Localized ^{18}F-fluorodeoxyglucose uptake at the pancreatic head during remission phase of autoimmune pancreatitis: A case report

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Abstract. Autoimmune pancreatitis (AIP) is a unique form of pancreatitis, histopathologically characterized by dense lymphoplasmacytic infiltration and fibrosis of the pancreas with obliterative phlebitis. AIP is associated with a good response to steroid therapy. Differentiation between AIP and pancreatic cancer to determine a preoperative diagnosis is often challenging, despite the use of various diagnostic modalities, including computed tomography (CT), magnetic resonance imaging and endoscopic retrograde cholangiopancreatography. It has been reported that ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-positron emission tomography (PET)/CT may be a useful tool for distinguishing between the two diseases. In the present case report, a 71-year-old male patient presented with a well-circumscribed, solitary, nodular and homogenous ^{18}F-FDG uptake at the pancreatic head, while receiving maintenance steroid therapy in the remission phase of AIP; preoperatively, the patient had been strongly suspected of having pancreatic cancer. Pathological examination revealed post-treatment relapse of AIP. The present case highlights the diagnostic and management difficulties with AIP in the remission phase. In certain cases, it remains challenging to differentiate the two diseases, even using the latest modalities.

Introduction

Autoimmune pancreatitis (AIP) is a unique form of pancreatitis that is histopathologically characterized by dense lymphoplasmacytic infiltration and fibrosis of the pancreas with obliterative phlebitis (1). Pancreatic cancer is one of the leading causes of mortality in Japan and Western countries (2). This type of tumor is associated with poor prognosis, due to its aggressive biology and the difficulty in making an early diagnosis. Patients with AIP share numerous clinical features with pancreatic cancer patients, including advanced age, painless jaundice, weight loss, new-onset diabetes mellitus and elevated serum levels of carbohydrate antigen (CA) 19-9 (3). Such factors commonly render the differentiation between AIP and pancreatic cancer rather challenging; however, distinguishing between the two diseases is crucial, as their treatments and prognoses are vastly different (4). An accurate preoperative diagnosis of AIP is required in order to avoid unnecessary surgery and to achieve clinical remission with steroid therapy. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/computed tomography (CT) has been reported to assist with this differentiation (2,3,5). The current study reports the case of a patient who presented with a new localized ^{18}F-FDG uptake at the pancreatic head and normal serum immunoglobulin G4 (IgG4) levels during the remission phase of AIP, and had been strongly suspected of having pancreatic cancer preoperatively. Written informed consent to publish was obtained from the patient.

Case report

A 71-year-old male patient was admitted to Shiritsu Oozu Hospital (Oozu, Japan) after presenting with worsening diabetes mellitus in April 2009. The patient had a history of two abdominal surgeries: A choledochectomy and choledochojejunostomy, due to choledocholithiasis 28 years prior to admission; and a right lateral hepatic sectoriectomy, due to intrahepatic stones 3 years prior to admission. AIP was suspected following a workup, which included examining the serum IgG4 levels and an ^{18}F-FDG-PET/CT, and the patient was referred to the Ehime University Hospital (Toon, Japan). Abdominal ultrasonography and CT imaging (Brilliance 64; Philips, Tokyo, Japan) revealed enlargement of the pancreatic head and body (Fig. 1A and B). Endoscopic retrograde cholangiopancreatography (ERCP; JF-260V; Olympus Corporation, Tokyo, Japan) showed diffuse narrowing of the main pancreatic duct (MPD) in the pancreatic head and body (Fig. 1C). ^{18}F-FDG-PET/CT (Discovery ST Elite; GE Healthcare Life Sciences, Hino, Japan), which had been performed during the previous hospital stay, revealed a strong and diffuse uptake of

