Case report

Seronegative Sjögren syndrome with asymptomatic autoimmune sclerosing pancreatitis

Masayuki Matsuda*, Hideaki Hamano**, Takuhiro Yoshida*, Shigeyuki Kawa**, Shu-ichi Ikeda*

*Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine

**Department of Medicine (Gastroenterology), Shinshu University School of Medicine

Short running headline: Autoimmune pancreatitis manifesting as seronegative Sjögren

Correspondence and reprint requests to: Dr. Masayuki Matsuda, Third Department of Medicine, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan

Tel: +81-263-37-2673

Fax: +81-263-37-3427

e-mail: matsuda@hsp.md.shinshu-u.ac.jp

Abstract

We report two elderly patients with asymtomatic autoimmune sclerosing pancreatitis (ASP) who initially manifested dry mouth with or without chronic swelling of bilateral submandibular glands. Histopathology of the lip biopsy and reduced excretion of saliva with negative results of anti-SS-A and SS-B antibodies were compatible with the clinical picture of seronegative Sjögren syndrome, but benign swelling of the pancreas were concurrently seen in both patients. Increased production of IgG4 was confirmed by immunostaining of the biopsied lip tissue or serum examination, leading to the diagnosis of ASP as a cause of the swelling of the pancreas. This disease often shows multi-organ involvement, and should be actively considered as a possible etiology in patients with seronegative Sjögren syndrome, particularly in elderly people, even though there are no signs or symptoms suggestive of pancreatitis.

Key words: autoimmune sclerosing pancreatitis, IgG4, immunostaining, lip biopsy, seronegative Sjögren syndrome

Introduction

Autoimmune sclerosing pancreatitis (ASP) is characterized by swelling of the pancreas with narrowing of the main pancreatic duct, which is pathologically ascribed to fibrosis with infiltration of plasma cells and lymphocytes [1]. Immunological abnormalities are considered to play an important role in the pathogenesis of ASP based on the presence of autoantibodies and hypergammaglobulinemia, particularly IgG4 in the active phase [2, 3]. ASP is often associated with other disorders, including retroperitoneal fibrosis and sclerosing cholangitis [4, 5]. Here, we describe two elderly patients with ASP who showed dry mouth and/or remarkable swelling of bilateral submandibular glands as initial symptoms despite the lack of anti-SS-A and anti-SS-B antibodies. Both patients were clinically diagnosed as having seronegative Sjögren syndrome, but the coexistence of ASP was identified by radiological examination and immunological abnormalities such as increased levels of IgG4 in serum and predominant infiltration of IgG4-positive plasma cells in the biopsied lip tissue. We postulate that seronegative Sjögren syndrome and ASP may result from the common immunopathogenesis, particularly in elderly people.

Case report

Case 1

A 68-year-old man noticed sense of dryness in both eyes and the mouth with no precipitating cause or significant previous history. He visited our hospital because of gradual worsening of these symptoms two years later. Physical examination showed dryness of the oral mucosa and tongue without obvious swelling of salivary glands. Routine laboratory data demonstrated no abnormal findings in either hematology or blood chemistry. Both the erythrocyte sedimentation rate (ESR, 3 mm/hr, normal 3-11

mm/hr) and C-reactive protein (CRP, 0.02 mg/dl, normal <0.1 mg/dl) were within normal limits, and no positive results were obtained for anti-nuclear antibodies, including anti-SS-A and anti-SS-B, or rheumatoid factor. An increase in gammaglobulin or IgG in serum was not seen, and the IgG subclass showed normal levels of IgG4 (25 mg/dl, normal <70 mg/dl). Both the Schirmer and gum tests were positive. The lip biopsy demonstrated remarkable infiltration of lymphocytes and plasma cells, predominantly IgG4-positive cells, in the minor salivary gland (Fig. 1). Diffuse swelling of the pancreas was seen on computed tomography (CT) (Fig. 2A). The patient was successfully treated only with sedatives, and the follow-up CT demonstrated spontaneous improvement of swelling of the pancreas two months later (Fig. 2B).

