Association of Sarcoidosis and other Granulomatous Disorders. *Sarcoidosis Vasc Diffuse Lung Dis* 1999;**16**:149–73.
17 Kubo K, Yamazaki Y, Masubuchi T, Takamizawa A, Yamamoto H, Koizumi T *et al.* Pulmonary infection with mycobacterium avium-intracellulare leads to air trapping distal to the small airway. *Am J Respir Crit Care Med* 1998;**27**:979–84.
18 Kubo K, Hanaoka M, Hayano T, Miyahara T, Hachiya T, Hayasaka M *et al.* Inflammatory cytokines in BAL fluid and pulmonary hemodynamics in high-altitude pulmonary edema. *Respir Physiol* 1998;**111**:301–10.
19 Kamisawa T. Diagnostic criteria for autoimmune pancreatitis. *J Clin Gastroenterol* 2008;**42**:404–7.
20 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.

Proposal for a new clinical entity, IgG_4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG_4-related disorders

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ABSTRACT

Background: Mikulicz's disease (MD) has been considered as one manifestation of Sjögren's syndrome (SS). Recently, it has also been considered as an IgG_4-related disorder.

Objective: To determine the differences between IgG_4-related disorders including MD and SS.

Methods: A study was undertaken to investigate patients with MD and IgG_4-related disorders registered in Japan and to set up provisional criteria for the new clinical entity IgG_4-positive multiorgan lymphoproliferative syndrome (IgG_4+MOLPS). The preliminary diagnostic criteria include raised serum levels of IgG_4 (>135 mg/dl) and infiltration of IgG_4^+ plasma cells in the tissue (IgG_4+/IgG+ plasma cells >50%) with fibrosis or sclerosis. The clinical features, laboratory data and pathologies of 64 patients with IgG_4+MOLPS and 31 patients with typical SS were compared.

Results: The incidence of xerostomia, xerophthalmia and arthralgia, rheumatoid factor and antinuclear, antiSS-A/Ro and antiSS-B/La antibodies was significantly lower in patients with IgG_4+MOLPS than in those with typical SS. Allergic rhinitis and autoimmune pancreatitis were significantly more frequent and total IgG, IgG_2, IgG_4 and IgE levels were significantly increased in IgG_4+MOLPS. Histological specimens from patients with IgG_4+MOLPS revealed marked IgG_4+ plasma cell infiltration. Many patients with IgG_4+MOLPS had lymphocytic follicle formation, but lymphoepithelial lesions were rare. Few IgG_4+ cells were seen in the tissue of patients with typical SS. Thirty-eight patients with IgG_4+MOLPS treated with glucocorticoids showed marked clinical improvement.

Conclusion: Despite similarities in the involved organs, there are considerable clinical and pathological differences between IgG_4+MOLPS and SS. Based on the clinical features and good response to glucocorticoids, we propose a new clinical entity: IgG_4+MOLPS.

In 1888, Johann von Mikulicz-Radecki reported a man with symmetrical swelling of the lacrimal, submandibular and parotid glands of unknown aetiology.[1] Histologically, the swollen glands showed massive mononuclear cell infiltration, and this condition is called Mikulicz's disease (MD).[2 3] Since Morgan *et al* reported in 1953 that MD was not a distinct clinical and pathological disease but merely one manifestation of Sjögren's syndrome (SS),[4] MD has attracted very little interest.

However, more than 20 cases of MD were reported between 1960 and 2006 in Japan, and differences between MD and SS have been investigated.[5–10] Previous case reports indicated that MD may differ from SS in a number of respects:[7–10] (1) MD occurs in both men and women whereas SS occurs mainly in women; (2) patients with MD show significant enlargement of the lacrimal and salivary glands but relatively mild xerostomia and xerophthalmia; (3) more complications such as autoimmune pancreatitis have been reported in MD; (4) raised levels of serum IgG_4 and IgG_4+ plasma cell infiltration in tissues were reported in patients with MD; (5) a better response to glucocorticoid therapy is achieved in patients with MD than in those with SS.

For analysis of IgG_4-related disorders including MD, autoimmune pancreatitis and other conditions, we performed a retrospective analysis of data from patients with MD and similar cases from all over Japan. From these results, we propose a new clinical entity for these disorders with characteristic features: IgG_4-positive multiorgan lymphoproliferative syndrome (IgG_4+MOLPS).

METHODS

Case reports of MD involving two or three sets of swollen lacrimal, parotid or submandibular glands on physical examination and IgG_4-related disorders have been collected from all over Japan since 2004. A total of 85 patients from 10 collaborating institutes were registered retrospectively. The diagnosis of IgG_4+MOLPS was defined as both raised serum IgG_4 levels (>135 mg/dl)[11] and histopathological features including lymphocyte and IgG_4+ plasma cell infiltration (IgG_4+ plasma cells/IgG+ plasma cells >50%)[12 13] with typical fibrosis or sclerosis in the tissue. Sixty-four of these 85 cases were diagnosed as IgG_4+MOLPS. Of these 64 patients with IgG_4+MOLPS (mean age 57.0 years; median age 60.0 years; range 17–80), 33 were women (mean age 54.7 years; median age 56.0 years; range 17–77) and 31 were men (mean age 59.4 years; median age 62.0 years; range 23–83).

