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Xanthogranulomatous cholecystitis mimicking gallbladder carcinoma: A diagnostic and therapeutic dilemma

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Abstract
Xanthogranulomatous cholecystitis (XGC) is a rare condition, very difficult to diagnose preoperatively. It resembles carcinoma of the gallbladder (Ca G.B) clinically, radiologically and intra-operatively and this confusion between XGC and Ca G.B risk the patients being over or under-treated. Awareness about this rare entity and its characteristic radiological features can be used to alert clinicians to the possibility of XGC masquerading as gallbladder carcinoma.

Keywords: xanthogranulomatous cholecystitis, gallbladder carcinoma, chronic cholecystitis, laparoscopic cholecystectomy, radical cholecystectomy

Introduction
Xanthogranulomatous cholecystitis (XGC) is an uncommon variant of cholecystitis with intense inflammatory destruction of the gallbladder [1]. The disease is benign but locally invasive and may involve adjacent organs such as the liver, duodenum, stomach, colon and common bile duct, mimicking carcinoma of the gallbladder [2].
This rare but distinct clinical entity was first described in 1970 by Christensen *et al*. [3]. They noted a pseudotumoral form of chronic cholecystitis that was characterized by the presence of Xanthoma- like foam cells (lipid-laden macrophages) and scarring and that contained ceroid (wax-like) nodules in the wall of inflamed gallbladder. Latter, the nomenclature was done by Mc Coy *et al* in 1976 [4].
XGC is characterized by a focal or diffuse destructive inflammatory process involving gallbladder wall and adjacent structures resulting in dense adhesions, perforation, abscess formation, and fistulous communication with adjacent bowel. Striking gallbladder wall thickening and dense local adhesions can be easily mistaken for carcinoma of the gallbladder, both intraoperatively as well as on preoperative imaging [5]. Besides, cases of concomitant gallbladder carcinoma complicating XGC have also been reported in literature. This study is presented to make awareness about this entity as well as to increase the diagnostic yield of the disease by summarizing the characteristic findings and associations of XGC.

Case 1
A 50 year old male patient, with previous history of gallbladder sludge, diagnosed 3 months back on abdominal sonological screening for dyspepsia presented with pain right lower chest and right upper abdomen for 3 days. It was associated with fever and vomiting. The patient was also having mild icteric tinge. The patient was not on any other medications and he did not report any family history of gastro-intestinal cancers. No abdominal mass was palpated on physical examination. Initial laboratory tests showed leucocytosis (TLC= 17,000/cumm), S. bilirubin of 5.9mg/dl, SGOT= 118 U/L, SGPT= 210 U/L. Ultasonography (USG) abdomen showed well distended gallbladder with 5mm thick wall with doubtful, irregular, isoechoeic lesion (3.7x4.7mm) in posterior wall of body. Neck of gallbladder shows intraluminal mass like lesion (Fig.1) with minimal pericholecystic fluid with hapatomegaly with moderate hepatic steatosis with slightly bulky pancrease and with grossly normal CBD. His C.T scan (Fig.2) showed thick walled (5mm), distended GB with ill-defined fat planes with liver at fundus and body of GB. Neck of GB shows few calculi with intraluminal sludge/? mass.

Pericholecystic fat stranding and peri-pancreatic nodes (40x38mm) and nodes around celiac axis were seen. Minimal right pleural effusion was present. Liver was normal in size on C.T scan with no any metastasis or ascitis. Detailed counseling was done with patient and relatives after consultation with the gastrointestinal onco-surgeon and he was planned for USG guided FNAC. The patient had a normal (0 – 35kU/L) CA 19-9 level of 18 kU/L preoperatively. On the night of 7th day of admission, the patient complained of severe pain abdomen and an USG abdomen was advised which showed peritoneal collection which came out to be bile on aspiration. GB rupture with biliary leak was suspected and he was taken to O.T immediately to put drain percutaneously after diagnostic laparoscopy.

