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Histopathologically Proven Autoimmune Pancreatitis Mimicking Neuroendocrine Tumor or Pancreatic Cancer

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Key Words
Differential diagnosis · Endoscopic ultrasonography · Fine-needle biopsy · IgG4

Abstract
Autoimmune pancreatitis (AIP) can be difficult to distinguish from pancreatic cancer. We report a case of histopathologically proven AIP mimicking neuroendocrine tumor (NET) or pancreatic cancer in a 53-year-old man. He was referred to our hospital for further evaluation of a pancreatic mass detected on ultrasonography at a medical check-up. Abdominal ultrasonography showed a 15-mm hypoechoic mass located in the pancreatic body. Computed tomography revealed a tumor without any contrast enhancement, and magnetic resonance imaging demonstrated the mass to be hyperintense on diffusion-weighted image. Endoscopic retrograde cholangiopancreatography revealed slight dilatation of a branch of the pancreatic duct without stricture of the main pancreatic duct. The common bile duct seemed intact. Under suspicion of a non-functioning NET or malignant neoplasm, laparotomy was performed. At laparotomy, an elastic firm and well-circumscribed mass was found suggestive of a non-functioning NET, thus enucleation was performed. Histopathologically, the lesion corresponded to AIP.

Introduction

Autoimmune pancreatitis (AIP) is a type of chronic pancreatitis characterized by an autoimmune inflammatory process in which prominent lymphocyte infiltration with associated fibrosis of the pancreas causes organ dysfunction. AIP is a rare disease.

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Although there has been an increase in the number of reports of AIP in recent years, the overall number of patients is still relatively small. Three series have reported the prevalence of AIP as between 5 and 6% of all patients with chronic pancreatitis [1]. Clinically, AIP is characterized by a preponderance of elderly males, jaundice as a frequent initial symptom, an association with various sclerosing extrapancreatic lesions, such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis, showing similar histological findings to the pancreas with elevated serum IgG or IgG4 levels. Therefore, AIP can be considered to be a pancreatic lesion of IgG4-related systemic disease, and its extrapancreatic lesions are clinical manifestations of organs involved in this systemic disease. AIP sometimes forms a pancreatic mass lesion, which can often be difficult to distinguish from pancreatic cancer, and this diagnostic uncertainty can lead to pancreatic resection for benign disease. We report a case of AIP with the formation of a mass mimicking neuroendocrine tumor (NET) or pancreatic cancer without any specific findings and review the relevant literature.

Case Report

In December 2007, a 53-year-old man was referred to our hospital for further evaluation of a pancreatic mass detected on ultrasonography at a medical check-up. He denied abdominal pain, nausea, vomiting, or weight loss. Vital signs were stable and the findings of physical examination were unremarkable. He had no history of alcohol consumption, smoking, or family history of pancreatic or any other gastrointestinal disease. The results of the laboratory test were almost within normal limits except for slightly elevated gastrin. Levels of pancreatic hormones such as insulin and glucagon were within the normal ranges. IgG serum level was normal and antinuclear antibody test was negative (**table 1**). Abdominal ultrasonography showed a 15-mm hypoechoic mass located in the pancreatic body without dilatation of the main pancreatic duct (**fig. 1**a). Computed tomography revealed a tumor in the pancreatic body without any contrast enhancement (fig. 1b). Magnetic resonance imaging demonstrated the mass to be hyperintense on diffusion-weighted image (fig. 1c). Endoscopic retrograde cholangiopancreatography revealed slight dilatation of a branch of the pancreatic duct in the pancreatic body without stricture of the main pancreatic duct (fig. 1d). The common bile duct seemed intact, and cytology of the pancreatic juice was class II. Endoscopic ultrasonography revealed a partially encapsulated hypoechoic mass in the body of the pancreas abutting the splenic vein. On the basis of these findings, a non-functioning NET or malignant neoplasm were suspected, and laparotomy was performed. At laparotomy, an elastic firm mass well circumscribed by a thin wall suggestive of a NET was found at the pancreatic body. Therefore enucleation was performed (**fig. 2**a). The tumor could be easily dissected. Intraoperative frozen section revealed no evidence of malignancy, thus further excision was not attempted. Histologically, the tumor was partially indiscrete and showed extensive fibrosis, and demonstrated infiltration of lymphocytes, plasma cells, and eosinophils with lymphoid follicles around the pancreatic duct and pancreatic parenchyma, and obliterative venulitis, which are typical features of AIP (fig. 2b). Subsequently, immunohistological examination demonstrated that the pancreatic duct was surrounded by abundant IgG4-positive plasma cells (fig. 2c). On the basis of these findings, the tumor was diagnosed as AIP. Postoperatively, the level of serum IgG increased but then decreased to normal limits without any treatment, and the patient is currently doing well.

