

Clinical Characteristics of Patients with Autoimmune Pancreatitis with or without Mikulicz's Disease and Mikulicz's Disease Alone

Sawako Kuruma*, Terumi Kamisawa*, Taku Tabata*, Seiichi Hara*, Takashi Fujiwara*, Go Kuwata*, Hideto Egarashira*, Koichi Koizumi*, Keigo Setoguchi*, Junko Fujiwara†, Takeo Arakawa†, Kumiko Momma†, Toshio Mitsuhashi‡, and Tsuneo Sasaki§

Departments of *Internal Medicine, †Endoscopy, ‡Otorhinolaryngology, and §Chemotherapy, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

Background/Aims: The objective of this study was to compare the clinical characteristics of patients with autoimmune pancreatitis (AIP) with or without Mikulicz's disease (MD) and with MD alone. **Methods:** We investigated the clinical findings in 15 AIP patients with MD (group A+M), 49 AIP only patients (group A), and 14 MD only patients (group M). **Results:** The male-female ratio was significantly higher in group A+M (73%, $p<0.05$) and group A (78%, $p<0.01$) than group M (21%). Serum immunoglobulin G (IgG) levels were significantly higher in group A+M than in group A ($p<0.01$) and group M ($p<0.05$). Serum IgG4 levels were significantly higher in group A+M than in group A ($p<0.01$). Other organ involvement was observed in 73% (11/15) of patients in group A+M. The number of patients with diabetes mellitus was significantly higher in group A+M (66%, $p<0.01$) and group A (51%, $p<0.05$) than in group M (7%). All of the patients responded well to steroid therapy, but the relapse rate in group A+M (33%) was significantly higher than that in group A (3%, $p<0.01$). Salivary gland function was impaired in all groups compared with the control group, but the degree of dysfunction was less in group A compared with group A+M and group M. **Conclusions:** The relapse rate of AIP in MD patients was significantly higher than that of AIP in patients without MD. (*Gut Liver* 2013;7:96-99)

Key Words: Autoimmune pancreatitis; Mikulicz' disease; Immunoglobulin G; IgG4-related disease; Steroid therapy

INTRODUCTION

Mikulicz's disease (MD) refers to idiopathic, bilateral, painless, and symmetrical swelling of the lacrimal, parotid, and submandibular glands.¹ Due to histological similarity, MD has been con-

sidered a subtype of Sjögren's syndrome.² However, in contrast to Sjögren's syndrome, MD responds well to steroid therapy and lacks anti-SS-A and anti-SS-B antibodies.^{3,4} Recently it was revealed that MD patients showed high immunoglobulin G4 (IgG4) concentrations and abundant infiltration of IgG4-positive cells as well as lymphocytes and fibrosis was detected in the lacrimal and salivary glands of MD patients,^{3,4} leading to the suggestion that MD is an IgG4-related disease.⁵

Autoimmune pancreatitis (AIP) is frequently associated with sclerosing extrapancreatic lesions such as stenosis of the bile ducts (sclerosing cholangitis), gallbladder wall thickening (sclerosing cholecystitis), swelling of the salivary and lacrimal glands (sclerosing sialadenitis and dacryoadenitis), retroperitoneal fibrosis, and pseudotumors. Histological findings for these extrapancreatic lesions are similar to those of the pancreas in AIP patients, and included dense fibrosis with abundant infiltration of IgG4-positive plasma cells and lymphocytes.⁶ We proposed the existence of a novel clinicopathological entity, an "IgG4-related sclerosing disease." IgG4-related sclerosing disease represents a systemic disease characterized by extensive IgG4-positive plasma cells and T lymphocyte infiltration of various organs. Clinical manifestations are apparent in organs such as the pancreas, bile duct, gallbladder, salivary and lacrimal glands, retroperitoneum, lung, and prostate gland, where tissue fibrosis is pathologically induced. AIP is not simply a pancreatitis, but rather a pancreatic lesion reflecting an IgG4-related sclerosing disease. In some cases, only one or two organs are clinically involved, while in other cases three or four organs are affected.^{7,8}

Some patients have AIP complicated by MD, but the difference between AIP cases complicated MD, AIP alone patients, and MD alone patients is not clear. We compared clinical characteristics of AIP patients with and without MD and MD patients alone.

