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Xanthogranulomatous Cholecystitis: A Diagnostic and Therapeutic Dilemma

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ABSTRACT
Introduction: The atypical thickening of the gallbladder (GB) wall can be caused by a malignant condition like gallbladder carcinoma or benign lesions such as chronic cholecystitis or xanthogranulomatous cholecystitis (XGC). XGC can be difficult to differentiate from malignant lesions using imaging tools like ultrasonography (USG), computed tomography scan, or even fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) scan. Histopathology is the gold standard for diagnosis of XGC. In this retrospective study, we report seven cases of histopathology proven XGC.
Methods: This study was conducted at a tertiary care teaching hospital in North India from Jan 2018 to Dec 2019, during which period our hospital treated 184 patients who had cholecystectomies. Based on histopathological results, 7 patients were diagnosed with XGC. We analyzed the clinicopathological parameters, preoperative imaging and intraoperative results, surgical procedures, and postoperative outcomes of these 7 patients in this retrospective study.
Results: The mean patient age was 67.6 years, and female predominance was observed. Abdominal pain and obstructive jaundice were noted in 5 and 3 patients with XGC, respectively. Gallbladder stones were observed in 6 patients. The preoperative diagnoses were acute cholecystitis and chronic cholecystitis, in 1 and 4 patients, respectively, whereas gallbladder cancer was preoperatively suspected in 2 patients.
A significant difference was observed in the conversion rate to open cholecystectomy between XGC and other gallbladder diseases. Our analysis revealed that conversion to open cholecystectomy was associated with significantly higher amount of bleeding, longer operation time, and longer hospital stays compared with laparoscopic cholecystectomy.
Conclusion: Due to the presence of significant inflammation, laparoscopic cholecystectomy for XGC is possible but often difficult. Furthermore, patients with XGC had a higher rate of conversion to open surgery than those with other types of cholecystitis. Based on clinical and diagnostic imaging results, XGC may indicate gallbladder cancer. Intraoperative frozen section analysis is helpful in discriminating between XGC and cancer, as well as avoiding unnecessary surgery.
Keywords: Xanthogranulomatous cholecystitis, Open cholecystectomy, Carcinoma gallbladder

I. INTRODUCTION

Xanthogranulomatous cholecystitis (XGC) is an uncommon inflammatory disease of the gallbladder wall marked by extensive fibrosis, lipid-laden macrophages and acute and chronic inflammatory cells [1, 2]. It was first described by Christensen and Ishak in 1970 as "fibroxanthogranulomatous inflammation" and later in 1976 as XGC by McCoy. It is largely seen in the Japanese or South Asian population with the age of presentation between 44 and 63 years. Its occurrence ranges from 0.7% in the USA to 10% in India, with no obvious gender difference [21]. Although the condition is benign, XGC can involve adjacent organs and its macroscopic appearance can be mistaken for gallbladder cancer [3–5]. XGC might manifest as acute or chronic cholecystitis in the clinic.

It can be difficult to tell the difference between XGC and gallbladder cancer, especially in patients who have significant proliferative fibrosis encompassing the gallbladder and surrounding organs [1, 3, 4]. The current gold standard for the treatment of benign gallbladder disease is laparoscopic cholecystectomy. However, in XGC, laparoscopic cholecystectomy is linked to a significant likelihood of conversion to open cholecystectomy [5–7]. The goal of this study was to assess the clinical and radiological aspects of XGC, as well as the outcomes of surgical treatment, in order to determine the best treatment options for these individuals.

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II. METHODS

This study was conducted in the Department of General Surgery at a tertiary care teaching hospital in North India from Jan 2018 to Dec 2019, during which period our hospital treated 184 patients who had cholecystectomies.

Based on histopathological results, 7 (3.8 percent) patients were diagnosed with XGC. We analyzed the clinicopathological parameters, preoperative imaging and intraoperative results, surgical procedures, and postoperative outcomes of these 7 patients in this retrospective study.

Acute cholecystitis, chronic cholecystitis, and suspicious gallbladder cancer were among the preoperative diagnosis for these 7 individuals with XGC. The data regarding clinical symptoms, the presence or absence of gallbladder stones, preoperative biliary drainage, cholecystectomy technique characteristics, rate of conversion to open surgery, and patient characteristics with probable gallbladder cancer were all recorded.

