Autoimmune Pancreatitis with Extreme Elevation of DUPAN-2

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Abstract

An 80-year-old woman was admitted to our hospital with complaints of jaundice and liver dysfunction. She was found to have a high titer of serum IgG4, positive rheumatoid factor and marked elevation of DUPAN-2 (11,148 U/ml). Computed tomography showed swelling of the pancreas, and endoscopic retrograde cholangiopancreatography revealed diffuse irregular narrowing of the main pancreatic duct, which are typical findings of autoimmune pancreatitis. There was no evidence of malignancy. Administration of 30 mg/day of prednisolone was started. Computed tomography showed significant regression in the size of the pancreas, and the stenosis of the main pancreatic duct was improved on ERCP. The serum level of DUPAN-2 was also markedly decreased after the treatment.

Key words: autoimmune pancreatitis, DUPAN-2, IgG4, steroid

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Introduction

Autoimmune pancreatitis (AIP) is a recently described clinical entity that is thought to involve an autoimmune mechanism (1-5). AIP is characterized by pancreatic swelling with stenosis of the pancreatic duct. Common presenting symptoms include jaundice, weight loss, and mild abdominal pain, which clinically mimic pancreatic carcinoma (2, 3, 6, 7). It is important to obtain precise knowledge of this condition in order to differentiate it from pancreatic cancer. We encountered a rare case of AIP with a markedly high elevation of DUPAN-2, which improved remarkably after steroid therapy. Though cases of AIP occasionally show a slight elevation of tumor markers, a significant raise of DUPAN-2, as in the present case, has not been reported to date (7-9). In this paper, we also discuss the mechanism of elevated DUPAN-2 in AIP, and highlight the clinical and radiological features which make it possible to differentiate this disorder from pancreatic carcinoma.

Case Report

An 80-year-old woman was admitted to our hospital complaining of jaundice and liver dysfunction. Neither the patient nor her family had any history of liver or pancreas diseases. There was no history of chronic alcohol abuse. Physical examination revealed no particular findings except for jaundice. Laboratory tests revealed liver dysfunction and hyperglycemia, as shown by the following findings: aspartate aminotransferase (AST) 140 IU/L (12-35 IU/L), alanine aminotransferase (ALT) 202 IU/L (6-38 IU/L), γ-glutamyl transpeptidase (γGTP) 990 IU/L (10-47 IU/L), alkaline phosphatase (ALP) 1,642 IU/L (115-359 IU/L), lactate dehydrogenase (LDH) 110 IU/L (119-229 IU/L), total bilirubin (T.Bil) 4.4 mg/dl (0.2-1.2 mg/dl), direct bilirubin (D.Bil) 3.3 mg/dl (0-0.4 mg/dl), amylase (Amy) 41 IU/L (40-131 IU/L), glucose (GLU) 334 mg/dl (70-110 mg/dl), hemoglobin A1c (HbA1c) 7.5% (4.3-5.8%). Carcinoembryonic antigen (CEA) and carbohydrate antigen determinant 19-9 (CA19-9) were within normal limits. DUPAN-2 was 11,148 U/ml (0.150 U/...
Figure 1. Abdominal contrast-enhanced CT on admission showed diffuse enlargement of the pancreas, with homogonous contrast enhancement in the arterial phase. A capsule-like hypoattenuating rim is seen (a, b). The pancreas showed a reduction in size towards normal on the CT taken after the treatment with prednisolone (c, d).

ml) and Span-1 was 417.0 U/ml (0-30 U/ml). Though IgG level was normal, IgG4 was elevated to 237 mg/ml (0-80 mg/dl). Rheumatoid factor was positive. Hepatitis A virus antibody (HA Ab), hepatitis B surface antigen (HBs Ag), hepatitis C virus antibody (HCV Ab), anti-mitochondrial antibody (AMA), anti-nuclear antibody (ANA), anti-smooth muscle antibody, anti-SS-A/Ro (SS-A) and anti-SS-B/La (SS-B) were all negative. Contrast-enhanced CT demonstrated diffuse enlargement of pancreas and dilatation of the intrahepatic bile ducts. The pancreas was typically enhanced with a capsule-like change surrounding it. There were no masses in the pancreas and no swelling of the lymph nodes (Fig. 1a, 1b).

Endoscopic retrograde cholangiopancreatography (ERCP) showed diffuse irregular narrowing of the main pancreatic duct throughout the whole pancreas (Fig. 2a). Stenosis of the lower bile duct with upstream dilation was observed on magnetic resonance cholangiopancreatography (MRCP) (Fig. 3). A diagnosis of AIP was made, based on the criteria of the Japan Pancreas Society (JPS) (10). After informed consent was obtained, the patient was started on oral prednisolone at an initial dose of 30 mg/day. Two months after admission, the size of the whole pancreas was normalized on CT (Fig. 1c, 1d). ERCP (Fig. 2b) showed improvement of both irregularity and narrowing of the main pancreatic duct and stenosis of the lower bile duct. After the treatment, the level of serum DUPAN-2 also decreased significantly to 366 U/ml. The levels of serum IgG4, Span-1, T.Bil and ALP improved to normal range and γGTP decreased to 330 IU/L (Fig. 4).

Discussion

AIP is a relatively new clinical entity which has received increased attention from clinical and basic researchers in the last few years. AIP is characterized by the following: 1) enlargement of the pancreas or irregular narrowing of main pancreatic duct, 2) massive lymphoplasmacytic inflammation of pancreatic parenchyma, 3) hypergammaglobulinemia, and 4) effective steroid therapy (1, 3).

Since AIP can present with obstructive jaundice without severe pain as in acute pancreatitis and frequently causes stenosis of the bile duct, elevation of serum tumor markers, segmental pancreatic enlargement, and angiographic abnormalities, difficulties can arise in making the differential diagnosis of AIP from pancreatic cancer (3).

