

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2017 December 28; 23(48): 8439-8678





### EDITORIAL

- 8439 Serum levels of angiotensin converting enzyme as a biomarker of liver fibrosis

*Miranda AS, Simões e Silva AC*

### MINIREVIEWS

- 8443 Mechanisms of autophagy activation in endothelial cell and their targeting during normothermic machine liver perfusion

*Boteon YL, Laing R, Mergental H, Reynolds GM, Mirza DF, Afford SC, Bhogal RH*

### ORIGINAL ARTICLE

#### Basic Study

- 8452 Human small intestine is capable of restoring barrier function after short ischemic periods

*Schellekens DH, Hundscheid IH, Leenarts CA, Grootjans J, Lenaerts K, Buurman WA, Dejong CH, Derikx JP*

- 8465 Stable gastric pentadecapeptide BPC 157 in treatment of colitis and ischemia and reperfusion in rats: New insights

*Duzel A, Vlainic J, Antunovic M, Malekinusic D, Vrdoljak B, Samara M, Gojkovic S, Krezic I, Vidovic T, Bilic Z, Knezevic M, Sever M, Lojo N, Kokot A, Kolovrat M, Drmic D, Vukojevic J, Kralj T, Kasnik K, Siroglavic M, Seiwerth S, Sikiric P*

- 8489 Exploring pathogenesis of primary biliary cholangitis by proteomics: A pilot study

*Deng CW, Wang L, Fei YY, Hu CJ, Yang YJ, Peng LY, Zeng XF, Zhang FC, Li YZ*

- 8500 Influence of TBX21 T-1993C variant on autoimmune hepatitis development by Yin-Yang 1 binding

*Sun W, Wu HY, Chen S*

- 8512 Astragaloside IV inhibits pathological functions of gastric cancer-associated fibroblasts

*Wang ZF, Ma DG, Zhu Z, Mu YP, Yang YY, Feng L, Yang H, Liang JQ, Liu YY, Liu L, Lu HW*

#### Retrospective Cohort Study

- 8526 Prevalence and outcomes of pancreatic cystic neoplasms in liver transplant recipients

*Liu K, Joshi V, van Camp L, Yang QW, Baars JE, Strasser SI, McCaughan GW, Majumdar A, Saxena P, Kaffes AJ*

#### Retrospective Study

- 8533 Analysis of 12 variants in the development of gastric and colorectal cancers

*Cavalcante GC, Amador MA, Ribeiro dos Santos AM, Carvalho DC, Andrade RB, Pereira EE, Fernandes MR, Costa DF, Santos NP, Assumpção PP, Ribeiro dos Santos Á, Santos S*

- 8544** Childhood-onset inflammatory bowel diseases associated with mutation of Wiskott-Aldrich syndrome protein gene

*Ohya T, Yanagimachi M, Iwasawa K, Umetsu S, Sogo T, Inui A, Fujisawa T, Ito S*

- 8553** Comparison of totally laparoscopic total gastrectomy using an endoscopic linear stapler with laparoscopic-assisted total gastrectomy using a circular stapler in patients with gastric cancer: A single-center experience

*Gong CS, Kim BS, Kim HS*

- 8562** Prognostic significance of pretreatment serum carcinoembryonic antigen levels in gastric cancer with pathological lymph node-negative: A large sample single-center retrospective study

*Xiao J, Ye ZS, Wei SH, Zeng Y, Lin ZM, Wang Y, Teng WH, Chen LC*

- 8570** Fecal microbiota transplantation induces remission of infantile allergic colitis through gut microbiota re-establishment

*Liu SX, Li YH, Dai WK, Li XS, Qiu CZ, Ruan ML, Zou B, Dong C, Liu YH, He JY, Huang ZH, Shu SN*

- 8582** Prognostic value of lymph node metastasis in patients with T1-stage colorectal cancer from multiple centers in China

*Sun ZQ, Ma S, Zhou QB, Yang SX, Chang Y, Zeng XY, Ren WG, Han FH, Xie X, Zeng FY, Sun XT, Wang GX, Li Z, Zhang ZY, Song JM, Liu JB, Yuan WT*

**Clinical Trial Study**

- 8591** Association between acute pancreatitis and small intestinal bacterial overgrowth assessed by hydrogen breath test

*Zhang M, Zhu HM, He F, Li BY, Li XC*

**Observational Study**

- 8597** Endoscopic papillary large balloon dilatation with sphincterotomy is safe and effective for biliary stone removal independent of timing and size of sphincterotomy

*Aujla UI, Ladep N, Dwyer L, Hood S, Stern N, Sturgess R*

- 8605** Person-centered endoscopy safety checklist: Development, implementation, and evaluation

*Dubois H, Schmidt PT, Creutzfeldt J, Bergenmar M*

**Randomized Clinical Trials**

- 8615** Multicenter, randomized study to optimize bowel preparation for colon capsule endoscopy

*Kastenber D, Burch WC, Romeo DP, Kashyap PK, Pound DC, Papageorgiou N, Fernández-Urien Sainz I, Sokach CE, Rex DK*

**SYSTEMATIC REVIEWS**

- 8626** *Fusobacterium's* link to colorectal neoplasia sequenced: A systematic review and future insights

*Hussan H, Clinton SK, Roberts K, Bailey MT*

- 8651** Psychiatric morbidity after surgery for inflammatory bowel disease: A systematic review

*Zangenberg MS, El-Hussuna A*

**CASE REPORT**

- 8660** Stricturing Crohn's disease-like colitis in a patient treated with belatacept

*Bozon A, Jeantet G, Rivière B, Funakoshi N, Dufour G, Combes R, Valats JC, Delmas S, Serre JE, Bismuth M, Ramos J, Le Quintrec M, Blanc P, Pineton de Chambrun G*

