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**Clinical and pathological differences between serum immunoglobulin G4-positive and -negative type 1 autoimmune pancreatitis**

**Paik WH *et al.*** IgG4-positive and negative type 1 autoimmune pancreatitis

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**Abstract**

**AIM:** To find clinical and pathological differences between serum immunoglobulin G4 (IgG4)-positive (SIP) and IgG4-negative (SIN) type 1 autoimmune pancreatitis (AIP) in South Korea.

**METHODS:** AIP was diagnosed by the international consensus diagnostic criteria. The medical records and pathology was retrospectively reviewed and IgG4 positive cells were counted in high power filed (HPF). The type I AIP was defined as a high serum level of IgG4 or histological finding. The SIN type 1 AIP was defined as a histological evidence of type 1 AIP and normal serum IgG4 level. The clinical and pathologic findings were compared between two groups. The analysis was performed using Student’s *t* test, Fischer’s exact test and Mann-Whitney’s *U* test. A value of < 0.05 was considered statistically significant. As repeated comparison was made, *P* values of less than 5% (*P* < 0.05) were considered significant.

**RESULTS:** Twenty five patients with definite type 1 AIP (19 histologically and 6 serologically diagnosed cases) were enrolled. The mean tissue IgG4 concentrations were significantly higher in SIP than SIN group (40 cells per HPF *vs* 18 cells per HPF, *P* = 0.02). Among 8 SIN patients, the tissue IgG4 concentrations were less than 15 cells per HPF in most of cases except one. The sensitivity of serum IgG4 was 68% (17 SIP and 8 SIN AIP). Other organ involvement was more frequently associated with SIP than SIN AIP (59% *vs* 26%, *P* = 0.016). However, the relapse rate and diffuse swelling of pancreas were not associated with serum IgG4 level. The concentrations of IgG4 positive cells per HPF were higher in SIP than SIN AIP (40 *vs* 18, *P* = 0.02).

**CONCLUSION:** The sensitivity of serum IgG4 was 68% in type I AIP. The high serum IgG4 level was associated with other organ involvement and tissue IgG4 concentration but did not affect the relapse rate in type 1 AIP.

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**Key words:** Autoimmunity; Chronic pancreatitis; IgG4-related systemic disease; Lymphoplasmacytic sclerosing pancreatitis; Immunoglobulin G4

**Core tip:** Type 1 autoimmune pancreatitis (AIP) is one of the immunoglobulin G4 (IgG4) related diseases and serum IgG4 is known as a useful diagnostic marker. However, the sensitivity of serum IgG4 is variable. The sensitivity of serum IgG4 was not enough (68%) in definite type I AIP. The demographic findings were not different between SIP and SIN type 1 AIP, but other organ involvement was significantly more common in SIP than SIN type 1 AIP. High serum IgG4 level was associated with other organ involvement and tissue IgG4 concentration, but did not affect relapse rate in type 1 AIP.

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**INTRODUCTION**

Autoimmune pancreatitis (AIP) is a kind of chronic pancreatitis with irregular narrowing of the pancreatic duct and systemic fibroinflammatory disease and is characterized by a remarkable response to steroid therapy. According to a multicenter nationwide study in Korea, the prevalence of AIP was 2.0% among 814 patients with chronic pancreatitis[1]. The early report from Japan that proposed the term lymphoplasmacytic sclerosing pancreatitis (LPSP) described some specific morphologic features of AIP such as diffuse lymphoplasmacytic infiltration with marked interstitial fibrosis and obliterative phlebitis[2].

The Japan Pancreas Society proposed the diagnostic criteria for the first time in 2002, and the characteristic features of AIP were the elevation of serum immunoglobulin G4 (IgG4) and LPSP on pathology[3]. However, many evolving evidences suggest the presence of two AIP types which have different clinical profiles and outcomes. In 2003, a Mayo clinic group found two distinct histologic patterns which were designated LPSP and idiopathic duct-centric chronic pancreatitis (IDCP)[4]. IDCP was characterized by inflammatory infiltrates that were denser in the lobules than interlobular fibrotic areas.

Recently, the expert panel in the international consensus study has agreed that there are two distinct histopathologic types of AIP[5]. Type 1 AIP has dense periductal lymphoplasmacytic infiltrate with storiform fibrosis and obliterative phlebitis, whereas type 2 is distinguished from type 1 by granulocyte epithelial lesion, less prominent lymphoplasmacytic infiltrate, and less prominent storiform fibrosis. Recently, the international consensus diagnostic criteria (ICDC) for AIP were developed based on the agreement of an international panel of experts and ICDC include both types 1 and 2 AIP[6].

