An Extremely High Preoperative CA19-9 Cannot Exclude the Diagnosis of Xanthogranulomatous Cholecystitis: A Case Report and Literature Review

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Abstract

Xanthogranulomatous Cholecystitis is a rare idiopathic benign chronic inflammatory condition with a locally aggressive spread. Its clinical and radiological manifestation is variable and unpredictable. It shares great similarities and association with gallbladder cancer; yet, does not require by itself aggressive surgical treatment. However, the considerable challenge to reach a pre-operative diagnosis of this condition makes a paramount need for aggressive surgical approach. Adding to the challenge, extremely elevated CA19-9 is not a distinguishing factor anymore.

Keywords: Xanthogranulomatous; Cholecystitis; CA19-9.

Introduction

Xanthogranulomatous Cholecystitis is rare benign inflammatory condition with a variable clinical presentation. Its etiology remained to be unknown, but the pathological features and its variations is well known. Moreover, pre-operative diagnosis of this condition remains extremely challenging given its locally aggressive behavior. Adding to that, tumor marker such as Carbohydrate antigen 19-9 (CA 19-9) might be somewhat raised in such condition. Yet, extremely- high levels are usually attributed to biliopancreatic malignancy. However, there are three cases reported extremely high pre-operative CA19-9 that have normalized after cholecystectomy.[1] Moreover, there are reported cases of concomitant malignancy in patient with Xanthogranulomatous Cholecystitis.[2] Hence, we present a puzzling clinical manifestation of Xanthogranulomatous Cholecystitis case with extremely high-levels of CA19-9 without the presence of malignancy component which contribute to the ongoing dilemma of best management approach.

Case Report

A sixty-two years old gentleman complained of episodes of colicky right upper quadrant pain with associated nausea, vomiting and loss of appetite for the last two months. Recently, he developed a very painful episode with associated jaundice without itchiness. He was evaluated in the regional hospital and was found to have obstructive jaundice biochemically and radiologically. He was referred to our institute for further work-up and management. On examination, he had normal vital signs. His abdominal examination revealed a fullness in the right upper quadrant with associated tenderness.

His laboratory investigation showed a hemoglobin of 11.1 g/dL (NR: 11.5-15.5 g/dL), platelet count was 375 10^9/L (NR: 150-400 10^9/L) and the white cell count was 5.6 10^9/L (NR: 4.5-11 10^9/L). His electrolytes and renal function were within normal limits. His liver enzymes were as follow; alanine aminotransferase 171 iU/L (NR: 7-55 iU/L), aspartate aminotransferase 131 iU/L (NR: 8-33 iU/L), alkaline phosphatase 545 iU/L (NR: 44-147

iU/L). He had a normal albumin of 39g/L (NR: 34-54 g/L) and a raised total bilirubin of 179 µmol/L (NR: 1.71-20.5 µmol/L). His coagulation was as follow; prothrombin time 12.7s (NR: 10-13s), activated partial thromboplastin time 39.7s (NR: 30-40s), international normalized ratio of 1.16. His hepatitis screen was negative. His tumor markers profile was as follow; alpha fetoprotein 4.2 µg/L (NR: 0.5-15 µg/L), carcinoembryonic antigen 0 U/mL (NR:0-2.5 U/mL), CA19-9 2364 U/mL (NR: 0-37 U/mL).

Computed Topographic CT scan demonstrate irregular diffuse mural wall thickening of the gallbladder along with few hypoattenuating mural nodules. In addition to multiple hyperdense calculi and pericholecystic fluid collection with poor fat planes to the adjacent liver parenchyma [Figure 1]. Abdominal Magnetic resonance imaging (MRI) has demonstrated a diffusely thickened gallbladder wall which shows iso- to slightly hyperintense signal along with a few mural nodules within the thickened wall denoting fat deposition of xanthogranuloma. In addition to a focal area of early enhancement of adjacent liver parenchyma is seen [Figure 2].