- 8666** Emphysematous pancreatitis associated with penetrating duodenal ulcer

*Tana C, Silingardi M, Giamberardino MA, Cipollone F, Meschi T, Schiavone C*

- 8671** Infiltrative xanthogranulomatous cholecystitis mimicking aggressive gallbladder carcinoma: A diagnostic and therapeutic dilemma

*Nacif LS, Hessheimer AJ, Rodríguez Gómez S, Montironi C, Fondevila C*

**ABOUT COVER**

Editorial board member of *World Journal of Gastroenterology*, Paola Iovino, MD, Associate Professor, Lecturer, Department of Medicine and Surgery, AOU San Giovanni di Dio e Ruggi di Aragona, Salerno 84131, Italy

**AIMS AND SCOPE**

*World Journal of Gastroenterology* (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7<sup>th</sup>, 14<sup>th</sup>, 21<sup>st</sup>, and 28<sup>th</sup> each month. The *WJG* Editorial Board consists of 1375 experts in gastroenterology and hepatology from 68 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

**INDEXING/ABSTRACTING**

*World Journal of Gastroenterology* (*WJG*) is now indexed in Current Contents<sup>®</sup>/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch<sup>®</sup>), Journal Citation Reports<sup>®</sup>, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2017 edition of Journal Citation Reports<sup>®</sup> cites the 2016 impact factor for *WJG* as 3.365 (5-year impact factor: 3.176), ranking *WJG* as 29<sup>th</sup> among 79 journals in gastroenterology and hepatology (quartile in category Q2).

**FLYLEAF**

**I-IX** Editorial Board

**EDITORS FOR THIS ISSUE**

**Responsible Assistant Editor:** *Xiang Li*  
**Responsible Electronic Editor:** *Yu-Jie Ma*  
**Proofing Editor-in-Chief:** *Lian-Sheng Ma*

**Responsible Science Editor:** *Ze-Mao Gong*  
**Proofing Editorial Office Director:** *Jin-Lei Wang*

**NAME OF JOURNAL**  
*World Journal of Gastroenterology*

**ISSN**  
 ISSN 1007-9327 (print)  
 ISSN 2219-2840 (online)

**LAUNCH DATE**  
 October 1, 1995

**FREQUENCY**  
 Weekly

**EDITORS-IN-CHIEF**  
**Damian Garcia-Olmo, MD, PhD, Doctor, Professor, Surgeon**, Department of Surgery, Universidad Autonoma de Madrid; Department of General Surgery, Fundacion Jimenez Diaz University Hospital, Madrid 28040, Spain

**Stephen C Strom, PhD, Professor**, Department of Laboratory Medicine, Division of Pathology, Karolinska Institutet, Stockholm 141-86, Sweden

**Andrzej S Tarnawski, MD, PhD, DSc (Med), Professor of Medicine, Chief Gastroenterology**, VA Long Beach Health Care System, University of California, Irvine, CA, 5901 E. Seventh Str., Long Beach,

CA 90822, United States

**EDITORIAL BOARD MEMBERS**  
 All editorial board members resources online at <http://www.wjgnet.com/1007-9327/editorialboard.htm>

**EDITORIAL OFFICE**  
 Jin-Lei Wang, Director  
 Ze-Mao Gong, Vice Director  
*World Journal of Gastroenterology*  
 Baishideng Publishing Group Inc  
 7901 Stoneridge Drive, Suite 501,  
 Pleasanton, CA 94588, USA  
 Telephone: +1-925-2238242  
 Fax: +1-925-2238243  
 E-mail: [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com)  
 Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>

**PUBLISHER**  
 Baishideng Publishing Group Inc  
 7901 Stoneridge Drive, Suite 501,  
 Pleasanton, CA 94588, USA  
 Telephone: +1-925-2238242  
 Fax: +1-925-2238243  
 E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
 Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>

**PUBLICATION DATE**  
 December 28, 2017

**COPYRIGHT**  
 © 2017 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

**SPECIAL STATEMENT**  
 All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

**INSTRUCTIONS TO AUTHORS**  
 Full instructions are available online at <http://www.wjgnet.com/bpg/gerinfo/204>

**ONLINE SUBMISSION**  
<http://www.f6publishing.com>

## Infiltrative xanthogranulomatous cholecystitis mimicking aggressive gallbladder carcinoma: A diagnostic and therapeutic dilemma

Lucas Souto Nacif, Amelia Judith Hessheimer, Sonia Rodríguez Gómez, Carla Montironi, Constantino Fondevila

Lucas Souto Nacif, Amelia Judith Hessheimer, Constantino Fondevila, Department of Surgery, Institut de Malalties Digestives i Metabòliques (IMDM), Hospital Clínic, Barcelona 08036, Spain

Lucas Souto Nacif, Amelia Judith Hessheimer, Constantino Fondevila, CIBERehd, IDIBAPS, University of Barcelona, Barcelona 08036, Spain

Sonia Rodríguez Gómez, Department of Radiology, Hospital Clínic, Barcelona 08036, Spain

Carla Montironi, Department of Pathology, Hospital Clínic, Barcelona 08036, Spain

ORCID number: Lucas Souto Nacif (0000-0002-7059-3978); Amelia Judith Hessheimer (0000-0002-7247-5051); Sonia Rodríguez Gómez (0000-0002-1257-2757); Carla Montironi (0000-0002-1453-2193); Constantino Fondevila (0000-0002-6161-6824).

**Author contributions:** Nacif LS and Hessheimer AJ contributed equally to this work; Nacif LS and Fondevila C designed the work; Nacif LS, Hessheimer AJ, Rodríguez Gómez S and Montironi C acquired and analyzed the data; Nacif LS and Hessheimer AJ wrote the manuscript; Rodríguez Gómez S, Montironi C and Fondevila C provided critical appraisal of the manuscript.

**Supported by** Nacif LS was supported by an International Travel Scholar Award from the International Liver Transplantation Society (ILTS).