These were compared with 31 patients with patients with typical primary SS (male:female ratio

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Table 1 Comparison of frequencies of symptoms and complications in patients with IgG_4-positive multiorgan lymphoproliferative syndrome (IgG_4+MOLPS) and those with typical Sjögren's syndrome (SS)

	IgG_4+MOLPS			Typical SS					
	All (n = 64)	Women (n = 33)	Men (n = 31)	All (n = 31)	Women (n = 29)	Japanese*	p Value†	p Value‡	p Value§
Xerophthalmia	32.8% (21)	42.4% (14)	22.6% (7)	93.5% (29)	93.1% (27)		<0.001	<0.001	0.114
Xerostomia	37.5% (24)	45.5% (15)	29.0% (9)	87.1% (27)	86.2% (25)		<0.001	0.001	0.205
Arthralgia	15.6% (10)	15.2% (5)	16.1% (5)	48.4% (15)	51.7% (15)		0.001	0.002	1.000
Allergic rhinitis	40.6% (26)	54.5% (18)	25.8% (8)	6.5% (2)	6.9% (2)	5–10%	0.001	<0.001	0.024
Bronchial asthma	14.1% (9)	18.2% (6)	9.7% (3)	3.2% (1)	3.4% (1)	3–5%	0.158	0.109	0.476
Autoimmune pancreatitis	17.2% (11)	3.0% (1)	32.3% (10)	0.0% (0)	0.0% (0)	<0.001%	0.014	0.532	0.002
Interstitial nephritis	17.2% (11)	9.1% (3)	25.8% (8)	6.5% (2)	6.9% (2)	<0.005%	0.210	1.000	0.074
Interstitial pneumonitis	9.4% (6)	9.1% (3)	9.7% (3)	32.3% (10)	31.0% (9)	<0.005%	0.008	0.051	1.000

Incidence rates (numbers of positive patients) are shown.
*Incidence rates in Japanese population.
†All IgG_4+MOLPS vs all typical SS.
‡Female IgG_4+MOLPS vs female typical SS.
§Female vs male IgG_4+MOLPS.

2:29; mean age 52.0 years; median age 49.0 years; range 34–76). Typical patients with SS fulfilled both Japanese[14] and European[15] SS criteria and were positive for both anti-SS-A/Ro and anti-SS-B/La antibodies.

Histopathological findings were examined by haematoxylin and eosin staining and immunohistochemical staining using anti-CD3 antibody (rabbit polyclonal anti-human CD3 A0452; Dako, Glostrup, Denmark), anti-CD20 antibody (mouse monoclonal anti-human CD20 M0755; Dako), anti-CD38 antibody (mouse monoclonal anti-human CD38 NCL-CD38-290; Novocastra, Newcastle-upon-Tyne, UK), anti-IgG antibody (mouse anti-IgG antibody, M0828; Dako) and anti-IgG_4 antibody (mouse anti-human IgG4 antibody MC011; The Binding Site, Birmingham, UK). Biopsy specimens of minor salivary glands from 22 typical patients with SS with marked lymphocytic infiltration were also examined by IgG_4 immunostaining.

Laboratory data and the clinical response to treatment were investigated. The study was approved by the review board of Kanazawa Medical University and those of each collaborating institute. All data and samples from patients were collected with their informed consent.

Statistical analysis

The frequencies of symptoms, complications and laboratory data were compared between the groups. IgG_4+MOLPS was seen in both men and women, while the majority of patients with typical SS were women. We therefore compared data of all patients with IgG_4+MOLPS patients and only female patients with IgG_4+MOLPS with those of typical SS patients. We also compared female vs male patients with IgG_4+MOLPS. Comparisons between the two groups were performed using the χ^2 or Fisher exact test with regard to the frequencies of symptoms of xerostomia, xerophthalmia and arthralgia, and complications of allergic rhinitis, bronchial asthma, autoimmune pancreatitis, interstitial nephritis and interstitial pneumonia, and the incidences of rheumatoid factor, antinuclear antibody, anti-SS-A/Ro antibody, anti-SS-B/La antibody and

Table 2 Comparison of frequencies of laboratory findings in patients with IgG_4-positive multiorgan lymphoproliferative syndrome (IgG_4+MOLPS) and those with typical Sjögren's syndrome (SS)

