

Original article

Allergic diseases, immunoglobulin E, and autoimmune pancreatitis: a retrospective study of 22 patients

Zhang Li, Guo Limei, Huang Yonghui, Wang Tianli, Shi Xueying, Chang Hong, Yao Wei and Huang Xuebiao

Keywords: hypersensitivity; pancreatitis; immunoglobulin E; mast cells

Background Autoimmune pancreatitis (AIP) is a chronic inflammatory disease of pancreas. We evaluated the clinical manifestations, imaging, and histological presentations of AIP in Chinese patients, and investigated the roles of immunoglobulin E (IgE) and allergic diseases in the diagnosis and pathogenesis of AIP.

Methods The clinical records of 22 patients diagnosed with AIP were reviewed and analyzed. All patients with AIP fulfilled the 2006 revised diagnostic criteria proposed by Japan Pancreas Society or the Korean Criteria for AIP.

Results Half (11/22) of AIP patients had allergic diseases. Twenty-one patients had elevated serum IgE levels, and 14 patients had IgE levels more than 3 times that of normal. There were no significant differences between the patients with higher or lower IgE, with or without allergic disease, in clinical features, laboratory tests, diffuse or focal lesions, or the choice of treatment methods; however, more complaints of body weight loss were observed in patients with higher IgE levels. Patients with higher IgE levels and with allergic diseases were more likely to have onset in March, April, May, August, September, or October. IgE levels decreased after therapy, but increased again during recurrence. Increased number of mast cells was found in the pancreatic tissue in AIP.

Conclusions IgE maybe a useful marker for monitoring therapeutic response and recurrence of AIP. Allergic processes may play an important role in the pathogenesis of AIP.

Chin Med J 2014;127 (23): 4104-4109

Autoimmune pancreatitis (AIP) is a chronic inflammatory disease of pancreas characterized by enlargement of the pancreas, hyperglobulinemia, fibrosis and lymphoplasmacytic infiltration of the pancreas, involvement of extrapancreatic organs, and response to corticosteroid therapy.^{1,2} Despite growing awareness of the condition, differentiating between AIP and pancreatic cancer remains challenging. Type 1 AIP is defined as pancreatic lesions of IgG4-related systemic disease (IgG4RD); however, there is no evidence supporting the direct immunopathological role of IgG4 in AIP.² Autoimmune mechanisms are thought to cause AIP, but the etiology and pathogenesis of AIP are still largely unknown, and only a few studies have described potential relationships between allergic disease and AIP.³⁻⁵ In this retrospective study, we evaluated the clinical manifestations, imaging findings, and histological presentations of AIP in Chinese patients. Additionally, we discussed the role of the immunoglobulin E (IgE) in the diagnoses and treatment of AIP and the possible involvement of allergic mechanisms in the pathogenesis of AIP.

METHODS

From May 2007 to August 2013, 22 patients were diagnosed with AIP at Peking University Third Hospital, Beijing, China. These patients' clinical records were reviewed and analyzed. The data included patients' main symptoms, physical signs, medical history, allergic history, laboratory studies. The patients received endoscopy, radiological imaging, and/or biopsy studies, as summarized

in Table 1. Two patients were misdiagnosed with pancreatic cancer and underwent from partly pancreatectomy. All slides were reviewed by 2 experienced histopathologists. All patients with AIP fulfilled the 2006 revised diagnostic criteria proposed by Japan Pancreas Society⁶ or the Korean Criteria for AIP.⁷

For statistical analysis, variables were represented as percentages or means $\pm$ standard deviation. The χ^2 test and Student *t* test were used for comparative statistical evaluation among groups, and differences with *P*-values of less than 0.05 were considered significant. Correlation analyses were evaluated by Spearman's correlation. Statistical analyses were performed using SPSS 18.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

General states and clinical features of patients

The duration of symptoms prior to diagnosis ranged from 1 week to 3 years, and abdominal pain, jaundice, and body weight loss were the most common symptoms of AIP. The other main complaints included the presence of pancreatic

DOI: 10.3760/cma.j.issn.0366-6999.20141684

Department of Gastroenterology (Zhang L, Huang YH, Chang H, Yao W and Huang XB), Department of Radiology (Wang TL), Peking University Third Hospital, Beijing 100191, China

Department of Pathology, Peking University Health Science Center, Beijing 100191, China (Guo LM and Shi XY)

