JOP. J Pancreas (Online) 2007; 8(5):621-627.

MULTIMEDIA ARTICLE - Clinical Imaging

An Autopsy Case of Autoimmune Pancreatitis

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ABSTRACT

Context Autoimmune pancreatitis is an increasingly recognized type of chronic pancreatitis, but little is known about the long-term outcome of the disease.

Case report We report an autopsy case of autoimmune pancreatitis. The patient was an 81-year-old Japanese male. He was referred to our department with jaundice in February 1996. ERCP images revealed a severe stricture of the lower part of the common bile duct and irregular narrowing of the main pancreatic duct. A diagnosis of extrahepatic cholangiocarcinoma was made and endoscopic biliary drainage was performed. A stricture of the common bile duct and narrowing of the pancreatic duct had improved on ERCP images when a follow-up examination was performed in November 1998. He was followed up for chronic pancreatitis. The serum IgG and IgG4 levels were increased on serological examination. He died of interstitial pneumonia and congestive heart failure in May 2003. At the autopsy examination, fibrosis was found in the periductal, interlobular and intralobular parts of the pancreas. Focal atrophy of the acinar cells was also identified. There was little infiltration of inflammatory cells into the parenchyma or the stroma of the pancreas. These pathological findings were similar to those of 'conventional' chronic pancreatitis.

Conclusion We present an autopsy case of autoimmune pancreatitis which is a rare finding.

INTRODUCTION

Autoimmune pancreatitis is an increasingly recognized type of chronic pancreatitis, characterized by the following unique clinical, diagnostic imaging and pathological features: high incidence in middle to advanced aged men, pancreatic enlargement, irregularly narrowed pancreatic duct and bile duct stricture on endoscopic retrograde cholangiopancreatography (ERCP) images, increased levels of serum IgG and IgG4, presence of serum autoantibodies, and lymphoplasmacytic infiltration with fibrosis in the pancreas [1, 2]. Little is known about the long-term outcome of autoimmune pancreatitis. Nishino *et al*. [3] reported on the long-term outcome of autoimmune pancreatitis after prednisolone therapy. They found that the pancreatic enlargement and pancreatic duct narrowing improved in all cases, and that pancreatic atrophy developed in some. Bile duct stricture also improved in all patients but recurred in one. There are other follow-up reports about morphological or functional changes [4, 5, 6, 7, 8] but very few reports about pathological changes. The pathological findings of autoimmune pancreatitis in the inactive state are not

well-known. We experienced a case of autoimmune pancreatitis and followed its natural course until death. We herein present the changes in clinical manifestation and the autopsy findings.

CASE REPORT

The patient was an 81-year-old Japanese male. He noticed general pruritus and malaise in January 1996 and was admitted to our Department with jaundice on February 23rd, 1996. He was not a habitual drinker and did not smoke. Past history and family history were not contributory. Physical examination on admission revealed jaundice of the bulbar conjunctiva, slight resistance in the right hypochondrium, and normal body temperature. Laboratory data showed the following values: 20.6 mg/dL total bilirubin, 16.4 mg/dL direct bilirubin, 1,604 IU/L alkaline phosphatase, 48 IU/L serum amylase, 0.89 mg/dL C-reactive protein, 9.0 g/dL total protein, and 3.3 g/dL serum albumin (Table 1). Abdominal CT showed diffuse enlargement of the pancreas (Figure 1). ERCP images revealed a severe stricture of the distal common bile duct, and cholangiography via a nasobiliary drainage tube showed irregularity of the intrahepatic

Table 1. Laboratory data at first admission (February 23rd, 1996).

