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World J Gastrointest Surg 2020 March 27; 12(3): 85-128



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The WJGS is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yu-Jie Ma*
Proofing Production Department Director: *Xiang Li*

NAME OF JOURNAL

World Journal of Gastrointestinal Surgery

ISSN

ISSN 1948-9366 (online)

LAUNCH DATE

November 30, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Varut Lohsirawat, Shu-You Peng

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9366/editorialboard.htm>

EDITORIAL OFFICE

Ruo-Yu Ma, Director

PUBLICATION DATE

March 27, 2020

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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>



Evolution and current status of the subclassification of intermediate hepatocellular carcinoma

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Author contributions: Li JS proposed the idea; Yi PS and Wang H wrote the paper; Yi PS collected literatures and abstracted data.

Conflict-of-interest statement: No conflict of interest is reported by the authors.

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Manuscript source: Invited Manuscript

Received: November 11, 2019

Peer-review started: November 11, 2019

First decision: December 11, 2019

Revised: December 21, 2019

Accepted: February 17, 2020

Article in press: February 17, 2020

Published online: March 27, 2020

P-Reviewer: Hann HW, Manesis EK

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Abstract

The staging and treatment of intermediate hepatocellular carcinoma (HCC) remains controversial. According to the recommendations of Barcelona Clinic Liver Cancer staging system, patients with intermediate HCC are candidates for transcatheter arterial chemoembolization. However, not all patients with intermediate HCC benefit from transcatheter arterial chemoembolization. Therefore, it is meaningful to propose a novel staging system of intermediate HCC in order to allocate different treatments for different subgroups. Bolondi *et al* proposed the first subclassification system of intermediate HCC. Subsequently, investigators performed studies to validate the feasibility of Bolondi's criteria and proposed several novel staging systems. The present study reviewed the literatures and provided a general overview of the evolution and current status of the subclassification of intermediate HCC. We propose to expand the indication of liver resection and add radical treatments as the first option of the treatment for patients with intermediate HCC.

Key words: Subclassification; Intermediate hepatocellular carcinoma; Treatment; Staging; Transcatheter arterial chemoembolization; Liver resection

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Core tip: The present study reviewed the literatures and provided a general overview of the evolution and current status of the subclassification of intermediate hepatocellular carcinoma. We propose to expand the indication of liver resection and add radical treatments as the first option of the treatment for patients with intermediate hepatocellular carcinoma.

S-Editor: Gong ZM**L-Editor:** A**E-Editor:** Ma YJ

Citation: Yi PS, Wang H, Li JS. Evolution and current status of the subclassification of intermediate hepatocellular carcinoma. *World J Gastrointest Surg* 2020; 12(3): 85-92
URL: <https://www.wjgnet.com/1948-9366/full/v12/i3/85.htm>
DOI: <https://dx.doi.org/10.4240/wjgs.v12.i3.85>

INTRODUCTION

Hepatocellular carcinoma (HCC) ranks the fifth cause of cancer-associated mortality worldwide, and > 50% of patients with HCC are diagnosed in China^[1,2]. Considering the etiology of HCC, hepatitis C virus infection and alcohol abuse are the main causes of HCC in Western countries. However, patients in China are mainly derived from the trilogy chronic hepatitis B virus infection-liver cirrhosis-HCC onset^[3]. Novel staging and treatment recommendations are critical for improving the prognosis of HCC. The Barcelona Clinic Liver Cancer (BCLC) staging system is widely accepted by investigators and endorsed by the American Association for the Study of Liver Diseases and European Association for the Study of the Liver^[4]. According to the recommendations of BCLC staging system, patients with very early and initial stage HCC within the Milan criteria and without associated diseases are suitable for radical treatments, including liver transplantation, liver resection and radiofrequency ablation. Patients with intermediate HCC (BCLC B stage) are recommended to receive transcatheter arterial chemoembolization (TACE), which is a palliative treatment^[5]. However, 50% of patients with HCC are diagnosed at intermediate stage when the first presentation of symptoms occur^[6], and the prognosis of these patients remains unsatisfactory.

Intermediate HCC comprises heterogeneous patients with varying tumor burden, liver function and performance status, and TACE cannot provide survival benefit for all these patients. The survival benefit of radical treatments for intermediate HCC has been explored in recent years. Mazzaferro *et al*^[7] analyzed the survival of patients beyond the Milan criteria based on largest tumor size, tumor nodule and microvascular invasion (MVI). Patients beyond the Milan criteria but within the sum of largest tumor size and tumor number < 7 had comparable 5-year survival rates to those within the Milan criteria. Thus, they proposed novel criteria for selecting patients with HCC for liver transplantation, called the “up to-7 criteria”^[7]. To improve the prognosis of intermediate HCC, it is of great importance to divide these patients into subgroups and allocate feasible treatments to different subgroups. Bolondi *et al*^[8] proposed a subclassification of intermediate HCC in 2012. The Bolondi criteria sub-divides intermediate HCC into 4 groups and provides first-line and alternative treatment options for different subgroups^[8]. Numerous subsequent studies were conducted to validate or clarify this subclassification system. Certain studies demonstrated the ability of the Bolondi criteria in predicting prognosis of intermediate HCC and supported the application of this system in clinical practice^[9-11]. By contrast, other studies advocated to modify this system and proposed novel subclassification systems^[12-14]. To date, the staging and management of intermediate HCC remains controversial. The present review aims to provide a clear summary of the evolution and general view of current status of the subclassification of intermediate HCC.

PROPOSAL AND VALIDATION OF THE BOLONDI CRITERIA

Patients with intermediate HCC are defined as those with a single tumor > 5 cm, or with 2-3 > 3 cm in maximum diameter, or with > 3 tumors regardless of tumor size, without portal vein thrombosis and extra-hepatic metastasis^[8]. Due to the varying tumor burden, liver function and physical status, patients differ significantly in terms of survival outcomes and treatment response. Bolondi *et al*^[8] proposed to subdivide intermediate HCC into 4 subgroups: Stage B1, which comprises patients with compensated cirrhosis and preserved liver function, who have a Child-Pugh score of 5-7, are within the up to-7 criteria, and have a ECOG PS completely preserved (PS0). The treatment recommendation is controversial in this subgroup, with TACE being recommended to be the first option and liver transplantation or TACE plus ablation being considered alternative options. Stage B2 comprises patients with Child-Pugh A, who are beyond the up to-7 criteria and have good well PS (PS0). TACE or transarterial radioembolization are suggested for these patients, and sorafenib is

recommended as an alternative option. Stage B3 comprises patients with Child-Pugh score of 7, who are beyond the up to seven criteria and have a good PS (PS0). No particular treatment recommendation for this subgroup has been provided thus far, although these patients may be suitable for inclusion in a research randomized clinical trial, with TACE or sorafenib being potential treatment options. Stage B4 comprises patients with decompensated Child-Pugh class B (score of 8 or 9) with severe ascites or jaundice. The treatment allocation for this subgroup is also controversial, the first recommendation is basic supportive care and the alternative option is liver transplantation (Table 1).

Ciria *et al*^[9] performed a retrospective analysis of 80 patients with intermediate HCC, and subdivided these patients according to the Bolondi criteria. Taken together, the study revealed that the 5-year survival rate did not differ between the liver resection group and the TACE group, in the subgroups of intermediate HCC, the 5-year survival rate was higher in stage B1 when compared with stages B2 and B3-4 who had been subjected to liver resection or TACE. However, the overall survival was not significantly different among continuous substages. By multivariate analysis, total bilirubin and subclassification stages B2 and B3-4 *vs* B1 to be independent risk factors of survival. Ciria *et al*^[9] proposed to perform liver resection for stage B1 and partial of patients at B2 and B3-4 stage when the pathological and anatomical criteria were matched. Other retrospective studies obtained similar results to those reported by Ciria *et al*^[9]. Two previous studies did not find significant difference in survival outcomes among continuous subgroups according to the Bolondi criteria^[13,14], while a previous study even reported poor survival outcomes in patients at stage B3 compared with stage B4^[14]. However, several studies also obtained different results compared with above studies. Various studies observed significantly different survival outcomes among continuous subgroups of patients with intermediate HCC. Therefore, they recommended that the Bolondi criteria could feasibly predicting the prognosis of intermediate HCC and advocated the allocation of such criteria in clinical practice^[9-11]. In addition, several studies demonstrated that the subclassification of intermediate HCC was an independent prognostic factor of survival outcomes^[9,11,12]. In summary, Bolondi criteria can predict the prognosis of intermediate HCC to certain extent. However, additional prospective studies are required to clarify its feasibility (Table 2).

PROPOSAL OF A NOVEL SUBCLASSIFICATION OF INTERMEDIATE HCC

Although the feasibility of the Bolondi criteria have been validated by numerous studies, there are certain limitations of this subclassification system. First, the Bolondi criteria stratify intermediate HCC based on 4 factors, but, ECOG PS is a relatively subjective factor; thus, it is difficult to definitely evaluate it and does not discriminate between cancer or cirrhosis-associated symptoms. Second, none of the radical treatments are recommended as first option for intermediate HCC. However, recent studies have demonstrated the survival benefit of radical treatments for intermediate HCC, and liver resection and liver transplantation have been demonstrated to prolong survival in superselective patients with intermediate HCC^[15,16]. Third, no first treatment option for stage B3 is recommended by the Bolondi criteria, which limits the application of this subclassification system in clinical practice.

In order to develop a more reasonable subclassification system for intermediate HCC, previous studies have attempted to modify the Bolondi criteria in recent years. Yamakado *et al*^[17] subdivided BCLC B stage based on the tumor number, size and Child-Pugh grade of patients receiving TACE. They observed that presence of 4 tumors of 7 cm in diameter and Child-Pugh score were significant prognostic factors of intermediate HCC. Therefore, the authors subdivided intermediate HCC into 4 substages based on these two prognostic factors. According to this subclassification, stage B1 had better survival than stage B2, B3 and B4. However, no significant difference was observed in survival among continuous stages (Table 3). The authors concluded that the best candidates for TACE were patients with Child-Pugh grade A and HCC lesions with the tumor criteria of exhibiting 4 tumors and 7 cm in diameter. Subsequently, Kudo *et al*^[18] proposed the Kinki Criteria criteria based on a modified version of the Bolondi criteria. Intermediate HCC in this case was subclassified into 3 stages based on Child-Pugh score, the Milan criteria and the up to-seven criteria. The Kinki Criteria is similar to the Bolondi criteria to certain extent, although the Kinki Criteria is simplified version and the treatment recommendations are more rational, since even radical treatments are recommended as first option for selected patients. Thus, the Kinki Criteria appears to provide more strategies than the Bolondi criteria

Table 1 Bolondi criteria

| BCLC sub-stage | B1 | B2 | B3 | B4 |
|------------------------------|--------------------|--------------|--------------------------|------------------|
| CPT score | 5-7 | 5-6 | 7 | 8-9 ¹ |
| Beyond Milan and within Ut-7 | In | Out | Out | Any |
| ECOG (tumor related) PS | 0 | 0 | 0 | 0-1 |
| PVT | No | No | No | No |
| 1 st option | TACE | TACE or TARE | | BSC |
| Alternative | LT TACE + ablation | SOR | Research trials TACE SOR | LT ² |

¹With severe/refractory ascites and/or jaundice.

²Only if Up-to-7 IN and PS0. CPT: Child Pugh score; BSC: Best supportive care; LT: Liver transplantation; SOR: Sorafenib; TACE: Transcatheter arterial chemoembolization; TARE: Transarterial radioembolization; PVT: Portal vein thrombosis; Ut-7: Up to-7 criteria.

for intermediate HCC. However, further studies are required to clarify the predicting value of prognosis of the Kinki Criteria (Table 4). Arizumi *et al.*^[19,20] compared survival outcomes among subgroups according to the Kinki Criteria, they noticed significant differences in survival among continuous subgroups. However, no significant difference in survival between BCLC A and B1 stage or BCLC C and B3 stage was observed^[19,20]. Wang *et al.*^[12] validated the feasibility of the Bolondi criteria in predicting prognosis of intermediate HCC, and they demonstrated that alpha-fetoprotein (AFP) levels > 200 ng/mL and AST levels > 40 IU/L were prognostic factors. Thus, they proposed stratifying stages B1 and B2 according to AFP levels. Stages B1 and B2 were consequently subdivided into B1a (AFP < 200 ng/mL) and B1b (AFP > 200 ng/mL) and B2a (AFP < 200 ng/mL) and B2b (AFP > 200 ng/mL), respectively. The newly proposed substaging system comprises modified B1, B2 and B3 (Table 5). Survival difference is observed among continuous substages of this modified criteria.

Recently, Lee *et al.*^[21] proposed a subclassification system similar to that of Yamakado, which was based on Child-Pugh score (A or B) and tumor size (< 5 or > 5 cm). This newly proposed subclassification system comprises 3 substages, and survival differences were observed among continuous substages (Table 6). Kim *et al.*^[14] compared survival outcomes in different subgroups according to the Bolondi criteria, but no significantly differences in survival among substages were observed. Thus, they proposed a novel subclassification system based on Child-Pugh score, within up to-11 and ECOG PS. Instead of the up-to-7 criteria, up-to-11 was used as a measure of tumor burden. When patients were stratified using this substaging system, significantly differences in survival were observed among continuous substages of intermediate HCC following TACE treatment (Table 7). A recent study proposed a subclassification system based on the up to-7 criteria and the levels of two serum biomarkers, namely AFP and des-r-carboxy prothrombin^[22]. This subclassification system subdivides BCLC B stage into B1, B2 and B3 (Table 8). Notably, B2 stage in this staging system is not clearly defined and treatment recommendation is not provided, which limits its utilization in clinical practice.

