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

Shigeaki Sawada, Yutaka Shimada, Shinichi Sekine, Kazuto Shibuya, Isaku Yoshioka, Koshi Matsui, Tomoyuki Okumura, Toru Yoshida, Takuya Nagata, Hideyuki Uotani, Kazuhiro Tsukada

Department of Surgery and Science, Graduate School of Medicine and Pharmaceutical Sciences for Research, University of Toyama, Toyama, Japan

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

Corresponding author: Shigeaki Sawada, Department of Surgery and Science, Graduate School of Medicine and Pharmaceutical Science for Research, University of Toyama, 2630 Sugitani, Toyama, 930-0194, Japan.
Tel.: +81 76 434 7331; Fax: +81 76 434 5043; E-mail: sawadas@med.u-toyama.ac.jp

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 (¹⁸F-FDG PET) is useful for differentiating between benign and malignant lesions of the gallbladder,^{4–8} ¹⁸F-FDG is not only accumulated in malignant lesions but also in inflammatory lesions with glucose metabolism and therefore a positive result on ¹⁸F-FDG PET is not specific to malignant lesions.⁹ It was reported previously that the most important pathway for ¹⁸F-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 ¹⁸F-FDG PET. This is the first report to reveal the correlation between ¹⁸F-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: $309 \times 10^4/\mu\text{L}$; normal $364\text{--}471 \times 10^4/\mu\text{L}$, 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). ¹⁸F-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.

Discussion

The entity of XGC was first described by Christensen and Ishak in 1970¹¹ 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 hypo-attenuated 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

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.

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 ¹⁸F-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 cells²³ and ¹⁸F-FDG accumulation is thought to be due to enhanced exogenous glucose utilization in the tumor lesion.²⁴ The GLUT family plays a role in ¹⁸F-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 ¹⁸F-FDG accumulation in several cancers;^{25,26} however, ¹⁸F-FDG is not specific to malignant lesions and can accumulate in inflammatory lesions with increased glucose metabolism. The molecular basis of ¹⁸F-FDG uptake in white blood cells (WBCs) of granulation tissue and granulomas

Fig. 3 ¹⁸F-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 ¹⁸F-FDG in tumors. It is already known that GLUT-1 together with GLUT-3 is the most important isotype for understanding ¹⁸F-FDG uptake in WBCs.⁹

Although several authors have previously reported XGC mimicking gallbladder carcinoma with a false-positive result on ¹⁸F-FDG PET,^{27,28} no correlative clinical report has been revealed between ¹⁸F-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 ¹⁸F-FDG was accumulated on PET examination. This is the first report to reveal the correlation between ¹⁸F-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 ¹⁸F-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 transmurular infiltration of histiocytes, neutrophils, plasmocytes, and lymphocytes with proliferative fibrosis and Rokitansky-Aschoff sinuses (H.E. b $\times$ 40, c $\times$ 100). CA19-9 was expressed in epithelial cells of the gallbladder by immunohistochemical staining (d $\times$ 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

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is noncommercial and is otherwise in compliance with the license. Non-commercial License, which permits

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

use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is noncommercial and is otherwise in compliance with the license³⁵.

