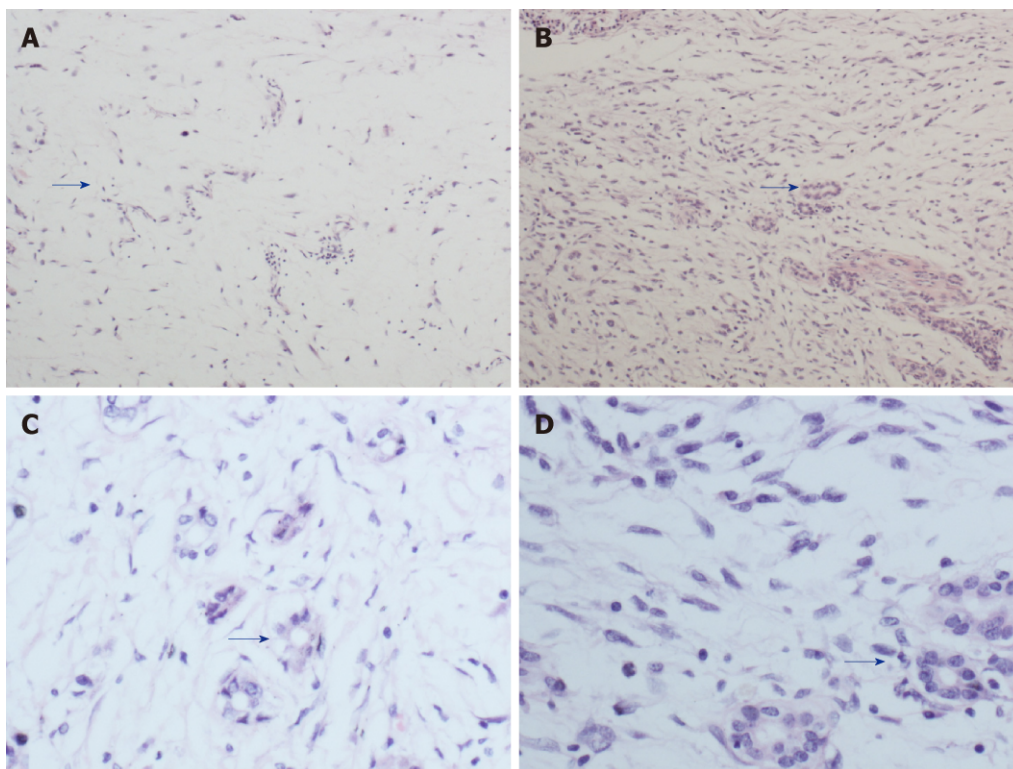


Figure 3 Histopathology. A: Coexisting areas of well-differentiated liposarcoma and the pancreatic canal (H and E \times 100); B: Coexisting areas of dedifferentiated liposarcoma and the pancreatic canal (H and E \times 100); C: Coexisting areas of well-differentiated liposarcoma and the pancreatic canal (H and E \times 400); D: Coexisting areas of dedifferentiated liposarcoma and the pancreatic canal (H and E \times 400). Blue arrows show areas containing the pancreatic canal. H and E: Hematoxylin and eosin.

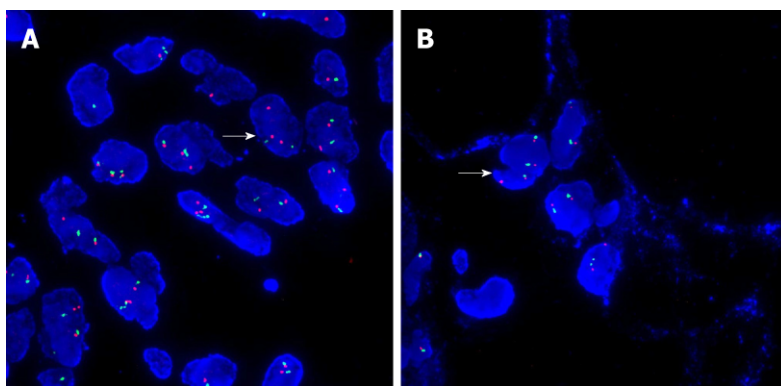


Figure 4 Fluorescence *in situ* hybridization results. A: *MDM2* gene amplification of the mass was positive (White arrow; as shown by three red dots and two green dots); B: *MDM2* gene amplification of adjacent retroperitoneal tissue was negative (White arrow; as shown by two red dots and two green dots).

REFERENCES

- 1 Mankin HJ, Mankin KP, Harmon DC. Liposarcoma: a soft tissue tumor with many presentations. *Musculoskelet Surg* 2014; **98**: 171-177 [PMID: 25047632 DOI: 10.1007/s12306-014-0332-1]
- 2 Dei Tos AP. Liposarcomas: diagnostic pitfalls and new insights. *Histopathology* 2014; **64**: 38-52 [PMID: 24118009 DOI: 10.1111/his.12311]
- 3 Mullinax JE, Zager JS, Gonzalez RJ. Current diagnosis and management of retroperitoneal sarcoma. *Cancer Control* 2011; **18**: 177-187 [PMID: 21666580 DOI: 10.1177/107327481101800305]
- 4 Matthews M, Nelson S, Hari D, French S. Well differentiated liposarcoma, sclerosing type, of the pancreas a case report. *Exp Mol Pathol* 2016; **101**: 320-322 [PMID: 27840110 DOI: 10.1016/j.yexmp.2016.11.002]
- 5 Elliott TE, Albertazzi VJ, Danto LA. Pancreatic liposarcoma: case report with review of retroperitoneal liposarcomas. *Cancer* 1980; **45**: 1720-1723 [PMID: 7370927]
- 6 Dodo IM, Adamthwaite JA, Jain P, Roy A, Guillou PJ, Menon KV. Successful outcome following resection of a pancreatic liposarcoma with solitary metastasis. *World J Gastroenterol* 2005; **11**: 7684-7685 [PMID: 16437699]

- 7 **Kuramoto K**, Hashimoto D, Abe S, Chikamoto A, Beppu T, Iyama K, Baba H. Education and imaging. Hepatobiliary and pancreatic: large pancreatic liposarcoma. *J Gastroenterol Hepatol* 2013; **28**: 1800 [PMID: 24261954 DOI: 10.1111/jgh.12433]
- 8 **Machado MC**, Fonseca GM, de Meirelles LR, Zacchi FF, Bezerra RO. Primary liposarcoma of the pancreas: A review illustrated by findings from a recent case. *Pancreatol* 2016; **16**: 715-718 [PMID: 27423533 DOI: 10.1016/j.pan.2016.07.003]
- 9 **Han T**, Luan Y, Xu Y, Yang X, Li J, Liu R, Li Q, Zheng Z. Successful treatment of advanced pancreatic liposarcoma with apatinib: A case report and literature review. *Cancer Biol Ther* 2017; **18**: 635-639 [PMID: 28678611 DOI: 10.1080/15384047.2017.1345394]
- 10 **Gyorki DE**, Brennan MF. Management of recurrent retroperitoneal sarcoma. *J Surg Oncol* 2014; **109**: 53-59 [PMID: 24155163 DOI: 10.1002/jso.23463]
- 11 **Zhu H**, Sun J, Wei S, Wang D, Brandwein M. Well-Differentiated Laryngeal/Hypopharyngeal Liposarcoma in the MDM2 Era Report of Three Cases and Literature Review. *Head Neck Pathol* 2017; **11**: 146-151 [PMID: 27492446 DOI: 10.1007/s12105-016-0747-0]
- 12 **Arvinus C**, Torrecilla E, Beano-Collado J, García-Coiradas J, García-Maroto R, Puerto-Vázquez M, Cebrián-Parra JL. A clinical review of 11 cases of large-sized well-differentiated liposarcomas. *Eur J Orthop Surg Traumatol* 2017; **27**: 837-841 [PMID: 28536819 DOI: 10.1007/s00590-017-1968-y]
- 13 **Moreau LC**, Turcotte R, Ferguson P, Wunder J, Clarkson P, Masri B, Isler M, Dion N, Werier J, Ghert M, Deheshi B; Canadian Orthopaedic Oncology Society (CANOOS). Myxoid/round cell liposarcoma (MRCLS) revisited: an analysis of 418 primarily managed cases. *Ann Surg Oncol* 2012; **19**: 1081-1088 [PMID: 22052112 DOI: 10.1245/s10434-011-2127-z]
- 14 **Gronchi A**, Collini P, Miceli R, Valeri B, Renne SL, Dagrada G, Fiore M, Sanfilippo R, Barisella M, Colombo C, Morosi C, Stacchiotti S, Casali PG, Dei Tos AP, Pilotti S. Myogenic differentiation and histologic grading are major prognostic determinants in retroperitoneal liposarcoma. *Am J Surg Pathol* 2015; **39**: 383-393 [PMID: 25581729 DOI: 10.1097/PAS.0000000000000366]
- 15 **Ortega P**, Suster D, Falconieri G, Zambrano E, Moran CA, Morrison C, Suster S. Liposarcomas of the posterior mediastinum: clinicopathologic study of 18 cases. *Mod Pathol* 2015; **28**: 721-731 [PMID: 25475695 DOI: 10.1038/modpathol.2014.152]
- 16 **Hostein I**, Pelmus M, Aurias A, Pedetour F, Mathoulin-Pélissier S, Coindre JM. Evaluation of MDM2 and CDK4 amplification by real-time PCR on paraffin wax-embedded material: a potential tool for the diagnosis of atypical lipomatous tumours/well-differentiated liposarcomas. *J Pathol* 2004; **202**: 95-102 [PMID: 14694526 DOI: 10.1002/path.1495]
- 17 **Tamborini E**, Della Torre G, Lavarino C, Azzarelli A, Carpinelli P, Pierotti MA, Pilotti S. Analysis of the molecular species generated by MDM2 gene amplification in liposarcomas. *Int J Cancer* 2001; **92**: 790-796 [PMID: 11351297 DOI: 10.1002/ijc.1271]
- 18 **Coindre JM**, Hostein I, Maire G, Derré J, Guillou L, Leroux A, Ghnassia JP, Collin F, Pedetour F, Aurias A. Inflammatory malignant fibrous histiocytomas and dedifferentiated liposarcomas: histological review, genomic profile, and MDM2 and CDK4 status favour a single entity. *J Pathol* 2004; **203**: 822-830 [PMID: 15221942 DOI: 10.1002/path.1579]
- 19 **Coindre JM**, Mariani O, Chibon F, Mairal A, De Saint Aubain Somerhausen N, Favre-Guillevin E, Bui NB, Stoeckle E, Hostein I, Aurias A. Most malignant fibrous histiocytomas developed in the retroperitoneum are dedifferentiated liposarcomas: a review of 25 cases initially diagnosed as malignant fibrous histiocytoma. *Mod Pathol* 2003; **16**: 256-262 [PMID: 12640106 DOI: 10.1097/01.MP.0000056983.78547.77]



