INTERNAL MEDICINE

□ CASE REPORT □

Two Siblings with Type 1 Autoimmune Pancreatitis

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Abstract

Type 1 autoimmune pancreatitis (AIP) is characterized by a high serum IgG4 concentration and is closely associated with the *HLA-DRB1*04:05-DQB1*04:01* haplotype, for which family studies may disclose its immunogenetic significance. In the present study, we encountered two male siblings with type 1 AIP who exhibited diffuse pancreatic swelling with a capsule-like rim and diffuse pancreatic duct stricture. The younger brother also displayed characteristic IgG4-related sialadenitis and retroperitoneal fibrosis. Contrary to our expectations, the siblings showed only normal or slightly elevated values of serum IgG4 and no *HLA DRB1*04:05-DQB1*04:01* haplotype, suggesting that type 1 autoimmune pancreatitis is associated with multiple immunogenetic factors.

Key words: autoimmune pancreatitis, IgG4, sibling

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Introduction

Autoimmune pancreatitis (AIP) is a specific type of chronic pancreatitis that is believed to be caused by autoimmune mechanisms (1). AIP was recently classified into two types, of which type 1 AIP has been exclusively reported in the Japanese literature (2, 3). The major clinical findings of type 1 AIP, including an older male preponderance, obstructive jaundice, pancreatic swelling and narrowing of the pancreatic duct, mimic those of pancreatic cancer and indicate that differentiating between AIP and pancreatic cancer is a crucial clinical issue. Other characteristic features of type 1 AIP include a high serum IgG4 concentration (4) and abundant IgG4-bearing plasma cell infiltration in the affected pancreatic tissue (5), which are considered to be the serological and pathological hallmarks of this condition, respectively. Patients with type 1 AIP frequently exhibit various extrapancreatic lesions, such as dacryoadenitis, sialadenitis, sclerosing cholangitis and retroperitoneal fibrosis (6). These lesions commonly share the pathological finding of IgG4-bearing plasma cell infiltration in the affected organ with pancreatic lesions (5), which suggests the presence of a common pathogenic background now termed the comprehensive disease concept of IgG4-related disease (7). AIP is now recognized to be a pancreatic manifestation of IgG4-related disease.

Similar to other autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus, both environmental and genetic factors seem to contribute to the pathogenesis of AIP. Regarding genetic factors, the human leukocyte antigen (HLA) and various susceptibility genes related to autoimmunity have been intensively investigated (8-11). Although genetic factors are likely closely related to familial occurrence, there are no reports of familial AIP and no familial surveys clinically investigating genetic factors. In this report, we present the cases of two male siblings with AIP, which may provide useful information related to commonly shared genetic aspects within families regarding the pathogenesis of this disease, with special reference to IgG4 and HLA alleles such as *DRB1*04:05* and *DQB1*04:01*.

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Table 1. Laboratory Findings

	Normal range	Patient 1: Elder brother	Patient 2: Younger brother
WBC	2.97-9.13 × 10^3 /μL	4.09 × 10^3	5.48 × 10^3
Eo	0.58-10.06 %	6.0	3.0
RBC	4.14-5.63 × 10^6 /μL	4.01 × 10^6	4.36 × 10^6
Plt	14.3-33.3 × 10^4 /μL	28.8 × 10^4	17.3 × 10^4
TP	6.8-8.3 g/dL	7.5	6.4
Alb	4.2-5.1 g/dL	4.1	3.6
BUN	9-22 mg/dL	26	7
Cr	0.6-1.0 mg/dL	1.14	0.82
Total bilirubin	0.3-1.2 mg/dL	2.3	0.66
AST	12-37 IU/L	220	15
ALT	7-45 IU/L	312	14
ALP	124-367 IU/L	1,049	549
γ-GTP	8-50 IU/L	373	179
Amylase	44-127 IU/L	129	128
Lipase	13-55 IU/L	125	13
HbA1c	4.3-5.8 %	5.7	6.5
CRP	< 0.1 mg/dL	0.16	0.05
CA19-9	< 37 U/mL	13.5	25.6
IgG	<1,800 mg/dL	1,523	1,199
IgG4	<135 mg/dL	206	33
C3	86-160 mg/dL	137	97
C4	17-45 mg/dL	25.5	18.1
FANA	<×40	×80	(-)
RF	<10	74	2
Circulating immune complex	<4.2 μg/mL	4.9	< 2.0
Soluble interleukin 2-receptor	122-496 U/mL	806	715
β_2-microgloburin	0.9-1.9 mg/dL	4.2	2.2