Discussion

AIP is a particular type of pancreatitis that is thought to have an autoimmune etiology. Since Yoshida et al. proposed AIP as a disease entity in 1995, many cases of AIP have been reported in Japan, and AIP has received increasing awareness and better understanding worldwide [2]. The diagnosis of focal forms can be difficult as AIP may

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mimic pancreatic adenocarcinoma [3–5]. Therefore, there have been several cases of AIP in whom resection was performed because of a high suspicion of pancreatic cancer [6, 7]. In the past decade, many different diagnostic criteria for AIP have been proposed from Asia, Europe and North America [8–11]. In 2002, diagnostic criteria for AIP were proposed first in the world by the Japan Pancreas Society and revised in 2006 [8, 9]. These criteria are based on the minimum consensus of AIP and aim to avoid misdiagnosing pancreatic cancer as much as possible, but not to screen for AIP. These criteria consist of the following radiological, serological, and histopathological items: (1) radiological imaging showing narrowing of the main pancreatic duct and enlargement of the pancreas, which are characteristic of the disease; (2) laboratory data showing abnormally elevated levels of serum gamma globulin, IgG or IgG4, or the presence of autoantibodies; (3) histopathological examination of the pancreas demonstrating marked fibrosis and prominent infiltration of lymphocytes and plasma cells, which is called lymphoplasmacytic sclerosing pancreatitis (LPSP). For a diagnosis of AIP, criterion 1 must be present, together with criterion 2 and/or criterion 3. However, it is necessary to exclude malignant diseases such as pancreatic or biliary cancer. In 2006, two new sets of diagnostic criteria for AIP were proposed, in Korea and the United States (Mayo Clinic), respectively [10, 11]. These criteria included 'response to steroid' as one of the diagnostic items. When response to steroid therapy is added to the criteria, the diagnostic sensitivity is increased. However, in the diagnostic criteria in Japan, 'response to steroid' is excluded. It is possible that the ready use of steroids by general physicians inexperienced in pancreatic disease will delay the diagnosis of pancreatic cancer, which may lead to cancer progression in some cases [12]. We agree that a trial of steroid therapy should be avoided in the absence of the typical features of AIP, such as in our case, for whom non-functioning NET or pancreatic cancer were suspected without considering AIP in the differential diagnosis, and laparotomy was performed because no specific findings in the criteria of AIP had been seen. Endoscopic ultrasonography-guided fine-needle aspiration is frequently used worldwide to rule out pancreatic cancer, however its yield for cancer is not perfect, and negative biopsy does not rule out cancer [13, 14].

In 2011, the international consensus diagnostic criteria for AIP were proposed. AIP was classified into two types [15]. In one form the histological description is called LPSP or AIP without granulocyte epithelial lesions. The other form is idiopathic duct-centric pancreatitis (IDCP) or AIP with granulocyte epithelial lesions. Clinically, LPSP seems to be the pancreatic manifestation of an IgG4-related systemic disease characterized by elevated serum IgG4 levels and extrapancreatic lesions such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis associated with infiltration with abundant IgG4-positive plasma cells. In contrast, IDCP usually has no or very few IgG4-positive plasma cells, although this can vary. IDCP does not seem to be a systemic disease; rather, it seems to be a pancreas-specific disorder. Since IDCP patients are seronegative and lack other organ involvement, a definitive diagnosis requires pancreatic histology.

