Original Article

Is Final Histopathological Examination the Only Diagnostic Criteria for Xanthogranulomatous Cholecystitis?

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Abstract

Background: Xanthogranulomatous cholecystitis (XGC) is an uncommon inflammatory disease of gallbladder (GB) and can mimic GB cancer in extensive form. This study aims to assess the predictability of XGC on the basis of clinical presentation, laboratory tests, and radiological or intraoperative findings on frozen section analysis. **Materials and Methods:** This is a retrospective study, conducted over a period of 4 years from October 2013 to November 2017. In this study, all patients with histopathological reports of XGC, who underwent cholecystectomy or a radical cholecystectomy, were included. Clinical records of these patients were reviewed for clinical features, laboratory tests, and findings on radiological imaging. **Results:** Out of 700 consecutive cholecystectomies reviewed, 34 had histologically proven XGC (4.85%). Two patients had simultaneous presence of GB carcinoma with XGC. The most common presenting symptoms were right upper quadrant pain in 32 (94%) patients, jaundice in 9 (36%) patients, and fever in 5 (14%) patients. The most common radiological finding was cholelithiasis in 85.2% of cases. Thick-walled GB was present in 79.4% of patients; irregular wall thickening was present in 20.5% of patients. Intramural nodule was present in two patients, whereas hepatic invasion was observed in 11% and pericholecystic infiltration was present in 8.8% of patients. Regional lymphadenopathy was present in 9 (26.4%) patients. **Conclusion:** Clinical presentation and laboratory parameters were unequivocal due to considerable overlap. Despite recent advances in radiology, none have significant sensitivity and specificity to accurately diagnose XGC preoperatively. Intraoperative frozen section can add to the diagnosis with limited accuracy. The diagnosis of XGC can be confirmed only on histopathological examination.

Keywords: *Carcinoma gall bladder, frozen section, xanthogranulomatous cholecystitis*

Introduction

Xanthogranulomatous cholecystitis (XGC), first described in 1981 by Goodman and Ishak,[1] is characterized by acute or chronic inflammation, abnormal thickening of gallbladder (GB) wall, and severe proliferative fibrosis with formation of multiple yellow-brown intramural nodules.[2] Adjacent organs such as liver, duodenum, colon, and omentum may be involved in this inflammatory process. It is often difficult to differentiate between XGC, chronic cholecystitis, and carcinoma GB clinically as well as on radiological imaging techniques.

GB disease is very common in our clinical practice, with many cases presenting with thick-walled GB (TWGB) or mass in GB. Owing to considerable overlap in clinical presentation and radiological findings, XGC remains a histopathological diagnosis posing significant clinical challenges both in diagnosis and management.

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Thus, this study aims to assess the predictability of XGC on the basis of clinical presentation, laboratory tests, and radiological or intraoperative findings. We would like to elucidate the role of intraoperative frozen section examination in predicting XGC and to rule out malignancy. As a secondary objective, we strive to evolve an optimal approach for patients with TWGB with suspected XGC.

Materials and Methods

This is a retrospective review of prospectively collected data, conducted at a tertiary care center in North India, over a period of 4 years from October 2013 to November 2017.

In this study, all patients with histopathological reports of XGC, who underwent cholecystectomy (laparoscopic or open) or radical cholecystectomy, were included. Clinical records of these patients were reviewed retrospectively for clinical features, laboratory investigations, and findings on radiological imaging. Ultrasonography (USG) abdomen was done as an initial examination in all patients; in case of TWGB or contracted GB with mass lesion, a contrast-enhanced computed tomography (CECT) was done. In patients with jaundice or suspected obstructive biliopathy, a magnetic resonance cholangiopancreatography (MRCP) was also performed.

As protocol, all patients with TWGB underwent staging laparoscopy followed by open cholecystectomy and intraoperative frozen section examination. Patients with GB mass were managed with open cholecystectomy with >2 cm liver wedge resection along with frozen section examination. If the frozen section was suggestive of malignancy, the patient underwent frozen section analysis of interaortocaval lymph node, followed by formal lymphadenopathy.

Follow-up of patients was done after every 3 months for 1 year and then half yearly for 2 years. Clinical examination and an abdominal USG were done to predict disease recurrence or evidence of new pathology.

