[症例報告]Xanthogranulomatous cholecystitis mimicking carcinoma of the gallbladder : Report of four cases

Xanthogranulomatous cholecystitis mimicking carcinoma of the gallbladder: Report of four cases

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ABSTRACT

We herein present four cases of xanthogranulomatous cholecystitis (XGC) that involved the adjacent structures and clinically mimicked carcinoma of the gallbladder (diffuse-infiltrating type). The patients consisted of two males and two females, with a mean age of 64.5 years (range, 51 to 77 years). Three of them had an episode of acute cholecystitis one to five months before the operation. An elevation of CA19-9 and Span-1 was recognized in one case. Gallstones were present in all cases with a thickening of the gallbladder wall on either ultrasonography (US) or computed tomography (CT). Furthermore, three cases revealed either intramural hyperechoic spots or comet-like echoes on US. Three cases were erroneously diagnosed as carcinoma based on the operative findings and underwent a cholecystectomy with a partial hepatic resection of the gallbladder bed and/or a resection of the surrounding structures involved. In the remaining case, an intraoperative pathological study revealed chronic inflammation without malignancy and a cholecystectomy was thus performed. The resected gallbladders histologically revealed many granulomas (abundant pigment-laden foamy histiocytes, fibroblasts and inflammatory cells) which extended to the liver and/or colon. Therefore, in such a situation, an intraoperative pathological study is recommended in order to avoid any excessive and unnecessary surgery when determining the optimal method of treatment. *Ryukyu Med. J., 20(1)25~29, 2001*

Key words: Xanthogranulomatous cholecystitis, Carcinoma of the gallbladder

INTRODUCTION

Xanthogranulomatous cholecystitis (XGC) is a relatively rare benign disease which is sometimes clinically difficult to discriminate from carcinoma of the gallbladder (diffuse-infiltrating type). The frequency of XGC varies from 0.7% to 4.2% of all surgically resected gallbladders[1-4]. Houston *et al*[5] and Robert *et al*[3] reported the incidence of XGC at their hospital to be greater than that of carcinoma of the gallbladder. However, there is a broad spectrum of xanthogranulomatous changes from small and localized brown nodules to a diffuse involvement of the entire gallbladder with extension into the surrounding tissues[6]. Severe XGC with a markedly thickened gallbladder wall and involvement of the adjacent structures, which cannot be differentiated from carcinoma of the gallbladder based on both the diagnostic imaging and macroscopic findings, is uncommon[7].

We herein review four cases of XGC that clinically mimicked carcinoma of the gallbladder, and also discuss the clinical and pathological characteristics of XGC.

PATIENTS AND METHODS

We reviewed four cases of XGC which were difficult to differentiate from carcinoma of the gallbladder based on the clinical, imaging and/or operative findings. The patients were collected from Ryukyu University Hospital and the National Leprosarium Okinawa Airaku-en from 1986 to 1998. There were two males and two females, with a mean age of 64.5 years (range, 51 to 77 years).

The clinical records of these patients were reviewed regarding clinical features, laboratory data, radiological imaging, operative findings and histological findings, together with the immunohistochemical findings of a case which showed an abnormal serum CA19-9 level. An immunohistochemical examination for CA19-9 was performed using the labeled streptavidin biotin (LSAB) method. Primary antibody against CA19-9 (Toray-Fuji Bionics, Tokyo, Japan) was used.

Table 1 Clinical Features

Case	Age	Sex	Symptom	Concomitant diseases	IOO
1	55	F	Fever RUQ pain	Cholecystolithiasis	3M
2	77	M	RUQ pain	Cholecystolithiasis Adrenal tumor (Non functional)	1M
3	75	M	RUQ pain	Cholecystolithiasis Leprosy	5M
4	51	F	None	Cholecystolithiasis Diabetes Mellitus	N/A

IOO: Interval between onset and operation
RUQ pain : right upper quadrant pain
N/A : not applicable

Table 2 Radiological features

	Case 1	Case 2	Case 3	Case 4
Ultrasonography (US)				
Calculi in gallbladder	+	+	+	+
Comet-like echo or calculi in gallbladder wall	+	+	+	−
Thickened gallbladder wall	+	+	+	+
Mass within gallbladder	−	−	−	+
Dilatation of common bile duct	−	−	+	−
Sludge in gallbladder	−	−	+	+
Computed Tomography (CT)				
Calculi in gallbladder	*	+	+	+
Thickened gallbladder wall	*	+	−	+
Enhancement	*	−	−	+
LAA in thickened gallbladder wall	*	−	+	+
Gas in gallbladder	*	−	−	+
Cholangiography				
Negative study of gallbladder	*	+	+	+
Angiography				
Irregularity of the cystic artery	*	*	*	+
Tumor stain	*	*	*	+

LAA: Low Attenuation Area, * : not performed

RESULTS

Clinical features

Table 1 summarizes clinical features of all the cases. Three of the patients presented with an episode of acute cholecystitis such as right upper quadrant pain or a high fever one to five months before the operation. No symptoms were observed in case 4 who had diabetes mellitus. All patients presented with cholelithiasis.

