

Rapid communication

A new clinicopathological entity of IgG4-related autoimmune disease

TERUMI KAMISAWA¹, NOBUAKI FUNATA², YUKIKO HAYASHI², YOSHINOBU EISHI³, MORIO KOIKE³, KOUJI TSURUTA⁴,
ATSUTAKE OKAMOTO⁴, NAOTO EGAWA¹, and HITOSHI NAKAJIMA¹

¹Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan

²Department of Pathology, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

³Department of Pathology, Tokyo Medical and Dental University School of Medicine, Tokyo, Japan

⁴Department of Surgery, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

Background. Autoimmune pancreatitis (AIP) is occasionally associated with other autoimmune diseases.

Methods. To investigate the pathophysiology of AIP, we immunohistochemically examined the pancreas and other organs in eight patients with AIP, and in controls, using anti-CD4-T and CD8-T cell subsets, as well as IgG4 antibodies. **Results.** In AIP patients, severe or moderate infiltration of IgG4-positive plasma cells associated with CD4- or CD8-positive T lymphocytes was detected in the peripancreatic tissue (6/6), bile duct (8/8), gallbladder (8/8), portal area of the liver (3/3), gastric mucosa (5/7), colonic mucosa (2/2), salivary glands (1/2), lymph nodes (6/6), and bone marrow (2/2), as well as in the pancreas (8/8). There were few IgG4-positive plasma cells at the same sites in controls. **Conclusions.** These results suggest that AIP is not simply pancreatitis but that it is a pancreatic lesion involved in IgG4-related systemic disease with extensive organ involvement. We propose a new clinicopathological entity, of a systemic IgG4-related autoimmune disease in which AIP and its associated diseases might be involved.

Key words: autoimmune pancreatitis, IgG4, autoimmune disease

Introduction

Pancreatitis often coexists with an autoimmune disease, such as Sjogren's syndrome or primary sclerosing cholangitis.¹ A type of chronic pancreatitis in which an autoimmune mechanism may be involved in the pathogenesis is proposed as autoimmune pancreatitis (AIP).

This is a distinct condition characterized by the following clinical, morphological, and histological features: diffuse enlargement of the pancreas; diffuse, irregular narrowing of the main pancreatic duct; increased levels of serum gammaglobulin or IgG; presence of autoantibodies; fibrotic changes with lymphoplasmacytic infiltration; and clinical improvement by steroid therapy.² However, the autoimmune mechanisms that contribute to the pathogenesis or physiology of pancreatitis remain poorly understood. To investigate the pathophysiology of AIP, we immunohistochemically examined the pancreas and other organs of patients with AIP. We now propose a new clinicopathological entity of IgG4-related autoimmune disease.

Subjects and methods

We immunohistochemically examined the organs of seven male patients and one female patient (age range, 63–79 years; mean, 69.3 years) who were confirmed as having AIP according to the characteristic histological findings. The initial symptom was obstructive jaundice, and the extrahepatic bile duct was significantly stenosed in all patients. The main pancreatic duct had narrowed and the pancreas was swollen in all patients. Levels of serum IgG were elevated in four patients (patients 1, 2, 3, and 7). Levels of serum IgG4 were significantly elevated in two patients examined (patients 1 and 6). Autoantibodies were positive in all patients. Six patients underwent pancreatoduodenectomy due to suspected pancreatic tumor, and two underwent bypass surgery with pancreatic biopsy. Various organs from these patients were histologically examined during the course of AIP after we had obtained informed consent.

