

Extended resection for xanthogranulomatous cholecystitis mimicking gallbladder carcinoma: Cases and review of diagnostic approach

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Abstract

Xanthogranulomatous cholecystitis is a rare variant of chronic cholecystitis, which can involve adjacent organs including liver, colon and duodenum mimicking gallbladder cancer. Preoperative and intraoperative differentiation of xanthogranulomatous cholecystitis from gallbladder cancer is often difficult and the final diagnosis is made on histopathology of the resected specimen. We hereby report four cases of xanthogranulomatous cholecystitis which were misdiagnosed as cases of advanced gallbladder cancer based on presentation and radiological findings and underwent radical resections but the final histopathology was a diagnostic surprise. Xanthogranulomatous cholecystitis is still a diagnostic challenge as no single modality has been helpful to diagnose this entity till date. Radical resection seems justified in patients who present with the features mimicking gallbladder cancer.

Keywords: Xanthogranulomatous Cholecystitis, Gallbladder Cancer, Radical Cholecystectomy, Extended Resection, Hepatectomy.

Introduction

Xanthogranulomatous cholecystitis (XGC) is a rare inflammatory disorder of gallbladder first described in 1976 by McCoy et al.¹ The exact etiology of XGC is still unknown but is often associated with gallbladder stones and cholestasis. It is characterized by a focal or diffuse destructive inflammatory process.² It is traditionally a histopathological diagnosis of focal or diffuse acute and chronic cholecystitis. Microscopically, lipid containing histiocytes infiltrating into outer muscle layer of gallbladder wall may be seen to form xanthogranulomatous foci and fibrosis owing to extravasation of bile into gallbladder wall through Rokitansky-Aschoff sinuses or a small ulceration in the mucosa.³ Macroscopically, XGC lesion vary from yellow-brown nodules in the gallbladder wall to diffuse

involvement of the entire gallbladder with extension to the surrounding structures.⁴ The importance of XGC is that it mimics gallbladder carcinoma (GBC) preoperatively on imaging and intra-operatively. Radiological findings (sonography and computerized tomography) of uniformly thickened gallbladder wall, continuous mucosal enhancement, intramural hypodense bands (due to presence of foamy histiocytes), pericholecystic fluid and presence of gallstones are reported to be characteristic features of XGC.^{5,6} Intra-operatively pericholecystic infiltration, hepatic and colonic involvement and lymphadenopathy makes XGC difficult to differentiate from GBC.⁷ The definitive diagnosis is always on final histopathology.

Identification of preoperative differences between XGC and GBC is important to avoid unnecessary extended resection and morbidity in patients with XGC. We report four cases of XGC who underwent radical surgery based on the presentation and preoperative imaging features of GBC and final histopathology was a diagnostic surprise.

Cases

A 60 years old male presented with the history of right upper quadrant (RUQ) pain for one month. In his past history he had similar episode of pain and jaundice one and half years back and the work up showed cholelithiasis and choledocolithiasis for which he underwent endoscopic retrograde cholangiopancreatography (ERCP) with incomplete common bile duct clearance and stent placement in a local hospital. His symptoms subsided for a year followed by repeated episodes of pain and jaundice. He underwent repeat ERCP, complete duct clearance and removal of stent. However, computerized tomography (CT) scan revealed gallbladder mass inseparable from liver. On his presentation at our outpatient clinic he had vague right upper quadrant pain and no symptoms suggestive of malignancy. On examination, he was vitally stable, not icteric, and had mild RUQ tenderness. Lab workup showed normal blood

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counts and liver function tests however CA 19-9 was 22.9 U/ml. Patient was advised antibiotics and a repeat CT scan after four weeks which showed infiltrative mass in the gallbladder fundus involving right lobe of liver and hepatic flexure of colon. Considering the features consistent with malignancy patient underwent radical cholecystectomy, extended right hepatectomy and right hemicolectomy with ileotransverse anastomosis. Intra-operatively thick walled gallbladder was infiltrating into right hepatic lobe and hepatic flexure of colon. His postoperative course was complicated with intraabdominal collection and acute kidney injury managed with image guided drain placement and three sessions of haemodialysis. On his last visit to clinic one and half year after surgery patient was well with normal liver and renal function tests. (June, 2016 Aga Khan University)