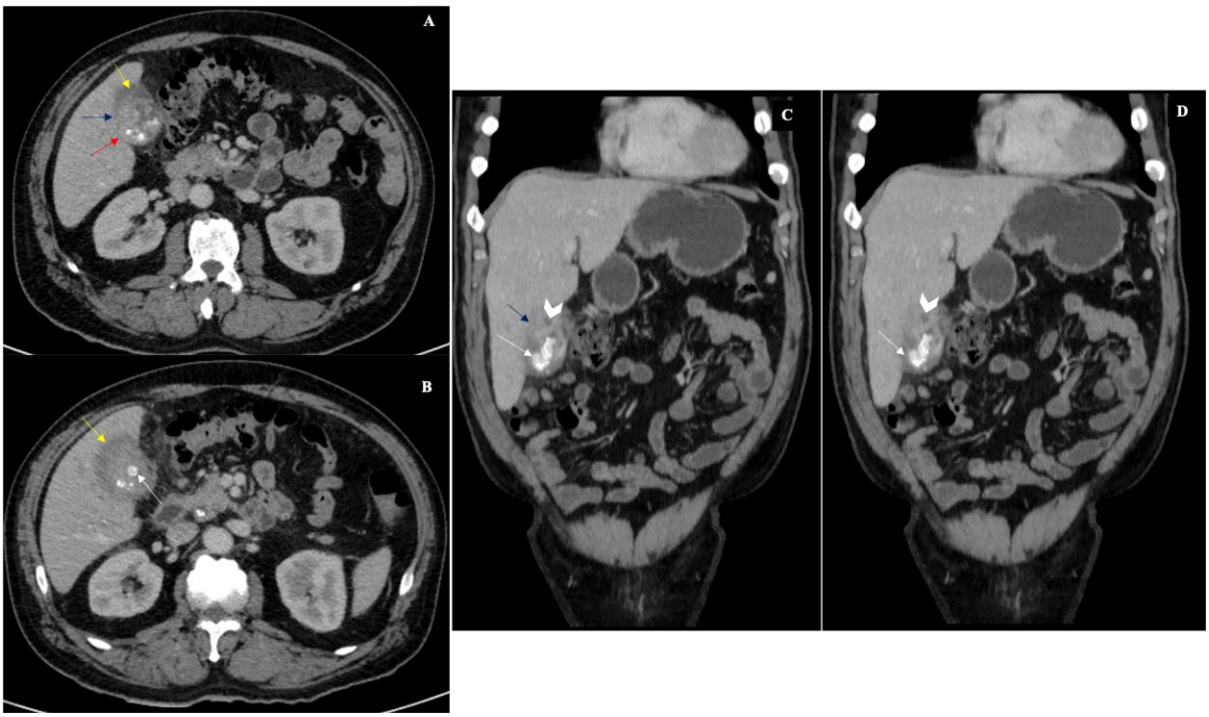

Figure 1: Contrast enhanced Computerized tomography (CT) scans of the abdomen in axial and coronal views from (A–D) demonstrate irregular diffuse mural wall thickening of the gallbladder (red arrows) along with few hypoattenuating mural nodules (white head arrows). Multiple hyperdense calculi (white arrows) and pericholecystic fluid collection(yellow arrows). Poor fat planes to the adjacent liver parenchyma are noted (blue arrows).