The work has been reported in line with the STROCSS criteria.[3]

Results

Out of 700 consecutive cholecystectomies reviewed, 34 had histologically proven XGC (4.85%). Two patients had simultaneous presence of gallbladder carcinoma (GBC) with XGC, with an incidence of 5.8% among all cases of XGC. The female: male ratio of the study population was 1:1, with a mean (± standard deviation) age of 54.69 (± 14.24) years (range, 26–90 years). Clinical presentations are summarized in Table 1. The most common presenting symptom was right upper quadrant (RUQ) pain in 32 (94%) patients.

Laboratory findings are summarized in Table 2. Specifically, tumor markers such as carcinoembryonic antigen (CEA) had a mean value of 1.71 ng/L, with no patient having a reading more than the cutoff value of >5 ng/ml. Similarly, median value of serum carbohydrate antigen (CA) 19-9 was 23.26 U/ml, with three patients having values greater than the cutoff of 35.

The most common radiological finding [Table 3] was cholelithiasis in 29 (85.2%) patients, with 21 (61.7%) patients having multiple stones. Eleven patients had cross-sectional imaging CECT and/or magnetic resonance imaging with a suspicion of GBC. Nine patients (26.47%) presented with obstructive jaundice and required a MRCP. Three patients had normal findings, and a dilated common bile duct (CBD) was found in six patients (two with stones and four without stones). Endoscopic retrograde cholangiopancreatography (ERCP) and CBD stone removal were performed in these two patients. One patient was diagnosed with spontaneous GB perforation which was managed with percutaneous drainage followed by delayed interval cholecystectomy.

Table 1: Clinical presentation of cases

Demographic data	*n*
Age (years), mean±SD	54.69±14.24
Gender	
Male	17
Female	17
Male:female	1:1
Simultaneous presence of CaGB with XGC	2 cases
Clinical presentation	
Abdominal pain	32 (94)
Jaundice	9 (36)
Fever	5 (14)
Weight loss	2 (5.8)
RUQ mass	2 (5.8)

SD: Standard deviation, XGC: Xanthogranulomatous cholecystitis, RUQ: Right upper quadrant, CaGB: Carcinoma gallbladder

Table 2: Laboratory findings of cases

Laboratory findings	Values
WBC counts (mean±SD)	9100±4400 cells/cumm
N/L ratio (mean±SD)	4.6±2
Total serum bilirubin (mean±SD)	1.35±2.6 mg/dl
CEA (mean±SD)	1.71±0.96 ng/ml
CA 19-9 (median)	23.26 U/ml

WBC: White blood cell, SD: Standard deviation, CEA: Carcino-embryonic antigen, CA: Carbohydrate antigen, N/L: Neutrophil:lymphocyte ratio

Table 3: Radiological finding (abdominal ultrasonography + contrast enhanced computed tomography abdomen + magnetic resonance imaging abdomen)

Findings	*n* (%)
Gallbladder wall thickening	27 (79.4)
Focal	3 (8.8)
Diffuse	24 (70)
Mucosal line	
Continues	24 (70)
Irregular	7 (20.5)
Intramural nodule	2 (5.58)
Cholelithiasis	29 (85.2)
Single	8 (23.5)
Multiple	21 (61.7)
Hepatic invasion	4 (11)
Pericholecystic infiltration	3 (8.8)
Lymphadenopathy	9 (26.4)
Bile duct dilation	6 (17.6)
GB perforation	1 (2.9)

GB: Gallbladder

Table 4: Surgical management

Procedures	*n* (%)
Laparoscopic cholecystectomy	15 (44.11)
Converted from laparoscopic to open cholecystectomy	7 (20.58)
Open cholecystectomy with intraoperative frozen	5 (14.7)
Open cholecystectomy with 2 cm liver wedge + intraoperative frozen	5 (14.7)
Open cholecystectomy with CBD exploration	1

CBD: Common bile duct

Table 5: Intraoperative findings

Findings	*n* (%)
Empyema	13 (38.23)
Mucocele	2 (5.88)
Choledochoduodenal fistula	1 (2.9)
Contracted GB	6 (17.6)
Mirrizi;s syndrome	2 (5.8)

