

Allergic manifestations in autoimmune pancreatitis

Terumi Kamisawa^a, Hajime Anjiki^a, Naoto Egawa^a and Naoko Kubota^b

Objective Autoimmune pancreatitis (AIP) is a peculiar type of pancreatitis of presumed autoimmune etiology. However, target antigens for AIP have not been detected. Furthermore, its preponderant occurrence in elderly men and the very dramatic response with no major residual deformity to oral steroid therapy within 2 weeks suggest that the pathogenesis of AIP might not involve autoimmune mechanism. Recently, it was reported that the immune reaction closely involved in the pathogenesis of allergic disorders was upregulated in the affected tissues of AIP. This study aimed to examine the allergic manifestations in AIP patients.

Methods This case series consisted of 45 AIP patients. Present and/or past histories of allergic diseases, clinical findings, and laboratory data were reviewed.

Results Twenty patients (allergic-type AIP) had histories of allergic diseases, such as acute allergic rhinitis ($n=11$), including rose and hay fever, atopic dermatitis ($n=5$), bronchial asthma ($n=3$), drug allergy ($n=2$), and hypersensitivity pneumonitis ($n=1$). Serum IgE levels were elevated in only 12 allergic-type AIP patients, and they were significantly higher in allergic-type AIP patients than in AIP patients without allergic manifestations ($P=0.0001$). The

peripheral eosinophil count was significantly elevated in allergic-type AIP patients ($P=0.048$). With respect to initial symptoms, obstructive jaundice was less frequent in allergic-type AIP patients ($P=0.012$), and abdominal pain was detected in only five patients with allergic-type AIP ($P=0.013$). Allergic-type AIP occurred predominantly from September to February in 19 of 20 patients ($P=0.001$).

Conclusion Allergic manifestations were detected in about half of the AIP patients, and allergic mechanisms may be related to the occurrence of AIP in these patients. *Eur J Gastroenterol Hepatol* 21:1136–1139 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

European Journal of Gastroenterology & Hepatology 2009, 21:1136–1139

Keywords: allergy, autoimmune pancreatitis, eosinophil, IgE, IgG4

Department of ^aInternal Medicine and ^bGeneral Medicine, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

Correspondence to Terumi Kamisawa, MD, PhD, Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan
Tel: +81 3 3823 2101; fax: +81 3 3824 1552; e-mail: kamisawa@cick.jp

Received 25 November 2008 Accepted 18 January 2009

Introduction

Autoimmune pancreatitis (AIP) is a peculiar type of pancreatitis of presumed autoimmune etiology, and it has become a distinct entity that is recognized worldwide [1–5]. In 1995, Yoshida *et al.* [6] first proposed the concept of AIP from analysis of their case and the 10 other reported cases, and they summarized the clinical features as follows: (i) increased serum γ -globulin or IgG levels; (ii) presence of autoantibodies; (iii) effectiveness of steroid therapy; (iv) occasional association with other autoimmune diseases, such as Sjogren's syndrome; (v) diffuse enlargement of the pancreas; (vi) diffuse irregular narrowing of the main pancreatic duct on endoscopic retrograde pancreatography; (vii) fibrotic change with lymphocyte infiltration histopathologically; (viii) mild symptoms, usually without acute attacks of pancreatitis; (ix) occasional association with stenosis of the lower bile duct, cholestatic liver dysfunction, and hyperbilirubinemia; (x) no pancreatic calcification; and (xi) no pancreatic cysts. Based on the first four findings, they suspected that the cause of the pancreatitis was an autoimmune mechanism, and named this pancreatitis as AIP.

However, target antigens for AIP have not been detected. On the basis of histological and immunohistochemical examinations of various organs and extrapancreatic lesions of AIP patients, AIP might be a pancreatic lesion of an IgG4-related systemic disease, and extrapancreatic lesions occasionally associated with AIP might not be a part of an autoimmune disease but organs involved in this systemic disease [5,7,8]. Furthermore, its preponderant occurrence in elderly men and the very dramatic response with no major residual deformity to oral steroid therapy within 2 weeks [1–5] suggest that the pathogenesis of AIP might not involve an autoimmune mechanism. Recently, it was shown that the expressions of Th2 cytokines (IL-4, IL-5, and IL-13) and regulatory cytokines (IL-10 and transformation growth factor- β) were upregulated in the affected tissues of AIP [9]. The immune reactions that are predominantly mediated by Th2 cells and regulatory T cells are not common in classical autoimmune diseases, but they are closely involved in the pathogenesis of allergic disorders such as bronchial asthma and atopic dermatitis [10].