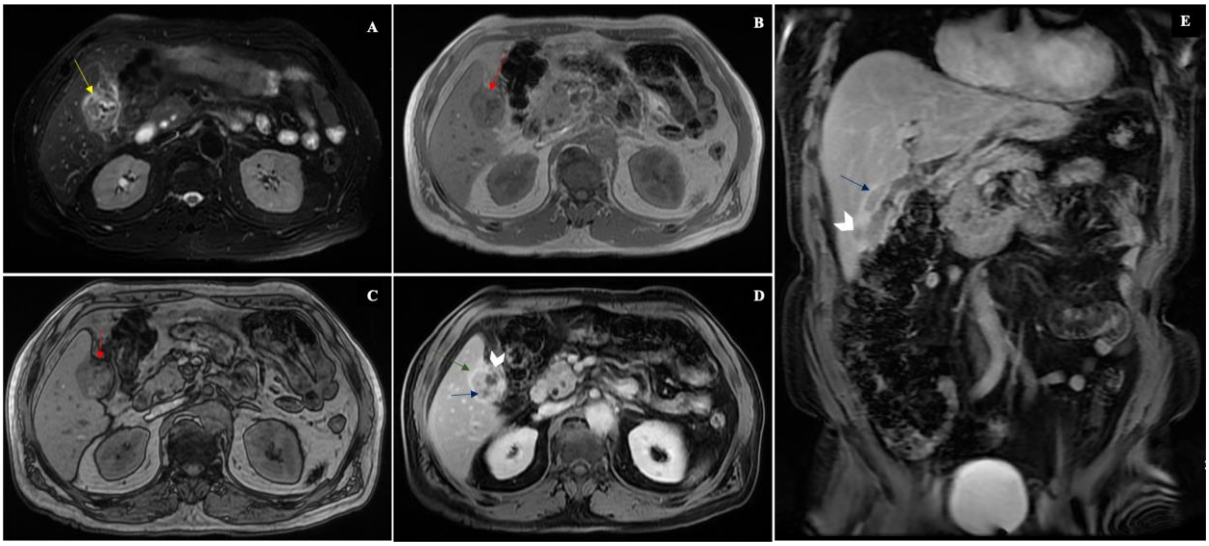

Figure 2: Magnetic Resonance images (MRI) of the abdomen from (A–E) including axial fat-suppressed T2WI (A), In-phase (IP) (B), Opposed-phase (OP) chemical shift images (C), T1WI post contrast in axial (D) and coronal (E) demonstrate a diffusely thickened gallbladder wall which shows iso- to slightly hyperintense signal in T2WI (yellow arrows) along with a few mural nodules within the thickened wall (white head arrows) some of which demonstrate signal drop out in opposed-phase images (OP) denoting fat deposition of xanthogranuloma (red arrows). Minimal pericholecystic fluid. Smooth luminal surface enhancement is noted in post contrast images (blue arrows). Focal area of early enhancement of adjacent liver parenchyma is seen (green arrows).

He was referred urgently to the gastroenterology for Endoscopic retrograde cholangiopancreatography (ERCP) to decompresses his biliary system. Two weeks later under conscious sedation a successful ERCP was done. A sphincterotomy, retrieval of CBD stone and placement of plastic stent. A week later he was admitted for radical surgical resection. During admission his total bilirubin showed significant reduction to 30 µmol/L. All his liver enzymes normalized, apart for his alkaline phosphatase which has showed significant reduction to 184 iU/L. His coagulation has normalized as well.

He underwent radical cholecystectomy with wedge resection of segment 4b and5 with porta hepatis lymph adenectomy via a right subcostal incision. During surgery a segment of the greater omentum and anterior wall of hepatic flexure colon was resected as en bloc with the specimen. The cystic margin was and hepatic margins frozen section were negative for malignancy. He lost around 100cc of blood. His post-operative was un remarkable, apart from a superficial wound infection.

His histopathology showed gallbladder wall exhibiting mucosal ulceration and dense infiltration by mixed inflammatory cell infiltrate comprising mainly foamy histiocytes containing bile pigment admixed with multinucleated giant cells, lymphocytes and plasma cells. Area of marked fibrosis are seen with adherent liver tissues. There is no evidence of dysplasia of malignancy [Figure 3].