A large basal cell adenoma extending to the ipsilateral skull base and mastoid in the right parotid gland: A case report

Lu-Yang Du, Xiu-Hong Weng, Zhen-Yu Shen, Bo Cheng

ORCID number: Lu-Yang Du (0000-0002-2965-1232); Xiu-Hong Weng (0000-0002-3094-2344); Zhen-Yu Shen (0000-0001-6194-8039); Bo Cheng (0000-0003-1916-0410).

Author contributions: Du LY analysed the data and wrote the paper; Weng XH collected the medical imaging materials and analysed the data; Shen ZY collected the medical imaging materials; Cheng B designed the report and performed the preliminary revision of the article. All authors contributed to this article.

Informed consent statement: Consent was obtained from the patient for publication of the report and accompanying images.

Conflict-of-interest statement: There are no conflicts of interest declared by the authors.

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).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and

Lu-Yang Du, Zhen-Yu Shen, Department of Stomatology, Union Hospital, Tongji Medical College, HuaZhong University of Science and Technology, Wuhan 430022, Hubei Province, China

Xiu-Hong Weng, Bo Cheng, Department of Stomatology, Zhongnan Hospital of Wuhan University, Wuhan 430071, Hubei Province, China

Corresponding author: Bo Cheng, DDS, PhD, Associate Professor, Department of Stomatology, Zhongnan Hospital of Wuhan University, 169 Donghu Road, Wuhan 430071, Hubei Province, China. chengbo@znhospital.cn
Telephone: +86-135-07190986

Abstract

BACKGROUND

Basal cell adenoma (BCA) is a rare benign tumour that has unique histological characteristics and primarily arises in the parotid glands. According to published reports, nearby tissue destruction by BCA seems impossible.

CASE SUMMARY

We presented a case of a 54-year-old woman with a mass in the deep lobe of the right parotid gland involving the ipsilateral skull base and mastoid. The patient exhibited gradual right facial swelling but no other obvious symptoms. Combined resection of the total right parotid gland and partial skull base excision were performed. The biopsy conducted before the surgery and sections cut from intraoperatively obtained tissues were not definitive for identifying the character of the neoplasm. A final diagnosis of tubular BCA without malignant elements was established based on postoperative pathology results and immunohistochemical analysis. The tumour did not recur during the 12-mo follow-up period.

CONCLUSION

A diagnosis of BCA can only be established based on a histopathological examination after an excisional biopsy, and tubular BCA should carefully be considered as a destructive type.

Key words: Basal cell adenoma; Mastoid; Parotid gland; Skull base; Total parotidectomy; Case report

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

the use is non-commercial. See:
<http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Received: January 17, 2019

Peer-review started: January 17, 2019

First decision: March 10, 2019

Revised: April 2, 2019

Accepted: April 9, 2019

Article in press: April 10, 2019

Published online: June 6, 2019

P-Reviewer: Vissink A, Mogulkoc R, Ciuman RR

S-Editor: Dou Y

L-Editor: Filipodia

E-Editor: Xing YX



Core tip: Basal cell adenoma (BCA) is a rare benign tumour that has unique histological characteristics and primarily arises in the parotid glands. Destruction of nearby tissue by BCA has not been reported. We presented a case of tubular BCA in the deep lobe of the parotid gland involving the ipsilateral skull base and mastoid. It suggests that a diagnosis of BCA can only be established after an excisional biopsy, and tubular BCA should carefully be considered as a destructive type.

Citation: Du LY, Weng XH, Shen ZY, Cheng B. A large basal cell adenoma extending to the ipsilateral skull base and mastoid in the right parotid gland: A case report. *World J Clin Cases* 2019; 7(11): 1351-1357

URL: <https://www.wjgnet.com/2307-8960/full/v7/i11/1351.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v7.i11.1351>

INTRODUCTION

Basal cell adenoma (BCA) is an uncommon benign tumour of the salivary glands, usually the parotid gland that accounts for no more than 3% of all salivary gland tumours^[1-3]. It frequently occurs in patients over 50 years of age and has a slightly higher prevalence in women^[4]. With regard for clinical presentation, BCAs exhibit slow growth and are asymptomatic, movable, round or oval, normal-coloured subcutaneous masses measuring less than 3 cm in diameter^[4]. Histologically, they are known to possess a prominent basal cell layer and a distinct basement membrane-like material and are classified into four subtypes according to cell arrangement^[5]. Its differential diagnosis with conditions with varied prognoses, such as pleomorphic adenoma (PA) and adenoid cystic carcinoma (ACC), makes it necessary to consider this entity in cases of glandular tumours of the maxillofacial area. A nonspecific presentation and difficulty in obtaining a histology-based diagnosis characterize this benign neoplasm. Total parotidectomy is preferred for tumours in the deep portion of the parotid gland or for membranous-type BCAs, which tend to be multi-centric, have multiple recurrences, and occasionally undergo malignant transformation.

Here, we report a case in which a mass that originated from the deep lobe of the right parotid gland resulted in skull bone destruction involving the mastoid process and cerebellar dura mater. The tumour was ultimately confirmed as a tubular BCA. The results of this report emphasize the complexity and difficulty of diagnosing BCA, which must be distinguished from PA, ACC, and adenocarcinoma. It is important to obtain a histopathological confirmation in a BCA diagnosis and to explore the potential for adjacent tissue destruction in tubular BCA.

CASE PRESENTATION

Chief complaints

In March 2017, a 58-year-old woman attended the outpatient oral and maxillofacial surgery clinic. Her chief complaint was the presence of a painless swelling in her right parotid gland for one year.

History of present illness

Ten years before, the patient had right facial paralysis without apparent cause, and then one year before, she stumbled across a peanut-sized nodule on her right postauricular region. The mass gradually increased in size during the previous half year and was accompanied by vertigo. Six days before her visit to our hospital, she went to Jiangnan Oilfield general hospital and received a fine-needle aspiration (FNA), which suggested a diagnosis of PA with cell hyperplasia. Then, she was advised to go to a higher-level hospital for further treatment. Since the onset of illness, the general condition of patients has had no significant change.

History of past illness

The patient underwent appendectomy in Houhu Farm Hospital 25 years ago. There is no other special trauma history, blood transfusion history, or allergy history. There was not a history of ear disease or past radiology.

Personal and family history

Non-apparent abnormality.

Physical examination upon admission

A physical examination revealed a mass measuring approximately 6 cm × 7 cm. The mass was firm, immovable, non-tender, smooth-surfaced, and well-demarcated. There was regional lymphadenopathy on the same side of the neck. She was diagnosed with right facial palsy more than ten years previously and showed clinical characteristics of peripheral facial paralysis (Figure 1), including an askew mouth, an inability to frown or to close the eye, and a smooth right nasolabial fold.

