Multidetector Computed Tomographic Findings of Xanthogranulomatous Cholecystitis: Correlation with Histopathologic Findings

Ksantogranülomatöz Kolesistitte Çok Dedektörlü Bilgisayarlı Tomografi Bulgularının Histopatolojik Bulgularla Korelasyonu

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ABSTRACT Objective: Xanthogranulomatous cholecystitis (XGC) is a rare presentation of chronic cholecystitis that is characterized by xanthogranulomas, severe fibrosis, and foam cells. We aimed to evaluate the features of xanthogranulomatous cholecystitis revealed via multidetector computed tomography (MDCT) and correlate the imaging findings with various pathologic findings. **Material and Methods:** A retrospective analyses was done in 19 patients with pathologically diagnosed XGC between January 2002 and July 2008. Preoperative MDCT examinations were evaluated in all patients. The following MDCT features were evaluated: maximum wall thickness, patterns of wall thickening and enhancement, intramural hypodense nodules, preservation of the mucosal line, presence of stones, surrounding fat and liver. **Results:** The most characteristic MDCT findings were thickening of the gallbladder wall (100%), the presence of intramural hypodense nodules (100%), and preservation of the mucosal line (79%). Microscopically, the thickened gallbladder wall consisted of proliferation of foamy cells and fibrous tissue with infiltration of inflammatory cells in all patients (100%). Intramural hypodense areas on the wall on MDCT were microscopically composed of xanthogranulomas consisting of foamy histiocytes and inflammatory cells in 79% of the patients. Microscopic examination revealed preservation of the epithelial layer in 68% of the patients. Our results indicate that MDCT findings correlate well with the histopathologic findings of XGC. **Conclusion:** Although the preoperative imaging diagnosis of XGC is difficult, characteristic MDCT findings are highly suggestive for the diagnosis of XGC.

Key Words: Gallbladder; cholecystitis; tomography, X-ray computed

ÖZET Amaç: Ksantogranülomatöz kolesistit, kronik kolesistitin nadir görülen bir formu olup ksantogranülomlar, şiddetli fibrozis ve köpük hücrelerle karakterizedir. Bu çalışmanın amacı, ksantogranülomatöz kolesistitin çok kanallı bilgisayarlı tomografi (ÇKBT) bulgularının değerlendirilmesi ve histopatolojik bulgular ile karşılaştırılmasıdır. **Gereç ve Yöntemler:** Ocak 2002 - Temmuz 2008 tarihleri arasında patolojik olarak ksantogranülomatöz kolesistit tanısı almış 19 hasta retrospektif olarak analiz edildi. Tüm hastaların cerrahi öncesi yapılan ÇKBT incelemeleri değerlendirildi. ÇKBT ile en kalın yerinde duvar kalınlığı, duvar kalınlaşmasının şekli ve kontrastlanma, intramural hipodens nodüller, mukozal çizginin korunması, taş varlığı, çevre yağ dokusu ve karaciğer değerlendirildi. **Bulgular:** ÇKBT ile saptanan en karakteristik bulgular safra kesesi duvar kalınlaşması (%100), intramural hipodens nodüller (%100) ve mukozal çizginin korunması (%79) idi. Mikroskobik olarak, kalınlaşmış safra kesesi duvarında inflamatuar hücre infiltrasyonu ile beraber fibröz doku ve köpük hücre proliferasyonu izlendi. Kese duvarında izlenen intramural hipodens alanlar hastaların %79'unda mikroskobik olarak köpük histiositler ve yangı hücrelerinden oluşan ksantogranülomlara karşılık geliyordu. Mikroskopik olarak hastaların %68'inde epitelin korunduğu görüldü. Çalışmanın sonucunda ÇKBT'de saptanan bazı karakteristik bulguların histopatolojik bulgularla korele olduğu görüldü. **Sonuç:** Ksantogranülomatöz kolesistitin cerrahi öncesi görüntüleme ile tanısı zor olmasına rağmen, karakteristik ÇKBT bulgularının bilinmesi hastalığın tanısında son derece önemlidir.