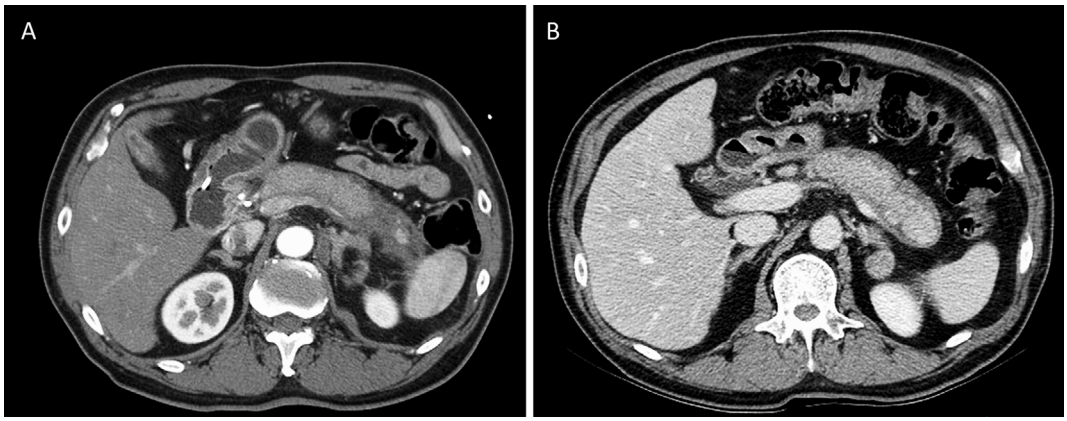

Figure 1. Enhanced CT of pancreatic parenchymal imaging showing diffuse swelling and a capsule-like rim in (A) the elder brother and (B) the younger brother.

Case Reports

Case 1: Elder brother

Patient 1 was a 59-year-old man at the time of diagnosis. In 2003, he visited a nearby clinic complaining of epigastralgia and anorexia, where he was diagnosed to have jaundice. A physical examination disclosed ocular jaundice without lachrymal or salivary gland swelling and no hepatosplenomegaly. The patient's blood test results revealed obstructive jaundice and various abnormal activity marker values, as summarized in Table 1. The IgG4 level was slightly elevated at 206 mg/dL. Computed tomography (CT) and magnetic resonance imaging (MRI) showed diffuse swelling and a capsule-like rim of the pancreas (Fig. 1A). Endoscopic retrograde cholangiopancreatography (ERCP) disclosed diffuse narrowing of the main pancreatic duct (Fig. 2A) and lower bile duct stricture with dilatation of the extrapancreatic bile duct. Gallium 67 scintigraphy showed positive images in the hilar lymph node and pancreas; however, CT and MRI showed no other extrapancreatic lesions, including dacryoadenitis, sialadenitis, sclerosing cholangitis or retroperitoneal fibrosis. Prednisolone treatment resulted in amelioration of the clinical, laboratory and imaging findings. The patient was diagnosed as having type 1 AIP based on

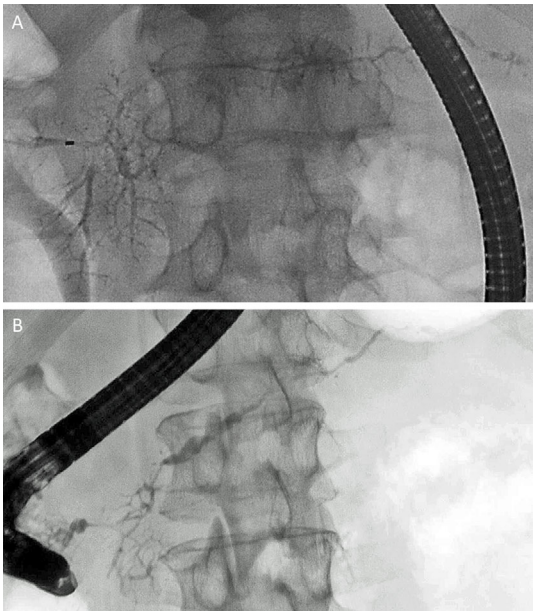

Figure 2. Duct imaging endoscopic retrograde pancreatography (ERP) of (A) the elder brother and (B) the younger brother showing long (1/3 the length of the main pancreatic duct) and multiple strictures without any marked upstream dilatation.

the International Consensus Diagnostic Criteria (ICDC) for AIP (Table 2) (12). His HLA typing results were *A*24:02/-*, *B*52:01/-*, *DRB1*15:02/-* and *DQB1*06:01/-*.

