Int Surg 2013;**98:**372–378
DOI: 10.9738/INTSURG-D-13-00092.1

Case Report

Expression of GLUT-1 and GLUT-3 in Xanthogranulomatous Cholecystitis Induced a Positive Result on ^{18}F-FDG PET: Report of a Case

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Although several reports have revealed that fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is useful for differentiating between benign and malignant lesions in the gallbladder, the positive results of ^{18}F-FDG PET are not specific for malignancy because ^{18}F-FDG is also accumulated in inflammatory lesions. It is known that the most important pathway for ^{18}F-FDG to enter the cell body is mediated by the facilitative glucose transporter-1 (GLUT-1) through GLUT-3. We herein present a case of xanthogranulomatous cholecystitis (XGC) with a positive result on ^{18}F-FDG PET. In this case, GLUT-1 and GLUT-3 were both positively expressed in inflammatory cells at the gallbladder wall of XGC and this is the first report to reveal GLUT expression in XGC. This report reveals that surgeons should carefully consider the appropriate treatment of gallbladder tumor, even with a positive result on ^{18}F-FDG PET.

Key words: Xanthogranulomatous cholecystitis – Fluorine-18 fluorodeoxyglucose positron emission tomography – GLUTs

Xanthogranulomatous cholecystitis (XGC) is an uncommon inflammatory disease of the gallbladder and is characterized by marked proliferative fibrosis, macrophage infiltration, and foam cells involving the wall of the gallbladder.[1] Despite recent advances in imaging techniques of ultrasonography

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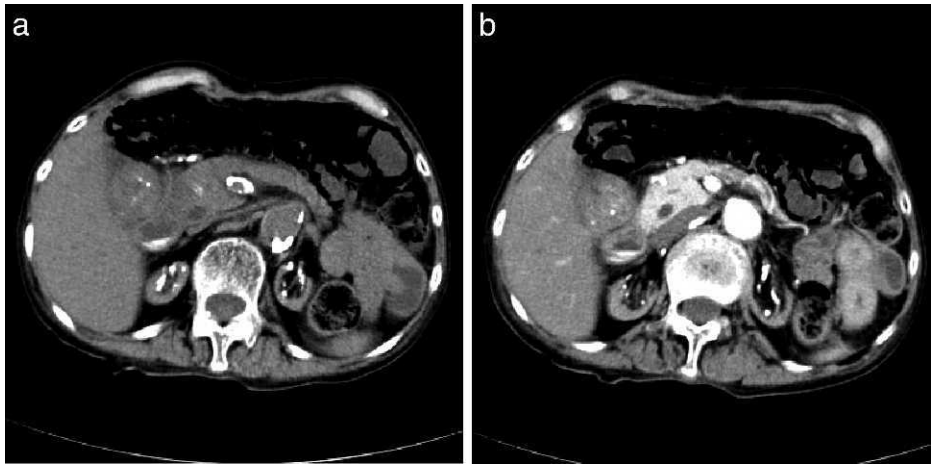

Fig. 1 Plain computed tomography revealed irregular thickening of the whole wall of the gallbladder from body to bottom with tiny gallstones (a). The thickened wall was slightly enhanced by contrast medium (b).

(US), computed tomography (CT), and magnetic resonance imaging (MRI), it is still quite difficult to distinguish XGC from gallbladder carcinoma preoperatively.[2,3] Although several reports have revealed that fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is useful for differentiating between benign and malignant lesions of the gallbladder,[4–8] ^{18}F-FDG is not only accumulated in malignant lesions but also in inflammatory lesions with glucose metabolism and therefore a positive result on ^{18}F-FDG PET is not specific to malignant lesions.[9] It was reported previously that the most important pathway for ^{18}F-FDG to enter the cell body of almost all human cells is mediated by the facultative glucose transporter-1 (GLUT-1) through GLUT-3.[10]

We here report a case of XGC mimicking gallbladder carcinoma with a false-positive result on ^{18}F-FDG PET. This is the first report to reveal the correlation between ^{18}F-FDG PET and GLUT expression in XGC.