	IgG_4+MOLPS			Typical SS					
	All (n = 64)	Women (n = 33)	Men (n = 31)	All (n = 31)	Women (n = 29)	Normal range	p Value†	p Value‡	p Value§
RF	26.6% (17)	33.3% (11)	19.4% (6)	87.1% (27)	86.2% (25)		<0.001	<0.001	0.263
ANA	23.4% (15)	15.2% (5)	32.3% (10)	90.3% (28)	89.7% (26)		<0.001	<0.001	0.143
A-SSA	1.6% (1)	0.0% (0)	3.2% (1)	100.0% (31)	100.0% (29)		<0.001	<0.001	0.484
A-SSB	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (31)	100.0% (29)		<0.001	<0.001	NE
Low CH50	57.8% (37)	57.6% (19)	58.1% (18)	48.4% (15)	51.7% (15)		0.510	0.799	1.000
IgG (mg/dl)	2960.1 (1.7)	2661.3 (1.7)	3315.9 (1.7)	2473.4 (1.4)	2459.2 (1.4)	870–1700	0.042	0.458	0.104
IgG_1 (mg/dl)	1155.3 (1.6)	1025.2 (1.5)	1338.4 (1.7)	1437.1 (1.5)	1417.1 (1.5)	320–748	0.039	0.004	0.038
IgG_2 (mg/dl)	786.5 (1.5)	737.2 (1.6)	851.7 (1.5)	566.6 (1.6)	545.8 (1.5)	208–754	0.001	0.009	0.206
IgG_3 (mg/dl)	57.6 (2.8)	48.2 (2.8)	71.9 (2.8)	81.9 (1.8)	83.5 (1.8)	6.6–88.3	0.047	0.013	0.147
IgG_4 (mg/dl)	697.7 (2.6)	690.9 (2.6)	705.5 (2.7)	23.5 (2.1)	21.3 (1.9)	4.8–105	<0.001	<0.001	0.933
IgA (mg/dl)	194.7 (1.80)	178.3 (2.0)	213.8 (1.5)	389.7 (1.7)	377.1 (1.7)	110–410	<0.001	<0.001	0.199
IgM (mg/dl)	63.0 (2.0)	69.6 (2.0)	56.6 (2.1)	147.3 (1.7)	145.7 (1.7)	35–220	<0.001	<0.001	0.249
IgE (IU/ml)	307.4 (4.0)	182.6 (4.3)	566.5 (2.8)	15.3 (1.4)	15.2 (1.3)	<173	0.005	0.030	0.033

Values are shown as geometrical means (geometrical SD) for IgG, IgG_1, IgG_2, IgG_3, IgG_4, IgE, IgA and IgM.
Incidence rates (numbers of positive patients) are shown for RF, ANA, A-SSA, A-SSB and low CH50.
IgE was examined in 50 patients (not all) with IgG_4+MOLPS. IgG_1, IgG_2 and IgG_3 were examined in 58 patients (not all) with IgG_4+MOLPS.
†All IgG_4+MOLPS vs typical SS.
‡Female IgG_4+MOLPS vs typical SS.
§Female vs male IgG_4+MOLPS.
ANA, antinuclear antibody; A-SSA, anti-SS-A/Ro antibody; A-SSB, anti-SS-B/La antibody; CH50, 50% haemolytic unit of complement; NE, not examined; RF, rheumatoid factor.