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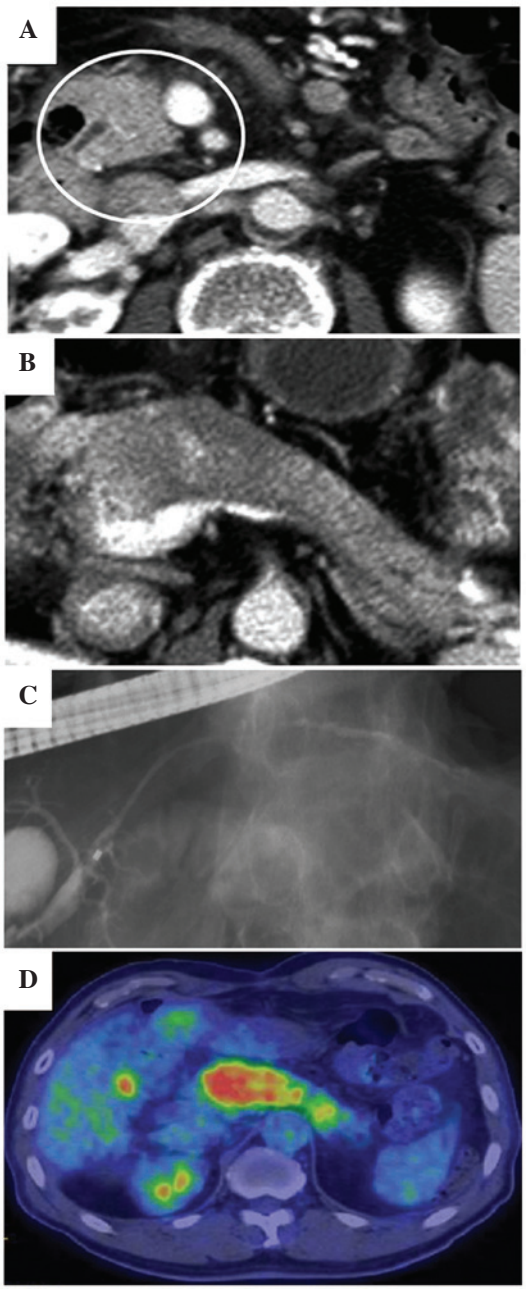

Figure 1. Images prior to initiation of steroid therapy. (A and B) CT scans showing enlargement of the pancreatic head (circle) and body upon initial diagnosis. (C) Endoscopic retrograde cholangiopancreatography showing diffuse narrowing of the main pancreatic duct in the pancreatic head and body, upon initial diagnosis. (D) ^{18}F-FDG-positron emission tomography/CT showing a strong and diffuse uptake of ^{18}F-FDG throughout the entire pancreas. CT, computed tomography; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose.

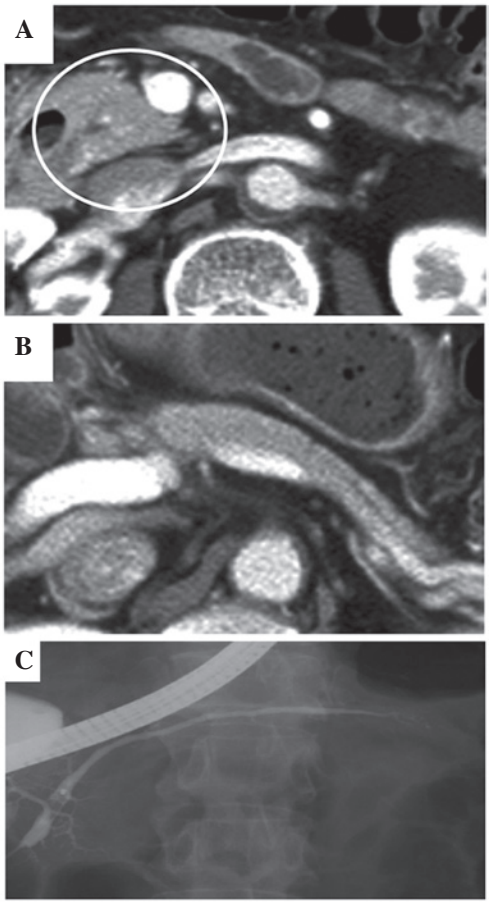

Figure 2. Follow-up images acquired 3 months after the initiation of steroid therapy. (A and B) Computed tomography showing that the enlargement of the pancreatic head (circle) and body had markedly improved. (C) Endoscopic retrograde cholangiopancreatography showing that the diffuse narrowing of the main pancreatic duct had fully recovered.