Second case was a 42 year old male with recurrent episodes of acute cholecystitis and 10 kg weight loss over a year. General physical and abdominal examination was unremarkable. Complete blood counts and liver function tests were normal. Ultrasound showed gallbladder mass and CT scan revealed soft tissue thickening in gallbladder fundus and adjacent body with loss of fat planes between gallbladder and liver. Intra-operatively, gallbladder was thick, hard and dense adhesions with omentum and hepatic flexure of colon. Patient underwent extended cholecystectomy with en-bloc resection of segment IVb and V of liver, portal lymphadenectomy and segmental resection of colon. Postoperative course was unremarkable and patient was discharged on 7th post-operative day. At one year follow up in clinic patient was well and had gained weight. (July, 2012 Aga Khan University)

Third case was a 55 year old female with recurrent episodes of RUQ pain for two years. No other features in the history were suggestive of malignancy. General physical and abdominal examination was unremarkable. Blood counts and liver function tests were within normal range. Ultrasound showed gallstones and thick walled gall bladder and subsequent CT scan showed thick gallbladder infiltrating into segment V of liver. Intra-operatively there was thick walled gallbladder with omental adhesions and enlarged portal and hepatic lymph nodes. Patient underwent radical cholecystectomy and portal lymphadenectomy. Patient was discharged on 6th postoperative day. On 5th postoperative week

patient presented in the clinic with fever and swelling under the surgical scar. CT scan revealed subcutaneous collection and she underwent drainage under general anaesthesia. Patient was well after two years at her last follow up in clinic. (September, 2015 Aga Khan University)

Fourth case was a 67 years old hypothyroid male with history of recurrent RHC pain, progressive jaundice and weight loss for two months. Initial workup was done in another hospital where an ERCP was done which showed stricture at the hepatic hilum and plastic stent was placed. On presentation at our outpatient clinic he was mildly jaundiced, abdominal examination was unremarkable. Blood counts were normal with mild derangement in liver function tests. CT scan showed a mass lesion at hepatic hilum likely originating from gallbladder. Intra-operatively there was thick walled gallbladder infiltrating into pericholecystic fat and common hepatic duct, closely abutting duodenum. Radical cholecystectomy with en-bloc resection of bile duct, portal lymphadenectomy with roux -en-y hepaticojejunostomy was done. Postoperatively patients course was complicated with bile leak from a small segmental duct from liver resection bed which sealed off subsequently with biliary diversion by percutaneous biliary drainage. At one year follow up patient was well with normal liver function tests and no collection on ultrasound (December, 2016 Aga Khan University)

Discussion

XCG is a rare form of chronic cholecystitis seen in 1.3% to 5.2% of resected GB specimen.⁸ The exact etiology of XCG is unknown, it is suggested that presence of gallstones, obstruction and cholestasis results in the extravasation of bile into the GB wall. The process is supposed to start as an inflammatory process, followed by a granulomatous reaction with the involvement of Rokitsansky-Aschoff sinuses⁹ leading to formation of submucosal abscesses or xanthogranulomas. Macroscopically, XCG is characterized by formation of multiple yellowish nodules within gallbladder wall. Histologically, there is diffuse or focal mural changes in the form of xanthoma cells (foamy histiocytes containing lipids and bile pigments), giant multinucleate histiocytes and acute and chronic inflammatory cells. Microabscesses also tend to form in the gallbladder wall and finally a fibrous reaction and scarring results from healing of the inflammatory reaction.⁴ Rupture of gallbladder serosal

linning and spread of inflammatory response leads to adhesions with adjacent liver, duodenum and transverse colon.