DISCUSSION

The clinicopathological characteristics of patients with intermediate HCC vary in tumor burden, liver function and physical status. The treatment and subclassification of intermediate HCC remains controversial. Therefore, it is necessary to develop a novel substaging system for intermediate HCC. Bolondi *et al.*^[8] proposed the first substaging system and provided treatment options for each substage. Subsequently, several studies investigated its feasibility, and a number of them proposed modifying this system. The Bolondi criteria subdivide intermediate HCC based on liver function, tumor burden and ECOG PS. However, ECOG PS is difficult to be objectively evaluated, and treatment recommendation does not include radical treatments, which limits the utilization of this system.

Subsequent studies proposed various novel subclassification systems. Several of them stratified intermediate HCC based on prognostic factors of survival, and reported the predicting value for survival of these systems. Notably, radical treatments were recommended as treatment options for patients with intermediate HCC^[18], which may prolong short and long-term survival of intermediate HCC. However, there are various limitations of these newly proposed systems. First, all these studies were retrospective analyses of cohort of consecutive patients, thus,

Table 2 Studies validation and modification of Bolondi criteria

| Patients (n) | Treatment | Median follow-up | Ref. | B1 | B2 | B3 | B4 | Independent risk factor of survival |
|--------------|---------------|------------------|---------------------------------------|---|---|---|---|--|
| 80 | LR, TACE | 28.19 mo | Ciria <i>et al</i> ^[9] | OS rate: 43.75%; 5-yr survival rate (62.9%) | OS rate: 40%; 5-yr survival rate (28.1%) | OS rate: 11.25%; 5-yr survival rate (28.1%) | OS rate: 5%; 5-yr survival rate (15.1%) | Total bilirubin, subclassification stages B2 and B3-4 vs B1 |
| 90 | TAE | NR | Scaffaro <i>et al</i> ^[10] | Mean OS: 33.6 mo | Mean OS: 28.6 mo | Mean OS: 19.0 mo | Mean OS: 13.0 mo | NR |
| 580 | TAE | NR | Wang <i>et al</i> ^[12] | Median OS: 28.8 mo; 1, 3, 5-yr survival rate: 80%, 39.5%, 21.4% | Median OS: 15.6 mo; 1, 3, 5-yr survival rate: 59.2%, 23%, 13.9% | Median OS: 6 mo; 1, 3, 5-yr survival rate: 39.5%, 11.2%, 7.4% | Median OS: 9.6 mo; 1, 3, 5-yr survival rate: 46.2%, 23.1%, 7.7% | AFP level, AST, and substage B2, B3, and B4 vs B1 |
| 254 | TACE, LR, OLT | 15.4 mo | Weinmann <i>et al</i> ^[13] | Median OS: 31.9 mo; 1, 2-yr survival rate: 82.93%, 60.98% | Median OS: 26.9 mo; 1, 2-yr survival rate: 72.9%, 52.44% | Median OS: 13.5 mo; 1, 2-yr survival rate: 65%, 40% | Median OS: 10.9 mo; 1, 2-yr survival rate: 48.98%, 38.35% | Total bilirubin, MELD score, presence of ascites, and the therapies resection and OLT. |
| 269 | NR | NR | Giannini <i>et al</i> ^[11] | Median OS: 25 mo | Median OS: 16 mo | Median OS: 9 mo | Median OS: 5 mo | Subclassification of BCLC B, MELD score, and platelet count. |
| 821 | TACE | NR | Kim <i>et al</i> ^[14] | 1, 3, 5-yr survival rate: 95.1%, 66.4%, 41.2% | 1, 3, 5-yr survival rate: 78.4%, 33%, 20.3% | 1, 3, 5-yr survival rate: 59.3%, 10.5%, 0 | 1, 3, 5-yr survival rate: 57.4%, 43.7%, 17% | NR |

LR: Liver resection; OS: Overall survival; TACE: Transcatheter arterial chemoembolization; OLT: Orthotopic liver transplantation; MELD: Model of end-stage liver disease; NR: Not reported.

further prospective studies are required to clarify the feasibility of these systems. Second, only a few newly proposed systems provide treatment recommendations for a specific substage, resulting in difficult decision making in clinical practice.

CONCLUSION

Substaging and treatment of intermediate HCC remains confounded for clinicians. Since the survival benefit of radical treatments has been previously demonstrated^[23,24], the present study proposes expanding the indication of radical treatments and adding radical treatments into first option for patients with intermediate HCC.

Table 3 Yamakado criteria

| Substage | B1 | B2 | B3 | B4 |
|---------------------------------------|--------|--------|--------|--------|
| Child-Pugh grade | A | A | B | B |
| 4 tumors and 7 cm of maximal diameter | Within | Beyond | Within | Beyond |

Table 4 Kinki Criteria

| BCLC substage | B1 | B2 | B3 |
|---------------------------------|---|---|--|
| Child-Pugh score | 5-7 | 5-7 | 8-9 |
| Beyond Milan and within up-to-7 | In | Out | Any |
| Sub-substage | | | In Out |
| Concept of treatment strategy | Curative intent | Non-curative, palliative | B3-a B3-b |
| Treatment option | Resection Ablation Superselective c-TACE | DEB-TACE ¹ HAIC ² Sorafenib ³ | Curative intent if within up-to-7 Transplantation Ablation Superselective c-TACE |
| Alternative | DEB-TACE (large, C-P 7) B-TACE ⁴ | c-TACE | Palliative, no treatment HAIC Selective DEB-TACE DEB-TACE B-TACE, HAIC BSC |

¹DEB-TACE is recommended for huge tumors that are > 6 cm;²HAIC is recommended for multiple tumors > 6;³Sorafenib is recommended for patients with liver function of Child-Pugh score 5 and 6;⁴B-TACE is recommended for fewer tumors. TACE: Transcatheter arterial chemoembolization; c-TACE: Conventional subsegmental lipiodol TACE; DEB-TACE: TACE with drug-eluting beads; B-TACE: Balloon occluded TACE; HAIC: Hepatic arterial infusion chemotherapy; BSC: Best supportive care; C-P: Child-Pugh score; BCLC: Barcelona Clinic Liver Cancer.**Table 5 Wang criteria**

| Bolondi substage | Modified B1 | Modified B2 | Modified B3 |
|-----------------------|-------------|-------------|-------------|
| B1a (AFP < 200 ng/mL) | B1a | | |
| B1b (AFP > 200 ng/mL) | | B1b + B2a | |
| B2a (AFP < 200 ng/mL) | | | |
| B2b (AFP > 200 ng/mL) | | | B2b + B3 |
| B3 | | | |

AFP: Alpha-fetoprotein.

Table 6 Lee criteria

| Substage | B1 | B2 | B3 |
|-------------------|---------------|-----|-----|
| Tumor size < 5 cm | In | Out | Out |
| Child-Pugh | Not concerned | A | B |

Table 7 Kim criteria

| BCLC substage | B1 | B2 | B3 |
|---|----|-----|--------|
| Child-Pugh | A | A | B |
| Within up to-11 | In | Out | In Out |
| ECOG performance status (tumor related) | 0 | 0 | 0 |
| Portal vein thrombosis | No | No | No No |

Table 8 Kimura criteria

| Substage | B1 | B2 | B3 |
|-------------------------|---------------|---------------------------------------|---------------|
| Within up to-7 criteria | In | Other than those include in B1 and B3 | Out |
| DCP < 150 mAU/mL | In | | Not concerned |
| AFP > 100 ng/mL | Not concerned | | In |

AFP: Alpha-fetoprotein; DCP: Des-r-carboxy prothrombin.

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Observational Study

Fluorescence cholangiography enhances surgical residents' biliary delineation skill for laparoscopic cholecystectomies

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Institutional review board

statement: The study was reviewed and approved by the Ramathibodi Hospital Institutional Review Board Committee on Human Rights Related to Research Involving Human Subjects (protocol number ID MURA2018/558).

Informed consent statement: The population in this study signed informed consent.

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

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Abstract

BACKGROUND

Laparoscopic cholecystectomy (LC) is a minimally invasive procedure, often performed by surgical residents (SRs). Fluorescence cholangiography (FC) enables real-time identification of biliary anatomy.

AIM

To investigate the benefit of FC for enhancing SRs' identification skills.

METHODS

Prospective data was collected from January 2018 to June 2018 at our hospital. The study cohorts were the SRs (study group, $n = 15$) and the surgical staff (SS; control group, $n = 9$). Participants were assigned to watch videos of LCs with FC from five different patients who had gallbladder disease, and identify structures in the video clips (including cystic duct, common bile duct, common hepatic duct, and cystic artery), first without FC, and then with FC.

RESULTS

In the without-FC phase, the overall misidentification rate by SRs (21.7%) was greater than that of the SS (11.8%; $P = 0.018$). However, in the FC phase, the two groups did not significantly differ in misidentification rates (23.3% vs 23.3%, $P = 0.99$). Paired-structure analysis of the without-FC and with-FC phases for the SR group found a significantly higher misidentification rate in the without-FC phase than the with-FC phase (21.9% vs 10.9%; $P < 0.01$). However, misidentification rates in the with-FC phase did not significantly differ between SRs and SS.

CONCLUSION

FC enhanced identification skills of inexperienced surgeons during LC compared with conventional training. Combined with simulation-based video training, FC

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE-statement, and the manuscript was prepared and revised according to the STROBE-statement.

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Manuscript source: Invited manuscript

Received: October 17, 2019

Peer-review started: October 17, 2019

First decision: December 4, 2019

Revised: December 19, 2019

Accepted: January 19, 2020

Article in press: January 19, 2020

Published online: March 27, 2020

P-Reviewer: Augustin G, Iwasaki T

S-Editor: Dou Y

L-Editor: A

E-Editor: Ma YJ



is a promising tool for enhancing technical and decision skills of trainees and inexperienced surgeons.

Key words: Laparoscopic cholecystectomy; Fluorescence; Cholangiography; Residency; Education

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Core tip: Laparoscopic cholecystectomy (LC) is often performed by surgical residents. Avoiding bile duct injury (BDI) is a critical aspect of learning to perform this procedure safely. Landmark misperception is a high-risk factor for bile duct injury. Fluorescence cholangiography (FC) enables real-time identification of biliary anatomy during LC. We studied changes in biliary identification skills among surgical residents when FC was applied during LC, with staff surgeons as the control group. FC is a promising tool for enhancing biliary identification skills of surgeons-in-training.

Citation: Rungsakulkij N, Thewmorakot S, Suragul W, Vassanasiri W, Tangtawee P, Muangkaew P, Mingphruedhi S, Aeesoa S. Fluorescence cholangiography enhances surgical residents' biliary delineation skill for laparoscopic cholecystectomies. *World J Gastrointest Surg* 2020; 12(3): 93-103

URL: <https://www.wjgnet.com/1948-9366/full/v12/i3/93.htm>

DOI: <https://dx.doi.org/10.4240/wjgs.v12.i3.93>

INTRODUCTION

The adoption of minimally invasive surgery has significantly affected training of surgical residents (SRs). Laparoscopic cholecystectomy (LC) is an minimally invasive surgery procedure that is performed by SRs in nearly 50% of cases^[1]. According to the Accreditation Council of Graduated Medical Education, LC is a core-level surgery, of which a graduate should possess significant knowledge and procedural competency^[2]. In our center, where the general residency training is based on Accreditation Council of Graduated Medical Education standards, LC is a core procedure that SRs are required to master, which includes avoiding bile duct injury (BDI) or other major serious complications^[3]. Although various techniques and tools described in the literature and expert consensus can facilitate trainees' performance^[4,5], achieving a critical view of safety (CVS), proposed by Strasberg *et al*^[6], is widely regarded as the most crucial step. It has three criteria, including (A) dissecting and clearing the hepatocystic triangle of fat and fibrous tissue; (B) identifying two, and only two, structures [cystic duct (CD) and cystic artery] entering the gallbladder; and (C) dissecting the gallbladder off and away from the liver, exposing at least the bottom third of the cystic plate^[5,7,8].

Way *et al*^[9], reported that the principal risk factor associated with BDI during LC was misperception, rather than errors of skill, knowledge, or judgement. The surgeon's experience is reportedly a risk factor for BDI^[10]. Optical or real-time surgery is being increasingly reported in the literature. Fluorescence cholangiography (FC) enables real-time identification of biliary anatomy during dissection of Calot's triangle^[11,12]. FC involves administering indocyanine green (ICG) by intravenous injection before surgery. ICG is taken up by the liver, then excreted exclusively in the bile. The excitation of protein-bound ICG by near-infrared light causes it to fluoresce, thereby delineating components of the biliary system for the surgeon. FC is a feasible, low-cost and effective imaging modality^[13]. Conrad *et al*^[14], reported that FC may prove beneficial in preventing BDI. Recently, FC is considered as one of the supporting imaging techniques for achieving safe LC in the rationale of FC would reduce the misinterpretation rate of the biliary tree^[14]. Thus, whereas the benefits of enhanced visualization through FC would be limited for experienced surgeons, its identification benefits for less experienced surgeons might be very helpful. To our knowledge, no studies have been conducted on FC use during LC for SRs and less-experienced surgeons. Thus, the aim of this pilot study is to investigate the benefit of FC for enhancing the abilities of SRs to identify important structures during LC, compared with experienced surgeons.

MATERIALS AND METHODS

Prospective data were collected between October 2018 to March 2019 at Department of Surgery, Faculty of Medicine Ramathibodi Hospital, Bangkok, Thailand. Inclusion criteria for the SR group were (A) was an in-training general surgery resident during that period; (B) had been first surgeon in fewer than 10 LC procedures; and (C) had not worked with FC before. Inclusion criteria for the control group were surgical staff members who had performed at least 50 LC procedures and had not previously performed an LC with FC.

Procedure

A standardized setup was applied for all procedures. ICG was injected intravenously immediately after induction phase of anesthesiology (about 15 min before skin incision), at a dose of 1 mL of 10 mL dilution of a 2.5 mg/mL stock solution. The patient was positioned supine with the surgeon standing on the left side of the patient. A zero-degree telescope (10 mm diameter, 31 cm length, Karl Storz) was inserted through a 11-mm subumbilical trocar. Two or three further trocars were inserted with a 5-mm epigastric port, followed by a 5-mm port in the right upper quadrant. A 5-mm port was additionally inserted in the right lumbar region of the abdomen if a difficult situation was encountered during surgery. The dissection of Calot's triangle was routinely performed. FC was periodically applied during surgery, but was always applied before dissecting Calot's triangle and after dissecting Calot's triangle. All procedures were video-recorded.