Anahtar Kelimeler: Safra kesesi; kolesistit; bilgisayarlı tomografi

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Xanthogranulomatous cholecystitis (XGC) is a relatively rare chronic inflammatory disease of the gallbladder characterized by a thickening gallbladder wall consisting of proliferation of foamy cells and fibrous tissue with an infiltration of inflammatory cells. Although it is well-defined pathologically, XGC is difficult for the radiologist to recognize because some of the sonographic and computed tomographic (CT) features of the disease are nonspecific.[1-3] The clinical and radiologic characteristics of XGC are often similar to those of gallbladder cancer. Patients with XGC are frequently misdiagnosed intraoperatively as having carcinoma of the gallbladder and are treated with extensive excision.[4] It is thus important to make a correct diagnosis preoperatively; however, only a few studies have characterized the CT findings of XGC. The aims of this study were to evaluate multidetector computerized tomography (MDCT) findings of XGC and to correlate those findings with pathologic findings. In our study, XGC showed certain characteristic MDCT findings, which correlate well with the histopathologic findings. Awareness of these findings is helpful for the diagnosis of XGC.

MATERIALS AND METHODS

SUBJECTS

A retrospective analysis was done in 19 patients with pathologically diagnosed XGC from January 2002 to July 2008. The patients were 9 women and 10 men with a mean age of 63 years. The symptoms included right-sided quadrant pain and tenderness (n= 14), fever and chills (n= 8), nausea (n= 10), vomiting (n= 6) and jaundice (n= 2) with a duration of 12 days to 6 months. Seven (36.8%) patients had a history of acute cholecystitis and 6 (31.5%) patients biliary colic. Six patients had presented with obstructive jaundice and six with acute cholecytitis. All patients had undergone preoperative MDCT examination. The mean time from the onset of symptoms to the date of the MDCT examination was 22 days (range, 3-67 days). The mean time from the initial MDCT to surgery was 28 days (range, 1-85 days). In the initial 7 patients, MDCT scans of the abdomen were done with a 4-row MDCT (Volume Zoom, Siemens, Erlangen, Germany), and in the last 12 patients, CT scans of the abdomen were performed with a 16-row MDCT (Sensation, Siemens, Erlangen, Germany) with a 5 mm thickness and in 5 mm intervals, 120 kVp, 110-120 mA, both before and after the intravenous administration of contrast material. A triple-phase CT was performed with a scanning delay of 30 seconds (arterial phase), 60 seconds (portal phase) and 120 seconds (delayed phase) with the intravenous rapid injection (3-3.5 mL/sec) of 100-120 mL of contrast material (Iopamiro 300; Bracco, Milan, Italy). Scanning was done with 1.5 mm collimation and 0.75 mm pitch.

HISTOPATHOLOGIC TECHNIQUE

All patients underwent cholecystectomy. All tissue specimens used for histopathologic diagnosis were obtained during surgery. All the specimens were fixed in formalin and were stained with hematoxylin and eosin.

MULTIDETECTOR COMPUTERIZED TOMOGRAPHY EVALUATION

All images were retrospectively reviewed by two radiologists who were blinded to the pathologic results. After the review, a conference was held to discuss the cases and (when there was disagreement) to arrive at a consensus. The following MDCT features were analyzed: measurement of maximum wall thickness, patterns of wall thickening and enhancement (homogeneous vs heterogeneous), degree of enhancement of the thickened wall, intramural hypodense areas, mucosal line, surrounding fat, surrounding liver and the presence of stones. Thickening of the gallbladder wall was considered abnormal if it exceed 3 mm and was defined as diffuse (> 50% involvement) or focal (< 50%).[5] The gallbladder wall thickness was measured at the thickest portion. The degree of enhancement of the thickened gallbladder wall was evaluated by comparing to normal liver parenchyma areas. The degree of enhancement of the thickened wall was characterized as poor or mild (less than that of the liver), moderate (equal to that of the liver), or marked (greater than that of liver). We graded the degree of the involved area occupi-

ed by the intramural hypodense areas in the thickened gallbladder wall as follows: none (less than 30%), 30% to 60% or greater than 60%. The mucosal line was evaluated if it was visualized and was categorized as continuous or disrupted.[6] The surrounding gallbladder tissue was evaluated for surrounding fat and was categorized as clear or obliterated and the surrounding hepatic parenchyma was evaluated for the presence or absence of abnormal enhancement on arterial phase. The same pathologist evaluated the pathologic findings and we then examined the correlation between the radiologic and pathologic findings.

