Distinguishing Xanthogranulomatous Cholecystitis from the Wall-Thickening Type of Early-Stage Gallbladder Cancer

Byung Jin Chang*, Seong Hyun Kim[†], Ho Yong Park*, Seong Woo Lim*, Jeong Kim*, Kwang Hyuck Lee*, Kyu Taek Lee*, Jong Chul Rhee*, Jae Hoon Lim[†], and Jong Kyun Lee*

Departments of *Medicine and [†]Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Background/Aims: Xanthogranulomatous cholecystitis (XGC) mimics early-stage gallbladder (GB) cancer with wall thickening on computed tomography (CT), both clinically and radiologically. Preoperative differentiation of XGC from early-stage GB cancer is important for selecting the most appropriate surgical management. Therefore, we evaluated the clinical features and multidetector CT (MDCT) findings of XGC to determine whether it can be distinguished from early-stage GB cancer. **Methods:** We retrospectively evaluated 25 patients with XGC and 56 patients with the wall-thickening type of T1- and T2-stage GB cancer, where all of the diagnoses were pathologically confirmed by surgical treatment. All of the patients underwent preoperative MDCT. The clinical symptoms, laboratory findings, and CT findings were compared. **Results:** Abdominal pain, fever, and jaundice were noted more frequently in the patients with XGC. Serum aspartate aminotransferase and alanine aminotransferase levels were more elevated in patients with XGC, whereas carbohydrate antigen (CA 19-9) was higher in the patients with GB cancer. When the T-category cancer staging of XGC and early-stage GB cancer were compared, diffuse GB wall thickening, intramural hypoattenuated nodule, gallstone, and pericholecystic infiltration were consistent significant findings associated with XGC, regardless of the cancer staging. **Conclusions:** MDCT findings such as diffuse GB wall thickening, intramural hypoattenuated nodule, gallstone, and pericholecystic infiltration together with the clinical symptoms, can provide clues for physicians to differentiate XGC from early-stage GB cancer

with wall thickening on CT. (*Gut Liver* 2010;4:518-523)

Key Words: Xanthogranulomatous cholecystitis; Gallbladder cancer; Multidetector computed tomography

INTRODUCTION

Xanthogranulomatous cholecystitis (XGC) is a rare inflammatory disease of the gallbladder that is characterized by diffuse thickening of the gallbladder wall. Its importance lies in the fact that it is a benign condition that may be confused with gallbladder (GB) cancer.¹⁻³ Among GB cancers, intraluminal polypoid masses or advanced diseases that invade adjacent organs and vessels are easy to be differentiated from XGC. However, it is often troublesome to differentiate wall thickening type of early-stage GB cancer from XGC. In such cases, making the correct diagnosis of XGC is important to avoid an extended operation including hepatic resection.⁴⁻⁶

The common imaging techniques, for example ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI), are able to detect abnormalities of the gallbladder, but they are not always able to differentiate XGC from GB cancer,⁷ and the final diagnosis is usually made by histological examination of the resected specimen. Previous studies have reported that the CT findings can provide clues concerning the differentiation, but these enrolled all stages of GB cancer and

Correspondence to: Jong Kyun Lee

Division of Gastroenterology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, Korea

Tel: +82-2-3410-3407, Fax: +82-2-3410-6983, E-mail: jongk.lee@samsung.com

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Byung Jin Chang and Seong Hyun Kim contributed equally to this article.

was generally not achieved with multidetector CT (MDCT),⁸⁻¹⁰ which has improved temporal and spatial resolution with thinner section acquisition. To the best of our knowledge, there is no data for making comparisons between XGC and wall thickening type of early-stage GB cancer according to the cancer staging in spite that the CT images are much affected by the progression of tumors.

Therefore, we evaluated the preoperative MDCT findings, in addition to the clinical symptoms and the laboratory findings, to differentiate XGC from wall thickening type of early-stage GB cancer, especially according to the T category of the cancer staging.

MATERIALS AND METHODS

From November 2001 to June 2009, a total of 49 patients underwent cholecystectomy and they were pathologically diagnosed as having XGC at Samsung Medical Center, South Korea. Of these, 24 patients were excluded from the analysis for one of the following reasons: XGC with concomitant cancer (n=13), which included 7 cases of GB cancer, 2 cases of hilar cholangiocarcinoma, 1 case of common bile duct cancer, 1 pancreatic cancer, 1 hepatocellular carcinoma and 1 ampulla of Vater tumor: an MDCT examination was not performed (n=11).