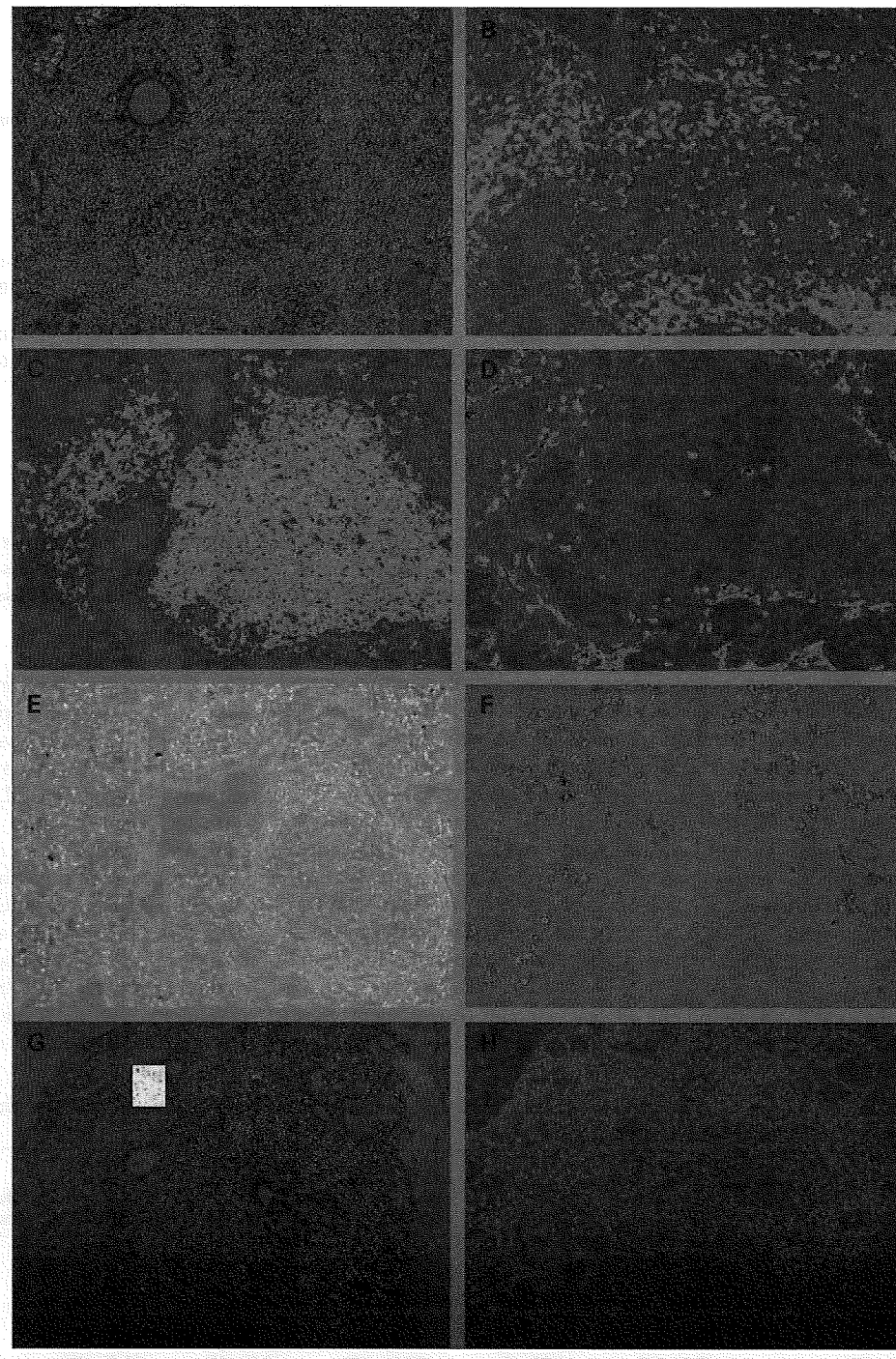

Figure 1 Histopathological findings of labial minor salivary gland biopsy in (A–F) patients with IgG_4+MOLPS/Mikulicz's disease and (G, H) patients with Sjögren's syndrome. (A, G) H&E staining; (B) CD3; (C) CD20; (D) CD38; (E) IgG; (F, H) IgG_4 immunostaining. Massive lymphocyte and plasmacyte infiltration and lymphoid follicle formation were seen in IgG_4+MOLPS. The ducts remained clearly without lymphocytic infiltration. CD20+ B cells remained in the follicle and CD3+ T cells were seen around the follicle. CD38+ plasma cells, IgG+ cells and IgG_4+ plasma cells were scattered in the periphery of the follicle. The ratio of IgG_4+ plasma cells/IgG+ plasma cells was > 50%. On the other hand, there were few or no IgG_4+ cells in typical SS, even in cases with severe lymphocytic infiltration.

decreased CH50 (50% haemolytic unit of complement). Comparisons of immunoglobulin classes and subclasses (IgG, IgG_1, IgG_2, IgG_3, IgG_4, IgA, IgM and IgE) were performed using the Mann-Whitney U test. All analyses were performed using SPSS V.11 (SPSS, Chicago, Illinois, USA).

RESULTS

As shown in table 1, the numbers of patients with symptoms of xerostomia, xerophthalmia and arthralgia were significantly lower in all cases of IgG_4+MOLPS than in typical cases of SS (32.8% vs 93.5%, 37.5% vs 87.1% and 15.6% vs 48.4%, respectively). Similar results were seen in the comparison of female patients with IgG_4+AMOLPS compared with patients with typical SS. Allergic rhinitis and autoimmune pancreatitis were significantly more common in IgG_4+MOLPS than in typical SS (40.6% vs 6.5%, 17.2% vs 0%, respectively). Interstitial pneumonitis was significantly rarer in all patients with IgG_4+MOLPS than in patients with typical SS (9.4% vs 32.3%). We compared gender differences among IgG_4+MOLPS cases and found that autoimmune pancreatitis was significantly more common in men than in women (32.3% vs 3%).

The incidences of rheumatoid factor, antinuclear antibody, anti-SS-A/Ro antibody and anti-SS-B/La antibody were significantly lower in patients with IgG_4+MOLPS than in those