Correspondence to: Huang Yonghui, Department of Gastroenterology, Peking University Third Hospital, Beijing 100191, China (Fax: 86-10-82801250. Email: huangyonghui@medmail.com.cn)

Table 1. The number of patients receiving endoscopy, radiological imaging, and/or biopsy studies

Diagnostic method	Number of cases
ERCP	20
MRI/MRCP	17/17
CT/PET-CT	20/6
EUS (+FNA)	7 (+3)
IDUS	3
BCE	9
Duodenal biopsy	14
Lung biopsy	1
Submaxillary salivary gland biopsy	1
Lymph node biopsy	1
Renal biopsy	1
Liver biopsy	2

ERCP: endoscopic retrograde the cholangiopancreatography; CT: computed tomography; MRI/MRCP: magnetic resonance imaging/magnetic resonance cholangiopancreatography; EUS (+FNA): endoscopic ultrasonography (-guided fine-needle aspiration); IDUS: intraductal ultrasonography; Duodenal biopsy means biopsy specimens obtained from duodenal papilla and duodenal mucosa from the opposite side of the papilla; BCE: brushing cytological examination of stenotic biliary lesion.

masses, elevated serum CA19-9 levels, and fatigue. One patient underwent distal pancreatectomy because of misdiagnosed pancreatic cancer 3 years prior at another hospital, and was diagnosed as AIP based on postoperative histopathological studies. This patient was admitted to our hospital for obstructive jaundice. Concomitant allergic diseases were observed in half (11/22) of patients, including allergic rhinitis in 9 patients and bronchial asthma in 2 patients. Five patients had a history of allergy to medicine or protein foods (Table 2).

Laboratory studies

Peripheral leucocytes and classifications were normal in all patients, but only one patient had a high percent of eosinophilic cells (8.7%; normal is less than 5%), with a normal eosinophilic cell count (0.36×10^9 cells/L). Eleven out of 15 patients had IgG4 elevation. Interestingly, serum IgG4 levels were normal in 2 patients when they were diagnosed with AIP, but were higher than 135 mg/dl after corticosteroid therapy. Elevated IgG was observed more

frequently in patients with allergic diseases than in those without allergic diseases. IgE levels were elevated in 21 out of 22 patients, ranging from 135 U/ml to more than 2 500 U/ml (normal, <100 U/ml). Serum IgE levels were more than 300 U/ml in 14 cases. Allergic history was more frequent in patients with higher IgE levels (> 300 U/ml) than in patients with lower IgE levels (< 300 U/ml; 10/14 vs. 4/8). Mean serum IgE levels were higher in patients with allergic diseases than in patients without allergic disease (927.7 ± 842.2) U/ml, range: 135 to >2 500 U/ml; vs. (463.1 ± 371.4) U/ml, range: 85 to 1 364 U/ml). The mean percentage of $\alpha 2$ -globulin was higher ($P=0.021$) and the mean percentage of γ -globulin was lower ($P=0.028$) in patients with lower IgE levels than those in patients with higher IgE levels. Although the mean values of IgG and IgG4 were higher in patients with allergic diseases or in patients with higher IgE level than the controls, but there were no statistical significance between them (Table 3). There were no correlations between the levels of serum IgE and the levels of serum IgG or IgG4.

Imaging findings

Thirteen patients had diffuse enlargement of the pancreas. In 1 patient, the body and tail of pancreas had been involved 3 years prior, whereas the head of the pancreas was involved at the current evaluation. On endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP), the intrapancreatic segment of the common bile duct (CBD) showed narrowing in all patients, and the narrowness was smooth and gradual, resulting in dilation of the proximal bile ducts. Twelve patients were found to have thickened bile duct walls on computed tomography (CT), endoscopic ultrasonography (EUS), or intraductal ultrasonography (IDUS). Narrowed bile duct of the hepatic hilum was found in 3 patients. There were no differences in imaging manifestations between patients with higher or lower IgE levels or between the patients with or without allergic diseases.