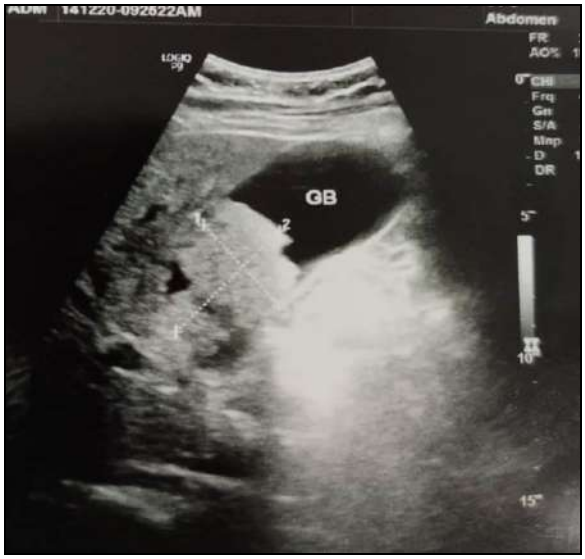

Fig 1: Ultrasound showing mass like lesion with distended GB.

On diagnostic laparoscopy, there was an inflamed distended GB, and having pus collection between the posterior surface of GB and liver, along with biliary leak from the posterior surface of GB. Intraoperatively, there was no any sign of malignancy, mass, enlarged nodes or extension of pathology to any adjacent structures. It was decided to proceed with laparoscopic cholecystectomy after irrigation of pus and bile and a drain was kept in Morrison's space. Post-operative period was uneventful and drain was removed on 3rd post-operative day (POD). Patient was discharged on 7th POD. His histopathological report came out to be Xanthogranulomatous cholecystitis with superadded acute inflammation.

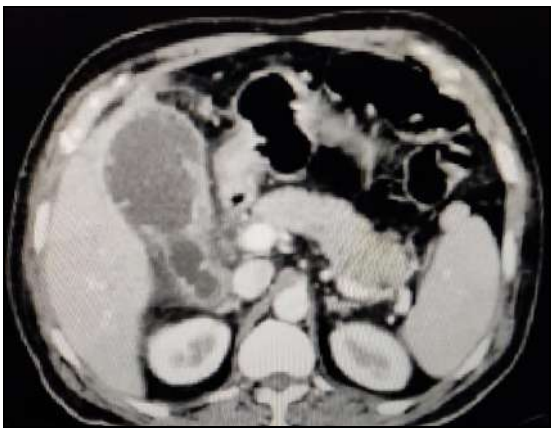

Fig 2: Contrast enhancing CT showing thickened gallbladder wall with significant pericholecystic fat stranding.

Case 2

Another patient, 49 year old male, presented with mild fever, naseua and pain right upper abdomen of 2 weeks duration. He was having a mild icteric tinge, and a vague, tender lump right upper abdomen. His investigations showed leucocytosis (TLC= 13,000/cumm), S.Billirubin=2.6mg%, SGOT=90U/L, and SGPT=86U/L. Ultasonography abdomen showed cholelithiasis with cholecystitis, distended, thick walled gall-bladder with breach in the wall with pericholecystic fluid collection. C.T scan abdomen showed diffuse wall thickening, disrupted mucosal lines, pericholecystic infiltration and fat stranding. The patient was operated (Open procedure) with the provisional diagnosis of gall bladder lump with empyema gall bladder. Intra-operatively patient was having ruptured empyema gall bladder secondary to multiple stones and a stone stuck in the neck of gall-bladder. He was having pericholecystic and peri-hepatic abscess (Fig.3), grossly thickened fundus and ruptured anterior wall with impending cholecysto-colonic fistula. Subtotal cholecystectomy (Fig. 4) with drainage of pus with lavage and mopping was done. Histopathology showed Xanthogranulomatous cholecystitis (Fig.5).

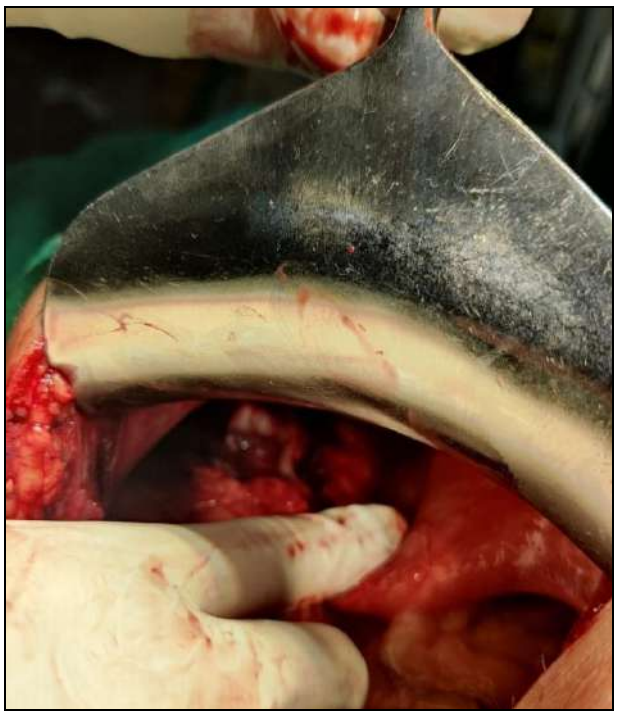

Fig 3: Showing peri-hepatic pockets after drainage of pus, along with dense adhesions.