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

**Conflict-of-interest statement:** None of the authors have any conflicts of interest to declare.

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

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

**Manuscript source:** Unsolicited manuscript

**Correspondence to:** Constantino Fondevila, MD, PhD, Associate Professor of Surgery, Hepatobiliary Surgery and Liver Transplant, Hospital Clínic, University of Barcelona, C/ Villarroel 170, Barcelona 08036, Spain. [cfonde@clinic.ub.es](mailto:cfonde@clinic.ub.es)  
**Telephone:** +34-93-2275718  
**Fax:** +34-93-2275589

**Received:** September 13, 2017

**Peer-review started:** September 13, 2017

**First decision:** October 10, 2017

**Revised:** October 13, 2017

**Accepted:** November 21, 2017

**Article in press:** November 21, 2017

**Published online:** December 28, 2017

### Abstract

Xanthogranulomatous cholecystitis (XGC) is an uncommon variant of chronic cholecystitis. The perioperative findings in aggressive cases may be indistinguishable from those of gallbladder or biliary tract carcinomas. Three patients presented mass lesions that infiltrated the hepatic hilum, provoked biliary dilatation and jaundice, and were indicative of malignancy. Surgical excision was performed following oncological principles and included extirpation of the gallbladder, extrahepatic bile duct, and hilar lymph nodes, as well as partial hepatectomy. Postoperative morbidity was minimal. Surgical pathology demonstrated XGC and absence of malignancy in all three cases. All three

patients are alive and well after years of follow-up. XGC may have such an aggressive presentation that carcinoma may only be ruled out on surgical pathology. In such cases, the best option may be radical resection following oncological principles performed by expert surgeons, in order that postoperative complications may be minimized if not avoided altogether.

**Key words:** Hepaticojejunostomy; Xanthogranulomatous cholecystitis; Gallbladder carcinoma; Hepatectomy; Hilar cholangiocarcinoma

© **The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Though it is a benign disease process, xanthogranulomatous cholecystitis may have an aggressive presentation suggestive of a carcinoma of the gallbladder or biliary tract. In such cases, the best option may be surgical resection performed by expert surgeons following oncological principles, in order to cure affected patients without provoking postoperative morbidity.

Nacif LS, Hessheimer AJ, Rodríguez Gómez S, Montironi C, Fondevila C. Infiltrative xanthogranulomatous cholecystitis mimicking aggressive gallbladder carcinoma: A diagnostic and therapeutic dilemma. *World J Gastroenterol* 2017; 23(48): 8671-8678 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i48/8671.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i48.8671>

## INTRODUCTION

Xanthogranulomatous cholecystitis (XGC) is an uncommon variant of chronic cholecystitis characterized by focal or diffuse severe inflammatory destruction of the gallbladder. The incidence of XGC is variable and has been described among series of cholecystectomies to range between 0.6% and 10%<sup>[1]</sup>. Regarding pathogenesis, the prevailing theory holds that chronic outflow obstruction provokes mucosal ulceration and/or rupture of Rokitsky-Aschoff sinuses and extravasation of mucin and bile into subepithelial tissue. Extravasated bile provokes inflammation, and macrophages phagocytose bile lipids and cholesterol to form ceroid-laden and foamy histiocytes (xanthoma cells). The chronic phase is characterized by repair of the inflammatory reaction, resulting in fibrosis<sup>[2-6]</sup>. The inflammatory process may be severe and extend into adjacent organs, such as the liver, and fistulae may develop into surrounding hollow viscuses (namely the duodenum and transverse colon)<sup>[7]</sup>.

Given the relative scarcity of the disease process and the fact that it may be difficult to differentiate from gallbladder carcinoma (GBC) based on clinical presentation and preoperative imaging, it is not

uncommon that patients with XGC are taken to the operating room without a clear diagnosis. We describe three such cases in which preoperative studies and intraoperative findings were highly suggestive for malignancy, and radical resection following oncological principles was performed. In all three, surgical pathology was ultimately benign, and the postoperative courses were uneventful.