Case Report

A 67-year-old Japanese woman receiving treatment for renal dysfunction after kidney transplantation because of chronic glomerulonephritis developed right upper abdominal pain. Her laboratory data showed anemia (red blood cell count: $309 \times 10^4/\mu L$; normal 364–471 $\times$ $10^4/\mu L$, hemoglobin: 8.8 g/dL; 10.8–14.6 g/dL, hematocrit: 26.6%; 33.3%–44.1%), a decreased serum level of total protein: 4.3 g/dL; 6.7–8.3 g/dL and albumin: 2.0 g/dL; 4.0–5.0 g/dL, and an increased serum level of C-reactive protein: 0.63 mg/dL; –0.29 mg/dL. Tumor markers including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were elevated, 6.9 ng/mL (–3.4 ng/mL) and 70 U/mL (–37 U/mL), respectively. CT scan revealed irregular thickening of the whole wall of the gallbladder from the body to bottom with enhancement by contrast medium, and tiny gallstones (Figs. 1a and 1b). Endoscopic ultrasonography (EUS) also showed irregular thickening of the gallbladder wall with an acoustic shadow inside the bottom of the gallbladder, and the border between the gallbladder and liver was unclear in some areas (Fig. 2). ^{18}F-FDG PET revealed a focal hot lesion [standardized uptake value (SUV) = 5.15] at the same site of the tumorous lesion of the gallbladder on CT (Fig. 3). We suspected the lesion preoperatively to be a gallbladder carcinoma with direct invasion to the gallbladder liver bed and planned to perform gallbladder liver bed resection, extrahepatic bile duct resection and regional lymph node dissection. At surgery the gallbladder tumor was located mainly at the fundus without serosa invasion, and gallbladder liver bed infiltration was not observed on intraoperative US examination. According to our decision against gallbladder tumor, for which we could not completely exclude carcinoma, we performed all-layer cholecystectomy and placed the great omentum over the gallbladder liver bed. A frozen section of the cut end of the cystic duct showed no malignancy. Macroscopic examination of the resected specimen demonstrated no obvious tumor on the mucosa surface, and the gallbladder wall from the body to bottom was thickened with tiny black stones and yellowish

tumors located between the serosa and mucosa (Fig. 4a). Histopathologic examination revealed transmural infiltration of histiocytes, neutrophils, plasmocytes, and lymphocytes with proliferative fibrosis and Rokitansky–Aschoff sinuses (Figs. 4b and 4c). The expression of CA19-9 (mouse monoclonal, 1116-NS-19-9; Dako, Glostrup, Denmark; diluted 1:50) was shown in the epithelial cells of the gallbladder by immunohistochemical staining (Fig. 4d). We also carried out immunohistochemical staining to investigate GLUT-1 (rabbit polyclonal, prediluted; ab15310; Abcam, Cambridge, UK; no dilution) and GLUT-3 (rabbit polyclonal, E3270; Spring Bioscience, California, USA; diluted 1:50) expression in the resected specimen. As shown in Fig. 5, GLUT-1 and GLUT-3 were both positively expressed in inflammatory cells. The postoperative course was uneventful and the patient was discharged on postoperative day 11. She is now in good health 2 years after surgery.

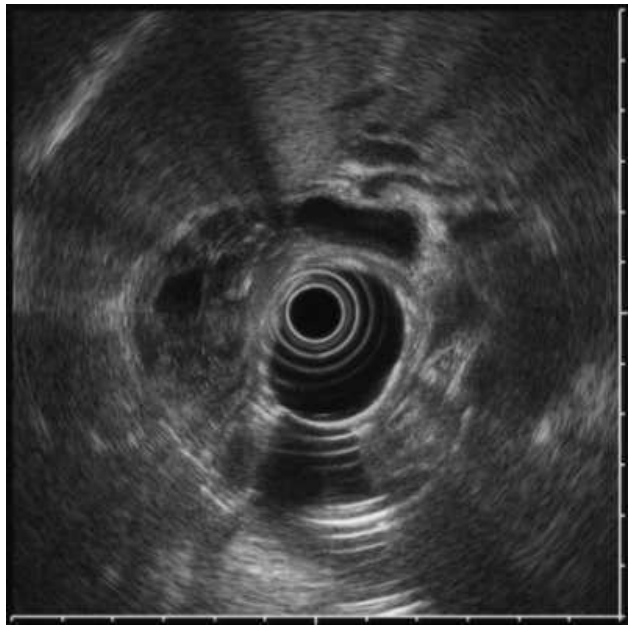

Fig. 2 Endoscopic ultrasonography showed irregular thickening of the gallbladder wall with an acoustic shadow inside. The border between the gallbladder and liver was unclear in some areas.