Table 2. General state, clinical features and treatments of patients with AIP

Clinical features	Total (n=22)	IgE<300 (n=8)	IgE≥300 (n=14)	Without AD (n=11)	With AD (n=11)
Age (range (mean), years)	41–82 (64.1)	41–74 (63.0)	45–82 (64.8)	41–82 (62.2)	45–76 (66.1)
Male: female	18:4	7:1	11:3	10:1	8:3
Duration before diagnosis	1 week to 3 years				
<1 month (n)	3	1	2	1	2
≥1 month to <6 months (n)	9	3	6	6	3
≥6 months (n)	10	4	6	4	6
Season (3, 4, 5, 8, 9, 10th month) (n)	13	2	11*	3	10†
Abdominal pain (n)	15	6	9	10	5
Jaundice (n)	14	5	9	7	7
Body weight loss (≥3 kg) (n)	17	4	13*	7	10
Allergic history (n)	11	3	8	–	–
HBV infection (n)	12	3	9	4	8
Smoke (n)	11	5	6	9	2†
Alcohol (n)	4	2	2	2	2
Diabetes mellitus (n)	9	4	5	5	4
Diffuse involvement (n)	13	6	7	7	6
Focal involvement (n)	9	2	7	4	5
Bile duct stent (n)	16	5	11	9	7
Pancreatic duct stent (n)	3	2	1	3	0
Steroid treatment (n)	16	5	11	7	9

HBV: hepatitis B virus; AD: allergic diseases. * $P < 0.05$, patients with IgE ≥300 U/ml vs. those with IgE <300 U/ml; † $P < 0.05$, patients with AD vs. those without AD.

Table 3. Laboratory studies of AIP patients

Laboratory studies	<i>n</i> /total (<i>n</i> =22)	IgE<300 (<i>n</i> =8)	IgE≥300 (<i>n</i> =14)	Without AD (<i>n</i> =11)	With AD (<i>n</i> =11)
ESR>20 mm/h					
<i>n</i>	17/20	6/8	11/12	7/10	10/10
Value (mm/h)	45.15±30.86	47.50±37.78	43.58±27.02	42.40±37.57	47.90±24.12
ALT>3N (N≤40 U/L)					
<i>n</i>	9/22	3/8	6/14	4/11	5/11
Value (U/L)	139.91±160.03	181.16±233.47	109.71±99.94	124.55±174.53	147.28±151.78
CA19-9>37 U/ml					
<i>n</i>	14/22	5/8	9/14	6/11	8/11
Value (U/ml)	146.35±233.14	140.58±143.61	149.65±276.89	103.98±139.08	188.73±301.41
High serum IgG					
<i>n</i>	11/22	3/8	8/14	1/11	10/11 [†]
Value (g/L)	20.10±10.55	15.51±3.52	22.72±12.36	16.59±10.99	23.60±9.71
IgG4>135 mg/dl					
<i>n</i>	11/15	4/6	7/9	4/7	7/8
Value (mg/dl)	448.6±769.1	249.1±321.1	581.7±959.7	292.3±314.7	585.5±1025.9
Low serum C50					
<i>n</i>	6/22	1/8	5/14	1/11	5/11
Value (kU/L)	37.73±21.67	39.75±16.44	36.57±24.68	44.55±16.01	30.91±25.05
Low serum C3					
<i>n</i>	11/22	5/8	6/14	4/11	7/11
Value (g/L)	0.901±0.469	0.914±0.360	0.893±0.535	1.047±0.411	0.754±0.497
Low serum C4					
<i>n</i>	8/22	3/8	5/14	2/11	6/11
Value (g/L)	0.171±0.110	0.19±0.12	0.159±0.107	0.200±0.109	0.141±0.108
High α1-globulin					
<i>n</i>	9/15	4/6	5/9	2/5	7/10
Value (%)	3.413±1.148	3.633±1.269	3.267±1.112	3.240±1.766	3.500±0.799
High α2-globulin					
<i>n</i>	13/15	6/6	7/9	4/5	9/10
Value (%)	10.633±2.223	12.183±2.386	9.600±1.447 [*]	11.640±3.454	10.130±1.243
High β-globulin					
<i>n</i>	4/15	2/6	2/9	2/5	2/10
Value (%)	9.56±3.08	11.20±2.24	8.47±3.18	10.14±4.20	9.27±2.58
High γ-globulin					
<i>n</i>	12/15	4/6	8/9	3/5	9/10
Value (%)	30.25±9.76	23.72±5.83	34.60±9.60 [*]	25.92±11.80	32.41±8.41

AD: allergic diseases; N: normal limit; 3N: three times of normal value; ^{*}*P*<0.05, patients with IgE ≥300 U/ml vs. those with IgE <300 U/ml; [†]*P*<0.05, patients with AD vs. those without AD.