In the same period, there were 324 patients with proven GB cancer according to surgical treatment at Samsung Medical Center. Among these patients, 268 patients were excluded from the analysis because 208 patients underwent US or conventional CT preoperatively, 34 patients had polypoid or mass forming gallbladder lesions seen on CT and 26 patients were staged as T3 or T4 cancer pathologically that were clearly different from the findings of XGC. Finally, we selected 25 consecutive patients with XGC and 56 patients with wall thickening type of T1 and T2 GB cancer, and we reviewed the clinical symptoms, the laboratory findings and the preoperative MDCT findings. On the histopathologic examination of the GB cancer, 9 patients were staged as T1 (16%), 47 were staged as T2 (84%). On the analysis of the CT findings, the patients with GB cancer were classified according to the T category of the TMN staging based on the American Joint Committee on Cancer Staging Manual, 6th edition (2002).

Triple phase helical CT examinations were performed using one of these MDCT scanners: LightSpeed QX/I, Ultra 8 or Ultra 16 (GE Healthcare, Milwaukee, WI, USA), Brilliance 40 (Philips Medical System, Eindhoven, Netherlands) and Aquilion 64 (Toshiba Medical, Tokyo, Japan). After unenhanced CT scanning (5 mm slice thick-

ness), a total 120 mL of nonionic iodinated contrast material (Ultravist 300 [300 mg I/mL iopromide]; Schering AG, Berlin, Germany) was administered intravenously with an automatic injector at a rate of 3-4 mL/sec. The arterial phase (2.5 mm slice thickness) was obtained at 45 seconds, and the portal phase (5 mm slice thickness) was obtained at 70 seconds after initiation of the contrast material injection, respectively. The CT scans acquired in the 81 patients were reviewed by two radiologists who were unaware of the diagnosis and cancer staging.

The CT findings used for comparison between the two diseases in the gallbladder were the maximum gallbladder thickness, the patterns of gallbladder thickening (>3 mm, focal or diffuse), the presence of gallbladder distension, the enhancement pattern of the gallbladder (homogeneous or heterogeneous, early or delayed), continuity of the mucosal line, the presence of hypoattenuated intramural nodule, the coexistence of gallstone, hepatic invasion, pericholecystic infiltration, bile duct dilatation and lymph node enlargement (>10 mm, regional or distant).

The chi-square test, Fisher's exact test, Student's t-test and the Mann-Whitney test were used to determine the parametric differences and nonparametric proportions between the two groups. Multivariable logistic regression analysis was used to determine the CT findings that favored the diagnosis of XGC. A p-value less than 0.05 indicated statistically significant. The statistical analysis was performed using SPSS statistical software version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The 25 patients with XGC consisted of 17 men and 8 women (mean age, 64.4 ± 13 years), whereas the 56 patients with GB cancer consisted of 31 men and 25 women (mean age, 62.1 ± 10.3). Of XGC group, 2 cases were diagnosed as GB cancer preoperatively beyond doubt; 6 cases of differential diagnosis between XGC and GB cancer. Preoperative diagnosis of GB cancer group were; GB cancer (n=49), possibility of chronic cholecystitis or GB cancer (n=3), possibility of adenomyomatosis or GB cancer (n=3), possibility of XGC or GB cancer (n=1). There was no significant difference of age and gender between the two groups. For the clinical symptoms, abdominal pain, fever and jaundice were more prevalent in the patients with XGC ($p=0.002$, $p=0.001$, $p=0.008$, respectively). The serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) level was more increased in the patients with XGC ($p=0.040$, $p=0.028$, respectively), and carbohydrate antigen (CA 19-9), by contrast, was more increased in the patients with GB cancer. But there was

no significant difference in the serum levels of total bilirubin, alkaline phosphatase (ALP) and the white blood cell count (WBC). The clinical symptoms and laboratory findings are summarized in Table 1.