Test	Value (reference range)
Peripheral blood	
White blood cells (mL^{-1})	4,700 (3,500-8,500)
Red blood cells ($x10^4\ mL^{-1}$)	334 (425-571)
Hemoglobin (g/dL)	10.5 (13.4-17.6)
Hematocrit (%)	32.9 (39.6-52.0)
Platelets ($x10^4\ mL^{-1}$)	21.2 (12.0-37.0)
Blood chemistry	
Total protein (g/dL)	9.0 (6.0-8.0)
Albumin (g/dL)	3.3 (3.8-5.3)
Total bilirubin (mg/dL)	20.6 (0.2-1.0)
Direct bilirubin (mg/dL)	16.4 (0.1-0.6)
Alkaline phosphatases (IU/L)	1,604 (96-284)
AST - GOT) (IU/L)	101 (8-40)
ALT - GPT (IU/L)	127 (5-37)
LDH (IU/L)	500 (230-460)
GGT (IU/L)	590 (7-32)
Blood urea nitrogen (mg/dL)	15 (6-20)
Creatinine (mg/dL)	0.8 (0.4-1.3)
Amylase (IU/L)	48 (38-175)
Lipase (IU/L)	9 (17-52)
CRP (mg/dL)	0.89 (0-0.30)
Coagulation tests	
Prothrombin time (sec)	11.6 (10.1-12.1)
APTT (sec)	27.1 (22.5-34.5)
Fibrinogen (mg/dL)	353 (200-400)
Tumor markers	
CEA (ng/mL)	3.6 (0-4.9)
CA 19-9 (U/mL)	184 (0-29)
Alpha-fetoprotein (ng/mL)	2 (0-19)
Serology	
HBs Ag	Negative
HBs Ab	Negative
HCV	Negative

APTT: activated partial thromboplastin time

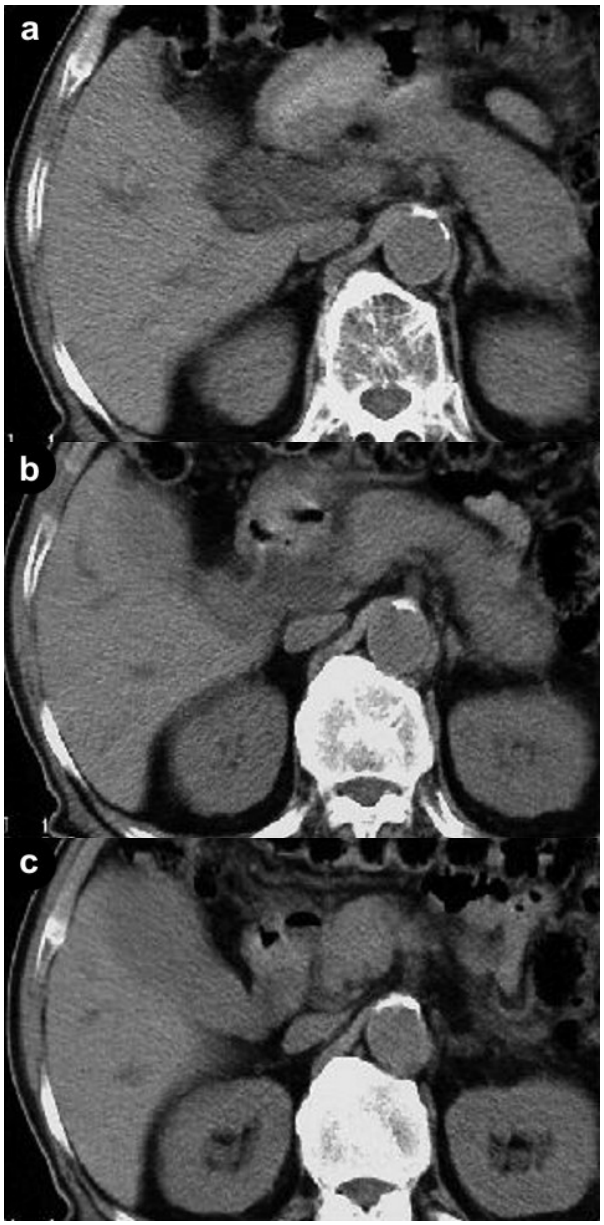

Figure 1. a. b. c. Abdominal computed tomography findings at first admission (February 1996). Note the diffuse enlargement of the pancreas and dilatation of the biliary tract.

