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SYSTEMATIC REVIEWS

CASE REPORT

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Contents

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CASE REPORT

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

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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: Hepaticojejuostomy; Xanthogranulomatous cholecystitis; Gallbladder carcinoma; Hepatectomy; Hilar cholangiocarcinoma

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%[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 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

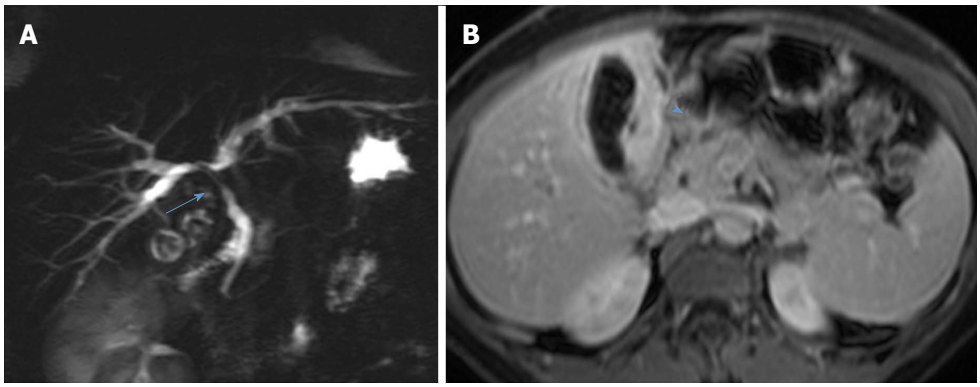

Figure 1 Preoperative magnetic resonance cholangiopancreatography from case 1 demonstrates stenosis of the common bile duct and biliary confluence (arrow, A) and retrograde biliary dilatation. The transverse section demonstrates diffuse asymmetrical gallbladder wall thickening (arrowhead, B) and contiguous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

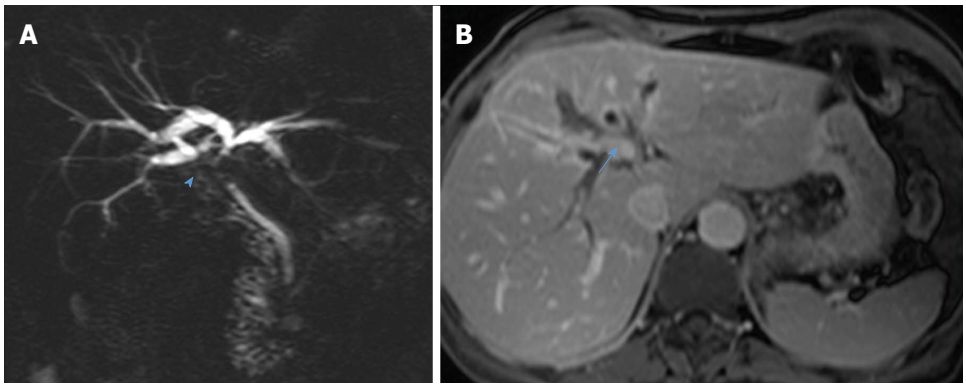

Figure 2 Preoperative magnetic resonance cholangiopancreatography from case 2 demonstrates stenosis of the proximal and middle thirds of the common bile duct, biliary confluence (arrowhead, A), and right hepatic duct and second-order biliary radicals, with retrograde biliary dilatation; a suspicious-appearing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

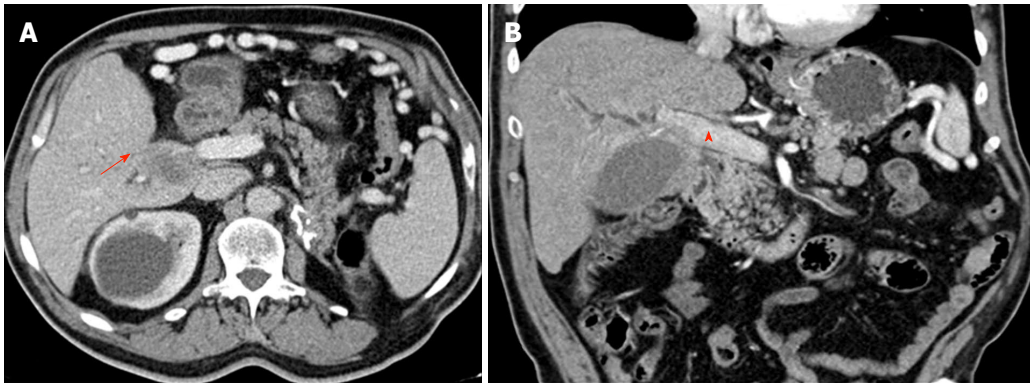

Figure 3 Preoperative CT images from case 3 demonstrating a dilated intrahepatic bile duct (arrow, A) that ends abruptly at the biliary confluence. An ill-defined hilar mass is seen infiltrating the right hepatic artery (arrow, B) and bilateral hepatic ducts and contacting focally with the portal vein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