Diffuse gallbladder wall thickening was more frequent in the patients with XGC (18 patients, 72%) than that in the patients with GB cancer (14 patients, 25.0%) ($p < 0.001$). For the enhancement pattern of the gallbladder, early enhancement of the gallbladder was observed in 17 patients with XGC (68%) and in 53 patients with GB cancer (94.6%) ($p = 0.003$). The continuous mucosal line was seen in 9 patient with XGC (36%) and in only 4 patients with GB cancer (7.1%) ($p = 0.002$). A hypoattenuated intramural nodule were found in 13 patients with XGC (52%) and in only 3 patients with GB cancer (5.4%) ($p < 0.001$). Gallstone was also more frequently observed in the patients with XGC (14 patients, 56%) than that in the patients with GB cancer (6 patients, 10.7%) ($p < 0.001$). A pericholecystic infiltration to the duodenum, colon and omentum was noticed in 14 patients with XGC (56%) and in 12 patients with GB cancer (21.4%) ($p = 0.002$). In contrast, lymph node enlargement (> 10 mm in minimum diameter) was seen in 33 patients with GB cancer (58.9%) and in 7 patients with XGC (28%) ($p = 0.010$). There were no significant differences between XGC and

GB cancer for the gallbladder wall thickness ($9.8 \text{ mm} \pm 3.9$ and 10.8 ± 4.7 , respectively), homogenous gallbladder enhancement, the extent of bile duct dilatation. The CT findings of the XGC and GB cancer are summarized in Table 2. Multivariable logistic analysis revealed that hypoattenuated intramural nodule ($p = 0.040$), and the absence of LN enlargement ($p = 0.014$) were the independent variables for making the diagnosis of XGC (Table 3).

On analyzing the CT findings according to the T category of the TMN staging, diffuse gallbladder wall thickening ($p = 0.017$), hypoattenuated intramural nodule ($p = 0.006$), gallstone ($p = 0.047$) and pericholecystic infiltration ($p = 0.04$) were more frequently observed in the patient with XGC than those of patients with T1 GB cancer. On comparing XGC and T2 GB cancer, diffuse gallbladder thickening ($p < 0.001$), gallbladder distension ($p = 0.022$), a continuous mucosal line ($p = 0.002$), hypoattenuated intramural nodule ($p < 0.001$), gallstone ($p < 0.001$) and pericholecystic infiltration ($p = 0.019$) were more associated with XGC; early gallbladder wall enhancement ($p = 0.012$) and LN involvement ($p = 0.014$) were more frequently ob-

Table 1. The Baseline Characteristics and Clinical Features of the Patients with XGC and GB Cancer

	XGC (n=25)	GB cancer (n=56)	p-value
Age, yr	64.4 $\pm$ 13	62.1 $\pm$ 10.3	0.397
Gender, M/F	17/8	31/25	0.285
Laboratory findings*			
WBC, /mm ³	7,443 $\pm$ 2,241	7,504 $\pm$ 2,731.5	0.866
AST, U/L	57.6 $\pm$ 53.8	41.2 $\pm$ 56.0	0.040
ALT, U/L	72.9 $\pm$ 66.3	34.8 $\pm$ 33.3	0.028
ALP, U/L	171.3 $\pm$ 159.6	115.5 $\pm$ 105.4	0.216
Total bilirubin, mg/dL	2.6 $\pm$ 4.2	1.3 $\pm$ 3.4	0.192
CA 19-9, U/mL	261.5 $\pm$ 740.2	408.5 $\pm$ 1,535.7	0.045
Presenting symptoms and signs			
Abdominal pain	19 (76.0)	22 (39.3)	0.002
Jaundice	9 (36.0)	5 (8.9)	0.008
Fever	8 (32.0)	2 (3.6)	0.001
Fatigue	7 (28.0)	11 (19.6)	0.403
Anorexia	11 (44.0)	13 (23.2)	0.058
Weight loss	5 (20.0)	13 (23.3)	0.074
RUQ mass	2 (8.0)	3 (5.4)	0.642

Data are presented as numbers of patients (%). XGC, xanthogranulomatous cholecystitis; GB, gallbladder; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; CA 19-9, carbohydrate antigen 19-9; RUQ, right upper quadrant.

*The data are shown as means $\pm$ standard deviations.

Table 2. The CT Findings of the Patients with XGC and GB Cancer

	XGC (n=25)	GB cancer (n=56)	p-value
GB wall thickness, mm*	9.8 $\pm$ 3.9	10.8 $\pm$ 4.7	0.371
GB wall thickening patterns			<0.001
Focal	7 (28)	42 (75.0)	
Diffuse	18 (72)	14 (25.0)	
GB distension	10 (40)	8 (14.3)	0.010
Enhancement pattern of the GB wall			0.489
Homogenous	4 (16)	6 (10.7)	
Heterogenous	21 (84)	50 (89.3)	
GB wall enhancement			0.003
Early	17 (68)	53 (94.6)	
Delayed	8 (32)	3 (5.4)	
Mucosal line			0.002
Continuous	9 (36)	4 (7.1)	
Disrupted	16 (64)	52 (92.9)	
Intramural hypoattenuated nodule	13 (52)	3 (5.4)	<0.001
Gallstone	14 (56)	6 (10.7)	<0.001
Hepatic invasion	15 (60)	20 (35.7)	0.042
Pericholecystic infiltration	14 (56)	12 (21.4)	0.002
Bile duct dilatation	13 (52)	29 (51.7)	0.986
Lymph node enlargement (> 10 mm)	7 (28)	33 (58.9)	0.010
Regional: distant	7:0	23:10	0.161
Size, mm*	12.2 $\pm$ 2.3	16.5 $\pm$ 8.1	0.144

Data are presented as numbers of patients (%).