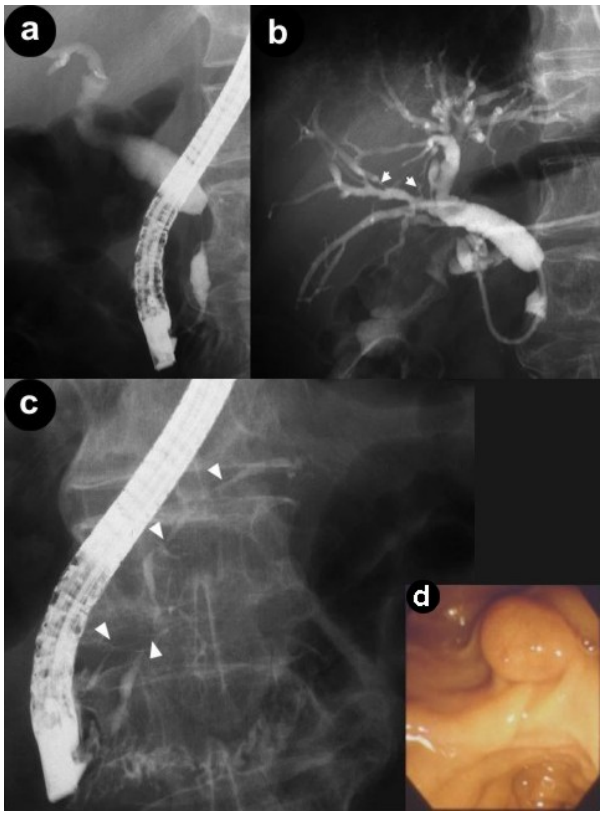

Figure 2. Findings at first admission (February 1996): **a.** endoscopic retrograde cholangiography; **b.** cholangiography via nasobiliary drainage tube; **c. d.** endoscopic retrograde pancreatography. **a.** Note the severe stricture of the distal bile duct. **b.** Irregularity of intrahepatic bile ducts (arrows). **c.** Irregular narrowing of the main pancreatic duct. **d.** Swelling of the papilla of Vater.

and hilar bile ducts (Figures 2a, 2b). Endoscopic retrograde pancreatography revealed irregular narrowing of the main pancreatic duct and swelling of the papilla of Vater (Figures 2c, 2d). Following ERCP, we performed a transpapillary forceps biopsy.

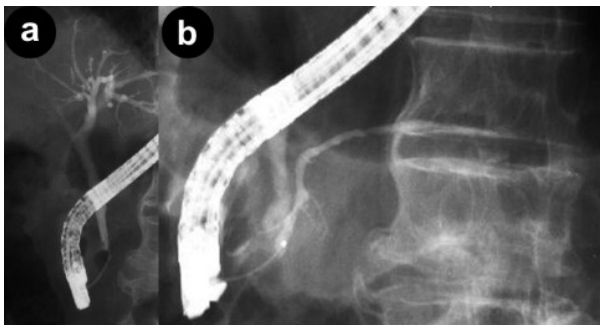

Figure 3. Endoscopic retrograde cholangiopancreatography findings (**a.** cholangiogram; **b.** pancreatogram) at second admission (November 1998). Bile duct stricture and narrowing of the main pancreatic duct obviously improved.

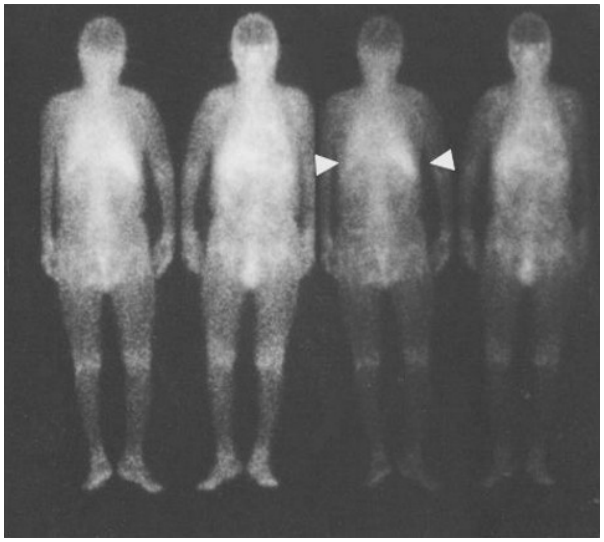

Figure 4. Gallium scintigraphy findings (January 1999). Abnormal uptake was seen in the bilateral lower lung fields. No hilar adenopathy or sialadenitis was found.