According to ICDC, the radiologic imaging and the response to steroids are common features of both type 1 and 2 AIP. However, typical serological abnormalities such as serum IgG4 elevation and other organ involvement can be seen only in type 1. So, for the definite diagnosis of type 2 AIP, the histological confirmation is always necessary. Type 2 AIP has been shown to be associated with inflammatory bowel disease and to affect younger patients without a gender predilection[7]. Both types of AIP respond to steroid very well but type 2 AIP has the rare relapse rate[7].

Even if the elevation of serum IgG4 is the one of the characteristic features in type 1 AIP, the sensitivity of serum IgG4 is variable. The initial Japanese study reported that the sensitivities of IgG4 were 90.9%[8]. However, other studies reported the sensitivity of IgG4 as approximately 70.0%[9-12]. The problem of the previous studies was that there was no clear classification of AIP type because the study was performed before the concept of type 2 AIP was established. If the study population had included more type 2 AIP, the sensitivity of IgG4 would have been low. However, the recent multicenter study also showed that the sensitivity was only 63.0% among histologically proven type 1 AIP[13]. Type 1 AIP is considered as the pancreatic manifestation of IgG4-related systemic disease in which tissue infiltration of IgG4 positive plasma cell is a characteristic feature[14-16]. However, the reason of variable level of serum IgG4, the relation between serum level and tissue concentration of IgG4, and clinical significance of serum IgG4 level in type 1 AIP is unknown and still an interesting issue till now.

The aim of this study was to find clinical and pathological differences between serum IgG4-positive (SIP) and serum IGg4-negative (SIN) type 1 AIP in Korea.

**MATERIALS AND METHODS**

***Patients***

From January 2005 to May 2011, all patients with AIP were retrospectively reviewed at Seoul National University Hospital. The diagnosis of AIP was based on the ICDC[6] and the patients without available serum IgG4 level were excluded. We enrolled the patients with definite AIP. The study was approved by the institutional review board of Seoul National University Hospital.

***Definition of AIP type***

The histology was obtained before steroid therapy in all cases. If histology was available, type 1 AIP was defined as LPSP and type 2 as IDCP. The serum IgG4 level was obtained before steroid therapy and tissue acquisition. If tissue was not obtained, type 1 AIP was also defined if the serum IgG4 level was higher than upper limit of normal value (134 mg/dL). If the patients had no or unclear pathologic findings and serum IgG4 level was normal, the patients were classified as indeterminate type and excluded in this study.

***Radiological analysis***

Pancreatic imaging was categorized as diffuse or segmental swelling by computed tomography (CT) scan. The presence of extrapancreatic lesion included sclerosing cholangitis, sclerosing sialoadenititis, lymphadenopathy, retroperitoneal fibrosis, and ulcerative colitis. The sclerosing cholangitis was defined as the presence of benign stricture of the bile duct on cholangiography. The stricture of only lower bile duct was not included in sclerosing cholangitis. The presence of sialoadenitis, lymphadenopathy and retroperitoneal fibrosis was determined based on CT findings.

***Steroid therapy and relapse***

Steroid therapy was done at 0.6 mg/kg/d of prednisolone for one month and gradually tapered to maintenance dose during three months. Steroid maintenance therapy (5 mg/d) was done for 6 mo to prevent relapse. Relapse was defined as a recurrence of symptom with the development of pancreatic or extrapancreatic abnormal findings on imaging studies.

***Histological examination***

Surgically resected or core biopsied specimens were reviewed by one special pathologist without any clinical information. Fine needle aspiration specimens were not considered as available histology and not reviewed. All specimens were stained with anti-IgG4 antibody for immunohistochemical examination. The number of IgG4-positive plasma cells was counted in high power field (HPF). In surgical specimen, LPSP was defined with at least 3 of the 4 characteristic features which are (1) dense infiltration of plasma cells and lymphocytes, particularly periductal; (2) peculiar storiform fibrosis; (3) venulitis with lymphocytes and plasma cells often leading to obliteration of the affected veins; and (4) abundant (> 10 cells per HPF) IgG4 positive plasma cells. In biopsy specimen, AIP was considered with lymphoplasmacytic infiltration with fibrosis and abundant (> 10 cells per HPF) IgG4 positive plasma cells.

***Statistical analysis***

Statistical analysis was done with statistical software (SPSS version 19.0 for Windows, SPSS Inc, Chicago, IL, USA; MedCalc version 11.5.0.0, MedCalc Software, Mariakerke, Belgium). The data were compared between two groups. The analysis was performed using Student’s *t* test, Fischer’s exact test and Mann-Whitney’s *U* test. A value of < 0.05 was considered statistically significant. As repeated comparison was made, *P* values of less than 5% (*P* < 0.05) were considered significant.