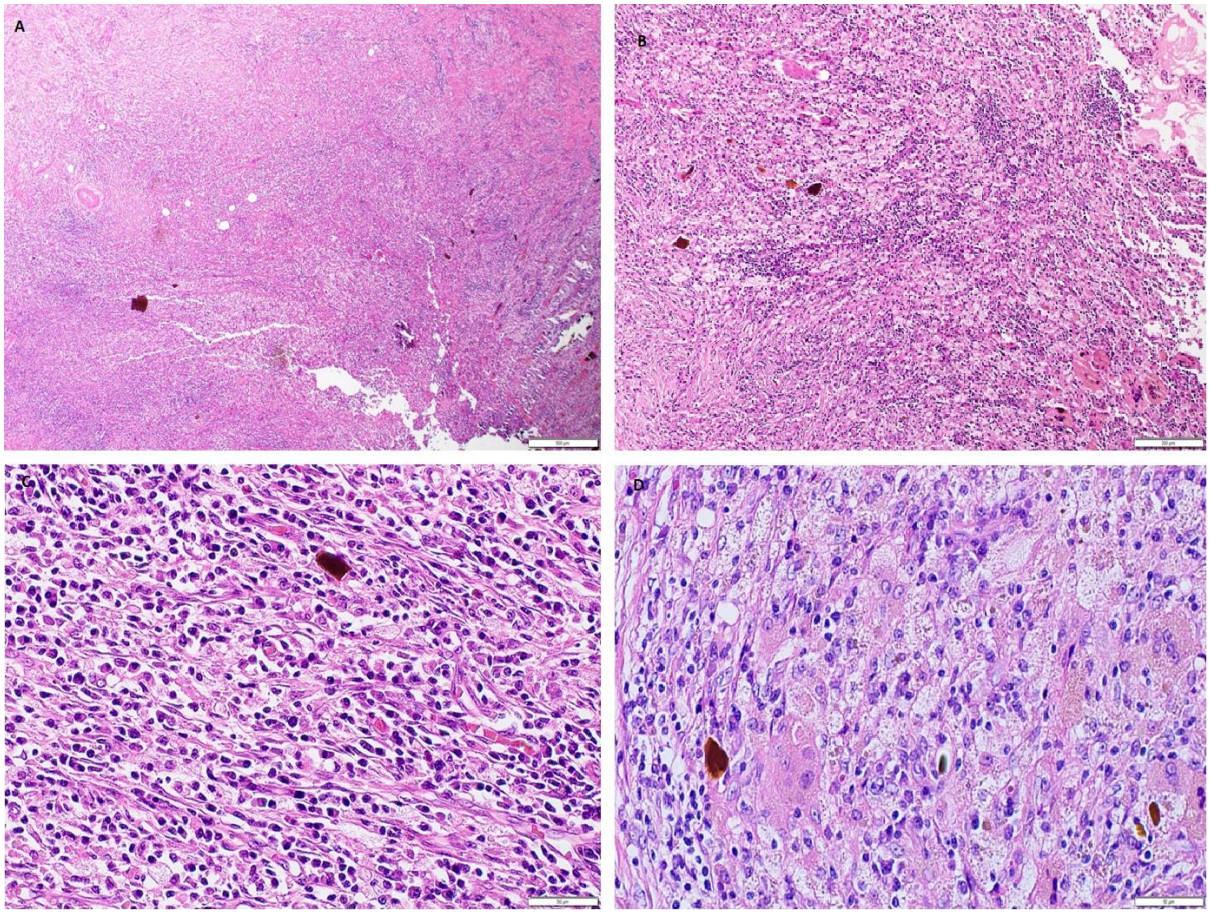

Figure 3: Histopathological Slides of the gallbladder from (A-D), Low power (4 ×) histologic appearance of gallbladder wall showing mucosal ulceration and dense inflammation (A), Medium power (10 ×) histologic appearance showing the dense inflammation with abundant histiocytes, multinucleated giant cells admixed with lymphoplasmacytic cell infiltrate (B), 40 × showing abundant plasma cells (C), High power (40 ×) demonstrating the details of the inflammatory cells (D).

On follow up outpatient visit he was doing well and asymptomatic. His Ca 19-9 has normalized to 13 U/mL. He was discharged from clinic with no further follow-ups.

Discussion

Xanthogranulomatous Cholecystitis is a rare benign idiopathic gallbladder pathology that may simulate malignancy both radiologically and pathologically. It is characterized by marked increase in gallbladder wall thickness with lymphocytes and plasma cells in a focal or diffuse inflammatory process which can extended into the adjacent structures like the liver in our case. The gross examination may reveal yellow masses within thickened gallbladder wall. Nevertheless, the definitive diagnosis can only be obtained by pathological examination.[2]

Xanthogranulomatous reaction secondary to inflammation is different from the xanthomatous lesions due to hypercholesterolemia. Cozzutto C. and colleagues review of xanthogranulomatous process, have postulated a hypothesis for the formation of foamy macrophages. They found that they are formed in medias where hemorrhage, suppuration and necrosis occur profoundly and for long period such as chronic or remittent severe inflammation. Basically, the macrophages lysosomes phagocytic activity cannot cope-up with the digestion of huge amount of destructed blood cells by-products such as phospholipids.[3]

Although the imaging diagnosis of xanthogranulomatous cholecystitis (XGC) is challenging, some characteristic imaging findings could suggest the diagnosis pre-operatively.[4] The main differential diagnoses of XGC are carcinoma of the gallbladder (GB), actinomycosis and adenomyomatosis of the GB.[5,6]

In ultrasound, the main finding of XGC is marked mural thickening of the GB with associated gallstones or sludge. Parra et al[5] noted that the wall thickening was hyperechoic compared to the liver parenchyma in all cases. Hypoechoic nodules or bands in the thickened wall can be seen in approximately 19% of XGC cases[5,7] and considered to be a characteristic finding. Ultrasound also can demonstrate some associated complications like perforation, abscess formation and adjacent hepatic parenchymal infiltration.[5,8]

Computed Tomography (CT) findings include diffuse or focal wall thickening, intramural hypodense nodules in thickened walls, luminal surface enhancement (LSE) with continuous or focal disruption of mucosal lines. GB calculi and pericholecystic fluid collection are commonly associated with XGC.[9] Infiltration to adjacent liver parenchyma or bowel can also be seen.[9] CT may also demonstrate other complications like perforation, abscess or fistula formation.[4,7]

Ito et al[4] concluded that using CT scoring system which assessed the presence of five components including diffuse wall thickening, absence of polypoid lesions, intramural nodules or bands, pericholecystic infiltration and pericholecystic abscess collection likely increase the sensitivity and specificity of CT diagnosis of xanthogranulomatous cholecystitis. Presence of three or more findings had sensitivity of 77% and specificity of 94% (with 95% Confidence Interval (CI)). Zhao et al[9] studied the CT findings in 49 proven cases of XGC and found that diffuse wall thickening seen in 87.8% and intramural hypodense nodules in the thickened wall noted in 85.7% of cases. Luminal surface enhancement with continuous mucosal line were observed in 85.7% of cases. Gallbladder stones were seen in 69.4% of patients. These CT findings were observed in 40% of cases and 80% of them had four or more of these features. Coexistent malignancy of gallbladder has been documented.[6,10] Krishnani et al[10] found that 19.6% of XGC cases had associated carcinoma of the gallbladder. In our patient, the CT showed irregular diffuse GB mural thickening with a few hypoattenuating mural nodules, multiple hyperdense calculi along with pericholecystic fluid collection and poor fat planes to the adjacent liver parenchyma.