Case 2: Younger brother

Patient 2 was a 61-year-old man at the time of diagnosis. In 2011, a blood test performed at a routine health examination revealed a high serum γ-GTP concentration. Two months later, the patient visited a nearby clinic complaining of a 5-kg weight loss. A physical examination disclosed symmetrical salivary gland swelling without jaundice. Blood tests indicated slight serum elevations in the levels of biliary enzymes, soluble interleukin 2 receptor (sIL2R), β2 microglobulin (β2MG) and HbA1c, but not IgG4 or other activity markers (Table 1). CT and MRI showed diffuse swelling and a capsule-like rim of the pancreas (Fig. 1B). ERCP revealed diffuse narrowing of the main pancreatic duct (Fig. 2B) and lower bile duct stricture with dilatation of the extrapancreatic bile duct. CT, MRI and Gallium 67 scintigraphy revealed extrapancreatic lesions of sialadenitis and retroperitoneal fibrosis with a soft tissue mass around the iliac artery (Fig. 3). During admission, spontaneous remission was achieved without the administration of prednisolone treatment. AIP was diagnosed based on the ICDC criteria (Table 1) (12). The patient's HLA typing results were as follows: *A*24:02/A*24:02*, *B*15:01/B*52:01*, *DRB1*04:06/DRB1*15:02* and *DQB1*03:02/DQB1*06:01*.

Discussion

The ICDC for AIP enables clinicians to diagnose AIP based on an international standard and to classify the disease as type 1 or type 2 (12). The siblings in the present study exhibited the typical pancreatic parenchymal imaging findings of diffuse enlargement with delayed enhancement associated with rim-like enhancement, which is rated as a level 1 finding by the ICDC, and the pancreatic duct imaging of long or multiple strictures without marked upstream dilatation (a level 1 finding). The serology results revealed slight IgG4 elevation in the elder brother (1-2x the upper limit of normal; a level 2 finding). Other organ involvement (OOI) findings revealed typical radiological evidence of retroperitoneal fibrosis (a level 1 finding) and symmetrically enlarged salivary glands (a level 2 finding) in the younger brother (Table 2). These parenchymal imaging and non-ductal level 1 and level 2 findings met the ICDC criteria for definitive type 1 AIP (12). Type 2 AIP has been predominantly described in Europe as "granulocyte epithelial lesion (GEL)-positive pancreatitis" or "idiopathic duct-centric pancreatitis (IDCP)" and is characterized by ductal epithelial granulocytic infiltration. Type 2 AIP patients are on average a decade or more younger than type 1 patients and do not show the male gender bias seen in type 1 AIP. Type 2 AIP also does not appear to involve IgG4-related systemic diseases such as sialadenitis and retroperitoneal fibrosis (2). Based on this background, the clinical features of the two siblings were distinct from those of type 2 AIP and more consistent with those of type 1 AIP.

Type 1 AIP exhibits a close association with a high serum IgG4 concentration and IgG4-bearing plasma cell infiltration in affected organs (4, 5). Although the exact role of IgG4 in this disease has not been disclosed, it may be associated with acquired or innate immunity involved in the pathogenesis of AIP (13, 14). IgG4 has also been reported to display dynamic Fab-arm exchange and rheumatoid factor-like activity, both of which seem to exert protective effects on the inflammatory process of AIP (15, 16). Dynamic Fab-arm exchange in the IgG4 molecule results in bispecific activity towards antigens and a loss of monospecific cross-linking activity and the ability to form immune complexes, thus resulting in decreased inflammation (15). Similarly, IgG4 can bind to IgG-Fc via an Fc-Fc interaction, which may promote the formation of large circulating immune complexes that are easily eliminated from the circulation (16). Accordingly, elevated levels of serum IgG4 play pivotal roles in the pathophysiology of AIP. Contrary to our expectations, however, the IgG4 values in the two siblings exhibited at most a slight elevation, suggesting that further studies are needed to disclose the roles of IgG4, especially in AIP patients without marked serum IgG4 elevation.