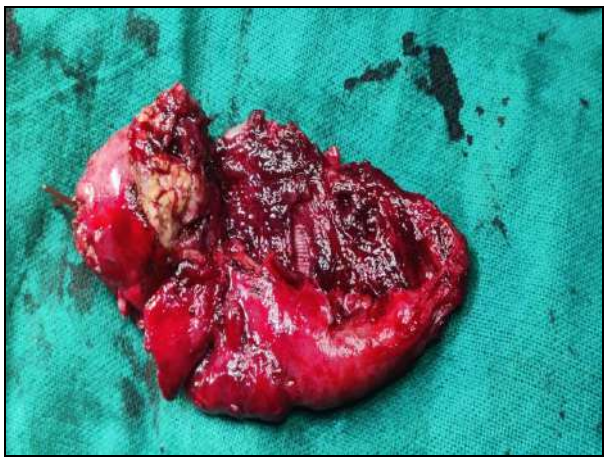

Fig 4: Specimen after sub-total Cholecystectomy

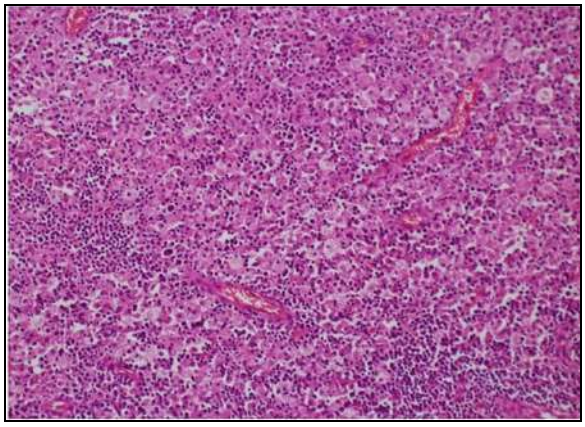

Fig 5: Histopathology of the gallbladder mucosa showing diffuse inflammatory infiltrate consisting of giant histiocytes and foamy histiocytes with clear lipid- containing cytoplasm, lymphocytes, and polymorphonuclear cells.

Discussion

The diagnosis of Xanthogranulomatous cholecystitis (XGC) is often a post-operative histological surprise. XGC exhibits similar imaging and intraoperative findings as those of gallbladder cancer (GBC), leading to its frequent misdiagnosis and unnecessary radical surgery [6].

The true incidence of XGC is unknown, ranging widely from 0.7% to 13.2% of all inflammatory gallbladder pathology [7]. Geographical variations in incidence are also considerable, with most case being reported from East and Southern Asian populations while there is very limited research in North America [8]. The incidence of XGC in males and females largely appears equal and occurs mostly in patients between 50-60 years age. Clinical presentation of XGC is variable and often non-specific. Most of the patients present with chronic cholecystitis while others have acute cholecystitis (as in these cases) or Mirrizi's syndrome. A majority of the patients present with XGC report abdominal pain, naseua, vomiting and fever. Jaundice occurs in about 20% of patients with XGC [9]. Jaundice may develop as a result of choledocholithiasis or excessive inflammation and transmural fibrosis that extends to the common bile duct. A history of repeated episodes of biliary colic or pancreatitis is also fairly common [10].