^{18}F-FDG throughout the entire pancreas (Fig. 1D). The serum IgG4 level was markedly elevated (158 mg/dl; normal range, 4.8-105.0 mg/dl). A diagnosis of AIP was thereby established, and steroid therapy was initiated.

The initial oral prednisolone dose administered was 30 mg/day. Following the initiation of the steroid therapy, the enlargement of the pancreatic head and body markedly improved, the diffuse narrowing of the MPD fully recovered (Fig. 2A-C), and the IgG4 level dropped to within normal limits. The oral steroid therapy regimen was as follows: The initial dose was administered daily for 2 weeks, followed by gradual tapering of the dose by 5 mg every 2 weeks, until a daily dose of 5 mg was reached. Subsequently, maintenance steroid therapy (5 mg/day) was administered, based on the Japanese consensus guidelines for the management of AIP (6). Follow-up examinations were performed on an outpatient basis.

At 10 months after the initiation of the steroid therapy, elevated serum levels of amylase (255 IU/l; normal range, 37-124 IU/l) and lipase (91 IU/l; normal range, 13-49 IU/l) were detected, and a CT scan revealed a 2-cm low-attenuation mass at the pancreatic head and dilation of the MPD (Fig. 3A and B). The patient was readmitted to the hospital due to a suspected relapse of AIP. Magnetic resonance imaging (MRI) revealed tumor-like enlargement at the pancreatic head, and obstruction of the MPD with dilatation of the upstream MPD. ERCP showed a ~2-cm long stricture of the MPD at the pancreatic head and a dilatation of the body and tail portion of MPD that measured 5 mm in diameter (Fig. 3C). Based on these radiographic findings, it was difficult to decide between recurrence of AIP and pancreatic cancer. The serum levels of CA19-9, duke pancreatic monoclonal antigen type 2, and Span-1 were normal. The serum level of carcinoembryonic antigen was slightly elevated (7.1 ng/ml; normal range, <5.0 ng/ml). The serum level of IgG4 was 106 mg/dl, which was below the cutoff value (≥135 mg/dl) of the Japanese clinical diagnostic criteria for AIP (1). ^{18}F-FDG-PET/CT