Magnetic resonance imaging (MRI) can add further characterization of XGC. In T2 weighted images, the thickened gallbladder wall with xanthogranuloma accumulation shows areas of iso- to slightly hyperintense signal which show variable enhancement in post contrast study.[11] Luminal surface enhancement (LSE) of gallbladder wall denotes intact epithelial layer.[7,9] Early enhancement of adjacent liver parenchyma indicates liver involvement. In-phase (IP) and opposed-phase (OP) chemical shift imaging is useful to detect the presence of fat within intramural nodules in XGC.[11] This sign is likely highly specific and can lead to the diagnosis. Diffusion-weighted images (DWI) helps to further differentiate between thickened gallbladder wall in XGC and gallbladder cancer. Kang et al[12] noticed that diffusion restriction was commonly observed in gallbladder cancer (68%) compared to 7% of XGC cases. In our patient, MRI revealed a diffusely thickened gallbladder wall which shows iso- to slightly hyperintense signal in T2-wieghted images along with few mural nodules within the thickened wall, some of which demonstrate signal drop-out in opposed-phase images (OP) denoting microscopic fat deposition of xanthogranuloma. Minimal pericholecystic fluid is seen. Smooth luminal surface enhancement is noted in post contrast images. The presence of microscopic fat on MRI helped in reaching the diagnosis pre-operatively.

CA19-9 is cell surface glycoprotein complex produced by ductal cells from different gastrointestinal and non-gastrointestinal organs. Its expression and metabolism are effect by many factors including, enzymes deficiency, ethnicity, dietary and comorbidities. However, over expression is known to occur more commonly with pancreaticobiliary pathology and pancreaticobiliary malignancy specifically. Carcinogenesis related epigenetic silencing factor is responsible for malignant overexpression of CA9-9, owing to considering it as a tumor marker. Nevertheless, the emerging terminology now is tumor-associated consequent to its significant association with vast benign pathology. Nonetheless, extremely high levels of CA19-9 are generally found in advance cases of pancreaticobiliary malignancy, though it's not exclusive.[13,14]

In begin biliary condition, acute cholangitis, choledocholithiasis and cholecystitis are the most reported case associated with extremely high CA19-9. This suggest that obstructive inflammation is probably the culprit for raises of CA19-9. Although, the exact cause of extremely high levels of CA19-9 in benign condition is unknown, there are few theories that have been postulated. The first one is that the raised inflammatory cytokines lead to over expression of CA19-9 and the second one is that the extensive inflammation led to ductal obstruction and large amount of cellular destruction leading to increase production and hematogenous leakage.[14,15]

In Xanthogranulomatous Cholecystitis, CA 19-9 have played a significant role in assessment long side clinical and radiological evaluation to distinguish between Gallbladder adenocarcinoma and xanthogranulomatous cholecystitis. However, with emerging evidence of extremely high levels of CA19-9 seen in xanthogranulomatous

Cholecystitis, question the its significance. Hong and colleagues[16] have reported a raised CA19-9 in 45.95% of patients with Xanthogranulomatous Cholecystitis and to reach a maximum 536.29 U/mL. On the other hand, Zhuang et al[17] have studied the association of Xanthogranulomatous Cholecystitis to gallbladder carcinoma and found that CA19-9 although is significantly higher in gallbladder carcinoma it cannot be used to distinguish between them. The raise in CA19-9 in patients with Xanthogranulomatous Cholecystitis is yet not fully understood as it may raise in the absence of jaundice. Furthermore, it is reported that the diseased gallbladder epithelium in Xanthogranulomatous Cholecystitis express CA19-9 signifying the raise is to be disease related.[1]

Conclusion

Although, Xanthogranulomatous Cholecystitis is considered as a benign disease, its complexity and variability dictate an aggressive approach in assessment. Likewise, the local aggressive nature of the condition, as well as its association and similarity with gallbladder carcinoma propels us to make drastic measures in management in evade suboptimal treatment.

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