Video preparation

We collected video-recordings from five patients with different gallbladder diseases who underwent LC with FC. Their diagnoses were (A) gallbladder polyp in an obese patient; (B) history of biliary pancreatitis; (C) symptomatic gallstone; (D) acute cholecystitis; and (E) gallbladder polyp in a non-obese patient (Figure 1). Inform consent was applied to all populations as standard of care. All procedures were performed by the same surgeon (Rungsakulkij N). There was no BDI in these patients. The unedited video-recordings were analyzed for their quality by a blinded assessor. Consequently, each video-recording was divided into four short clips (for a total of 20 clips from the 5 patients) by the blinded assessor into the following segments: (A) Before dissecting Calot's triangle without FC; (B) Before dissecting Calot's triangle with FC; (C) After dissecting Calot's triangle without FC; and (D) After dissecting Calot's triangle with FC (Figure 2).

Defining answers and examination method

The correct identifications in each video clip were reviewed by two experienced surgeons. They defined "identified structures" as structures which one or both reviewers could identify from the video clips; and "unidentified structures" as structures which these two reviewers could not clearly identify; the latter were excluded from the scoring system.

For the examinations, first, the mechanism of FC was briefly reviewed by all participants in the study. The participants then watched all twenty video clips in random order. For identified structures, they pointed to the pictures to indicate the CD, common bile duct (CBD), common hepatic duct, and cystic artery in each video clip, for a total of 80 points. If participants could not clearly see or were uncertain of a structure in the video, they answered "unidentified." Accuracy of their identifications in each video clip were reviewed by two reviewers. Whether the identifications were "true" or "false" were judged by the assessors. For structures that were clearly shown in the video and correctly identified by the participant, were considered "true"; structures that were clearly shown but identified incorrectly or "unidentified", were considered "false." The flow chart for the video preparation and examination method is shown in Figure 3.

Statistical analysis

An independent χ^2 test was used to determine possible significant differences between false identification rate of extrahepatic bile ducts; comparing SS with SRs. A paired McNemar's test was used to determine possible significant differences between false identification rates of extrahepatic bile ducts; comparing without FC with FC. $P \leq 0.05$ was considered significant. All statistical analysis was performed with STATA software (version 14).

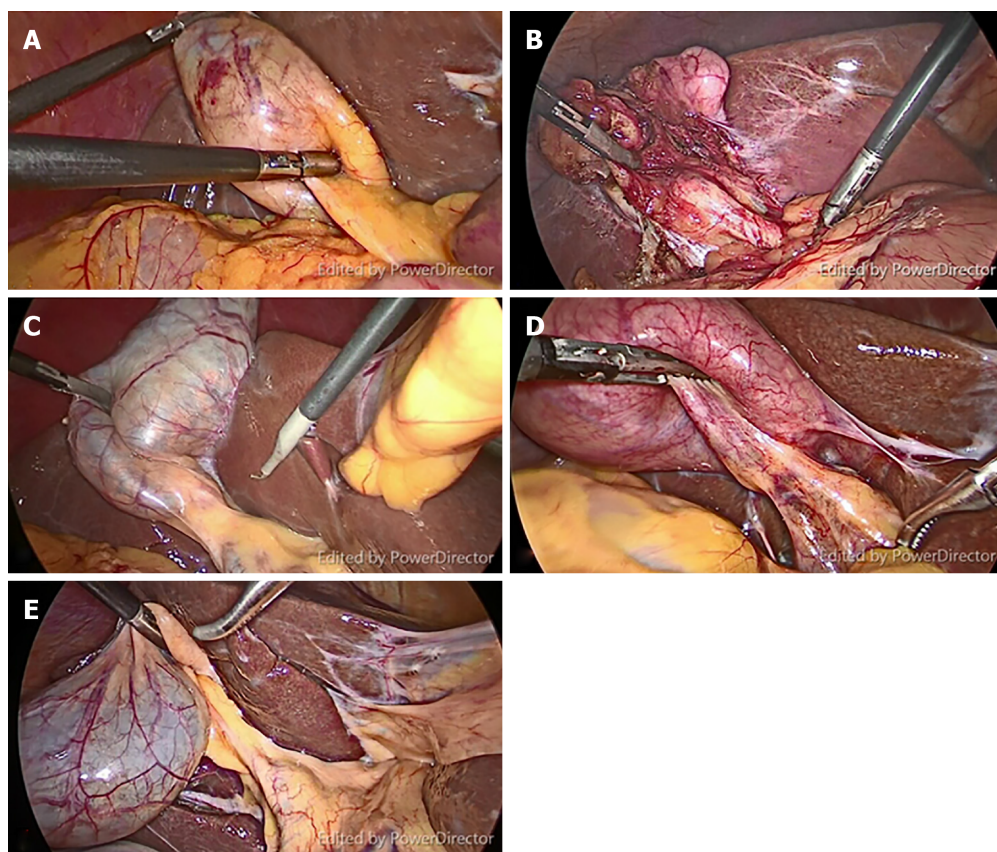


Figure 1 Representative still images from video clips of five patients with different gallbladder diseases. A: The obese patient with gallbladder polyp; B: Biliary pancreatitis; C: Symptomatic gallstone; D: Acute cholecystitis; E: Gallbladder polyp in a non-obese patient.

RESULTS

There were twenty-four participants including in this study, including nine experienced surgeons (staff group) and fifteen SRs (resident group). We excluded forty-five points from the analysis, for structures were not clearly identified, either with or without FC; all participants considered them to be “unidentified.” Thus, thirty-five points, based on clear structures, were included for the analysis.

Analysis of overall answers

Table 1 shows the overall answers of staff and residents during with-FC and without-FC phases. In the without-FC phase, the incorrect rate of the resident group was significantly greater than staff group (21.78% *vs* 11.85%, $P = 0.018$). However, in the FC phase, the two groups did not significantly differ (23.3% *vs* 23.3%, $P = 0.99$). Among the SRs, the misidentification rate did not significantly differ between with- and without-FC phases (23.3% *vs* 21.7%, $P = 0.674$) is shown in **Table 2**.

Paired structures analysis

The major limitation of FC is that the delineation of the deeply located bile ducts might fail because near-infrared light can penetrate tissues only to a depth of about 5 mm. Therefore, in patients with thick connective tissue or severe cholecystitis, FC may fail to elucidate the extrahepatic bile ducts. However, we proposed that analyzing paired structures would increase the accuracy of the analysis. We defined paired structures as those structures that could be identified in both with- and without-FC phases, in the same patient, for each dissection phase (before or after dissection phase); for example, the CD in Patient 1, seen in with-FC and without-FC phases, before dissection (**Figure 4**). Eventually, only fourteen points were included as match-paired structures. **Table 3** shows the effect of the FC between paired and unpaired structures. The result was in the without-FC phase have significantly higher misidentification rate than with-FC phase (17.8% *vs* 10.4%, $P < 0.001$) in paired group. Nevertheless, in the unpaired group, the with- and without-FC groups did not significantly differ (18.0% *vs* 23.3%, $P = 0.063$). Thus, for the analysis of the accuracy of this study, we included only paired structures. The analysis of accuracy between the with- and without-FC phases in each participant groups showed the misidentification

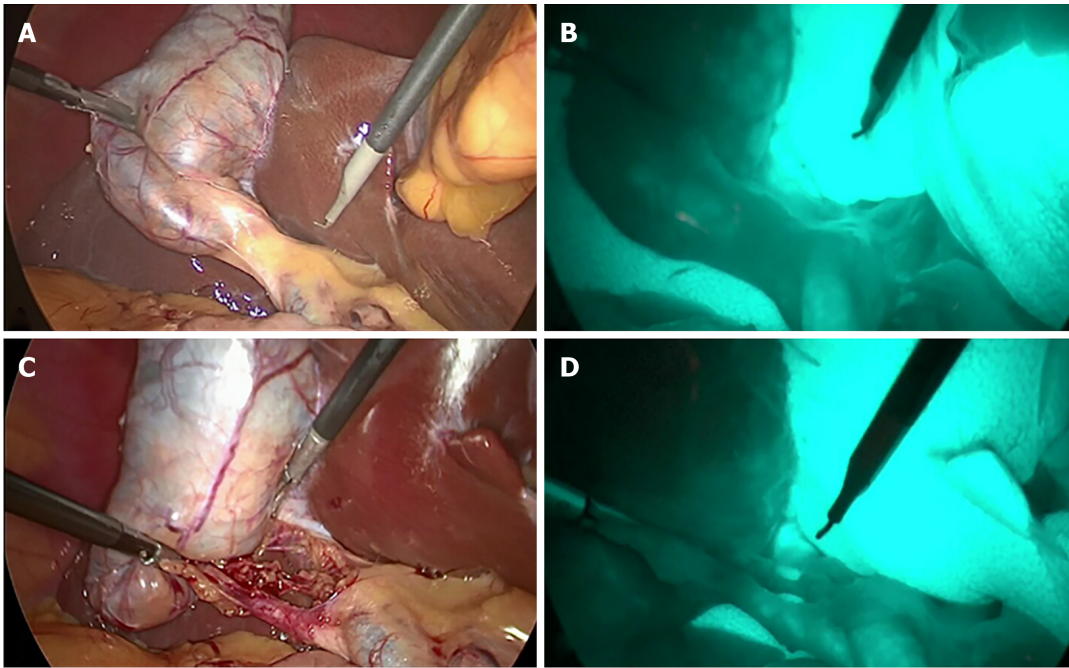


Figure 2 Representative still images from video clips of each phase of procedure. A: Before dissection of Calot's triangle without fluorescence cholangiography (FC); B: Before dissection of Calot's triangle with FC; C: After dissection of Calot's triangle without FC; D: After dissection of Calot's triangle with FC.

rate was significantly higher in the without-FC phase than the with-FC phase in both the RS group (21.9% *vs* 10.9%, $P < 0.01$) and the SS group (11.1% *vs* 9.5%, $P < 0.01$; Table 4).

SR results for the before- and after-dissection phases

Table 5 showed the analysis of the performance of the SR group. The without-FC phase had a significantly greater misidentification rate than the with-FC phase, in both before dissection (55.5% *vs* 22.2%, $P < 0.01$) and after dissection (12.73% *vs* 7.88%, $P = 0.045$). Table 6 showed the analysis between the two participant groups. In the without-FC phase, the SR group had significantly greater misidentification rate than the SS group (21.9% *vs* 11.1%, $P = 0.012$). Nevertheless, the two groups did not significantly differ in the with-FC phase (10.9% *vs* 9.5%, $P = 0.67$; Table 6).

DISCUSSION

LC is one of the most common procedures performed by general surgeons. It is essential that the SRs are adequately trained and competent, and are able to deliver high-standard care to patient after graduation^[15]. Surgical training commonly sets minimum numbers of operations required during general surgical training^[15]. However, the minimal procedural numbers of LC are not standardized worldwide for general surgical training and varies in each country^[16]. Moreover, evidence that correlates the numbers of a specific procedure that trainees must perform and the achievement of procedural competency is weak^[16]. Various tools for improving and assessing clinical performance of LC by SRs have been reported^[17-20]. Harrysson *et al*^[17], reported three core elements of the curriculum and framework for LC training: knowledge, technical skill, and attitudes and behaviors. The technical skills are the mainstay of surgical education and can be taught in many different ways^[17]. An emerging technique for training is simulator-based training. SRs who practice on simulators before performing procedures and operations on actual patients deliver better patient safety^[20,21]. Nagendran *et al*^[22], reported the virtual reality training appears to decrease operating time and improve the performance of surgical trainees with limited laparoscopic experience, compared with no training or with box-trainer training. Skills acquired by simulation-based training seem to be transferable to the operative setting for LCs^[19]. From our result, the misidentification rate did not differ between with- and without-FC phase from overall answer in resident group. However, we proposed the analysis of paired structures in order to avoid the limitation of FC which deeply located bile ducts might fail to be demonstrated. The result of paired structure analysis showed the significant ability of the FC in

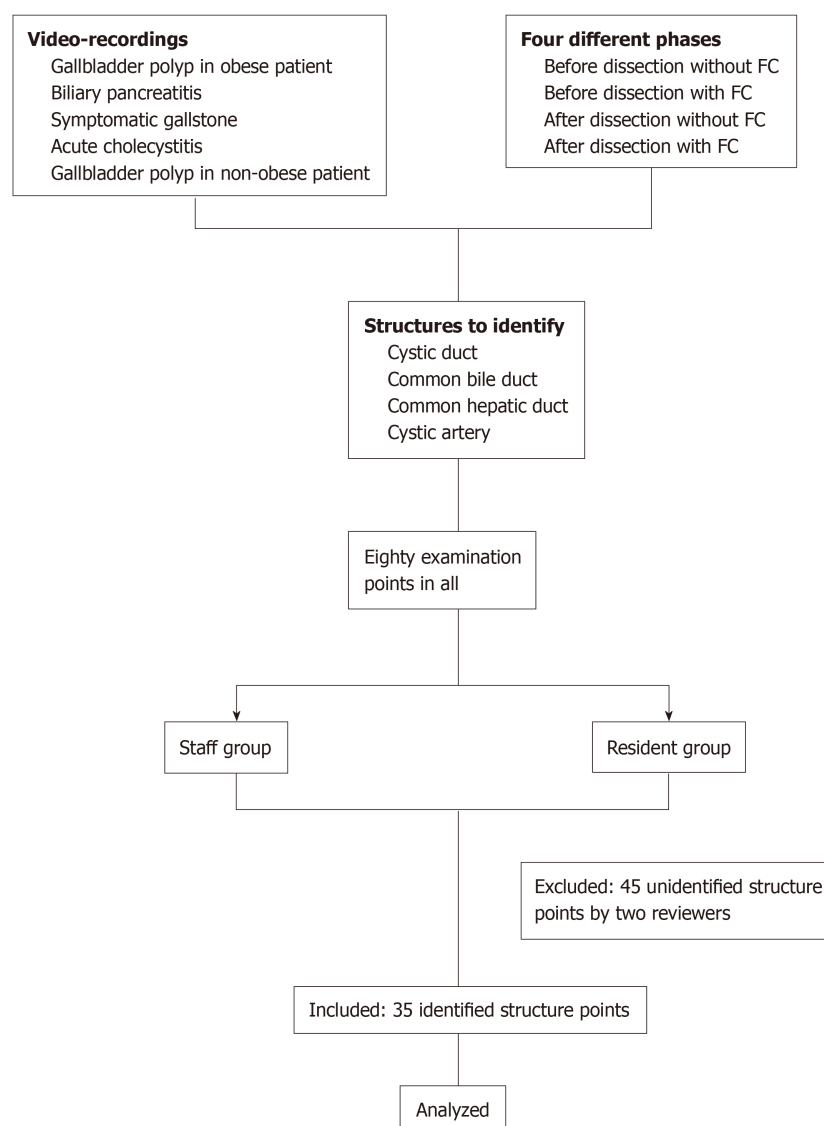


Figure 3 Study protocol flow chart.

enhancing the skill of the SR. Eventually, our pilot study indicates that FC increases the delineation of the biliary tree significantly for SRs. Thus, FC, which is considered to be a tool of real-time surgery, can be easily applied to simulation-based training as preoperative preparation tool for trainees. Ultimately, FC might be used as the adjunct to the clinical operative setting for LC. However, the further well-designed prospective study should be conducted to confirm this hypothesis.