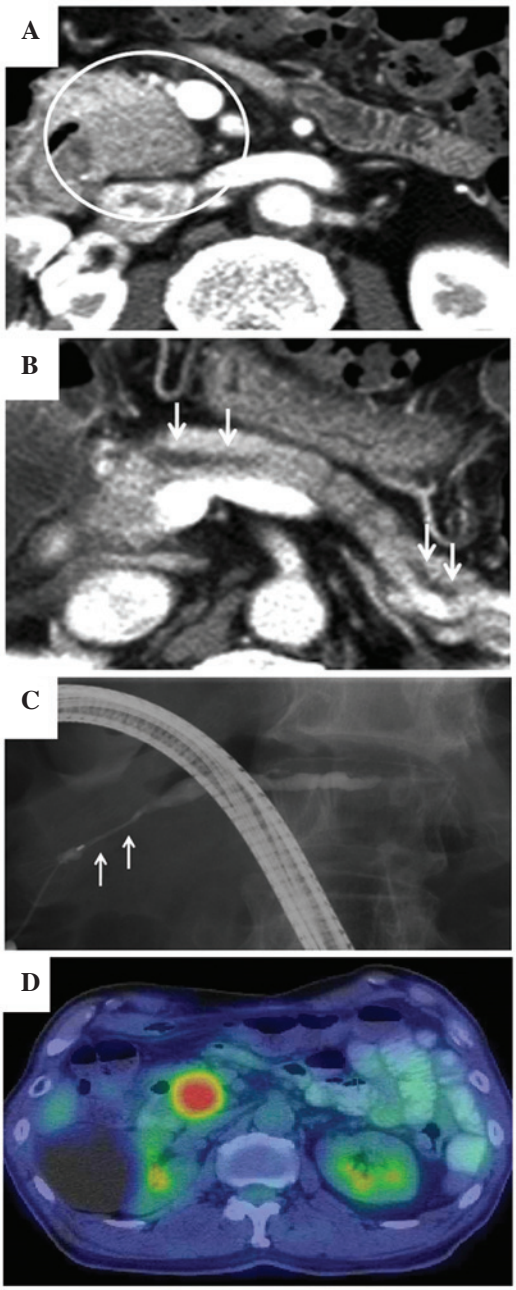

Figure 3. Follow-up images acquired 10 months after the initiation of steroid therapy. (A and B) CT scan showing a low-attenuation mass measuring 2 cm at the pancreatic head (circle) and dilation of the MPD (arrow), which had not been observed in previous CT scans (Figs. 1 and 2). (C) Endoscopic retrograde cholangiopancreatography showing an ~2-cm long stricture of the MPD at the pancreatic head and dilatation of the the body and tail portion of MPD measuring 5 mm in diameter. (D) ^{18}F-FDG-positron emission tomography/CT showing a well-circumscribed uptake of ^{18}F-FDG at the location where the pancreatic head mass was identified by CT scan. CT, computed tomography; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; MPD, main pancreatic duct.

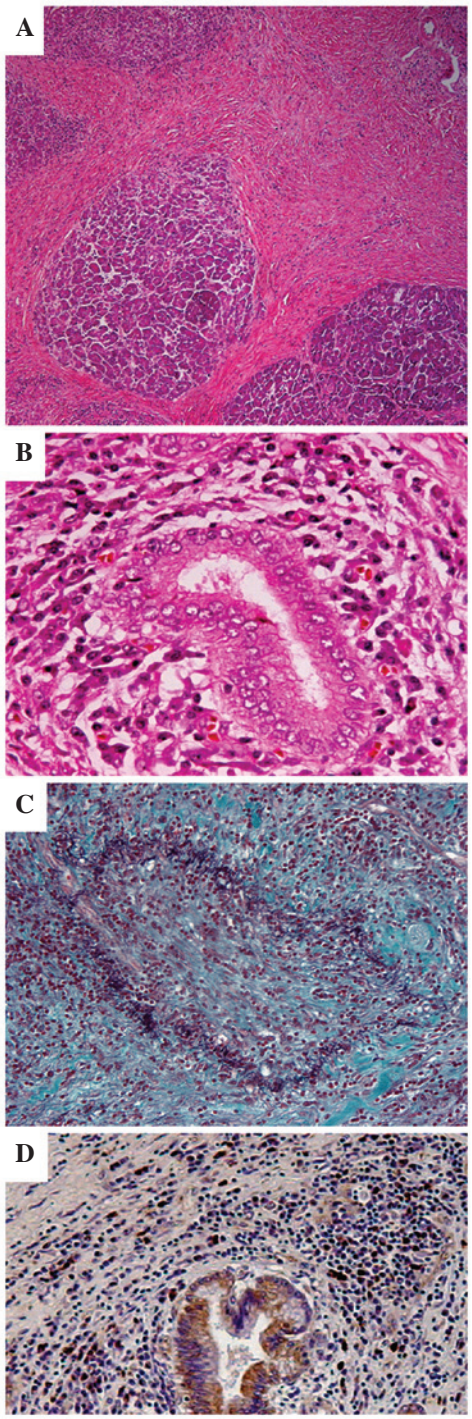

Figure 4. Pathological examination revealing diffuse lymphoplasmacytic infiltrate with fibrosis, periductal lymphoplasmacytic infiltrate in the pancreatic head mass: (A) x40 and (B) x400 magnification. (C) Elastica-Masson staining showing obliterative phlebitis in this specimen. (D) An abundance of IgG4-positive cells was observed in the lymphoplasmacytic infiltrate (>10 cells/high power field).