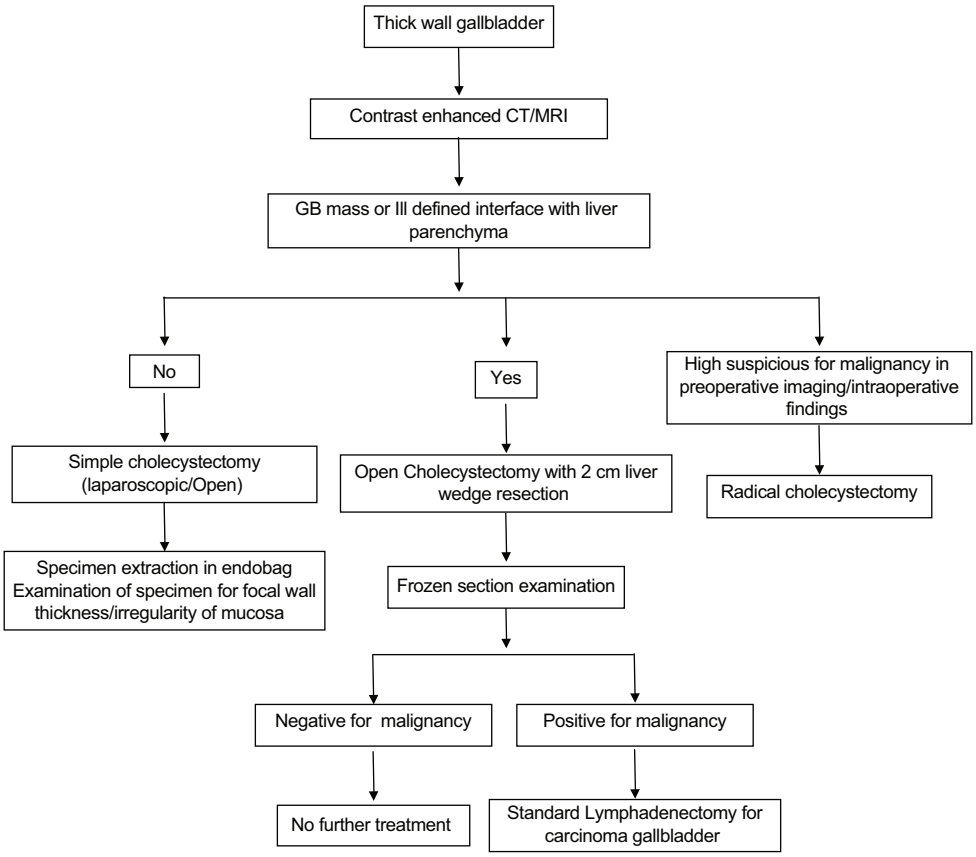
GB: Gallbladder

Laparoscopic cholecystectomy was successfully performed in only 15 (44.11%) patients. Conversion from laparoscopic to open cholecystectomy was done in 7 (20.58%) patients; the cause of conversion was dense adhesion and frozen Calot's triangle in 5 patients. In one patient, choledochoduodenal fistula was the cause of conversion. In one patient, conversion was done due to spontaneous GB perforation with frozen Calot's triangle. In one patient, open cholecystectomy with open CBD exploration was performed because of impacted CBD stone and spontaneous GB perforation. In five patients, an elective open cholecystectomy with intraoperative frozen section of GB was performed due to high index of preoperative suspicion of GBC. Open cholecystectomy with 2-cm liver wedge resection and intraoperative frozen section of specimen was done in five (14.7%) patients because of high preoperative and intraoperative suspicion of malignancy and presence of mass [Table 4]. Intraoperative finding of cases are mentioned in Table 5.

Coexisting XGC and GBC was found in two cases. The first case was a 65-year-old female admitted with a 3-month history of right upper abdominal pain, fever, and jaundice, without any anorexia or weight loss. The initial diagnosis was cholelithiasis and choledocholithiasis. ERCP and CBD clearance and stenting were done in view of cholangitis. CECT examination revealed overdistended GB and ill-defined enhancing polypoidal endophytic lesion measuring approximately 14 mm × 8.6 mm in the anterior body with pericholecystic fat stranding. In view of suspected GBC, the patient underwent open surgery; intraoperative finding revealed conglomerate mass of GB, hepatic flexure of colon and duodenum. An open cholecystectomy with >2 cm liver wedge resection was performed with intraoperative frozen section. This was reported as negative for malignancy and reported as XGC. The final histopathology turned out to be well-differentiated infiltrating adenocarcinoma GB, pT1bNx lesion with coexisting XGC. Further, completion of formal lymphadenectomy was not consented by the patient, and thus is on close follow-up.