Correspondence to: Terumi Kamisawa

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 on January 13, 2012. Accepted on February 9, 2012. Published online on November 13, 2012.

pISSN 1976-2283 eISSN 2005-1212 <http://dx.doi.org/10.5009/gnl.2013.7.1.96>

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

MATERIALS AND METHODS

1. Patients

The subjects of this study were 64 patients with AIP and 14 patients with MD (group M) treated in Tokyo Metropolitan Komagome Hospital between 1990 and 2010. AIP was diagnosed according to the Asian Diagnostic Criteria for AIP:⁹ enlargement of the pancreas on computed tomography and/or ultrasonography (n=64); irregular narrowing of the main pancreatic duct on endoscopic retrograde pancreatography (n=64); elevation of serum IgG4 levels (n=48); elevation of serum IgG levels (n=22); presence of autoantibodies (n=30); histology of lymphoplasmacytic sclerosing pancreatitis (n=18); and steroid responsiveness (n=49). MD was diagnosed according to diagnostic criteria of MD proposed by Japanese Sjögren's Syndrome Society:¹⁰ 1) symmetrical swelling of at least two pairs of the lacrimal, parotid, or submandibular glands continuing for more than 3 months (n=14), and 2) elevated serum IgG4 levels (>135 mg/dL) (n=12), or 3) histological features including lymphocyte and IgG4-positive plasma cell infiltration with typical tissue fibrosis or sclerosis (n=11). Patients in group M showed no abnormality in pancreatic imaging. The 64 AIP patients were divided into 15 AIP patients complicated by MD (group A+M) and 49 AIP patients without MD (group A). The 15 patients of group A+M had bilateral salivary gland swelling (n=15) and lacrimal gland swelling (n=2). Histological confirmation of MD was performed in 11 of the 15 AIP patients complicated by MD. AIP occurred in eight conservatively followed-up MD patients during 3 months to 4 years. MD and AIP were diagnosed simultaneously in the other seven patients. Steroid therapy was used in 12 patients in group A+M, 36 patients in group A, and 11 patients in group M according to the standard regimen.¹¹

2. Clinical analysis

We investigated age, sex, serum IgG levels (11 patients in group A+M, 35 patients in group A, and 13 patients in group M), serum IgG4 levels (15 patients in group A+M, 44 patients in group A, and 14 patients in group M), anti-nuclear antibody (ANA) (10 patients in group A+M, 35 patients in group A, and 14 patients in group M), rheumatoid factor (RF) (11 patients in group A+M, 32 patients in group A, and 13 patients in group M), and association with diabetes mellitus (DM). Other organ involvement including intrahepatic or hilar sclerosing cholangitis, sclerosing cholecystitis, retroperitoneal fibrosis, and distant lymphadenopathy were examined.

Remission after steroid therapy was defined as disappearance of clinical symptoms, and resolution of the imaging manifestations of the pancreas, salivary and/or lacrimal glands, and/or other organ involvements.¹² Relapse after steroid therapy was defined as reappearance of symptoms with development of imaging abnormalities.¹²

3. Salivary gland function

To examine salivary gland function, submandibular scintigraphy was performed in six patients in group A+M, 15 patients in group A, and seven patients in group M. After intravenous injection of 180 to 200 Mbq (^{99m}Tc) pertechnetate, anterior sequential imaging was performed every minute for 30 minutes using a gamma camera. At 15 minutes after injection of radionuclide, ascorbic acid (20 mg) was administered intraorally to stimulate salivary secretion. The region of interest was set manually on the submandibular glands and time-activity curves were generated. The ratio of cumulative peak count to injected radionuclide (PCR) and washout ratio (WR, peak count before ascorbic acid administration—lowest count after administration/peak count before administration) was examined as a functional parameter. The minimum levels of PCR and WR were analyzed.^{13,14} Data for salivary gland function examined before in 30 normal individuals were used as controls.¹⁴

4. Statistical analysis

Data for three groups were compared to each other using Fisher's exact probability test and the Mann-Whitney U test. The p-value was corrected by Bonferroni's method, and p-values of less than 0.05 were considered statistically significant.