Histopathological findings

Characteristic histopathological features of AIP were confirmed in surgical samples from the pancreases of patients. The lobular architecture of the pancreas became irregular. The most characteristic changes included a dense mature lymphoplasmacytic inflammatory infiltrate in the atrophic acinar tissue, fibrous deposition, and surrounding medium- to large-sized interlobular ducts. By immunohistochemical staining, plenty of IgG4-positive cells were observed. The ratio of IgG4-positive cells to IgG-positive cells was above 40%. In addition, mast cells, identified by immunoreactivity of anti-CD117 antibodies, were unevenly distributed. Some mast cells were present focally and were accompanied by lymphoplasmacytic cells, while some were scattered in the acini (Figure 1).

IgG4-related sclerosing sialitis, intrahepatic cholangitis, inflammatory pseudotumors in the lung, and interstitial nephritis were found in 4 patients.

Treatment and follow up

Sixteen patients were treated with prednisone at an initial dose of 30–40 mg/d for 2 weeks. Prednisone was then tapered by 5 mg every 2–4 weeks, and 2.5–5

mg/d was continued as maintenance therapy for 6 months or longer. Sixteen patients received bile duct stents, and 3 received pancreatic duct stents to relieve symptoms. Six patients were followed up without prednisone because they were asymptomatic, asymptomatic after biliary drainage, had hepatitis B virus infection, or rejected further therapy. One patient discontinued steroid therapy because of exacerbated diabetes mellitus.

The patients were followed up for 8–64 months (mean follow-up, 31 months). Relief of symptoms and improved imaging findings were found in all patients, and persistent improvement was noted in most cases, even though 6 patients did not receive corticosteroid therapy. Two patients suffered from relapse of AIP during the tapering or discontinuation of corticosteroid therapy. One patient, who had no obvious relapse of AIP (according to clinical and imaging criteria) after therapy, was diagnosed with IgG4-related interstitial nephritis 6 months later. Fifteen patients were monitored for changes in IgE levels at least once during the follow up, and IgE levels decreased after therapy in all of these patients (Figure 2). In 2 patients with recurrence, IgE levels rose again. In 1 patient with recurrence, both IgG and IgE levels fluctuated synchronously (correlation coefficient: 0.629, *P*=0.012; Figure 3).

DISCUSSION

AIP was first described by Sarles et al⁸ in 1961 as idiopathic chronic pancreatitis with hypergammaglobulinemia. The concept of autoimmune pancreatitis was first proposed by Yoshida et al⁹ in 1995 based on the clinical features of increased serum γ-globulin or IgG levels, presence of autoantibodies, effectiveness of steroid therapy, and occasional association with other autoimmune diseases, in addition to abnormalities of the morphology and histopathology of the pancreas. Elevated levels of IgG, IgG4, or γ-globulin are characteristics of AIP and required criteria for AIP in several well established diagnostic criteria guidelines;^{6,7,10} thus, immunoglobulins are generally evaluated during suspected diagnoses of AIP. Because serum IgE levels are always measured simultaneously with IgG levels at our hospital, we found that IgE levels were usually elevated in AIP patients, but not in patients with acute pancreatitis or pancreatic carcinoma. Moreover, because patients with allergic diseases generally exhibited elevated IgE, we sought to investigate the relationships among allergic diseases, IgE, and AIP.