RESULTS

On MDCT, the gallbladder wall was thickened in all 19 patients (mean maximum thickness 12 mm; range 5-20 mm). Diffuse thickening was found in 17 (89%) patients, and focal thickening (Figure 1A) in 2 (11%). The thickened gallbladder wall was mildly enhanced in 8 (42%) patients, moderately enhanced in 9 (47%), and markedly enhanced in 2 (11%). The pattern of enhancement was heterogeneous in 13 (68%) patients and homogeneous in 6 (32%).

Intramural hypodense areas were seen in all patients (Figure 2A). Ten (53%) patients had a degree of involvement of less than 30%, 3 (16%) had 30% to 60% and 6 (31%) had greater than 60%. The mucosal line was observed in 15 (79%) patients; it was continuous in 3 and focally disrupted (Figure 2B) in 12. The mucosal line was absent (Figure 1B, 1D) in 4 patients (21%). Gallbladder stones were identified in 14 (74%) patients and the mean diameter of the stones was 10.2 mm. Extension of the inflammatory process into the liver was seen in 7 (37%) patients as early parenchymal enhancement adjacent to the inflamed gallbladder (Figure 3A). The diffuse and irregular thickening of the gallbladder wall with nearly complete loss of mucosal line was seen in 1 patient who was misdiagnosed via MDCT as having cancer of the gallbladder (Figure 4A). Mild and heterogeneous enhancement of the gallbladder wall was seen. The liver parenchyma adjacent to the gallbladder showed hypodense and ill-defined areas and surrounding fat showed diffuse increased densities corresponding with pericholecystic fat infiltration (Figure 4B). Pericholecystic fat infiltration was seen in 14 (74%) patients. Dilation of the intrahepatic and extrahepatic biliary systems was observed in 5 (26%) patients. Pericholecystic fluid was detected in 2 (11%) patients and gallbladder perforation was found in 1 patient.

All patients underwent cholecystectomy and gallbladder stones were detected in 16 (84%) patients. Open surgery was planned and done in 5 (26%) patients. A malignant lesion was suspected preoperatively in one of those subjects. Frozen-section analysis was done in that patient (in whom a conventional approach was used) and no malignancy was found. Laparoscopic cholecystectomy was planned in 14 (74%) patients, but that operation was converted to open surgery in 6 patients who had severe adhesions.

Microscopically, the thickened gallbladder wall consisted of proliferation of foamy cells and fibrous tissue with an infiltration of inflammatory cells in all patients.

Measurement of the pathologic specimens showed that the gallbladder wall ranged from 6 to 25 mm (mean, 11.2 mm) in thickness and was thickened in all patients. Intramural hypodense areas in the wall that were noted on MDCT were composed microscopically of a xanthogranuloma consisting of foamy histiocytes and inflammatory cells in 15 (79%) patients (Figure 1C). Those areas were consistent with the nonenhanced cystic areas within the intramural hypodense nodules shown via MDCT. In 4 patients (21%), intramural hypodense areas in the gallbladder wall were noted on MDCT (in 1 patient the area of involvement ranged from 30% to 60%, and in 3 patients it was greater than 60%) and corresponded with the diffuse accumulation of foamy and giant cells and necrosis and/or abscess in the gallbladder wall.

Preservation of the epithelial layer was noted on microscopic examination in 13 out of 19 (68%) patients. In 10 of those 13 (77%) patients, the epithelial layer was focally disrupted (Figure 2C), and in 3 (23%), the epithelial layer was continuous on

