Tubular adenoma of the common bile duct with uptake in ^{18}F-FDG PET: A case report

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Abstract. A 64-year-old man presented with epigastric discomfort and nausea. Laboratory analyses revealed increased levels of total and direct bilirubin, and increased levels of aminotransferases. Computed tomography revealed the presence of a mass in the distal common bile duct. Endoscopic retrograde cholangiopancreatography and intraductal ultrasonography revealed a 25 mm filling defect in the distal common bile duct, and biopsy of the lesion disclosed the presence of tubular adenoma. Using fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) revealed an increased accumulation of the tracer in the lesion, with a maximum standard uptake value (SUV_{max}) of 3.3. The patient received a pylorus-preserving pancreatoduodenectomy. The histopathological examination revealed a tubular adenoma with low-grade atypia. The patient remains alive 15 months following the surgery, with no evidence of recurrence of the adenoma. ^{18}F-FDG PET has been successfully applied in clinical practice to detect a wide variety of tumor types, including lymphoma, lung, colon and bile duct cancer. In the present study, a case of bile duct adenoma with low-grade atypia was reported, revealing the uptake of ^{18}F-FDG. ^{18}F-FDG PET may be able to detect premalignant tumors of the bile duct, although whether ^{18}F-FDG PET is able to differentially discriminate between diagnoses of adenoma and carcinoma of the bile duct remains to be fully elucidated, and the assessment of further case studies is required.

Introduction

Adenomas of the colon and rectum are very common benign neoplasms, but adenomas of the common bile duct (CBD) are very rare diseases (1,2). Since bile duct adenomas often cause obstructive jaundice, patients are suspected to have CBD stones or malignant neoplasms. Adenomas of the bile duct are essentially benign tumors, although they are occasionally considered to be premalignant tumors. Intraductal papillary neoplasms of the bile duct (IPNB) have been proposed to be the biliary counterpart of intraductal papillary mucinous neoplasms of the pancreas, and the processes of the adenoma-to-carcinoma sequence in bile duct neoplasms have been identified (3-5). Treatments for bile duct adenoma are necessarily based on diagnostic results, and local resections of the CBD may be performed if the distal and proximal cut ends are free from the tumor, and the tumor is diagnosed to be benign. When a bile duct resection is insufficient for complete resection, or if a malignant transformation of the tumor is suspected, consequently, pancreatoduodenectomy should be considered (5).

Fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is used for cancer diagnosis and staging, and is often used for CBD tumors. ^{18}F-FDG PET is known to have 92.3% sensitivity, and 92.9% specificity, in the diagnosis of bile duct cancer (6), although whether ^{18}F-FDG PET is able to differentially discriminate between diagnoses of adenoma and carcinoma of the bile duct remains to be fully elucidated. In the present study, a case of bile duct adenoma with low-grade atypia was reported, demonstrating the uptake of ^{18}F-FDG, which was successfully treated by surgical resection.

Case report

A 64-year-old man was admitted to hospital with epigastric discomfort and nausea. He had diabetes mellitus and hypertension, which were controlled by the use of oral medicines. A physical examination revealed normal findings in the patient's abdomen. Laboratory analyses, however, revealed increased levels of total bilirubin (40.4 μmol/l), direct bilirubin (21.0 μmol/l), alkaline phosphatase (507 units/l), γ-glutamyl transpeptidase (364 units/l), aspartate aminotransferase (1,578 units/l) and alanine aminotransferase (1,132 units/l). Tumor markers, including carcinoembryonic antigen and carbohydrate antigen 19-9, were shown to be within the normal range. Computerized tomography (CT) revealed a

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slight dilation of the CBD, with the identification of a mass in the distal CBD (Fig. 1A). Following a diagnosis of obstructive jaundice, endoscopic nasobiliary drainage was performed after the admission of the patient. Radiological examinations revealed the presence of a 25 mm fixed filling defect in the distal CBD, and intraductal ultrasonography revealed an isoechoic, and partially high echoic, mass (Figs. 1B and C). A biopsy of this lesion revealed the presence of tubular adenoma with low-grade atypia. ^{18}F-FDG PET demonstrated an accumulation of focal increased tracer in this lesion, with a maximum standard uptake value (SUV_{max}) of 3.3, and the position where uptake of the ^{18}F-FDG occurred was separate from the drainage tube (Fig. 1D).

On the basis of these findings, a pylorus-preserving pancreatoduodenectomy and regional lymph-node dissection were performed. The tumor was impacted in the bile duct lumen, occupying 2.5 cm in length (Fig. 2A). Histological examinations revealed that the tumor was composed of relatively uniform tubules, with a bland cellular appearance. Neither necrotic foci nor mitotic figures were observed. Furthermore, invasion was not observed in the duct wall, and no intraductal mass was identified (Fig. 2B and C). Lymph node metastasis was not detected. A grade B pancreatic fistula was identified following the surgery, although the patient was discharged 40 days post-surgery. The patient remains alive, with no evidence of any recurrence of the tumor, 15 months following the surgery.