The second case was a 66-year-old female admitted with dull-aching pain abdomen in the RUQ with an ill-defined mass. CECT revealed moderate smooth thickening of GB wall with focally effaced pericholecystic planes. There was no definite hepatic infiltration with few mildly enlarged periportal lymph nodes. CEA was 1.63 and CA19-9 was 50.63. The patient underwent open cholecystectomy with >2 cm liver wedge resection and intraoperative frozen section. This was reported as infiltrating adenocarcinoma GB, and a standard lymph node clearance was done. The final histopathological examination reported as moderately differentiated infiltrating adenocarcinoma, T2N1 with clear margin, and coexisting XGC.

In another case, a 61-year-old male admitted with abdominal pain and jaundice, CECT revealed diffuse irregular wall thickening and the lesion was infiltrating the adjacent liver parenchyma with periportal lymphadenopathy. With a suspicion of malignancy, he underwent open chlolecystectomy with >2 cm of liver wedge resection. Frozen section examination was positive for malignancy, and standard lymph node dissection was completed. Interestingly, the final histopathological examination was reported as XGC,



Flow Chart 1: Proposed management algorithm for thickwall gallbladder

which was reviewed at multiple centers. The patient is doing well on follow-up.

In our study, the diagnosis of GBC was missed in one patient on intraoperative frozen section analysis, which was reported as XGC. An intriguing case of false-positive frozen section occurred, when one of our patients was diagnosed as GBC intraoperatively on frozen section examination, and the final histopathology turned out to be XGC.

Discussion

The clinical presentation of XGC is varied; RUQ pain, fever, jaundice, or a mass with or without weight loss. This may overlap with the presentation of other inflammatory condition and malignant pathology. Radiological imaging does not adequately distinguish between the two, with findings ranging from mild wall thickening to extensive pericholecystic inflammation extending to the liver and rarely adjacent organs. Therefore, differentiation between acute and chronic inflammatory processes and localized GB cancer is difficult. In its extensive form with involvement of the liver and adjacent organs, XGC may be impossible to differentiate from malignancy, creating a diagnostic dilemma.

Chronic inflammation and GBC have a high prevalence in North India. Despite recent advances in investigation and therapeutics, GBC has a poor prognosis and overall survival. Only in early GBC is there a possibility of potential cure with good long-term outcomes. On the other hand, XGC is a chronic inflammatory disease and may not require the radical treatment recommended for GBC. In our study, out of the total 700 specimens, only 34 (4.8%) were reported as XGC. This is similar to other series,[4] wherein an overall incidence of 1.3%[5] to 5.5% was reported.[6] The male-to-female ratio was 1:1 in our study. A male preponderance in XGC has been reported in one study.[7] Although females are more affected by gall stone disease, XGC appears to affect both sexes equally.

The clinical presentation in our study was in congruence with reported literature, with common symptom being right hypochondrial pain in 94% of cases. Abdominal pain and fever are nonspecific findings, seen in most inflammatory or neoplastic processes of the biliary system. Bile duct involvement and jaundice have been found to be reliable clinical features to differentiate XGC from GBC in few reports.[8] However, in other series, no significant difference was found.[4] Weight loss and RUQ mass more commonly indicate neoplastic

disease; two cases in our review had presented as such. Therefore, clinical presentation is unequivocal in most cases, and accurate prediction of XGC cannot be done solely on the same.

Serum tumor markers also have a nonspecific role with regard to diagnosis in XGC. In our study, four cases of XGC had raised CA19-9, whereas none had raised CEA levels. A previous report had concluded that serum CA19-9 can be elevated in XGC, albeit an inflammatory condition.[9] Two other similar studies[6,10] reported the unreliability of serum tumor marker levels in preempting the diagnosis of XGC.

