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Autoimmune pancreatitis with multifocal lesions

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Abstract
Two cases of a focal type of autoimmune pancreatitis (AIP) with distinct double mass lesions within the pancreas are described. In both patients, computed tomography (CT) showed localized pancreatic masses with delayed enhancement, and magnetic resonance cholangiopancreatography (MRCP) revealed localized stenoses of the main pancreatic duct (MPD) with mild upstream dilatation. Fluorodeoxyglucose positron emission tomography (FDG-PET) examination, performed in one patient, showed intense uptake concordant with tumors. Both patients received pancreatic resection with a presumptive diagnosis of pancreatic carcinoma. Histologic evaluation of the tumors showed marked lymphoplasmacytic infiltration and fibrosis around the large and medium pancreatic ducts, without any evidence of malignancy. Serum IgG4 concentration, measured postoperatively, was elevated in both patients. The characteristic morphological features of AIP are diffuse swelling of the pancreatic parenchyma and diffuse narrowing of the MPD. Recently, a focal type of AIP, which mimics pancreatic carcinoma, has been recognized. Considering the favorable response of AIP to steroid therapy, it is clinically important to differentiate the focal type of AIP from pancreatic carcinoma and to know that AIP sometimes exhibits multiple lesions within the pancreas.

Key words Autoimmune pancreatitis · Multifocal lesions · IgG4 staining

Introduction

Autoimmune pancreatitis (AIP) is a unique form of chronic pancreatitis associated with an autoimmune inflammatory process.[1] Although diffuse swelling of the pancreatic parenchyma and diffuse irregular narrowing of the pancreatic duct system are morphologically characteristic of AIP, a focal type of this clinical entity has been recently recognized.[2–4]

The focal type of AIP exhibits a localized mass lesion in the pancreas, similar to pancreatic carcinoma, and it often exhibits obstructive jaundice,[5] which is also characteristic of pancreatic carcinoma, when the lesion involves the head of the pancreas. Consequently, some patients with these features have been subjected to surgical exploration with a presumed diagnosis of pancreatic carcinoma.[6] Considering that AIP shows a favorable response to steroid therapy, the differentiation of these two entities is clinically important.

Although patients with AIP sometimes show multifocal or skipped narrowing of the main pancreatic duct (MPD), there have been only a few cases of AIP with multifocal lesions.[7] In this report, we describe the clinical, radiological, and histopathological features of two patients with AIP who exhibited distinct double masses in the pancreas; the masses were resected on the suspicion of pancreatic carcinoma.

Case reports

Case 1

A 62-year-old male patient with mild epigastralgia was referred for further investigation of pancreatic masses. He had no medical history of autoimmune disease, but he had a history of hypertension. The results of laboratory examinations, including complete blood count, electrolytes, bilirubin, liver function tests, and pancreatic enzymes and tumor markers (carbohydrate antigen [CA] 19-9, and carcinoembryonic antigen [CEA]), were all within normal limits. Computed tomography (CT) showed irregular mass lesions in the head and body of the pancreas (Fig. 1a, b); the lesions were 30 mm and 25 mm in diameter, respectively. The tumors showed slight attenuation in the delayed phase with contrast

