BRIEF COMMUNICATION

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Unusual Multiorgan Immunoglobulin G4 (IgG4) Inflammation: Autoimmune Pancreatitis, Mikulicz Syndrome, and IgG4 Mastitis

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Autoimmune pancreatitis (AIP) type 1 is commonly associated with simultaneous involvement of extrapancreatic organs. Sclerosing cholangitis, sialadenitis, retroperitoneal fibrosis, Sjögren syndrome, and other extrapancreatic lesions are often observed concurrently with AIP. High levels of immunoglobulin G4 (IgG4) in the blood serum and affected tissues are typical of this diagnostic entity. We describe a case report of a 58-year-old female with findings of AIP (according to Asian criteria), IgG4-positive mastitis, and histologically verified Mikulicz syndrome. The effect of corticoid therapy supported the diagnosis of AIP and simultaneously led to the eradication of recurrent mastitis. To the best of our knowledge, this is the first reported case of concurrent findings of AIP and IgG4 mastitis. Our case report supports the concept of systemic IgG4 syndrome with multisystem involvement. Timely diagnosis and appropriate therapy can be effective in a high percentage of patients. **(Gut Liver 2013;7:621-624)**

Key Words: Autoimmune; Pancreatitis; Immunoglobulin G; Mikulicz syndrome; Mastitis

INTRODUCTION

Idiopathic chronic pancreatitis associated with minimal clinical symptoms, icterus and notable hypergammaglobulinaemia was first described in 1961 by Sarles *et al*.[1]

In 1995, Yoshida *et al*.[2] documented a case of a 68-year-old woman with obstructive icterus, diffusely enlarged pancreas with irregular caliber of pancreatic duct (without significant stenosis or dilatations), significantly increased γ-globulin levels, and histologically verified pancreatic fibrosis. Steroid treatment led to amelioration of clinical symptoms and morphological changes. This disease was labeled autoimmune pancreatitis (AIP; as a parallel for autoimmune hepatitis).

AIP is currently classified into two subgroups.[3] Type 1 AIP, also known as lymphoplasmacytic sclerosing pancreatitis (LPSP), usually affects men between 50 and 60 years of age, with histological findings of periductal lymphoplasmacytic infiltrates, oblitering arteritis, and excessive fibroproduction.[4,5] In 95% to 98% of cases, AIP type 1 is accompanied by immunoglobulin G4 (IgG4) positivity in tissue samples and/or elevated IgG4 levels in blood serum. AIP type 1 is frequently combined with simultaneous involvement of extrapancreatic organs (e.g., sclerosing cholangitis,[6] retroperitoneal fibrosis,[7] IgG4 positive tubulointestitial nephritis,[8] chronic sclerosing sialadenitis,[9] and sicca syndrome[10]) and other extrapancreatic lesions.

In contrast, AIP type 2 is most commonly diagnosed in the fourth decade of life, with the same incidence in men and women and is usually combined with the presence of inflammatory bowel disease. IgG4 positive biopsy and/or elevated IgG4 serum levels (diagnostic for AIP type 1) are usually absent in AIP type 2. Besides the lymphoplasmacytic infiltrates, typical histological findings of AIP type 2 also include ductuli destructing inflammation with granulocytic epithelial lesions with partial or full obstruction of the pancreatic ducts.[11] The presence of icterus is uncommon.[12]

We present a case report of concurrent findings of AIP, IgG4 positive mastitis, and Mikulicz syndrome. A publication of unidentified case reports is allowed by Ethical Committee of the University Hospital Brno.

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CASE REPORT

A 58-year-old woman was referred to our institution for nonspecific dyspepsia. She had been medically followed for several years for recurring mastitis of unclear etiology.

Medical history was significant for thyroiditis diagnosed in 1976. For the last 3 years, she was followed by the Department of Ophthalmology, University Hospital Brno for histologically verified Mikulicz syndrome. Subsequently, salivary function was also tested, but only nonsignificant decrease in function was revealed.

In 2006, the patient noticed right-sided submandibular induration; extirpation was carried out for suspected malignancy which was ruled out by histological findings of a fibrotised salivary gland.

In 2009, she was examined by the oncology department for recurring mastitis; biopsy findings showed IgG4 infiltrates (Figs 1 and 2). A gastroenterology consult was then recommended for the patient's dyspepsia.