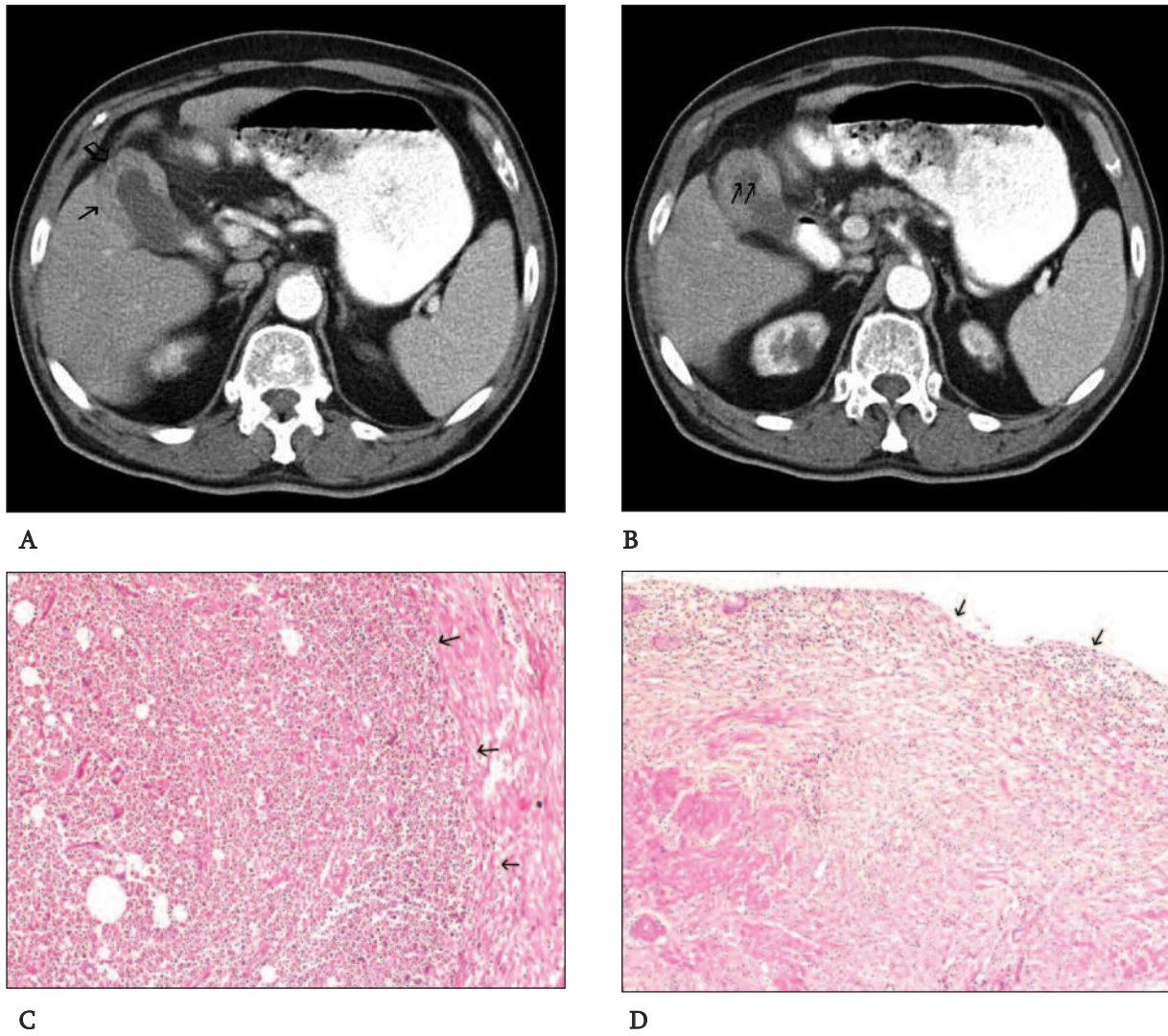

FIGURE 1: A 59-year-old woman with xanthogranulomatous cholecystitis. **A.** A contrast-enhanced multidetector computed tomography scan shows focal thickening of the gallbladder wall predominantly in the fundus (arrow) and an intramural hypodense nodule (open arrow). **B.** The mucosal line is absent (arrows). **C.** A pathologic specimen shows a small intramural nodule that represents a xanthogranuloma within the focally thickened gallbladder wall. **D.** Microscopic examination shows destructions of epithelial layer (HE stain; x10).

microscopic examination. Rokitansky-Aschoff sinuses were identified in 14 (74%) patients.

