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CASE REPORT

Three Cases of Bronchial Asthma Preceding IgG4-Related Autoimmune Pancreatitis

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ABSTRACT

Background: Autoimmune pancreatitis is characterized by diffuse swelling of the pancreas and a high serum immunoglobulin (Ig) G4 concentration. Histopathologically, dense infiltration of lymphocytes and IgG4-positive plasma cells with fibrosis are seen in the pancreas. Although allergic diseases complicating autoimmune pancreatitis have been reported, the clinical features of bronchial asthma complicated by autoimmune pancreatitis remain unclear.

Case Summary: We report three cases of bronchial asthma preceding the onset of type 1 autoimmune pancreatitis by 3 months to 30 years. All three cases were males with high serum IgG, IgG4, and IgE concentrations. The radioallergosorbent tests were positive for common allergens such as mites and house dust. One case had a pulmonary manifestation that proved to be an inflammatory pseudotumor of the lung with an accumulation of IgG4-positive plasma cells. The asthma symptom was ameliorated by oral prednisolone therapy for autoimmune pancreatitis, and when the corticosteroid doses were reduced, asthma became worse in all three cases.

Discussion: It is possible that atopy and increased Th2 cell activity are related to a higher coincidence of IgG4-related diseases such as type 1 autoimmune pancreatitis. Because the present cases are few in number, further studies are necessary.

KEY WORDS

asthma, atopy, autoantibody, immunoglobulin E (IgE), Th2

INTRODUCTION

Autoimmune pancreatitis is characterized by diffuse swelling of the pancreas and a high serum immunoglobulin (Ig) G4 concentration.[1-6] Dense infiltration of lymphocytes including IgG4-positive plasma cells with fibrosis in the pancreas is a histopathological feature of this disease.[4] It is at least twice as common in men as in women.[1] Because autoimmune pancreatitis is part of a clinical syndrome that involves systemic disorders including pulmonary lesions, the new concept "IgG4-related sclerosing diseases" has been proposed.[7]

Concomitant allergic diseases and high serum IgE levels have been demonstrated in patients with autoimmune pancreatitis.[8,9] In fact, bronchial asthma is reported to be one of the complications of autoimmune pancreatitis.[8-11] The clinical features of bronchial asthma complicating autoimmune pancreatitis still remain unclear. Here we report three cases of asthma, all of whom were males, of the atopic type with elevated serum IgE levels and that preceded the onset of type 1 autoimmune pancreatitis, one of major IgG4-related diseases.

CLINICAL SUMMARY

CASE ONE

A 38-yr-old male current smoker who had been diagnosed with autoimmune pancreatitis by clinical and radiological findings with positive anti-nuclear anti-

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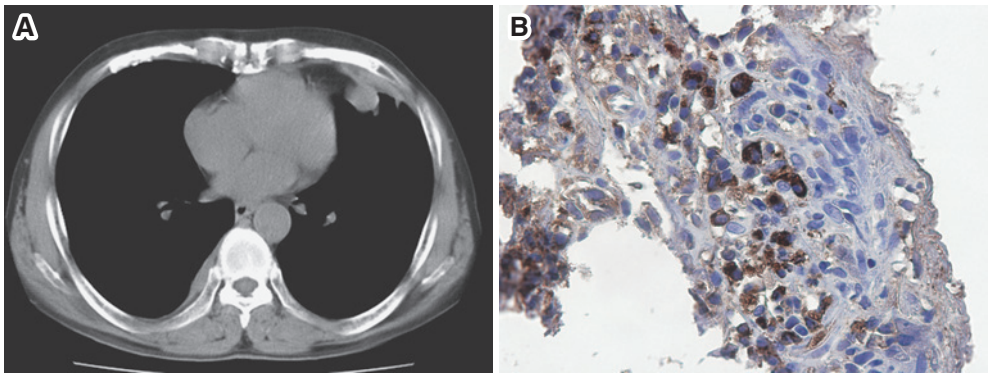

Fig. 1 **A:** Chest CT demonstrates subpleural nodular opacities in the left upper lobe in case two. **B:** Specimens of the lung obtained by CT-guided cutting needle biopsy reveal abundant IgG4-positive plasma cells (brown) assessed by anti-IgG4 antibody stain without malignant cells (x40 objective).

body in another hospital at the age of 32 years was referred to the Department of Gastroenterology, Nagoya University Hospital because he had moved. Systemic corticosteroid was given as maintenance treatment (1 mg of prednisolone daily) for autoimmune pancreatitis at the first visit. Two months later, he presented with acute abdominal pain with cholestasis. The serum levels of total bilirubin (2.5 mg/dL), aspartate aminotransferase (AST) (621 IU/L), alanine aminotransferase (ALT) (756 IU/L), and lipase (91 IU/L) were elevated. An abdominal enhanced computed tomography (CT) scan revealed swelling of the pancreas and stenosis of the biliary duct. After a replace of autoimmune pancreatitis with sclerosing cholangitis was diagnosed, the dose of prednisolone was increased to 30 mg daily.