Thus, we studied allergic manifestations in 45 AIP patients and compared the clinical features of AIP patients with and without allergic manifestations.

Patients and methods

Patients

Between April 1990 and July 2008, 48 patients were consecutively diagnosed with AIP based on the Asian diagnostic criteria for AIP [11]. All patients showed pancreatic enlargement and irregular narrowing of the main pancreatic duct. Forty patients were also diagnosed based on the revised clinical diagnostic criteria of AIP 2006 [12] in Japan, and the other eight patients were diagnosed based on the imaging criterion and good responsiveness to steroid therapy.

Methods

Allergy clinic charts of the patients were reviewed for present and/or past histories of allergic diseases, such as acute allergic rhinitis, atopic dermatitis, and bronchial asthma. Of 48 AIP patients, three patients whose allergy clinic charts were not fully described were excluded from this study. They were treated before 1995 and were not followed up. Finally, 45 AIP patients (37 men and 8 women, median age 67 years) were enrolled in this study. Authors confirmed allergic histories by interview in 36 followed up patients again.

Clinical findings and laboratory data (antinuclear antigen in 45 patients, rheumatoid factor in 38 patients, serum IgG4 level in 41 patients, serum IgE level in 35 patients, and peripheral eosinophil count in 45 patients) were also reviewed. Peripheral blood eosinophilia was identified when the absolute eosinophil count was greater than 600 cells/mm³ [13]. This study was approved by the institutional review board of Tokyo Metropolitan Komagome Hospital.

Statistical analysis

Statistical analysis was performed using Wilcoxon's rank-sum test and Fisher's exact test. A *P* value of less than 0.05 was considered statistically significant.

Results

Of the 45 AIP patients, 20 had present and/or past histories of allergic diseases, such as acute allergic rhinitis (*n*=11), including rose and hay fever, atopic dermatitis (*n*=5), bronchial asthma (*n*=3), drug allergy (*n*=2), and hypersensitivity pneumonitis (*n*=1). The clinical features of the 20 AIP patients with allergic manifestations (allergic-type AIP) and the 25 AIP patients without allergic manifestations (nonallergic-type AIP) were compared.

There were no significant differences between the two types: in age at diagnosis, sex ratio, serum IgG4 levels, positivity of autoantibodies, and frequency of associated extrapancreatic lesions, such as sclerosing sialadenitis and retroperitoneal fibrosis. Elevated serum IgG4 levels were detected in 16 (84%) of 19 allergic-type AIP patients, and in 18 (82%) of 22 nonallergic-type AIP patients. Serum IgE levels (normal, 580 IU/ml) were elevated in 12 (80%) of 15 allergic-type AIP patients, and in none of 20 nonallergic-type AIP patients (*P*<0.0001). Serum IgE levels were significantly higher in allergic-type AIP patients than in nonallergic-type AIP patients (*P*=0.0001). Peripheral blood eosinophilia was identified in five (25%) of allergic-type AIP patients (600–1390 cells/mm³), and in none of nonallergic-type AIP patients (*P*=0.013). The peripheral eosinophil count was significantly elevated in allergic-type AIP patients (*P*=0.048). With respect to initial symptoms, obstructive jaundice was less frequent in allergic-type AIP patients (*P*=0.012), and abdominal pain was detected in only five patients with allergic-type AIP (*P*=0.013).

Allergic-type AIP occurred predominantly from September to February in 19 of 20 patients, whereas nonallergic-type AIP occurred from September to February in 12 of 25 patients (*P*=0.009) (Table 1).

Discussion

The concept of AIP was first proposed based on the frequent increases in serum IgG, the presence of autoantibodies, and responsiveness to steroid therapy [6]. However, target antigens for AIP have not been detected.

Table 1 Clinical differences between autoimmune pancreatitis patients with and without allergic aspects

	With allergic aspects (<i>n</i> =20)	Without allergic aspects (<i>n</i> =25)	<i>P</i> value
Age at diagnosis ^a (years)	65 (54.25–69.50)	68 (61.00–76.00)	0.166
Male/female	14/6	23/2	0.113
Obstructive jaundice +	9 (45%)	19 (76%)	0.062
Abdominal pain +	5 (25%)	0 (0%)	0.012
Autoantibody +	3 (15%)	6 (24%)	0.709
Serum IgG4 ^a (mg/dl)	298.00 (198.00–450.00)	368 (125.75–796.00)	0.647
Serum IgE ^a (IU/ml)	793.50 (310.75–1288.00)	176 (98.500–221.00)	0.00001
Eosinophils ^a (cells/mm ³)	292.50 (106.00–582.00)	160 (104.50–284.00)	0.048
Extrapancreatic lesion +	5 (25%)	8 (32%)	0.744
On-set month, March–August/September–February	2/18	12/13	0.0009

+, present.