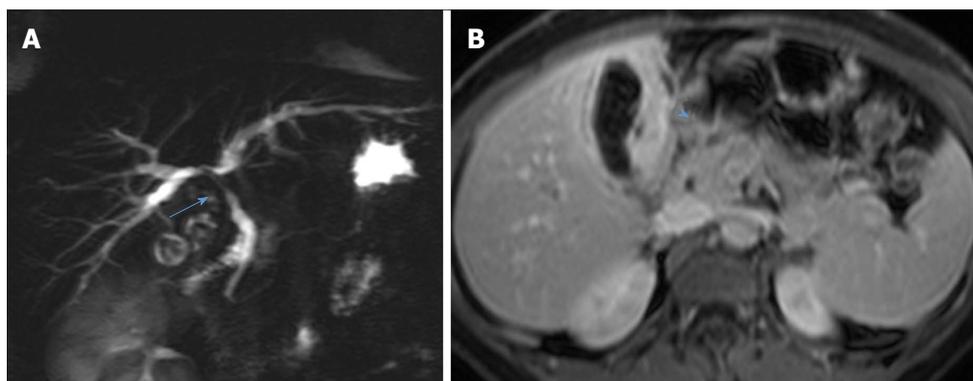
## CASE REPORT

### Case 1

The first patient is a 42-year-old woman with no significant past medical history who presents with loss of 6 kg over the course of two months and a two-week history of epigastric pain and jaundice. No abdominal mass is palpated on physical exam. Initial laboratory tests are significant for cholestasis, with serum bilirubin of 9.3 mg/dL. Computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) imaging reveal a gallbladder with stones and asymmetrical malignant-appearing wall thickening and a contiguous hepatic hilar mass. The mass infiltrates hepatic segment IVb as well as the common and bilateral hepatic ducts, with intrahepatic biliary dilatation (Figure 1). There is extensive contact between the mass and the right portal vein, without any apparent plane of separation. No hilar lymphadenopathy is observed. Given these imaging findings suggestive for resectable biliary tract cancer, the decision is made to perform radical surgery. Intraoperatively, a petrous lesion enveloping the gallbladder and the biliary confluence, with retrograde biliary dilatation, is observed. Right trisectionectomy with cholecystectomy and complete extirpation of the extrahepatic bile duct, hilar lymphadenectomy, and double Roux-en-Y hepaticojejunostomy is performed. The specimen is not opened, but the proximal and distal bile duct margins are sent for perioperative frozen-section analysis (negative for malignancy). The intraoperative and postoperative courses are uneventful, and the patient is discharged home on postoperative day thirteen. Pathological analysis of the surgical specimen reveals chronic cholecystitis with areas of xanthogranulomatous inflammation and absence of malignancy. With over ten years of follow-up, the patient remains well and asymptomatic.

### Case 2

The second patient is a 66-year-old man with no significant past medical history that is referred to our center for suspected gallbladder versus hilar cholangiocarcinoma. The patient arrives at our emergency department with complaints of abdominal pain, fever, jaundice, acholic stools, and choluria. A left-sided external biliary drain has been placed at the referring center. The patient is cachectic and presents pain on palpation of the right upper quadrant, but



**Figure 1** Preoperative magnetic resonance cholangiopancreatography from case 1 demonstrates stenosis of the common bile duct and biliary confluence (arrow, A) and retrograde biliary dilatation. The transverse section demonstrates diffuse asymmetrical gallbladder wall thickening (arrowhead, B) and contiguous hilar mass.

no mass is appreciated. Initial laboratory evaluation at our center is significant for a serum bilirubin of 3 mg/dL (status post biliary drainage) and white blood cell count of  $18.5 \times 10^3/L$ . The external biliary drain is exchanged for an internal-external biliary drain. Imaging studies, including CT and MRCP, are performed, revealing gallstones and a collapsed gallbladder, with focal malignant-appearing wall thickening. There is apparent contiguous infiltration of hepatic segment IVb, the biliary confluence, the right hepatic duct and second-order biliary radicals on the right, and the proximal and middle thirds of the common bile duct, with intrahepatic biliary dilatation. There is also focal contact with the right hepatic artery and a suspicious-appearing spiculated 1-cm hilar lymph node (Figure 2). Exploratory laparoscopy is performed to rule out peritoneal carcinomatosis and intraabdominal metastatic disease followed by laparotomy. Perioperative frozen-section analysis of the suspicious hilar lymph node is negative for malignancy. Radical surgery, including right trisectionectomy with cholecystectomy and complete extirpation of the extrahepatic bile duct, hilar lymphadenectomy, and double Roux-en-Y hepaticojejunostomy, is performed. The postoperative course is complicated by signs of mild hepatic insufficiency (grade 1-2 hepatic encephalopathy and peak serum bilirubin of 8.5 mg/dL on postoperative day 2) and self-limited bile-tinged output in the abdominal drain. The patient is ultimately discharged home on postoperative day thirteen. Pathological analysis of the surgical specimen reveals XGC, without any evidence of malignancy. With almost nine years of follow-up, the patient remains well and asymptomatic.

### Case 3

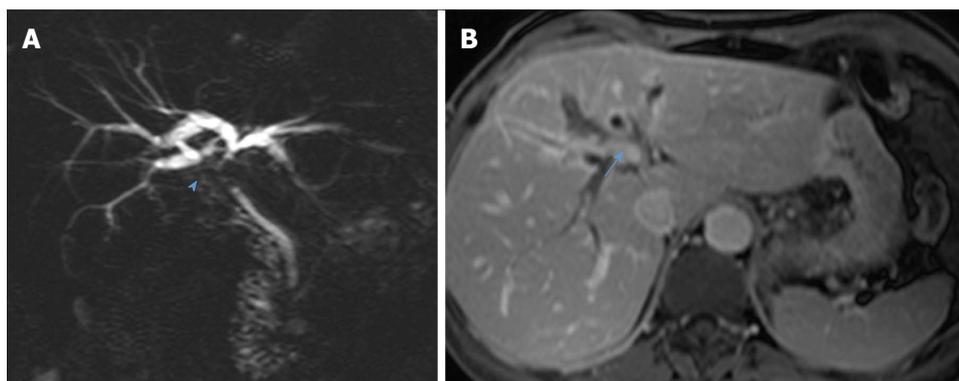
The third case is a 65-year-old man with active cigarette use (one pack per day), and a personal history of arterial hypertension, glucose intolerance, and left nephrectomy over forty years prior. He presents to the emergency department with a five-day history of jaundice, choluria, and anorexia. Initial laboratory

examination is remarkable for a serum bilirubin of 6.8 mg/dL. Abdominal imaging demonstrates gallstones and asymmetric gallbladder wall thickening, affecting primarily the infundibulum, with a contiguous hilar mass infiltrating bilateral hepatic ducts and contacting the right hepatic artery and portal vein, without any apparent plane of separation (Figure 3). Intrahepatic biliary dilatation was also present. Given a differential diagnosis including GBC centered at the infundibulum versus hilar cholangiocarcinoma, radical surgery is indicated. Perioperative frozen-section analysis of hilar lymphadenopathy is negative for malignancy. Ultimately, *en bloc* resection of the gallbladder, hepatic segments IVb and V, and the extrahepatic bile duct, as well as hilar lymphadenectomy and Roux-en-Y hepaticojejunostomy, is performed. The intraoperative and postoperative courses are uneventful, and the patient is discharged home on postoperative day nine. Pathological analysis of the surgical specimen reveals chronic cholecystitis with focal areas of xanthogranulomatous inflammation and absence of malignancy (Figure 4). The patient remains well after almost seven years of follow-up.