Discussion

The entity of XGC was first described by Christensen and Ishak in 1970[11] and the name XGC was first reported by McCoy *et al* in 1976.[12] The etiology of XGC is still unknown; however, it is thought that XGC results due to an inflammatory process and a granulomatous reaction followed by the extravasation of bile into the gallbladder wall through the broken Rokitansky–Aschoff sinus or ulcer lesions due to gallbladder stones, acute inflammation, or both.[13,14] As the disease progresses with lesion expansion, fibrous tissue hyperplasia forms, causing inflammatory granuloma, which leads to gallbladder wall thickening and adhesion with or infiltration to the liver, omentum, duodenum, and colon.[12,14]

Although XGC is unusual and accounts for 0.7%–13.2% of all cholecystitis cases,[15,16] it has attracted attention recently because it is often misdiagnosed as gallbladder carcinoma. It was previously reported that CT findings of XGC were intramural hypoattenuated nodules with a mucosal line in the gallbladder wall,[17,18] a soft tissue mass in the region of the gallbladder,[19] a gallbladder with an irregular, sometimes lobulated, greatly thickened wall,[20] and poorly defined borders of the underlying liver and/or the adjacent organs.[16,21] B-mode ultrasonography showed hypo-echoic nodules and a low-level echo band that are the most characteristic features of XGC;[17] however, these findings mimic carcinoma in most cases and in fact, in our case, we could not exclude the irregular thickened wall from being malignant. Kang *et al* recently revealed the benefit of diffusion-weighted magnetic resonance imaging (DWI) in differentiating XGC from the wall-thickening type of gallbladder cancer. The addition of DWI to conventional MRI improves discrimination and its sensitivity and specificity in gallbladder carcinoma are 79%–86% and 94.7%, respectively.[22] DWI might be the main imaging technique to distinguish XGC from gallbladder carcinoma.

Recently it has been reported that ^{18}F-FDG PET is useful in the differential diagnosis of gallbladder carcinoma and its sensitivity in gallbladder carcinoma was 75%–78% and specificity was 82%–100%.[4–8] It has long been recognized that cancer cells have an increased rate of glucose metabolism compared with benign cells[23] and ^{18}F-FDG accumulation is thought to be due to enhanced exogenous glucose utilization in the tumor lesion.[24] The GLUT family plays a role in ^{18}F-FDG accumulation and, in particular, GLUT-1 and GLUT-3 have been suggested to show a strong correlation between their expression level and the degree of ^{18}F-FDG accumulation in several cancers;[25,26] however, ^{18}F-FDG is not specific to malignant lesions and can accumulate in inflammatory lesions with increased glucose metabolism. The molecular basis of ^{18}F-FDG uptake in white blood cells (WBCs) of granulation tissue and granulomas