The present case seems to be LPSP because of histological features of abundant IgG4-positive cells infiltrating the pancreatic duct. The patient therefore is followed up as an outpatient, with special attention for the appearance of extrapancreatic lesions. Although pancreatic tumor in the present case was incidentally detected during medical check-up, he was asymptomatic, seronegative and revealing atypical features

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on imaging, which seems to be a rare presentation of AIP. Clinically, this type of AIP is difficult to diagnose or to differentiate from pancreatic cancer.

In conclusion, we report a rare case of histopathologically proven AIP in whom the lesion was small and no characteristic findings were obtained by imaging or blood tests.

Disclosure Statement

The authors have no conflict of interest.

Table 1. Laboratory data on admission

Total bilirubin	1.6 mg/dl
Direct bilirubin	0.4 mg/dl
Alkaline phosphatase	287 IU/l
Gamma-glutamyl transpeptidase	36 IU/l
Amylase	91 IU/l
Lipase	24 IU/l
Trypsin	410 IU/l
Elastase-1	160 IU/l
CA19-9	11 ng/ml
DUPAN-2	<25 U/ml
SPan-1	8.1 U/ml
Glucagon	92 pg/ml
Gastrin	340 pg/ml
Insulin	4 mU/ml
IgG	1,260 mg/dl
Antinuclear antibody test	negative

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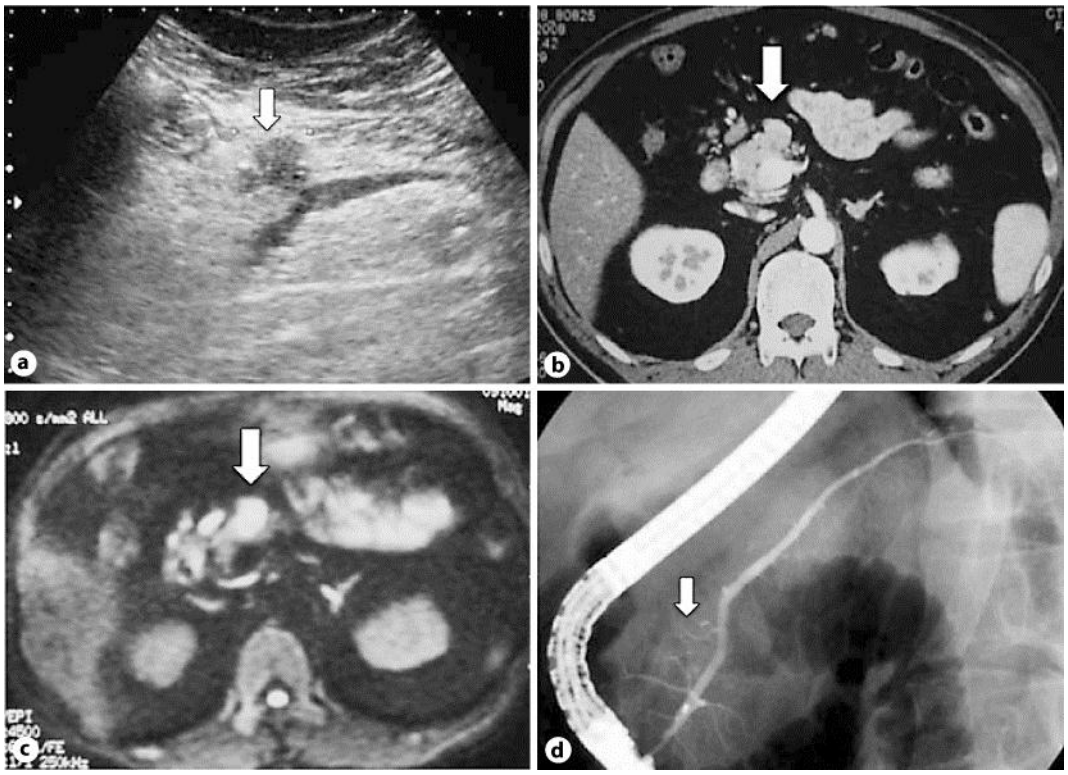

Fig. 1. a Abdominal ultrasonography showed a 15 mm hypoechoic mass located in the pancreatic body without dilatation of the main pancreatic duct (arrow). **b** Computed tomography revealed a tumor in the pancreatic body without any contrast enhancement (arrow). **c** Magnetic resonance imaging demonstrated the mass to be hyperintense on diffusion-weighted image (arrow). **d** Endoscopic retrograde cholangiopancreatography revealed slight dilatation of a branch of the pancreatic duct in the pancreatic body without stricture of the main pancreatic duct and the common bile duct (arrow).