Based on the patient's prior medical history, AIP was strongly suspected; therefore, serum immunoglobulin levels were tested. Total IgG was elevated (29.77 g/L; normal range, 7 to 16 g/L); IgG4 was more than 3-times the normal limit (920 mg/L; normal range, 8 to 140 mg/L) and rheumatoid factor and antipancreatic duct antibodies also tested positive. According to Japanese criteria, the findings indicated AIP with synchronous IgG4 mastitis and Mikulicz syndrome.

Abdominal sonography and computed tomography revealed the typical picture of AIP—an enlarged sausage-like pancreas. The steroid treatment led to a normalization of sonographic finding (Figs 3 and 4).

Further endosonography confirmed a diffusely enlarged pancreas with rough, unclear outlines, and a small caliber duct.

The patient was treated with prednisone at an initial dose of 40 mg for 2 weeks. The dose was then tapered by 5 mg with a maintenance dose of 10 mg of prednisone prescribed for 3 months.

The patient has been followed for 1 year after completion of steroid treatment and she is symptoms free with normalized

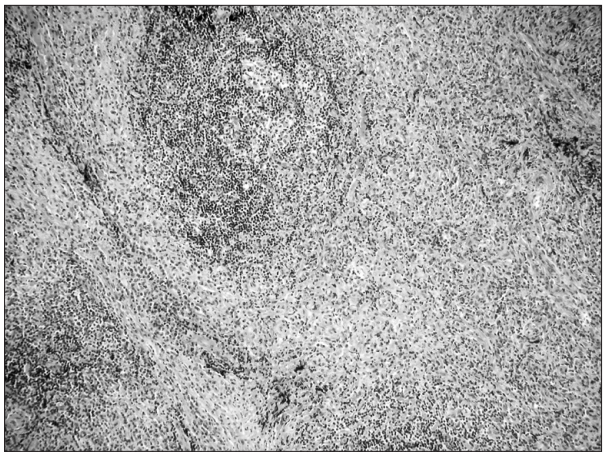

Fig. 1. Lymphoplasmacytic infiltrates of the mammary gland with signs of fibrosis (Standard H&E stain, ×200).

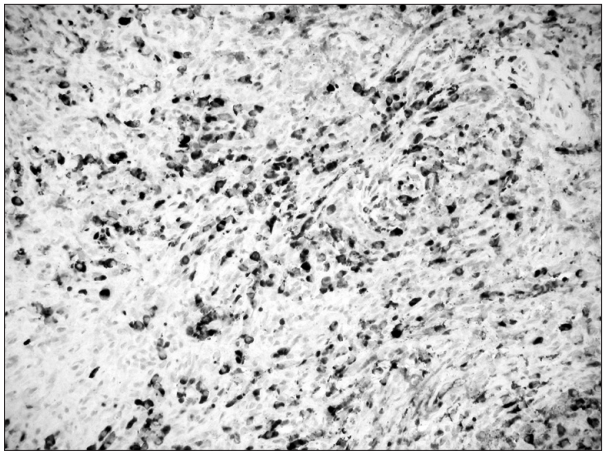

Fig. 2. Diffuse expression of immunoglobulin G4 (IgG4) in polyclonal plasmacytic cells (IgG4 immunohistochemistry, ×400).