Laboratory data

No obvious characteristics could be identified in the hematological or biochemical findings except for an abnormal CA19-9 level (680 U/ml) and Span-1 (250 U/ml) level without any obstructive jaundice or cholangitis in Case 3. The serum CA19-9 level increased from 150 U/ml on admission to 680 U/ml before the operation, although the clinical and laboratory findings such as abdominal pain, tenderness and a CRP elevation all improved before the operation. After the operation, the elevated levels of serum CA19-9 and Span-1 returned to almost within the normal limits, and at the time of writing the patient has been doing well for the past 4 years and 6 months since the operation.

Radiological imaging

All patients had gallstones in the gallbladder and also demonstrated a thicker than normal gallbladder wall on ultrasonography (US) or computed tomography (CT) (Table 2). In three cases, intramural hyperechoic spots or comet-like echoes were observed on US. A low attenuation area in the thickened gallbladder wall was

Table 3 Operative findings

Case	Preoperative diagnosis	Operation performed	IOB
1	1) Cholecystolithiasis	CC with PRGBB	−
2	1) Cholecystolithiasis	CC with PRGBB + partial resection of the colon and diaphragma	−
3	1) Choledocholithiasis 2) Adenomyomatosis or XGC or GBCa	CC with PRGBB + partial colectomy	−
4	1) Cholecystolithiasis 2) XGC or GBCa	CC	+

IOB : Intraoperative biopsy, CC : Cholecystectomy, PRGBB : partial resection of the gallbladder bed, XGC : Xanthogranulomatous cholecystitis, GBCa : Gallbladder Carcinoma

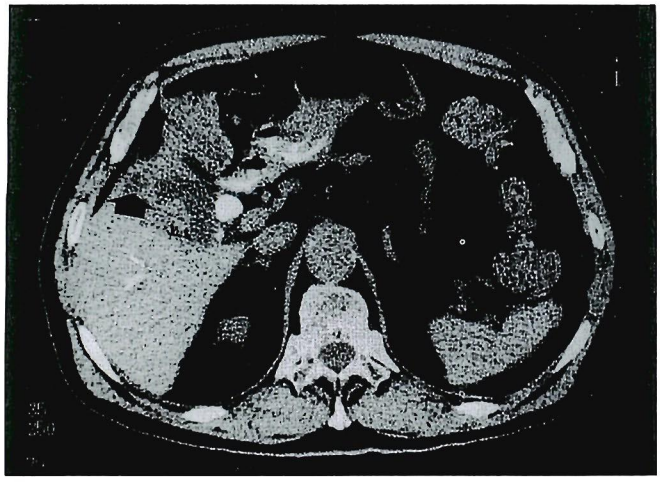

Fig. 1 A CT scan revealing a low attenuation (arrow) area in the thickened gallbladder wall (Case 3).

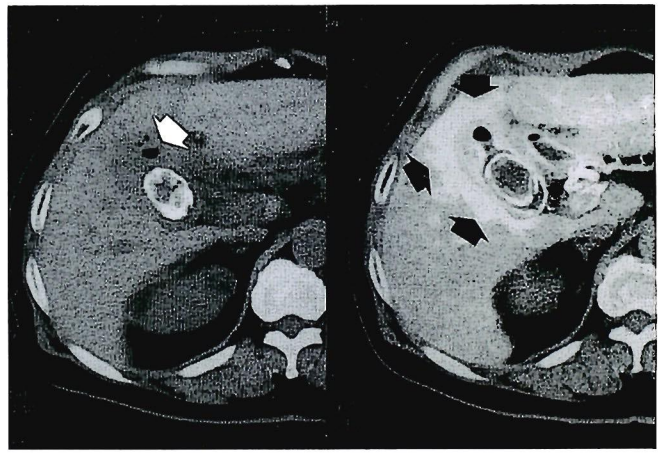

Fig. 2 A CT scan showing the presence of gas (white arrow) in the gallbladder (Left, Case 4), and an angio-CT scan revealing a hypervascular mass (arrow) in the liver bed with a clear border in the gallbladder wall (Left, Case 4).

detected by CT (Fig 1) in two cases, and gas in the gallbladder (Fig 2, Left) was observed in one case. A clear border between the thickened gallbladder wall and mass in the gallbladder bed was detected by angio CT (Fig 2, Right). Cholangiography showed negative findings in all three examined cases.