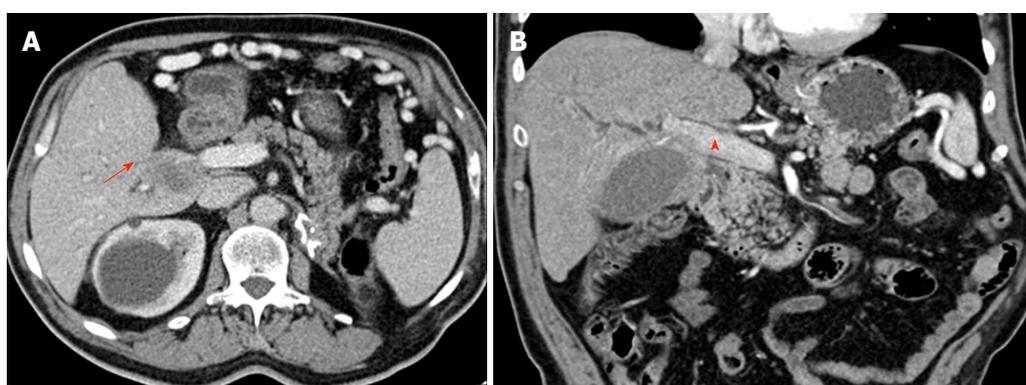
## DISCUSSION

Herein, we present three cases of aggressive XGC where the preoperative studies and intraoperative findings demonstrated widely infiltrative disease processes that could only be removed by radical surgical excision. From a technical standpoint, when severe chronic inflammatory changes of XGC have extended into the hepatic hilum, resection of adjacent organs and the extrahepatic bile duct might be necessary, regardless of the ultimate diagnosis. Such radical interventions should always be performed by surgeons with appropriate expertise, in order that postoperative complications may be minimized, if not avoided altogether.

The difficulty in reaching a definitive diagnosis preoperatively in cases of aggressive XGC lies in the considerable overlap they may present with GBC. Both share peak incidences in the sixth and seventh



**Figure 2** Preoperative magnetic resonance cholangiopancreatography from case 2 demonstrates stenosis of the proximal and middle thirds of the common bile duct, biliary confluence (arrowhead, A), and right hepatic duct and second-order biliary radicals, with retrograde biliary dilatation; a suspicious-appearing spiculated hilar lymph node is seen on transverse section (arrow, B).



**Figure 3** Preoperative CT images from case 3 demonstrating a dilated intrahepatic bile duct (arrow, A) that ends abruptly at the biliary confluence. An ill-defined hilar mass is seen infiltrating the right hepatic artery (arrow, B) and bilateral hepatic ducts and contacting focally with the portal vein (arrowhead, B).

decades of life, arise more commonly in women<sup>[8]</sup>, have been associated with cholelithiasis and chronic inflammation, and present vague clinical signs and symptoms suggestive of biliary colic or acute or chronic cholecystitis<sup>[9]</sup>. Jaundice and cholestasis may be seen in both, though jaundice in the setting of GBC portends worse prognosis.

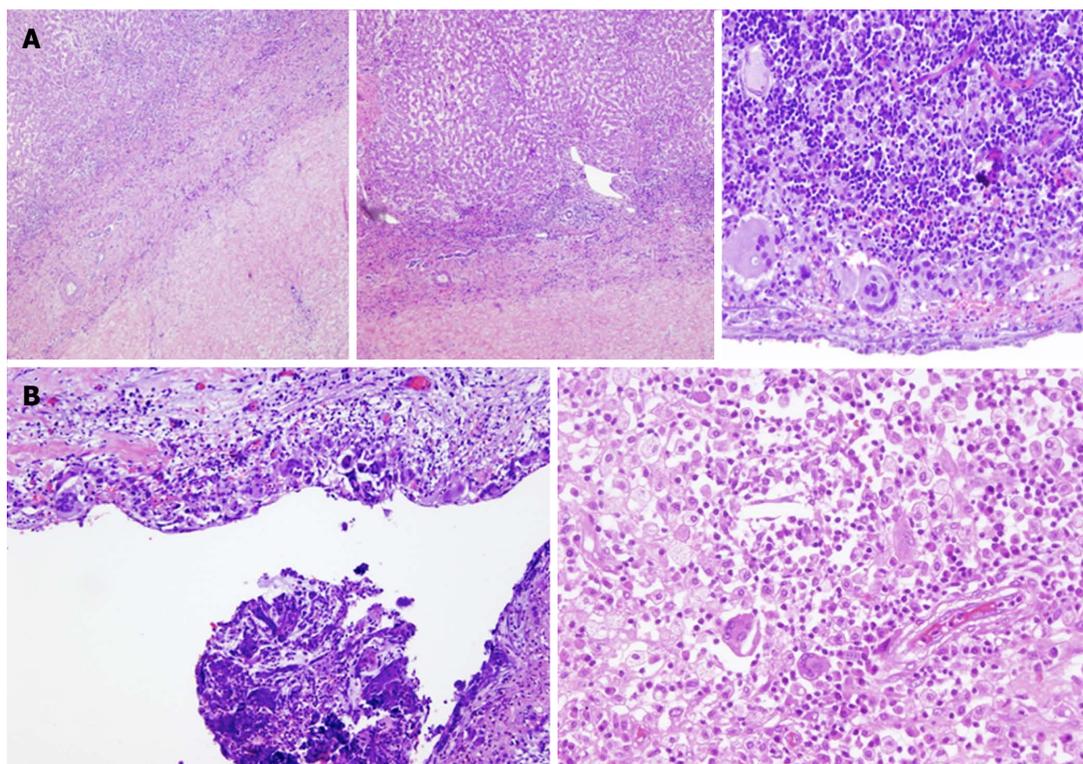
None of the three patients in our series had elevated serum tumor markers. However, in the diagnosis of patients with XGC, serum tumor markers (*e.g.*, CA-19.9) are of little utility, as they are not infrequently elevated (and in some cases extremely so)<sup>[3,9]</sup>. Also, patients who are Lewis antigen negative (10% of the Caucasian population) do not express CA-19.9.