We immunohistochemically examined various sites in these eight patients, as follows. The pancreas, peripancreatic tissue, bile duct, gallbladder, duodenum, stomach, and peripancreatic lymph nodes were obtained

from six pancreatoduodenectomy procedures. The following were obtained from biopsy specimens: pancreatic tissues ($n = 2$), hepatic tissues ($n = 3$), gastric mucosa ($n = 1$), colonic mucosa ($n = 2$), pulmonary tissues ($n = 1$) salivary glands ($n = 2$), and cervical lymph node ($n = 1$). Two bile ducts and gallbladders were resected, and two bone marrow samples were aspirated. Sections were immunostained using anti-CD4-T (Novocastra, Newcastle upon Tyne, UK), CD8-T (DakoCytomation, Glostrup, Denmark), and CD20-B (DakoCytomation) cell subsets, as well as IgG (MBL, Nagoya, Japan) and IgG4 (The Binding Site, Birmingham, UK) antibodies with avidin-biotin-peroxidase complex (ABC). The number of immunohistochemically identified cells per high power field (HPF) in each specimen was counted. The degree of infiltrated inflammatory cells was classified as severe, more than 30/HPF; moderate, 30–10/HPF; slight, 10–5/HPF; or few, fewer than 5/HPF. We also similarly examined pancreatoduodenectomy specimens from ten patients with chronic alcoholic pancreatitis; biopsied salivary glands from five patients with Sjogren's syndrome; and biopsied or resected liver, stomach, colon, lung, and bone marrow of five control patients.

Results and discussion

Histologically, diffuse lymphoplasmacytic infiltration and fibrosis were significant in the pancreas, peripancreatic retroperitoneal tissue, bile duct wall, and salivary glands of patients with AIP. Diffuse infiltrates in the pancreas predominantly consisted of CD4- or CD8-positive T lymphocytes and IgG4-positive plasma cells rather than CD20-positive B lymphocytes. This profile of cellular infiltration was identical to that of the peripancreatic tissue, bile duct, and gallbladder. Severe or moderate IgG- and IgG4-positive plasmacytic infiltration was associated with CD4- or CD8-positive T lymphocytes in the portal area of the liver (3/3), the stomach (5/7), colon (2/2), salivary glands (1/2), lymph nodes (6/6), and bone marrow (2/2) (Fig. 1 and Table 1). Few IgG4-positive plasma cells were detected in identical control specimens.

Hamano et al.³ reported that serum concentrations of IgG4 were significantly increased in patients with AIP, and they demonstrated abundant infiltration of IgG4-positive plasma cells in the ureteral and pancreatic lesions of patients with AIP associated with retroperitoneal fibrosis.⁴ We previously suggested a close relationship between AIP and multifocal fibrosclerosis, including sclerosing cholangitis, retroperitoneal fibrosis, and Sjogren's syndrome, from the development of specific inflammation in the biliary tract and salivary gland, as well as in the pancreas of patients with AIP.⁵

Table 1. Distribution of IgG4-positive plasma cells in the organs and tissues of eight patients with IgG4-related autoimmune pancreatitis

IgG4-positive plasma cells	Peripancreatic		Bile duct	Gallbladder	Liver	Stomach	Duodenum	Colon	Lung	Salivary gland	Lymph node	Bone marrow
	Pancreas	tissues										
>30/HPF	1, 2, 3, 4, 5, 6, 7, 8	1, 2, 3, 4, 5, 6	1, 3, 4, 5, 6, 7, 8	1, 4, 5, 7, 8	6, 7	1, 3, 6		8		1	1, 2, 3, 5, 6	
30–10/HPF			2	2, 3, 6	1	5, 8		7			4	
10–5/HPF						2, 4	1, 3, 6			2		1, 5
<5/HPF							2, 4, 5		3			

Numbers in the table denote patients 1 to 8 with autoimmune pancreatitis
HPF, high-power field