Discussion

Benign tumors arising from the extrahepatic biliary tree are very rare, and are reported to occupy 6% of all tumors of the bile ducts (2). In benign tumors, adenomas and papillomas are commonly encountered. Adenomas arise from the epithelial lining of the biliary duct, and grow in a tubular, papillary or a tubulopapillary manner. Adenomas of the bile duct are considered to be premalignant tumors. The adenoma-to-carcinoma sequence has been well established to occur in the colon and the rectum, and this also applies in the ampullary region (7-10). In carcinoma of the ampulla of Vater, adenomatous areas were revealed to co-exist with high frequency in >40% of the surgically resected specimens (11,12). Previously, IPNB have been proposed to be the biliary counterpart of intraductal papillary mucinous neoplasms of the pancreas (3,4). IPNB are a major intraductal neoplasm, which is capable of progressing to an invasive carcinoma, and the types of cytoarchitectural atypia in IPNB were characterized as adenoma, borderline, carcinoma *in situ* and invasive carcinoma (3). The development of IPNB was reported to follow an adenoma-to-carcinoma sequence, which correlated with the stepwise activation of common oncogenic pathways, including mutated Kirsten rat sarcoma viral oncogene homolog, the overexpression of tumor protein 53 and loss of p16 (13). Kim *et al* (1) summarized the 26 cases of adenomas arising from CBD, and reported that the histological findings ranged from adenoma without atypia to carcinoma *in situ* with an adenoma component. Therefore, complete resection of the lesion is required in order to avoid the postoperative development of bile duct carcinoma.

Appropriate modalities to resect CBD adenoma have not been clearly defined. Endoscopic resection for bile duct

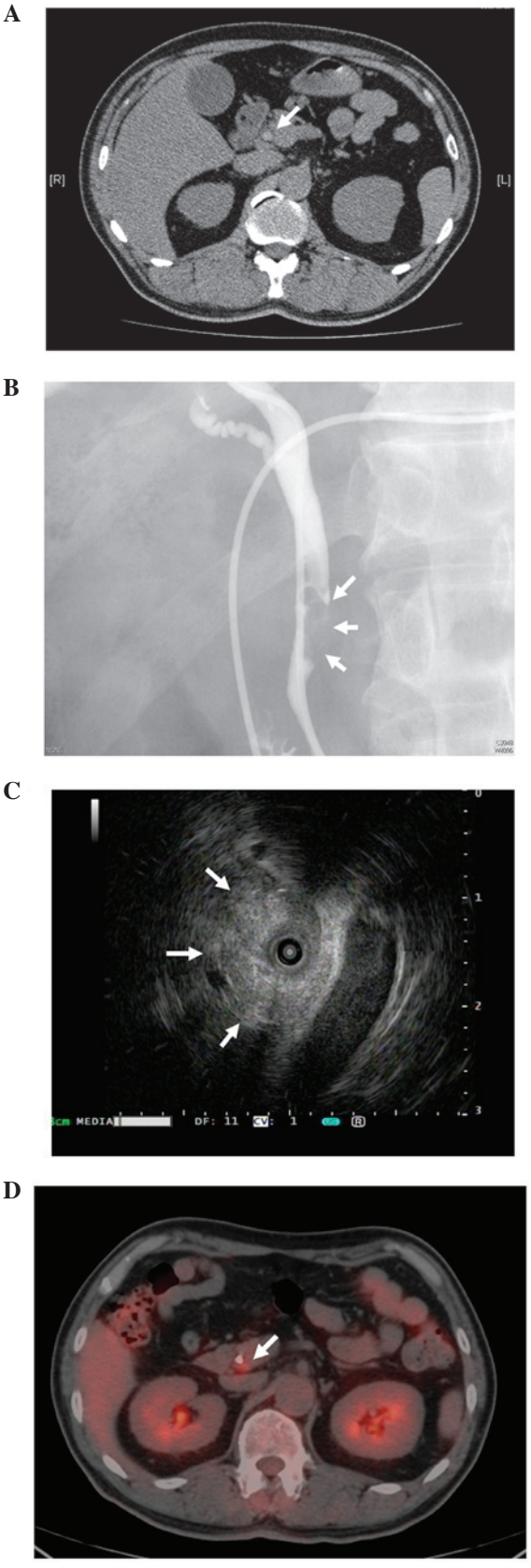

Figure 1. (A) Computed tomography revealed slight dilation of the common bile duct, with a mass in the distal common bile duct (revealed by the arrow). (B) Endoscopic retrograde cholangiopancreatography revealed a 25 mm fixed filling defect in the distal common bile duct (indicated by the arrows). (C) Intraductal ultrasonography revealed an iso-high echoic mass in the distal bile duct (indicated by the arrows). (D) Fluorine-18 fluorodeoxyglucose positron emission tomography demonstrated an increased accumulation of tracer in the distal bile duct, with a maximum standard uptake value (SUV_{max}) of 3.3 (highlighted by the arrow).