Radiological findings in XGC may include the presence of gallstones and gallbladder wall thickening (diffuse 80%-90%, focal 10%-20%), intramural hypoattenuated nodules, and continuous mucosal line enhancement. Though typically considered characteristic of XGC, intramural nodules may also be seen in well-differentiated GBC with abundant mucin production<sup>[8]</sup>. Features more commonly associated with malignant pathology, including mass lesion, hepatic invasion, and enlarged lymph nodes, may also be seen in XGC<sup>[5,9]</sup>. While involvement of the biliary tree

by the inflammatory process (“xanthogranulomatous cholelithiasis”) may be present, intrahepatic biliary dilatation is often absent<sup>[7,8]</sup>. Findings in our cases that were indicative of potentially malignant processes include hilar mass lesions, intrahepatic biliary dilatation, and images suggestive of vascular infiltration in all three.

When the diagnosis is clear at the time of surgical intervention, simple cholecystectomy is sufficient therapy<sup>[1,5,6]</sup>. Contiguous organ involvement may necessitate performing more extensive resection, however, even when it is known preoperatively that the underlying disease process is entirely benign. The three cases presented in our series were rather complex, due to the presence of widely infiltrative hilar mass lesions with associated vascular affection and retrograde biliary dilatation and jaundice, and the interventions that were performed were necessary to remove the masses and adequately relieve biliary obstruction. In general, the laparoscopic approach is not indicated for XGC (associated with conversion rates of up to 80%)<sup>[1]</sup>, and open approaches are often used initially due to suspicion of cancer and/or the anticipation of technical difficulty.

It has been repeatedly suggested that intra-



**Figure 4** Histological examination of the surgical specimens from the three cases of xanthogranulomatous cholecystitis reveals findings of chronic cholecystitis and marked inflammatory infiltrate, including lymphocytes, plasma cells, foamy histiocytes, and spindle-shaped cells. A: Focal formations of pseudocysts, with multinucleated foreign-body giant cells and cholesterol clefts, are also observed; B: Hyalinization and fibrosis of the gallbladder wall reflects chronic inflammation. Typically, the xanthogranulomatous reaction occupies a limited portion of the gallbladder wall, while the remainder shows signs of conventional chronic cholecystitis. Polymorphonuclear lymphocytes, reflecting acute inflammation, are also occasionally seen. The mucosa presents focal ulceration and erosion and reactive changes that consist in papillary hyperplasia and mucinous and cardiac-type glandular metaplasia. Dysplastic changes and malignant features are absent in all three cases.

operative frozen-section analysis may be useful when diagnosis is in doubt, in order to avoid an unnecessarily aggressive/“mutilating” intervention<sup>[3,4,9]</sup>. This approach is problematic, however, for a couple of reasons. GBC may co-exist with XGC in up to 31% of cases (and may actually provoke outflow obstruction or serve as an entry point for bile, lipids, etc., into subepithelial tissues)<sup>[2,4,9-13]</sup>, and GBC may be missed due to sampling error when the two are present simultaneously<sup>[4,9,10,14]</sup>. Also, opening a potentially cancerous gallbladder to examine the mucosa risks cutting across tumor and disseminating malignant disease. Authors who describe doing so relate cases where surgical pathology was ultimately benign (XGC), but they typically do not describe cases operated in this manner where the ultimate diagnosis was GBC. In general, retrospective series of rare and highly selected patients that criticize the “overtreatment” of this benign disease with an oncological resection can be misleading and should be regarded with caution. In order to adequately analyze the risk for overtreatment, it is important to take into account the percentage of patients with aggressive radiological features that are ultimately diagnosis with GBC, which is the great majority<sup>[3]</sup>.

Complete resection with negative margins remains

the only curative treatment for patients with GBC. According to the National Comprehensive Cancer Network (NCCN) 2017 Guidelines for the management of GBC, if there is a mass on imaging suspicious for GBC, perioperative biopsy is not necessary. Also, suspicious mass lesions found during cholecystectomy should not be biopsied, as doing so might risk peritoneal dissemination. If expertise is available and there is convincing clinical evidence of cancer, definitive resection (radical cholecystectomy including segments IVb and V, lymphadenectomy, and extended hepatectomy or biliary resection as needed to obtain negative margins) should be performed. If expertise is not available, the patient should be referred to a center/surgeon capable of performing radical/definitive resection<sup>[15]</sup>.

Table 1 provides an overview of single-center series (including our own) and case reports published to date that include patients undergoing radical resection following oncological principles (associating, at a minimum, cholecystectomy with resection of hepatic segments IVb and V and hilar lymphadenectomy) for what ultimately turned out to be XGC. Among these 68 patients, the great majority (72%) presented mass lesions and almost half (47%) hepatic invasion. Postoperative outcomes were reported for 42 patients,