Laboratory examinations

Biochemical blood tests were within normal limits. The results of a preliminary FNA biopsy suggested PA with positive immunostaining for cytokeratin, nuclear associated antigen Ki-67 (< 5%), and markers for luminal cells [epithelial membrane antigen, cluster of differentiation-17] and myoepithelial cells [soluble protein-100, transformation-related protein 63, cytokine-14, and calponin]. A possible diagnosis of ACC could not be ruled out at the time.

Imaging examinations

Magnetic resonance imaging was performed and revealed a well-defined, heterogeneously enhancing mass with a size of 3.9 cm × 2.9 cm × 5.3 cm that was mostly derived from the deep lobe of the right parotid gland. The signs showed invasion in adjacent structures (right mastoid and occipital bone) (Figure 2). It also indicated that the branches of right lateral carotid artery adjacent to the mass were pushed and squeezed.

FINAL DIAGNOSIS

The excised specimen was sent for histopathological and immunohistochemical analysis to obtain more detailed and accurate histopathology-based diagnosis. Hematoxylin-eosin staining showed that the tumour possessed relatively uniform-appearing basaloid epithelial cells arranged in clusters around ducts, an abundant basal cell layer, and a distinctive basement membrane-like material (Figure 3). The immunohistochemical analysis showed that the tumour was positive for epithelial membrane antigen, transformation-related protein 63, calponin and Ki67 (5%). Its overall features were indicative of tubular BCA of the right parotid gland.

TREATMENT

In April 2017, a total excision including the removal of the mass with the right parotid gland and involving the right mastoid process and cerebellar dura mater was planned in cooperation with a neurosurgeon. The intramastoid part of the tumour was exposed, and a partial right mastoid osteotomy followed by a total parotidectomy was performed (Figure 4). The tumour was encapsulated by fine fibrous connective tissue originating in the parotid gland and intramastoid parts. Dura mater was not involved, so we successfully departed the tumour and cerebellar dura mater. The results of an analysis of frozen sections of intraoperatively obtained tissues provided an unclear diagnosis of a benign tumour. The cut surface of the tumour was greyish-white in colour, and no necrotic and haemorrhagic changes were found in the tumour.

OUTCOME AND FOLLOW-UP

In July 2017, a post-operative magnetic resonance imaging showed no mass residual and an absence of the right parotid gland (Figure 5). Except for the right facial paralysis, there was no sign of recurrence and neurosis after one year of follow-up.

DISCUSSION

BCAs are uncommon benign tumours with an appearance dominated by basaloid cells. The parotid gland, and especially its superficial lobe, is the most common site of BCA occurrence and is followed by tumour occurrence by the palate and buccal mucosa^[4]. A thorough review of the literature revealed that no previous study has described a case with a BCA in the deep lobe of the parotid gland with adjacent bone

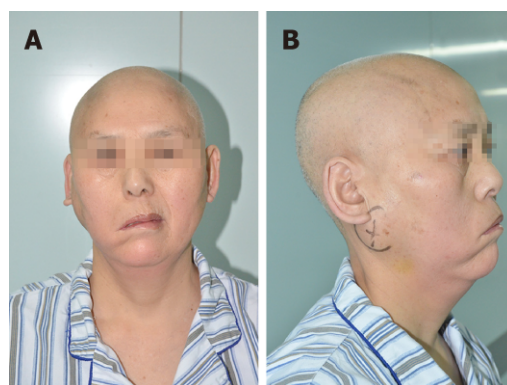


Figure 1 Clinical photographs of the right parotid swelling and characteristics of right facial palsy. A: Front photograph; B: Right side photograph. (March 2017)

destruction and intracranial invasion.

Clinically, BCA tends to be an asymptomatic, slowly enlarging, well-encapsulated tumour with a diameter of no more than 3 cm^[6]. One unusual feature observed in this case was a BCA of the parotid gland that measured up to 6 cm in diameter, far exceeding the normal size of such tumours. Grossly, BCAs appear as round or oval tumours encapsulated by fine fibrous connective tissue. In many cases, cystic formations, predominantly found in tubular and trabecular BCAs, are noted in the central area of the tumour, and the lumens are usually filled with mucinous material^[4]. In our case, a preliminary radiological assay seemed to show several small cysts within the tumour, leading to a suspected diagnosis of BCA.

Pathology examination is acknowledged as the most accurate method for diagnosing BCA. Histologically, BCA is divided into the following four subtypes based on morphologic patterns: solid, trabecular, tubular, and membranous. Solid variants are the most common type^[7], and membranous BCAs are normally expected to be non-encapsulated, multicentric, and multilobular^[8,9]. Other primary tumours, such as PA, ACC, and basal cell adenocarcinoma, can simulate its basal cell features, making this tumour difficult to diagnose and differentiate. However, the appearance of BCAs, including the lack of a chondromyxoid stroma and the presence of a distinctive basal membrane, in addition to the absence of an infiltrative growth pattern, perineural invasion, and mitotic features, and their particular pattern of immunohistochemical staining, including epithelial membrane antigen, α smooth muscle actin, and focal staining for Ki-67 (< 5%), can help to distinguish a BCA from another primary tumour, such as a PA or ACC and basal cell adenocarcinoma^[2,4,10,11]. However, it is not easy to confirm a BCA diagnosis.

In our case, findings based on primary FNA and immunohistochemistry initially suggested a probable diagnosis of PA without ruling out ACC. We decided in our surgical plan to take several factors into consideration, including the patient's clinical features, radiological examination, and histopathological findings. The results of our analysis of intraoperatively obtained sections produced an ambiguous diagnosis of a benign lesion derived from the right parotid gland. A final diagnosis of tubular BCA can be established only when a histopathological examination is performed after the tumour removal. By combining the clinical manifestations (bone destruction and local invasive behaviour) and histological features (Ki67, 5%) of the tumour, we were inclined to consider the tumour a borderline lesion, even though it was a BCA.

BCA can be managed by conservative resection resulting in a negative surgical margin. Additionally, the results of an accurate surgical treatment can differ based on the preoperative and intraoperative diagnoses. While superficial or total parotidectomy is generally considered the primary treatment for BCA, the membranous subtype requires complete resection of the entire gland^[8]. In contrast to the high recurrence rate for this specific BCA type (24%), the recurrence rates for the other three types of BCA is nearly zero. We observed no recurrence after a follow-up of one year. Malignant transformation is also more common in membranous BCA, although it remains extremely rare^[8]. However, signs of invasion into adjacent structures were evident in our case, which was a tubular BCA, and these tend to occur in membranous type BCAs or malignant neoplasms. Further studies aimed at increasing our understanding of BCA should be performed in the future. Overall, when treatment achieves a wide excision exhibiting a negative surgical margin and regular follow-up is performed, the prognosis of BCA is good.



Figure 2 Pre-operative magnetic resonance imaging of the tumour (coronal, April 2017). A 3.9 cm × 2.9 cm × 5.3 cm sized lobulated, well-encapsulated, and heterogeneously enhancing mass on the deep lobe of the right parotid gland (arrow). It extended into the mastoid and was associated with bone destruction in the wall of the ear canal and mastoid.

CONCLUSION

It is rare for a BCA in the parotid gland to extend into the mastoid and ear canal, and this is the first such case to be reported in the literature. A diagnosis of BCA can only be established based on a histopathological examination after an excisional biopsy, and FNA, immunohistochemistry, and magnetic resonance imaging scans should not be considered conclusive. Both the membranous and tubular types of BCA should prompt attention to the possibility of local tissue invasion. The goal of the present paper was to add our case to the literature related to BCAs that arise from the parotid gland and extend into the skull base and to prompt clinicians to carefully consider tubular BCA with parotid gland swelling that shows adjacent tissue destruction. Long-term follow-up and more research are indeed necessary to prevent recurrence and improve the prognosis in this group of patients.

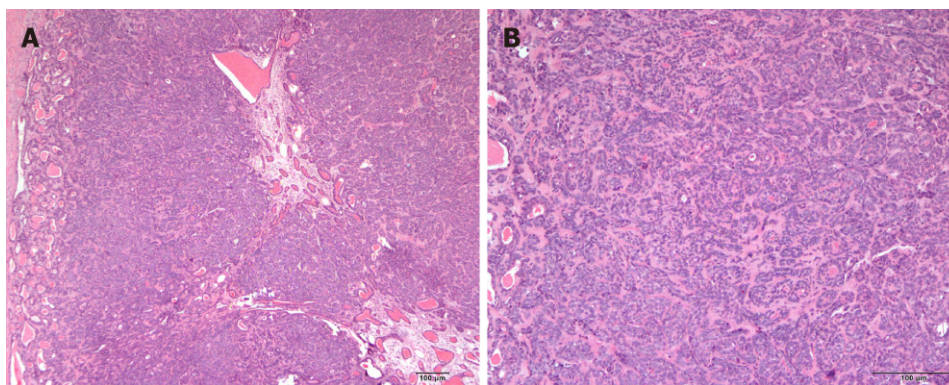


Figure 3 Photomicrographs of the trabecular type of basal cell adenoma. A: A capsule and an eosinophilic basal membrane-like structure (hematoxylin-eosin staining, $\times 40$); B: Small cuboidal to columnar epithelial cells arranged in strands with round hyperchromatic nuclei and relatively rounded central cells. The strands are surrounded by hyalinised connective tissue (hematoxylin-eosin staining, $\times 100$).