XGC, xanthogranulomatous cholecystitis; GB, gallbladder.

*The data are shown as means $\pm$ standard deviations.

Table 3. Multivariable Logistic Regression Analysis for the Diagnosis of Patient with XGC according to the CT Findings

	Odds ratio	95% CI	p-value
Intramural hypoattenuated nodule	13.472	1.123-161.589	0.040
Gallstone	8.253	0.785-86.721	0.079
Continuous mucosal line	9.154	0.338-247.666	0.188
Absence of lymph node enlargement	44.029	2.150-901.826	0.014

XGC, xanthogranulomatous cholecystitis; CT, computed tomography; CI, confidence interval.

Table 4. Comparison of the CT Findings between XGC and GB Cancer according to the T Stage

	XGC (n=25)	T1 (n=9)	T2 (n=47)
Diffuse GB wall thickening	18 (72)	2 (22.2)*	12 (25.5)*
Intramural hypoattenuated nodule	13 (52)	0 (0)*	3 (6.4)*
Gallstone	14 (56)	1 (11.1)*	5 (10.6)*
Early GB wall enhancement	17 (68)	9 (100)	44 (93.6)*
GB distension	10 (40)	1 (11.1)	7 (14.9)*
Continuous mucosal line	9 (36)	1 (11.1)	3 (6.4)*
Pericholecystic infiltration	14 (56)	0 (0)*	12 (25.5)*
Hepatic invasion	15 (60)	3 (33.3)	17 (36.2)
Bile duct dilatation	13 (52)	2 (22.2)	27 (57.4)
Lymph node enlargement (>10 mm)	7 (28)	5 (55.6)	28 (59.6)*

Data are presented as the numbers of patients (%).

CT, computed tomography; XGC, xanthogranulomatous cholecystitis; GB, gallbladder.

* The difference between XGC and each T stage of GB cancer was statistically significant ($p < 0.05$).

served in the patients with T2 GB cancer. Diffuse GB wall thickening, intramural hypoattenuated nodule, gallstone and pericholecystic infiltration were the consistent, significant findings associated with XGC, regardless of the cancer staging (Table 4).

DISCUSSION

Patient with XGC can be frequently misdiagnosed as GB cancer, two different respects are linked to clinical importance of precise diagnosis between two diseases. First, if a correct diagnosis of XGC is made before operation, radical resection including hepatic resection with high morbidity and mortality may be avoided. Second, in high risk operative group the patient with XGC may be treated with non-operative management, but patient with

Fig. 1. A 42-year-old woman with XGC. The contrast-enhanced computed tomography image shows severe, diffuse wall thickness and a continuous mucosal line. An intramural hypoattenuated nodule is also seen (arrow). XGC, xanthogranulomatous cholecystitis.

GB cancer should be considered to undergo operation bearing complication.⁵

The characteristic CT features of XGC, for example continuous mucosal line, intramural hypoattenuated nodule and gallstone, have been reported, but these studies had limitations that conventional CT was used or polypoid mass lesion and advanced GB cancer that were easily differentiated from XGC, was included in the studies.^{8,11} MDCT has currently superseded conventional CT because it allows dynamic images to assess enhancement pattern, improved spatial resolution with thinner sections, and provides the multiplanar reconstruction images in addition to the axial images.^{12,13} Previous studies included all kinds of GB cancer to compare with XGC. However, we evaluated the diagnostic accuracy of MDCT for differentiating XGC from wall thickening types of early-stage GB cancer which looks like XGC. And because the CT findings are affected by the extent of local tumor spread,^{14,15} we classified the GB cancers according to the T category of the TMN staging to reveal consistent CT finding for differentiating two diseases regardless of T staging.