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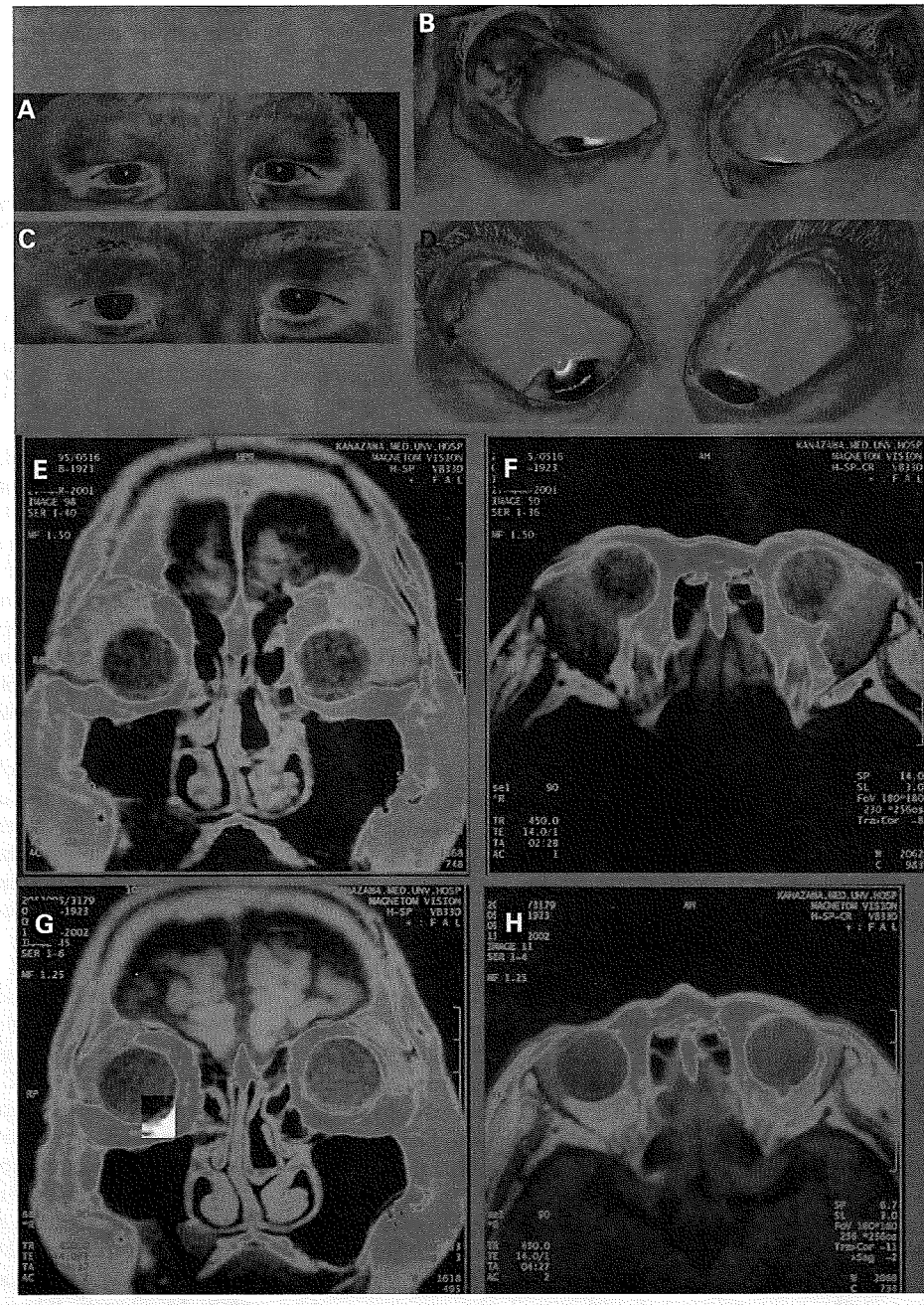

Figure 2 Effect of glucocorticoid therapy on swollen lacrimal glands. (A–D) Photographs of face and eyes. (E–H) MRCT T1 imaging of another patient. (E, G) Frontal cross-section. (F, H) Coronal cross-section. (A, B, E, F) Before treatment, markedly swollen lacrimal glands were seen. (C, D, G, H) After glucocorticoid treatment, lacrimal swelling was reduced.

with typical SS (table 2). The same tendency was seen when women with IgG_4+MOLPS were compared with patients with typical SS. We compared immunoglobulin classes and subclasses and found that not only IgG_4 but also total IgG, IgG_2 and IgE levels were significantly higher in IgG_4+MOLPS than in typical SS. In contrast, IgG_1, IgG_3, IgA and IgM levels were significantly lower in IgG_4+MOLPS than in typical SS.

Patients with IgG_4+MOLPS showed marked lymphocyte and IgG_4+ plasma cell infiltration with fibrosis (sclerotic lesions). Furthermore, lymphocytic follicle formation was observed in many patients (fig 1). Lymphocytic infiltration into the ducts (formation of lymphoepithelial lesions) was rare, and many IgG_4+ cells were scattered in the periphery of the follicles. In situ hybridisation of kappa and lambda indicated polyclonal B cell proliferation (see figure in online supplement). In contrast, few or no IgG_4+ cells were seen in biopsy specimens of minor salivary glands from 22 patients with typical SS with severe lymphocytic infiltration.

Thirty-eight of the 64 patients with IgG_4+MOLPS were treated with glucocorticoids. The starting dose of prednisolone was 10–30 mg/day for the majority of patients (n = 25), and higher doses of 40–60 mg/day for those patients suffering severe complications (n = 13) such as pancreatitis, interstitial nephritis, interstitial pneumonitis or hydronephrosis due to retroperitoneal fibrosis. Twenty-six patients were followed up without glucocorticoid treatment because their symptoms were mild or they refused glucocorticoid treatment. Glucocorticoid treatment markedly improved clinical signs and symptoms such as gland swelling (fig 2), but recurrence was seen in some cases (n = 15) when the glucocorticoid was tapered early or

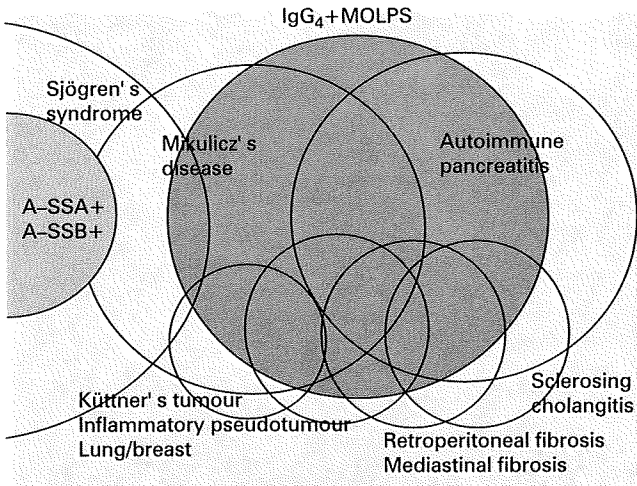

Figure 3 Spectrum of IgG_4+MOLPS. IgG_4+MOLPS included Mikulicz's disease, autoimmune pancreatitis and many other inflammatory conditions. A-SSA, anti-SS-A/Ro antibody; A-SSB, anti-SS-B/La antibody.

discontinued. A maintenance dose of 2.5–10 mg/day prednisolone was then used in most patients (37/38 patients).