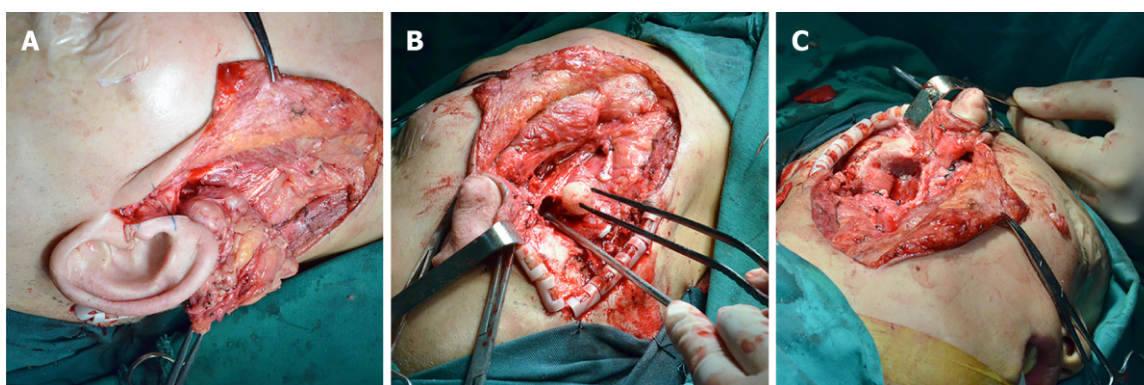


Figure 4 Intra-operative appearance of the tumour mass. A: The right parotid gland part of the tumour was separated; B: The basicranial part of the tumour was removed; C: The right mastoid process and cerebellar dura mater were resected. The mass was clearly lobular in shape, and the mastoid was partially destroyed. (April 2017)

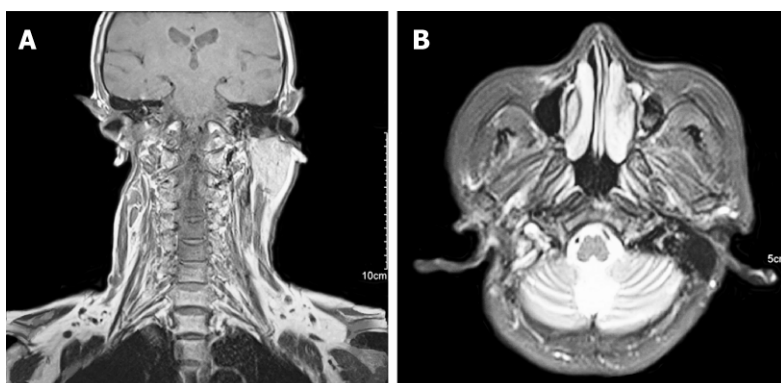


Figure 5 Post-operative magnetic resonance imaging of the patient 3 mo after operation. No obvious residual tissue and no recurrence of the tumour. A: Coronal; B: Axial. (July 2017)

REFERENCES

- 1 **Jang M**, Park D, Lee SR, Hahm CK, Kim Y, Kim Y, Park CK, Tae K, Park MH, Park YW. Basal cell adenoma in the parotid gland: CT and MR findings. *AJNR Am J Neuroradiol* 2004; **25**: 631-635 [PMID: 15090357]
- 2 **González-García R**, Nam-Cha SH, Muñoz-Guerra MF, Gamallo-Amat C. Basal cell adenoma of the parotid gland. Case report and review of the literature. *Med Oral Patol Oral Cir Bucal* 2006; **11**: E206-E209 [PMID: 16505803 DOI: 10.1007/s00233-015-9754-9]
- 3 **Chawla AJ**, Tan TY, Tan GJ. Basal cell adenomas of the parotid gland: CT scan features. *Eur J Radiol* 2006; **58**: 260-265 [PMID: 16414228 DOI: 10.1016/j.ejrad.2005.12.001]

- 4 **Yadav AB**, Narwal A, Devi A, Kumar S, Yadav SK. Basal Cell Adenoma of Palate, a Rare Occurrence with Review of Literature. *J Dent (Shiraz)* 2015; **16**: 291-295 [PMID: [26535412](#)]
- 5 **El-Naggar**, Adel K. Diagnostic Surgical Pathology of the Head and Neck. American Journal of Surgical Pathology. 2001; **25**: 976
- 6 **Chung WY**, Kim CH. Basal cell adenoma in the deep portion of the parotid gland: a case report. *J Korean Assoc Oral Maxillofac Surg* 2015; **41**: 352-356 [PMID: [26733071](#) DOI: [10.5125/jkaoms.2015.41.6.352](#)]
- 7 **Machado de Sousa SO**, Soares de Araújo N, Corrêa L, Pires Soubhia AM, Cavalcanti de Araújo V. Immunohistochemical aspects of basal cell adenoma and canalicular adenoma of salivary glands. *Oral Oncol* 2001; **37**: 365-368 [PMID: [11337269](#) DOI: [10.1016/S1368-8375\(00\)00086-5](#)]
- 8 **Lambade PN**, Rajkhokar D, Lambade D. Basal Cell Adenoma of Submandibular Salivary Gland: A Case Report and Literature Review. *J Maxillofac Oral Surg* 2015; **14**: 999-1003 [PMID: [26604476](#) DOI: [10.1007/s12663-014-0709-6](#)]
- 9 **Junquera L**, Gallego L, de Vicente JC, Fresno MF. Bilateral parotid basal cell adenoma: an unusual case report and review of the literature. *J Oral Maxillofac Surg* 2010; **68**: 179-182 [PMID: [20006174](#) DOI: [10.1016/j.joms.2009.04.091](#)]
- 10 **Jeddy N**, Prasannamoorthy L, Thavarajah R, Radhika T, Ramachandran A. Membranous Basal Cell Adenoma - A Rare Entity in an Unusual Location. *J Clin Diagn Res* 2017; **11**: ZD21-ZD22 [PMID: [28571291](#) DOI: [10.7860/JCDR/2017/25940.9692](#)]
- 11 **Veeresh M**, Bavle RM, Vinay KN, Nandakumar H. Basal cell adenoma of the submandibular gland. *J Maxillofac Oral Surg* 2010; **9**: 289-291 [PMID: [22190808](#) DOI: [10.1007/s12663-010-0035-6](#)]

Novel *ATL1* mutation in a Chinese family with hereditary spastic paraplegia: A case report and review of literature

Xue-Wen Xiao, Juan Du, Bin Jiao, Xin-Xin Liao, Lu Zhou, Xi-Xi Liu, Zhen-Hua Yuan, Li-Na Guo, Xin Wang, Lu Shen, Zhang-Yuan Lin

ORCID number: Xue-Wen Xiao (0000-0001-9151-8937); Juan Du (0000-0002-0051-6125); Bin Jiao (0000-0002-6337-0784); Xin-Xin Liao (0000-0003-1461-900X); Lu Zhou (0000-0001-7499-3971); Xi-Xi Liu (0000-0002-0854-9677); Zhen-Hua Yuan (0000-0003-0957-0280); Li-Na Guo (0000-0002-3752-6079); Xin Wang (0000-0001-7254-0100); Lu Shen (0000-0002-3393-8578); Zhang-Yuan Lin (0000-0002-0777-8347).

Author contributions: Xiao XW reported the case and drafted manuscript; Du J, Jiao B, Liao XX and Zhou L studied the HSP family; Liu XX, Yuan ZH, Guo LN, Wang X and Shen L reviewed the relevant literatures; Lin ZY reviewed the literatures and revised the manuscript

Supported by National Natural Science Foundation of China, No. 81171068.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report.