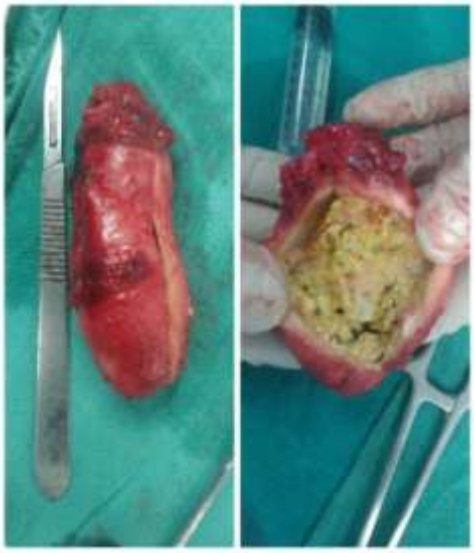

Figure 1: Specimen of Gallbladder with Xanthogranulomatous cholecystits

Ultrasonography and abdominal computed tomography were the most common preoperative diagnostic procedures (CT). When cancer was suspected, magnetic resonance imaging (MRI) was used to investigate. Furthermore, positron emission tomography (PET) using fluorine-18-labeled fluorodeoxyglucose (FDG-PET) was used to distinguish between malignant and benign gallbladder illnesses in two patients. CT scans demonstrated focal thickening of the gallbladder wall and/or ambiguous boundaries between the gallbladder and liver in suspected instances of gallbladder cancer, and ultrasonography revealed irregular thickening of the gallbladder wall.

Surgical operations were carried out depending on the results of the preoperative examination. Patients with preoperative suspicion of gallbladder cancer and other concurrent illnesses had open cholecystectomy.

The presence of widespread or focal mural alterations, as well as xanthoma cells (i.e., foamy histiocytes carrying lipid and bile pigment), multi-nucleated large histiocytes, and acute or chronic inflammatory cells, were used to make the pathological diagnosis of XGC [1]. (Fig. 1).

III. RESULTS

Thirty-nine laparoscopic hernia repairs were performed in 32 inguinal hernia patients during the time period mentioned above. There were 23 females and 9 males with a mean age at surgery of 6.1years (range 2yr – 8yr). At the time of presentation, after clinical history and examination, 15 patients were diagnosed as right-sided inguinal hernia, 12 patients with left-sided and 5 patients with bilateral inguinal hernia. In addition, contralateral patent processus vaginalis (CPPV) was identified intraoperatively in 2 patients and repaired in the same sitting.

Surgery time was calculated as time from umbilical incision to the dressing of skin incisions. Mean surgery time was 36.4 minutes (range 14 – 47 min) for unilateral and 47.8 minutes (range 28 – 55 min) for bilateral PIRS. Operative times demonstrated a decreasing trend as the authors got more proficient with the technique. There was no incidence of conversion.

There was no recurrence identified with a median follow up of 6 months. All parents were satisfied with the operative scar which was minimal except for one patient who developed suture granuloma, which was managed conservatively and improved.Among a total of 184 patients who underwent cholecystectomy during the study period, gallbladder stones were observed in 165 (89.6%) patients while 19 (10.3%) patients had acalculous cholecystitis. After histopathological analysis of the gallbladder specimen, 142 (77.1%) patients were diagnosed as chronic cholecystitis, 4 (2.1%) patients as acute cholecystitis and 7 (3.8%) patients were diagnosed with XGC.

The clinical characteristics of these 7 patients are presented in Table 1. Briefly, the mean patient age was 67.6 (range, 52–81) years, and female predominance was observed (3 males and 4 females). Abdominal pain and obstructive jaundice were noted in 5 (71.4%) and 3 (42.8%) patients with XGC, respectively. Gallbladder stones were observed in 6 (85.7%) patients. The preoperative diagnoses were acute cholecystitis and chronic

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cholecystitis, in 1 (14.2%) and 4 (57.1%) patients, respectively, whereas gallbladder cancer was preoperatively suspected in 2 (28.5%) patients.

	n=7
Age (years)	67.6 (range, 52–81)
Sex	
Male	3 (42.8%)
Female	4 (57.1%)
Presenting symptoms	
Abdominal pain	5 (71.4%)
Jaundice	3 (42.8%)
Fever	3 (42.8%)
Nausea and vomiting	2 (28.5%)
Abdominal distension	1 (14.2%)
Preoperative diagnosis	
Acute cholecystitis	1 (14.2%)
Chronic cholecystitis	4 (57.1%)
Suspicious gallbladder cancer	2 (28.5%)
Gallbladder stone	6 (85.7%)

Table 1: Characteristics of patients with xanthogranulomatous cholecystitis

Biliary drainage was performed preoperatively in 1 (14.2%) patient to improve the symptoms of acute cholangitis and obstructive jaundice. Endoscopic retrograde biliary drainage (ERBD) was performed in 1 (14.2%) patient with acute cholangitis.

	n=7
Operative procedures	
Laparoscopic cholecystectomy	1 (14.2%)
Conversion to open cholecystectomy	4 (57.1%)
Open cholecystectomy	2 (28.5%)
CBD exploration	1 (14.2%)
Postoperative complications	
Intra-abdominal abscess	1 (14.2%)
Wound infection	1 (14.2%)

Table 2: Operative procedures and postoperative complications

Operative procedures and postoperative complications are summarized in Table 2. Initial laparoscopic cholecystectomy was performed in 5 (71.4%) of the 7 patients. In these patients, laparoscopic cholecystectomy was performed in 1 (20%) patients, whereas conversion to open cholecystectomy was necessary in 4 (80%) patients.