XCG due to its close resemblance with GBC is responsible for approximately 1 in 10 patients being either over treated with unnecessary extended resection or under-treated for a missed GBC. Careful identification of clinical symptoms and radiological features of XCG is therefore desirable to avoid unnecessary morbidity associated with radical surgery.¹⁰ Clinically no symptoms or signs are specific for XCG and they are similar to those of acute and chronic cholecystitis.¹¹ The clinical presentation of all four of our patients was that of recurrent episodes of acute cholecystitis for the span of one year with one patient's course complicated with common bile duct stone for which he had to undergo ERCP twice for duct clearance while other had a history of significant weight loss favoring GBC. However, clinical features are considered to be less useful in differentiating XCG from GBC.⁴

On ultrasonography the common and characteristic feature of all of our patients was either thickened gallbladder wall or mass which warranted further confirmation with triphasic CT scan which confirmed gallbladder mass infiltrating into right lobe of liver in all patients and involvement of hepatic flexure of colon in two patients with associated portal lymphadenopathy favouring GBC. Although imaging characteristics of XCG closely resemble those of GBC in terms of gallbladder wall thickening and tendency to involve neighbouring organs, presence of gallstones indicate high likelihood of XCG. On the other hand, there is some debate as to coexistence of stones with GBC. Uchiyama et al⁵ reported continuous mucosal enhancement as a pathognomic for XCG and Kim et al reported that combined ultrasonographic findings of diffuse wall thickening and intramural nodule formation are highly suggestive of XCG.¹² No such features were reported in any of our patients which was probably due to low index of suspicion and the rare incidence of this benign condition, however CT scan did show infiltrative mass involving liver and colon raising high suspicion for malignancy as shown in Figure 1 and 2.

XCG can be more easily mistaken for GBC intra-operatively than radiologically due to the fact that severe proliferative fibrosis involves gallbladder and surrounding organs leading to hardening of gallbladder wall,



Figure-1: An ill-defined soft tissue thickening in the gallbladder wall infiltrating into adjacent right lobe of liver and hepatic flexure of colon.



Figure-2: Soft tissue thickening of gallbladder fundus and body with loss of fat planes between liver and gallbladder.

infiltration into liver parenchyma and dense adhesions with colon, duodenum and stomach. All cases had common intra-operative picture of thick walled gallbladder with infiltration into right lobe of liver or common hepatic duct and two cases with colonic involvement requiring formal right hemicolectomy and ileotransverse anastomosis in one patient and segmental resection in other. Intra-operative findings of infiltration to the surrounding organs favoured GBC mandating radical operation requiring hepatic resection, lymphadenectomy and bowel resection.

The ideal approach to XCG needs an integrated review of clinical presentation, radiological features and preoperative cytology. The most common clinical presentation is typical of cholecystitis.¹¹ Symptoms suggestive of malignancy like anorexia and weight loss may be present in some patients. There is a strong

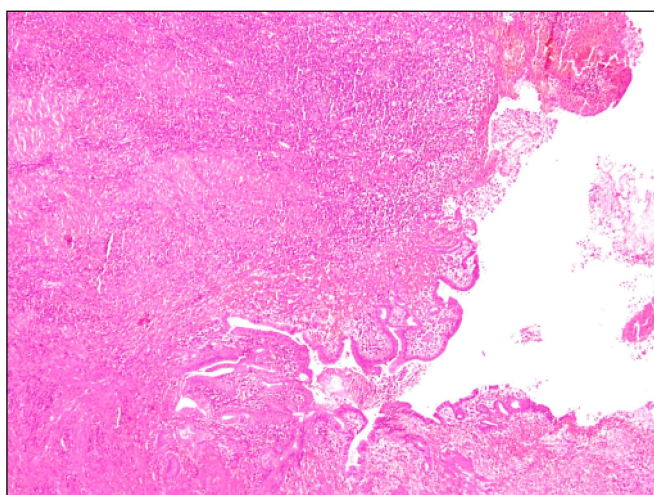


Figure-3: Microscopic section showing gallbladder mucosa with underlying muscularis propria and serosa. Dense acute and chronic inflammation with collection of foamy macrophages.

association of XCG with gallstones. European studies have reported an incidence between 92% to 100%.¹⁰