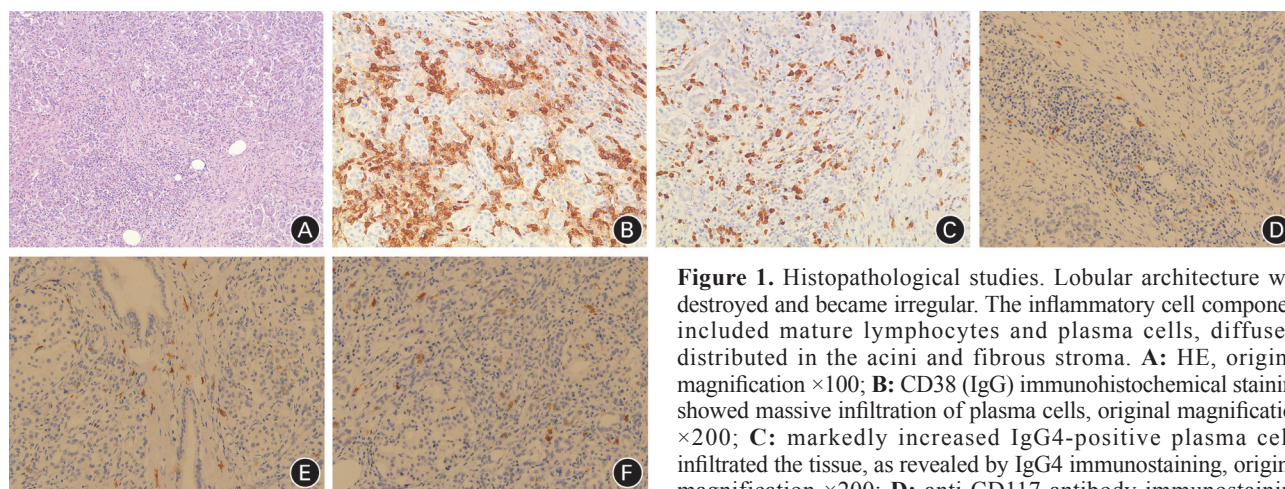


Figure 1. Histopathological studies. Lobular architecture was destroyed and became irregular. The inflammatory cell component included mature lymphocytes and plasma cells, diffusely distributed in the acini and fibrous stroma. **A:** HE, original magnification $\times 100$; **B:** CD38 (IgG) immunohistochemical staining showed massive infiltration of plasma cells, original magnification $\times 200$; **C:** markedly increased IgG4-positive plasma cells infiltrated the tissue, as revealed by IgG4 immunostaining, original magnification $\times 200$; **D:** anti-CD117 antibody immunostaining revealed an increased number of mast cells in the fibrous stroma, original magnification $\times 200$; **E:** HE, original magnification $\times 100$; **F:** HE, original magnification $\times 100$.

accompanied by lymphoplasmacytic cells that were scattered close to the duct (E) or located in the acini (F), original magnification $\times 100$.

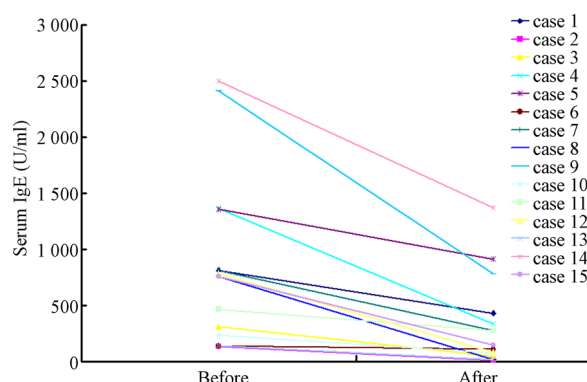


Figure 2. Changes in serum IgE levels before and after therapy in 15 patients. Serum IgE levels were decreased when patients' conditions improved. All patients were treated with corticosteroids except for case 4.

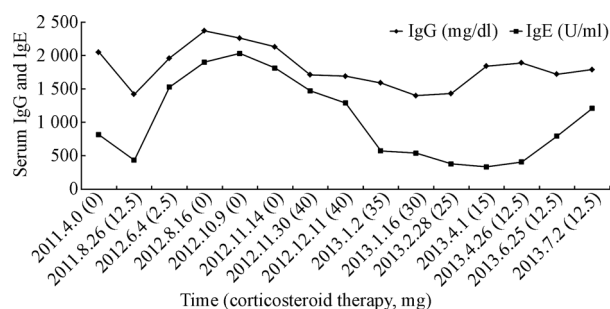


Figure 3. Changes in serum IgG and IgE levels in a patient with recurrence. The patient complained of progressive fatigue when he discontinued corticosteroid therapy; serum IgG and IgE levels were elevated, and B-mode ultrasonography showed enlargement of the pancreas. When the patient was re-treated with corticosteroids, his symptoms were relieved, and serum IgG and IgE levels were decreased.

In limited previous reports, 37.5%–44.4% of patients with AIP had histories of allergic diseases, such as acute allergic rhinitis, atopic dermatitis, bronchial asthma, drug allergy, and hypersensitivity pneumonitis.³⁻⁵ In the present series, 11/22 of patients suffered from allergic diseases. These diseases were problematic several months to 2 years before

and during symptoms of AIP. Notably, only 4 patients reported actively a history of allergic rhinitis or bronchial asthma, and the other 7 patients complained of symptoms of persistent nasal discharge or sneezing, and were diagnosed as allergic disease by experts of otorhinolaryngology or respiration this time. Among these 11 patients, 5 patients had a history of allergy to medicines or protein foods.