**RESULTS**

***Enrolled patients and classification of AIP***

Thirty seven patients with AIP were enrolled and histology was available in 23 patients (Figure 1). Among 23 patients with histology, 19 patients showed typical finding of type 1 AIP and was confirmed as type 1 AIP. Only one patient was histologically confirmed as a type 2 AIP and had a history of ulcerative colitis. The pathologic diagnosis was inconclusive in 3 cases among 8 core biopsies. One type 2 and 3 SIN AIP patients with inconclusive pathology were excluded in this study. Among 19 patients with type 1 AIP, 11 patients had high serum IgG4 level and 8 patients had normal level. Among 14 patients without histology, 6 patients had elevated serum IgG4 levels (146, 213, 250, 279, 300, 4000 mg/dL) and were included in type 1 AIP. Another 8 patients with normal serum IgG4 level were classified as indeterminate AIP and excluded in this study. Finally, 17 patients with SIP type 1 AIP and 8 patients with SIN type 1 AIP were enrolled in this study. The median age was 61 years (range, 33-84 years) and males were predominant (72%). The sensitivity of serum IgG4 was 68.0%.

***Comparison of SIP and SIN type 1 AIP***

The mean age of two groups was similar (62 years *vs* 60 years in SIP and SIN type 1 AIP) and there was no difference in sex between two groups (Table 1). The diffuse type of AIP seemed to be more common in SIP than SIN group (47% *vs* 31%) but the difference was not significant (*P* = 0.39). The median serum IgG4 level was 312 mg/dL (normal range, 145-4000) in SIP group and that was 33 mg/dL (normal range, 6-75 mg/dL) in SIN group and the difference was significant (*P* = 0.03). The patients of SIP group were more likely to have other organ involvement than those of SIN group (59% *vs* 26%, *P* = 0.016). Among SIP group, sclerosing cholangitis was the most common (4 cases) and sialoadenitis was also common (3 cases) as other organ involvement. Retroperitoneal fibrosis, mediastianl lymphadenitis and lacrimal gland were another other organ involvements. Among SIN group, one patient had retroperitoneal fibrosis. Only one patient with sclerosing cholangitis was pathologically confirmed as an other organ involvement and other patients were diagnosed with only image and steroid responsiveness. The surgical resection rate was higher in SIN than SIP group (75% *vs* 26% in, *P* = 0.018). The mean follow up duration was not different between two groups (30 *vs* 16 mo in SIP and SIN groups, *P* = 0.075). All patients except surgical resection received steroid treatment and the response rate was 100% in both SIP and SIN groups. The relapse rate was not different between two groups (36% *vs* 25% in SIP and SIN group, *P* = 0.80). The mean interval from steroid treatment and relapse was not different between two groups (14 mo *vs* 11 mo in SIP and SIN groups, *P* = 0.82).

***Correlation between serum and tissue IgG4 concentrations***

Among total 25 patients with type 1 AIP, 19 patients had tissue specimens which included 11 SIP and 8 SIN groups. The mean tissue IgG4 concentrations were significantly higher in SIP than SIN group (40 cells per HPF *vs* 18 cells per HPF, *P* = 0.02). Among 8 SIN patients, the tissue IgG4 concentrations were less than 15 cells per HPF in most of cases except one (Figure 2). Among 11 SIP patients, the tissue IgG4 concentrations were more than 25 cells per HPF except 1 case (15 cells per HPF). However, there was no linear correlation between serum and tissue IgG4 concentration among 11 SIP patients.

***Clinical features of 8 patients with SIN type 1 AIP***

The clinical features of 8 patients with SIN type 1 AIP were summarized in Table 2. Three cases were typical diffuse type AIP. However, surgical resection was done in two cases because serum IgG4 was normal and possibility of malignancy could not be excluded in early period (2005). Four cases with segmental type, surgical resections were performed because the possibility of malignancy could not be excluded with image at that time. Only one patient had retroperitoneal fibrosis and experienced disease relapse. Six patients who received surgical resection could be confirmed as type I AIP with LPSP (level 1 criterion) and level 1/2 parenchymal imaging. One patient (Case 3) had level 1 parenchymal imaging and level 2 histology. The other patient (Case 4) could be diagnosed as type 1 AIP with level 1 ductal imaging, level 2 histology and response to steroid.

One patient had a relatively high tissue IgG4 concentration (80 cells per HPF) despite low serum IgG4 level (43 mg/dL). He was 61-year -old male and mass was detected incidentally at the body of pancreas. Magnetic resonance image (MRI) finding also showed slightly exophytic mass of iso-attenuation at the body of pancreas with distal parenchymal atrophy and abrupt cutting of pancreatic duct was noticed with upstream ductal dilatation (Figure 3). Image findings were compatible with pancreatic cancer and distal pancreatectomy was performed. Gross pathologic finding showed 1.3 cm × 1.2 cm × 3 cm sized white solid mass with uncertain margin. Microscopic finding showed dense periductal lymphoplasmacytic infiltration, storiform fibrosis and obliterative phlebitis (Figure 4A). The IgG4 immunohistochemistry also showed dense infiltration (80 cells per HPF) (Figure 4B). After operation, he did not develop any symptoms and signs of recurrencefor 3 years of follow-up.