Conversely, two (28.5%) patients underwent open surgery. In these patients, open approach was performed with preoperative suspicion of gallbladder cancer.

Postoperative complications greater than grade II according to the Clavien-Dindo classification were observed in two (28.5%) patients, including one (14.2%) with intraabdominal abscesses and one (14.2%) with a wound infection. Both patients were treated with antibiotics and experienced an uneventful recovery.

Gallbladder disease	Laparoscopic cholecystectomy	Conversion to open cholecystectomy
XGC (n=7)	1 (20%)	4 (80%)
Other diseases (n=147)	139 (94.6%)	8 (5.4%)

Table 3: Rate of conversion to open cholecystectomy in XGC and other forms of gallbladder diseases

Laparoscopic cholecystectomy, performed in 5 (71.4%) patients, was converted to open cholecystectomy in 4 (80%) of these 5 patients. Among patients with other gallbladder diseases, laparoscopic cholecystectomy was performed in 147 patients and was converted to open surgery in 8 (5.4%) of these patients (Table 3). A significant difference was observed in the conversion rate to open cholecystectomy between XGC and other gallbladder diseases. Our analysis revealed that conversion to open cholecystectomy was associated with significantly higher amount of bleeding, longer operation time, and longer hospital stays compared with laparoscopic cholecystectomy. Furthermore, the operation time was significantly longer with conversion to open cholecystectomy than with open cholecystectomy. Gallbladder cancer was suspected in two patients on preoperative ultrasonography and CT scan. Ultrasonography showed irregular wall thickening of gallbladder in two patients. CT scan revealed focal and diffuse wall thickening of gallbladder in one patient each, whereas bowel invasion was suspected in one patient with unclear borders between the gallbladder and adjacent colon. In one patient, CT scan revealed dilatation of the intrahepatic bile duct. MRI, which was performed in two of the seven patients, showed focal and diffuse wall thickening of the gallbladder in one patient each. FDG-PET was performed in two of the seven patients with suspected gallbladder cancer, revealed

abnormal accumulation in both patients. Standardized uptake value max (SUV max) ranged from 3.4 to 6.1. Increases in the levels of the tumor markers carbohydrate antigen 19–9 (CA19-9, > 37 U/mL) and carcinoembryonic antigen (CEA, > 5.0 ng/mL) were observed in both patients. Two of these seven patients with suspicious gallbladder cancer underwent only open cholecystectomy. Furthermore, one patient with suspicious gallbladder cancer underwent partial cholecystectomy and CBD exploration with T-tube placement. In this patient, the postoperative course was uneventful, and the patient was discharged without any complications. Both the patients with suspected gallbladder cancer received the definitive diagnosis of XGC based on the analysis of histopathology sections. There were no mortalities in this study.

IV. DISCUSSION

XGC is an uncommon, chronic gallbladder (GB) disease distinguished by the proliferation of xanthoma within the GB wall. Macroscopically, it looks like a yellowish mass in the gall bladder wall. It is a sporadic chronic granulomatous inflammation of the gall bladder, first described by Christensen and Ishak in 1970 as "Fibroxanthogranulomatous inflammation." The term XGC was created by McCoy et al. in 1976 [22]. XGC has been reported as having incidence of 1.3–5.2 percent of all gallbladder specimens removed [8, 9]. Our study found a 3.8 percent XGC incidence, which is comparable with earlier reports. Gallbladder stones and biliary obstruction may contribute to the development of XGC by allowing bile to extravasate into the gallbladder wall through ruptured Rokitansky-Aschoff sinuses and/or mucosal surface ulcers [4, 5, 10 and 11]. XGC has a substantial connection with cholelithiasis [5, 8]. Gallbladder stones were found in large numbers in this investigation, with 6 (85.7 percent).

XGC is frequently biologically aggressive, spreading through the gallbladder wall into neighboring structures and causing substantial morbidity. As a result, XGC is regarded as a separate clinical entity or invasive version of chronic cholecystitis [6, 12]. XGC has no distinct clinical signs, however it frequently involves acute or chronic cholecystitis. Right upper quadrant discomfort, epigastric pain, fever, jaundice, nausea, and vomiting are the most prevalent complaints [5, 8]. These nonspecific symptoms are quite similar to those of gallbladder cancer and are frequently ineffective in distinguishing between the two illnesses [4].