In 4 of 7 patients with early-enhanced areas of the liver parenchyma adjacent to the inflamed gallbladder on MDCT the liver parenchyma adjacent to the gallbladder was resected. In 3 of those 4 patients, the early-enhanced areas of the liver parenchyma adjacent to the inflamed gallbladder on MDCT corresponded with the accumulation of inflammatory cells and various degrees of abundant fibrosis (Figure 3B).

Pericholecystic fat infiltration noted on MDCT also corresponded with abundant fibrosis and the accumulation of inflammatory cells. Pericholecystic fat infiltration was identified on MDCT in 14 (74%) patients and was noted microscopically in all patients (100%). The patient who was misdiagnosed via MDCT as having gallbladder carcinoma showed an absence of the mucosal line, diffuse and irregular gallbladder wall thickening, and mild heterogeneous enhancement of gallbladder wall on CT. In that individual, ill-defined and hypodense

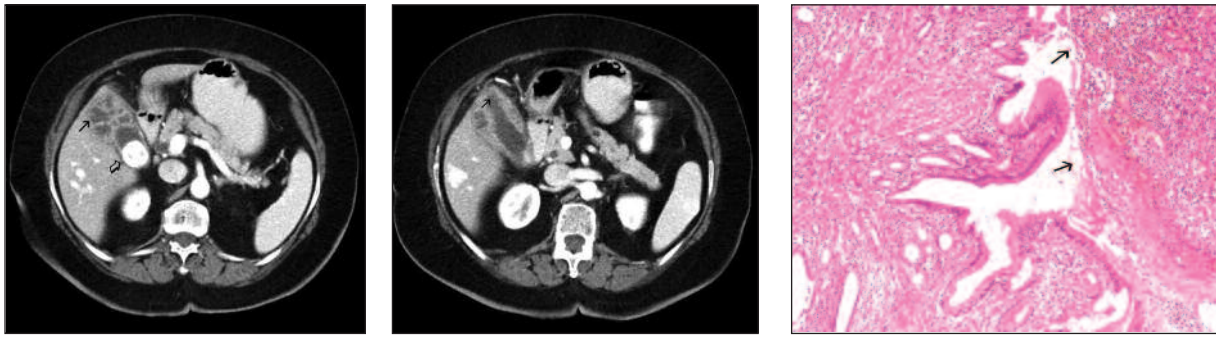

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FIGURE 2: A 75-year-old woman with xanthogranulomatous cholecystitis. **A.** A contrast-enhanced multidetector computed tomography scan shows diffuse gallbladder wall thickening with multiple intramural hypodense nodules (arrow) and a gallstone (open arrow). **B.** The mucosal line is preserved but focally disrupted (arrow). As an incidental finding, flash-filling haemangioma on dynamic contrast-enhanced CT showing intense homogeneous blush on the arterial phase in the liver parenchyma. **C.** Pathologic specimen shows that mucosal and muscular layers are relatively well preserved. Severe inflammation and fibrin accumulation is seen in focal disrupted area (arrows) of the mucosal line (HE stain; x10).