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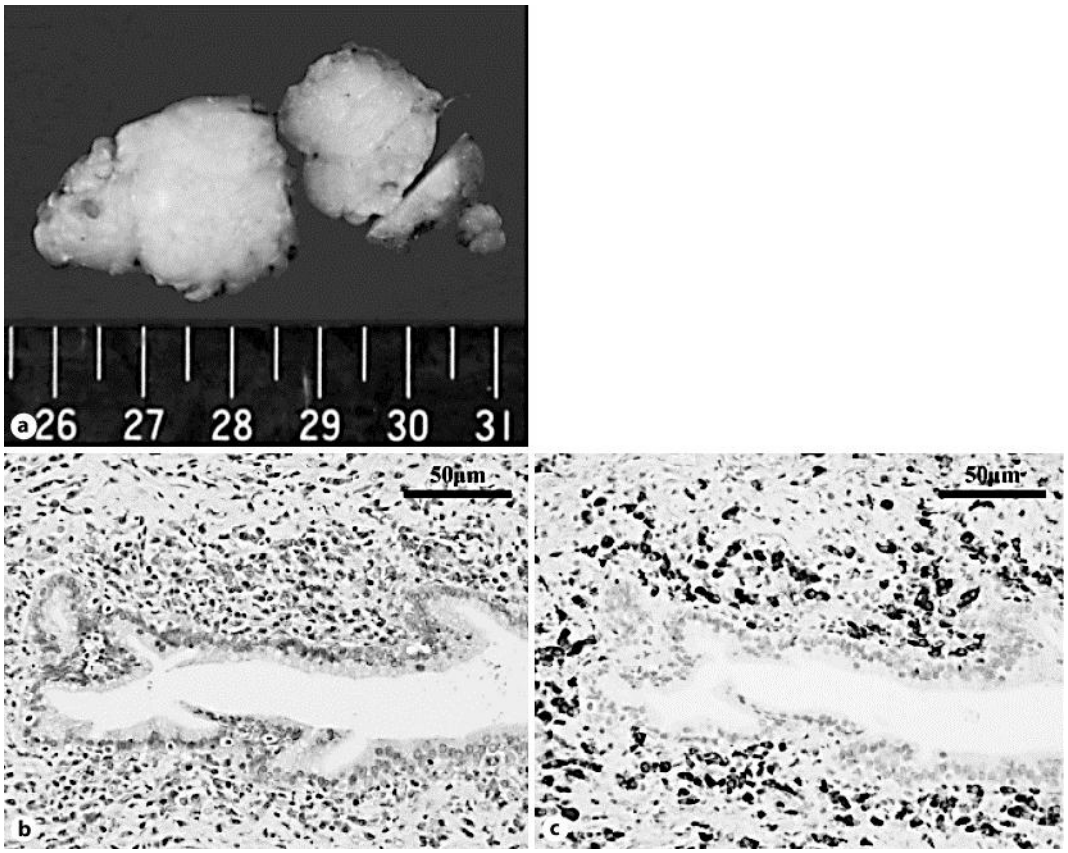

Fig. 2. **a** Macroscopically, a well-circumscribed solid and elastic firm tumor about 2 cm in diameter with gray-yellow coloration was found. **b** Histologically, the tumor was not well-circumscribed partially and showed extensive fibrosis and infiltration of lymphocytes, plasma cells, and eosinophils with lymphoid follicles around the pancreatic duct and pancreatic parenchyma, and obliterative venulitis was seen, which are typical features of AIP. H&E staining, × 40. **c** Immunohistological examination demonstrated that the pancreatic duct was surrounded by abundant IgG4-positive plasma cells. IgG4 staining, × 40.

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