Case 2

A 67-year-old man developed non-painful swelling in bilateral submandibular glands and sense of dryness in the mouth with no precipitating cause. He visited our hospital because of gradual increasing in the size of these glands six months later. Physical examination showed no abnormal findings other than the remarkable swelling of bilateral submandibular glands (Fig. 3A) and the dry tongue. Inflammatory reactions, including CRP (0.11 mg/dl) and ESR (3 mm/hr), were within normal limits, and no abnormal findings were seen in other routine laboratory data such as hepatic and renal indices. No positive results were obtained for the anti-nuclear antibody, including anti-SS-A and anti-SS-B, or rheumatoid factor, but serum immunoglobulin showed an elevated level of IgG (4500 mg/dl), particularly IgG4 (1185 mg/dl). Both the Schirmer and gum tests were positive. The lip biopsy demonstrated slight infiltration of lymphocytes and plasma cells in the minor salivary gland, but a predominant increase in IgG4-positive cells was not obvious. Abdomen CT demonstrated swelling in the body and tail of the pancreas (Fig. 3B), and in these parts irregular narrowing of the main

pancreatic duct was seen on endoscopic retrograde cholangiopancreatography. Positron emission tomography (PET) showed remarkable uptake in bilateral submandibular glands and the pancreas body (Figs. 3C and D).

Six months later oral prednisolone was started at a dose of 40 mg/day because of persistent swelling of both submandibular glands and the pancreas with a gradual increase in serum levels of IgG. Sense of dryness in the mouth quickly improved in parallel with a decrease in the size of submandibular glands and serum levels of IgG.

Discussion

These two elderly patients showed dryness in the oral cavity, positive results of Schirmer and gum tests, infiltration of mononuclear cells in the biopsied lip tissue, but the absence of the anti-SS-A and anti-SS-B antibodies, leading to the diagnosis of seronegative Sjögren syndrome according to the classification criteria [6]. mouth eosinophilia and non-pitting edema localized to both hands and lower legs with no recurrent attacks in a follow-up of approximately 5 months, leading to the clinical diagnosis of NEAE. There were no clinical findings or preceding events suggestive of parasitic or autoimmune disorders. Skin lesions are sometimes seen also in idiopathic hypereosinophilic syndrome [4], but our patients lacked any affected visceral organs. RS3PE can also be excluded from the diagnosis in our patients, because this disease is characterized by pitting edema and polyarthralgia in the extremities with remarkable inflammatory reactions, predominantly in elderly people [5, 6].

The clinical findings in our two patients and 33 previously described cases of NEAE are summarized in Table 1 [2, 3, 7-19]. EAE has been reported mainly from Europe and the United States, while all the patients with NEAE were Japanese. NEAE has been considered as a less severe form of EAE because there are several similarities

in the clinical picture other than peripheral edema and eosinophilia between both diseases. One similarity is a predominant incidence in young women. The male-to-female ratio and the mean onset age in EAE were 1:2 and 15.9 years, respectively [16], while in NEAE all the patients were women and the onset age ranged from 21 to 37 years with a mean of 25.9 years. The other is the clear effectiveness of corticosteroid therapy. In NEAE 8 patients were treated with low-dose oral prednisolone, and all of them showed a good response.

The most characteristic aspect of NEAE is of course the absence of recurrence, but there are also several other differences in the clinical picture between NEAE and EAE. The first difference is the distribution of angioedema. In NEAE, angioedema is usually localized to hands and feet as seen in our patients, whereas it frequently extends also to the proximal portion of the extremities and sometimes to the face in EAE [16, 20]. The second is the presence of urticaria and an increase in serum IgM, which are commonly seen in EAE [16]. Skin lesions and an increase in serum levels of IgM were present only in 33.3% and 3.3% of the previously reported patients with NEAE, respectively. In our patients, serum IgM was within normal limits and urticaria was seen only in case 1. The third is the frequency of spontaneous remission. Almost all the patients with EAE need corticosteroid therapy [16], while spontaneous remission frequently occurred in those with NEAE, including our cases, in parallel with a decrease in eosinophils in the peripheral blood. These three differences may be explainable by the lower severity of disease in NEAE compared with EAE. The fourth difference is transient arthralgia, which was seen in 45.7% of the patients with NEAE, including our case 2. This symptom has not been noted in EAE. The fifth difference is a tendency to preferentially occur in the autumn. Approximately 69 % of NEAE cases, including ours, developed in the autumn, whereas such a tendency has not been reported in EAE. This clinical

observation suggests that the pathogenesis of NEAE might be more closely related to a reaction to some environmental factors than that of EAE.