Radiological findings (USG and CT) have been reliable in distinguishing XGC from GBC. One series reported that thickening, hypoechoic nodules and bands in the GB wall, pericholecystic fluid collection, and presence of gallstones on ultrasound were indicators of XGC. Hypoechoic bands, due to the presence of foamy histiocytes in GB wall, have been reported to be a characteristic feature of XGC.[5] In our study, only two (5.58%) patients had findings suggestive of hypoechoic intramural nodules. Gall stones were associated with 85.2% cases of XGC in our study, similar to the incidence of 75%–90% in GBC patients in different series.[11]

One study reported that presence of continuous mucosal line enhancement on CT is a reliable finding in XGC.[7] This was present in nearly 70% of our cases. This finding may be explained by the inflammatory process predominantly affecting GB wall, while the overlying mucosal line is usually intact. This may not be true for extensive disease with destructive fibrosis. Other studies have reported the combined ultrasound findings of diffuse wall thickening and intramural nodule formation to be highly suggestive of XGC.[12] In our study, we found diffuse wall thickening in 70% and focal thickening in 8.8% of cases, suggesting that diffuse wall thickening is commonly associated but not specific to XGC.

Liver infiltration is usually a feature of neoplastic disease, and absence of hepatic invasion was reported to be diagnostic of XGC.[4] However, in the present study, liver infiltration was seen in 11% of cases. In addition, lymphadenopathy was present in 26.4% and pericholecystic infiltration was present in 8.8% of cases. Hepatic invasion and lymphadenopathy can be helpful to rule out early cases of XGC, but the same is not true for extensive disease.

Recently, fluorodeoxyglucose-positron emission tomography (FDG-PET) has also been found to be useful in differentiating XGC from GBC in few reports,[13] while other studies have not found it useful.[14] XGC shows a positive image due to FDG uptake by active inflammatory cells.[15] In two of our cases with TWGB, FDG-PET which was reported as carcinoma GB with SUV_{max} 9 but on final histopathological examination, the diagnosis of XGC was confirmed.

In the present study, coexisting XGC and GBC was found in two cases. Interestingly, in different studies, the incidence of coexisting XGC and GBC was reported between 5% and 12.5%.[16] XGC can be seen as a small focus in a background of malignancy, or vice versa; in a diffuse background of XGC, there can be a small focus of malignancy.

Frozen section analysis is an important tool for diagnosis, but can be falsely negative in cases of coexistent malignancy. In our study, the diagnosis of GBC was missed in one patient, which was reported as XGC on intraoperative frozen section analysis. Other studies also reported similar fallacies of frozen section.[3,6] An intriguing case of false-positive frozen section occurred, when one of our patients was diagnosed as GBC intra operatively on frozen section examination, and final histopathology turned out to be XGC. Thus, it can be concluded that frozen section examination is helpful in the diagnosis of XGC. However, in cases of coexisting GBC and due to high risk of false negative, final diagnosis is confirmed on histopathological examination.

There exists confusion and dilemma regarding the adequate surgical management of XGC. On one hand, where radical surgery increases morbidity and has a risk of mortality; a more conservative approach has the risk of being oncologically inadequate. We follow a standard protocol for the management of such patients with thick walled gall bladder. If preoperative imaging shows no evidence of mass with well defined interface with liver parenchyma and no lymphadenopathy, a simple cholecystectomy is performed. The choice of laparoscopy versus open procedure is decided by grade of inflammation and fibrosis at calot's triangle. In case of laparoscopic cholecystectomy, specimen is extracted in endobag to minimize spillage. The cut surface of GB specimen is examined for suspicious lesions, in which case, frozen section examination is done to rule out unapparent GBC.

If there is focal GB mass with liver infiltration, an open cholecystectomy with >2 cm of liver wedge resection and frozen section examination of the specimen is done. In case frozen section examination is positive for malignancy, standard lymphadenectomy is performed. If there is high suspicion of malignancy on preoperative finding and intraoperative examination a radical

cholecystectomy with standard lymphadenectomy will be the procedure of choice [Flow Chart 1].

GB cancer has high prevalence in the gangetic belt of Northern India; thick walled and focal mass in gall bladder are common presentations requiring adequate management. In the presence of dense inflammation, XGC is difficult to diagnose and distinguish from GBC on pre-and intra-operative findings. Intra-operative frozen section may also be misleading. Localized early GBC have better prognosis and survival, only when managed radically. Thus, in cases of co-existing XGC and GBC, final diagnosis and management depends on histopathology. Owing to an undetermined management protocol, and preoperative and intra-operative dilemma, it is safe to err towards radicality; especially in the tertiary care setting, where such procedures can be performed with limited morbidity and mortality.