The MDCT findings of XGC have a tendency to be correlated with the pathologic parameters, as was previously mentioned.^{8,11} The diffuse wall thickening, intramural hypoattenuated nodule, continuous mucosal line and gallstone were highly suggestive of XGC in our study (Figs. 1 and 2). Characteristically, early GB wall enhancement was more common in GB cancer than XGC, it seems that enhancement pattern between inflammatory lesion and cancer is different.¹⁶⁻¹⁸ This phenomenon may be related that angiogenesis is central to tumor growth. Although the in-

Fig. 2. An 87-year-old man with XGC. The contrast-enhanced computed tomography image shows diffuse wall thickness, distension, and multiple intramural hypoattenuated nodules (short arrows). The interface between the gallbladder wall and the liver is not apparent, suggesting spread of inflammation into the liver; infiltration to the duodenum and stomach was also seen (long arrows).
XGC, xanthogranulomatous cholecystitis.

Fig. 3. An 80-year-old woman with T1-stage gallbladder cancer. The contrast-enhanced computed tomography image shows focal enhancement in the wall thickness involving the fundus of the gallbladder (arrows).

flammation also increase local blood flow than normal condition, angiogenesis is lacking in inflammation may explain why early perfusion is less than in cancer.¹⁷ This different enhancement pattern has never been studied in gallbladder cancer and chronic cholecystitis, more studies will be needed for using this as differential finding by development of MDCT.

Diffuse gallbladder wall thickening, hypoattenuated in-

Fig. 4. A 52-year-old woman with T2-stage gallbladder cancer. The contrast-enhanced computed tomography image shows diffuse wall thickness, distension, and continuous mucosal lines. However, there are no intramural hypoattenuated nodules, gallstones, or infiltration to the adjacent organs.

tramural nodule, gallstone and pericholecystic infiltration were the consistent, significant CT findings of XGC regardless of the cancer staging, but focal gallbladder wall thickening was more often observed in early GB cancer patients. Because mucosal line was disrupted with T2 GB cancer, disrupted mucosal line is important finding of GB cancer. But T1 GB cancer may show continuous, preserved mucosal line in the individual cases, we suggest cautiously considering this variable when differentiating XGC and GB cancer. In that equivocal cases, the presence of intramural hypoattenuated nodule, gallstone, diffuse wall thickening can be helpful. XGC can have tendency to extend into the adjacent liver, hepatic flexure of the colon or duodenum, our study revealed that local infiltration to colon, duodenum, adjacent liver are more prevalent in XGC than early-stage GB cancer. Therefore, local infiltration to adjacent organ may also discriminative finding between XGC and early GB cancer, although advanced GB cancer may infiltrate into local organs like XGC. This feature for the involvement of adjacent organs indicates that XGC may have a aggressive presentation like advanced GB cancer, and so it is important to preoperatively differentiate XGC from GB cancer to avoid incorrect surgical treatment (Figs. 3 and 4).

Clinically, no symptoms and signs are specific for XGC and they are similar to those of acute and chronic cholecystitis.^{6,10,19} And, there were no significant differences of the presenting sign and symptoms on comparing XGC with GB cancer in a previous study.⁷ However, in our study, abdominal pain, jaundice, and fever were more frequently observed in the patients with XGC compared

with that of the patients with GB cancer. These differences seems to be due to the facts that patients with early-stage GB cancer may be asymptomatic or have non-specific symptoms. In general, CA 19-9 is commonly measured in the serum of patients with suspected pancreatobiliary malignancy, however, moderate elevations of CA 19-9 may be seen in patients with benign disease like XGC. Previous studies have observed that the serum CA-19-9 is not helpful for making the differential diagnosis between the two diseases.^{5,20} Although elevated serum CA 19-9 level was prevalent even in early-stage GB cancer compared with XGC in our study, this tumor marker needs careful consideration in differentiating until now. By contrast, more elevated level of serum AST and ALT in the XGC patients appears to be related with a local inflammatory reaction of the liver.

In addition to the intrinsic limitations of a retrospective study, this study has several limitations. First of all, because our study population was composed of patients who underwent only MDCT preoperatively and they had GB cancer that was curable with surgical treatment, there could have been a selection bias. The limitations also included the non-proportionate number of patients in both groups, usage of three different MDCT scanners and no evaluation of the interobserver variability among the radiologists who analyzed the CT findings.

In conclusion, we demonstrated that the MDCT findings such as diffuse GB wall thickening, the presence of intramural hypoattenuated nodule, gallstone and pericholecystic infiltration are more associated with XGC than with early-stage GB cancer regardless of the cancer staging. These CT findings, in addition to the clinical symptoms, can provide clues to help physicians differentiate XGC from early-stage GB cancer.

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