Although the biopsy specimen did not reveal malignancy, cholangiocarcinoma was thought to be the most likely diagnosis. Surgery was not performed due to the advanced age of the patient. The patient was discharged after endoscopic biliary drainage was performed . A plastic stent, 12 Fr in diameter, was used for the endoscopic biliary drainage. At his second admission in November 1998, enlargement of the pancreas, narrowing of the main pancreatic duct and a stricture of the common bile duct had improved on CT and ERCP (Figure 3) without steroid therapy. The serum IgG level was elevated (2,490 mg/dL; reference range: 607-1,621 mg/dL). The antinuclear antibody (ANA) was positive and the titer was x320. After these investigations, he was diagnosed conclusively as having chronic pancreatitis, and the biliary stent was removed. The stent had never been exchanged until this time because he had temporarily dropped out from follow-up from 1996 to 1998. A Gallium scintigraphy in January 1999 revealed no abnormal uptake, except in the bilateral lower lung fields, which was suspected to be interstitial pneumonia (Figure 4). On follow-up ERCP, 4 years after onset (November 2000), the common bile duct stricture had not recurred, and the papilla of Vater swelling had improved (Figures 5a, 5b). The narrowing of the main pancreatic duct had

improved further (Figure 5c). Abdominal CT in January 2002 showed atrophy of the pancreas (Figure 6). The serum IgG level was higher than the upper reference limit throughout the course after 1998, although it was not determined at the first admission. The serum IgG4 level was checked once in October 2001 (264 mg/dL; reference range 6-140 mg/dL). On two occasions, the N-benzoyl-L-tyrosyl-para-aminobenzoic acid (BT-PAVA) excretion value showed abnormally low levels (27% and 28%, respectively; reference range 73.4-90.4%). The hemoglobin A1c (HbA1c) level was within the reference range.

He died on June 2nd, 2003 from interstitial pneumonia and congestive heart failure. There had been no steroid administration during the entire period. At autopsy, fibrosis was found in the periductal, interlobular and intralobular parts of the pancreas, and atrophy of the acinar cells was identified (Figure 7). There was very little periductal lymphoplasmacytic infiltration.

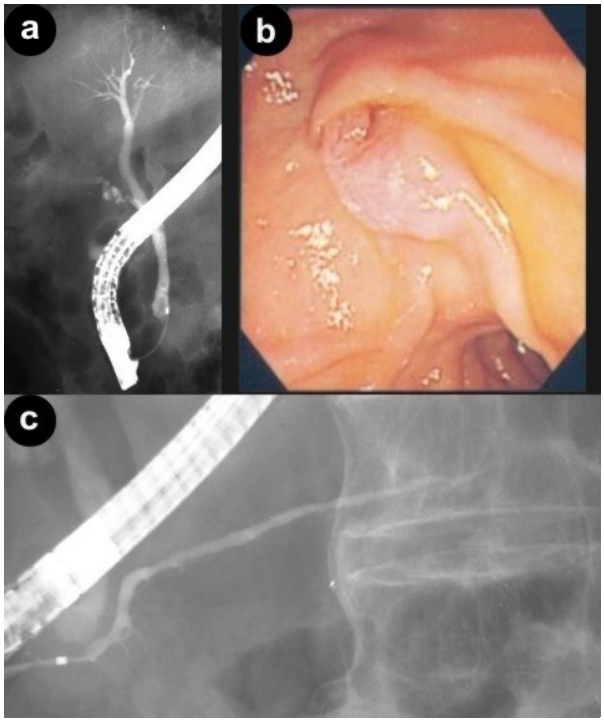

Figure 5. Endoscopic retrograde cholangiopancreatography findings on third admission (November 2000). **a.** No stricture was seen on cholangiography. **b.** Swelling of the papilla of Vater had improved. **c.** Pancreatography findings improved further. Only a slight irregularity of the main pancreatic duct remained.