From our results, even after dissecting Calot's triangle, SRs still had a high rate of misidentifying structures. However, the misidentification rate declined when FC was applied. Moreover, in term of ability to identify biliary structures, FC use decreased the misidentification rate for both SS and SRs. Consistent with previous reports, FC used during LC are increasing used in clinical practice^[13]. FC can delineate the extrahepatic biliary tree, especially in difficult clinical situations^[23-25]. However, FC is only one method to achieve safer LCs; the CVS is still crucial. From our result, CDs and CBDs were better seen after dissecting Calot's triangle. Consistent with the report of Kono *et al*^[26], FC improved identification of the CD, common hepatic duct, and CBD. They concluded that FC is a simple navigation tool for obtaining a biliary roadmap to reach the CVS during LC. However, this procedure needs sufficient extension of connective tissues around the bile ducts^[26]. Osayi *et al*^[27] reported using FC to identify biliary anatomy during LC compared with conventional intra-operative cholangiogram; they concluded that FC is a safe and effective alternative for imaging extrahepatic biliary structure.

Although LC is a safe procedure with very low mortality (< 1%), it has some associated major morbidity^[28]. BDI is the most serious complication of LC. Although

Table 1 Overall answers of staff and residents during with-fluorescence cholangiography and without-fluorescence cholangiography phases

| | Without FC | | | | With FC | | | |
|-------|----------------|------------|------------|----------------|----------------|------------|------------|----------------|
| | <i>n</i> = 360 | Staff | Residents | <i>P</i> value | <i>n</i> = 480 | Staff | Residents | <i>P</i> value |
| False | 65 (18.0) | 16 (11.8) | 49 (21.7) | 0.018 | 112 (23.3) | 42 (23.3) | 70 (23.3) | 0.999 |
| True | 295 (81.9) | 119 (88.1) | 176 (78.2) | | 368 (76.6) | 138 (76.6) | 230 (76.6) | |
| Total | 360 (100) | 135 (100) | 225 (100) | | 480 (100) | 180 (100) | 300 (100) | |

FC: Fluorescence cholangiography.

BDI reportedly has very low incidence (0.3%-0.5%)^[29,30], it incurs significant costs, including increased hospital cost, need for additional interventions, prolonged hospital stays, and readmission rate. The sequelae of major BDI is a catastrophic occurrence and is associated with a 1-year mortality of 1.7%-3.9%^[7]. The factors most associated with BDI are reported to be the surgeon's misidentification/perception and experience^[9,10]. Way *et al*^[9] and Schwaitzberg *et al*^[10] report that surgeons in their learning curve periods have a higher rate of BDI than experienced surgeon, and surgeons with certificates for fundamental laparoscopic skill have a lower rate of BDI than surgeons who do not have the certificate. Nevertheless, some studies reported different results^[31,32]. However, current literature supports use of FC with respect to improved identification of biliary structure, feasibility, cost effectiveness, safety, and simplicity^[13]. Little evidence supports the use of FC in preventing BDI. A randomized controlled trial (RCT) protocol is currently underway to establish the clinical efficacy of FC for prevention of BDI^[33]. Thus, to prove the effect of FC in preventing BDI by less-experienced surgeons, a well-designed RCT should be conducted. However, the number of patients required for the RCT to prove this hypothesis would be overwhelming because of the very low incidence of BDI.

This study has some limitations. Firstly, this study uses video-based material that does not affect SRs' psychomotor skills. Second, structure identification with FC may depend on the thickness of the soft tissue; in some situations, the video could not clearly delineate the structure in question. We excluded 45 points from the analysis, because of unclear structures. Third, this study had only a few participants.

In conclusion, FC is a surgery navigation tool that can be easily applied to simulation-based video training for SR to improve identification and decision analysis. In the simulation video, FC enhanced identification skills of surgeons-in-training during LC, especially for biliary structures, and seems to be a useful adjunct to clinical operative training. However, further prospective studies should be conducted to confirm our findings.

Table 2 Subgroup analysis of the effect of fluorescence cholangiography on overall answers from the resident group

| Identified | n (%) | Resident group, n = 525 | | |
|------------|-------------|-------------------------|-------------|---------|
| | | Without-FC | With-FC | P value |
| False | 119 (22.67) | 49 (21.78) | 70 (23.33) | 0.674 |
| True | 406 (77.33) | 176 (78.22) | 230 (76.67) | |
| Total | 525 (100) | 225 (100) | 300 (100) | |

FC: Fluorescence cholangiography.

Table 3 Effect of fluorescence cholangiography on match-paired and non-match-paired structures

| Identified | Match-paired | | | Non-match-paired | | |
|------------|--------------|-------------|---------|------------------|-------------|---------|
| | Without FC | With FC | P value | Without FC | With FC | P value |
| False | 60 (17.86) | 35 (10.42) | < 0.01 | 65 (18.06) | 112 (23.33) | 0.063 |
| True | 276 (82.14) | 301 (89.58) | | 295 (81.94) | 368 (76.67) | |
| Total | 336 (100) | 336 (100) | | 360 (100) | 480 (100) | |

FC: Fluorescence cholangiography.

Table 4 Accuracy of match-pairing analysis, comparing between with- and without-fluorescence cholangiography phases in each participant group

| Identified | Staff, n = 126 | | | Resident, n (%) n = 210 | | |
|------------|----------------|-------------|---------|-------------------------|-------------|---------|
| | Without FC | With FC | P value | Without FC | With FC | P value |
| False | 14 (11.11) | 12 (9.52) | < 0.01 | 46 (21.90) | 23 (10.95) | < 0.01 |
| True | 112 (88.89) | 114 (90.48) | | 164 (78.10) | 187 (89.05) | |
| Total | 126 (100) | 126 (100) | | 210 (100) | 210 (100) | |

FC: Fluorescence cholangiography.

Table 5 Subgroup analysis of the resident group, before and after dissection of Calot's triangle

| Identified | Resident group | | | | | |
|------------|----------------------------|------------|---------|----------------------------|-------------|---------|
| | Before dissection (n = 45) | | | After dissection (n = 165) | | |
| | Without FC | With FC | P value | Without FC | With FC | P value |
| False | 25 (55.56) | 10 (22.22) | < 0.001 | 21 (12.73) | 13 (7.88) | 0.045 |
| True | 20 (44.44) | 35 (77.78) | | 144 (87.27) | 152 (92.12) | |
| Total | 45 (100) | 45 (100) | | 165 (100) | 165 (100) | |

FC: Fluorescence cholangiography.

Table 6 Accuracy of match-pairing analysis, comparing between staff and residents, in with-fluorescence cholangiography and without-fluorescence cholangiography phases

| Identified | Without FC, <i>n</i> (%), <i>n</i> = 336 | | | With FC, <i>n</i> (%), <i>n</i> = 336 | | |
|------------|--|-------------|----------------|---------------------------------------|-------------|----------------|
| | Staff | Residents | <i>P</i> value | Staff | Residents | <i>P</i> value |
| False | 14 (11.11) | 46 (21.90) | 0.012 | 12 (9.52) | 23 (10.95) | 0.678 |
| True | 112 (88.89) | 164 (78.10) | | 114 (90.48) | 187 (89.05) | |
| Total | 126 (100) | 210 (100) | | 126 (100) | 210 (100) | |

FC: Fluorescence cholangiography.

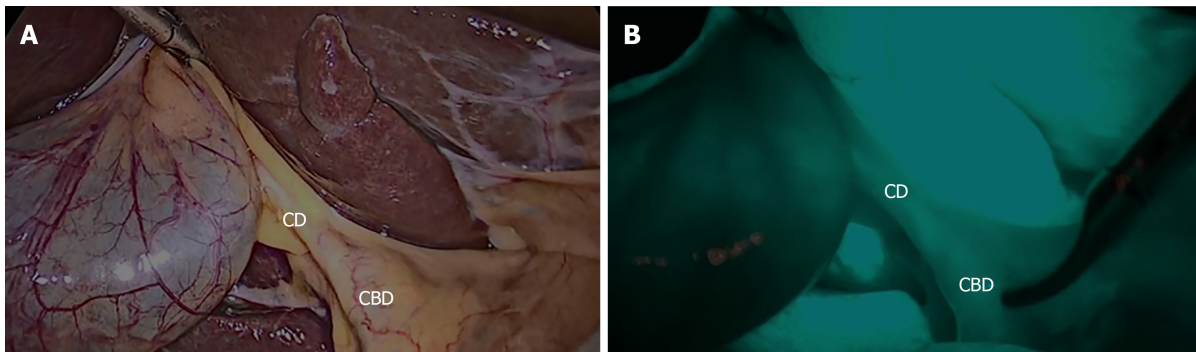


Figure 4 Representative still images from paired structures identified in both with-and without-fluorescence cholangiography phases from before dissection in the same patient. A: Before dissection of Calot's triangle without fluorescence cholangiography; B: Before dissection of Calot's triangle with fluorescence cholangiography. CD: Cystic duct; CBD: Common bile duct.

ARTICLE HIGHLIGHTS

Research background

Fluorescence cholangiography (FC) is considered as one of the supporting imaging techniques for achieving safe laparoscopic cholecystectomy (LC) in the rationale of FC would reduce the misinterpretation rate of the biliary tree.

Research motivation

The identification benefit of FC might be very helpful for inexperienced surgeons.

Research objectives

To investigate the benefit of FC for enhancing the skill of surgical resident (SR) to identify the important structure during LC when comparing with experienced surgeon.

Research methods

The prospective observational study in university hospital. The data collected from participants including surgical staff and resident which were assigned to watch videos of LC with FC from different patients, and identify structures in the video clips.

Research results

The result indicates that FC increases the delineation of the biliary tree significantly for SR.

Research conclusions

FC enhanced identification skills of surgeons-in-training during LC, especially for biliary structures.

Research perspectives

The further well-designed prospective study should be conduct to confirm the ability of FC which enhancing the skill of SR.

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Acute esophageal necrosis: A systematic review and pooled analysis

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

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript

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Abstract

BACKGROUND

Acute esophageal necrosis (AEN) is a rare entity with multifactorial etiology, usually presenting with signs of upper gastrointestinal bleeding.

AIM

To systematically review all available data on demographics, clinical features, outcomes and management of this medical condition.

METHODS

A systematic literature search was performed with respect to the PRISMA statement (end-of-search date: October 24, 2018). Data on the study design, interventions, participants and outcomes were extracted by two independent reviewers.

RESULTS

Seventy-nine studies were included in this review. Overall, 114 patients with

was prepared and revised according to the PRISMA 2009 Checklist.

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Manuscript source: Invited manuscript

Received: October 19, 2019

Peer-review started: October 19, 2019

First decision: November 19, 2019

Revised: December 2, 2019

Accepted: December 23, 2019

Article in press: December 23, 2019

Published online: March 27, 2020

P-Reviewer: Aktekin A, Cremers I, Dogan U, Isik A, Mercado MA, Okamoto H, Yeh HZ

S-Editor: Yan JP

L-Editor: A

E-Editor: Ma YJ



AEN were identified, of whom 83 were males and 31 females. Mean patient age was 62.1 ± 16.1 . The most common presenting symptoms were melena, hematemesis or other manifestations of gastric bleeding (85%). The lower esophagus was most commonly involved (92.9%). The most widely implemented treatment modality was conservative treatment (75.4%), while surgical or endoscopic intervention was required in 24.6% of the cases. Mean overall follow-up was 66.2 ± 101.8 d. Overall 29.9% of patients died either during the initial hospital stay or during the follow-up period. Gastrointestinal symptoms on presentation [Odds ratio 3.50 (1.09-11.30), $P = 0.03$] and need for surgical or endoscopic treatment [surgical: Odds ratio 1.25 (1.03-1.51), $P = 0.02$; endoscopic: Odds ratio 1.4 (1.17-1.66), $P < 0.01$] were associated with increased odds of complications. A sub-analysis separating early versus late cases (after 2006) revealed a significantly increased frequency of surgical or endoscopic intervention (9.7 % *vs* 30.1% respectively, $P = 0.04$)

CONCLUSION

AEN is a rare condition with controversial pathogenesis and unclear optimal management. Although the frequency of surgical and endoscopic intervention has increased in recent years, outcomes have remained the same. Therefore, further research work is needed to better understand how to best treat this potentially lethal disease.

