Strategies for Differentiating Gallbladder Carcinoma from Xanthogranulomatous Cholecystitis—a Tertiary Care Centre Experience

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Abstract Xanthogranulomatous cholecystitis (XGC) is an uncommon variant of chronic cholecystitis, characterized by focal or diffuse destructive inflammatory process. The importance of XGC is that it mimics gallbladder carcinoma (GBC) both preoperatively and intra-operatively, since it can present with pericholecystic infiltration, hepatic involvement and lymphadenopathy. As a result of this misdiagnosis which is not infrequent, the patient may need to undergo an unnecessary radical cholecystectomy rather than only a cholecystectomy which is associated with greater morbidity and mortality. Patients who underwent gallbladder and gallbladder-related operations during period of 5 years between 2010 and 2014 were reviewed ($n = 462$). A comparison of clinical, biochemical, radiological and operative features were made between patients with carcinoma gallbladder ($n = 101$) and xanthogranulomatous cholecystitis ($n = 22$). Patient with a long history of recurrent abdominal pain with leucocytosis and who on imaging are found to have a diffusely thickened gallbladder wall ($p < 0.01$), with cholelithiasis, choledocholithiasis and sub-mucosal hypoattenuated nodules ($p < 0.05$) are likely to have XGC while those with anorexia, weight loss, focal thickening of the gallbladder wall on imaging ($p < 0.01$) and dense local organ infiltration are more likely to have GBC. The presence of lymph nodes on imaging and the loss of fat plane interface between the liver and gallbladder are not differentiating factors. Differentiating XGC from GBC in pre-operative setting is necessary to avoid radical procedures

being done for a benign process. Certain clinical, radiological and intra-operative features aid in differentiating these benign and malignant process. However, the definitive diagnosis still remains a histopathological examination to avoid radical resection in patients who have a benign condition.

Keywords Xanthogranulomatous cholecystitis · Carcinoma gallbladder · Radical cholecystectomy · Sub-mucosal nodules

Introduction

Xanthogranulomatous cholecystitis (XGC) is an uncommon variant of chronic cholecystitis, characterized by a focal or diffuse destructive inflammatory process. The importance of XGC is that it mimics gallbladder carcinoma (GBC) both preoperatively and intra-operatively, since it can present with pericholecystic infiltration, hepatic involvement and lymphadenopathy [1, 2].

As a result of a misdiagnosis which is not infrequent, the patient may undergo an unnecessary radical cholecystectomy rather than only a gallbladder excision which is associated with a greater morbidity and mortality [3]. We postulated that a preoperative diagnosis of XGC might benefit patients by avoiding radical procedures and attempted to identify the features of XGC which differentiated it from GBC before and during operation.

Patients and Methods

We conducted a retrospective cohort study in the Department of Surgical Gastroenterology and Liver Transplantation, Sir Ganga Ram Hospital in New Delhi over a period of 5 years from 2010 to 2014. All the patients who underwent gallbladder

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and gallbladder-related operations (benign and malignant) during this time period were reviewed ($n = 462$). Out of these patients, a histopathological report of XGC was received in 22. These patients were placed in group A, and 101 patients who were reported to have GB malignancy were included in group B (2 patients who had concomitant XGC and GBC were excluded).

We recorded the following data—clinical features, biochemical, radiological results including the presence of gallstones/common bile duct (CBD) stones, focal or diffuse wall thickening of the GB, the presence of intra-mural bands or nodules in the wall, lymph node enlargement, mucosal enhancement and the status of the interface between the liver bed and gallbladder, and a comparison was made between the groups.

Statistical Analysis

The means and Student's *t* test were used to compare continuous variables, and the chi-square and Fisher's exact tests were used to compare nominal variables. The statistical comparisons were performed using SPSS 20.0.

A *p* value was considered significant if it was less than 0.05.

Results

Out of the 462 patients, 22 were included in group A (histologically proven XGC) and 101 in group B (histologically proven GBC). The mean age of the patients with XGC was 53.7 years (range 20–68) with a M:F ratio of 2.2:1 while for GBC the mean age was 56 years (range 30–82) with a M:F ratio of 1:1.3.

The clinical features of the XGC and GBC patients were compared, and these are summarized in Table 1. A significantly greater number of patients in group A (XGC) presented with fever and abdominal pain, while group B (GBC) patients presented more frequently with anorexia and weight loss. The

average duration of abdominal pain was 11.4 months with a history of recurrent episodes in group A while in group B it was a constant pain with an average duration of 4.7 months. However, the presence of jaundice, vomiting and a palpable right upper quadrant mass was not distinguishing factors.

Imaging (USG/CT) showed gallstones more frequently in group A (72%) than in group B (29%). In group A, multiple stones were present in 10 patients (63%) and a single stone (>1.5 cm) was seen in 6 (40%). The presence of a CBD stone was more common in group A than in group B (80% in A and 42% in B). Group A patients also were more likely to present with cholecystitis ($p < 0.01$).