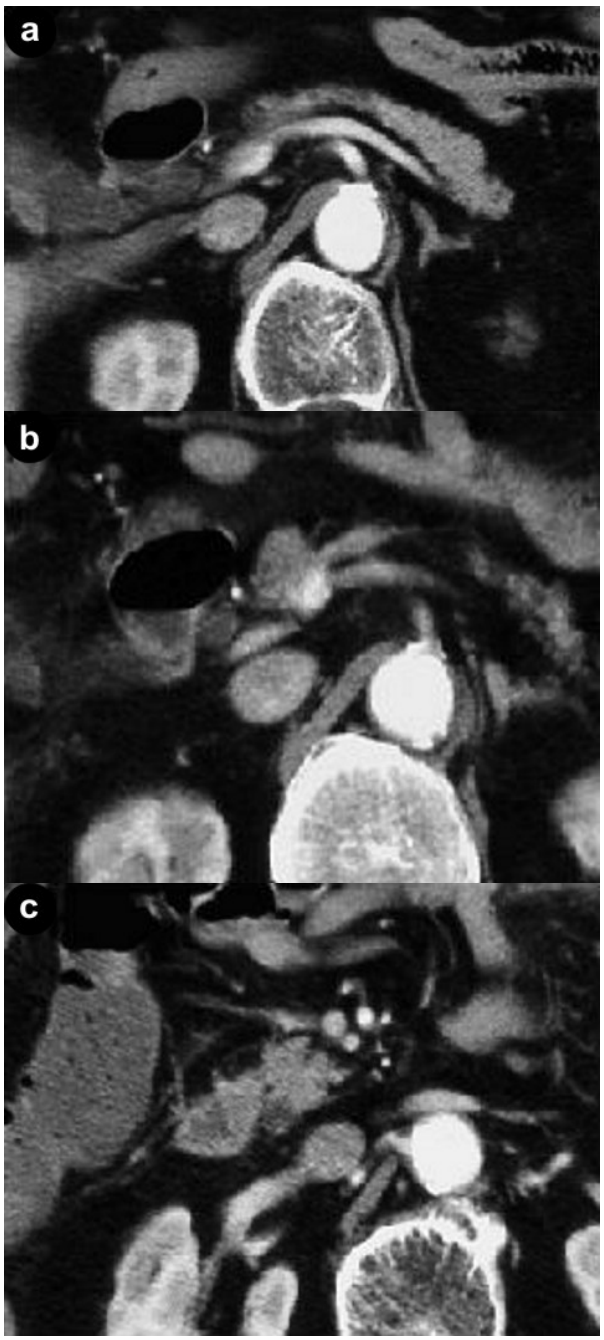

Figure 6. a. b. c. Abdominal computed tomography findings 6 years after onset (January 2002). Note that atrophy of the pancreas has become evident.

IgG4 positive plasmacyte infiltration was not identified on immunohistostaining. There was no obliterative phlebitis, and neither pseudocysts nor calculi were seen in the pancreas. Examination of the kidneys revealed partial necrosis of the glomeruli with mild interstitial lymphocyte infiltration. There was interstitial nephritis but no IgG4 positive plasmacyte infiltration. There was periductal fibrosis of both the intrahepatic and the extrahepatic bile ducts, but very little