Operative findings

The gallbladders appeared as a hard mass on palpation and extensive adhesions was found to such adjacent organs as the liver, colon and diaphragm in all cases (Table 3). Three cases were erroneously diagnosed as carcinoma based on the operative findings and, as a result, they underwent a cholecystectomy with a partial hepatic resection of the gallbladder bed, a partial colectomy and/or a partial resection of the diaphragm. In one case, the intraoperative pathological diagnosis revealed chronic inflammation without malignancy. Consequently, a cholecystectomy was performed.

Macroscopic features

The gallbladder wall was remarkably thickened and whitish in color with yellowish-brown nodules in all cases. In all cases, cholesterol gallstones were impacted in the neck of the gallbladder. Intramural calculi were seen in two (Fig 3, Top) and mucosal ulcerations of the gallbladder in three (Fig 3, Bottom).

Histological study

The histological examination of the resected gallbladders revealed many ill defined granulomatous lesion composed of abundant brown pigment-laden foamy histiocytes, fibroblasts and inflammatory cells (Fig 4, Top), and non-specific chronic inflammation extended to the liver and/or colon. In case 3, an immunohistochemical study showed a positive reaction for CA19-9 in both the preserved gallbladder epithelium and foamy histiocytes in granulomatous lesions (Fig 4, Bottom), having no remarkable differences in the intensity of the immunoreactivity between them.

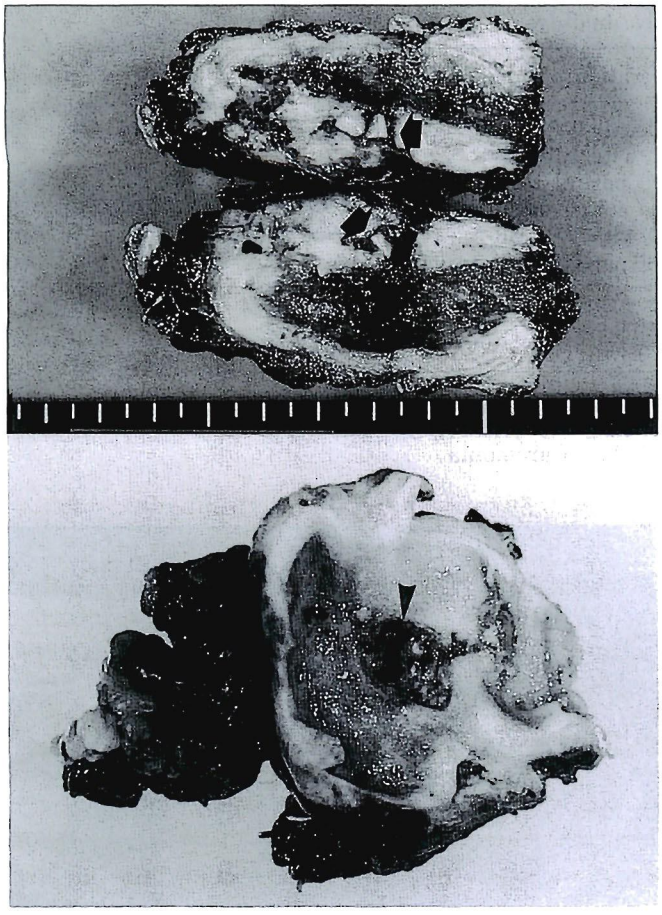

Fig. 3 Resected specimens revealing a thicker gallbladder wall than normal along with the presence of intramural calculi (arrow) (Top, Case 1), or mucosal ulceration (arrow head) (Bottom, Case 3).