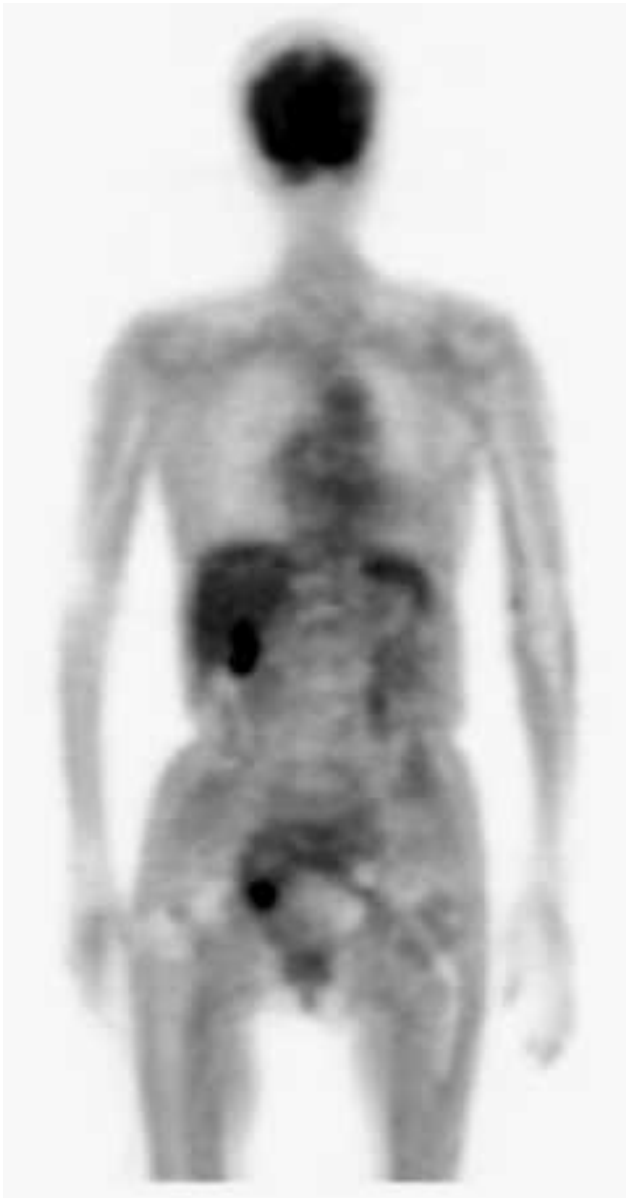

Fig. 3 ^{18}F-FDG-PET revealed a focal hot lesion (SUV = 5.15) at the same site of the tumorous lesion of the gallbladder on CT.

exhibits similarities to the metabolism of ^{18}F-FDG in tumors. It is already known that GLUT-1 together with GLUT-3 is the most important isotype for understanding ^{18}F-FDG uptake in WBCs.[9]

Although several authors have previously reported XGC mimicking gallbladder carcinoma with a false-positive result on ^{18}F-FDG PET,[27,28] no correlative clinical report has been revealed between ^{18}F-FDG accumulation and the immunohistochemical expression of GLUTs in the resected XGC specimens. In our case, GLUT-1 and GLUT-3 were both positively expressed in inflammatory cells in the XGC gallbladder wall where ^{18}F-FDG was accumulated on PET examination. This is the first report to reveal the correlation between ^{18}F-FDG PET and GLUTs expression in XGC.

It was previously reported that an elevated serum level of CA19-9, a glycoprotein antigen tumor marker, has some suggestive value for differentiating gallbladder carcinoma from benign tumor,[3,29] whereas other authors revealed that it could not be easily diagnosed as gallbladder carcinoma based on elevated serum CA19-9 and 44% of patients with XGC had high serum CA19-9.[30] In our case, serum CA19-9 was high and immunohistochemical staining showed the positive expression of CA19-9 in epithelial cells at the gallbladder wall. These results suggest that CA19-9 was expressed not only in carcinoma cells but also in epithelial cells at the gallbladder wall with XGC, and these expressions influenced the serum CA19-9 level.

It was previously suggested that XGC was more strongly associated with gallbladder carcinoma than with ordinary chronic cholecystitis/cholelithiasis because the incidence of XGC in neoplasm-free gallbladder was 1.8%, contrasting with the incidence of 8.6% in carcinomatous gallbladder. This association is thought to be due to structural changes in the cells brought on by the chronic inflammatory process.[31] Recently, Zhuang *et al* revealed that XGC is an uncommon inflammatory condition distinct from cholecystitis and may be associated with the precancerous nature of gallbladder carcinoma because of its upregulated oncogenes, BCL-2 and c-Myc, and increased number of macrophages.[32] However, no relationship has been demonstrated in the literature,[15,33] and the association of XGC and gallbladder cancer is controversial and remains a matter of discussion. In our case, carcinoma did not coexist in the gallbladder with XGC and we performed an all-layer cholecystectomy and placed the great omentum over the gallbladder liver bed to prevent peritoneal dissemination of cancer cells in case of malignancy because we could not completely exclude carcinoma preoperatively. We should be aware that xanthogranulomatous inflammation and carcinoma are sometimes mixed and, therefore, if XGC is suspected, all-layer cholecystectomy should be performed.[34]

In conclusion, we have reported a case of XGC mimicking gallbladder carcinoma with a false-positive result on ^{18}F-FDG PET and serum CA19-9. In our case, GLUT-1 and GLUT-3, which play roles