Conclusion

XGC still is a diagnostic dilemma as it can mimic acute or chronic cholecystitis as well as GBC. Clinical presentation and laboratory parameters are unequivocal due to considerable overlap. Despite recent advances in radiology like triphasic CECT and PET scan, none have significant sensitivity and specificity to accurately diagnose XGC preoperatively. Intraoperative frozen section can add to the diagnosis and can differentiate XGC from GBC, with limited accuracy. The diagnosis of XGC can be confirmed only on histopathological examination. The recommended algorithm for management of XGC is described, and requires external validation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Goodman ZD, Ishak KG. Xanthogranulomatous cholecystitis. Am J Surg Pathol 1981;5:653-9.
2. Benbow EW. Xanthogranulomatous cholecystitis. Br J Surg 1990;77:255-6.
3. Agha RA, Borrelli MR, Vella-Baldacchino M, Thavayogan R, Orgill DP. The STROCSS statement: Strengthening the Reporting of Cohort studies in Surgery. Int J Surg 2017;46:198-202.
4. Agarwal AK, Kalayarasan R, Javed A, Sakhuja P. Mass-forming xanthogranulomatous cholecystitis masquerading as gallbladder cancer. J Gastrointest Surg 2013;17:1257-64.
5. Parra JA, Acinas O, Bueno J, Güezmes A, Fernández MA, Fariñas MC. Xanthogranulomatous cholecystitis: Clinical, sonographic, and CT findings in 26 patients. AJR Am J Roentgenol 2000;174:979-83.
6. Yoshida J, Chijiiwa K, Shimura H, Yamaguchi K, Kinukawa N, Honda H, *et al.* Xanthogranulomatous cholecystitis versus gallbladder cancer: Clinical differentiating factors. Am Surg 1997;63:367-71.
7. Rao RV, Kumar A, Sikora SS, Saxena R, Kapoor VK. Xanthogranulomatous cholecystitis: Differentiation from associated gall bladder carcinoma. Trop Gastroenterol 2005;26:31-3.
8. Guermazi A. Are there other imaging features to differentiate xanthogranulomatous cholecystitis from gallbladder carcinoma? Eur Radiol 2005;15:1271-2.
9. Clarke T, Matsuoka L, Jabbour N, Mateo R, Genyk Y, Selby R, *et al.* Gallbladder mass with a carbohydrate antigen 19-9 level in the thousands: Malignant or benign pathology? Report of a case. Surg Today 2007;37:342-4.
10. Adachi Y, Iso Y, Moriyama M, Kasai T, Hashimoto H. Increased serum CA19-9 in patients with xanthogranulomatous cholecystitis. Hepatogastroenterology 1998;45:77-80.
11. Serra I, Diehl AK. Number and size of stones in patients with asymptomatic and symptomatic gallstones and gallbladder carcinoma. J Gastrointest Surg 2002;6:272-3.
12. Kim PN, Lee SH, Gong GY, Kim JG, Ha HK, Lee YJ, *et al.* Xanthogranulomatous cholecystitis: Radiologic findings with histologic correlation that focuses on intramural nodules. AJR Am J Roentgenol 1999;172:949-53.
13. Oe A, Kawabe J, Torii K, Kawamura E, Higashiyama S, Kotani J, *et al.* Distinguishing benign from malignant gallbladder wall thickening using FDG-PET. Ann Nucl Med 2006;20:699-703.
14. Makino I, Yamaguchi T, Sato N, Yasui T, Kita I. Xanthogranulomatous cholecystitis mimicking gallbladder carcinoma with a false-positive result on fluorodeoxyglucose PET. World J Gastroenterol 2009;15:3691-3.
15. Anderson CD, Rice MH, Pinson CW, Chapman WC, Chari RS, Delbeke D. Fluorodeoxyglucose PET imaging in the evaluation of gallbladder carcinoma and cholangiocarcinoma. J Gastrointest Surg 2004;8:90-7.
16. Kwon AH, Sakaida N. Simultaneous presence of xanthogranulomatous cholecystitis and gallbladder cancer. J Gastroenterol 2007;42:703-4.