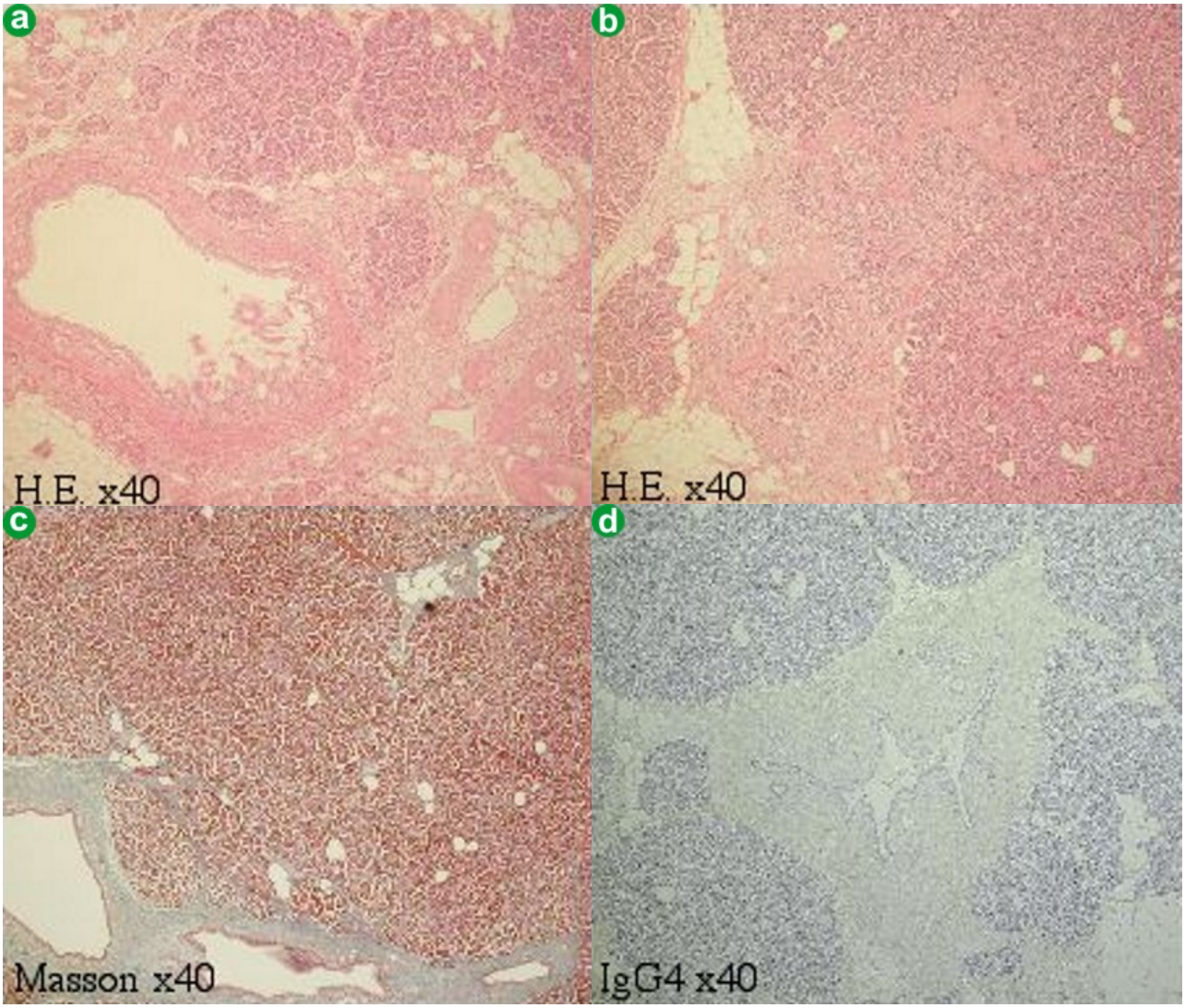

Figure 7. Histology of the autopsy specimens of the pancreas. **a. b.** Atrophy of the acinar cells and fibrosis. Very little infiltration of inflammatory cells (H&E x40). **c.** Periductal and interlobular fibrosis clearly seen (Masson x40). **d.** Immunohistostaining revealed no IgG4 positive plasmacytes (x40).

infiltration by inflammatory cells (Figure 8). Severe fibrosis and severe inflammatory cell infiltration were found in the alveolar walls and the alveoli of the lungs.

DISCUSSION

The number of reported cases of autoimmune pancreatitis is increasing and, recently, it has been widely recognized as a clinical entity of chronic pancreatitis. Many groups have cited the diagnostic criteria proposed by the Japan Pancreas Society [9], which include serological, imaging and pathological findings. American and Korean groups suggested other diagnostic criteria in 2006, which also include the response to steroid therapy [10, 11]. Our case showed diffuse enlargement of the gland, irregular narrowing of the main pancreatic duct, and abnormal levels of serum IgG, IgG4 and ANA. These findings fulfill all three diagnostic criteria for autoimmune pancreatitis. Swelling of the papilla of Vater is also sometimes found [12]. These imaging findings improved spontaneously in this case without steroid therapy, which has also been described in other reports [4, 8], and is compatible with autoimmune pancreatitis. Reduced pancreatic exocrine function is also compatible with autoimmune pancreatitis [7].

In this case there were no co-existing collagen diseases, and no clear extrapancreatic lesions such as hilar adenopathy, sialadenitis or retroperitoneal fibrosis. It is not known why the serum IgG levels remained high.