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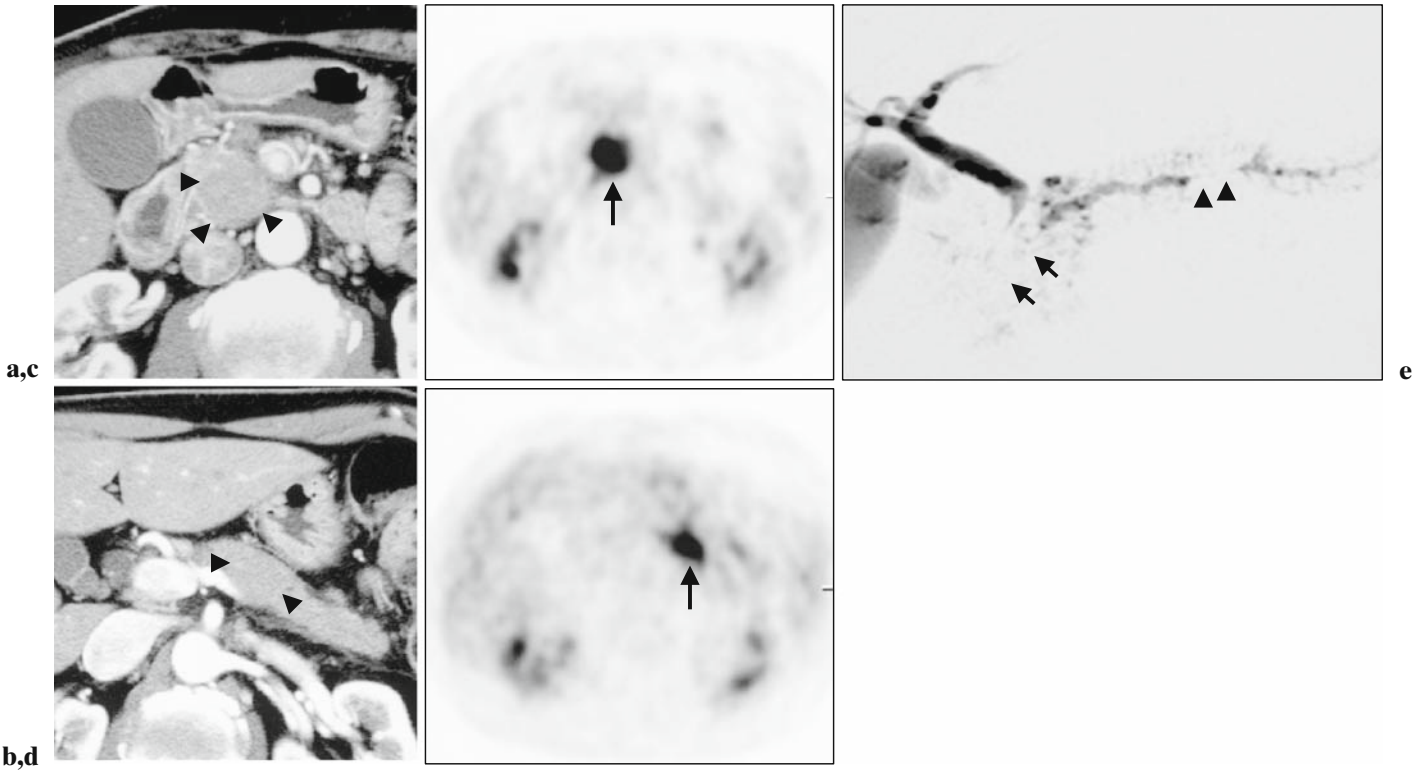

Fig. 1a–e. Case 1. Computed tomography (CT) revealed irregular mass lesions in the head (**a**) and body (**b**) of the pancreas (*arrowheads*); early phase. **c**, **d** Fluorodeoxyglucose positron emission tomography (FDG-PET) showed intense uptake in both lesions (*arrows*), and their standardized uptake values (SUVs) were 6.6 and 8.3, respectively. (**c**, head; **d**, body). **e** Magnetic resonance cholangiopancreatography (MRCP) revealed skipped stenoses in the main pancreatic duct (MPD) concordant with the tumors (head, *arrows*; body, *arrowheads*), and mild dilatation between the tumors and distally

medium. Fluorodeoxyglucose positron emission tomography (FDG-PET) showed intense uptake in both lesions, and their standardized uptake values (SUVs) were 6.6 and 8.3, respectively (Fig. 1c, d). Magnetic resonance cholangiopancreatography (MRCP) revealed skipped stenoses of the MPD, concordant with the tumors, and mild dilatation between the tumors and distally (Fig. 1e).

Case 2

A 64-year-old male patient without any symptoms or past medical history was admitted because of pancreatic masses that were picked up on a medical checkup. Laboratory tests showed slight elevation of blood glucose (126 mg/dl; normal, 69–104 mg/dl) and hepatic enzymes (aspartate aminotransferase, 41 IU/l [normal, 13–33 IU/l], alkaline aminotransferase, 75 IU/l [normal, 8–42 IU/l]). Dynamic CT showed two lesions, in the body and tail of the pancreas, 28 mm and 30 mm in diameter, respectively, and exhibited subtle delayed enhancement (Fig. 2a). MRCP revealed obstruction of the MPD in concordance with the tumors, and slight dilatation between the tumors (Fig. 2b).

The proximal lesions in both patients were considered to be pancreatic carcinomas because the finding of localized stenoses with upstream dilatation of the MPD was suggestive of pancreatic carcinoma. The distal lesions were deemed to be either obstructive pancreatitis demonstrating mass lesions because of severe inflammation, or other primary pancreatic carcinoma. In case 1, core needle biopsy of the tumor in the pancreatic body was performed during surgery, and this revealed parenchymal fibrosis and infiltration of inflammatory cells, including plasma cells, without any evidence of malignancy. Therefore, Whipple resection was performed to resect only the head lesion. In case 2, the patient received distal pancreatectomy.