Kamisawa et al⁵ observed elevation of IgE in 34% (12/35) of AIP patients (IgE > 580 U/L), and all patients with high IgE had present and/or past occurrence of allergic diseases. The authors believed that allergic mechanisms may be related to the occurrence of AIP in these patients. In the present study, 21/22 of patients had elevated serum IgE levels (IgE > 100 U/ml), 14/22 had more than 3 times that of normal levels, with levels varying from 135 U/ml to more than 2 500 U/ml. Moreover, patients with allergic diseases had higher levels of IgE than patients without allergic diseases. Elevated IgE in AIP patients had also been mentioned in a few additional studies,^{11,12} however, the reasons for these elevated IgE levels are not often discussed. In a study by van Toorenbergen et al,¹² serum total IgE levels appeared to differ significantly between AIP and pancreatic cancer, but the detailed roles of IgE were unknown.

In the present study, AIP mainly affected middle-aged to elderly men, and the most common symptoms were mild abdominal pain, obstructive jaundice, and weight loss. Increased ESR was found in 17/20 of patients, which suggested the occurrence of an active inflammation reaction. Elevated CA19-9 was associated with jaundice, and this symptom returned to normal after the jaundice was improved. A total of 11/15 of patients had elevated levels of serum IgG4, and asynchronization between elevated IgG4 levels and the onset of disease was noted in 2 patients in our study. Increased levels of serum $\alpha 1$ -globulin (9/15) and $\alpha 2$ -globulin (13/15) were also observed in many AIP patients; however, the pathogenesis and etiologies of these abnormalities in globulin levels were not clear. Decreased serum levels of C3 were found in 11/22 of

patients, indicating that the complement activation system was functioning in the pathogenesis of this disease, as mentioned in a prior report.¹³

Based on imaging findings, diffuse involvement of the pancreas was found in 13/22 of patients, and focal lesions could progress to diffuse lesions, or the remnant pancreas could relapse after partial pancreatectomy. This result supported the hypothesis that focal-type AIP is an initial stage of diffuse AIP. Stricture of the intrapancreatic segment of the CBD was detected in all patients in present study, regardless of the presence of jaundice or involvement of specific regions of the pancreas. Moreover, 12/22 of patients showed wall thickening in the CBD on CT, EUS, or IDUS. The biliary stenosis resulted from extrinsic pancreatic compression or inflammation of the bile duct itself in AIP.

In histopathological studies, besides characteristic histopathological features of AIP, increased numbers of mast cells were found in the pancreatic tissues. Generally, mast cells are scattered close to blood vessels in normal pancreatic tissue. However, in the present case, some mast cells were present focally and were accompanied by lymphoplasmacytic cells, while some were found in the acini; these characteristics were different from those of mast cells in normal pancreatic tissue. To our knowledge, this is first report that characteristic mast cells were found in the pancreatic tissue of patients with AIP.

In our study, EUS-FNA or brushing cytological examination yielded very low positive diagnoses, and moderately increased IgG4-positive plasma cell infiltrates were not seen in sample biopsies from these patients (> 10 cells per high-powered field). We experienced difficulties in diagnosing AIP by these examinations due to patchy distribution of the disease, insufficient specimens, or lack of tissue architecture. Some data suggested that swollen duodenal papilla or positive IgG4 staining in duodenal papilla tissue may be useful in both the diagnosis and prognosis of AIP;¹⁴ however, our study did not support these notions. One study has shown that IgG4+ plasma cells are not abundant in the digestive mucosa of AIP patients compared to healthy controls.¹⁵ Therefore, IgG4 immunostaining of the digestive mucosa may not be helpful for the diagnosis of AIP. Although these histological examinations could not suggest the diagnosis of AIP, they are useful to differentiate AIP from pancreatic cancer, neoplasia of the bile duct, or eosinophilic pancreatitis.