**DISCUSSION**

IgG4 related disease was recognized as a systemic disease since 2003[18] and AIP was proposed as one of the IgG4 related sclerosing diseases in 2006[19]. Since two histopathologic subtypes such as LPSP and IDCP have been recognized[20], type 1 AIP is now considered as the pancreatic manifestation of an IgG4 related systemic fibroinflammatory diseases involving the salivary gland, bile duct, and retroperitoneum. So, the serum IgG4 is a useful marker for the diagnosis of type 1 AIP and most diagnostic criteria of AIP include the serum IgG4 elevation as one of the criteria[6,9,17]. However, the sensitivity of serum IgG4 is variable and different among countries. If the study population includes more type 2 AIP, the sensitivity of IgG4 may be low because serum IgG4 is not usually elevated in type 2 AIP. The recent international multicenter study which enrolled 713 patients with AIP from 8 countries reported that sensitivity of serum IgG4 was only 63% among 204 patients with histologically proven type 1 AIP[13]. The relatively low sensitivity of serum IgG4 can make the diagnosis of AIP in clinical setting confusing. In our study, 4 patients with segmental type AIP underwent unnecessary surgical resection.

We had a question about the reason for not enough high sensitivity even if type 1 AIP is a kind of IgG4 related systemic disease. So, we conducted our study in order to analyze the clinical and pathological differences between SIP and SIN type I AIP. Unfortunately, there were a few studies about the normal serum IgG4 AIP till now[21,22]. One study included 58 AIP patients including 13 normal serum IgG4 AIP[21] but histology was available in only 14 cases (6 cases among 13 SIN AIP). Another study included 27 patients with AIP including 7 SIN AIP[22]. Histology was not available in any cases because endoscopic ultrasonography guided fine needle aspiration was performed in 26 cases using 22 gauge needle not to diagnose AIP but to exclude pancreatic malignancy. So, it can’t be accepted that all of the enrolled patients were really type I AIP in both studies. In order to exclude possible type 2 AIP, our study enrolled 19 patients with histologically proven type 1 AIP and 6 patients who were clinically diagnosed as type 1 AIP with elevated serum IgG4 level. Of course, there are possibilities of type 2 AIP in spite of elevated serum IgG4 level among 6 patients because the serum IgG4 elevation was detected in 23% among 47 patients with histological proven type 2 AIP according to recent study[13]. However, the possibility might be very low because the serum IgG4 level was relatively high (213, 250, 279, 300, 4000 mg/dL) except one case (146 mg/dL) and type 2 AIP was reported to be relatively rare in Asian countries including South Korea[13]. In addition, 5 patients had other organ involvement which could rarely be seen in type 2 AIP[7].

The surgical resection rate was higher in SIN than SIP group. The one reason could be a difficult diagnosis of AIP. If the lesion is in the body/tail and serum IgG4 is normal, the clinicians can’t suspect the possibility of AIP and don’t hesitate surgical resection. Another reason might be selection bias of this study because we excluded 8 patients with normal serum IgG4 and no histology. The 8 patients received steroid treatment and steroid responsiveness was 100%. One patient experienced relapse.

In this study, the clinical profiles of type 1 AIP are not different from recent other multicenter study including 327 Asian patients[12]. The old mean age (over 60 year), male predominance, common other organ involvement especially sclerosing cholangitis and frequent relapse are common features of Asian patients of AIP which are similar to our study. Interestingly, the important clinical difference between SIP and SIN type 1 AIP was the frequency of other organ involvement. Other organ involvement was significantly more common in SIP than SIN type 1 AIP (59% *vs* 26%). Only one patient among SIN group had retroperitoneal fibrosis. This result can assume that other organ involvement can affect the serum IgG4 level. Mikulicz’s disease refers to idiopathic symmetrical swelling of lacrimal, submandibular gland and is one of IgG4 related systemic disease. The recent study reported that the serum IgG4 level is very high (894 mg/dL) in Mikulicz’s disease and significantly higher in patients with extrasalivary gland involvement[23]. More frequent other organ involvement in our SIP type 1 AIP is similar to the results of previous studies[21,22,24].