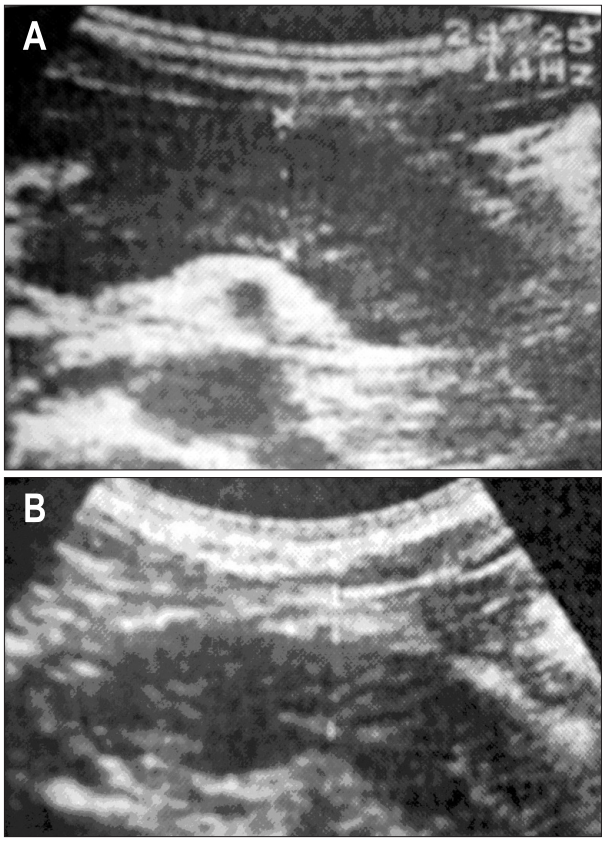

Fig. 3. (A) Sonographic picture of enlarged sausage-like pancreas prior to steroid treatment and (B) normalization of this finding after 6 months of steroid treatment.

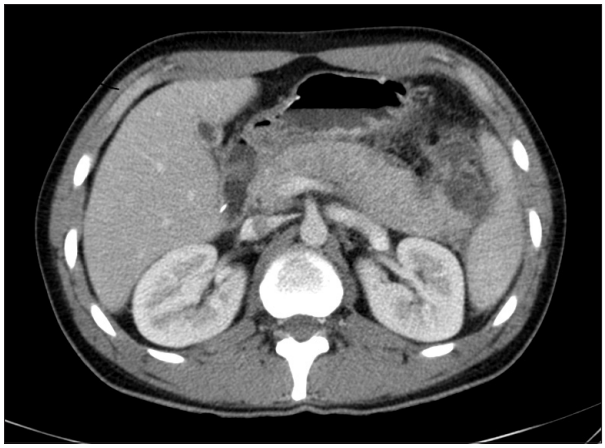

Fig. 4. Computed tomography scan of enlarged sausage-like pancreas prior steroid treatment.

biochemical and sonographic findings. Additionally, the mastitis did not recur during the 12 months period.

DISCUSSION

It is widely accepted that AIP is a part of multisystem disorder characterized by histomorphologic changes with concurrent presence of immunoglobin IgG4 in blood plasma and/or tissues.[13,14] As such, the term IgG4 related sclerosing disease is used for this entity by some authors.[15,16]

AIP is frequently associated with simultaneous involvement of extrapancreatic organs, in particular the hepatobiliary system,[6] kidneys,[17] salivary glands, retroperitoneal fibrosis, and pulmonary impairment.[7,9,18,19]

Currently, AIP is divided into two subgroups. AIP type 1, which is more common, has symptoms and diagnostic criteria equivalent to disorders described in earlier literature as an autoimmune form of pancreatitis or LPSP.[4] This type of AIP is often accompanied by concurrent extrapancreatic disorders and has recently been considered to be a part of IgG4 associated systemic disease.[13] Findings of high levels of IgG4 immunoglobulin in blood serum and/or affected tissues with their progressive fibrotization are typical for this diagnostic entity.

The presented case report documents a patient with histologically verified Mikulicz syndrome and recurring mastitis who we diagnosed with concurrent AIP. Asian criteria[20] were used for the AIP diagnosis, since the pancreas involvement was not focal and therefore, biopsy necessary for HISORt classification system[21] was not indicated.

While IgG4-related sclerosing mastitis has been described before,[22] to the best of our knowledge, this is the first reported case of concurrent findings of AIP and IgG4 positive mastitis. Levels of IgG4 tested highly positive both in blood serum and breast biopsy. Steroid treatment improved patient's dyspepsia making the AIP diagnosis even more likely. Neither AIP symptoms, nor mastitis recurred within the 12 months period following termination of steroid treatment.