In contrast CT of the abdomen, XGC patients mostly showed diffuse wall thickening of gallbladder (73 vs. 16%) whereas GBC patients mostly had focal wall thickening (76 vs. 27%). The mucosal enhancement was continuous (55%) in XGC patients when compared with group B patients (25%).

A retrospective analysis of the CT images showed sub-mucosal hypoattenuated nodules or bands in 55% of patients with XGC while only 9% of patients with GBC exhibited such nodules ($p < 0.01$). Three patients in group A (13%) showed evidence of CBD compression by the gallstones (Mirizzi type 1). In our study, the sensitivity of CT scans in diagnosing xanthogranulomatous cholecystitis was 45% (10/22). Out of the 101 patients in group B, 5 patients (5%) were misdiagnosed as having XGC on preoperative imaging and turned out to have carcinoma GB on the frozen section examination and hence underwent a radical cholecystectomy.

On imaging, enlarged lymph nodes and a loss of interface between the GB and liver bed were seen in both groups. The comparison of radiological findings between XGC and GBC are summarized in Table 2.

Nineteen out of twenty-two patients in group A underwent a simple cholecystectomy (14—open, 3—initial laparoscopic converted to open, 2—laparoscopic) while the other 3 underwent a radical cholecystectomy. Three of the patients also had a cholecysto-duodenal fistula which was repaired primarily. Though external compression of the duodenal wall was found in group B patients, fistula formation was not seen.

Table 1 Comparison of clinical features between XGC and GBC

Variables	Group A XGC ($n = 22$)	Group B GBC ($n = 101$)	<i>p</i> value
Age (years)	50.7 $\pm$ 11.2	56 $\pm$ 13.4	NS
Male/female	2.2:1	1:1.3	NS
Fever	10 (45%)	8 (8%)	<0.01
Abdominal pain	19 (87%)	41 (40%)	<0.01
Vomiting	10 (45%)	31 (30%)	NS
Jaundice	5 (22%)	41 (40%)	NS
Anorexia	7 (31%)	58 (57%)	<0.05
Weight loss	4 (19%)	59 (58%)	<0.01
Palpable mass	3 (17%)	26 (25%)	NS

Table 2 Comparison of radiological findings between XGC and GBC

Imaging findings	Group A XGC (<i>n</i> = 22)	Group B GBC (<i>n</i> = 101)	<i>p</i> value
Cholecystitis on imaging	19 (86%)	11 (11%)	<0.01
Gallstones/CBD stones	16 (72%)	23 (23%)	<0.05
Gallbladder wall thickening(>3 mm)	10 (45%)	67 (66%)	NS
Continuous mucosal line enhancement	12 (55%)	12 (12%)	<0.05
Diffuse wall thickening	16 (73%)	17 (16%)	<0.01
Sub-mucosal nodules/bands	12 (55%)	9 (9%)	<0.05
Loss of interface between GB and liver	14 (67%)	60 (59%)	NS
Presence of GB mass	5 (23%)	75 (74%)	<0.01
Large lymph nodes	13 (59%)	78 (77%)	NS

Lymph nodal enlargement was found almost equally in both groups [59% in group A, 77% in group B]. There was a higher rate of dense local infiltration into the surrounding organs such as the duodenum and colon in group B (60%) than in group A (31%) [$p < 0.05$]. The average postoperative stay was 7.18 days in group A, while in group B it was 11.4 days. Postoperative complications occurred in 8/22 patients (33%) in group A—2 patients had biliary leaks (one was managed conservatively and the other underwent re-exploration and CBD repair), 2 patients underwent aspiration for intra-abdominal collections and 4 had wound infections. In group B, 4 patients had biliary leaks (2 underwent re-

exploration), 6 had postoperative collections needing aspiration and upper gastrointestinal bleeding occurred in 1 patient who was managed conservatively. In group B, there were 5 deaths, from myocardial dysfunction and respiratory infection while there were none in group A.

Discussion

XGC is characterized by a diffuse, destructive inflammatory process with the gallbladder wall being infiltrated by foam cells and macrophages causing a proliferative

Fig. 1 Radiology in xanthogranulomatous cholecystitis

Fig. 2 Xanthogranulomatous cholecystitis-various presentations mimics carcinoma gallbladder intra-operatively

fibrosis (Fig. 3d). Since it closely resembles gallbladder carcinoma with pericholecystic infiltration, hepatic involvement and lymphadenopathy (Fig. 3c), it was termed a “pseudo tumour” by Christensen and Ishak in 1970 and later called a xanthogranulomatous gallbladder by McCoy in 1976 [4, 5]. Unnecessary radical resections are done for XGC because of its similar features with GBC, and this

may be accompanied by higher morbidity and mortality rates [3]. Hence a preoperative diagnosis is important to avoid more extensive operations in patients with a benign disease.

We found that simple clinical parameters like the presence of fever and recurrent abdominal pain with a longer average duration (11.4 months in XGC vs. 4.7 months in GBC), and

Fig. 3 Ultrasound images in xanthogranulomatous cholecystitis

the presence of leucocytosis favoured a diagnosis of XGC, while a history of anorexia and weight loss favoured GBC. However, jaundice, vomiting and the presence of a palpable right upper quadrant mass were not distinguishing features. Zhang et al. [6] found similar results in their study.