Another reason for various serum IgG4 level may be the number of IgG4 positive plasma cells in tissue. As expected, the mean tissue IgG4 concentration was significantly low in SIN than SIP type 1 AIP. All patients with SIP group had high IgG4 concentration (over 25 cells per HPF) except one case (15 cells per HPF). However, the patients with SIN group had very low IgG4 concentration (below 15 cells per HPF) except one case (80 cells per HPF). Our data might conclude that IgG4 concentration of pancreatic tissue can influence the sensitivity of serum IgG4 in type 1 AIP. However, the serum level of IgG4 had no correlation with tissue IgG4 concentration in SIP type 1 AIP. It can be explained that the serum level may be influenced by not only tissue concentration but also other factors such as size of involved pancreas, other organ involvement. We think that this is the first study about correlation between serum and tissue IgG4 concentration in type I AIP.

Other possible clinical roles of serum IgG4 rather than diagnostic marker are uncertain and interesting issue in type 1 AIP. The clinical use of serum IgG4 except diagnostic marker may be relevant in three settings: monitoring of therapy, monitoring for disease relapse and prediction of relapse. The large multicenter study in Japan reported that IgG4 levels failed to normalize in 115/182 (63%) of the patients treated with steroids[25]. The study suggested that serial IgG4 levels are helpful in identifying early relapse. However, only 30% of patients with persistent IgG4 elevation relapsed, whereas relapse was also seen in 10% of patients who normalized IgG4 levels. The results regarding the value of initial serum IgG4 levels in predicting relapse are various among studies, some reporting higher relapse rate in patients with elevated serum IgG4 levels[22,26], whereas others failed to observe any association[7,27-29]. In order to clarify the role of serum IgG4 in predicting relapse, type 2 AIP should be excluded in normal serum IgG4 group, because type 2 AIP is well known for rare relapse[7]. The positive study might include some patients with type 2 AIP. In our study, the relapse rate was not different between two groups of type 1 AIP. So, our data supports that initial serum IgG4 levels can’t predict relapse in type 1 AIP.

In conclusion, the sensitivity of serum IgG4 was not enough (68%) in definite type I AIP. The demographic findings were not different between SIP and SIN type 1 AIP, but other organ involvement was significantly more common in SIP than SIN type 1 AIP. High serum IgG4 level was associated with other organ involvement and tissue IgG4 concentration, but did not affect relapse rate in type 1 AIP.

**COMMENTS**

***Background***

Type 1 autoimmune pancreatitis (AIP) is one of the immunoglobulin G4 (IgG4)related diseases and serum IgG4 is known as a useful diagnostic marker. However, the sensitivity of serum IgG4 is variable. AIP is a kind of chronic pancreatitis with irregular narrowing of the pancreatic duct and systemic fibroinflammatory disease andis characterized by a remarkable response to steroid therapy.

***Research frontiers***

IgG4 related disease was recognized as a systemic disease since 2003 and AIP was proposed as one of the IgG4 related sclerosing diseases in 2006. Since two histopathologic subtypes such as lymphoplasmacytic sclerosing pancreatitis and idiopathic duct-centric chronic pancreatitis have been recognized, type 1 AIP is now considered as the pancreatic manifestation of an IgG4 related systemic fibroinflammatory diseases involving the salivary gland, bile duct, and retroperitoneum. So, the serum IgG4 is a useful marker for the diagnosis of type 1 AIP and most diagnostic criteria of AIP include the serum IgG4 elevation as one of the criteria. However, the sensitivity of serum IgG4 is variable and different among countries.

***Innovations and breakthroughs***

The sensitivity of serum IgG4 was not enough (68%) in definite type I AIP. The demographic findings were not different between serum IgG4-positive (SIP) and serum IgG4-negative (SIN) type 1 AIP, but other organ involvement was significantly more common in SIP than SIN type 1 AIP. High serum IgG4 level was associated with other organ involvement and tissue IgG4 concentration, but did not affect relapse rate in type 1 AIP.

***Peer review***

The authors compared the clinical and pathological differences between serum IgG4-positive and IgG4-negative type 1 autoimmune pancreatitis and demonstrated that the sensitivity of serum IgG4 was 68% in type I AIP. The high serum IgG4 level was associated with other organ involvement and tissue IgG4 concentration, but did not affect the relapse rate in type 1 AIP.

**REFERENCES**

1 **Ryu JK**, Lee JK, Kim YT, Lee DK, Seo DW, Lee KT, Kim HG, Kim JS, Lee HS, Kim TN, Rho MH, Moon JH, Lee J, Choi HS, Lee WJ, Yoo BM, Yoon YB. Clinical features of chronic pancreatitis in Korea: a multicenter nationwide study. *Digestion* 2005; **72**: 207-211 [PMID: 16260866 DOI: 10.1159/000089414]

2 **Kawaguchi K**, Koike M, Tsuruta K, Okamoto A, Tabata I, Fujita N. Lymphoplasmacytic sclerosing pancreatitis with cholangitis: a variant of primary sclerosing cholangitis extensively involving pancreas. *Hum Pathol* 1991; **22**: 387-395 [PMID: 2050373 DOI: 10.1016/0046-8177(91)90087-6]