DISCUSSION

We propose a new clinical entity, IgG_4+MOLPS, a syndrome characterised by hyper-IgG_4 gammaglobulinaemia and IgG_4+ plasma cell infiltration in the tissue (lymphoproliferative disorder). IgG_4+MOLPS includes MD, autoimmune pancreatitis,[11 16–21] sclerosing cholangitis,[18] Küttner's tumour,[15] inflammatory pseudotumour of the lung,[19] liver[18] and breast,[16 22] retroperitoneal and mediastinal fibrosis,[20] interstitial nephritis,[8 23] autoimmune hypophysitis[9] and many other inflammatory conditions in multiple organs (fig 3). The distribution of involved organs in IgG_4+MOLPS is similar to that in SS, but there are obvious differences in clinical and pathological features between these classifications. SS is also a very broad-spectrum syndrome, as both anti-SS-A/Ro antibody-positive and anti-SS-B/La antibody-positive SS patients are thought to be typical SS. We compared IgG_4+MOLPS with 31 cases of typical SS.

The age range of patients with IgG_4+MOLPS was broad in our series, ranging from 17 to 80 years with mean and median ages similar to those of SS. On the other hand, the gender distribution was quite different. Male patients with SS are very rare (2/31), but almost half (31/64) of the patients with IgG_4+MOLPS were men. These results suggest that the differential diagnosis of IgG_4+MOLPS should be re-examined in men with SS, even if they meet the SS criteria.

Although swollen glands are usually correlated with xerostomia and xerophthalmia in patients with SS, the incidence of xerostomia and xerophthalmia was significantly lower in IgG_4+MOLPS, even in cases where the lacrimal, parotid or submandibular glands were swollen. Histopathological examination showed that lymphocytic infiltration in the ducts and formation of lymphoepithelial lesions are rare in IgG_4+MOLPS, even in cases showing severe lymphocyte and plasma cell expansion. This may explain the marked swelling of the glands without severe dryness in IgG_4+MOLPS. The decreased numbers of apoptotic cells and abnormal expression and function of Fas ligand in MD tissue[5 6] are compatible with this observation.

Allergic rhinitis and bronchial asthma were more common in IgG_4+MOLPS than in typical SS. This tendency towards an increased incidence of these allergic conditions may be related to the observation that IgG_4 and IgE levels were significantly higher in IgG_4+MOLPS than in SS. With regard to gender differences, autoimmune pancreatitis and interstitial nephritis were more common in men with IgG_4+MOLPS than in women. Thus, the clinical picture was more severe in men with IgG_4+MOLPS.

The incidence of rheumatoid factor, antinuclear antibody, anti-SSA/Ro antibody and anti-SSB/La antibody was significantly lower in IgG_4+MOLPS than in SS. IgG_4+MOLPS should therefore be suspected in patients with symptoms of SS but without autoantibodies, and IgG subclasses should be examined in such patients. Total IgG, IgG_2, IgG_4 and IgE were significantly higher and IgG_1, IgG_3, IgA and IgM were significantly lower in patients with IgG_4+MOLPS than in patients with typical SS. The amount of immunoglobulin protein differed markedly between IgG_4+MOLPS and typical SS and, thus, immunoglobulin gene usage, rearrangement pattern or regulation by T cells may be different in the two groups. The gene fragments Cγ2, Cγ4 and Cε—which code IgG_2, IgG_4 and IgE, respectively—line up side by side and therefore gene linkage may explain the observed association.

Histopathological differences are important to differentiate IgG_4+MOLPS from SS. IgG_4+ plasma cell infiltration in tissue was seen in patients with IgG_4+MOLPS but not in those with SS. Expansion of IgG_4+ plasma cells with fibrosis or sclerosis is an important histopathological finding in IgG_4+MOLPS which is not usually seen in SS. Furthermore, lymphocytic follicle formation is commonly observed in IgG_4+MOLPS but lymphocytic infiltration in the ducts (formation of lymphoepithelial lesions) is rare. In cases in which differential diagnosis is difficult, serum IgG subclasses and IgG_4+/IgG+ immunostaining of tissue should be examined.

A good response to glucocorticoid therapy is usually seen in IgG_4+MOLPS, and this is the most important reason for separating IgG_4+MOLPS from SS. It will be necessary to develop guidelines for standard glucocorticoid therapy (indications, doses and tapering) based on the results of a larger study.

The differential diagnosis of IgG_4+MOLPS from multicentric Castleman's disease (MCD) or idiopathic plasmacytic lymphadenopathy (IPL) is important. Hyper-IgG_4 gammaglobulinaemia and IgG_4 plasma cell infiltration with fibrosis and sclerosis of tissue may be present in these conditions,[24] and therefore discrimination may sometimes be difficult based on histological findings. On serological analysis, increased levels of interleukin-6 are seen in MCD and IPL but not in IgG_4+MOLPS. IgG_4+MOLPS shows a good response to glucocorticoid therapy while MCD and IPL do not. Measurement of the serum interleukin-6 level in such cases is therefore necessary for differential diagnosis and to determine whether glucocorticoids should be used. Patients with raised interleukin-6 levels should be diagnosed as having MCD or IPL, and not IgG_4+MOLPS. An IgG_4+/IgG+ cell ratio of >50% is usually not seen in MCD or IPL.