Key words: Acute esophageal necrosis; Black esophagus; Acute necrotizing esophagitis

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Core tip: This manuscript's aim was to systematically review and synthesize all available data on demographics, clinical features, outcomes and the management of acute esophageal necrosis. According to our results, acute esophageal necrosis is a rare condition with controversial pathogenesis and unclear optimal management. Although the frequency of surgical and endoscopic intervention has increased in recent years, outcomes have remained the same. Therefore, further investigations are needed to better understand how to best treat this potentially lethal disease.

Citation: Schizas D, Theochari NA, Mylonas KS, Kanavidis P, Spartalis E, Triantafyllou S, Economopoulos KP, Theodorou D, Liakakos T. Acute esophageal necrosis: A systematic review and pooled analysis. *World J Gastrointest Surg* 2020; 12(3): 104-115

URL: <https://www.wjgnet.com/1948-9366/full/v12/i3/104.htm>

DOI: <https://dx.doi.org/10.4240/wjgs.v12.i3.104>

INTRODUCTION

Acute esophageal necrosis (AEN), also known as acute necrotizing esophagitis (ANE) or black esophagus is a rare and potentially devastating medical condition. Diagnosis is typically made with upper endoscopy. The most common endoscopic finding is a striking diffuse circumferential black discoloration of the esophageal mucosa which is associated with histologic evidence of extensive mucosal necrosis. The pathogenesis of AEN appears to be multifactorial. That said, ischemia has been reported as the most common etiology^[1,2]. Gastric outlet obstruction with massive reflux of gastric secretions, viral infection, hypersensitivity to antibiotics, hypothermia, and corrosive trauma can also lead to AEN^[1,3]. Typically, patients present at the emergency room with signs of upper gastrointestinal (GI) hemorrhage such as coffee-ground emesis, melena or hematemesis^[4]. Conservative management with adequate hydration, proton pump inhibitors, antibiotics, acid suppression or sucralfate suspension administration is employed either as definitive or first-line treatment depending on disease severity^[4]. Emergency surgical intervention followed by patient support until clinical stabilization can also be considered in case of necrosis and perforation^[5].

Given the rarity of AEN, our experience with this condition is primarily based on case reports and small case series. To better understand the demographics, clinical features, and outcomes of this uncommon esophageal disease, we performed a systematic review of literature published within the period 1990 to 2018. Our study

includes 160 cases of AEN and constitutes the largest to date review of “black esophagus”^[6]. Overall, the present work may serve as a useful guide to clinicians contemplating how to best treat this rare condition.

MATERIALS AND METHODS

Search strategy and data extraction

We performed a PubMed/Medline search for English-language case reports and case series, using the keywords "acute esophageal necrosis" OR "black esophagus" OR "acute necrotizing esophagitis". Articles were screened by 2 independent reviewers (Theochari NA, Schizas D) and conflicts were resolved by a third reviewer (Kanavidis P). The reference lists of systematically reviewed articles were hand-searched for potentially eligible, missed studies. Data extraction of the articles included in our review was performed by Theochari NA and Schizas D.

Eligibility criteria for inclusion and exclusion

Eligible articles were identified on the basis of the following inclusion criteria: (1) Papers published in English; (2) Primary research papers; (3) Papers that included patients older than 18 years old; and (4) Papers that included patients who were treated for AEN. Exclusion criteria were the following: (1) Papers that are not published in English; (2) Reviews, letters to the editor; and (3) Papers with inadequate data.

Statistical analysis

Variables were summarized as mean and standard deviation when continuous, or frequencies and percentages when categorical. Continuous variables were analyzed with independent samples student's *t*-test, for normally distributed variables, or Mann-Whitney *U*-test otherwise (Kolmogorov-Smirnov test of normality was used). For categorical variables Pearson's Chi-Square test was used, with Yates' continuity correction when appropriate, whereas for ordinal variables we used Wilcoxon rank sum test. Univariate logistic regression was performed with logit transformation of data. Exploratorily, the outcome “death” was dichotomized and logistic regression was utilized since performing valid time-to-event analyses was not deemed feasible due to missing data and inadequate follow-up data. The level of statistical significance was set at 5%. Statistical analysis was performed with R-project environment for statistical computing (<https://www.r-project.org/>).

Protocol registration

This study is registered with the PROSPERO registry and its unique identifying number is: CRD42018112571.

RESULTS

Literature search results

The search produced 820 PubMed results (October 24, 2018). The publications matching our selection criteria were 81. Ultimately, 79 studies satisfied our inclusion criteria and were selected for data collection (Figure 1). Of those, 69 were case reports^[3,5,7-64] and 10 were cases series^[2,65-73] including 69 and 45 patients respectively. A total of 114 of 160 patients were selected for the pooled analysis, as some case series did not publish individual patient data.

Demographics and clinicopathological features

There were 114 patients who were diagnosed with AEN included in our study, of which 83 male and 31 female (M:F ratio of 2.7:1). Mean age was 62.1 ± 16.1 . The most common presenting symptom was melena, hematemesis or other manifestation of gastric bleeding (85%), followed by epigastric or chest pain (29.2%) and other peptic symptoms (25.7%), including nausea, vomiting and dysphagia. Other symptoms such as fever, weakness, dyspnea, hypotension were less common (23.9%).

Patients had a diverse medical history, including diabetes mellitus or diabetic ketoacidosis, cardiopulmonary disease (chronic obstructive pulmonary disease, hypertension, heart failure, atrial fibrillation, myocardial infarct, angina), alcohol abuse, chronic kidney disease or other kidney-related disease (*i.e.*, nephrectomy), liver-related disease (cirrhosis, liver transplantation) and others (stroke, gastroesophageal reflux disease, GI ulcers, chronic pancreatitis, prostate hypertrophy). Relative frequencies are displayed in Table 1, grouped by affected

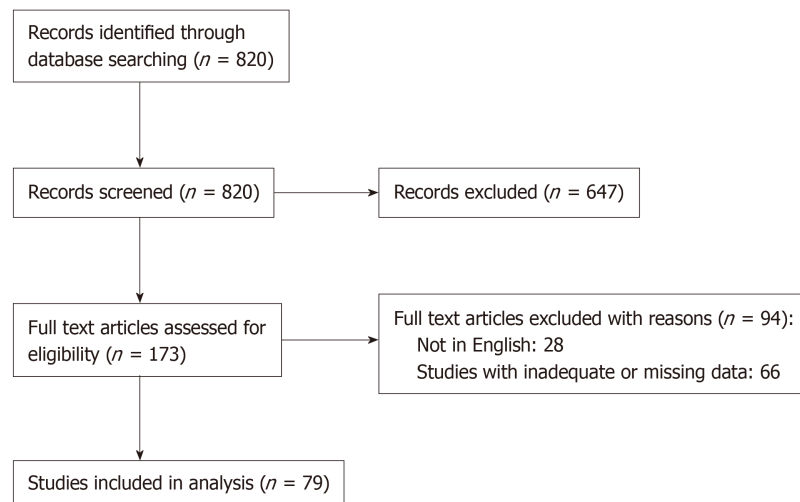


Figure 1 Prisma flow chart.

system.

Clinical findings on admission were not always reported, but the most severe among them were signs of hypovolemic or septic shock/multiple organ dysfunction/sepsis (73%), acute kidney injury (20%) and malnutrition (7%). Lower esophageal involvement was almost always present (92.9%), with extension to the middle esophagus in many cases (64.3%). Upper esophagus was involved in only 33.7% of the cases.

Treatment

Surgical or endoscopic intervention was required in 24.6% of the cases, whereas 75.4% were treated conservatively. Data available for the cases where intervention was required reveals that endoscopic treatment was preferred in 15 cases (14%), 2 of which later required surgical re-intervention, while surgical-first approach was used in 11 cases (10%). Most survivors received a follow-up endoscopy (89%), with a complication rate of 18.7%. A total of 32 patients died (29.9%), either during the initial hospital stay or during the follow-up period. Follow-up data was available for 78.9% of the patients. Mean overall follow-up was 66.2 ± 101.8 d, (or 82.9 ± 113.2 d among survivors) (Tables 2 and 3).

Outcomes

On univariate logistic regression, GI symptoms on presentation [Odds ratio (OR) 3.50 (1.09-11.30), $P = 0.03$] and need for surgical or endoscopic treatment [surgical: OR 1.25 (1.03-1.51), $P = 0.02$; endoscopic: OR 1.4 (1.17-1.66), $P < 0.01$] were associated with increased odds of complications (Table 4). Patients that underwent both endoscopic and surgical intervention had even higher complication rate; OR 2.58 (1.7-3.93), $P < 0.01$. Exploratory logistic regression for the dichotomized “death” endpoint (Table 5) did not reveal any statistically significant prognostic factors.

Publication year

A sub-analysis separating early versus late cases (after 2006) revealed a significantly increased frequency of surgical or endoscopic intervention of 30.1% for the late cases, compared to 9.7% for the early cases ($P = 0.04$). Mortality rate, however, was similar, for the late (30.3%) and the early cases (29%) ($P = 1.00$).

DISCUSSION

ANE was first described by Goldenberg *et al*^[1] in 1990. The largest case series of AEN published to date included 29 and 16 cases respectively^[74,75]. In 2007, Gurvits *et al*^[6] attempted for the first time to present a review of the literature and described 88 patients with black esophagus. Since then, no systematic or broad review of the published literature has been performed. To guide clinicians treating patients with AEN using up-to-date information we systematically reviewed relevant literature from 1990 until 2018. Our analysis includes 114 patients and provides a comprehensive overview of the demographics, clinical features, treatment options,

Table 1 Clinicopathological features

| Clinicopathological features | | | |
|--|-----------------|----------------|-------|
| Gender | | $\Sigma = 114$ | |
| | Male | 83 | 72.8% |
| | Female | 31 | 27.2% |
| Age (yr) | 62.1 \pm 16.1 | 114 | |
| Admission symptoms | | $\Sigma = 113$ | |
| | Bleeding | 96 | 85.0% |
| | Peptic | 29 | 25.7% |
| | Pain | 33 | 29.2% |
| | Other symptom | 27 | 23.9% |
| Medical history | | $\Sigma = 110$ | |
| | Cardiopulmonary | 52 | 47.3% |
| | Diabetes | 40 | 36.4% |
| | Alcohol | 31 | 28.2% |
| | Kidney | 17 | 15.5% |
| | Liver | 19 | 17.3% |
| | Other | 61 | 55.5% |
| Clinical findings | | $\Sigma = 38$ | |
| | Shock | 11 | 28.9% |
| | Malnutrition | 1 | 2.6% |
| | AKI | 3 | 7.9% |
| | Other | 24 | 63.2% |
| Involvement of esophagus (relative to GEJ) | | $\Sigma = 98$ | |
| | Upper | 33 | 33.7% |
| | Middle | 63 | 64.3% |
| | Lower | 91 | 92.9% |

AKI: Acute kidney injury; GEJ: Gastroesophageal junction.

and outcomes of patients with AEN.

Several theories have been proposed to explain the pathogenesis of AEN. The most popular is ischemia due to low flow rates or shock. Reichart *et al*^[3] reported that ischemic AEN is typically secondary to cardiac dysfunction, prolonged hypotension or sepsis. Our findings support this statement with 47.3% of the patients described in this review having a cardiopulmonary medical history. Another factor that argues in favor of an ischemic etiology in the present study is the predominance of esophageal necrosis in the middle and lower thirds of esophagus (64.3% and 92.9% respectively) which are usually less vascularized and thus more prone to ischemic injury. Other causes of AEN include gastric outlet obstruction with massive reflux of gastric secretions, viral infection, hypersensitivity to antibiotics, hypothermia and corrosive trauma^[3].

According to our analysis, AEN affects predominately men (72%) at a mean age of 62 years. Nevertheless, AEN can develop at virtually any age. In our review AEN, was seen in 6 patients in the third decade of life and in male patient at the age of 10 year^[17]. The majority (85%) of patients presented at the ER with symptoms of upper GI bleeding *i.e.*, melena, hematemesis or other manifestations of gastric bleeding. Associated clinical findings were not always reported, but the most commonly reported ones were hypovolemic or septic shock^[74]. Patients' medical history may also be a serious risk factor for AEN^[76]. Most patients included in this systematic review had history of a significant cardiopulmonary disease (47.3%) while others suffered from diabetes mellitus (36.4%), alcohol abuse (28.2%), as well as liver (17.3%) and kidney related disease (15.5%).

The diagnosis of AEN is made endoscopically by identifying diffuse circumferential progressive black discoloration of the esophagus with abrupt demarcation at the Z-line. In six cases reported in this review, the mucosa of the esophagus was also covered by yellow or white exudates at the time of initial scoping^[8,73]. Histologically, AEN specimens shows necrotic debris, mucosal and submucosal necrosis with a local inflammatory response^[8,73].

Table 2 Treatment modalities, follow-up

| Treatment modalities | | | |
|-------------------------|-----------------------|----------------|--------|
| Intervention | | $\Sigma = 114$ | |
| | Yes | 28 | 24.6% |
| | No | 86 | 75.4% |
| Management | | $\Sigma = 105$ | |
| | Conservative | 79 | 75.2% |
| | Surgical | 11 | 10.5% |
| | Endoscopic | 13 | 12.4% |
| | Endoscopic + surgical | 2 | 1.9% |
| Follow-up endoscopy | Yes | 67 | 58.8% |
| Complications | Yes | 14 | 12.3% |
| Death | Yes | 32 | 29.9% |
| FUP (overall; mean; SD) | 66.2 \pm 101.8 | 90 | 90/114 |
| FUP (dead; mean; SD) | 16.6 \pm 21.8 | 23 | 23/32 |
| FUP (alive; mean; SD) | 82.9 \pm 113.2 | 65 | 65/75 |

FUP: Follow up; SD: Standard deviation.