adenoma has been infrequently reported, and the technique is considered to be applicable only in a limited number of situations, for example, for patients for whom surgical resection would pose a high risk (14,15). Local resection of the CBD may be performed if the distal and proximal cut ends are free from the tumor and the tumor is diagnosed to be benign. If the extent of the bile duct adenoma occupies a range which reaches to the distal CBD and local resection is impossible, pancreatoduodenectomy should be considered for complete resection. In adenoma of the bile duct, predicting the presence of malignant foci preoperatively may be difficult. Kim *et al* (1) reported that radical resection may be required in cases where the size of the adenoma was >~20 mm, or where malignant transformation was suspected. In the present case study, the tumor was located in the distal bile duct in the pancreas, and consequently, pancreaticoduodectomy was selected as the procedure, not bile duct resection. Based on the results obtained from the ^{18}F-FDG PET, the regional lymph node was also dissected. Had the results of the ^{18}F-FDG PET proven to be negative, lymph node dissection would not have been necessary.

^{18}F-FDG PET has been applied in clinical practice to detect a wide variety of tumor types, including lymphoma, lung, esophageal, colon and bile duct cancer (16-19). For patients with extrahepatic cholangiocarcinoma, ^{18}F-FDG PET may be used in the diagnosis and staging of the patients (6,20). Furthermore, Choi EK *et al* (21) reported that the SUV_{max} value identified from PET-CT scans is a useful parameter to enable the differentiation of an extrahepatic biliary malignancy from benign disease. In the meta-analysis, Annunziata *et al* (22) reported that the sensitivity and specificity of ^{18}F-FDG PET were 76 and 74%, respectively, for extrahepatic cholangiocarcinoma. Several previous studies reported that false-negative results obtained in cases of ^{18}F-FDG PET were due to the morphology of extrahepatic cholangiocarcinoma (20,23). Infiltrative types of cholangiocarcinoma led to discrepancies in the diagnostic performance due to an insufficient uptake of FDG in the tumor. However, an explanation of how an uptake of FDG was observed with benign biliary tumors was not forthcoming, and neither was it discussed. ^{18}F-FDG PET detects premalignant colonic adenomas, and a focal FDG accumulation is detected in >50% of reported cases (24). The degree of FDG uptake was reported to be correlated with the size of the adenoma, or to the degree of dysplasia (25). For results obtained from ^{18}F-FDG-PET of the bile duct adenoma, Dong *et al* (26) reported two cases of IPNB, with uptake of FDG, in 2012. Histological findings revealed that these cases were adenomas, with a high-grade dysplasia in one case, and a low-grade dysplasia in the other. The authors reported that the reason for an uptake of FDG in the adenoma was, primarily, high-mitotic activity across the entire range, from low-grade to high-grade dysplasia, and, secondly, the larger tumor size, composed of a greater number of tumor cells (26). In the present case study, the adenoma was 25 mm in diameter with low-grade atypia, and it was hypothesized that the tumor size of the adenoma and the histological grade of atypia correlated with the extent of FDG accumulation.

False-positive results obtained with FDG uptake which are due to inflammatory causes are well recognized. Wakabayashi *et al* (27) reported that, in diagnosing malignant diseases in patients with biliary stricture, FDG-PET was superior as a method compared with CT examination in terms of both the sensitivity and the specificity, and superior to cytological examination of the bile in terms of its sensitivity. Anderson *et al* (28) described a false-positive result in a patient