It is possible that common immunogenetic factors exerted a role in the pathogenesis of the two present familial AIP cases. To date, various AIP-susceptible genes have been reported (8-11). Similar to other autoimmune diseases, such as rheumatoid arthritis, autoimmune hepatitis and type 1 diabetes mellitus, type 1 AIP exhibits a close association with the *DRB1*04:05-DQB1*04:01* haplotype (8). However, in the

Table 2. Diagnosis of the Two Siblings Based on the International Consensus Diagnostic Criteria for Autoimmune Pancreatitis

	Elder brother	Younger brother
P: Parenchymal imaging	Level 1 (Typical) diffuse swelling and a capsule-like rim	Level 1 (Typical) diffuse swelling and a capsule-like rim
D: Duct imaging (ERCP)	Level 1 long (1/3 the length of the main pancreatic duct) or multiple strictures without marked upstream dilatation	Level 1 long (1/3 the length of the main pancreatic duct) or multiple strictures without marked upstream dilatation
S: Serology	Level 2 (IgG4 206 mg/dL)	-
OOI: Other organ involvement	-	Level 1 (Typical radiological evidence of retroperitoneal fibrosis) Level 2 (Physical or radiological evidence of symmetrically enlarged salivary/lachrymal glands)
H: Histology of the pancreas	-	-
Rt: Response to steroids	+	Spontaneous remission
Diagnosis	Type 1 definite	Type 1 definite

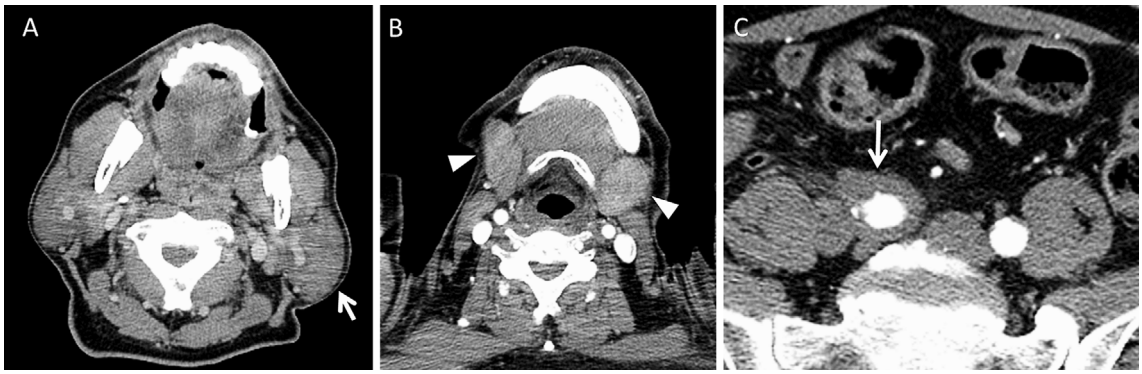

Figure 3. CT findings of the younger brother of other organ involvement demonstrating (A) parotid gland swelling, (B) submandibular gland swelling and (C) a soft tissue mass around the iliac artery showing retroperitoneal fibrosis.

present study, the siblings shared the common haplotype *A*24:02-B*52:01-DRB1*15:02-DQB1*06:01* but not the *DRB1*04:05-DQB1*04:01* haplotype. Close associations between AIP and other HLA class II antigens such as *DQB1*03:02*, *DQB1*06:02*, *DRB1*07:01* and *DQB1*02:02* have also been reported (17, 18). In addition, the *DRB1*15:02-DQB1*06:01* haplotype found in the present two siblings has been reported to be associated with other autoimmune diseases such as type 1 diabetes mellitus (19, 20). Since multiple HLA antigens may contribute to the pathogenesis of AIP, *A*24:02-B*52:01-DRB1*15:02-DQB1*06:01* may represent candidate antigens. Further studies are needed.

The two siblings in the present study shared a common genetic background but exhibited different clinical findings, such as the presence of other organ involvement, that might have been caused by environmental factors present throughout adulthood. Furthermore, spontaneous remission was seen in the younger brother only. The spontaneous remission rate for AIP is still not well understood because most patients receive corticosteroids as part of their standard therapy. Similar to the findings of the younger brother, however, AIP patients with IgG4 seronegativity have a high likelihood of achieving spontaneous remission (21, 22).

We encountered two siblings with type 1 AIP who exhibited typical imaging findings of pancreatic lesions and OOI. The patients were considered to share a common immunogenetic background for the pathogenesis of this disease, for example, a high serum IgG4 level and the *DRB1*04:05-DQB1*04:01* haplotype, but instead displayed normal to slightly elevated values of serum IgG4 and no such haplotype, thus suggesting that type 1 autoimmune pancreatitis is associated with multiple immunogenetic factors.

The authors state that they have no Conflict of Interest (COI).

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