Given the rarity of the condition, there are no clear guidelines regarding how to best manage patients with AEN. Most authors recommend a conservative treatment approach which includes correction of underlying disorders, total parenteral nutrition, adequate intravenous hydration, broad spectrum antibiotics, proton pump inhibitors and sucralfate suspension^[4]. Blood cell transfusion is also recommended when necessary. In case of necrosis or perforation, early surgical or endoscopic intervention is required^[5]. In this systematic review, surgery was performed as first line treatment in 11 cases whereas endoscopic treatment was used in 15 patients, 2 of which later required surgical re-intervention. Surprisingly, a sub-analysis that we conducted, separating cases before and after 2006 (*i.e.*, when the last systematic review was published) showed that the frequency of surgical or endoscopic intervention was significantly increased from 9.7% (before 2006) to 30.1% (after 2006) ($P = 0.04$). That said, the increased rate of operative intervention did not seem to affect overall patient outcomes.

The most commonly reported complication is stricture while others can be stenosis, abscesses, tracheoesophageal fistula and perforation of the esophagus^[1]. In this systematic review only 14 (12.3% of the patients) developed complications. Of them, 10 (70%) developed an esophageal stricture and four (30%) a tracheoesophageal fistula. Interestingly, univariate logistic regression revealed an association between the presence of GI symptoms on admission [OR 3.50 (1.09-11.30), $P = 0.03$] with increased odds of post-AEN complications. Patients that required surgical or endoscopic treatment [surgical: OR 1.25 (1.03-1.51), $P = 0.02$; endoscopic: OR 1.4 (1.17-1.66), $P < 0.01$] were also more likely to develop complications. This is not surprising since patients with more severe disease at presentation are more likely to receive surgical intervention. Moreover, patients that underwent both endoscopic and surgical intervention had an even higher complication rate [OR 2.58 (1.7-3.93), $P < 0.01$].

A total of 32 patients included in our study died (29.9%), either during the initial hospital stay or subsequently at follow-up. The high mortality rate that is seen in AEN may be potentially related to patient characteristics such as serious medical history, older age and higher incidence of malignancy^[1].

Methodological strengths of the present paper include: (1) Comprehensive literature search using rigorous and systematic methodology; and (2) Detailed data extraction. We also performed a sub-analysis separating early versus late cases^[6] (after 2006 when the last systematic review was published) which showed that the implementation of surgical/endoscopic interventions have increased threefold.

This analysis has certain limitations. As with any systematic review, certain studies did not report on all outcomes of interest and therefore all cumulative results were estimated based on available data. Only papers published in English were eligible and all included studies were retrospective case reports or small case series. Lastly, due to missing data, performing strong survival modeling was not possible and therefore we treated "death" as a binary outcome and performed logistic regression to provide an approximation of mortality predictors.

Table 3 Endoscopic intervention

| Endoscopic intervention | |
|-------------------------|--------------|
| Modalities | <i>n</i> (%) |
| Stenting | 1 (7.5) |
| Savary dilatations | 1 (7.5) |
| Balloon dilatations | 11 (85) |
| Total | 13 |

In conclusions, AEN is a rare condition with high mortality. Although, the etiology of this disease is likely multi-factorial, ischemia seems to play a pivotal role in pathogenesis. The diagnosis of AEN is mainly based on upper GI endoscopy revealing a black-appearing esophageal mucosa circumferentially. Although the rate of operative interventions has increased in recent years, conservative treatment still seems to be the most commonly used treatment approach. Black esophagus is anticipated to become a more commonly recognized and described entity. To that end, a staging system that classifies the patients with AEN according to their symptoms on admission, their medical history and the endoscopic findings would be meaningful. Overall, further investigations are needed to better understand the risk factors, pathogenesis, diagnostic challenges and optimum treatment approach for this rare but potentially lethal condition.

Table 4 Univariate logistic regression for complications

| | | OR | LCI | HCI | P value |
|-----------------------------------|-----------------------|-------|-------|-------|---------|
| Gender | Male | 0.95 | 0.83 | 1.09 | 0.45 |
| | Female | | | | (ref) |
| Age | +1 yr | 0.990 | 0.957 | 1.025 | 0.553 |
| Admission symptoms | Bleeding | 0.60 | 0.16 | 2.91 | 0.48 |
| | Peptic | 3.50 | 1.09 | 11.30 | 0.03 |
| | Pain | 2.00 | 0.61 | 6.29 | 0.24 |
| | Other symptom | 0.86 | 0.18 | 3.04 | 0.83 |
| | None | | | | (ref) |
| Medical history | Cardiac | 0.63 | 0.18 | 1.95 | 0.43 |
| | Diabetes mellitus | 1.46 | 0.45 | 4.53 | 0.52 |
| | Alcohol abuse | 1.08 | 0.28 | 3.54 | 0.90 |
| | Kidney diseases | 0.94 | 0.14 | 3.94 | 0.94 |
| | Liver diseases | 3.41 | 0.94 | 11.49 | 0.05 |
| | Other | 0.85 | 0.27 | 2.66 | 0.78 |
| Clinical findings | Malnutrition | 0.87 | 0.44 | 1.74 | 0.70 |
| | AKI | 0.87 | 0.58 | 1.30 | 0.50 |
| | Other | 1.15 | 0.77 | 1.73 | 0.50 |
| Involvement of esophagus (to GEJ) | | | | | |
| | Upper | 2.67 | 0.74 | 9.99 | 0.13 |
| | Middle | 0.97 | 0.27 | 3.94 | 0.96 |
| | Lower | 1.13 | 0.88 | 1.44 | 0.33 |
| Intervention | Yes | 11.39 | 3.41 | 45.44 | < 0.01 |
| | No | | | | (ref) |
| Management | Conservative | | | | (ref) |
| | Surgical | 1.25 | 1.03 | 1.51 | 0.02 |
| | Endoscopic | 1.4 | 1.17 | 1.66 | < 0.01 |
| | Endoscopic + surgical | 2.58 | 1.7 | 3.93 | < 0.01 |

OR: Odds ratio; LCI: Lower confidence interval; HCI: Higher confidence interval; AKI: Acute kidney injury; GEJ: Gastroesophageal junction.

Table 5 Univariate logistic regression for death

| | | OR | LCI | HCI | P value |
|-----------------------------------|-----------------------|------|------|------|---------|
| Gender | Male | 0.99 | 0.40 | 2.58 | 0.99 |
| | Female | | | | (ref) |
| Age | +1 yr | 1.02 | 0.99 | 1.05 | 0.30 |
| Admission symptoms | Bleeding | 1.33 | 0.42 | 5.09 | 0.64 |
| | Peptic | 0.72 | 0.26 | 1.85 | 0.51 |
| | Pain | 0.31 | 0.10 | 0.84 | 0.03 |
| | Other symptom | 0.83 | 0.29 | 2.15 | 0.70 |
| | None | | | | (ref) |
| Medical history | Cardiac | 1.06 | 0.46 | 2.44 | 0.88 |
| | Diabetes mellitus | 0.81 | 0.32 | 1.92 | 0.64 |
| | Alcohol abuse | 0.80 | 0.30 | 2.01 | 0.65 |
| | Kidney diseases | 2.34 | 0.75 | 7.21 | 0.13 |
| | Liver diseases | 1.47 | 0.50 | 4.10 | 0.47 |
| Clinical findings | Other | 0.55 | 0.23 | 1.26 | 0.16 |
| | malnutrition | 0.75 | 0.30 | 1.87 | 0.54 |
| | AKI | 1.05 | 0.61 | 1.83 | 0.85 |
| | Other | 0.95 | 0.55 | 1.65 | 0.85 |
| Involvement of esophagus (to GEJ) | Upper | 0.57 | 0.20 | 1.49 | 0.27 |
| | Middle | 0.59 | 0.24 | 1.49 | 0.26 |
| | Lower | 1.37 | 0.91 | 2.08 | 0.13 |
| Intervention | Yes | 0.63 | 0.21 | 1.69 | 0.38 |
| | No | | | | (ref) |
| Management | Conservative | | | | (ref) |
| | Surgical | 0.96 | 0.71 | 1.30 | 0.79 |
| | Endoscopic | 0.77 | 0.59 | 1.00 | 0.06 |
| | Endoscopic + surgical | 0.71 | 0.29 | 1.75 | 0.46 |

OR: Odds ratio; LCI: Lower confidence interval; HCI: Higher confidence interval; AKI: Acute kidney injury; GEJ: Gastroesophageal junction.

ARTICLE HIGHLIGHTS

Research background

Acute esophageal necrosis (AEN) is a severe medical condition with multifactorial etiology. Our experience is mainly based on case reports and small case series.

Research motivation

Given the rarity of this entity, further investigations are needed to better understand the risk factors, pathogenesis, diagnostic challenges and how to best treat this potentially lethal disease.

Research objectives

Our objective was to investigate all available data on demographics, clinical features, outcomes of this condition and to suggest the best management.

Research methods

We performed a systematic literature search with respect to the PRISMA statement. Univariate logistic regression was performed with logit transformation of data.

Research results

Overall, 114 patients with AEN were included in this study. The most common symptoms on admission were melena, hematemesis or other manifestations of gastric bleeding. With regards to treatment modalities, conservative treatment was the most widely implemented choice followed by surgical or/and endoscopic intervention. A sub-analysis separating early versus late cases (after 2006) revealed a significantly increased frequency of surgical or endoscopic intervention. Nevertheless, further research work is needed to better understand how to best treat this potentially deadly disease.

Research conclusions

To the best of our knowledge, this is the most up to date and comprehensive systematic review regarding AEN. This rare entity seems to have multi-factorial etiology, but ischemia seems to play the most significant role in pathogenesis. Diagnosis is made by upper gastrointestinal endoscopy, while conservative treatment seems to be still the most popular modality. Nevertheless, our study revealed that operative interventions have increased the last years. Black esophagus is a medical condition that is still difficult recognized. To that end, a staging system that classifies the patients with AEN according to their symptoms on admission, their medical history and the endoscopic findings would be meaningful.

Research perspectives

Further investigations are needed to better understand the risk factors, pathogenesis, diagnostic challenges and optimum treatment approach for this rare but potentially lethal condition.

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Colorectal cancer metastases to the thyroid gland: A case report

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Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: No conflicts of interest exist.

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

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Abstract

BACKGROUND

Secondary malignancies of the thyroid gland are a rare finding in clinical practice. In addition, colorectal metastasis to the thyroid (CMT) is even more infrequently diagnosed. The source of the primary tumor follows demographic and ethnic patterns, which reflects the most prevalent malignancies in the different populations. Colorectal cancer is one of the most common types of cancer worldwide; nevertheless, CMT is infrequently diagnosed. Most of them are identified during the follow-up of gastrointestinal primary malignancies. Due to the improvement of image techniques, oncological treatment, and follow-up, survival and consequent diagnosis of metastatic disease are more frequent. Those facts make this entity a diagnostic and therapeutic challenge, due to the lack of information and the difficulties performing clinical trials and research.

CASE SUMMARY

Here, we present a case report of a patient diagnosed with CMT of adenocarcinoma of the rectum evidenced during follow-up, 4 years after neoadjuvant chemoradiotherapy, who had subsequent curative surgical treatment of the primary tumor and inter-current lung bilateral metastases.

CONCLUSION

Thyroid metastases of extra-thyroid origin are an uncommon finding, even rarer in cases of CMT. The diagnostic process, as well as survival of oncologic patients is improving, and consequently the number of metastases to the thyroid gland is increasing.

Key words: Colorectal cancer metastases; Thyroid gland; Case report; Thyroid metastases

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Manuscript source: Unsolicited manuscript

Received: June 29, 2019

Peer-review started: July 1, 2019

First decision: September 10, 2019

Revised: October 1, 2019

Accepted: November 20, 2019

Article in press: November 21, 2019

Published online: March 27, 2020

P-Reviewer: Ding MX, Hu XT, Isik A, Sun XT, Xie Q

S-Editor: Yan JP

L-Editor: Filipodia

E-Editor: Ma YJ



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Core tip: Thyroid metastases of extra-thyroid origin are an uncommon finding, particularly in cases of gastrointestinal, colon, and rectum malignancies. The diagnostic process, as well as survival of oncological patients is improving. Consequently the number of diagnosed metastases to the thyroid gland is increasing. However, the management and outcome of these patients remain unclear, making it necessary to conduct more clinical research to define diagnostic and therapeutic protocols to provide a suitable treatment and a positive impact on outcome. Our objective was to review the current literature in the context of a recently diagnosed case in our hospital.

Citation: Ciriano Hernández P, Martínez Pinedo C, Calcerrada Alises E, García Santos E, Sánchez García S, Picón Rodríguez R, Jiménez Higuera E, Sánchez Peláez D, Herrera Montoro V, Martín Fernández J. Colorectal cancer metastases to the thyroid gland: A case report. *World J Gastrointest Surg* 2020; 12(3): 116-122

URL: <https://www.wjgnet.com/1948-9366/full/v12/i3/116.htm>

DOI: <https://dx.doi.org/10.4240/wjgs.v12.i3.116>

INTRODUCTION

The thyroid gland is an infrequent site for extra-thyroid metastases. This clinical finding accounts for 1.5%-7.5% of all malignant diseases of this organ. Despite its rarity, metastases to the thyroid seem to be more common in autopsies of oncologic patients, recording an incidence of up to 24%^[1-4].

The mechanisms involved in the low incidence of metastases to the thyroid gland are still unclear. Some authors support the hypothesis of rich and fast arterial flow through the gland, in addition to high values of oxygen and iodine, which would prevent the adhesion and growth of tumor cells^[5,6].

The most frequent origin of thyroid metastases is primary tumors of the kidney [clear cell carcinoma (CCC)], accounting for about half according to some authors^[4-6]. Other sources are the lung, breast, and gastrointestinal tract. The multiple origins of thyroid metastases are related to the most prevalent cancer types due to particular demographic, ethnic, and epidemiological issues of the different studied populations^[4]. Treatment and prognosis of colorectal metastasis to the thyroid (CMT) remain unclear, and its low incidence and prevalence makes clinical research almost impossible^[7].