In Wegener's granulomatosis, hyper-IgG_4 gammaglobulinaemia and IgG_4 plasma cell infiltration of tissue may be present.[25] However, it is not difficult to discriminate between Wegener's granulomatosis and IgG_4+MOLPS based on the histological differences between these two conditions. IgG_4+ plasma cells are also seen in other inflammatory or neoplastic conditions, and it is necessary to determine the IgG_4+/IgG+ cell ratio to make a definite diagnosis of IgG_4+MOLPS.

In conclusion, we propose a new clinical entity, IgG_4+MOLPS, which has a similar distribution of involved organs to SS but has clinical (symptoms, complications, immunological data, including autoantibodies and immunoglobulin classes/subclasses) and

histological (sclerosis or fibrosis and percentage of IgG_4+ cells) differences. Owing to the good response to glucocorticoid treatment, IgG_4+MOLPS should be excluded from the SS criteria. However, these conditions are still rare, and the aetiology and mechanism of development of IgG_4+ cells are still unknown. It is therefore necessary to collect and analyse more of data from patients worldwide.

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Patient consent: Obtained.

REFERENCES

1. **Mikulicz J.** Uber Eine Eigenartige Symmetrishe Erkrankung Der Tranen Und Mundspeicheldrusen. *Stuttgart: Beitr z Chir Fesrschr f Theodor Billroth* 1892:610–30.
2. **Napp O.** Über die Beziehungen der Mikuliczschen Erkrankung Tuberkulose. *Stschr Augenheilk* 1907;**17**:513.
3. **Schaffer AJ,** Jacobsen AW. Mikulicz's syndrome: a report of ten cases. *Am J Dis Child* 1927;**34**:327–46.
4. **Morgan WS,** Castleman B. A clinicopathologic study of Mikulicz's disease. *Am J Pathol* 1953;**29**:471–503.
5. **Tsubota K,** Fujita H, Tsuzaka K, Takeuchi T. Mikulicz's disease and Sjögren's syndrome. *Invest Ophthalmol Vis Sci* 2000;**41**:1666–73.
6. **Tsubota K,** Fujita H, Tadano K, Onoda N, Tsuzaka K, Takeuchi T. Abnormal expression and function of Fas ligand of lacrimal glands and peripheral blood in Sjögren's syndrome patients with enlarged exocrine glands. *Clin Exp Immunol* 2002;**129**:177–82.
7. **Yamamoto M,** Ohara M, Suzuki C, Naishiro Y, Yamamoto H, Takahashi H, *et al*. Elevated IgG4 concentrations in serum of patients with Mikulicz's disease. *Scand J Rhumatol* 2004;**33**:432–3.
8. **Shimoyama K,** Ogawa N, Sakai T, Karasawa H, Masaki Y, Kawabata H, *et al*. A case of Mikulicz's disease complicated with interstitial nephritis successfully treated by high-dose corticosteroid. *Mod Rheumatol* 2006;**16**:176–82.
9. **Yamamoto M,** Takahashi H, Ohara M, Suzuki C, Naishiro Y, Yamamoto H, *et al*. A case of Mikulicz's disease (IgG4-related plasmacytic disease) complicated by autoimmune hypophysitis. *Scand J Rheumatol* 2006;**35**:410–11.
10. **Yamamoto M,** Takahashi H, Ohara M, Suzuki C, Naishiro Y, Yamamoto H, *et al*. A new conceptualization for Mikulicz's disease as an IgG4-related plasmacytic disease. *Mod Rheumatol* 2006;**16**:335–40.
11. **Hamano H,** Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, *et al*. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001;**344**:732–8.
12. **Zen Y,** Kitagawa S, Minato H, Kurumaya H, Katayanagi K, Masuda S, *et al*. IgG4-positive plasma cells in inflammatory pseudotumor (plasma cell granuloma) of the lung. *Hum Pathol* 2005;**36**:710–7.
13. **Kitagawa S,** Zen Y, Harada K, Sasaki M, Sato Y, Minato H, *et al*. Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Küttner's tumor). *Am J Surg Pathol* 2005;**29**:783–91.
14. **Fujibayashi T,** Sugai S, Tojo T, Miyawaki S, Miyasaka N, Ichikawa Y, *et al*. Revised Japanese criteria for Sjögren's syndrome (1999): availability and validity. *Mod Rheumatol* 2004;**14**:425–34.
15. **Vitali C,** Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, *et al*; European Study Group on Classification Criteria for Sjögren's Syndrome. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;**61**:554–8.
16. **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**:982–4.
17. **Kamisawa T,** Funata N, Hayashi Y, Tsuruta K, Okamoto A, Amemiya K, *et al*. Close relationship between autoimmune pancreatitis and multifocal fibrosclerosis. *Gut* 2003;**52**:683–7.
18. **Zen Y,** Harada K, Sasaki M, Sato Y, Tsuneyama K, Haratake J, *et al*. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis. *Am J Surg Pathol* 2004;**28**:1193–203.
19. **Kamisawa T,** Okamoto A, Funata N. Clinicopathological features of autoimmune pancreatitis in relation of elevation of serum IgG4. *Pancreas* 2005;**31**:28–31.
20. **Zen Y,** Sawazaki A, Miyayama S, Notsumata K, Tanaka N, Nakanuma Y. A case of retroperitoneal and mediastinal fibrosis exhibiting elevated levels of IgG4 in the absence of sclerosing pancreatitis (autoimmune pancreatitis). *Hum Pathol* 2006;**37**:239–43.
21. **Nishimori I,** Tamakoshi A, Otsuki M, Research Committee on Intractable Disease of the Pancreas, Ministry of Health, Labour, and Welfare of Japan. Prevalence of autoimmune pancreatitis in Japan from a nationwide survey in 2002. *J Gastroenterol* 2007;**42**:6–8.
22. **Zen Y,** Kasahara Y, Horita K, Miyayama S, Miura S, Kitagawa S, *et al*. Inflammatory pseudotumor of the breast in a patients with a high serum IgG4 level. *Am J Surg Pathol* 2005;**29**:275–8.
23. **Saeki T,** Saito A, Hiura T, Yamazaki H, Emura I, Ueno M, *et al*. Lymphoplasmacytic infiltration of multiple organs with immunoreactivity for IgG4-related systemic disease. *Intern Med* 2006;**45**:163–7.
24. **Ishida F,** Kitano K, Kobayashi H, Saito H, Kiyosawa K. Elevated IgG4 levels in a case with mlticentric Castleman's disease. *Br J Haematol* 1997;**99**:981–2.
25. **Holland M,** Hewins P, Goodall M, Adu D, Jefferis R, Savage COS. Anti-neutrophil cytoplasm antibody IgG subclass in Wegener's granulomatosis: a possible pathogenic role for the IgG4 subclass. *Clin Exp Immunol* 2004;**138**:183–92.