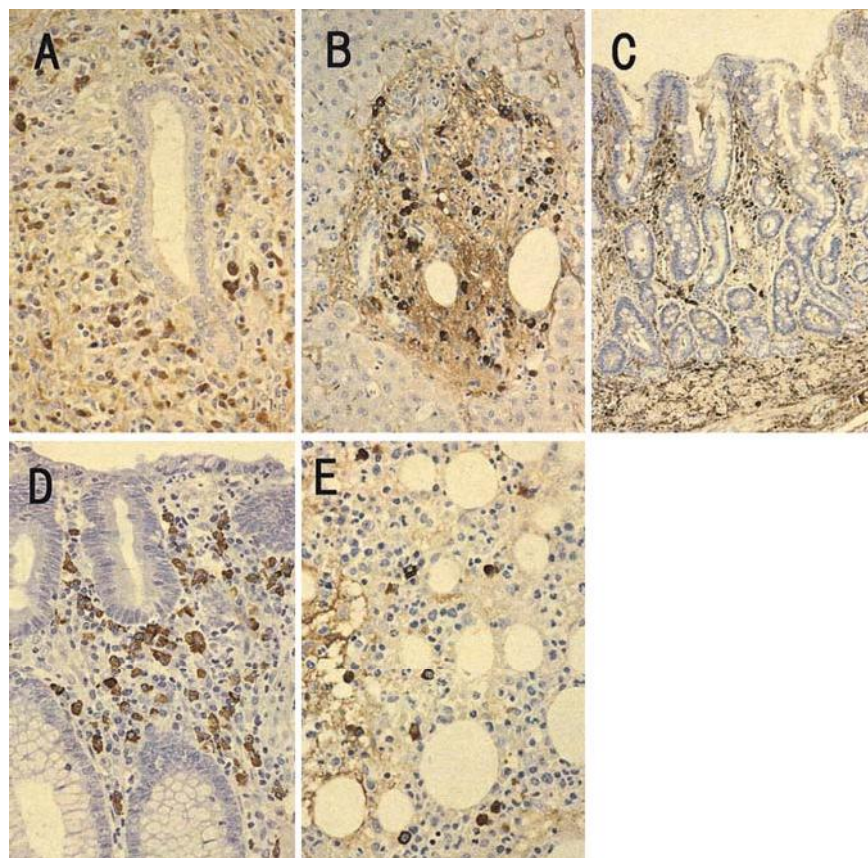


Fig. 1A–E. IgG4 immunostaining in organs and tissues of patients with autoimmune pancreatitis. IgG4-positive plasma cells are abundant in the pancreas (**A**), portal area of the liver (**B**), gastric mucosa (**C**), colonic mucosa (**D**), and bone marrow (**E**). **A** $\times 50$; **B** $\times 50$; **C** $\times 33$; **D** $\times 50$; **E** $\times 50$

However, the present study found that IgG4-positive plasma cells had extensively infiltrated the organs and tissues of patients with AIP, but not those of controls. These results suggest that AIP is not simply pancreatitis but that it is a pancreatic lesion involved in IgG4-related systemic disease. Furthermore, stenosis of the bile duct, sialoadenitis, and retroperitoneal mass associated with AIP may be induced by mechanisms that differ from those of primary sclerosing cholangitis, Sjogren's syndrome, and retroperitoneal fibrosis, because the bile duct, salivary glands, and retroperitoneum are involved in this systemic disease. We therefore propose a novel clinicopathological entity, of IgG4-related autoimmune disease characterized by extensive IgG4-positive plasma cell infiltration of organs together with CD4- or CD8-positive T lymphocytes.

In conclusion, we propose a new entity, of systemic IgG4-related autoimmune disease with extensive organ involvement. Clinical manifestations are apparent in

the pancreas, bile duct, retroperitoneum, and salivary glands, in which tissues fibrosis is pathologically induced.

References

1. Montefusco PP, Geiss AC, Bronzo RL, Randall S, Kahn E, Mckinley MJ. Sclerosing cholangitis, chronic pancreatitis, and Sjogren's syndrome: a syndrome complex. *Am J Surg* 1984;147:822–6.
2. Okazaki K, Chiba T. Autoimmune related pancreatitis. *Gut* 2002; 51:1–4.
3. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001;344:732–8.
4. Hamano H, Kawa S, Ochi Y, Unno H, Shiba N, Wajiki M, et al. Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. *Lancet* 2002;359:1403–4.
5. Kamisawa T, Funata N, Hayashi Y, Tsuruta K, Okamoto A, Egawa N, et al. Close relationship between autoimmune pancreatitis and multifocal fibrosclerosis. *Gut* 2003;52:683–7.

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