RESULTS

Although there were no differences in age in diagnosis in each group, the male-female ratio was significantly higher in group A+M (73%, $p < 0.05$) and group A (78%, $p < 0.01$) than group M (21%). Serum IgG levels were significantly higher in group A+M (median, 2,389 mg/dL) than group A (1,640 mg/dL, $p < 0.01$) and group M (1,708 mg/dL, $p < 0.05$). Serum IgG4 levels were significantly higher in group A+M (median, 970 mg/dL) than group A (267 mg/dL, $p < 0.01$). There were no significant differences in presence of ANA and RF among the three groups. In addition to salivary and/or lacrimal lesions, other organ involvement was seen in 11 (73%) of 15 patients in group A+M, but there were no significant differences among the three groups. Intrahepatic or hilar sclerosing cholangitis and sclerosing cholecystitis were detected in only group A+M and group A. The number of patients complicated by DM was significantly higher in group A+M (66%, $p < 0.01$) and group A (51%, $p < 0.05$) than group M (7%). All patients responded well to steroid therapy, but relapse rate in group A+M (33%) was significantly higher than in group A (3%, $p < 0.01$) (Table 1). Periods from initial diagnosis of AIP to its relapse were 0.5, 1, 1, and 1.8 years in group A+M, and 1 year in group A.

In terms of salivary gland function, PCR and WR by submandibular scintigraphy were significantly lower in group A+M ($p < 0.01$), group A ($p < 0.05$), and group M ($p < 0.01$) than controls. PCR was significantly lower in group A+M and group M than

Table 1. Clinical Differences between Group A+M, Group A, and Group M

Variables	Group A+M (n=15)	Group A (n=49)	Group M (n=14)
Age, yr*	67 (63-70)	64 (55-71)	60 (45-73)
Male/Female (%)	11/4 (73) [†]	38/11 (78) [†]	3/11 (21)
IgG, mg/dL*	2,389 ^{†,§} (1,990-2,710)	1,640 (1,270-1,912)	1,708 (1,512-2,033)
IgG4, mg/dL*	970 [§] (320-1,230)	267 (124-477)	480 (193-8,663)
ANA, +/- (%)	5/5 (50)	22/13 (63)	6/8 (43)
RF, +/- (%)	2/9 (18)	6/26 (19)	5/8 (38)
OOI, +/- (%)	11/4 (73)	20/29 (41)	4/10 (40)
Sclerosing cholangitis	3	3	0
Sclerosing cholecystitis	4	10	0
Retroperitoneal fibrosis	1	4	2
Distant lymphadenopathy	5	3	3
DM, +/- (%)	10/5 (66) [†]	25/24 (51) [†]	1/13 (7)
Steroid responsiveness, +/- (%)	12/0 (100)	36/0 (100)	11/0 (100)
Relapse after steroid, +/- (%)	4/8 (33) [§]	1/35 (3)	1/10 (9)

ANA, anti-nuclear antigen; RF, rheumatoid factor; OOI, other organ involvement; DM, diabetes mellitus.

*Median (quartile range); [†]p<0.05 compared with Group M; [‡]p<0.01 compared with Group M; [§]p<0.01 compared with Group A.

Table 2. Submandibular Gland Function Examined by Scintigraphy

	Group A+M	Group A	Group M	Controls
PCR, %	5 (3-17) ^{*,‡}	22 (14-35) [†]	8 (2-12) ^{*,‡}	35 (27-43)
WR, %	29 (22-50) [*]	59 (49-89) [†]	27 (19-51) ^{*,‡}	87 (78-96)

Data are presented as median (quartile range).