The probability of AIP recurrence after steroid withdrawal is 30% to 50%.[23-25] In this case, steroid, or azathioprine treatment would be indicated.[26,27]

In conclusion, by adding an additional organ affected with IgG4 derived inflammation, our findings support a concept of AIP as a systemic IgG4 disease with multisystem involvement.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Sarles H, Sarles JC, Muratore R, Guien C. Chronic inflammatory sclerosis of the pancreas: an autonomous pancreatic disease? Am J Dig Dis 1961;6:688-698.
2. 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.
3. Park DH, Kim MH, Chari ST. Recent advances in autoimmune pancreatitis. Gut 2009;58:1680-1689.
4. Sugumar A, Smyrk TC, Takahashi N, Levy MJ, Chari ST. Lymphoplasmacytic sclerosing pancreatitis (LPSP) and idiopathic duct centric pancreatis (IDCP) are distinct clinical forms of autoimmune pancreatitis (AIP). Pancreas 2008;37:497.
5. 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.
6. Kamisawa T, Egawa N, Nakajima H. Autoimmune pancreatitis is a systemic autoimmune disease. Am J Gastroenterol 2003;98:2811-2812.
7. Kamisawa T, Matsukawa M, Ohkawa M. Autoimmune pancreatitis associated with retroperitoneal fibrosis. JOP 2005;6:260-263.
8. Takahashi N, Kawashima A, Fletcher JG, Chari ST. Renal involvement in patients with autoimmune pancreatitis: CT and MR imaging findings. Radiology 2007;242:791-801.
9. Kamisawa T, Nakajima H, Hishima T. Close correlation between chronic sclerosing sialadenitis and immunoglobulin G4. Intern Med J 2006;36:527-529.
10. 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. Pancreatology 2006;6:132-137.
11. Sugumar A, Klöppel G, Chari ST. Autoimmune pancreatitis: pathologic subtypes and their implications for its diagnosis. Am J Gastroenterol 2009;104:2308-2310.
12. Frulloni L, Scattolini C, Falconi M, et al. Autoimmune pancreatitis:

differences between the focal and diffuse forms in 87 patients. Am J Gastroenterol 2009;104:2288-2294.
13. Kamisawa T, Funata N, Hayashi Y, et al. A new clinicopathological entity of IgG4-related autoimmune disease. J Gastroenterol 2003;38:982-984.
14. Deshpande V, Chicano S, Finkelberg D, et al. Autoimmune pancreatitis: a systemic immune complex mediated disease. Am J Surg Pathol 2006;30:1537-1545.
15. Deheragoda MG, Church NI, Rodriguez-Justo M, et al. The use of immunoglobulin g4 immunostaining in diagnosing pancreatic and extrapancreatic involvement in autoimmune pancreatitis. Clin Gastroenterol Hepatol 2007;5:1229-1234.
16. Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. J Gastroenterol 2006;41:613-625.
17. Watson SJ, Jenkins DA, Bellamy CO. Nephropathy in IgG4-related systemic disease. Am J Surg Pathol 2006;30:1472-1477.
18. Hirano K, Kawabe T, Komatsu Y, et al. High-rate pulmonary involvement in autoimmune pancreatitis. Intern Med J 2006;36:58-61.
19. Tsushima K, Tanabe T, Yamamoto H, et al. Pulmonary involvement of autoimmune pancreatitis. Eur J Clin Invest 2009;39:714-722.
20. 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;43:403-408.
21. Chari ST. Diagnosis of autoimmune pancreatitis using its five cardinal features: introducing the Mayo Clinic's HISORt criteria. J Gastroenterol 2007;42 Suppl 18:39-41.
22. Cheuk W, Chan AC, Lam WL, et al. IgG4-related sclerosing mastitis: description of a new member of the IgG4-related sclerosing diseases. Am J Surg Pathol 2009;33:1058-1064.
23. Park do H, Kim MH, Oh HB, et al. Substitution of aspartic acid at position 57 of the DQbeta1 affects relapse of autoimmune pancreatitis. Gastroenterology 2008;134:440-446.
24. Chari ST. Current concepts in the treatment of autoimmune pancreatitis. JOP 2007;8:1-3.
25. Sandanayake NS, Church NI, Chapman MH, et al. Presentation and management of post-treatment relapse in autoimmune pancreatitis/immunoglobulin G4-associated cholangitis. Clin Gastroenterol Hepatol 2009;7:1089-1096.
26. Kamisawa T, Satake K. Therapeutic strategy for autoimmune pancreatitis. Adv Med Sci 2008;53:145-148.
27. Kamisawa T, Okamoto A, Wakabayashi T, Watanabe H, Sawabu N. Appropriate steroid therapy for autoimmune pancreatitis based on long-term outcome. Scand J Gastroenterol 2008;43:609-613.