Several investigations have been performed in order to clarify the pathogenetic mechanism of EAE. Since sudden-onset angioedema is a main symptom in EAE, vascular permeability might temporarily increase via some mediators, including anti-endothelial cell antibody and cytokines, in the acute phase of the attack [21-25]. According to several recent reports the plasma histamine level was within normal limits, while IL-1, IL-5 and IL-6 were excessively produced by monocytes, endothelial cells, T cells and eosinophils, and serum levels of these cytokines were increased in the acute phase of EAE [22-25]. There are several pieces of evidence suggesting that a phenotypical change in eosinophils and activation of T cells might play an important role in the increased production of these cytokines [22, 25-27]. Our case 2 also showed an increased level of soluble IL-2R in serum, which was ascribable to the activation of lymphocytes. It remains unclear why recurrent attacks do not occur in NEAE, but the cytokine profile in the acute phase of NEAE is probably different from that of EAE [3]. Serum levels of cytokines, particularly IL-5, are relatively lower in the acute phase of NEAE than in that of EAE, and these mild changes might be related to the absence of recurrence in NEAE [3].

In conclusion, NEAE is important in the differential diagnosis of sudden-onset edema in both hands and lower legs, particularly in young women, because this disease frequently shows spontaneous remission without corticosteroid therapy. To clarify the pathogenesis of NEAE, accumulation of cases and further study are necessary.

References

1. Gleich GJ, Schroeter AL, Marcoux JP, Sachs MI, O'Connell EJ, Kohler PF (1985) Episodic angioedema associated with eosinophilia. N Engl J Med 313: 282-285
2. Chikama R, Hosokawa M, Miyazawa T, Miura R, Suzuki T, Tagami H (1998) Nonepisodic angioedema associated with eosinophilia: report of 4 cases and review of 33 young female patients reported in Japan. Dermatology 197: 321-325
3. Mizukawa Y, Shiohara T (2001) The cytokine profile in a transient variant of angioedema with eosinophilia. Br J Dermatol 144: 169-174
4. Barna M, Kemeny L, Dobozy A (1997) Skin lesions as the only manifestation of the hypereosinphilic syndrome. Br J Dermatol 136: 646-647
5. McCarty DJ, O'Duffy JD, Pearson L, Hunter JB (1985) Remitting seronegative symmetrical synovitis with pitting edema. RS3PE syndrome. JAMA 254: 2763-2767
6. Oide T, Ohara S, Oguchi K, Maruyama M, Yazawa M, Inoue K, Sekijima Y, Tokuda T, Ikeda S (2004) Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome in Nagano, Japan: clinical, radiological, and cytokine studies of 13 patients. Clin Exp Rheumatol 22: 91-98
7. Tsurumachi K, Sakurai M, Nogi N, Nakayama H, Sugi T (1990) Two cases of hypereosinophilic syndrome with transient swelling of legs. Jpn J Clin Dermatol 32: 999-1002 (in Japanese)
8. Tabe Y, Imayama S, Hori Y (1990) Two cases of hypereosinophilic syndrome associated with prolonged edematous skin eruption. Nishinihon J Dermatol 52: 896-900 (in Japanese)
9. Tsuda M, Mimura M (1990) A case of episodic angioedema. Rinsho Derma 32: 999-1002 (in Japanese)