References

1. Kwon AH, Matsui Y, Uemura Y. Surgical procedures and histopathologic findings for patients with xanthogranulomatous cholecystitis. *J Am Coll Surg* 2004;**199**(2):204–210
2. Spinelli A, Schumacher G, Pascher A, Lopez-Hanninen E, Al-Abadi H, Benckert C *et al*. Extended surgical resection for xanthogranulomatous cholecystitis mimicking advanced gallbladder carcinoma: a case report and review of literature. *World J Gastroenterol* 2006;**12**(14):2293–2296
3. Enomoto T, Todoroki T, Koike N, Kawamoto T, Matsumoto H. Xanthogranulomatous cholecystitis mimicking stage IV gallbladder cancer. *Hepatogastroenterology* 2003;**50**(53):1255–1258
4. Koh T, Taniguchi H, Yamaguchi A, Kunishima S, Yamagishi H. Differential diagnosis of gallbladder cancer using positron emission tomography with fluorine-18-labeled fluoro-deoxy-glucose (FDG-PET). *J Surg Oncol* 2003;**84**(2):74–81
5. Rodriguez-Fernandez A, Gomez-Rio M, Llamas-Elvira JM, Ortega-Lozano S, Ferron-Orihuela JA, Ramia-Angel JM *et al*. Positron-emission tomography with fluorine-18-fluoro-2-deoxy-D-glucose for gallbladder cancer diagnosis. *Am J Surg* 2004;**188**(2):171–175
6. 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**(1):90–97
7. 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**(10):699–703
8. Petrowsky H, Wildbrett P, Husarik DB, Hany TF, Tam S, Jochum W *et al*. Impact of integrated positron emission tomography and computed tomography on staging and management of gallbladder cancer and cholangiocarcinoma. *J Hepatol* 2006;**45**(1):43–50
9. Meller J, Sahlmann CO, Scheel AK. 18F-FDG PET and PET/CT in fever of unknown origin. *J Nucl Med* 2007;**48**(1):35–45
10. Shepherd PR, Kahn BB. Glucose transporters and insulin action: implications for insulin resistance and diabetes mellitus. *N Engl J Med* 1999;**341**(4):248–257
11. Christensen AH, Ishak KG. Benign tumors and pseudotumors of the gallbladder: report of 180 cases. *Arch Pathol* 1970;**90**(5):423–432
12. McCoy JJ, Vila R, Petrossian G, McCall RA, Reddy KS. Xanthogranulomatous cholecystitis. Report of two cases. *J S C Med Assoc* 1976;**72**(3):78–79
13. Benbow EW. Xanthogranulomatous cholecystitis. *Br J Surg* 1990;**77**(3):255–256
14. Guzman-Valdivia G. Xanthogranulomatous cholecystitis: 15 years' experience. *World J Surg* 2004;**28**(3):254–257
15. Guzman-Valdivia G. Xanthogranulomatous cholecystitis in laparoscopic surgery. *J Gastrointest Surg* 2005;**9**(4):494–497
16. Casas D, Perez-Andres R, Jimenez JA, Mariscal A, Cuadras P, Salas M *et al*. Xanthogranulomatous cholecystitis: a radiological study of 12 cases and a review of the literature. *Abdom Imaging* 1996;**21**(5):456–460
17. Parra JA, Acinas O, Bueno J, Guezmes A, Fernandez MA, Farinas MC. Xanthogranulomatous cholecystitis: clinical, sonographic, and CT findings in 26 patients. *Am J Roentgenol* 2000;**174**(4):979–983
18. Uchiyama K, Ozawa S, Ueno M, Hayami S, Hirono S, Ina S *et al*. Xanthogranulomatous cholecystitis: the use of preoperative CT findings to differentiate it from gallbladder carcinoma. *J Hepatobiliary Pancreat Surg* 2009;**16**(3):333–338
19. Cossi AF, Scholz FJ, Aretz HT, Larsen CR. Computed tomography of xanthogranulomatous cholecystitis. *Gastrointest Radiol* 1987;**12**(2):154–155
20. Houston JP, Collins MC, Cameron I, Reed MW, Parsons MA, Roberts KM. Xanthogranulomatous cholecystitis. *Br J Surg* 1994;**81**(7):1030–1032
21. Hanada K, Nakata H, Nakayama T, Tsukamoto Y, Terashima H, Kuroda Y *et al*. Radiologic findings in xanthogranulomatous cholecystitis. *AJR Am J Roentgenol* 1987;**148**(4):727–730
22. Kang TW, Kim SH, Park HJ, Lim S, Jang KM, Choi D *et al*. Differentiating xanthogranulomatous cholecystitis from wall-thickening type of gallbladder cancer: added value of diffusion-weighted MRI. *Clin Radiol* 2013 Apr 25, pii: S0009-9260(13)00130-X. doi:10.1016/j.crad.2013.03.022. [Epub ahead of print]
23. Warburg O. On the origin of cancer cells. *Science* 1956:309–314
24. Yonekura Y, Benua RS, Brill AB, Som P, Yeh SD, Kemeny NE *et al*. Increased accumulation of 2-deoxy-2-[18F]Fluoro-D-glucose in liver metastases from colon carcinoma. *J Nucl Med* 1982;**23**(12):1133–1137
25. Younes M, Brown RW, Stephenson M, Gondo M, Cagle PT. Overexpression of Glut 1 and Glut 3 in stage I non-small cell lung carcinoma is associated with poor survival. *Cancer* 1997;**80**(6):1046–1051
26. Higashi T, Tamaki N, Honda T, Torizuka T, Kimura T, Inokuma T *et al*. Expression of glucose transporters in human pancreatic tumors compared with increased FDG accumulation in PET study. *J Nucl Med* 1997;**38**(9):1337–1344
27. 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**(29):3691–3693
28. Mori A, Doi R, Yonenaga Y, Nakabo S, Yazumi S, Nakaya J *et al*. Xanthogranulomatous cholecystitis complicated with primary sclerosing cholangitis: report of a case. *Surg Today* 2010;**40**(8):777–782

29. Shukla VK, Gurubachan, Sharma D, Dixit VK, Usha. Diagnostic value of serum CA242, CA19-9, CA15-3, and CA125 in patient with carcinoma of gallbladder. *Trop Gastroenterol* 2006; **27**(4):160–165
30. Han SH, Chen YL. Diagnosis and treatment of xanthogranulomatous cholecystitis: a report of 39 cases. *Cell Biochem Biophys* 2012; **64**(2):131–135
31. Benbow EW. Xanthogranulomatous cholecystitis associated with carcinoma of the gallbladder. *Postgrad Med J* 1989; **65**(766): 528–531.
32. Zhuang PY, Zhu MJ, Wang JD, Zhou XP, Quan ZW, Shen J. Xanthogranulomatous cholecystitis: a clinicopathological study of its association with gallbladder carcinoma. *J Dig Dis* 2013; **14**(1):45–50
33. Dixit VK, Prakash A, Gupta A, Pandey M, Gautam A, Kumar M *et al.* Xanthogranulomatous cholecystitis. *Dig Dis Sci* 1998; **43**(5):940–942
34. Kwon AH, Sakaida N. Simultaneous presence of xanthogranulomatous cholecystitis and gallbladder cancer. *J Gastroenterol* 2007; **42**(8):703–704