The association of XGC with GBC is still a matter of debate [7–9]. Analogous to the results of Ros et al. [7], our study also supported the existence of this association (two patients had co-existent foci of GBC along with XGC).

On Imaging (USG—Fig. 3a, b) (CT—Fig. 1a–f), the presence of cholelithiasis, choledocholithiasis, cholecystitis, diffuse wall thickening (Fig. 1a–c) with continuous mucosal enhancement of gallbladder (Fig. 1d) and the presence of sub-mucosal hypoattenuated nodules [10] favoured XGC (Fig. 1e, f) whereas focal gallbladder wall thickening and the presence of GB mass favoured GBC.

Many researchers [11, 12] have reported that the most characteristic findings of XGC were the presence of sub-mucosal hypoechoic nodules (Fig. 1e, f) or bands in the gallbladder wall. In our study, nodules were observed in 12 patients (55%) fewer than the 8/11 (73%) patients reported by Kim et al. [12].

Chun et al. [10] reported that nodules occupying greater than 60% of a thickened gallbladder favoured XGC. Along with this finding, we also found a greater association of XGC with choledocholithiasis (40%) and with a sensitivity of 82%. The association of XGC with CBD stones ranges from 12 to 30% in various studies.

The presence of lymph nodes and the loss of interface between the GB and liver bed intra-operatively (Fig. 2a, b) were seen in both XGC and GBC, and these features on imaging may not be helpful in differentiating between the two diseases (Fig. 3). The various intra-operative presentations in our experience were shown in Fig. 2a–d.

The MRI findings which favours XGC are non-focal wall thickening, type I enhancement, THAD (transient hepatic attenuation difference) and the presence of intramural nodules. T2-weighted images showing areas of iso to slightly high signal intensity correspond to the presence of xanthogranulomas [13]. Hatakenaka et al. [14] have demonstrated the importance of chemical shift gradient—echo MRI imaging in differentiating XGC from GBC patients with a thickened gallbladder wall.

Kang et al. [15] found that diffusion weighted magnetic resonance imaging (DWI) had a higher sensitivity (79–86%) and specificity (94.7%) in differentiating XGC from GBC. XGC had a higher diffusion coefficient than in GBC, and diffusion restriction was more apparent in wall thickening type of GBC. Though 18-FDG PET is not specific for malignant lesions and the radio-isotope can also accumulate in inflammatory lesions with increased glucose metabolism, studies [16–18] have shown that in differentiating GBC from XGC, it had a sensitivity rate of

75.5–78% and specificity of 82–100%. In cases with suspicion of CBD involvement, procedures like ERCP and PTC have been found to be useful.

A preoperative USG guided FNAC biopsy shows promising results in differentiating XGC from GBC [11, 19] with an overall diagnostic accuracy around 96% [20]. Though a positive FNAC confirms the diagnosis of GBC, a negative sample does not rule it out owing to sampling from non-representative areas. The procedure may also lead to seeding of the track with tumour and fistula formation [21]. Though clinical, radiological [10] and preoperative FNAC or biopsy are helpful in diagnosing GBC and XGC, they are not entirely reliable. Intra-operative frozen section examination is probably the best modality for differentiating XGC and GBC [6, 22–25] which can avoid radical surgery for a benign disease. Immunohistochemistry done along with frozen section is highly sensitive in differentiating between the two conditions [26].

In our study, intra-operative findings like dense local infiltration to the surrounding organs favoured GBC. Even though 28% of XGC patients had local infiltration at the time of surgery, simple cholecystectomy was usually possible by careful dissection. Lymph nodal enlargement was found almost equally in both groups during operation.

In XGC patients, because of dense adhesions due to chronic inflammation, the dissection of Calot's triangle is often difficult if one is doing a laparoscopic procedure [27–29] and the incidence of surgical complications is also higher (postoperative morbidity was 33% in our study). Hence in difficult cases and those which mimic malignancy intra-operatively, open surgery [29] probably provides a better assessment of the gallbladder pathology and helps in performing a careful dissection.

Conclusion

The differentiation of XGC and GBC preoperatively remains a challenge. Patients with a long history of recurrent abdominal pain and who on imaging are found to have a diffusely thickened gallbladder wall, with cholelithiasis, choledocholithiasis and sub-mucosal hypoattenuated nodules are likely to have XGC while those with anorexia, weight loss, focal thickening of the gallbladder wall on imaging and dense local organ infiltration are more likely to have GBC. The presence of lymph nodes on imaging and the loss of a fat plane interface between the liver and gallbladder are not differentiating factors. However, the definitive diagnosis still remains a histopathological examination to avoid radical resection in patients who have a benign condition.

Compliance with Ethical Standards

Funding No funding information available during this study.

Conflict of Interest The authors disclose no conflicts of interest.

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