During the last decade, an increase in diagnosis of CMT has been noticed, probably due to improvements on image techniques and protocols of treatment and follow-up, which might be responsible for the longer survival of oncologic patients^[5,8,9]. Some case reports of CMT have been described in the literature^[10-14].

CASE PRESENTATION

Chief complaints

A 50-year-old woman was admitted to our hospital with the main complaint of a fast-growing thyroid node and appearance of a right cervical lymph node.

History of present illness

The patient was previously under levothyroxine treatment due to sub-clinical hypothyroidism, and subsequent thyroid function was normal.

History of past illness

On November 2014, the patient had undergone anterior rectal resection and mesorectal total excision due to a previous history of rectal bleeding, and was diagnosed with adenocarcinoma of the rectum on September 2014.

Laboratory examinations

Prior to surgical treatment, the patient had received neoadjuvant radiation (50 Gy) and capecitabine. Histological examination of the specimen confirmed adenocarcinoma of the rectum T3N0M0. She was discharged on the eighth postoperative day after a non-complicated postoperative course and received

adjuvant chemotherapy. After the third session of Xelox (capecitabine and oxaliplatin), she presented with a cutaneous adverse response, and thus was switched to Tomudex (Raltitrexed), finishing on July 2015 after eight cycles.

Imaging examinations

A year after achieving complete remission, 13 mo after diagnosis of the primary tumor, during routine follow-up, a positron emission tomography/computed tomography (PET/CT) scan showed bilateral lung metastases, and also unspecific and diffuse hyper-metabolism on both thyroid lobes (Figure 1).

A new adjuvant Folfiri (folinic acid, 5-fluorouracil, and irinotecan) therapy was administered, but unfortunately had to be suspended during the second cycle due to toxicity. Metastasectomy of the left lung was performed in October 2017, followed by subsequent lobectomy and linfadenectomy of the right lung in December 2017. After surgical treatment, the patient rejected more chemotherapy. At 1.5 year after lung surgery and 43 mo after diagnosis of primary tumor, the patient noticed a right thyroid nodule and hoarseness, which were confirmed by physical examination.

Fine needle aspiration biopsy (FNAB) was performed. Cytological analysis revealed epithelial cells, nuclear atypia, and oncotic changes, indicative of a papillary thyroid carcinoma (Bethesda V). Ultrasound confirmed a hypoecogenic nodule, and CT scan confirmed an enlarged thyroid gland and suspicious cervical right lymph node (Figures 2 and 3).

The patient underwent surgery on May 2019, finding an enlarged thyroid gland in contact with the trachea, esophagus, and right recurrent laryngeal nerve. A frozen section informed metastatic infiltration of the thyroid gland by adenocarcinoma of gastrointestinal origin. Total thyroidectomy, central lymph node dissection, and right lateral neck dissection were performed. During the postoperative course, the patient developed a clinical hypocalcemia and right vocal cord palsy. The patient was discharged 4 d after surgery.

Histological analysis of the specimen confirmed metastasis of adenocarcinoma of gastrointestinal origin, infiltration of 3/9 of central lymph nodes, and 4/9 of laterocervical lymph nodes. Immunological examination showed positive for CDX2 and cytokeratin 20 (CK20) expression (suggestive of gastrointestinal origin), and negative for CK7 and thyroid transcription factor 1 (suggestive of thyroid primary tumor, papillary type) (Figures 4 and 5).

The patient (5 mo after thyroidectomy and 61 mo after diagnosis of the primary tumor) is currently under oncologic follow-up, and a new type of chemotherapy based on raltitrexed, oxaliplatin, and bevacizumab has been proposed.

FINAL DIAGNOSIS

Thyroid metastasis of adenocarcinoma of the rectum.

TREATMENT

Total thyroidectomy, central lymph node dissection, and right lateral neck dissection.

OUTCOME AND FOLLOW-UP

The patient is currently under oncologic follow-up, and a new type of chemotherapy based on raltitrexed, oxaliplatin and bevacizumab has been proposed.

DISCUSSION

Metastases to the thyroid gland are a rare finding in scientific literature. Secondary malignancies of the thyroid account for an estimated percentage of 1.5%-7.5% of all malignant diseases of the thyroid gland in clinical practice. On the other hand, in autopsy studies this finding seems to be more prevalent, accounting for 24% of performed clinical autopsies^[1-4].

The reasons that explain the infrequent settlement of extra-thyroid metastases to the thyroid gland remain unclear. The thyroid gland has a high blood flow, which could be responsible for the difficulty of malignant cells to settle and grow. In addition, the elevated concentration of oxygen and iodine throughout the thyroid gland might also prevent the growth of tumor cells. Some authors have noticed a

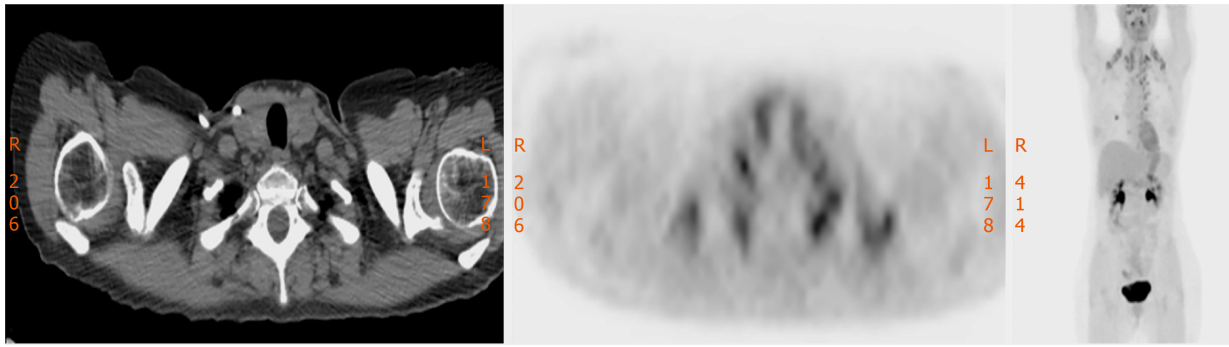


Figure 1 Thyroid gland hypermetabolism on positron emission tomography.

higher prevalence of thyroid metastases in the context of a diseased gland, with thyroid adenomas, multinodular goiter, and thyroiditis being the most frequent entities. The reduced blood flow and iodine content would probably explain the susceptibility to host metastases^[5,6].

A few groups have focused on this specific topic, developing retrospective studies with the aim of identifying and analyzing secondary malignancies of the thyroid gland. Wood *et al*^[1] presented a retrospective series of 15 metastases to the thyroid gland of a total of 1016 patients. They found a prevalence of 1.5%, according to literature, and a high prevalence of kidney CCC. In contrast, other authors have found a much lower incidence of thyroid metastases of extra-thyroid origin, accounting for 0.13%^[1,4]. If focusing on colorectal metastases, Lièvre *et al*^[2] found a prevalence of 0.1% of CMT during a period of 10 years.

The most frequent origins are renal CCC followed by lung, breast, and gastrointestinal tract, although some demographic variability has been observed. The review of Asiatic series by Chung *et al*^[5] found a higher prevalence of CCC accounting for almost half of the secondary disease of the thyroid gland (48%), followed by CMT (10.4%)^[5]. Other retrospective studies agree with these findings, showing a prevalence of CCC origin of the thyroid metastases up to 76%^[6].

On the contrary, Papi *et al*^[4] found the lung as the main primary source of thyroid malignancies, followed by CMT, probably due to the high prevalence of lung and colorectal cancer in European countries.

The most common clinical findings are fast enlargement of the thyroid gland, rapidly growing thyroid nodes, and hoarseness. In some cases, acute onset of compressive symptoms, particularly invalidating dyspnea, may lead to urgent surgical treatment to secure the airway, and occasionally with palliative intention^[1,5,6]. Incidental diagnosis during routine physical examination or its finding in the context of oncologic follow-up is also feasible^[3].

Most patients, including those affected by CMT are euthyroid. Changes on thyroid function are uncommon and tend to occur late. Hypothyroidism as well as thyrotoxicosis may be a consequence of massive infiltration of the thyroid gland^[3,5]. Most patients (60%-80%) according to Nixon *et al*^[9] are diagnosed with thyroid metastases in the clinical setting of a previous malignant disease, both incidentally, due to evident symptoms or during image techniques performed as part of the follow-up. That encourages many authors to alert a high index of suspicion, especially in the case of previous oncologic history^[3,8].

In addition, the accuracy and spread of diagnostic image techniques such as CT scan, magnetic resonance imaging, and PET/CT might be responsible for an increased number of CMT. Moreover, generalization and improvement of oncological therapies redounds on a longer overall survival of oncologic patients, which will probably lead to the late appearance of metastases to infrequent sites such as the thyroid gland^[2,8,9].

Also, differential diagnosis with primary malignancies of the thyroid gland, which can be complex, has to be taken into account. In order to simplify this diagnostic challenge, FNAB, cytology reports, and histological examination can be of great importance, all identifying primary thyroid malignancies or assessing the primary source of the metastases, although false negative and false positive rates have been described^[2,4,5,10,12].

CMT can be diagnosed as synchronous and metachronous to the primary tumor, and can also appear many years after curative treatment of the primary tumor^[1,7,8,11]. Lièvre *et al*^[2] found a median disease-free interval of 61 mo from diagnosis of colorectal cancer to the confirmation of the CMT.

There are controversial opinions regarding the treatment of thyroid metastases of



Figure 2 Computerized tomography image of a suspicious thyroid nodule.

extra-thyroid malignancies. Some authors have advocated surgical treatment based on total thyroidectomy, while others have considered lobectomy as a valid option. The main objective is the achievement of negative margins in the specimen^[1,3,6].

The lack of experience and clinical trials in specific cases of CMT make the decision-making process even more difficult. Some authors have advocated for surgical treatment, as in selected cases, it might improve the patient outcome. In other cases, it might prevent the wide spread of metastatic disease by achieving local control. Otherwise surgical treatment is recommended at the onset of compressive symptoms^[2,4,7].

Chung *et al*^[5] even defend a total thyroidectomy in cases of a diseased thyroid gland and a previous oncologic history, in spite of the cytological result after a FNAB. Mirallié *et al*^[7] agree and also recommend lymph node dissection if clinical or image evident cervical lymph nodes are detected^[5,7,13]. In some cases, palliative surgery is the only feasible option, in association with chemotherapy and/or radiotherapy^[7,13].

Thyroid invasion by malignant disease of extra-thyroid origin has been classically associated with extrathyroid metastases and a poor prognosis^[1,3,7,9]. Lièvre *et al*^[2] assessed an overall survival of 12 mo since the diagnosis of the CMT, and 77 mo since the diagnosis of primary colorectal cancer.

Some other authors have argued that thyroid metastases have the same impact on prognosis as metastases to other sites, and that thyroid invasion does not negatively impact overall survival. Overall survival depends on prognosis of the primary tumor and the metastatic burden^[3,14].

CONCLUSION

To summarize, secondary malignancies of the thyroid gland are a rare entity. In addition, CTMs are even more rare, despite the high prevalence of colorectal cancer in developed countries. Due to a more concerned follow-up of oncologic patients and improvements in diagnostic techniques and cancer treatment, the rate of distant metastatic disease has become more frequent, including its appearance in infrequent sites as the thyroid gland. The main objective is to correctly identify the CMT and discharge other clinical entities as primary disease of the thyroid gland. In this context, FNAB and cytological examination could be of great help, especially in cases of a previous oncologic history. Some authors have suggested different surgical techniques as a curative treatment, based on complete resection of the thyroid metastases, if tumor-free margins are guaranteed. On the other hand the infrequency of the situation makes it difficult to draw clear conclusions and management protocols, and makes us advocate for an individualized treatment.

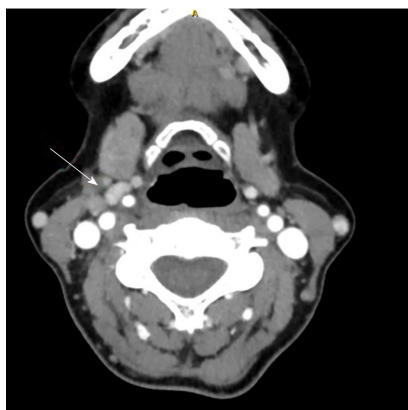


Figure 3 Computerized tomography image of a pericarotid lymph node.

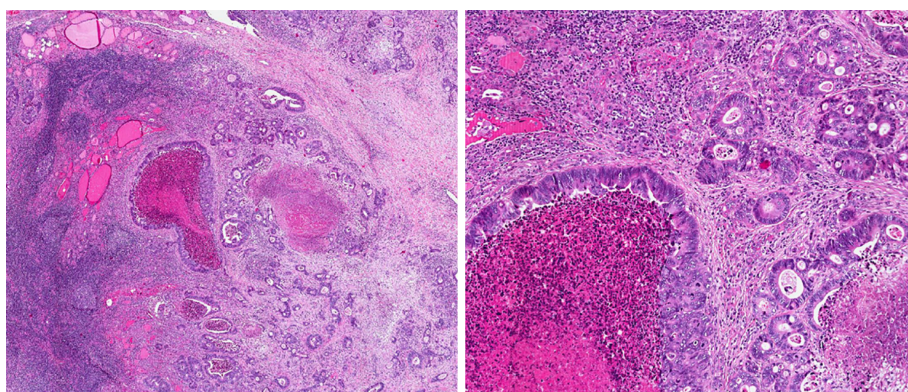


Figure 4 Hematoxylin-eosin stain of a specimen showing thyroid gland infiltration by metastasis of colorectal origin. Numerous mitosis and necrosis (2.5 ×).