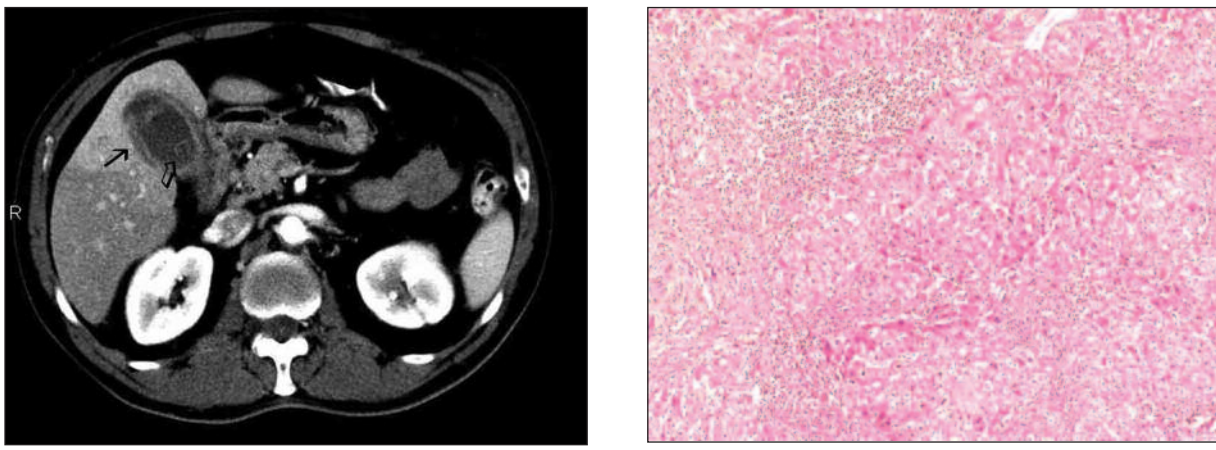

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FIGURE 3: A 56-year-old man with xanthogranulomatous cholecystitis. **A.** A contrast-enhanced multidetector computed tomography scan shows diffuse gallbladder wall thickening (arrow). Multiple stones can be seen in the gallbladder (open arrow). Geographic enhancement of the liver adjacent to the gallbladder suggests the spread of inflammation to the liver. **B.** Pathologic specimen shows extending of chronic inflammation to the liver parenchyma (HE stain; x10).

areas of the liver parenchyma that was adjacent to the gallbladder and a diffuse increased density of surrounding fat corresponded with the pericholecystic fat infiltration. The pathologic findings were consistent with the MDCT findings, but the changes in the liver parenchyma adjacent to the gallbladder corresponded with much more aggressive inflammation and fibrosis (Figure 4C) than that noted in other patients.

DISCUSSION

XGC is an uncommon form of chronic cholecystitis characterized by a focal or diffuse destructive inflammatory process, varying proportions of fibrous tissue, acute and chronic inflammatory cells, and the accumulation of lipid-laden macrophages in areas of inflammation.[7,8] Although the pathogenesis of this lesion is not fully understood, it is suggested that rupture and intramural extravasation of the inspissated bile and mucin from occlusion of the Rokitansky-Aschoff sinuses are the main causes for a xanthogranulomatous reaction in the gallbladder wall. Christensen and Ishak, who first established the pathologic diagnosis of XGC in 1970, described 7 patients with a pseudotumor of the gallbladder.[9] Microscopically, the early stage of

XGC is characterized by a large number of foamy histiocytes and acute inflammatory cells. Later stages show increasing fibrosis.[10]

The gallbladder wall is thickened (3-25 mm) in most patients with XGC.[11] In our study, the gallbladder wall was thickened in all 19 patients (mean thickness 12 mm; diffuse in 17 patients and focal in 2). Gallbladder wall thickening in patients with XGC was commonly diffuse, whereas it was usually focal in patients with gallbladder carcinoma.[6]

Chun and colleagues reported that except for the evidence of hematogenous metastasis to the liver, the presence of intramural hypoattenuated nodules occupying more than 60% of the thickened gallbladder wall had statistically significant specificity for the diagnosis of XGC.[6] Previous studies have reported that intramural hypodense areas on CT represented a xanthogranulomatous lesion, necrosis, and/or an abscess. Shuto and colleagues evaluated the CT scans of 13 patients with XGC and showed that intramural hypodense areas corresponded with necrosis and/or an abscess in 4 patients and with a xanthogranuloma in 9.[1] In our study, CT findings were similar to those reported by Shuto and colleagues: The CT scans showed a thick gallbladder wall within intramural hypodense areas that were consistent with a xanthogranulomatous lesion in 15 of 19 patients and with diffuse accumulation of foamy and giant cells, necrosis, and/or an abscess in 4 of 19 patients.

Chun and colleagues reported on CT information with regard to the mucosal line.[6] This mucosal line was composed of both mucosa and muscle layer in patients with XGC and indicated that the main lesion was in the intramural portion and that the mucosal surface overlying the lesion was either intact or focally denuded. Shuto and colleagues[1] also reported that luminal surface enhancement, which was noted in 7 of 10 (70%) patients, corresponded well with the presence of the epithelial layer. In our study, the CT findings were similar to the results of the previous study in which the mucosal line was seen in 15 patients on CT and it corresponded well with the presence of the epithelial layer in 13 of 15 patients.