He had been diagnosed with childhood asthma and had experienced frequent wheezing following airway infections and common colds. He had a cat inside of his house for ten years. His asthma was improved by high dose prednisolone. When the prednisolone dose was gradually decreased from 30 mg daily to 2.5 mg every two days, wheezing reappeared. Then he visited the Department of Respiratory Medicine, Nagoya University Hospital. After inhaled fluticasone propionate (250 μg)/salmeterol xinafoate (50 μg) combination therapy twice daily was added, his asthma was ameliorated.

CASE TWO

A 61-yr-old male current smoker was referred to the Department of Gastroenterology, Nagoya University Hospital, and diagnosed with autoimmune pancreatitis by laboratory and radiological findings. He had sometimes experienced wheezing and been diagnosed asthma at another medical clinic five years before. After treatment with oral prednisolone (30 mg daily) for autoimmune pancreatitis, his asthma disappeared but when the prednisolone dose was reduced to 5 mg every two days, his asthma reappeared. The previous asthma was supported by the positive result of an inhaled histamine challenge test. The maximal provocation concentration of histamine at which forced expiratory volume in one second (FEV_1) decreased by >20% was 78 μg/mL. Addition of inhaled fluticasone propionate (400 μg) therapy once daily was effective to control his asthma.

A chest CT scan revealed a sub-pleural nodular shadow in the left upper lobe (Fig. 1A). This shadow was not changed by steroid treatment. Histopathology obtained by a CT-guided cutting needle biopsy exhibited inflammatory cell accumulation and dense fibrosis consistent with an inflammatory pseudotumor of the lung. An immunohistochemical examination showed dense infiltration of IgG4-positive plasma cells (Fig. 1B).

CASE THREE

A 59-yr-old male nonsmoker with a history of chronic sinusitis was referred to the Department of Respiratory Medicine, Nagoya University Hospital, because he had asthma symptoms. Inhaled fluticasone propionate (400 μg) therapy once daily was effective. However, he had lost 7 kg in body weight in four months since his first visit. Laboratory tests showed positive rheumatoid factor (RF) and elevated serum levels of pancreatic enzymes including pancreatic-amylase (135 IU/L), lipase (91 IU/L), trypsin (696 ng/mL), and elastase-1 (895 ng/dL). An abdominal CT scan revealed diffuse swelling and partial calcification of the pancreas, indicating the presence of pancreatitis. An endoscopic ultrasonography-guided trucut biopsy of the pancreas revealed lymphoplasmacytic sclerosing pancreatitis. An immunohistochemical examination showed infiltration of IgG4-positive plasma cells consistent with type 1 autoimmune pancreatitis. Then oral prednisolone (30 mg daily) therapy was started. Because the prednisolone therapy di-

Table 1 Clinical and laboratory findings in three cases of asthma with autoimmune pancreatitis

Case No.	Age, y/Sex	Asthma onset	Steroid therapy	IgG (mg/dL)	IgG4 (mg/dL)	IgE (IU/mL)	Eosinophil (/μL)	RAST	Auto-antibody	Biopsy
1	32/M	Pre	Yes	1574	776	280	399	Positive	ANA	ND
2	61/M	Pre	Yes	1740	1090	7220	288	Positive	Negative	Lung
3	60/M	Pre	Yes	4480	1550	233	552	Positive	RF	Pancreas

RAST, radioallergosorbent test; ANA, positive anti-nuclear antibody; RF, positive rheumatoid factor.

Table 2 Findings of pulmonary function tests and respiratory resistance in three cases of asthma with autoimmune pancreatitis

Case No.	FEV_1 (L)	$\%FEV_1$ (%)	FEV_1/FVC (%)	Post-bronchodilator			R_5	R_{20}
				FEV_1 (L)	$\%FEV_1$ (%)	FEV_1/FVC (%)		
1	2.50	63.4	55.8	2.76	70.0	55.8	3.17	2.09
2	2.15	89.8	67.5	2.28	95.2	70.9	3.68	2.91
3	2.07	71.9	73.9	2.23	77.4	72.1	2.62	2.05

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity. R_5 and R_{20} are respiratory resistance at 5 Hz and 20 Hz, respectively ($cmH_2O/L/s$).

minished the asthma symptoms, he had stopped using inhaled fluticasone propionate. However, when the prednisolone dose was reduced to 5 mg daily, he presented with wheezing, and inhaled budesonide (800 μg daily) was added.