Although the mechanism that leads to this condition remains unclear, XGC is thought to start as a biliary obstruction with acute or chronic Cholecystitis and increasing intra-gallbladder pressure. This pressure provokes a rupture of the Rokitansky-Aschoff sinuses or mucosal ulcer with extravasation of bile in the interstitial tissues and a consequent Xanthogranulomatous inflammatory reaction, where by fibroblasts and macrophages phagocytose the biliary insoluble lipids in bile, such as cholesterol and phospholipids, leading to the formation of Xanthoma cells (foamy histiocytes with clear lipid-containing cytoplasm). These histiocytes are positive for CD 68 on immunohistochemistry. This inflammatory process is often extensive and may extend to adjacent organs, forming dense adhesions with a large mass of inflammatory tissue surrounding gallbladder [11]. A fibrous reaction and scarring result due to healing of the inflammatory reaction. Although gallstones and a strikingly thickened and echogenic gallbladder wall are frequent radiological findings, they are non-specific. The presence of sludge is also common and was observed in up to 50% of patients by Cases *et al.* [12]. Diffuse gallbladder wall thickening with intramural hypoechoiec nodules or bands are more characteristic features of XGC on ultrasound. The characteristic C.T findings include diffuse, or less often, focal wall thickening, intramural hypo attenuating nodules, luminal surface enhancement (LSE) in the presence of continuous mucosal lines, loss of interface between the gallbladder and liver, and other features of local inflammation. These findings are also associated with gallbladder cancer, but features such as continuous, rather than disrupted, mucosal lines and the presence of pericholecystic infiltration or fat stranding are thought to be especially suggestive of XGC [8, 13]. Features more commonly associated with malignant pathology including mass lesion, hepatic invasion, and enlarged lymph nodes, may also be seen in XGC. While involvement of the biliary tree by the inflammatory process ("Xanthogranulomatous Choledochitis") may be present, intrahepatic biliary dilatation is often absent, as in these cases [14].

The role of percutaneous and endoscopic ultrasound (EUS) guided fine needle aspiration (FNA) biopsy in the diagnostic workup of gallbladder lesions remain undefined. While a positive FNAC confirms the diagnosis of gallbladder cancer, a negative sample does not shed much light. The overall sampling adequacy is reported to be 86%. Sampling errors in the form of samples from non representative areas along with a confounding factor of coexistence of XGC and GBC limit the widespread applicability of EUS-FNA in XGC [6].

Elevated CA 19-9 correlates with an increased risk of coexistent GB cancer in XGC patients, so CA 19-9 may be considered as a marker for co-existing GB cancer. PET scan is not much helpful as it shows false positive result due to associated cholecystitis.

Owing to the invasiveness and destruction of XGC, surgery should be performed as soon as the diagnosis of XGC is made to prevent the occurrence of complications such as rupture and fistula. It is also reported that if there is no suspicion of cancer, percutaneous GB drainage may be an efficient method for the initial treatment of severe cases, which gives the opportunity for an elective cholecystectomy with an excellent outcome.

When the diagnosis is clear at the time of surgical intervention, simple cholecystectomy is sufficient therapy. In general, the open approaches are often used initially due to suspicion of cancer and/or the anticipation of technical difficulty as contiguous organ involvement may necessitate performing more extensive resection. However, multiple series have attested to the safety of laparoscopic cholecystectomy in XGC, with no increase in the morbidity as compared to an open procedure. There is indeed a higher incidence of conversion to an open procedure, but this low threshold for conversion to open surgery enables a better assessment of the lesion and result in superior outcomes with regard to mortality and morbidity [6].

It has been repeatedly suggested that intra-operative frozen section analysis may be useful when diagnosis is in doubt, in order to avoid an unnecessarily aggressive intervention. This approach is problematic, however, for a couple of reasons. Gallbladder cancer (GBC) may co-exist with XGC in up to 12% of cases and GBC may be missed due to sampling error when the two are present simultaneously. Also, opening a potentially cancerous gallbladder to examine the mucosa risks cutting across tumor and disseminating malignant disease [14]. Complete resection with negative margins (radical cholecystectomy) remains the only curative treatment for patients with GBC, if expertise is available. If expertise is not available, the patient should be referred to a center/ surgeon capable of performing radical/definitive resection.

Although XGC is not believed to be a premalignant lesion, the frequency of co-existing XGC and GBC is 10-20% [9, 15, 16]. Moreover, most of the reported cases with XGC and GBC were

discovered by histological examination of the cholecystectomy specimen. Careful gross observation during surgery and several frozen section examinations are necessary to treat XGC which can extend to surrounding organs.

Conclusion

An increased awareness of XGC combined with an increased accuracy of preoperative and intraoperative diagnosis could help avoid extended resections. Surgeon must also ensure that gallbladder cancer is not missed. XGC, or rather its association, with GBC is responsible for approximately 1 in 10 patients being either over-treated with unnecessary major surgery or under-treated for missed GBC. XGC must be managed with careful consideration of all findings and multidisciplinary input from a team of surgeons, radiologists and pathologists.

Conflict of interest

The author has no financial or any conflict of interest to declare.

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