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

CARE Checklist (2016) statement: The manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative

Xue-Wen Xiao, Juan Du, Bin Jiao, Lu Zhou, Xi-Xi Liu, Zhen-Hua Yuan, Li-Na Guo, Xin Wang, Lu Shen, Department of Neurology, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China

Juan Du, Bin Jiao, Lu Shen, Zhang-Yuan Lin, National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China

Bin Jiao, Lu Shen, Key Laboratory of Hunan Province in Neurodegenerative Disorders, Central South University, Changsha 410008, Hunan Province, China

Xin-Xin Liao, Department of Geriatrics Neurology, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China

Lu Shen, Key Laboratory of Organ Injury, Aging and Regenerative Medicine of Hunan Province, Changsha 410008, Hunan Province, China

Zhang-Yuan Lin, Department of Orthopedics, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China

Corresponding author: Zhang-Yuan Lin, MD, PhD, Surgeon, Department of Orthopedics, Xiangya Hospital, Central South University, No. 87 Xiangya Rd., Kaifu District, Changsha 410008, Hunan Province, China. linzhangyuan2505@sina.com

Telephone: +86-731-84327623

Fax: +86-731-84327332

Abstract

BACKGROUND

Hereditary spastic paraplegias (HSPs) refer to a group of heterogeneous neurodegenerative diseases characterized by lower limbs spasticity and weakness. So far, over 72 genes have been found to cause HSP (SPG1-SPG72). Among autosomal dominant HSP patients, spastic paraplegia 4 (SPG4/SPAST) gene is the most common pathogenic gene, and atlastin-1 (*ATL1*) is the second most common one. Here we reported a novel *ATL1* mutation in a Chinese spastic paraplegia 3A (SPG3A) family, which expands the clinical and genetic spectrum of *ATL1* mutations.

CASE SUMMARY

A 9-year-old boy with progressive spastic paraplegia accompanied by right hearing loss and mental retardation for five years was admitted to our hospital.

Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Received: February 2, 2019

Peer-review started: February 11, 2019

First decision: March 9, 2019

Revised: March 23, 2019

Accepted: April 9, 2019

Article in press: April 9, 2019

Published online: June 6, 2019

P-Reviewer: Demonacos C, Kiselev AV, Radenovic L, Rodrigues-Lisoni FC

S-Editor: Ji FF

L-Editor: A

E-Editor: Xing YX



Past history was unremarkable. The family history was positive, and his grandfather and mother had similar symptoms. Neurological examinations revealed hypermyotonia in his lower limbs, hyperreflexia in knee reflex, bilateral positive Babinski signs and scissors gait. The results of blood routine test, liver function test, blood glucose test, ceruloplasmin test and vitamin test were all normal. The serum lactic acid level was significantly increased. The testing for brainstem auditory evoked potential demonstrated that the right side hearing was impaired while the left was normal. Magnetic resonance imaging showed mild atrophy of the spinal cord. The gene panel test revealed that the proband carried an *ATL1* c.752A>G p.Gln251Arg (p.Q251R) mutation, and Sanger sequencing confirmed the existence of family co-segregation.

CONCLUSION

We reported a novel *ATL1* Q251R mutation and a novel clinical phenotype of hearing loss in a Chinese SPG3A family.

Key words: Hereditary spastic paraplegia; SPG3A; Atlastin-1 (*ATL1*) gene; Hearing loss; Case report

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Hereditary spastic paraplegias are a group of genetically and clinically heterogeneous neurodegenerative diseases characterized by lower limbs spasticity and weakness. Here we reported a novel *ATL1* Q251R mutation predicted to be pathogenic and a novel clinical phenotype of hearing loss in a Chinese SPG3A family, which expands the clinical and genetic spectrum of *ATL1* mutations.

Citation: Xiao XW, Du J, Jiao B, Liao XX, Zhou L, Liu XX, Yuan ZH, Guo LN, Wang X, Shen L, Lin ZY. Novel *ATL1* mutation in a Chinese family with hereditary spastic paraplegia: A case report and review of literature. *World J Clin Cases* 2019; 7(11): 1358-1366

URL: <https://www.wjgnet.com/2307-8960/full/v7/i11/1358.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v7.i11.1358>

INTRODUCTION

Hereditary spastic paraplegias (HSPs), also called spastic paraplegias (SPGs), are a group of genetically and clinically heterogeneous neurodegenerative diseases characterized by lower limbs spasticity and weakness. HSP can be classified into pure and complicated HSP based on symptoms. In pure HSP, the patient simply develops spasticity and weakness in lower limbs, while in complicated HSP, the patient presents with lower limbs spasticity accompanied by other symptoms, such as seizure and ataxia^[1]. Over 72 genes have been identified to cause HSP and named by the order of discovery (SPG1-SPG72). HSP can be inherited in autosomal dominant, autosomal recessive or X-linked forms^[2].

Among autosomal dominant HSP (AD-HSP) patients, spastic paraplegia 4 (SPG4/SPAST) is the most common pathogenic gene while the second most common one is atlastin-1 (*ATL1*)^[3,4]. The patients presenting with walking disturbances sometimes initially visit orthopaedic outpatient clinic for treatment. It is crucial to distinguish HSP from other orthopaedic diseases. Drugs, stretching and physiotherapy can reduce spasticity of HSP patients. In some severe HSP cases, orthopaedic surgery is also needed for improving contracture in the lower limbs^[5]. Here we reported a novel *ATL1* Q251R mutation in a Chinese family with spastic paraplegia 3A (SPG3A), with a novel phenotype of hearing loss.

CASE PRESENTATION

Chief complaints

A 9-year-old male student was admitted to our hospital orthopaedic outpatient clinic because of progressive spastic paraplegia accompanied by right hearing loss and

mental retardation for five years.

History of present illness

Five years ago, the patient began to have difficulty in walking and climbing stairs progressively accompanied by right hearing loss and mental retardation.

History of past illness

His medical history was not remarkable.

Personal and family history

His family history was positive for spastic paraplegia (Figure 1). His grandfather (subject I:1 Figure 1) developed unsteady walking at 3 years old, while his mother presented the same symptoms (subject II:2 Figure 1) at 8 years old. His mother had no other symptoms, while his grandfather had mental retardation (Table 1).

Physical examination upon admission

Vital signs were in the normal ranges: Body temperature, 37.0 °C, respiratory rate, 21 breaths/min, pulse rate, 92 bpm and blood pressure, 98/60 mmHg. Neurological examinations revealed hypermyotonia in his lower limbs, hyperreflexia in knee reflex, and bilateral positive Babinski signs. He had scissors gait when walking. His lower limbs' muscle strengths were grade 5-/5.

Laboratory examinations

The results of blood routine test, urine routine test, stool routine test, liver function test, renal function test, serum creatase, serum electrolyte, plasma ammonia, blood glucose, ceruloplasmin test and vitamin test were all within normal ranges. The serum lactic acid level was significantly raised to 4.36 mmol/L (normal range: 1.42-1.90 mmol/L). The gene panel included 72 known pathogenic genes associated with spastic paraplegia (Supplement Table 1). Genetic testing revealed that the proband carried an *ATL1* c.752A>G p.Gln251Arg (p.Q251R) mutation, and Sanger sequencing confirmed the existence of family co-segregation (Figure 2).

Imaging examinations

Magnetic resonance imaging (MRI) of the proband showed mild atrophy of the spinal cord (Figure 3), while the MRI results of his grandfather and mother were normal.

FINAL DIAGNOSIS

A diagnosis of autosomal-dominant SPG3A was made based on previously published criteria^[6].

TREATMENT

Mecobalamine 0.5 mg three times a day, coenzyme Q10 400 mg twice a day and baclofen 5 mg three times a day were administrated to the patient.

OUTCOME AND FOLLOW-UP

No adverse effects were observed. The patient's symptoms deteriorated gradually in a follow-up visit after two months.

DISCUSSION

To date, 68 *ATL1* pathogenic mutation types have been identified, most of which are missense mutations, followed by small insertions, small deletions and whole exon deletions. The mutation types were located in exon 12 (*n* = 29, 42.65%), exon 4 (*n* = 12, 17.65%), exon 8 (*n* = 8, 11.77%), exon 10 (*n* = 6, 8.82%), exon 7 (*n* = 4, 5.88%), exon 5 (*n* = 2, 2.94%), exon 11 (*n* = 2, 2.94%), exon 3 (*n* = 1, 1.47%), exon 6 (*n* = 1, 1.47%), exon 9 (*n* = 1, 1.47%), exon 13 (*n* = 1, 1.47%), and intron 1 (*n* = 1, 1.47%). The most common mutation genetic model is autosomal dominant (AD) inheritance (*n* = 57, 83.82%) while the sporadic is the second most common one (*n* = 7, 10.30%), and autosomal recessive (AR) inheritance is rare (*n* = 2, 2.94%) while two mutations' types are not available (*n* = 2, 2.94%) (Table 2)^[4,7-12]. Most *ATL1* mutation carriers develop pure

Table 1 Clinical characteristics of the patient and affected family members

Characteristics	I:1	II:2	III:1
Gender	Male	Female	Male
Age at onset (yr)	3	8	4
Past history	Lumbar disc herniation	None	None
Clinical presentations	Walking disturbance, mental retardation	Walking disturbance	Walking disturbance, mental retardation, right hearing loss
Physical examination			
Muscle strength	Normal	Normal	Lower limbs: grade 5-
Muscle tension	Lower limbs: increase	Lower limbs: increase	Lower limbs: increase
Sensory	Normal	Normal	Normal
Tendon reflex	Bilateral knee reflex ¹	Bilateral knee reflex ¹	Bilateral knee reflex ²
Babinski signs	Positive	Positive	Positive
Gait	Scissors gait	Scissors gait	Scissors gait
Auxiliary examination			
MRI	Normal	Normal	Mild atrophy of the spinal cord
EMG/NCS	NA	Normal	Right tibial nerve's F wave: Wide
BAEP	NA	NA	Right side hearing was impaired

¹Active;²Hyperreflexia. MRI: Magnetic resonance imaging; EMG: Electromyography; NCS: Nerve conduction study; BAEP: Brainstem auditory evoked potential; NA: Not available.