PCR, ratio of the cumulative peak count to injected radionuclide; WR, washout ratio.

*p<0.01 compared with controls; [†]p<0.05 compared with controls; [‡]p<0.05 compared with Group A.

group A (p<0.05). WR was significantly lower in group M than group A (p<0.05) (Table 2).

DISCUSSION

Salivary gland lesions, usually in the bilateral submandibular glands, are one of the common locations of other organ involvement in patients with AIP.^{6,15} The histology of swollen salivary glands in AIP patients is fibrosis with abundant infiltration of lymphocytes and IgG4-positive plasma cells, similar to findings in the pancreas in AIP patients. Therefore, swollen salivary glands associated with AIP are considered a salivary gland lesion of IgG4-related disease.⁶ MD is characterized by bilateral, painless, and symmetrical swelling of the lacrimal, parotid, and submandibular glands. From the findings of high IgG4 concentrations and abundant infiltration of IgG4-positive cells in the lacrimal and salivary glands of MD patients, MD is also considered an IgG4-related disease.³⁻⁵ Therefore, salivary gland lesions are thought to be the same as MD. However, it is unknown whether there are clinical differences among patients with AIP alone (group A), AIP with MD (group A+M), and MD alone (group M).

AIP showed a male preponderance even in AIP with MD, but

the sex ratio of the group M was 3:11 in favor of females. According to Yamamoto *et al.*,⁴ the sex ratio of M patients was approximately 3:1 in favor of females, which was similar to our results. The reason for the gender gap between AIP and MD is unknown.

Serum IgG and IgG4 levels were significantly higher in group A+M. In addition to salivary and/or lacrimal lesions, other organ involvement was seen in 73% of group A+M, although there were no significant differences among groups. In our previous study,¹⁶ AIP patients with serum IgG4 levels of more than 220 mg/dL frequently had other organ involvement. Ghazale *et al.*¹⁷ reported that AIP patients with serum IgG4 lesser than 140 mg/dL were less likely to present with other organ involvement compared with those with serum IgG4 greater than 140 mg/dL. It was also reported that AIP patients with organ involvement of three other organs had significantly higher IgG4 levels than those with no lesions.^{15,16} Serum IgG4 levels appear to show disease activity of an IgG4-related disease.

Salivary gland function was impaired in AIP patients without MD (group A) compared with controls, although the degree of salivary gland dysfunction was greater in group A+M and group M than group A. AIP occurred in eight conservatively followed-up MD patients during 3 months to 4 years. Compared with

AIP, swelling of the salivary or lacrimal glands can be easily noticed clinically even without symptoms. Given these findings, AIP might exist subclinically when preceding salivary or lacrimal gland lesions are diagnosed. Furthermore, salivary gland involvement may occur subclinically in most AIP patients. DM occurred in about half of AIP patients and improved in half of them after steroid therapy.^{11,13} The mechanisms for this effect were suggested to be due to regeneration of damaged islets and suppression of cytokines released from infiltrated lymphocytes.¹⁸ However, glucose intolerance was rare in MD patients.

The relapse rate was significantly higher in group A+M than group A. It has been reported that predictors for relapse are the presence of proximal bile duct stenosis and elevated serum IgG4 levels.^{12,19,20} However, Kubota *et al.*²¹ reported that three of five AIP patients with MD relapsed. AIP patients with MD should be treated more carefully with maintenance steroid therapy. Although there are several potential methods such as higher dose of initial steroids, longer duration of initial steroids, longer duration of maintenance therapy, and other immunosuppressive agents to reduce the relapse rate of highly active disease, further studies may be warranted.

In conclusion, the relapse rate of AIP with MD patients was significantly higher than AIP alone patients. AIP with MD may be associated with high disease activity of an IgG4-related disease and should be treated carefully with maintenance steroid therapy.