3 **Pearson RK**, Longnecker DS, Chari ST, Smyrk TC, Okazaki K, Frulloni L, Cavallini G. Controversies in clinical pancreatology: autoimmune pancreatitis: does it exist? *Pancreas* 2003; **27**: 1-13 [PMID: 12826899 DOI: 10.1097/00006676-200307000-00001]

4 **Notohara K**, Burgart LJ, Yadav D, Chari S, Smyrk TC. Idiopathic chronic pancreatitis with periductal lymphoplasmacytic infiltration: clinicopathologic features of 35 cases. *Am J Surg Pathol* 2003; **27**: 1119-1127 [PMID: 12883244 DOI: 10.1097/00000478-200308000-00009]

5 **Zhang L**, Chari S, Smyrk TC, Deshpande V, Klöppel G, Kojima M, Liu X, Longnecker DS, Mino-Kenudson M, Notohara K, Rodriguez-Justo M, Srivastava A, Zamboni G, Zen Y. Autoimmune pancreatitis (AIP) type 1 and type 2: an international consensus study on histopathologic diagnostic criteria. *Pancreas* 2011; **40**: 1172-1179 [PMID: 21975436 DOI: 10.1097/MPA.0b013e318233bec5]

6 **Shimosegawa T**, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, Kim MH, Klöppel G, Lerch MM, Löhr M, Notohara K, Okazaki K, Schneider A, Zhang L. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas* 2011; **40**: 352-358 [PMID: 21412117 DOI: 10.1097/MPA.0b013e3182142fd2]

7 **Sah RP**, Chari ST, Pannala R, Sugumar A, Clain JE, Levy MJ, Pearson RK, Smyrk TC, Petersen BT, Topazian MD, Takahashi N, Farnell MB, Vege SS. Differences in clinical profile and relapse rate of type 1 versus type 2 autoimmune pancreatitis. *Gastroenterology* 2010; **139**: 140-18; quiz 140-18; [PMID: 20353791 DOI: 10.1053/j.gastro.2010.03.054]

8 **Kawa S,** Hamano H. Assessment of serological markers for the diagnosis of autoimmune pancreatitis. *J Jpn Pancreas Soc* 2003; **17**: 607-610

9 **Chari ST**, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Zhang L, Clain JE, Pearson RK, Petersen BT, Vege SS, Farnell MB. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. *Clin Gastroenterol Hepatol* 2006; **4**: 1010-106; quiz 934 [PMID: 16843735 DOI: 10.1016/j.cgh.2006.05.017]

10 **Choi EK**, Kim MH, Lee TY, Kwon S, Oh HC, Hwang CY, Seo DW, Lee SS, Lee SK. The sensitivity and specificity of serum immunoglobulin G and immunoglobulin G4 levels in the diagnosis of autoimmune chronic pancreatitis: Korean experience. *Pancreas* 2007; **35**: 156-161 [PMID: 17632322 DOI: 10.1097/MPA.0b013e318053eacc]

11 **Ryu JK**, Chung JB, Park SW, Lee JK, Lee KT, Lee WJ, Moon JH, Cho KB, Kang DW, Hwang JH, Yoo KS, Yoo BM, Lee DH, Kim HK, Moon YS, Lee J, Lee HS, Choi HS, Lee SK, Kim YT, Kim CD, Kim SJ, Hahm JS, Yoon YB. Review of 67 patients with autoimmune pancreatitis in Korea: a multicenter nationwide study. *Pancreas* 2008; **37**: 377-385 [PMID: 18953249 DOI: 10.1097/MPA.0b013e31817a0914]

12 **Kamisawa T**, Kim MH, Liao WC, Liu Q, Balakrishnan V, Okazaki K, Shimosegawa T, Chung JB, Lee KT, Wang HP, Lee TC, Choudhuri G. Clinical characteristics of 327 Asian patients with autoimmune pancreatitis based on Asian diagnostic criteria. *Pancreas* 2011; **40**: 200-205 [PMID: 21404457 DOI: 10.1097/MPA.0b013e3181fab696]

13 **Kamisawa T**, Chari ST, Giday SA, Kim MH, Chung JB, Lee KT, Werner J, Bergmann F, Lerch MM, Mayerle J, Pickartz T, Lohr M, Schneider A, Frulloni L, Webster GJ, Reddy DN, Liao WC, Wang HP, Okazaki K, Shimosegawa T, Kloeppel G, Go VL. Clinical profile of autoimmune pancreatitis and its histological subtypes: an international multicenter survey. *Pancreas* 2011; **40**: 809-814 [PMID: 21747310 DOI: 10.1097/MPA.0b013e3182258a15]