AIP typically responds well to corticosteroid therapy, as shown in prior studies^{6,7,9,10} and in the present study. Biliary stents were implanted in some patients with stenosis bile duct, and rapid resolution of jaundice and abdominal pain was seen in these patients. Pancreatic duct stents were implanted in 3 patients; these procedures were performed by the doctors who completed the ERCP, but may not be necessary in AIP patients. Spontaneous remission in patients without corticosteroid therapy was also seen in this

study, as reported in a few prior studies.^{16,17}

There were no significant differences observed between patients with higher or lower IgE levels, or between patients with or without allergic diseases, in terms of clinical features, laboratory tests, diffuse or focal lesions, or the choice of treatment methods, except for loss of body weight, smoking history, levels of α 2-globulin, γ -globulin and IgG. Onset of AIP in March, April, May, August, September, or October occurred more frequently in patients with higher IgE levels or in patients with allergic diseases than in patients with lower IgE levels or without allergic diseases. Interesting, onset of allergic disease were also more frequent in this period in Beijing. These results were different from the results of the study by Kamisawa et al,⁵ in which allergic-type AIP occurred predominantly from September to February. This difference may be because of the different environments in which the patients lived, causing patients to be exposed to different allergic factors, such as cold air or pollens. Patients with allergic diseases reported relief of symptoms of rhinitis or asthma following AIP therapy, possibly resulting from the anti-inflammatory action of corticosteroids. In the study by Hirano et al,¹¹ there were no significant differences in the levels of IgE between patients with and without clinical relapse, before and after steroid treatment, and with or without past allergic disease. The authors believed that although IgE does not necessarily reflect the disease severity, IgE may be useful for the diagnosis of AIP during inactive stages. However, in our study, serum IgE levels decreased with relief of patients' conditions and then rose again during recurrence in 2 patients, indicating that IgE levels may be an indicator of AIP activity. In the study by van Toorenbergen et al,¹² there was a significant correlation between total IgE and total IgG4 levels in patients with AIP; however, in the study by Hirano et al,¹¹ there were no significant correlations between IgG, IgG4, and IgE. In our present study, a correlation between IgE and IgG or IgG4 levels was not shown, which may have been due to the significant variation in IgE levels among individual patients. Regardless, we did notice a consistent fluctuation in both IgG and IgE levels in one individual. These findings suggested that IgE may play a diagnostic role in AIP similar to that of IgG.

Recently, several studies have shown that T-helper type 2 (Th2) cells, Th2 cytokines (interleukin (IL)-4, IL-5, and IL-13), regulatory T cells (Tregs), and regulatory cytokines (IL-10 and TGF- β) play a critical role in the pathogenesis of AIP.¹⁸⁻²⁰ However, the inflammatory reactions predominantly mediated by Th2 cell and Treg responses are also closely involved in the pathogenesis of allergic disorders.^{19,20} Moreover, the regulation of both IgG4 and IgE depends on Th2 cells and Th2 cytokines, and high serum IgG4 levels are often observed in IgE-mediated allergic disorders.²¹⁻²³ Based on the relationship between IgG4, IgE, allergic diseases, and AIP, our study supported the hypothesis that allergic reactions may play a pathogenic role in some cases of AIP. And increased numbers of mast

cells exhibiting specialized localization in the target tissues of AIP by immunohistochemical studies supported this hypothesis further.

Although our study revealed important insights into AIP, many questions are still unanswered. Thus, further studies will need to address how allergic pathogenesis damages the pancreas or other target tissues, the relationship between susceptibility and allergic factors, the pathogenesis of AIP in patients without any medical history or symptoms suggestive of allergic conditions, and the variation in IgE values among groups of patients. The small sample size and incomplete data are limitations of this retrospective study. Further observation associated with IgE and allergic diseases in AIP patients is required.

The serum IgE level may be a useful marker for diagnosis, monitoring therapeutic response and recurrence of AIP. Allergic processes may play an important role in the pathogenesis of this condition. Further investigations to elucidate the possible pathogenic mechanisms through which IgG4 and IgE mediate inflammatory reactions and the diagnostic value of IgE in AIP are necessary.