(Aquiduo PCA-7000B; Toshiba Medical Systems, Ootawara, Japan) showed a well-circumscribed, solitary, nodular and homogenous ^{18}F-FDG uptake, with a maximum standardized uptake value of 7.82 at the location where the pancreatic head mass was identified by CT scan (Fig. 3D). No abnormal extrapancreatic uptake of ^{18}F-FDG was observed.

The patient was referred to the Department of Hepatobiliary-Pancreatic and Breast Surgery, Ehime University Hospital with a suspected diagnosis of concomitant pancreatic cancer with AIP, and pancreatoduodenectomy was performed. The formalin-fixed paraffin-embedded 4-μm sections were used for hematoxylin and eosin staining, Elastica-Masson staining and IgG4 immunostaining (mouse anti-human IgG4 monoclonal antibody; dilution, 1:400; catalog no., GTX75819; GeneTex, Irvine, CA, USA). Pathological examination revealed diffuse lymphoplasmacytic infiltrate with fibrosis, periductal lymphoplasmacytic infiltrate

and obliterative phlebitis (Fig. 4A-C). The lymphoplasmacytic infiltrate included an abundance of IgG4-positive cells [>10 cells/high power field (HPF)] (Fig. 4D), which forms one of the histological criteria for AIP proposed by the Mayo Clinic (7). No malignant cells were found. Recurrent AIP was therefore diagnosed. Maintenance steroid therapy was resumed following surgery, and, at the time of writing the present study, no recurrent AIP in the pancreatic remnant has been identified for 4 years after surgery.

Discussion

AIP is a distinct form of pancreatitis characterized by the involvement of autoimmune mechanisms, such as hypergammaglobulinemia, increased serum levels of IgG, increased serum levels of IgG4 or the presence of autoantibodies (1). AIP has been associated with an effective response to steroid therapy (1). The pathological features of this disorder are characterized by periductal lymphoplasmacytic infiltrate and lymphoplasmacytic infiltrate showing abundant (>10 cells/HPF) IgG4-positive cells (7). This lymphoplasmacytic infiltration is often accompanied by storiform fibrosis and obliterative phlebitis (7). These characteristic features can distinguish AIP from normal chronic pancreatitis (7). The clinical spectrum of AIP includes sclerosing cholangitis, retroperitoneal fibrosis, hilar lymphadenopathy, salivary gland swelling and interstitional pneumonia (8). Some of these extrapancreatic lesions show pathological findings similar to those of pancreatic lesions (8).

AIP and pancreatic cancer share several characteristics; however, the therapeutic methods for each of these diseases are vastly different. Pancreatic cancer requires surgery, while steroid therapy is effective for AIP without the need for surgical intervention (4). It is therefore crucial to distinguish AIP from pancreatic cancer; however, in certain cases, differential diagnosis is challenging, despite the use of numerous different diagnostic modalities, such as CT and MRI scans, and ERCP. Nakazawa *et al* (9) reported that 7/37 (18.9%) patients with AIP underwent surgical intervention due to having been misdiagnosed with pancreatic or bile duct cancer. Kamisawa *et al* (4) also reported that 6/17 (35.3%) patients with focal mass-forming AIP were surgically treated due to the suspicion of pancreatic cancer.

Other studies have reported the utility of ^{18}F-FDG-PET/CT for the differentiation of AIP from pancreatic cancer (2,3,5). ^{18}F-FDG-PET/CT is a sensitive modality used for the diagnosis of malignancies. Since ^{18}F-FDG uptake is caused by increased glucose utilization of tumor cells and is also observed at inflammatory sites, ^{18}F-FDG uptake is a shared finding between AIP and pancreatic cancer. Kamisawa *et al* (5) concluded that ^{18}F-FDG-PET/CT can assist in the differentiation between the two diseases by assessing ^{18}F-FDG uptake patterns in the pancreas and extrapancreatic lesions. Lee *et al* (3) indicated that, in severe cases, using PET/CT can detect the presence of diffuse ^{18}F-FDG uptake by the pancreas, or concomitant extrapancreatic uptake by the salivary glands, which can aid in differentiation. Ozaki *et al* (2) also reported that the typical ^{18}F-FDG-PET findings for AIP are an irregular contour, longitudinal shape, heterogeneous accumulation and multiple localizations, whereas those for pancreatic cancer are a smooth contour, nodular shape, homogenous accumulation and solitary localization. Shigekawa *et al* (8) indicated that the accumulation patterns of ^{18}F-FDG were nodular and solitary in the majority of cases of pancreatic cancer that they examined, and that the possibility of AIP was increased if the ^{18}F-FDG accumulation in the pancreas had a longitudinal shape; however, nodular and solitary ^{18}F-FDG accumulations were also observed in AIP, corresponding with focal changes in the pancreas on CT or ERCP. It was also reported that ^{18}F-FDG uptake in extrapancreatic lesions, including the extra-abdominal lymph nodes, salivary glands, eyes and biliary duct, may be helpful in differentiating between pancreatic cancer and AIP.