14 **Kamisawa T**, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, Okamoto A, Egawa N, Nakajima H. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003; **38**: 982-984 [PMID: 14614606 DOI: 10.1007/s00535-003-1175-y]

15 **Zhang L**, Smyrk TC. Autoimmune pancreatitis and IgG4-related systemic diseases. *Int J Clin Exp Pathol* 2010; **3**: 491-504 [PMID: 20606730]

16 **Sah RP**, Chari ST. Serologic issues in IgG4-related systemic disease and autoimmune pancreatitis. *Curr Opin Rheumatol* 2011; **23**: 108-113 [PMID: 21124093 DOI: 10.1097/BOR.0b013e3283413469]

17 **Otsuki M**, Chung JB, Okazaki K, Kim MH, Kamisawa T, Kawa S, Park SW, Shimosegawa T, Lee K, Ito T, Nishimori I, Notohara K, Naruse S, Ko SB, Kihara Y. Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis. *J Gastroenterol* 2008; **43**: 403-408 [PMID: 18600383 DOI: 10.1007/s00535-008-2205-6]

18 **Kamisawa T**, Egawa N, Nakajima H. Autoimmune pancreatitis is a systemic autoimmune disease. *Am J Gastroenterol* 2003; **98**: 2811-2812 [PMID: 14687846 DOI: 10.1111/j.1572-0241.2003.08758.x]

19 **Kamisawa T**, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. *J Gastroenterol* 2006; **41**: 613-625 [PMID: 16932997 DOI: 10.1007/s00535-006-1862-6]

20 **Chari ST**, Kloeppel G, Zhang L, Notohara K, Lerch MM, Shimosegawa T. Histopathologic and clinical subtypes of autoimmune pancreatitis: the Honolulu consensus document. *Pancreas* 2010; **39**: 549-554 [PMID: 20562576 DOI: 10.1097/MPA.0b013e3181e4d9e5]

21 **Kamisawa T**, Takuma K, Tabata T, Inaba Y, Egawa N, Tsuruta K, Hishima T, Sasaki T, Itoi T. Serum IgG4-negative autoimmune pancreatitis. *J Gastroenterol* 2011; **46**: 108-116 [PMID: 20824290 DOI: 10.1007/s00535-010-0317-2]

22 **Matsubayashi H**, Sawai H, Kimura H, Yamaguchi Y, Tanaka M, Kakushima N, Takizawa K, Kadooka M, Takao T, Hebbar S, Ono H. Characteristics of autoimmune pancreatitis based on serum IgG4 level. *Dig Liver Dis* 2011; **43**: 731-735 [PMID: 21515099 DOI: 10.1016/j.dld.2011.03.006]

23 **Himi T**, Takano K, Yamamoto M, Naishiro Y, Takahashi H. A novel concept of Mikulicz's disease as IgG4-related disease. *Auris Nasus Larynx* 2012; **39**: 9-17 [PMID: 21571468 DOI: 10.1016/j.anl.2011.01.023]

24 **Hamano H**, Arakura N, Muraki T, Ozaki Y, Kiyosawa K, Kawa S. Prevalence and distribution of extrapancreatic lesions complicating autoimmune pancreatitis. *J Gastroenterol* 2006; **41**: 1197-1205 [PMID: 17287899 DOI: 10.1007/s00535-006-1908-9]

25 **Kamisawa T**, Shimosegawa T, Okazaki K, Nishino T, Watanabe H, Kanno A, Okumura F, Nishikawa T, Kobayashi K, Ichiya T, Takatori H, Yamakita K, Kubota K, Hamano H, Okamura K, Hirano K, Ito T, Ko SB, Omata M. Standard steroid treatment for autoimmune pancreatitis. *Gut* 2009; **58**: 1504-1507 [PMID: 19398440 DOI: 10.1136/gut.2008.172908]

26 **Frulloni L**, Scattolini C, Falconi M, Zamboni G, Capelli P, Manfredi R, Graziani R, D'Onofrio M, Katsotourchi AM, Amodio A, Benini L, Vantini I. Autoimmune pancreatitis: differences between the focal and diffuse forms in 87 patients. *Am J Gastroenterol* 2009; **104**: 2288-2294 [PMID: 19568232 DOI: 10.1038/ajg.2009.327]

27 **Naitoh I**, Nakazawa T, Ohara H, Ando T, Hayashi K, Tanaka H, Okumura F, Miyabe K, Yoshida M, Sano H, Takada H, Joh T. Clinical significance of extrapancreatic lesions in autoimmune pancreatitis. *Pancreas* 2010; **39**: e1-e5 [PMID: 19924018 DOI: 10.1097/MPA.0b013e3181bd64a1]