Diagnostic radiological features of XCG can help distinguish it from GBC preoperatively. Sonographic findings include presence of gallstones or sludge with thickening of the gallbladder wall. The characteristic findings include presence of hypoechoic nodules or bands in thickened gallbladder wall. These characteristic nodules have been seen in 73% cases by Kim et al¹² and bands have been observed in 19% cases in XCG.⁶ CT findings include focal or diffuse wall thickening, intramural hypoattenuating nodules, luminal surface enhancement (LSE) with continuous mucosal lines or mucosal lines with focal breach. Gallbladder wall thickening can range from 4.0mm to 18.5mm and is usually diffuse.¹³ Diffuse thickening is observed in 88.9% and 87.8% of patients by Goshima et al¹⁴ and Zhao et al¹³ respectively. Focal thickening is less commonly seen in XCG and more common for GBC. Intramural nodules on CT (85.7% and 61.1% by Zhao et al¹³ and Goshima et al¹⁴ respectively) are either xanthogranulomas or abscesses characteristic of XCG. A continuous mucosal lining is more often noted in XCG (66.7% of cases) as shown in Figure 3, as compared to GBC where the lining is disrupted (82.2% of cases) because XCG is pathology of gallbladder wall and hence mucosal surface is intact or focally denuded. On the other hand carcinoma arises from epithelium and causes mucosal disruption.¹³ LSE was observed in 85.7% cases by Zhao et al¹³ in portal venous phase representing preservation of mucosal wall

which is characteristic of XCG. Additional findings on CT include organ infiltration involving liver, colon, duodenum, fistulae and abscesses. The magnetic resonance imaging findings that favour XCG are non-focal wall thickening, presence of intramural nodules and LSE. T2-weighted images showing areas of iso to slightly high signal intensity corresponds to the presence of xanthogranulomas. Thickened gallbladder wall in XCG contains intramural fat whereas GBC lacks it.

Endoscopic ultrasound guided fine needle aspiration cytology (EUS-FNAC) is a feasible and safe method for obtaining samples, its role in the diagnosis of gallbladder lesions is not well defined. Moreover, it is estimated that XCG and GBC coexist in upto 12%⁶ of cases and even if a preoperative diagnosis of XCG is made with FNAC it is important to be aware of the possible coexistence of XCG and cancer in the same gallbladder.¹⁵ The diagnostic accuracy of FNAC is around 96%,¹⁶ a negative sample does not rule it out owing to sampling from non-representative areas. The procedure has additional hazard of seeding of the tract with tumour and fistula formation.¹⁷ Intraoperative frozen section examination is the best modality for differentiating XCG and GBC which can avoid radical surgery and associated complications for benign disease.¹⁸⁻¹⁹ Immunohistochemistry along with frozen section is highly sensitive in differentiating between the two conditions.²⁰

With regard to the treatment of XCG, surgeon must show skepticism with advanced GBC. In patients with preoperative diagnosis of XCG based on clinical presentation and characteristic imaging features without local organ infiltration laparoscopic cholecystectomy is the ideal approach with low threshold for conversion because of difficult dissection due to chronic inflammatory process. In cases of liver or other organ infiltration open cholecystectomy with resection of segment IVB and V and intraoperative frozen section seems a reasonable approach for patients with preoperative diagnostic uncertainty. In case of evidence of GBC on frozen section one can proceed with portal lymph node dissection. Although associated with high morbidity, the risk of radical cholecystectomy may be offset by the procedure carrying a lower risk of potentially spilling bile in a patient with GBC than an open cholecystectomy alone, which significantly reduces survival in these patients.²¹

Conclusion

Preoperative or intraoperative differentiation of XCG from GBC is a challenge, especially in patients with pseudotumoral involvement of surrounding organs. Preoperative differentiation is often difficult and the definitive diagnosis is always on final histopathology. Integrated review of clinical features, characteristic radiological features and preoperative FNAC may help to avoid radical surgery in selected patients but in patients with preoperative and intraoperative diagnostic uncertainty, radical resection seems appropriate with the risk of added morbidity.

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Conflict of Interest: None

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