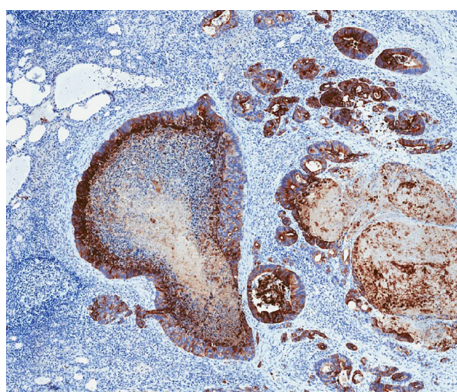


Figure 5 CK20-positive stain in a specimen (4.5 ×).

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Isolated gallbladder tuberculosis mimicking acute cholecystitis: A case report

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Author contributions: Chan KS wrote the paper; Shelat VG and Junnarkar SP performed the operation, supervised the study and designed the study; Tan CH and Tang YL provided advice and guidance on radiological and histopathological findings respectively.

Informed consent statement: Consent has been taken from the patient for publication of findings in a journal.

Conflict-of-interest statement: The authors declare that there is no conflict of interest.

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

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Abstract

BACKGROUND

Isolated tuberculosis of the gallbladder is extremely rare due to its intrinsic resistance to tuberculous infections. There are reports of gallbladder tuberculosis mimicking cholecystitis or malignancy. However, these presentations were chronic. The diagnosis of gallbladder tuberculosis warrants the need for investigation of additional sites of inoculation and contact tracing of all tuberculosis contacts. Gallbladder tuberculosis is a rare entity but should be suspected in patients from endemic regions with risk factors such as underlying immunosuppression or history of tuberculosis.

CASE SUMMARY

We present a case of gallbladder tuberculosis presenting as acute cholecystitis. A 44-year-old Filipino lady presented with a 11-d history of right hypochondrium and epigastric pain which worsened after meals with no significant past medical history. She underwent laparoscopic cholecystectomy on the presumptive diagnosis of acute cholecystitis and diagnosed as gallbladder tuberculosis after histopathological examination. The patient did not have features of pulmonary or systemic tuberculosis nor was she immunocompromised. She recovered uneventfully. She was subsequently discharged and followed-up at a hospital in her home country due to financial and social reasons.

CONCLUSION

Clinicians should have a high index of suspicion for patients in endemic regions

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Manuscript source: Invited manuscript

Received: October 14, 2019

Peer-review started: October 14, 2019

First decision: November 6, 2019

Revised: November 20, 2019

Accepted: December 14, 2019

Article in press: December 14, 2019

Published online: March 27, 2020

P-Reviewer: Donmez T, Gumbs A, Qayed E

S-Editor: Yan JP

L-Editor: A

E-Editor: Ma YJ



presenting with cholecystitis.

Key words: Cholecystectomy; Cholecystitis; Gallbladder; Extra-pulmonary tuberculosis; Case report

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Core tip: Isolated tuberculosis of the gallbladder is extremely rare due to its intrinsic resistance to tuberculous infections. We present a rare case of isolated gallbladder tuberculosis presenting as acute cholecystitis. Clinical examination revealed positive Murphy's sign. The patient underwent laparoscopic cholecystectomy within the same admission. Histology shows necrotizing granulomatous inflammation with rare acid-fast bacilli which was identified on Ziehl-Neelsen stain. This case highlights the multivariable clinical presentations of gallbladder tuberculosis. Clinicians should have a high index of suspicion for patients in endemic regions presenting with cholecystitis to obtain a pre-operative diagnosis.

Citation: Chan KS, Shelat VG, Tan CH, Tang YL, Junnarkar SP. Isolated gallbladder tuberculosis mimicking acute cholecystitis: A case report. *World J Gastrointest Surg* 2020; 12(3): 123-128

URL: <https://www.wjgnet.com/1948-9366/full/v12/i3/123.htm>

DOI: <https://dx.doi.org/10.4240/wjgs.v12.i3.123>

INTRODUCTION

Abdominal tuberculosis (TB) is uncommon, with an incidence of 3.5% of all extra-pulmonary TB^[1]. TB of the hepatobiliary system is rare and isolated gallbladder TB in the absence of any active pulmonary infection is extremely rare^[2-4]. Gallbladder TB remains a diagnostic challenge as clinical presentation mimics other gallbladder diseases such as cholecystitis and imaging features may mimic gallbladder carcinoma^[5]. There are reports describing varied clinical profile and associations with gallbladder TB^[2,4,6]. Majority of reports describe patients presenting with constitutional symptoms such as fever, anorexia, weight loss and/or an underlying immunosuppressed state in patients with gallbladder TB. In this report, we present a case of isolated gallbladder TB mimicking acute cholecystitis in an immunocompetent patient with no significant past medical history.

CASE PRESENTATION

Chief complaint

A 44-year-old Filipino lady presented with a 11-d history of right hypochondrium and epigastric pain which worsened after meals.

History of present illness

A 44-year-old Filipino lady presented with a 11-d history of right hypochondrium and epigastric pain which worsened after meals. There was no history of fever, night sweats, cough with hemoptysis, tea-coloured urine, pale stools or unintentional weight loss.

History of past illness

She had no significant past history.

Physical examination

On examination, there was no scleral icterus and Murphy's sign was positive. There was no cervical lymphadenopathy. Physical examination was otherwise unremarkable.

Laboratory examinations

Serum biochemistry revealed neutrophil-predominant leukocytosis with normal liver and renal function tests. Her blood cultures did not reveal microbial growth.

Imaging examinations

Chest x-ray was normal and computerized tomography scan of the abdomen and pelvis (CTAP) showed heterogeneous density of the gallbladder wall with marked gallbladder wall edema and a gallstone (Figure 1). The gallbladder wall thickness was 15 mm; the size of the extrahepatic common bile duct was 8.5 mm and the intrahepatic bile ducts were not dilated. CTAP also showed mesenteric and retroperitoneal lymphadenopathy which was deemed non-specific by size criteria.

FINAL DIAGNOSIS

A final diagnosis of acute on chronic cholecystitis secondary to gallbladder TB was made.

TREATMENT

She was started on empiric antibiotics according to local antibiogram^[7] and a laparoscopic cholecystectomy was scheduled during the admission^[8]. The 10-point intra-operative gallbladder scoring system (G10) operation score was 5^[9]. Intra-operatively, a chronically thickened and acutely inflamed gallbladder was covered by moderate grade omental adhesions. The gallbladder contained a 3 cm stone. On histology, the sections of the gallbladder revealed features of acute on chronic cholecystitis as well as necrotizing granulomatous inflammation. Rare acid-fast bacilli (AFB) was identified on Ziehl-Neelsen stain (Figure 2).

OUTCOME AND FOLLOW UP

The patient recovered uneventfully. She was subsequently discharged and followed-up at a hospital in her home country due to financial and social reasons. Details on her follow-up are unfortunately unavailable.

DISCUSSION

Gallbladder TB is a rare entity due to population vaccination and intrinsic resistance for tuberculous infections^[2,10]. It is associated with concomitant gallbladder lesions, especially cholelithiasis^[2-4,11]. Epidemiologically, TB involving the hepatobiliary system is more common in Filipino patients like ours^[1].

Four distinct clinical manifestations of gallbladder TB have been described^[12,13]: (1) As part of miliary TB; (2) As part of disseminated abdominal TB; (3) As isolated gallbladder TB often found incidentally on microscopic examination of resected gallbladder; and (4) As part of an immunocompromised state such as uraemia, cancer or acquired immunodeficiency syndrome^[10]. Our patient presented with a clinical profile consistent with acute cholecystitis and diagnosis was incidental on final histology.

Gallbladder TB remains a diagnostic challenge due to its rarity, non-specific presentation and investigation results. Common presentations of gallbladder TB include abdominal pain, fever, anorexia and weight loss^[14]. Gallbladder perforation with intrahepatic biloma is also described^[4]. Initial biochemical investigations for gallbladder TB are non-specific, such as a neutrophilic-predominant leukocytosis. A study by Xu *et al*^[5] also showed that CTAP imaging for gallbladder TB may mimic a polyp, cholecystitis or carcinoma. The presence of heterogenous enhancement of the gallbladder may suggest caseating or liquefactive necrosis, which was found in our patient (Figure 1). However, the possibility of gallbladder TB was not a consideration in this patient with no significant past medical history and absence of immunosuppression. Prominent retroperitoneal and mesenteric nodes are likely to be reactive and non-specific. The possibility of a gallbladder TB based on the CTAP finding is only able to be considered retrospectively after histopathological analysis reveals AFB. Ultrasound-guided fine needle aspiration cytology of the gallbladder, although not commonly performed in clinical practice, may suggest the presence of gallbladder TB: Multiple granulomas with inflammatory and multinucleated giant cells and a positive Ziehl-Neelsen stain^[15]. Histology is confirmatory and pre-operative predictors of gallbladder TB are not specific or validated due to paucity of data^[2,3,14,16]. Cholecystectomy during the initial hospitalisation is recommended for

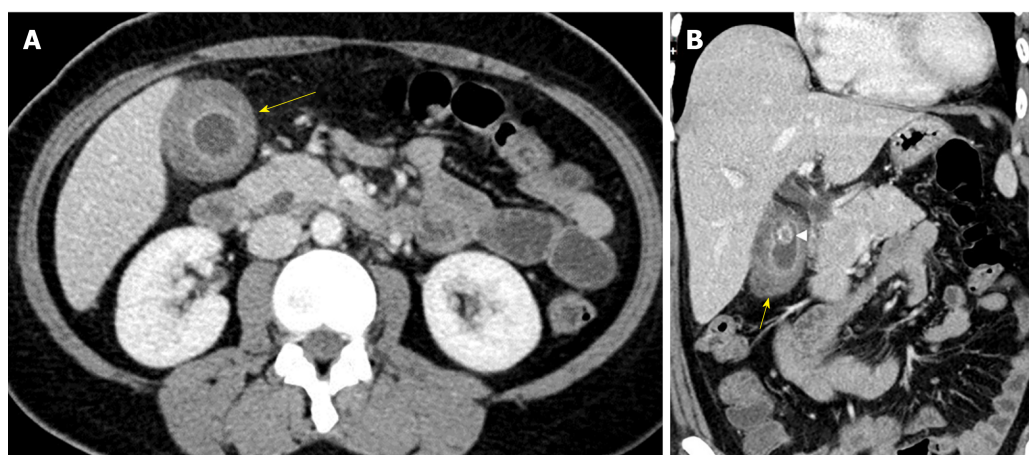


Figure 1 Contrast enhanced computed tomography of the abdomen and pelvis. A: Thickened gallbladder wall (arrow) with moderate increased density of the submucosa; B: Reformatted contrast enhanced computed tomography showing heterogeneous density of the gallbladder wall (arrow). A calculus (arrowhead) is present within the gallbladder.

patients with acute cholecystitis as it reduces length of stay, reduces cost and also restores quality of life^[17].

The diagnosis of gallbladder TB warrants the need for investigation of additional sites of inoculation of TB – *via* AFB smear and culture of induced sputum, blood culture and polymerase chain reaction (PCR) assay. Positive pulmonary TB results warrant the need for contact tracing and screening of all TB contacts under the local TB guidelines^[18]. This was not possible as our patient defaulted the follow-up. Should there be presence of biliary involvement, pre-operative diagnostic aids include the use of polymerase chain reaction of biliary aspirate *via* endoscopic retrograde cholangiopancreatography, which is more sensitive as compared to AFB staining^[19].

The management of gallbladder TB is similar to the management of pulmonary and/or intra-abdominal TB. The use of quadruple therapy (inclusive of rifampicin, isoniazid, pyrazinamide and ethambutol) remains the gold standard^[20]. If the disease is complicated by biliary obstruction, endoscopic or surgical management is still essential to relieve the obstruction in addition to anti-tuberculous treatment^[21].

CONCLUSION

This case illustrates gallbladder TB with acute presentation in a previously well patient. The findings on CTAP imaging similarly mimics acute cholecystitis and a definite diagnosis was only reached post-operatively after histopathological confirmation. This report highlights the multivariable clinical presentations of gallbladder TB. Clinicians should have a high index of suspicion for patients in endemic regions presenting with cholecystitis to obtain a pre-operative diagnosis. Gallbladder TB is a rare entity but should be suspected in patients from endemic regions with risk factors such as underlying immunosuppression or history of TB. Gallbladder TB may mimic various pathologies such as cholecystitis or malignancy.

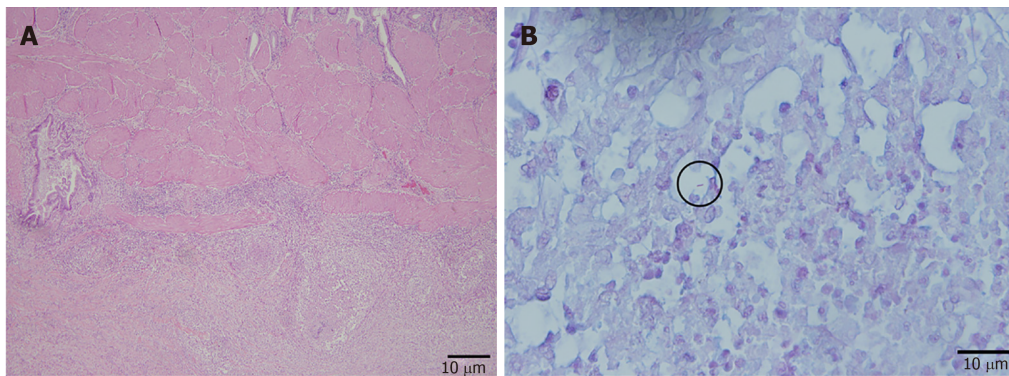


Figure 2 Histopathology of the gallbladder specimen post-cholecystectomy. A: Low power view of the gallbladder with acute and chronic cholecystitis and necrotizing granulomas (Hematoxylin-eosin, × 20); B: Rare acid-fast bacilli (circled) (Ziehl-Neelson × 60) were identified.

ACKNOWLEDGEMENTS

We would like to thank the Department of General Surgery, Radiology and Pathology of Tan Tock Seng Hospital for the support.

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