PATHOLOGICAL FINDINGS

A summary of the clinical characteristics and laboratory findings of the three patients is shown in Table 1. Cases two and three were included in previous studies reported by some of the co-authors.[12,13] All cases were male, and the ages at diagnosis of autoimmune pancreatitis were 32, 61, and 60 years old. All the patients fulfilled the diagnostic criteria of type 1 autoimmune pancreatitis proposed by the Mayo Clinic, the revised criteria of the Japan Pancreas Society, and the Honolulu Consensus Document.[14-16] The asthma complication preceded the appearance of autoimmune pancreatitis, and the asthma symptom was ameliorated by oral prednisolone therapy for autoimmune pancreatitis in all three cases. The levels of serum IgE, IgG, and IgG4 were elevated in all three cases, and the peripheral eosinophil count was high (>500/μL) in case three (Table 1). The radioallergosorbent test (RAST) was positive for *Dermatophagoides* (mites) (score 3), house dust (score 3), cat scurf (score 3), and dog scurf (score 2) in case 1, for *Dermatophagoides* (score 2) and house dust (score 2) in case 2, and for *Dermatophagoides* (score 3) and house dust (score 3) in case three. Autoantibodies were positive in cases one and three (Table 1). Biopsy of the left lung and pancreas was performed in cases two and three, respectively (Table 1).

Pulmonary function was examined by the standard spirometry method (Fudak70; Fukuda, Tokyo, Japan). The FEV_1/forced vital capacity (FVC) ratios in cases one, two, and three were 50%, 72%, and 67%, respectively (Table 2). The increase of FEV_1 after bronchodilation with inhaled procaterol was 260 mL (22%) in case one, demonstrating significant reversibility. Respiratory resistance at 5 Hz (R_5) and 20 Hz (R_{20}) was evaluated by impedance of the total respiratory system using a commercially available forced oscillation technique (MostGraph; Chest M.I., Inc., Tokyo, Japan). The R_5 values were 1.3-1.5 fold higher than the R_{20} values in all three cases (Table 2), suggesting the existence of heterogeneous bronchoconstriction in the airways due to asthma.[17,18]

DISCUSSION

This is the first report characterizing the clinical features of asthma complicating type 1 autoimmune pancreatitis. The immune mechanisms of pathogenesis of IgG4-related diseases including autoimmune pancreatitis have not been elucidated yet. There is accumulating evidence of allergic manifestations in patients with IgG4-related disorders such as autoimmune pancreatitis. Kamisawa *et al*. reported that 20 of 45 patients with autoimmune pancreatitis had allergic diseases, and of those three had asthma.[9] Increased mRNA expression of Th2 cytokines was found in the pancreatic lesions of patients with autoimmune pancreatitis.[19] In a recent review, Kamisawa *et al*.[20] described that IgG4-related autoimmune pancreatitis is mediated by an initial response to self-antigens induced by a decrease in levels of naïve regulatory T (T_{REG}) cells and Th1 cytokines. Then, the disease is progressed by upregulation of memory T_{REG} cells and Th2 cells, which results in increased IgG4 production. It is considered that regulation of IgG4 production is dependent on Th2 cells and that IgG4 acts as an blocking antibody against IgE-mediated allergic responses.[21] Consistent with this idea, asthma as a complication preceded the onset of autoimmune pan-

creatitis in all three cases of the present study. Moreover, asthma symptom became worse at the onset of autoimmune pancreatitis in all cases. It is possible that atopy and increased Th2 cell activity are related to a higher coincidence of IgG4-related diseases. Additionally, Th2-mediated inflammatory responses may be upregulated at the onset of IgG4-related diseases. Because the present cases are few in number, further studies are necessary.

IgG4-related sclerosing lesions which were first reported in autoimmune pancreatitis[2] were also found in the lung.[22] In case three, the histopathology of lung biopsy lesions revealed characteristics of inflammatory pseudotumor with lymphoplasmacytic infiltration and fibrosis. To our knowledge, this is the first report of an IgG4-related inflammatory pseudotumor complicated by asthma. Interestingly, the inflammatory pseudotumor was not changed by prednisolone therapy.