decades of life, arise more commonly in women[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[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)[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[8]. Features more commonly associated with malignant pathology, including mass lesion, hepatic invasion, and enlarged lymph nodes, may also be seen in XGC[5,9]. While involvement of the biliary tree by the inflammatory process ("xanthogranulomatous choledochitis") may be present, intrahepatic biliary dilatation is often absent[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[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%)[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-

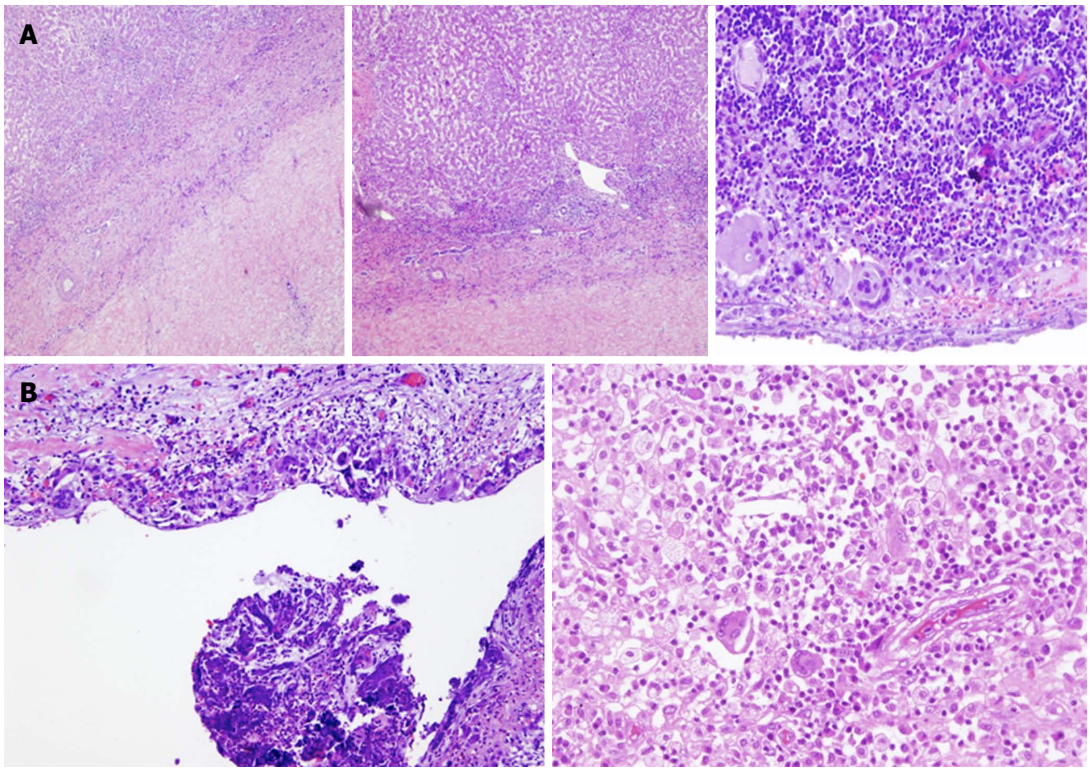

Figure 4 Histological examination of the surgical specimens from the three cases of xanthogranulomatous cholecystitis reveals findings of chronic cholecystitis and marked inflammatory infiltrate, including lymphocytes, plasma cells, foamy histiocytes, and spindle-shaped cells. A: Focal formations of 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 cardial-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[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 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[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 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 *et al*[12] *Gastrointest Surg*, 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 *et al*[3] *Gastroenterol Res*, Pract 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, *World J Gastroenterol* 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 Gastrointest Surg* 2008[7]	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, *Hepato-gastroenterology* 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 + hepaticojejunostomy	Asymptomatic
Goldar-Najafi A, *Semin Liver Dis* 2003	1	45	M	Cholelithiasis, GB wall thickening, jaundice, retrograde biliary dilatation	Whipple's procedure	NR
Kawate S, *World J Gastroenterol* 2006	1	34	F	Jaundice, mass lesion, retrograde biliary dilatation	Cholecystectomy + extended right hepatectomy + CBD excision + hepaticojejunostomy	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 + hepaticojejunostomy	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 + 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, 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 secuelae.

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 affectation 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.

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