CONFLICTS OF INTEREST

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

ACKNOWLEDGEMENTS

This study was supported by the Research Committee of Intractable Disease, provided by the Ministry of Health, Labour and Welfare of Japan.

REFERENCES

1. Mikulicz JH. Über eine eigenartige symmetrische Erkrankung der Tränen- und Mundspeicheldrüsen. In: Billroth GT, ed. Beitr Chir Fortschr. Stuttgart: [publisher unknown], 1892:610-630.
2. Morgan WS, Castleman B. A clinicopathologic study of Mikulicz's disease. *Am J Pathol* 1953;29:471-503.
3. Yamamoto M, Harada S, Ohara M, et al. Clinical and pathological differences between Mikulicz's disease and Sjogren's syndrome. *Rheumatology (Oxford)* 2005;44:227-234.
4. Yamamoto M, Takahashi H, Ohara M, et al. A new conceptualization for Mikulicz's disease as an IgG4-related plasmacytic disease. *Mod Rheumatol* 2006;16:335-340.
5. Umehara H, Okazaki K, Masaki Y, et al. A novel clinical entity,

- IgG4-related disease (IgG4RD): general concept and details. *Mod Rheumatol* 2012;22:1-14.
6. Kamisawa T, Takuma K, Egawa N, Tsuruta K, Sasaki T. Autoimmune pancreatitis and IgG4-related sclerosing disease. *Nat Rev Gastroenterol Hepatol* 2010;7:401-409.
7. Kamisawa T, Funata N, Hayashi Y, et al. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003;38:982-984.
8. Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. *J Gastroenterol* 2006;41:613-625.
9. 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.
10. Masaki Y, Sugai S, Umehara H. IgG4-related diseases including Mikulicz's disease and sclerosing pancreatitis: diagnostic insights. *J Rheumatol* 2010;37:1380-1385.
11. Kamisawa T, Okazaki K, Kawa S, Shimosegawa T, Tanaka M. Japanese consensus guidelines for management of autoimmune pancreatitis: III. treatment and prognosis of AIP. *J Gastroenterol* 2010;45:471-477.
12. Kamisawa T, Shimosegawa T, Okazaki K, et al. Standard steroid treatment for autoimmune pancreatitis. *Gut* 2009;58:1504-1507.
13. Kamisawa T, Egawa N, Inokuma S, et al. Pancreatic endocrine and exocrine function and salivary gland function in autoimmune pancreatitis before and after steroid therapy. *Pancreas* 2003;27:235-238.
14. Kamisawa T, Tu Y, Sasaki R, Egawa N, Kamata N, Sasaki T. The relationship of salivary gland function to elevated serum IgG4 in autoimmune pancreatitis. *Intern Med* 2007;46:435-439.
15. 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.
16. Kamisawa T, Imai M, Egawa N, Tsuruta K, Okamoto A. Serum IgG4 levels and extrapancreatic lesions in autoimmune pancreatitis. *Eur J Gastroenterol Hepatol* 2008;20:1167-1170.
17. Ghazale A, Chari ST, Smyrk TC, et al. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. *Am J Gastroenterol* 2007;102:1646-1653.
18. Tanaka S, Kobayashi T, Nakanishi K, et al. Corticosteroid-responsive diabetes mellitus associated with autoimmune pancreatitis. *Lancet* 2000;356:910-911.
19. Sah RP, Chari ST, Pannala R, et al. Differences in clinical profile and relapse rate of type 1 versus type 2 autoimmune pancreatitis. *Gastroenterology* 2010;139:140-148.
20. Takuma K, Kamisawa T, Tabata T, Inaba Y, Egawa N, Igarashi Y. Short-term and long-term outcomes of autoimmune pancreatitis. *Eur J Gastroenterol Hepatol* 2011;23:146-152.
21. Kubota K, Wada T, Kato S, et al. Highly active state of autoimmune pancreatitis with mikulicz disease. *Pancreas* 2010;39:e6-e10.