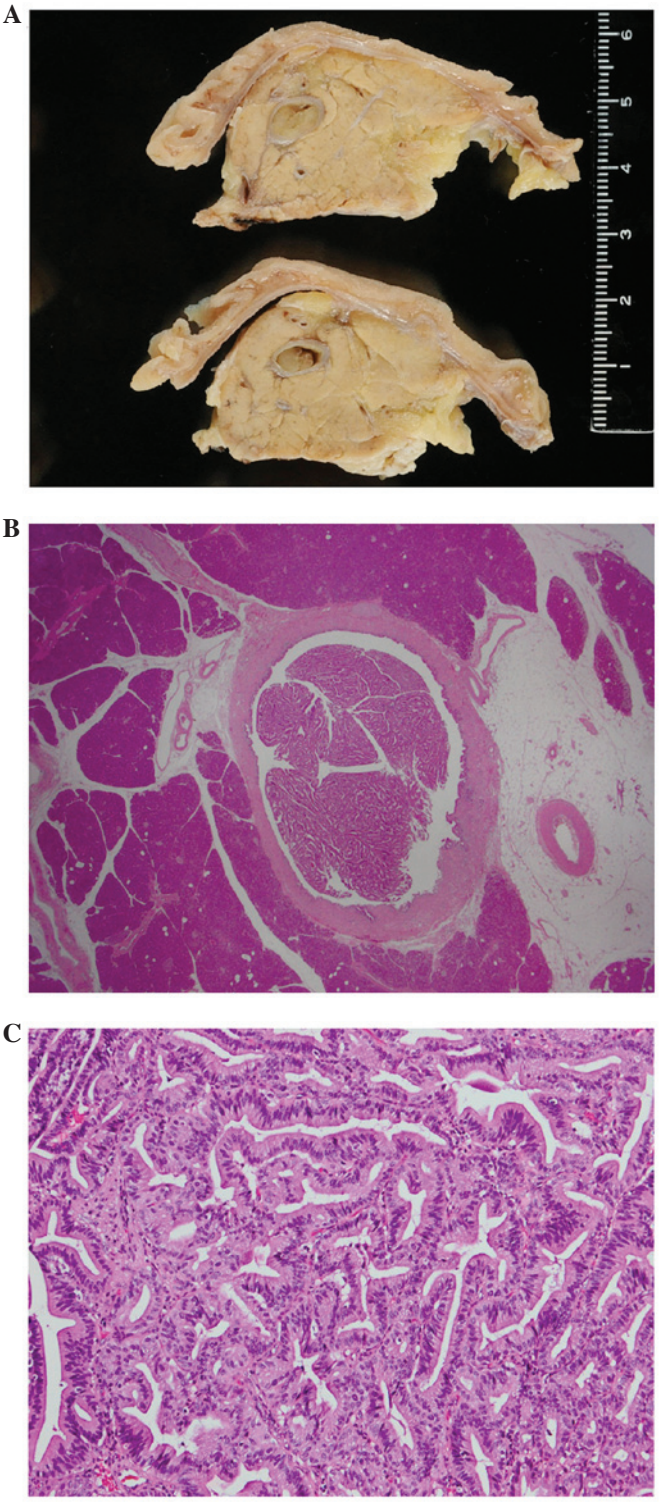

Figure 2. Surgical specimen and histological findings. (A) A macroscopic view of the resected specimen. A polypoid tumor is impacted in the intrapancreatic bile duct. (B) A low-power view (magnification x12.5) revealed that the intraductal neoplasm resided in the lumen. Neither necrotic foci nor invasion in the duct wall were observed. (C) The highest-power view (magnification x100) revealed that the tubules were relatively uniform, composed of cells of bland appearance. Nuclear stratification, nuclear pleomorphism and mitotic figures were not observed.

scanned following a cholecystectomy, with FDG uptake identified during the analysis of residual post-operative inflammatory changes. In the present case study, the bile duct drainage tube for obstructive jaundice was already inserted at the time of PET scan. In a previous report, Choi *et al* (21) evaluated the clinical value of ^{18}F-FDG PET for differentiating extrahepatic cholangiocarcinoma from benign disease. In that study, the final diagnosis was of cholangiocarcinoma in 34 patients, and of benign disease in five other patients. Of all 39 patients studied, 20 of them had either an endoscopic or external biliary drainage tube, or a biliary stent, at the time of the PET scan. Only one patient was false-positive, with a hyperplastic polyp in the ampulla of Vater, and the update of FDG was correlated with the drainage tube. In the present case study, the site of FDG uptake was observed to be separate from that of the drainage tube. In addition, Kitamura *et al* (18) examined the prognostic value of ^{18}F-FDG PET in extrahepatic bile duct cancers. The authors reported that no significant correlation was identified between FDG uptake and the presence of a biliary drainage tube, or the levels of C-reactive protein. Therefore, it was not possible to conclude that the presence of the biliary drainage tube did not affect the measurement of FDG uptake.

In conclusion, a case of bile duct adenoma with low-grade atypia showing FDG uptake has been reported in the present study. ^{18}F-FDG PET may be used to detect premalignant tumors of the bile duct, although whether ^{18}F-FDG PET is able to differentially discriminate between diagnoses of adenoma and carcinoma of the bile duct remains to be fully elucidated, and the assessment of further case studies is required.

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