The thickening of the gallbladder wall and the potential to engage surrounding organs are imaging characteristics of XGC that are similar to those of gallbladder cancer [6, 8, 9]. Ultrasonography indicates focal or widespread thickening of the gallbladder wall, as well as gallbladder stones and intramural hypoechoic nodules [5, 8]. These abnormalities have also been noted on CT tests. CT has also been suggested as a tool for distinguishing XGC from gallbladder cancer. Diffuse wall thickening, continuity of the mucosal line, intramural hypo-attenuated nodules, and absence of invasion to neighboring liver parenchyma are among the CT criteria for the diagnosis of XGC [5, 13]. Intramural T2 high signal intensity is a significant feature of XGC in MRI for diagnosis and differentiation from gallbladder cancer [9, 14].

This MRI finding was also seen in two of seven patients in the current investigation, suggesting that it could be useful in identifying XGC. FDG-PET may be able to provide useful information for determining the aggressiveness of gallbladder tumors [15, 16]. FDG, on the other hand, accumulates in both malignant tumor cells and activated inflammatory cells. The diagnostic performance of FDG-PET is influenced by the level of C-reactive protein (CRP) [16]. Inflammatory cells are relatively few in most individuals with chronic cholecystitis, and they do not show enhanced FDG uptake [16]. Both patients assessed by FDG-PET in this study were found to be false positive. As a result, FDG-PET may be ineffective in distinguishing XGC from gallbladder cancer.

In patients with gallbladder cancer, tumor markers such as CA19-9 and CEA tend to rise [4, 8]. However, in the current investigation, elevated CA19-9 and CEA values were found in both patients with suspected gallbladder cancer who were ultimately identified with XGC. CA19-9 and CEA tumor markers may not be useful in the differential diagnosis of XGC and gallbladder cancer as they can be high in both the conditions but useful in postoperative follow-up as CA 19-9 normalizes early after surgery for XGC, whereas it remains high for a longer duration in GB cancer. Increased CA19-9 level was observed in 32 (76%) patients, and increased CEA level was found only in 6 (14%) patients in a study by Deng et al [4].

In addition to sonography and CT, fine-needle aspiration cytology has been used in several cases with good results [23]. Preoperative FNAC in XGC is a distinct entity characterized by a spectrum of cytomorphologic features that can help in differentiating XGC from malignancy. It is less preferred as disadvantages of this procedure include seeding of the track with tumor and fistula formation.

The only definite treatment for XGC is surgery, and a simple cholecystectomy is generally enough. XGC can erode the gallbladder's border, cause thick fibrotic adhesions between surrounding organs, and lead to the creation of fistulas with nearby tissues, all of which mirror gallbladder cancer [9]. As a result, during surgery, the risk of gallbladder cancer should be ruled out. In this regard, intraoperative frozen section analysis is helpful in distinguishing between XGC and gallbladder cancer and in preventing unnecessary surgery.

All surgeries for patients with preoperative suspicion of gallbladder cancer in this study was done following oncological principles. For safe surgery, an initial laparoscopic cholecystectomy for XGC is conceivable, but proper evaluation by ultrasound, CT, and MRI is required. Due to acute inflammation, clouded anatomy, and thick adhesion, laparoscopic surgery is frequently challenging. Furthermore, conversion to open surgery is more common in patients with XGC than in patients with other types of cholecystitis, with conversion rates ranging from 10% to 80% [5, 7, 17–20]. The conversion rate in our study was 80 percent, which was almost 15 times greater than the conversion rate in patients with other gallbladder illnesses (5.4 percent). As a result, in patients with suspected malignancy and those who are predicted to have extensive fibrous adhesions and significant local inflammation, an open surgical approach is indicated [9, 10, 17]. Two (28.5%) of the patients in this study had a postoperative complication that was higher than grade II according to the Clavien-Dindo classification. All of the patients had a smooth recovery.

The current study has a number of flaws. First, the sample size was tiny, and all of the patients were enrolled at the same facility. Second, cholecystectomies was conducted by different surgeons, and any differences in the competence of the operators could not be ignored. Finally, because ultrasonography, CT, and MRI findings did not always coincide, a diagnosis of suspected gallbladder cancer was not always sufficient.

V. CONCLUSION

In conclusion, XGC is a rare inflammatory gallbladder disease with difficult diagnosis and management. Due to the presence of significant inflammation, laparoscopic cholecystectomy for XGC is possible but often difficult. Furthermore, patients with XGC had a higher rate of conversion to open surgery than those with other types of cholecystitis. Based on clinical and diagnostic imaging results, XGC may indicate gallbladder cancer. Intraoperative frozen section analysis is helpful in discriminating between XGC and cancer, as well as avoiding unnecessary surgery.

VI. DISCLOSURES

Authors have no conflicts of interest or financial ties to disclose.

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