HSP^[4,13,14], while a few of them present with complicated phenotypes, such as seizure, optic atrophy, mental retardation and ataxia^[15]. In China, the most common phenotype of *ATL1* mutation carriers is pure HSP while only one complicated phenotype was observed, namely muscular atrophy^[16-21].

The impairments of the upper motor system can lead to spastic paraplegia, including cerebral palsy, brain injury, spinal cord infection, spinal cord tumor, and spinal cord injury^[22-26]. Among them, the most common cause of spastic paraplegia in children is cerebral palsy, which can mimic HSP^[27]. Consequently, it is important to identify HSP in orthopedic patients presenting with spastic paraplegia. Lumbosacral dorsal rhizotomy, botulinum toxin, and physiotherapy are effective ways to treat spasticity in children^[28,29].

In the present study, we detected a novel *ATL1* Q251R mutation, which is located in exon 8. *ATL1* Q251R was considered as a novel mutation, as it is absent in the Human Gene Mutation Database (HGMD) (<http://www.hgmd.cf.ac.uk/ac/index.php>) and clinvar database (www.ncbi.nlm.nih.gov/clinvar/). Besides, no previous case has been reported with *ATL1* Q251R by searching it in PubMed and Web of Science. Protein Variation Effect Analyzer (PROVEN), Mutation Taster and Mutation Assessor were utilized to predict the pathogenicity of *ATL1* Q251R, and the results were described as deleterious, disease-causing and medium credible pathogenic, respectively. The amino-acid substitution replaced a neutrally charged glutamine for a positively charged arginine. Besides, *ATL1* Q251K was also reported to be a disease-causing mutation in HSP^[30]. Consequently, the above evidence suggests that *ATL1* Q251R is likely to be a pathogenic mutation of HSP. Further functional studies are warranted to confirm its pathogenicity.

ATL1 was firstly identified and reported to be pathogenic in five HSP kindreds^[31]. It encodes for atlastin-1 (*ATL1*) protein that belongs to the dynamin family of guanosine triphosphatases (GTPases). *ATL1* protein has a vital role in homotypic endoplasmic reticulum fusion, which is likely to be the underlying mechanism in the pathogenesis of HSP^[32].

In our SPG3A family, we found that the proband and affected family members exhibit different clinical manifestations despite having the same mutation. The proband developed progressive walking disturbance accompanied by hearing loss and mental retardation, while his mother exhibited pure HSP symptoms and his grandfather also had mental retardation but no hearing dysfunction. This clearly indicates that SPG3A is clinically heterogeneous. The intra-family variable penetrance may result from environmental modifiers as well as regulatory variants^[33]. Furthermore, sex and mutation types are of great importance in modifying the penetrance in HSP^[34]. In our SPG3A family, regulatory variants, gender differences and environmental factors may be the underlying contributors to different phenotypes.

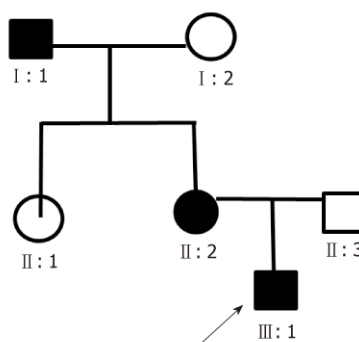


Figure 1 The pedigree of the SPG3A family. The patient is indicated with arrow (III:1) and the affected families are indicated by solid boxes (I:1 and II:2).

Our group previously analyzed the clinical spectrum of HSP in China and found that most of cases were pure one, whereas a few showed complicated phenotypes like atrophy in extremities^[35]. Only a few HSP patients develop deafness or hearing loss in the course of the disease, however, none of SPG3A patients with deafness or hearing loss has been reported^[36]. The patient we presented here developed progressive walking disturbance accompanied by hearing loss. Therefore, we also presented a novel clinical phenotype in SPG3A, hearing loss.

Furthermore, both neurological defects and orthopaedic diseases can result in movement abnormalities^[5]. In fact, orthopaedic surgeons are usually the first doctors who are visited by patients with walking disturbances or gait abnormalities, including HSP patients presenting with progressive spasmodic paraplegia. For example, a Caucasian girl was misdiagnosed with cerebral palsy and a final correct diagnosis of SPG3A was made by genetic testing^[12]. Consequently, careful medical history inquiry and physical examination are extremely important for diagnosis. In some cases, no definite diagnosis can be established by an orthopaedic surgeon alone. The evaluation of a neurologist or multidisciplinary team including a neurologist is essential for correct diagnosis. Besides, the treatments of HSP also involve appropriate orthopaedic therapies, such as surgery in severe HSP patients^[37].

CONCLUSION

In conclusion, we reported a novel *ATL1* Q251R mutation which is likely to be pathogenic and a clinically novel phenotype of hearing loss in a Chinese SPG3A family, which expands the clinical and genetic spectrum of *ATL1* mutations. SPG3A was clinically heterogeneous even with the same pathogenic mutation. In addition, this report emphasizes the importance of distinguishing HSP patients from other patients in orthopaedic outpatient clinic.

Table 2 *ATL1* pathogenic mutations in hereditary spastic paraplegia

Exon	Nucleotide changes	Amino acid changes	Genetic model
3	G353A	R118Q	AR
4	T452C	F151S	AD
4	G458C	S153T	AD
4	C460G	Q154E	AD
4	C467T	T156I	AD
4	T470G	L157W	AD
4	T470C	L157S	AD
4	G473C	R158T	AD
4	G481C	A161P	AD
4	A484C	T162P	AD
4	T488C	V163A	AD
4	G493A	A165T	AD
5	C565G	H189D	AD
5	A572G	Q191R	AD
6	A587G	Y196C	AD
7	C649T	R217*	AR
7	G650A	R217Q	AD
7	C715T	R239C	AD
7	G716T	R239L	AD
8	A740C	H247P	AD
8	T749C	L250P	AD
8	C751A	Q251K	AD
8	G757A	V253I	AD
8	A773G	H258R	AD
8	C777A	S259Y	AD
8	C776T	S259Y	AD
8	T776G	S259F	AD
9	T944G	I315S	AD
10	C1006T	Y336H	AD
10	C1025A	P342Q	AD
10	C1030T	P344S	S
10	T1036G	S346A	AD
10	T1040C	M347T	AD
10	G1048T	A350S	AD
11	A1064T	N355I	S
11	C1065A	N355K	S
12	T1123C	C375R	AD
12	C1193A	S398Y	AD
12	C1193T	S398F	S
12	T1202C	L401P	S
12	A1220G	K407R	AD
12	A1222G	M408V	AD
12	T1223C	M408T	AD
12	A1222G	M408T	AD
12	G1226A	G409D	S
12	G1228A	G410R	AD
12	A1237C	F413V	AD
12	T1239C	F413L	AD
12	C1242G	S414R	AD
12	C1243T	R415W	AD
12	A1244G	R415Q	AD
12	C1246T	R416C	AD

12	G1247A	R416H	AD
12	T1308A	N436K	S
12	A1319C	N440T	AD
12	A1376G	Y459C	AD
12	G1406C	G469A	AD
12	G1445T	G482V	AD
12	C1483T	R495W	AD
13	G1556A	S519N	AD
12	1306-1308delAAT	N436del	AD
4	Exon 4 del	140-174del	NA
Intron 1	c.35-3C>T	G13fsX16	AD
12	1462_1463insTG	T490Afs	NA
12	1466-1467insTG	T490fsX508	AD
12	1474insG	A492fsX522	AD
12	1504-1505insG	E502fsX522	AD
12	1520insA	I507fsX522	AD

AR: Autosomal recessive; AD: Autosomal dominant; S: Sporadic; NA: Not available.

