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

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:** Hepatojejunosotmy; 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, Rodriguez 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%.[1] Regarding pathogenesis, the prevailing theory holds that chronic outflow obstruction provokes mucosal ulceration and/or rupture of Rokitansky-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.[2-6]. 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) [7].

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 Vb 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 hepatojejunostomy is performed. The specimen is not opened, but the proximal and distal bile duct margins are sent for perireoperative 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 who 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
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 x 10^9/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 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
by the inflammatory process ("xanthogranulomatous choledochitis") may be present, intrahepatic biliary dilatation is often absent\textsuperscript{[7,8]}. 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\textsuperscript{[1,5,6]}. 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 affectation 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%)\textsuperscript{[1]}, 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-

decades of life, arise more commonly in women\textsuperscript{[8]}, have been associated with cholelithiasis and chronic inflammation, and present vague clinical signs and symptoms suggestive of biliary colic or acute or chronic cholecystitis\textsuperscript{[9]}. 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)\textsuperscript{[3,9]}. 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\textsuperscript{[8]}. Features more commonly associated with malignant pathology, including mass lesion, hepatic invasion, and enlarged lymph nodes, may also be seen in XGC\textsuperscript{[8,9]}. While involvement of the biliary tree

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).
operative frozen-section analysis may be useful when diagnosis is in doubt, in order to avoid an unnecessarily aggressive/"mutilating" intervention\[^3,4,9\]. 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)\[^2,4,9-13\], and GBC may be missed due to sampling error when the two are present simultaneously\[^4,9,10,14\]. 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\[^3\].

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 IV\(b\) and IV\(v\), 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\[^15\].

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 IV\(b\) and IV\(v\) 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 et al. Gastrointest Surg, 2013 | 31 | 50 ± 13 | 1:3.3 | Continuous mucosal line enhancement 48% GB wall thickening 19% Hepatic invasion 81% Intramural hypoattenuating nodules 42% Jaundice 7% | Radical cholecystectomy | Postoperative mortality 3% |
| Rammohan et al. Gastroenterol Res, Pract 2014 | 16 | 56 ± 12 | 1:1.5 | Continuous mucosal line enhancement 50% GB wall thickening 37% Intramural hypoattenuating nodules 56% Jaundice 13% | Radical cholecystectomy | NR |
| Suzuki H, World J Gastroenterol 2015 | 6 | 64 ± 10 | 2:1 | Continuous mucosal line enhancement 50% GB wall thickening 50% Intramural hypoattenuating nodules 50% Jaundice 17% | Radical cholecystectomy | NR |
| Nacif Souto L, 2017 | 3 | 65 (42-66) | 2:1 | Continuous mucosal line enhancement 100% GB wall thickening 100% Hepatic invasion 67% | Cholecystectomy + right trisectionectomy + CBD excision + hilar lymphadenectomy + double hepaticojejunosotmy (n = 2), radical cholecystectomy + CBD excision + hilar lymphadenectomy + hepaticojejunosotmy (n = 1) | Asymptomatic after ≥ 6 yr f/u |
| Krishna R, J Gastrointest Surg 2008 | 3 | 55 (48-56) | 2:1 | Continuous mucosal line enhancement 100% GB wall thickening 100% Jaundice 100% | Cholecystectomy + CBD excision + hepaticojejunosotmy (n = 1), right hepatectomy + CBD excision | Asymptomatic after ≥ 1 yr f/u |
| Enomoto T, Hepatogastroenterology 2003 | 1 | 64 | M | Hepatic invasion, jaundice, mass lesion, retrograde biliary dilatation | Cholecystectomy + right hepatectomy + Whipple’s procedure | NR |
| Garg P, J Gastrointest Canc 2014 | 1 | 32 | F | Hepatic invasion, jaundice, mass lesion, retrograde biliary dilatation | Radical cholecystectomy + CBD excision + hepaticojejunosotmy + Whipple’s procedure | Asymptomatic |
| Goldar-Najafi A, Semin Liver Dis 2003 | 1 | 45 | M | Cholelithiasis, GB wall thickening, jaundice, retrograde biliary dilatation | Cholecystectomy + extended right hepatectomy + CBD excision + hepaticojejunosotmy | NR |
| Kawate S, World J Gastroenterol 2006 | 1 | 34 | F | Jaundice, mass lesion, retrograde biliary dilatation | Cholecystectomy + extended right hepatectomy + CBD excision + hepaticojejunosotmy | NR |
| Makino I, World J Gastroenterol 2009 | 1 | 76 | M | GB wall thickening, hepatic invasion | Radical cholecystectomy | Asymptomatic after 8 mo f/u |
| Martins P, Hepatobiliary Pancreat Dis Int 2012 | 1 | 35 | M | GB wall thickening, hepatic invasion, jaundice | Cholecystectomy + left trisectionectomy + CBD excision + hilar lymphadenectomy + hepaticojejunosotmy | Asymptomatic after 6 mo f/u |
| Pantanowitz L, Pathol Int 2004 | 1 | 75 | F | Mass lesion, retrograde biliary dilatation | Cholecystectomy + extended left hepatectomy | NR |
| Sharma D, ANZ J Surg 2009 | 1 | 52 | F | Cholelithiasis, hepatic invasion, mass lesion | Radical cholecystectomy | Uneventful postoperative course |
| Spinelli A, World J Gastroenterol 2006 | 1 | 46 | F | Cholelithiasis, jaundice, mass lesion, retrograde biliary dilatation | Cholecystectomy + right hepatectomy + CBD excision + segmental duodenal resection + right hemicolectomy + partial omentectomy + hepaticojejunosotmy + ileotransversostomy | Asymptomatic after 1 yr f/u |
| Total | 68 | 53 ± 7 | 1:1.7 | 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, thought 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 aetification 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, mucus 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 Qasaihme GR, Matalapah I, Bakkar S, Al Omari A, Qasaihme 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: 2540941 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 YJ, 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: R36-841 [PMID: 18266047 DOI: 10.1007/s11605-008-0478-y]
8 Singh VP, Rajesh S, Bhiar 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, Wu 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.i144.12653]
10 Ueda J, Yoshida H, Arima Y, Mamada Y, Taniai 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, Facucci M. Xanthogranulomatous cholecystitis mimicking gallbladder cancer and causing obstructive cholestasis. Hepatobiliary Pancreat Dis Int 2012; 11: 549-552 [PMID: 23060404]
12 Agarwal AK, Kalayasan R, Javed A, Sakhija P. Mass-forming xanthogranulomatous cholecystitis masquerading as gallbladder cancer. J Gastrointest Surg 2013; 17: 1257-1264 [PMID: 23618507 DOI: 10.1007/s11605-013-2209-2]
13 Rajaguru K, Mehoitra S, Lahwani 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:
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