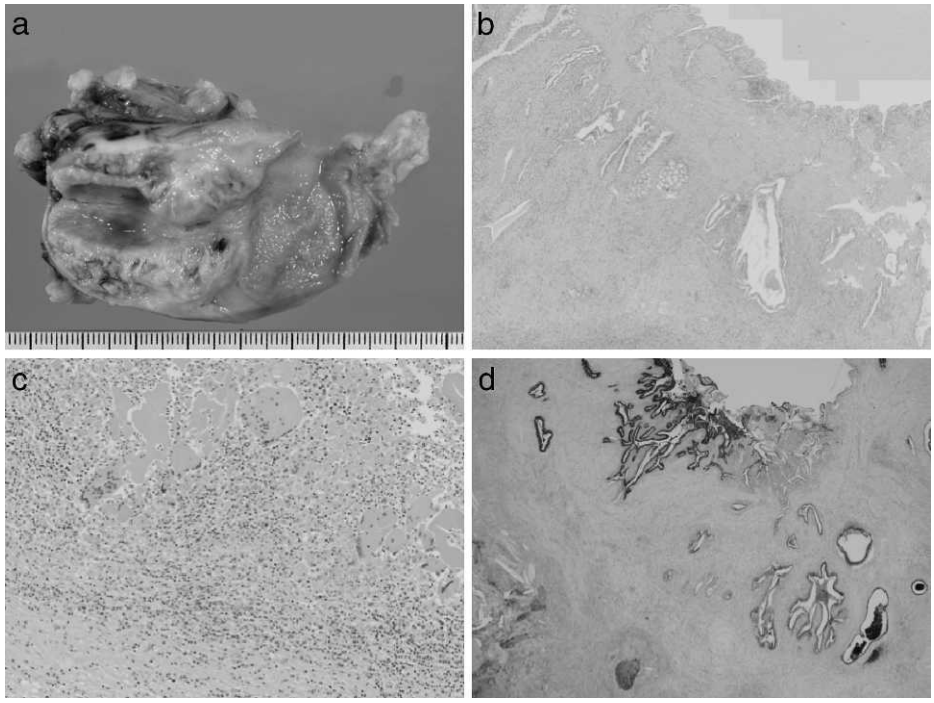

Fig. 4 Thickened gallbladder wall was observed macroscopically. Inside of the wall, black stones and yellowish tumors were located between the serosa and mucosa (a). Histopathologic examination revealed transmural infiltration of histiocytes, neutrophils, plasmocytes, and lymphocytes with proliferative fibrosis and Rokitansky-Aschoff sinuses (H.E. b × 40, c × 100). CA19-9 was expressed in epithelial cells of the gallbladder by immunohistochemical staining (d × 40).

in ^{18}F-FDG accumulation, were both positively expressed in inflammatory cells at the gallbladder wall of XGC and this is the first report to reveal GLUTs expression in XGC. It is quite difficult preoperatively to differentiate XGC from carcinoma even with several precise examinations, such as MDCT, MRI, and ^{18}F-FDG PET; therefore, surgeons should carefully consider the appropriate treatment in all cases of gallbladder tumor.

Acknowledgments

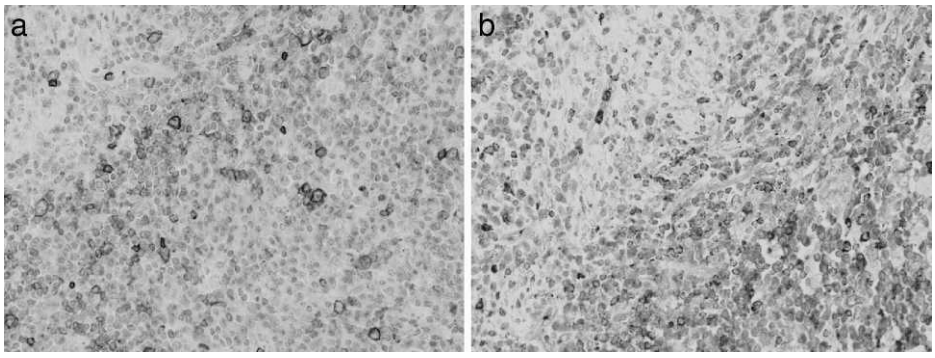

Fig. 5 Immunohistochemical staining of GLUT-1 (a × 200) and GLUT-3 (b × 200) was positive in inflammatory cells.

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