Shuto and colleagues observed early enhancement of the liver surrounding the gallbladder in 4 patients.[1] Matsui and colleagues reported that on dynamic CT, increased staining of the liver adjacent to the gallbladder was caused by increased venous drainage in patients with acute cholecystitis.[12] Ito and colleagues noted that the relatively rapid and direct return from the dilated and increased cystic vein into the liver parenchyma contributed to the early enhancement of the distant hepatic parenchyma.[13] In our study, early enhancement of the hepatic parenchyma, which was observed via CT in 3 patients, corresponded with the accumulation of inflammatory cells and various degrees of abundant fibrosis.

Because XGC is associated with a high frequency of complications and coexistent malignancy, early diagnosis is important.[8] If a correct diagnosis of XGC is made, then aggressive surgery (ie, partial or segmental hepatic resection or a Whipple operation) may be averted. The most characteristic findings of XGC (intramural hypodense areas, preservation of the mucosal line, diffuse wall thickening, gallbladder stones), which are described in this report, could be helpful in diagnosing that disorder. If intramural hypodense nodules and the preservation of mucosal line are not detected on CT, but focal wall thickening, a greater degree of hepatic parenchymal involvement and biliary duct dilation are present, then, gallbladder carcinoma or other forms of cholecystitis should be considered. Previous studies have shown that gallbladder carcinoma can coexist with XGC. Kim and colleagues reported that 3 of 19 patients with XGC had gallbladder carcinoma.[11,14] In our study, we did not detect concomitant XGC and gallbladder carcinoma.

CT is helpful in evaluating coexistent malignancy and in making differential diagnosis. The major advantages of the MDCT technology allow for acquisition of different image thicknesses from the same acquisition data set. Moreover, its increased speed, thin collimation, large volume, and extreme flexibility provide additional superiority over single slice helical CT. MDCT, as used in our cases, revealed preservation of mucosal line and intramural hypodense nodules in XGC patients,

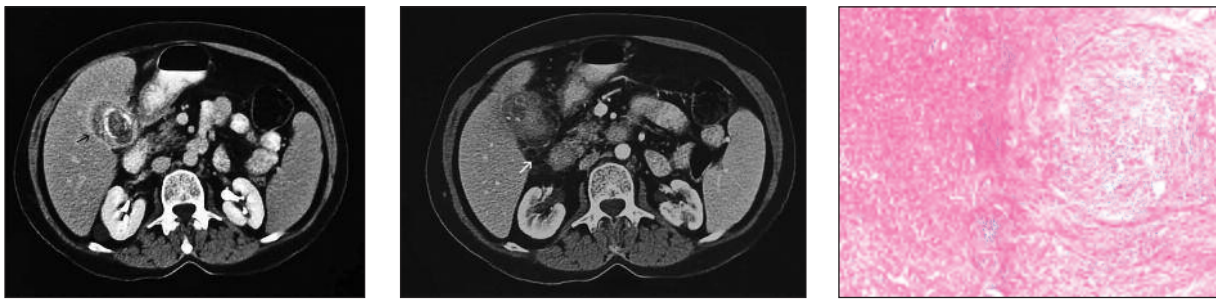

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FIGURE 4: A 64-year-old woman with xanthogranulomatous cholecystitis who was misdiagnosed with gallbladder carcinoma on CT. **A.** A contrast-enhanced multidetector computed tomography scan shows diffuse and irregular thickening of the gallbladder wall with nearly complete loss of mucosal line (arrow). **B.** The liver parenchyma adjacent to the gallbladder shows hypodense and ill-defined areas and surrounding fat shows diffuse increased densities corresponding with pericholecystic fat infiltration (white arrow). **C.** Pathologic specimen shows extending of severe fibrosis and chronic inflammation to the liver parenchyma (HE stain; x4).

which are important features in differentiating from GB cancer.

Our study has some limitations. Because it was retrospective, the correlation of pathologic specimens with CT findings was difficult. We suggest that our qualitative results are reliable because CT examinations were done by the same method.

CONCLUSION

We suggest that on MDCT, the presence of calculi and intramural hypodense nodules in a thickened gallbladder wall are highly suggestive of XGC. The preoperative diagnosis of XGC can be important in the proper surgical management of patients with that disorder and in the differential diagnosis of other chronic gallbladder diseases.

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