10. Take C, Kurasawa T, Ikeda K, Yamane Y (1992) Four Japanese cases of episodic angioedema with eosinophilia. Intern Med 31: 470-473
11. Ohashi A, Ishida T, Yamamoto M, Tamaki S (1992) Three cases of episodic angioedema with eosinophilia. Rinsho Derma 34: 1751-1754 (in Japanese)
12. Nishimoto M, Nakashima K, Sasaki K, Sasaki M, Takaiwa T (1993) Angioedema with eosinophilia. Jpn J Dermatol 103: 533-538 (in Japanese)
13. Nishii Y, Kawatsu T (1993) A case of episodic angioedema associated with eosinophilia. Jpn J Clin Dermatol 47: 991-995 (in Japanese)
14. Hara Y, Inoue T (1994) Two cases of episodic angioedema associated with eosinophilia. Jpn J Clin Dermatol 48: 367-370 (in Japanese)
15. Okahara K, Horiuchi K, Iwamoto T, Yamura M (1996) Two cases of episodic angioedema associated with eosinophilia. Nishinihon J Dermatol 58: 764-766 (in Japanese)
16. Shikiji T, Urano Y, Takiwaki H, Arase S (1997) A case of episodic angioedema associated with eosinophilia. J Med Invest 44: 103-108
17. Toyoda M, Suzuki D, Uehara G, Umezono T, Horiki T, Yagame M, Endoh M, Kurokawa K, Sakai H (2001) Two cases of episodic angioedema associated with eosinophilia. Nippon Jinzo Gakkai Shi 43: 44-48 (in Japanese with English abstract)
18. Shimasaki AK (2001). Five case of nonepisodic angioedema with eosinophilia. Rinsho Ketueki 42: 639-643 (in Japanese with English abstract)
19. Yamabe H, Takanashi S, Osawa H, Nakamura N, Shirato K, Sugawara T, Nakamura M, Tamura M, Okumura K (2003) Angioedema associated with eosinophilia. Intern Med 42: 626

20. Oktenli C, Bulucu F, Gurbuz M, Bozoglu E, Oguz Y, Koc B (2001) Observations on edema formation and resolution in Gleich syndrome: essential role of the kidneys in effective arterial blood volume regulation. Am J Nephrol 21: 154-161
21. Lassalle P, Gosset P, Gruart V, Prin L, Capron M, Lagrue G, Kusnierz JP, Tonnel AB, Capron A (1990) Presence of antibodies against endothelial cells in the sera of patients with episodic angioedema and hypereosinophilia. Clin Exp Immunol 82: 38-43
22. Putterman C, Barak V, Caraco Y, Neuman T, Shalit M (1993) Episodic angioedema with eosinophilia: a case associated with T cell activation and cytokine production. Ann Allergy 70: 243-248
23. Okubo Y, Sato E, Hossain M, Ota T, Yoshikawa S, Sekiguchi M (1995) Periodic angioedema with eosinophilia: increased serum level of interleukin 5. Intern Med 34: 108-111
24. Tillie-Leblond I, Gosset P, Janin A, Salez F, Prin L, Tonnel AB (1998) Increased interleukin-6 production during the acute phase of the syndrome of episodic angioedema and hypereosinophilia. Clin Exp Allergy 28: 491-496
25. Morgan SJ, Prince HM, Westerman DA, McCormack C, Glaspole I (2003) Clonal T-helper lymphocytes and elevated IL-5 levels in episodic angioedema and eosinophilia (Gleich's syndrome). Leuk Lymphoma 44: 1623-1625
26. Kawano M, Muramoto H, Tsunoda S, Koni I, Mabuchi H, Yachie A, Miyawaki T (1996) Absence of CD69 expression on peripheral eosinophils in episodic angioedema and eosinophilia. Am J Hematol 53: 43-45
27. Nakashima K, Sakurada T, Imayama S, Masukawa S, Ember JA, Hugli TE, Abe M (1998) A case of episodic engioedema associated with blood eosinophilia: upregulated C5a receptor expression on eosinophils. Allergy 53: 320-323

Figure legends

Figure 1: A photograph of case 1, showing remarkable edema in both hands and feet.

Figure 2: Clinical course of case 2. Change in clinical symptoms was judged subjectively on the basis of the degree of edema and the patient's complaints. Closed circles: number of white blood cells, closed squares: number of eosinophils.