**Table 1 Case series and reports on radical resection for xanthogranulomatous cholecystitis**

Ref.	n	Age (yr)	M:F	Perioperative findings	Intervention	Outcome
Agarwal <i>et al</i> <sup>[12]</sup> <i>Gastrointest Surg</i> , 2013	31	50 ± 13	1:3.3	Cholelithiasis 55% Continuous mucosal line enhancement 48% GB wall thickening 19% Hepatic invasion 81% Intramural hypoattenuating nodules 42% Jaundice 7% Mass lesion 100%	Radical cholecystectomy	Postoperative mortality 3%
Rammohan <i>et al</i> <sup>[31]</sup> <i>Gastroenterol Res, Pract</i> 2014	16	56 ± 12	1:1.5	Cholelithiasis 69% Continuous mucosal line enhancement 50% GB wall thickening 37% Intramural hypoattenuating nodules 56% Jaundice 13%	Radical cholecystectomy	NR
Suzuki H, <i>World J Gastroenterol</i> 2015	6	64 ± 10	2:1	Cholelithiasis 83% Continuous mucosal line enhancement 50% GB wall thickening 50% Intramural hypoattenuating nodules 50% Jaundice 17% Retrograde biliary dilatation 17%	Radical cholecystectomy	NR
Nacif Souto L, 2017	3	65 (42-66)	2:1	Cholelithiasis 100% Continuous mucosal line enhancement 100% GB wall thickening 100% Hepatic invasion 67% Intramural hypoattenuating nodules 33% Jaundice 100% Mass lesion 67% Retrograde biliary dilatation 100%	Cholecystectomy + right trisectionectomy + CBD excision + hilar lymphadenectomy + double hepaticojejunostomy (n = 2), radical cholecystectomy + CBD excision + hilar lymphadenectomy + hepaticojejunostomy (n = 1)	Asymptomatic after ≥ 6 yr f/u
Krishna R, J <i>Gastrointest Surg</i> 2008 <sup>[7]</sup>	3	55 (48-56)	2:1	Cholelithiasis 100% GB wall thickening 100% Jaundice 100% Mass lesion 33%	Cholecystectomy + CBD excision + hepaticojejunostomy (n = 1), right hepatectomy + CBD excision	Asymptomatic after ≥ 1 yr f/u
Enomoto T, <i>Hepato-gastroenterology</i> 2003	1	64	M	Hepatic invasion, jaundice, mass lesion, retrograde biliary dilatation	Cholecystectomy + right hepatectomy + Whipple's procedure	NR
Garg P, J <i>Gastrointest Canc</i> 2014	1	32	F	Hepatic invasion, jaundice, mass lesion, retrograde biliary dilatation	Radical cholecystectomy + CBD excision + hepaticojejunostomy	Asymptomatic
Goldar-Najafi A, <i>Semin Liver Dis</i> 2003	1	45	M	Cholelithiasis, GB wall thickening, jaundice, retrograde biliary dilatation	Whipple's procedure	NR
Kawate S, <i>World J Gastroenterol</i> 2006	1	34	F	Jaundice, mass lesion, retrograde biliary dilatation	Cholecystectomy + extended right hepatectomy + CBD excision + hepaticojejunostomy	NR
Makino I, <i>World J Gastroenterol</i> 2009	1	76	M	GB wall thickening, hepatic invasion	Radical cholecystectomy	Asymptomatic after 8 mo f/u
Martins P, <i>Hepatobiliary Pancreat Dis Int</i> 2012	1	35	M	GB wall thickening, hepatic invasion, jaundice	Cholecystectomy + left trisectionectomy + CBD excision + hilar lymphadenectomy + hepaticojejunostomy	Asymptomatic after 6 mo f/u
Pantanowitz L, <i>Pathol Int</i> 2004	1	75	F	Mass lesion, retrograde biliary dilatation	Cholecystectomy + extended left hepatectomy	NR
Sharma D, <i>ANZ J Surg</i> 2009	1	52	F	Cholelithiasis, hepatic invasion, mass lesion	Radical cholecystectomy	Uneventful postoperative course
Spinelli A, <i>World J Gastroenterol</i> 2006	1	46	F	Cholelithiasis, jaundice, mass lesion, retrograde biliary dilatation	Cholecystectomy + right hepatectomy + CBD excision + segmental duodenal resection + right hemicolectomy + partial omentectomy + hepaticojejunostomy + ileotransversostomy	Asymptomatic after 1 yr f/u
Total	68	53 ± 7	1:1.7	Cholelithiasis 62% Continuous mucosal line enhancement 43% GB wall thickening 35% hepatic invasion 47% Intramural hypoattenuating nodules 38% Jaundice 25% Mass lesion 72% Retrograde biliary dilatation 15%		Postoperative mortality 1%

Single-center series and case reports published to date in which radical resection following oncological principles was performed for what ultimately turned out to be xanthogranulomatous cholecystitis. CBD: Common bile duct; f/u: Follow-up; GB: Gallbladder; NR: Not reported.

and the majority experienced an uneventful postoperative course. There was only one postoperative death (1%).

In conclusion, though it is ultimately a benign condition, XGC may have such an aggressive presentation that carcinoma may only be definitively ruled out on surgical pathology. Considering the implications of undertreatment when diagnosis is in doubt, the fact that both XGC and GBC may co-exist, and the fact that lesser surgery might not be technically feasible (especially when there is a mass lesion with extensive involvement of the biliary tree), the best option may be to err on the side of overtreatment. In such cases, surgical intervention should be undertaken by a skilled surgeon capable of performing radical resection and reconstruction and curing the patient of his or her disease process, with little-to-no short- or long-term sequelae.

## ARTICLE HIGHLIGHTS

### Case characteristics

Three patients presented with jaundice and variable other symptoms, including abdominal pain and weight loss.

### Clinical diagnosis

Clinical findings were suggestive of neoplastic processes affecting directly or indirectly the biliary tree.

### Differential diagnosis

Serum bilirubin was elevated in all three cases, while serum CA-19.9 levels were normal.

### Laboratory diagnosis

Laboratory tests and imaging studies were performed to clarify the diagnosis.

### Imaging diagnosis

Abdominal imaging studies, including CT and magnetic resonance cholangiopancreatography, demonstrated widely infiltrative hilar mass lesions with associated vascular affection and retrograde biliary dilatation.

### Pathological diagnosis

Since all three patients had aggressive yet apparently resectable lesions, surgery was undertaken without previous biopsy.

### Treatment

All three interventions were performed according to oncological principles and included, at a minimum, radical cholecystectomy, common bile duct excision, hilar lymphadenectomy, and hepaticojejunostomy.