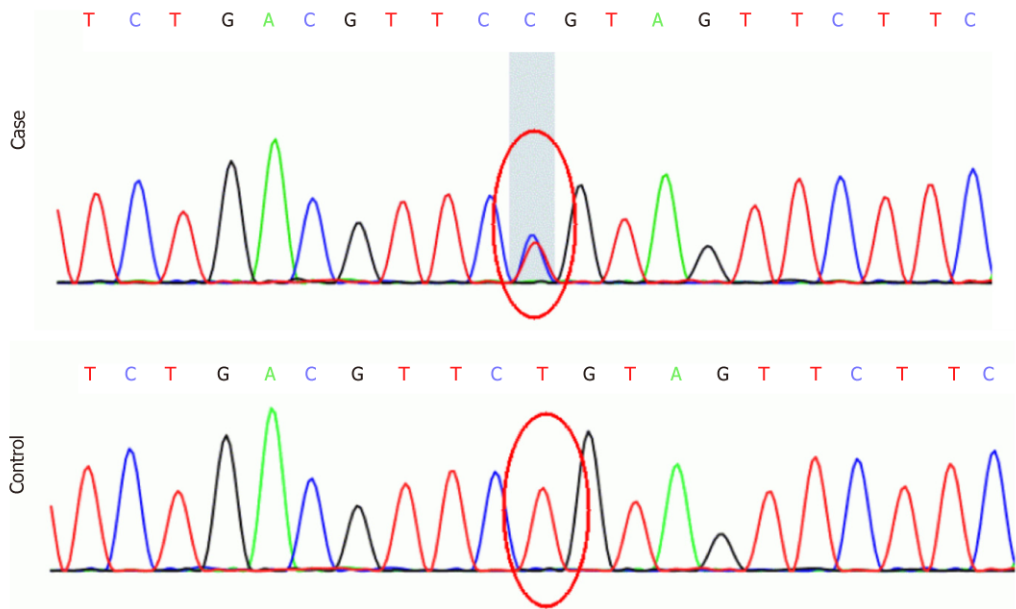


Figure 2 DNA sequencing identified a novel *ATL1* c.752A>G, p.Q251R mutation (top: sequence of the patients; bottom: sequence of healthy individuals).

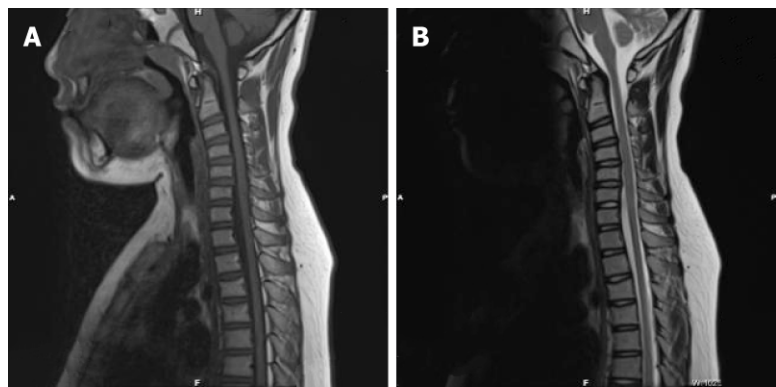


Figure 3 Magnetic resonance imaging showed the mild atrophy the spinal cord. A: T1 sagittal view B: T2 sagittal view.

ACKNOWLEDGEMENTS

The authors are grateful to all subjects for participation in our study.

REFERENCES

- Kara E**, Tucci A, Manzoni C, Lynch DS, Elpidorou M, Bettencourt C, Chelban V, Manole A, Hamed SA, Haridy NA, Federoff M, Preza E, Hughes D, Pittman A, Jaunmuktane Z, Brandner S, Xiromerisiou G, Wiethoff S, Schottlaender L, Proukakis C, Morris H, Warner T, Bhatia KP, Korlipara LV, Singleton AB, Hardy J, Wood NW, Lewis PA, Houlden H. Genetic and phenotypic characterization of complex hereditary spastic paraplegia. *Brain* 2016; **139**: 1904-1918 [PMID: [27217339](#) DOI: [10.1093/brain/aww111](#)]
- Gan-Or Z**, Bouslam N, Birouk N, Lissouba A, Chambers DB, Vérièpe J, Androschuk A, Laurent SB, Rochefort D, Spiegelman D, Dionne-Laporte A, Szuto A, Liao M, Figlewicz DA, Bouhouche A, Benomar A, Yahyaoui M, Ouazzani R, Yoon G, Dupré N, Suchowersky O, Bolduc FV, Parker JA, Dion PA, Drapeau P, Rouleau GA, Ouled Amar Bencheikh B. Mutations in *CAPN1* Cause Autosomal-Recessive Hereditary Spastic Paraplegia. *Am J Hum Genet* 2016; **98**: 1038-1046 [PMID: [27153400](#) DOI: [10.1016/j.ajhg.2016.04.002](#)]
- Vandebona H**, Kerr NP, Sue CM. Mutation Analysis of Spastin (SPG4) in Patients with Hereditary Spastic Paraplegia. *J Clin Neurosci* 2009; **16**: 476 [DOI: [10.1016/j.jocn.2008.07.049](#)]
- Zhao GH**, Liu XM. Clinical features and genotype-phenotype correlation analysis in patients with *ATL1* mutations: A literature reanalysis. *Transl Neurodegener* 2017; **6**: 9 [PMID: [28396731](#) DOI: [10.1186/s40035-017-0079-3](#)]
- Houlden H**, Charlton P, Singh D. Neurology and orthopaedics. *J Neurol Neurosurg Psychiatry* 2007; **78**: 224-232 [PMID: [17308288](#) DOI: [10.1136/jnnp.2006.092072](#)]
- Gasser T**, Finsterer J, Baets J, Van Broeckhoven C, Di Donato S, Fontaine B, De Jonghe P, Lossos A, Lynch T, Mariotti C, Schöls L, Spinazzola A, Szolnoki Z, Tabrizi SJ, Tallaksen CM, Zeviani M, Burgunder JM, Harbo HF; EFNS. EFNS guidelines on the molecular diagnosis of ataxias and spastic paraplegias. *Eur J Neurol* 2010; **17**: 179-188 [PMID: [20050888](#) DOI: [10.1111/j.1468-1331.2009.02873.x](#)]
- Dong EL**, Wang C, Wu S, Lu YQ, Lin XH, Su HZ, Zhao M, He J, Ma LX, Wang N, Chen WJ, Lin X. Clinical spectrum and genetic landscape for hereditary spastic paraplegias in China. *Mol Neurodegener* 2018; **13**: 36 [PMID: [29980238](#) DOI: [10.1186/s13024-018-0269-1](#)]
- Mészárosová AU**, Grečmalová D, Brázdilová M, Dvořáčková N, Kalina Z, Čermáková M, Vávrová D, Smetanová I, Staněk D, Seeman P. Disease-Causing Variants in the *ATL1* Gene Are a Rare Cause of Hereditary Spastic Paraplegia among Czech Patients. *Ann Hum Genet* 2017; **81**: 249-257 [PMID: [28736820](#) DOI: [10.1111/ahg.12206](#)]
- Willkomm L**, Heredia R, Hoffmann K, Wang H, Voit T, Hoffman EP, Cirak S. Homozygous mutation in *Atlastin* GTPase 1 causes recessive hereditary spastic paraplegia. *J Hum Genet* 2016; **61**: 571-573 [PMID: [26888483](#) DOI: [10.1038/jhg.2016.6](#)]
- Lu C**, Li LX, Dong HL, Wei Q, Liu ZJ, Ni W, Gitler AD, Wu ZY. Targeted next-generation sequencing improves diagnosis of hereditary spastic paraplegia in Chinese patients. *J Mol Med (Berl)* 2018; **96**: 701-712 [PMID: [29934652](#) DOI: [10.1007/s00109-018-1655-4](#)]
- Duz MB**, Dasdemir S, Kalayci Yigin A, Akalin MA, Seven M. Three novel mutations in 20 patients with hereditary spastic paraparesis. *Neurol Sci* 2018; **39**: 1551-1557 [PMID: [29907907](#) DOI: [10.1007/s10072-018-3454-7](#)]
- Andersen EW**, Leventer RJ, Reddihough DS, Davis MR, Ryan MM. Cerebral palsy is not a diagnosis: A case report of a novel *atlastin-1* mutation. *J Paediatr Child Health* 2016; **52**: 669-671 [PMID: [27333849](#) DOI: [10.1111/jpc.13200](#)]
- Alvarez V**, Sánchez-Ferrero E, Beetz C, Díaz M, Alonso B, Corao AI, Gámez J, Esteban J, Gonzalo JF, Pascual-Pascual SI, López de Munain A, Moris G, Ribacoba R, Márquez C, Rosell J, Marín R, García-Barcina MJ, Del Castillo E, Benito C, Coto E; Group for the Study of the Genetics of Spastic Paraplegia. Mutational spectrum of the *SPG4* (SPAST) and *SPG3A* (*ATL1*) genes in Spanish patients with hereditary spastic paraplegia. *BMC Neurol* 2010; **10**: 89 [PMID: [20932283](#) DOI: [10.1186/1471-2377-10-89](#)]
- Elert-Dobkowska E**, Stepniak I, Krysa W, Rajkiewicz M, Rakowicz M, Sobanska A, Rudzinska M, Wasielewska A, Pilch J, Kubalska J, Lipczynska-Lojkowska W, Kulczycki J, Kurdziel K, Sikorska A, Beetz C, Zaremba J, Sulek A. Molecular spectrum of the *SPAST*, *ATL1* and *REEP1* gene mutations associated with the most common hereditary spastic paraplegias in a group of Polish patients. *J Neurol Sci* 2015; **359**: 35-39 [PMID: [26671083](#) DOI: [10.1016/j.jns.2015.10.030](#)]
- Orlacchio A**, Montieri P, Babalini C, Gaudiello F, Bernardi G, Kawarai T. Late-onset hereditary spastic paraplegia with thin corpus callosum caused by a new *SPG3A* mutation. *J Neurol* 2011; **258**: 1361-1363 [PMID: [21336785](#) DOI: [10.1007/s00415-011-5934-z](#)]
- Chen SQ**, Zhou Y, Li XY, La B, Huang S, Huang WJ, Zhou CL, Maxwell PH, Wang YM. Severe hereditary spastic paraplegia caused by a de novo *SPG3A* mutation. *Sci China* 2005; **51**: 1854-1856 [DOI: [10.3321/j.issn.0023-074X.2006.15.021](#)]
- Li XH**, Song C, Chen SQ, Zhou Y, Guo H, Zhou CL, Yang ZY, Liang YX, Wang YM. A *SPG3A* mutation with a novel foot phenotype of hereditary spastic paraplegia in a Chinese Han family. *Chin Med J (Engl)* 2007; **120**: 834-837 [PMID: [17531128](#) DOI: [10.1136/bmj.39190.610127.BE](#)]
- Ming L**. [SPG3A-hereditary spastin paraplegia with genetic anticipation and incomplete penetrance]. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 2007; **24**: 15-18 [PMID: [17285536](#) DOI: [10.3760/j.issn.1003-9406.2007.01.004](#)]
- Chan KY**, Ching CK, Mak CM, Lam CW, Chan AY. Hereditary spastic paraplegia: identification of an *SPG3A* gene mutation in a Chinese family. *Hong Kong Med J* 2009; **15**: 304-307 [PMID: [19652243](#)]
- Lu X**, Cen Z, Xie F, Ouyang Z, Zhang B, Zhao G, Luo W. Genetic analysis of *SPG4* and *SPG3A* genes in a cohort of Chinese patients with hereditary spastic paraplegia. *J Neurol Sci* 2014; **347**: 368-371 [PMID: [25454648](#) DOI: [10.1016/j.jns.2014.10.017](#)]
- Shin JW**, Jung KH, Lee ST, Moon J, Seong MW, Park SS, Lee SK, Chu K. Novel mutation in the *ATL1* with autosomal dominant hereditary spastic paraplegia presented as dysautonomia. *Auton Neurosci* 2014; **185**: 141-143 [PMID: [24969372](#) DOI: [10.1016/j.autneu.2014.06.001](#)]