The histological finding of fibrotic change with lymphocyte infiltration in the pancreas is useful for making the diagnosis of AIP (11). However, since it can be technically difficult to obtain biopsy specimens from the pancreas, it is important to evaluate the clinical features of AIP. Numerous cases are associated with other autoimmune diseases such as
Figure 2. Initial ERCP revealed diffuse irregular narrowing of the main pancreatic duct (a). Two months after the admission, the irregularity and narrowing of the main pancreatic duct showed improvement (b).

Figure 3. MRCP on admission showed stenosis of the lower bile duct with upstream dilation. Severe stenosis of the main pancreatic duct was also seen.

Mikulicz’s disease and primary sclerosing cholangitis (12, 13).

A typical imaging feature of AIP is known as diffuse enlargement of the pancreas (14-19). Although the diffuse form is commonly reported in the literature, focal forms have been also observed, which can be deceptively similar to those of pancreatic cancer (16). Enhanced CT usually shows homogeneous contrast enhancement of swollen pancreas parenchyma (17). This may be useful to differentiate pancreatic carcinoma, as the majority of carcinomas show less contrast enhancement than the normal pancreas (17). Irie et al reported a capsule-like low density rim of contrast enhancement at CT and MR imaging examination in patients with AIP, which was also seen in the present case (18). This rim is presumed to represent fluid collection, peripheral inflammation, or fibrosis and is considered to be one of the characteristics of images in AIP (17, 18). Pancreatic calcification or pseudocyst is seldom observed (15, 17).

ERCP images usually show focal or diffuse irregular narrowing of the main pancreatic duct. Although severe stenosis can be observed, complete occlusion of the MPD is not commonly seen. Stricture of the distal common bile duct is also frequently observed (17). One of the important characteristics of AIP is that these radiological abnormalities are usually normalized after steroid therapy as seen in the present case.

In laboratory data, increased serum gamma-globulin or IgG levels, and the presence of autoantibodies suggest the presence of AIP. Previous studies also indicate a significant rise of IgG4 in serum in AIP patients (20). Since this finding is seldom observed in patients with pancreatic carcinoma, it contributes to the differentiation of pancreatic carcinoma with a high rate of sensitivity (95%) and specificity (97%) (3).

Our case presented with markedly high elevation of DUPAN-2, requiring more careful differential diagnosis of pancreatic and bile duct cancer than in a typical case of AIP. DUPAN-2 is a high molecular weight glycoprotein defined by a monoclonal antibody elicited against a human pancreatic cell line, which has been reportedly increased in the sera of pancreatic adenocarcinoma patients (21) and is also known to be produced in the epithelium of the biliary duct (22). According to the previous studies, DUPAN-2 is elevated in 64-81% and 62-63% of serum samples obtained from pancreatic carcinoma patients and biliary tract carcinoma patients, respectively (23, 24). There are some case reports of benign diseases such as chronic pancreatitis, liver cirrhosis and primary biliary disease with a high level of DUPAN-2 (25, 26). Some of the patients with AIP also show a slight or moderate elevation of serum tumor markers (3). However, it has been reported that the elevated levels of DUPAN-2 in AIP are usually within six times the upper limit of normal range (3, 7-9). Notably, in the present case, serum DUPAN-2 was elevated to 11,148 U/ml without the presence of malignancy. It is demonstrated that CA19-9 and DUPAN-2 is intensely stained in the tissues of chronic pan-
creatitis, especially in the lesion of hyperplasia and ductular proliferation (25). These pancreatic cancer-associated carbohydrate antigens tend to be elevated in patients with stagnation of pancreatic juice due to pancreatic calcification, obstruction, or stenosis of the main pancreatic duct and in those with obstruction of Santorin’s duct (26). And more, Ohshio et al reported that false positives for DUPAN-2 in patients with benign pancreatic and biliary tract disease with obstructive jaundice were more frequent compared to patients without obstructive jaundice (23). In the present case, severe stenosis of the pancreatic duct and obstructive jaundice was observed, which possibly destroyed the epithelium of the pancreatic duct and bile duct, leading to the release of DUPAN-2 into the blood vessels.

CA19-9 and Span-1, also serum markers for pancreatic cancer, can be elevated in cases of AIP. Despite the extreme elevation of DUPAN-2, serum CA19-9 was within the normal range and SPAN-1 was moderately elevated in the present patient. This condition is frequently observed in pancreatic cancer patients with Lewis negative blood groups (24). It is reported that CA19-9 and DUPAN-2 assay systems specifically recognize sialyllacto-N-fucopentaose II (SLF II), and its precursor, sialyllacto-N-tetraose (LSTa), respectively (24). In Lewis-negative phenotype, LSTa is not converted to SLF II because of the lack of the Lewis enzyme. It results in accumulation of the LSTa and the lack of the SLF II, making the characteristic difference among the titer of CA19-9 and DUPAN-2 (24). On the other hand, Span-1 antibody has an affinity for both LSTa and SLF II. Thus, the serum Span-1 tends to be higher than the serum CA19-9 in Lewis negative blood phenotype (24). It has been reported that 4~10% of the Japanese population is negative for Lewis blood phenotype (15). The present patient was possibly Lewis negative, though the Lewis blood type was unfortunately not examined in this case.

In summary, we reported a rare case of AIP with markedly high elevation of DUPAN-2. Our findings show that in patients with obstructive jaundice, enlargement of the pancreas and a high titer of DUPAN-2 should alert us to the differential diagnosis of AIP. In order to avoid an unnecessary operation for suspected pancreatic cancer in AIP patients, a constellation of clinical findings and imaging features is necessary.

References

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