The three resected tumors (case 1, head; case 2, body and tail) resembled each other on both macroscopic and microscopic examinations. On gross appearance, all cut surfaces of the tumors demonstrated swelling of the parenchyma, but the border between the tumor and the surrounding pancreatic tissue was unclear, while the existing lobular structure and narrowed MPD were clearly identified (Fig. 2c). Microscopic examination confirmed marked lymphoplasmacytic infiltration and fibrosis around the large and medium pancreatic ducts

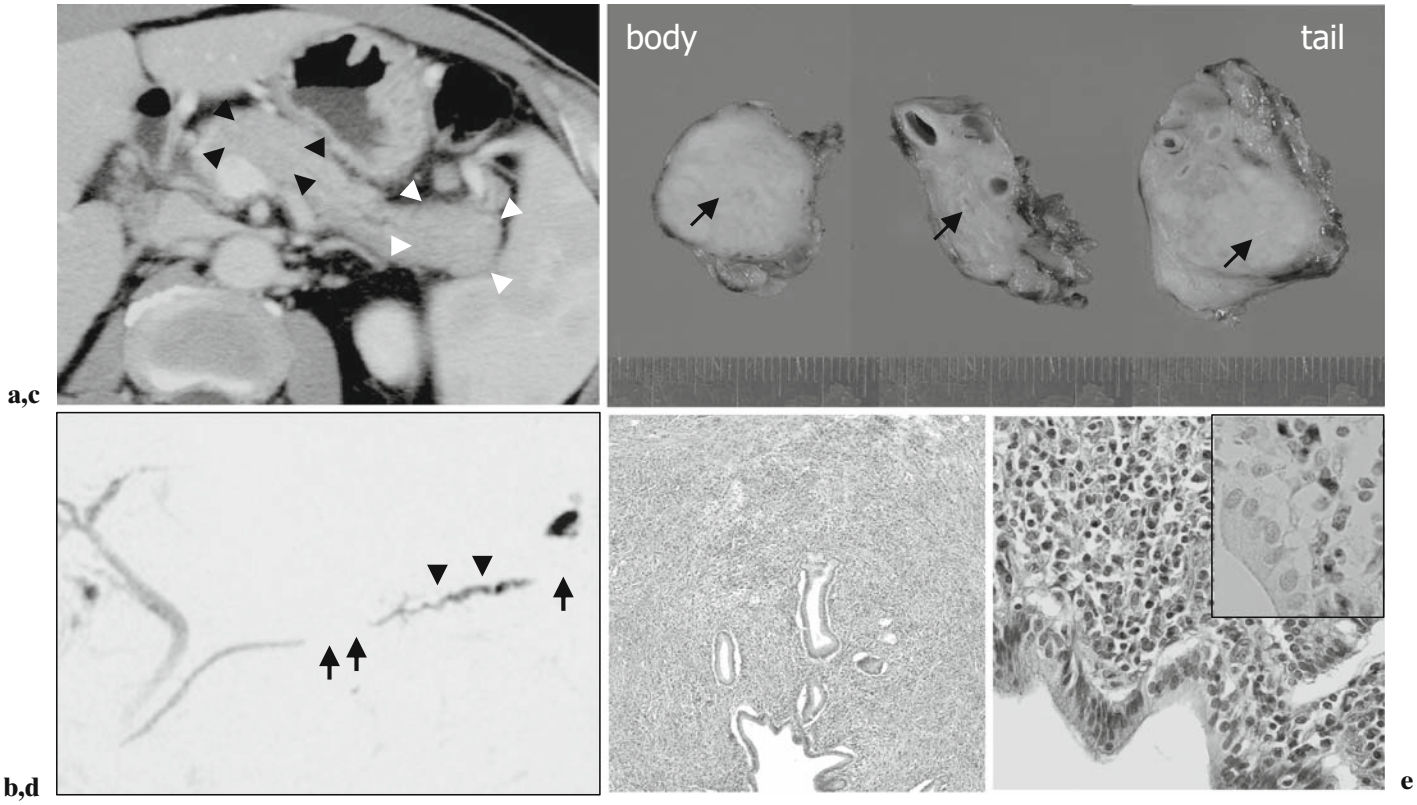

Fig. 2a–e. Case 2. **a** CT showed two lesions, in the body and tail of the pancreas (*arrowheads*), and exhibited subtle delayed enhancement; delayed phase. **b** MRCP revealed obstruction of the MPD concordant with the tumors (*arrows*), and slight dilatation between the tumors (*arrowheads*). **c** On macroscopic examination, the cut surface of the tumors showed swelling of the parenchyma, and the border between the tumor and the surrounding pancreatic tissue was unclear. The parenchyma between the two lesions was markedly atrophic. The MPD was narrowed in the tumor lesions, but was normal in the area between the tumors (*arrows*). **d** Microscopic examination confirmed that the MPD was narrowed, with dense lymphoplasmacytic infiltration and severe periductal fibrosis around the MPD. **e** Lymphocytes and plasma cells around the MPD. *Inset* shows IgG4-positive plasma cells. **d** H&E, × 40; **e** H&E, × 200; *inset* in **e** IgG4 staining, × 400

(Fig. 2d, e). Lobular inflammation, atrophy of the parenchyma, and obliterative phlebitis were also observed. No cystic lesion or calcification was detected. On immunohistochemical staining, abundant plasma cells showing strong immunoreactivity for IgG4 were observed, predominantly around the pancreatic ducts (Fig. 2e, inset).