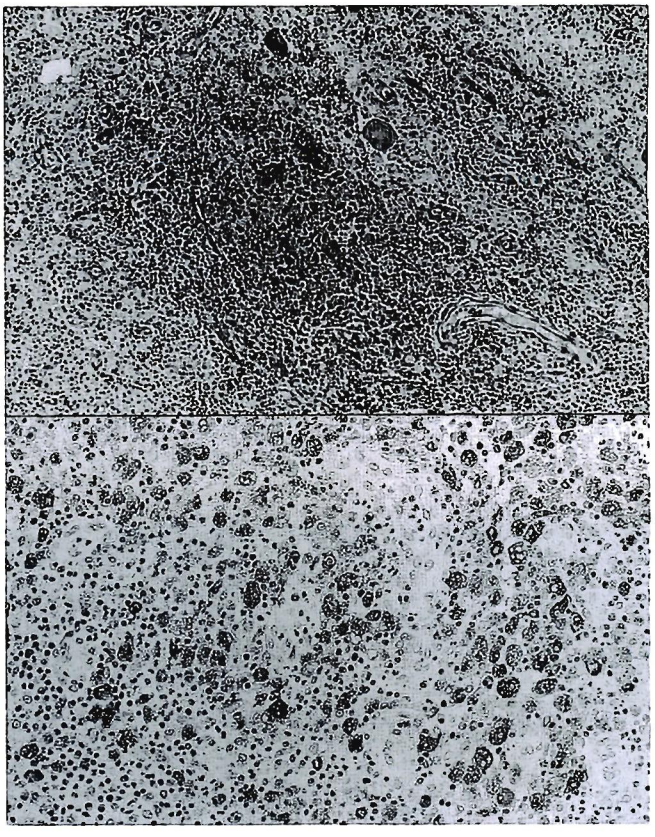

Fig. 4 A histological examination of the resected gallbladder showing accumulation of foamy histiocytes, inflammatory cells and fibroblasts (Top, HE, X 25, case 3), and immunohistochemical examination showing a positive reaction for CA19-9 in foamy histiocytes in the granulomas (Bottom, CA19-9, X 50, case 3).

DISCUSSION

The pathogenesis of XGC has not yet been clearly elucidated. Our many accumulated studies show that XGC is generally assumed to be the sequela of acute cholecystitis, i.e., the intermediate healing state of a subsiding acute cholecystitis[8]. In clinical practice, the great majority of acute cholecystitis cases are directly associated with an obstruction of the cystic duct by either the entry of a gallstone into the cystic duct or due to an impacted gallstone in the neck[9]. Therefore, acute cholecystitis should be called acute obstructive cholecystitis. Most cases of acute cholecystitis form intramural and/or pericystic abscesses which invariably contain inspissated bile, cholesterin crystals and other components in their centers, thus indicating an inflammatory reaction to these extravasated foreign bodies, and finally resulting in the formation of xanthogranuloma. As time elapses, these xanthogranulomas eventually form XGC.

In this study, three of the patients had an episode of acute cholecystitis from one to five months before the operation. Many studies have reported that most of the patients with XGC have a history of at least one previous episode of acute cholecystitis[3, 10]. To distinguish XGC from carcinoma of the gallbladder, a history of acute cholecystitis may be helpful for accurate diagnosis of XGC.

Unfortunately, there was no clear trends in the hematological or biochemical findings of the patients with XGC. Although CA19-9 is a useful tumor marker for diagnosing carcinoma of the gallbladder, the serum levels of CA19-9 in patients with XGC are often high[11]. A normalization of the serum CA19-9 level after successful treatment indicates a benign disease rather than a malignancy[12]. In our case 3, however, the serum CA19-9 levels tended to elevate despite the improvement in the inflammatory findings and this case thus led us into confusion when making the diagnosis.

Regarding the diagnostic imaging findings, the presence of comet-like echoes, hyperechoic spots and hypoechoic lesions by US or low attenuation areas within the gallbladder wall on the CT findings played an important role in making the diagnosis. These imaging characteristics are reportedly caused by cystic Rokitansky-Aschoff sinuses within a thickened gallbladder wall and the presence of in

tramural calculi[11]. Chun *et al*[13] mentioned that there were some differences between XGC and carcinoma of the gallbladder regarding the pattern of gallbladder wall thickening, the continuity of the mucosal line and the severity or heterogeneity of lymphadenopathy. However, they concluded that because of a statistically significant overlap in the CT features, XGC is thus only suggested when intramural hypoattenuated nodules occupy a large area of the thickened gallbladder wall. In cases with XGC involving the adjacent tissues, it is not possible to make a definite diagnosis based on either the diagnostic imaging or operative findings[13]. Such lesions may thus often be preoperatively diagnosed as carcinoma, or when unexpectedly encountered during an elective cholecystectomy they may also be mistaken for carcinoma[6,14]. Therefore, in order to avoid any excessive and unnecessary surgery, intraoperative frozen-sections or a fine-needle aspiration biopsy is thus recommended in such cases with the findings of a comet-like echo on US and/or an intramural low attenuation area on CT[15,16].

The association between XGC and carcinoma of the gallbladder has been described in previous reports[5, 17, 18]. However, this association remains controversial. It is generally accepted that many years are required for the development of carcinoma, whereas XGC can develop in only a few months. Therefore, in patients with XGC concomitant with carcinoma, it is naturally accepted that carcinoma is a prerequisite and not a consequence of XGC. Actually, the acute inflammation is superimposed on carcinoma of the gallbladder. Therefore, carcinoma theoretically precedes, not follows, XGC. The clinical frequency of carcinoma of the gallbladder with superimposed acute cholecystitis also tends to support this conclusion. In clinical practice, care should be taken not to overlook carcinoma of the gallbladder or overestimate on the stage of the tumor due to the presence of XGC.

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