- 22 **Matsuura E**, Yoshimura A, Nozuma S, Higuchi I, Kubota R, Takashima H. Clinical presentation of axial myopathy in two siblings with HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP). *BMC Neurol* 2015; **15**: 18 [PMID: [25884435](#) DOI: [10.1186/s12883-015-0275-7](#)]
- 23 **Lee JY**, Kim SN, Lee IS, Jung H, Lee KS, Koh SE. Effects of Extracorporeal Shock Wave Therapy on Spasticity in Patients after Brain Injury: A Meta-analysis. *J Phys Ther Sci* 2014; **26**: 1641-1647 [PMID: [25364134](#) DOI: [10.1589/jpts.26.1641](#)]
- 24 **Chang CH**, Chen YY, Yeh KK, Chen CL. Gross motor function change after multilevel soft tissue release in children with cerebral palsy. *Biomed J* 2017; **40**: 163-168 [PMID: [28651738](#) DOI: [10.1016/j.bj.2016.12.003](#)]
- 25 **Yan X**, Lan J, Liu Y, Miao J. Efficacy and Safety of Botulinum Toxin Type A in Spasticity Caused by Spinal Cord Injury: A Randomized, Controlled Trial. *Med Sci Monit* 2018; **24**: 8160-8171 [PMID: [30423587](#) DOI: [10.12659/MSM.911296](#)]
- 26 **Celiktas M**, Asik MO, Gezercan Y, Gulsen M. Pigmented villonodular synovitis of the thoracic vertebra presenting with progressive spastic paraparesis. *Case Rep Orthop* 2013; **2013**: 870324 [PMID: [24159395](#) DOI: [10.1155/2013/870324](#)]
- 27 **Lee RW**, Poretti A, Cohen JS, Levey E, Gwynn H, Johnston MV, Hoon AH, Fatemi A. A diagnostic approach for cerebral palsy in the genomic era. *Neuromolecular Med* 2014; **16**: 821-844 [PMID: [25280894](#) DOI: [10.1007/s12017-014-8331-9](#)]
- 28 **Health Quality Ontario**. Lumbosacral Dorsal Rhizotomy for Spastic Cerebral Palsy: A Health Technology Assessment. *Ont Health Technol Assess Ser* 2017; **17**: 1-186 [PMID: [28757906](#)]
- 29 **Pavone V**, Testa G, Restivo DA, Cannavò L, Condorelli G, Portinaro NM, Sessa G. Botulinum Toxin Treatment for Limb Spasticity in Childhood Cerebral Palsy. *Front Pharmacol* 2016; **7**: 29 [PMID: [26924985](#) DOI: [10.3389/fphar.2016.00029](#)]
- 30 **Dürr A**, Camuzat A, Colin E, Tallaksen C, Hannequin D, Coutinho P, Fontaine B, Rossi A, Gil R, Rousselle C, Ruberg M, Stevanin G, Brice A. Atlastin1 mutations are frequent in young-onset autosomal dominant spastic paraplegia. *Arch Neurol* 2004; **61**: 1867-1872 [PMID: [15596607](#) DOI: [10.1001/archneur.61.12.1867](#)]
- 31 **Zhao X**, Alvarado D, Rainier S, Lemons R, Hedera P, Weber CH, Tükel T, Apak M, Heiman-Patterson T, Ming L, Bui M, Fink JK. Mutations in a newly identified GTPase gene cause autosomal dominant hereditary spastic paraplegia. *Nat Genet* 2001; **29**: 326-331 [PMID: [11685207](#) DOI: [10.1038/ng758](#)]
- 32 **Bian X**, Klemm RW, Liu TY, Zhang M, Sun S, Sui X, Liu X, Rapoport TA, Hu J. Structures of the atlastin GTPase provide insight into homotypic fusion of endoplasmic reticulum membranes. *Proc Natl Acad Sci U S A* 2011; **108**: 3976-3981 [PMID: [21368113](#) DOI: [10.1073/pnas.1101643108](#)]
- 33 **Castel SE**, Cervera A, Mohammadi P, Aguet F, Reverter F, Wolman A, Guigo R, Iossifov I, Vasileva A, Lappalainen T. Modified penetrance of coding variants by cis-regulatory variation contributes to disease risk. *Nat Genet* 2018; **50**: 1327-1334 [PMID: [30127527](#) DOI: [10.1038/s41588-018-0192-y](#)]
- 34 **Parodi L**, Fenu S, Barbier M, Banneau G, Duyckaerts C, Tezenas du Montcel S, Monin ML, Ait Said S, Guegan J, Tallaksen CME, Sablonniere B, Brice A, Stevanin G, Depienne C, Durr A; SPATAX network. Spastic paraplegia due to SPAST mutations is modified by the underlying mutation and sex. *Brain* 2018; **141**: 3331-3342 [PMID: [30476002](#) DOI: [10.1093/brain/awy285](#)]
- 35 **Luo Y**, Chen C, Zhan Z, Wang Y, Du J, Hu Z, Liao X, Zhao G, Wang J, Yan X, Jiang H, Pan Q, Xia K, Tang B, Shen L. Mutation and clinical characteristics of autosomal-dominant hereditary spastic paraplegias in China. *Neurodegener Dis* 2014; **14**: 176-183 [PMID: [25341883](#) DOI: [10.1159/000365513](#)]
- 36 **Tesson C**, Koht J, Stevanin G. Delving into the complexity of hereditary spastic paraplegias: how unexpected phenotypes and inheritance modes are revolutionizing their nosology. *Hum Genet* 2015; **134**: 511-538 [PMID: [25758904](#) DOI: [10.1007/s00439-015-1536-7](#)]
- 37 **Cottalorda J**, Violas P, Seringe R; French Society of Pediatric Orthopaedics. Neuro-orthopaedic evaluation of children and adolescents: a simplified algorithm. *Orthop Traumatol Surg Res* 2012; **98**: S146-S153 [PMID: [22939865](#) DOI: [10.1016/j.otsr.2012.04.015](#)]



Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