28 **Ghazale A**, Chari ST, Zhang L, Smyrk TC, Takahashi N, Levy MJ, Topazian MD, Clain JE, Pearson RK, Petersen BT, Vege SS, Lindor K, Farnell MB. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. *Gastroenterology* 2008; **134**: 706-715 [PMID: 18222442 DOI: 10.1053/j.gastro.2007.12.009]

29 **Kubota K**, Iida H, Fujisawa T, Yoneda M, Inamori M, Abe Y, Kirikoshi H, Saito S, Ohshiro H, Kakuta Y, Nakajima A. Clinical factors predictive of spontaneous remission or relapse in cases of autoimmune pancreatitis. *Gastrointest Endosc* 2007; **66**: 1142-1151 [PMID: 18061714 DOI: 10.1016/j.gie.2007.06.059]

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**Figure 1 Enrolled patients and classification of autoimmune pancreatitis.** Among 37 patients with autoimmune pancreatitis (AIP), one case was type 2 AIP and 19 patients was type 1 AIP by histology. The pathologic diagnosis was inconclusive in 3 cases among 23 tissue samples. Among 14 patients without histology, 8 patients were excluded due to normal serum immunoglobulin G4 (IgG4) level. Finally, 25 patients with definite type 1 AIP (19 histologically and 6 serologically diagnosed cases) were enrolled in this study. LPSP: Lymphoplasmacytic sclerosing pancreatitis; IDCP: Idiopathic duct-centric chronic pancreatitis.

**Figure 2 Correlation between serum and tissue immunoglobulin G4 concentrations.** Among 8 IgG4-negative (SIN) patients, the tissue immunoglobulin G4 (IgG4) concentrations were less than 15 cells per high power filed (HPF) in most of cases except one. Among 11 serum IgG4-positive (SIP) patients, the tissue IgG4 concentrations were more than 25 cells per HPF except 1 case (15 cells per HPF). There was no linear correlation between serum and tissue IgG4 concentration among 11 SIP patients.

**Figure 3 Magnetic resonance image of 61 year old male patients with normal serum immunoglobulin G4.** Magnetic resonance image finding shows slightly exophytic mass of iso-attenuation at the body of pancreas with distal parenchymal atrophy and abrupt cutting of pancreatic duct with upstream ductal dilatation .

**Figure 4 Histology and immunoglobulin G4 immunohistochemical staining.** A: HE staining shows typical finding of lymphoplasmacytic sclerosing pancreatitis (× 200); B: Immunoglobulin G4 (IgG4) staining shows dense infiltration of IgG4 positive cells (× 400).

 **Table 1 Comparison of clinical characteristics of serum immunoglobulin G4-positive and negative type 1 autoimmune pancreatitis *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **SIP** | **SIN** | ***P*-value** |
| Patients | 17 | 8 |  |
| Mean age, yr | 62 (33-84) | 60 (42-72) | 0.359 |
| Sex (M/F) | 13 : 4 | 5 : 3 | 0.172 |
| Diffuse type | 8 (47) | 3 (31) | 0.390 |
| Median serum IgG4 (mg/dL) | 312 (145-4000) | 33 (6-75) | 0.030 |
| Other organ involvement | 10 (59) | 1 (26) | 0.016 |
| Histologic examination |  |  |  |
| Resection | 5 (26) | 6 (75) | 0.018 |
|  Biopsy | 6 (32) | 2 (25% |  |
|  Not done | 6 (32) |  |  |
| Mean follow up, mo | 30 | 16 | 0.075 |
| Relapse  | 6 (35) | 2 (25) | 0.85 |

SIP: Serum immunoglobulin G4 (IgG4)-positive; SIN: Serum IgG4-negative; F: Female; M: Male.

**Table 2 Clinical features of 8 patients with serum immunoglobulin G4-negative type 1 autoimmune pancreatitis**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Patients** | **Age/sex** | **Tissue** | **Image** | **OOI** | **Serum IgG4****(mg/dL)** | **Tissue IgG4****In HPF** | **Relapse** |
| Case 1 | 72/F | Resection | Diffuse | No | 75 | 5 | No |
| Case 2 | 42/M | Resection | Diffuse | No | 26 | 5 | Yes |
| Case 3 | 71/F | Biopsy | Diffuse | RF | 33 | 15 | Yes |
| Case 4 | 61/M | Biopsy | Tail | No | 39 | 11 | No |
| Case 5 | 61/M | Resection | Body | No | 43 | 80 | No |
| Case 6 | 51/M | Resection | Tail | No | 21 | 5 | No |
| Case 7 | 66/M | Resection | Head | No | 6 | 12 | No |
| Case 8 | 53/F | Resection | Body | No | 11 | 12 | no |

OOI: Other organ involvement; RF: Retroperitoneal fibrosis; HPF: High power field; F: Female; M: Male; IgG4: Immunoglobulin G4.