Systemic corticosteroid, specifically oral prednisolone, is established as a standard therapy for autoimmune pancreatitis.[12,23] Prednisolone was effective for autoimmune pancreatitis in our cases. Therefore, it must have improved the control of asthma and may even have masked the asthma symptoms. Indeed, when the corticosteroid doses were reduced, asthma became worse in all three of our cases. Although the appearance of IgG4 antibodies is proposed to be associated with a decrease in symptoms of allergic diseases,[21] an increased serum IgG4 was not related to decreased asthma severity in our cases. It is still unclear whether co-existing IgG4-related diseases affect asthma severity.

In summary, we experienced three male cases of asthma with autoimmune pancreatitis. Monitoring of IgG4 levels may be helpful to determine the incidence of IgG4-related diseases in patients with atopic type asthma for an overall statistical study.

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REFERENCES

1. Finkelberg DL, Sahani D, Deshpande V, Brugge WR. Autoimmune pancreatitis. *N Engl J Med* 2006;**355**:2670-6.
2. Hamano H, Kawa S, Horiuchi A *et al*. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001;**344**:732-8.
3. 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**:387-95.
4. Otsuki M, Chung JB, Okazaki K *et al*. Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis. *J Gastroenterol* 2008;**43**:403-8.
5. Sarles H, Sarles JC, Muratore R, Guien C. Chronic inflammatory sclerosis of the pancreas—an autonomous pancreatic disease? *Am J Dig Dis* 1961;**6**:688-98.
6. 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**:1561-8.
7. Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. *J Gastroenterol* 2006;**41**:613-25.
8. Hirano K, Tada M, Isayama H *et al*. Clinical analysis of high serum IgE in autoimmune pancreatitis. *World J Gastroenterol* 2010;**16**:5241-6.
9. Kamisawa T, Anjiki H, Egawa N, Kubota N. Allergic manifestations in autoimmune pancreatitis. *Eur J Gastroenterol Hepatol* 2009;**21**:1136-9.
10. Masaki Y, Dong L, Kurose N *et al*. Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. *Ann Rheum Dis* 2009;**68**:1310-5.
11. Roggin KK, Rudloff U, Klimstra DS, Russell LA, Blumgart LH. Adult-onset asthma and periocular xanthogranulomas in a patient with lymphoplasmacytic sclerosing pancreatitis. *Pancreas* 2007;**34**:157-60.
12. Ko SB, Mizuno N, Yatabe Y *et al*. Corticosteroids correct aberrant CFTR localization in the duct and regenerate acinar cells in autoimmune pancreatitis. *Gastroenterology* 2010;**138**:1988-96.
13. Mizuno N, Bhatia V, Hosoda W *et al*. Histological diagnosis of autoimmune pancreatitis using EUS-guided trucut biopsy: a comparison study with EUS-FNA. *J Gastroenterol* 2009;**44**:742-50.
14. 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**:549-54.
15. Chari ST, Smyrk TC, Levy MJ *et al*. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. *Clin Gastroenterol Hepatol* 2006;**4**:1010-6; quiz 934.
16. Okazaki K, Kawa S, Kamisawa T *et al*. Clinical diagnostic criteria of autoimmune pancreatitis: revised proposal. *J Gastroenterol* 2006;**41**:626-31.
17. Ito S, Lutchen KR, Suki B. Effects of heterogeneities on the partitioning of airway and tissue properties in normal mice. *J Appl Physiol* 2007;**102**:859-69.
18. LaPrad AS, Lutchen KR. Respiratory impedance measurements for assessment of lung mechanics: focus on asthma. *Respir Physiol Neurobiol* 2008;**163**:64-73.
19. Zen Y, Fujii T, Harada K *et al*. Th2 and regulatory immune reactions are increased in immunoglobin G4-related sclerosing pancreatitis and cholangitis. *Hepatology* 2007;**45**:1538-46.
20. Kamisawa T, Takuma K, Egawa N, Tsuruta K, Sasaki T. Autoimmune pancreatitis and IgG4-related sclerosing disease. *Nat Rev Gastroenterol Hepatol* 2010;**7**:401-9.
21. Aalberse RC, Stapel SO, Schuurman J, Rispens T. Immunoglobulin G4: an odd antibody. *Clin Exp Allergy* 2009;**39**:469-77.
22. Zen Y, Kitagawa S, Minato H *et al*. IgG4-positive plasma cells in inflammatory pseudotumor (plasma cell granuloma) of the lung. *Hum Pathol* 2005;**36**:710-7.
23. Kamisawa T, Shimosegawa T, Okazaki K *et al*. Standard steroid treatment for autoimmune pancreatitis. *Gut* 2009;**58**:1504-7.