Kamisawa *et al* (4) proposed an algorithm for the clinical management of a mass-like lesion on the pancreatic head, with particular emphasis on the differentiation between AIP and pancreatic cancer. They identified 6 imaging characteristics, a combination of CT and ERCP findings, that were highly suggestive of AIP. The findings were as follows: i) Delayed enhancement of the enlarged pancreas on CT scan; ii) a capsule-like rim on CT scan, iii) the presence of extrapancreatic lesions, such as salivary gland swelling, retroperitoneal mass or stenosis of the upper or intrahepatic bile duct on CT scan or ERCP; iv) ≥3 cm-long narrowed portion of the MPD on ERCP; v) skipped lesions of the MPD on ERCP, and vi) a maximal diameter of <5 mm of the upstream MPD on ERCP. In the present case, none of these imaging characteristics were observed. According to this algorithm, in cases with no positive imaging factors for AIP, surgery should be considered under the provisional diagnosis of pancreatic cancer.

Several studies have reported cases of pancreatic cancer complicated with AIP simultaneously (10-13) or during follow-up (14-18). Loos *et al* (15) reported a case of a patient who developed a metastatic adenocarcinoma of the pancreatobiliary system within a year after the histologically confirmed diagnosis of AIP. In addition, among the reports, 3 patients were diagnosed with pancreatic cancer during maintenance steroid therapy (16-18). In general, the risk of pancreatic cancer is markedly increased in patients with chronic pancreatitis (14); however, the association between AIP and pancreatic cancer remains unknown. Based on earlier reports of cancer development during the course of maintenance steroid therapy for AIP, three key findings of the present study, and the algorithm proposed by Kamisawa *et al* (4), the patient was diagnosed with pancreatic cancer during the course of maintenance steroid therapy for AIP, and pancreatoduodenectomy was performed. The aforementioned key findings of the present study were the following: i) Detection by PET/CT scan of a well-circumscribed, solitary, nodular and homogenous ^{18}F-FDG uptake at the same area where a pancreatic head mass was identified; ii) no extrapancreatic uptake; and iii) normal serum IgG4 levels. Pathological examination revealed diffuse lymphoplasmacytic infiltrate with fibrosis, periductal infiltrate, obliterative phlebitis, IgG4-positive cells and absence of malignant cells; therefore, post-treatment relapse of AIP was eventually diagnosed.

At the time of writing the present study, no recurrent AIP in the pancreatic remnant of the patient had been identified for 4 years after surgery. Of note, authors from the Mayo Clinic recently reported that the relapse rate of AIP patients who underwent pancreatoduodenectomy as the initial treatment

was markedly lower than that of patients who had not undergone pancreatoduodenectomy (the corticosteroid-treated group) (19). While the underlying mechanisms are unclear, this is a noteworthy observation that requires further study.

In summary, the current study reported the case of a patient who presented with a new mass at the pancreatic head and an upstream dilatation of the MPD while receiving a maintenance dosage of steroids in the remission phase of AIP. The present study highlights the challenges faced by clinicians in the diagnosis and management of AIP in remission. In certain cases, the differentiation between pancreatic cancer and AIP remains difficult, despite the use of the latest diagnostic modalities.

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