^aMedian (quartile range).

Its preponderant occurrence in elderly men and the very dramatic response with no major residual deformity to oral steroid therapy within 2 weeks [1–5] suggest that the pathogenesis of AIP might not involve an autoimmune mechanism. Although it has been reported that Sjogren's syndrome or primary sclerosing cholangitis is occasionally associated with AIP [14,15], it has become obvious that the salivary gland lesion in AIP is not Sjogren's syndrome but sclerosing sialadenitis with infiltration of abundant IgG4-positive plasma cells, and the bile duct lesion in AIP is not primary sclerosing cholangitis but sclerosing cholangitis with infiltration of abundant IgG4-positive plasma cells [16–18]. It has also been recognized that AIP might be a pancreatic lesion of an IgG4-related systemic disease, and extrapancreatic lesions occasionally associated with AIP might not be a part of an autoimmune disease but organs involved in this systemic disease [5,7,8]. Elevation of serum IgG4 concentrations is detected in 67–95% of AIP patients [19,20], and a close relationship between IgG4 and some allergic diseases has been reported [21]. Zen *et al.* [9] demonstrated that the expressions of Th2 cytokines and regulatory cytokines were upregulated in the affected tissues of AIP. The immune reactions that are predominantly mediated by Th2 cells and regulatory T cells are not common in classical autoimmune diseases, but they are closely involved in the pathogenesis of allergic disorders such as bronchial asthma and atopic dermatitis [10]. These findings led us to this study of allergic manifestations in AIP patients.

This study showed that 44% of AIP patients had allergic manifestations, and these allergic-type AIP patients frequently showed elevated serum IgE levels and peripheral eosinophil counts. According to a nationwide survey of AIP in Japan [22], an elevated peripheral eosinophil count (> 500 cells/mm³) was detected in 21% of AIP patients. Ito *et al.* [23] reported three AIP patients who had mild peripheral eosinophilia (less than 696 cells/mm³). Sasahira *et al.* [24] reported an AIP patient showing peripheral eosinophilia (1343 cells/mm³) who was associated with sclerosing cholangitis and inflammatory pseudotumor of the liver with histological findings of infiltration of abundant lymphocytes, plasma cells, and eosinophils. According to the report by Abraham *et al.* [25], moderate eosinophilic infiltration in the pancreas was observed histologically in five (21%) of 24 AIP patients, and these patients also had prominent eosinophilic infiltrates elsewhere in the biliary tract, but the eosinophilic infiltration was scattered within lymphoplasmacytic infiltration, which differed from the diffuse and dense eosinophilic infiltration seen in eosinophilic pancreatitis. They also reported that 10 (41%) of the 24 AIP patients had allergic and/or atopic manifestations, including asthma ($n=8$), allergic rhinitis ($n=6$), chronic urticaria ($n=1$), and nasal polyp ($n=1$), and in the 13 patients in whom a peripheral eosinophil count was performed, three

showed mild eosinophilia (400–550 cells/mm³) and one showed marked eosinophilia (1500 cells/mm³) [25]. It has also been reported that patients with eosinophilic pancreatitis, a rare pancreatic condition usually showing systemic eosinophilic manifestations, have histories of allergies, asthma, or eczema [26,27].

This is the second report dealing with allergic manifestations in AIP patients following the study by Abraham *et al.* [25]. Interestingly, in this study, the occurrence of allergic-type AIP showed seasonality (September to February) that might be similar to that of other allergic diseases, such as bronchial asthma and acute allergic rhinitis [28,29]. This may also suggest a relationship between AIP and allergy. Although the reason for the difference is unknown, obstructive jaundice was a less frequent initial symptom in allergic-type AIP patients, and abdominal pain was detected in only five patients with allergic-type AIP.

The small sample size and the incomplete data set as a result of the retrospective nature of the study are limitations of this study. However, if some AIP cases are caused with allergic mechanisms, a new therapeutic strategy, such as antiallergic treatment, may be effective in these patients.

In conclusion, allergic manifestations were detected in about half of the AIP patients, and allergic mechanisms may be related to the occurrence of AIP in these patients.

Acknowledgement

Conflicts of interest: none declared.