The parenchyma between the two lesions in case 2 was markedly atrophic, and the acinar cells were almost all replaced by fibrous tissue. The MPD was infiltrated with lymphoplasmacytes, including IgG4-positive plasma cells, as observed in the tumorous area.

The serum IgG4 level, measured postoperatively, was elevated in both patients (case 1, 149 mg/dl; case 2, 183 mg/dl [normal, 0–135 mg/dl[8]]).

Discussion

Since Yoshida et al.[1] proposed the term "autoimmune pancreatitis (AIP)" to describe a type of chronic pancreatitis with an autoimmune mechanism in 1995, the concept of AIP has been widely recognized. The characteristics of AIP are described as follows: mild symptoms, increased serum γ-globulin or IgG level and the presence of autoantibodies, diffuse enlargement of the pancreas, diffuse irregular narrowing of the MPD, fibrotic change with lymphoplasmacyte infiltration histopathologically, and a favorable response to steroid therapy.[1] In addition, an elevated concentration of serum IgG4 is reported to be supportive of the diagnosis of AIP.[8]

AIP is frequently associated with other autoimmune disorders such as inflammatory bowel disease and sclerosing cholangitis. Recently, IgG4-related sclerosing diseases of organs other than the pancreas have been documented.[9] Various organs, including the bile duct, gallbladder, salivary gland, and retroperitoneum are considered to be affected multifocally. These organs are characterized by dense infiltrations of IgG4-positive plasma cells.

With an increase of AIP cases being reported, some AIP patients have presented with focal involvement

showing localized narrowing of the MPD and focal swelling of the pancreas.[2–4] As this focal variant of AIP sometimes shows clinical and radiological findings resembling those of pancreatic carcinoma, patients with such findings have frequently been treated surgically for suspected malignancy.[6] Although some diagnostic clues have been reported to differentiate the focal type of AIP from pancreatic carcinoma, such as a fluctuating course of jaundice,[3] homogeneous delayed enhancement on dynamic CT, longer stenosed MPD without upstream dilatation,[4] and raised concentration of serum IgG4,[8] definite discrimination is still difficult in spite of the advances in imaging technology. Even with FDG-PET examination, when the lesion is localized, it can be confused with pancreatic malignancy, because it has been reported to show increased uptake at the affected site of AIP.[10]

Our preoperative diagnosis in both the present patients was pancreatic carcinoma with obstructive pancreatitis demonstrating mass lesions, or double primary pancreatic carcinomas. However, the possibility of mass-forming pancreatitis should have been entertained, considering the fact that cases of double pancreatic carcinomas have seldom been encountered in clinical settings and considering the finding that the tumor markers in both patients were within normal limits. From a retrospective point of view, stenotic or obstructive findings of the MPD on MRCP are not only characteristic of pancreatic carcinoma but may also be suggestive of AIP, because of the low resolution of MRCP.

Interestingly, the parenchyma between the two lesions in case 2, which appeared almost normal on radiological images, was markedly atrophic, and the acinar cells were almost all replaced by fibrosis on microscopic examination. The MPD was infiltrated with lymphoplasmacytes, including IgG4-positive plasma cells. This suggested that this area had suffered from autoimmune inflammation previously and was almost burned out. In other words, the intensity of inflammation may be related to the degree of swelling of the pancreas, and parenchyma that appears normal on radiological examination may be either actually normal or mildly affected without clinical manifestation, or it may already be burned out as in our case 2.

Considering a reported case of AIP that started as a localized form and progressed to diffuse swelling of the pancreas,[11] the focal type of AIP may be regarded as part of the same clinical spectrum as the diffuse type of AIP. Whether the distribution is diffuse or focal may merely reflect the stage or extent of the disease.[12]

The serum IgG4 level, measured postoperatively, was elevated in both of our patients. However, a case of pancreatic cancer in a patient with a high serum IgG4 concentration was recently reported.[13] Without definite criteria, it is still difficult to discriminate the focal type of AIP from pancreatic carcinoma. Therefore, it is clinically important to know that AIP sometimes exhibits multiple lesions within the pancreas.

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