REFERENCES

- Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas* 2011; 40: 352-358.
- Okazaki K, Uchida K, Koyabu M, Miyoshi H, Takaoka M. Recent advances in the concept and diagnosis of autoimmune pancreatitis and IgG4-related disease. *J Gastroenterol* 2011; 46: 277-288.
- Ito S, Ko SB, Morioka M, Imaizumi K, Kondo M, Mizuno N, et al. Three cases of bronchial asthma preceding IgG4-related autoimmune pancreatitis. *Allergol Int* 2012; 61: 171-174.
- Abraham SC, Leach S, Yeo CJ, Cameron JL, Murakata LA, Boitnott JK, et al. Eosinophilic pancreatitis and increased eosinophils in the pancreas. *Am J Surg Pathol* 2003; 27: 334-342.
- Kamisawa T, Anjiki H, Egawa N, Kubota N. Allergic manifestations in autoimmune pancreatitis. *Eur J Gastroenterol Hepatol* 2009; 21: 1136-1139.
- Okazaki K, Kawa S, Kamisawa T, Naruse S, Tanaka S, Nishimori I, et al. Clinical diagnostic criteria of autoimmune pancreatitis: revised proposal. *J Gastroenterol* 2006; 41: 626-631.
- Park SW, Chung JB, Otsuki M, Kim MH, Lim JH, Kawa S, et al. Conference report: Korea-Japan symposium on autoimmune pancreatitis. *Gut Liver* 2008; 2: 81-87.
- Sarles H, Sarles JC, Muratore R, Guieu C. Chronic inflammatory sclerosis of the pancreas--an autonomous pancreatic disease? *Am J Dig Dis* 1961; 6: 688-698.
- Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. *Dig Dis Sci* 1995; 40: 1561-1568.
- Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Zhang L, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. *Clin Gastroenterol Hepatol* 2006; 4: 1010-1016; quiz 1934.
- Hirano K, Tada M, Isayama H, Kawakubo K, Yagioka H, Sasaki T, et al. Clinical analysis of high serum IgE in autoimmune pancreatitis. *World J Gastroenterol* 2010; 16: 5241-5246.
- van Toorenbergen AW, van Heerde MJ, van Buuren HR. Potential value of serum total IgE for differentiation between autoimmune pancreatitis and pancreatic cancer. *Scand J Immunol* 2010; 72: 444-448.
- Muraki T, Hamano H, Ochi Y, Komatsu K, Komiyama Y, Arakura N, et al. Autoimmune pancreatitis and complement activation system. *Pancreas* 2006; 32: 16-21.
- Kamisawa T, Tu Y, Nakajima H, Egawa N, Tsuruta K, Okamoto A. Usefulness of biopsying the major duodenal papilla to diagnose autoimmune pancreatitis: A prospective study using IgG4-immunostaining. *World J Gastroenterol* 2006; 12: 2031-2033.
- Rebours V, Le Baleur Y, Cazals-Hatem D, Stefanescu C, Hentric O, Maire F, et al. Immunoglobulin G4 immunostaining of gastric, duodenal, or colonic biopsies is not helpful for the diagnosis of autoimmune pancreatitis. *Clin Gastroenterol Hepatol* 2012; 10: 91-94.
- Kamisawa T, Shimosegawa T, Okazaki K, Nishino T, Watanabe H, Kanno A, et al. Standard steroid treatment for autoimmune pancreatitis. *Gut* 2009; 58: 1504-1507.
- Kubota K, Iida H, Fujisawa T, Yoneda M, Inamori M, Abe Y, et al. Clinical factors predictive of spontaneous remission or relapse in cases of autoimmune pancreatitis. *Gastrointest Endosc* 2007; 66: 1142-1151.
- Zen Y, Fujii T, Harada K, Kawano M, Yamada K, Takahira M, et al. Th2 and regulatory immune reactions are increased in immunoglobulin G4-related sclerosing pancreatitis and cholangitis. *Hepatology* 2007; 45: 1538-1546.
- Kusuda T, Uchida K, Miyoshi H, Koyabu M, Satoi S, Takaoka M, et al. Involvement of inducible costimulator- and interleukin 10-positive regulatory T cells in the development of IgG4-related autoimmune pancreatitis. *Pancreas* 2011; 40: 1120-1130.
- Uchida K, Kusuda T, Koyabu M, Miyoshi H, Fukata N, Sumimoto K, et al. Regulatory T cells in type 1 autoimmune pancreatitis. *Int J Rheumatol* 2012; 2012: 795026.
- Robinson DS, Larche M, Durham SR. Tregs and allergic disease. *J Clin Invest* 2004; 114: 1389-1397.
- Romagnani S. Regulation of the development of type 2 T-helper cells in allergy. *Curr Opin Immunol* 1994; 6: 838-846.
- Aalberse RC, Stapel SO, Schuurman J, Rispens T. Immunoglobulin G4: an odd antibody. *Clin Exp Allergy* 2009; 39: 469-477.

(Received July 17, 2014)

Edited by Guo Lishao