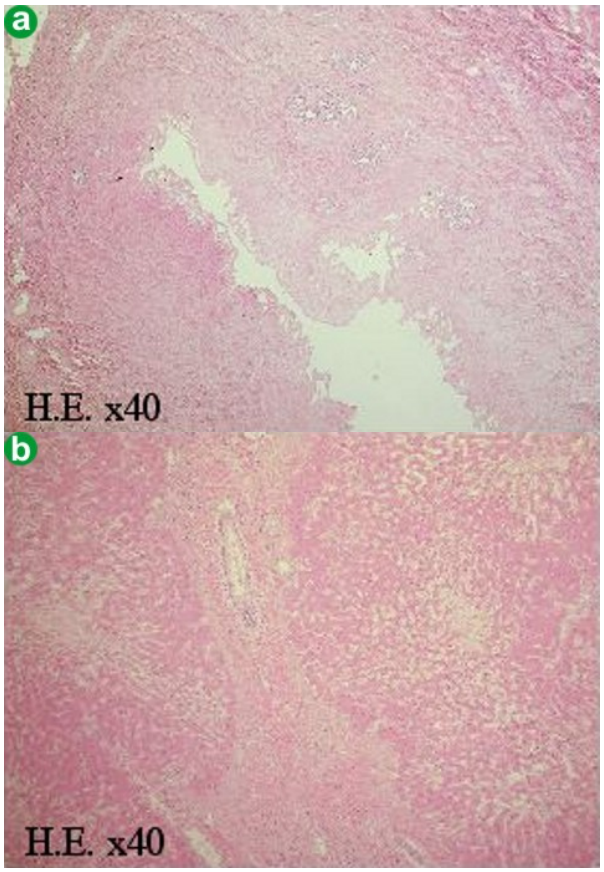

Figure 8. a. Histology of the intrapancreatic bile duct (H&E x40). Periductal fibrosis is obvious and there is minor inflammatory cell infiltration. **b.** Histology of the intrahepatic bile duct (H&E x40). Periductal fibrosis can be clearly seen. Minor infiltration of the inflammatory cells. Hepatic sinusoids dilated due to congestion.

Histopathological findings of autoimmune pancreatitis have been reported as follows: infiltration of inflammatory cells around large and medium sized pancreatic ducts, IgG4 positive plasma cell infiltration, fibrotic changes, atrophy of acinar cells and obliterated phlebitis [13, 14, 15]. At autopsy, very few inflammatory cells and IgG4 positive plasma cells were found in the pancreas, but fibrotic changes and acinar cell atrophy were detected. There have only been two reports in the English literature about histological changes in autoimmune pancreatitis after steroid therapy [16, 17]. These reports describe histological improvement including amelioration of the fibrosis and inflammatory cell infiltration, and a substantial increase in the number of pancreatic acinar cells. These findings may support reversibility of the histological findings if autoimmune pancreatitis patients are treated with steroids, but the follow-up period seems short in these reports. Other reports on the long-term outcome of autoimmune pancreatitis after steroid therapy described pancreatic atrophy and stone formation in some cases [3, 8, 18]. It is not clear whether histological and morphological findings improve or deteriorate after steroid therapy in the long term.

In our case, there was no steroid administration through the course because the patient had had no symptoms of autoimmune pancreatitis after the second admission in 1998. The pathological findings and atrophy of the pancreas on CT images seemed more compatible with ‘conventional’ chronic pancreatitis than with autoimmune pancreatitis. This implies that some autoimmune pancreatitis cases may change into ‘conventional’ chronic pancreatitis without steroid therapy and that a diagnosis of autoimmune pancreatitis should be made in an early phase of the disease. It is also possible that IgG4 positive plasma cell infiltration is of use in diagnosis only in an early phase of autoimmune pancreatitis. In the late phase, the diagnosis of autoimmune pancreatitis may be made difficult by other pathological findings.

To our knowledge, this is the first autopsy case of autoimmune pancreatitis which has evolved according to its natural history. Additional experience is needed to clarify whether some autoimmune pancreatitis cases change to ‘conventional’ chronic pancreatitis or not.

Received May 15th, 2007 - Accepted June 5th, 2007

Keywords Autoimmune Diseases; Autopsy; Pancreatitis, Chronic

Conflict of interest The authors have no potential conflicts of interest

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Document URL: http://www.joplink.net/prev/200709/02.html

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