References

- Okazaki K, Chiba T. Autoimmune related pancreatitis. *Gut* 2002; **51**:1–4.
- Kim KP, Kim MH, Song MH, Lee SS, Seo DW, Lee SK. Autoimmune chronic pancreatitis. *Am J Gastroenterol* 2004; **99**:1605–1616.
- Finkelberg DL, Sahani D, Deshpande V, Brugge WR. Autoimmune pancreatitis. *N Engl J Med* 2006; **355**:2670–2676.
- 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.
- Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. *J Gastroenterol* 2006; **41**:613–625.
- 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.
- Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, *et al.* A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003; **38**:982–984.
- Kamisawa T, Nakajima H, Egawa N, Funata N, Tsuruta K, Okamoto A. IgG4-related sclerosing disease incorporating sclerosing pancreatitis, cholangitis, sialadenitis and retroperitoneal fibrosis with lymphadenopathy. *Pancreatol* 2006; **6**:132–137.
- 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.
- Robinson DS, Larche M, Durham SR. Tregs and allergic disease. *J Clin Invest* 2004; **114**:1389–1397.
- Otsuki M, Chung JB, Okazaki K, Kim MH, Kamisawa T, Kawa S, *et al.* Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis. *J Gastroenterol* 2008; **43**:403–408.

- 12 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.
- 13 Tefferi A. Blood eosinophilia: a new paradigm in disease classification, diagnosis, and treatment. *Mayo Clin Proc* 2005; **80**:75–83.
- 14 Waldram R, Kopelman H, Tsantoulas D, Williams R. Chronic pancreatitis, sclerosing cholangitis, and Sicca complex in two siblings. *Lancet* 1975; **1**:550–552.
- 15 Muntefuso 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**:822–826.
- 16 Kamisawa T, Egawa N, Tsuruta K, Okamoto A, Funata N. Primary sclerosing cholangitis may be overestimated in Japan. *J Gastroenterol* 2005; **40**:318–319.
- 17 Kamisawa T, Egawa N, Nakajima H, Tsuruta K, Okamoto A. Extrapaneatic lesions in autoimmune pancreatitis. *J Clin Gastroenterol* 2005; **39**:904–907.
- 18 Kamisawa T, Nakajima H, Hishima T. Close correlation between chronic sclerosing sialadenitis and immunoglobulin G4. *Intern Med J* 2006; **36**:527–529.
- 19 Hamano H, Kawa S, Horiuchi A, Unno H, Furuta N, Akamatsu T, *et al.* High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001; **344**:732–738.
- 20 Kamisawa T, Okamoto A, Funata N. Clinicopathological features of autoimmune pancreatitis in relation to elevation of serum IgG4. *Pancreas* 2005; **31**:28–31.
- 21 Aalberse RC, Milligen FV, Tan KY, Stapel SO. Allergen-specific IgG4 in atopic disease. *Allergy* 1993; **48**:559–569.
- 22 Nishimori I, Suda K, Oi I, Ogawa M. Autoimmune pancreatitis [in Japanese with English abstract]. *Nippon Shokakibyo Gakkai Zasshi* 2000; **97**:1355–1363.
- 23 Ito T, Nakano I, Koyanagi S, Miyahara T, Migita Y, Ogoshi K, *et al.* Autoimmune pancreatitis as a new clinical entity – three cases of autoimmune pancreatitis with effective steroid therapy. *Dig Dis Sci* 1997; **42**:1458–1468.
- 24 Sasahira N, Kawabe T, Nakamura A, Shimura K, Shimura H, Itobayashi E, *et al.* Inflammatory pseudotumor of the liver and peripheral eosinophilia in autoimmune pancreatitis. *World J Gastroenterol* 2005; **11**:922–925.
- 25 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.
- 26 Flejou JF, Potet F, Bernades P. Eosinophilic pancreatitis: a rare manifestation of digestive allergy? *Gastroenterol Clin Biol* 1989; **13**:731–733.
- 27 Wagué J, Benamara MA, Chardot C, Pariente D. Common bile duct stenosis with hypereosinophilia and pancreatitis in childhood: report of 2 cases. *Pediatr Radiol* 2000; **30**:383–385.
- 28 Okuda M. Epidemiology of Japanese cedar pollinosis throughout Japan. *Ann Allergy Asthma Immunol* 2003; **91**:288–296.
- 29 Okubo K, Gotoh M, Fujieda S, Okano M, Yoshida H, Morikawa H, *et al.* A randomized double-blind comparative study of immunotherapy for cedar pollinosis. *Allergology International* 2008; **57**:265–275.