### Related reports

There are a few previous reports that describe radical resection of very aggressive cases of what ultimately turned out to be xanthogranulomatous cholecystitis, and most describe little-to-no postoperative morbidity or mortality.

### Term explanation

In xanthogranulomatous cholecystitis, mucin and bile are extravasated into subepithelial tissues and phagocytosed, resulting in inflammation, xanthoma formation, and processes of repair and fibrosis that, in some cases, produce

pseudotumors that may be confused with malignancy.

## Experiences and lessons

For clinicians confronting similar cases, we recommend direct surgical intervention performed by an experienced hepatobiliary surgeon capable of removing all diseased tissue, reconstructing the patient's anatomy, and effectively curing the patient of his or her disease process.

## REFERENCES

- 1 **Qasaimeh GR**, Matalqah I, Bakkar S, Al Omari A, Qasaimeh M. Xanthogranulomatous cholecystitis in the laparoscopic era is still a challenging disease. *J Gastrointest Surg* 2015; **19**: 1036-1042 [PMID: 25895976 DOI: 10.1007/s11605-015-2818-z]
- 2 **Hale MD**, Roberts KJ, Hodson J, Scott N, Sheridan M, Toogood GJ. Xanthogranulomatous cholecystitis: a European and global perspective. *HPB (Oxford)* 2014; **16**: 448-458 [PMID: 23991684 DOI: 10.1111/hpb.12152]
- 3 **Rammohan A**, Cherukuri SD, Sathyanesan J, Palaniappan R, Govindan M. Xanthogranulomatous cholecystitis masquerading as gallbladder cancer: can it be diagnosed preoperatively? *Gastroenterol Res Pract* 2014; **2014**: 253645 [PMID: 25404941 DOI: 10.1155/2014/253645]
- 4 **Yabanoglu H**, Aydogan C, Karakayali F, Moray G, Haberal M. Diagnosis and treatment of xanthogranulomatous cholecystitis. *Eur Rev Med Pharmacol Sci* 2014; **18**: 1170-1175 [PMID: 24817291]
- 5 **Lee ES**, Kim JH, Joo I, Lee JY, Han JK, Choi BI. Xanthogranulomatous cholecystitis: diagnostic performance of US, CT, and MRI for differentiation from gallbladder carcinoma. *Abdom Imaging* 2015; **40**: 2281-2292 [PMID: 25952571 DOI: 10.1007/s00261-015-0432-x]
- 6 **Truant S**, Chater C, Pruvot FR. Greatly enlarged thickened gallbladder. Diagnosis: Xanthogranulomatous cholecystitis (XGC). *JAMA Surg* 2015; **150**: 267-268 [PMID: 25565381 DOI: 10.1001/jamasurg.2014.492]
- 7 **Krishna RP**, Kumar A, Singh RK, Sikora S, Saxena R, Kapoor VK. Xanthogranulomatous inflammatory strictures of extrahepatic biliary tract: presentation and surgical management. *J Gastrointest Surg* 2008; **12**: 836-841 [PMID: 18266047 DOI: 10.1007/s11605-008-0478-y]
- 8 **Singh VP**, Rajesh S, Bihari C, Desai SN, Pargewar SS, Arora A. Xanthogranulomatous cholecystitis: What every radiologist should know. *World J Radiol* 2016; **8**: 183-191 [PMID: 26981227 DOI: 10.4329/wjr.v8.i2.183]
- 9 **Deng YL**, Cheng NS, Zhang SJ, Ma WJ, Shrestha A, Li FY, Xu FL, Zhao LS. Xanthogranulomatous cholecystitis mimicking gallbladder carcinoma: An analysis of 42 cases. *World J Gastroenterol* 2015; **21**: 12653-12659 [PMID: 26640342 DOI: 10.3748/wjg.v21.i44.12653]
- 10 **Ueda J**, Yoshida H, Arima Y, Mamada Y, Tani N, Mineta S, Yoshioka M, Kawano Y, Naito Z, Uchida E. A case of xanthogranulomatous cholecystitis preoperatively diagnosed with contrast-enhanced ultrasonography. *J Nippon Med Sch* 2011; **78**: 194-198 [PMID: 21720095]
- 11 **Martins PN**, Sheiner P, Facciuto M. Xanthogranulomatous cholecystitis mimicking gallbladder cancer and causing obstructive cholestasis. *Hepatobiliary Pancreat Dis Int* 2012; **11**: 549-552 [PMID: 23060404]
- 12 **Agarwal AK**, Kalayarsan R, Javed A, Sakhuja P. Mass-forming xanthogranulomatous cholecystitis masquerading as gallbladder cancer. *J Gastrointest Surg* 2013; **17**: 1257-1264 [PMID: 23615807 DOI: 10.1007/s11605-013-2209-2]
- 13 **Rajaguru K**, Mehrotra S, Lalwani S, Mangla V, Mehta N, Nundy S. New scoring system for differentiating xanthogranulomatous cholecystitis from gall bladder carcinoma: a tertiary care centre experience. *ANZ J Surg* 2016; Epub ahead of print [PMID: 26981227]

27599003 DOI: 10.1111/ans.13733]

- 14 **Kwon AH**, Sakaida N. Simultaneous presence of xanthogranulomatous cholecystitis and gallbladder cancer. *J Gastroenterol* 2007;

42: 703-704 [PMID: 17701136 DOI: 10.1007/s00535-007-2072-6]

- 15 **National Comprehensive Cancer Network**. NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers. 2017 May 25.

**P- Reviewer:** Catena F, Ramakrishna HK **S- Editor:** Chen K  
**L- Editor:** A **E- Editor:** Huang Y





Published by **Baishideng Publishing Group Inc**  
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA  
Telephone: +1-925-223-8242  
Fax: +1-925-223-8243  
E-mail: [bpgooffice@wjgnet.com](mailto:bpgooffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>



ISSN 1007-9327