Sonographic diagnosis for Mikulicz disease

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Objective. The aim was to investigate the diagnostic imaging characteristics of Mikulicz disease (MD), especially sonographic ones, and to clarify the differences between them and those in Sjögren syndrome (SS), based on new criteria of MD.
Study design. The sonographic and sialographic images, as well as clinical, histopathologic, and serologic findings of 9 patients satisfying the new criteria of MD were analyzed and compared with those in SS.
Results. All swollen submandibular glands showed bilateral nodal hypoechoic areas with high vascularization on sonograms and a parenchymal defect on sialograms, whereas parotid glands showed normal or slight change on both images. Nodal areas in submandibular gland sonograms were unclear on computerized tomography and on magnetic resonance imaging, but showed accumulation on gallium scintigraphy.
Conclusion. Mikulicz disease showed a high rate of bilateral nodal change in submandibular glands, which was completely different from SS. For detection and follow-up of these changes, sonography may be the best imaging modality. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108:105-113)**

Mikulicz disease (MD) was first reported by Johann von Milulicz-Radecki in 1888 as a disease of unknown etiology with symmetric swelling of bilateral lacrimal and salivary glands.[1] In 1927, Schaffer and Jacobsen[2] classified the disease into 2 types based on whether patients had certain underlying diseases, such as leukemia, malignant lymphoma, sarcoidosis, tuberculosis and syphilis, or whether they did not have any such diseases. In the former case, the illness was named "Mukulicz syndrome," and in the latter case "Mikulicz disease." In 1953, Morgan and Castleman[3] analyzed histopathologic findings of 18 cases of MD and concluded that MD was a less highly developed subtype of Sjögren syndrome (SS). After that, however, there were very few reports about MD for about a half-century.

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Regarding imaging examination, sialograms of MD and those of SS have been reported as having similar punctate or globular sialectasis in periphery.[4-9] Only 1 report demonstrated the sialographic differences between MD and SS.[10] It reported none of the punctate or globular sialectasis typically seen in SS, but demonstrated a defect of the parenchymal image in MD. Unfortunately, because the criteria of MD were still confused with those of SS, that report did not attract much attention.

More recently, however, Tsubota et al.[11] reported that the frequency of gland cell apoptosis in MD was significantly lower compared with that in SS. Furthermore, Yamamoto et al.[12,13] announced the clinical and serologic differences between SS and MD. These differences include persistent gland swelling in MD, whereas that in SS was periodic. Moreover, salivary function was either normal or improved with the administration of glucocorticoid in MD, whereas salivary function decreased and was not affected by treatment in SS. A further difference showed marked elevation of the level of immunoglobulin (Ig) G4 in MD serum although it tested negative for antiSS-A and/or antiSS-B antibodies, whereas SS showed normal IgG4 level but a high positive rate for antiSS-A and/or antiSS-B antibodies. Prominent infiltration of IgG4-positive plasmacytes was observed with immunostaining in MD, whereas there were no IgG4-positive plasmacytes seen in SS. In addition, no punctate or globular sialectasis was observed on sialograms in MD, whereas they were generally observed in SS. Therefore, Yamamoto et al.[14] considered MD to be an

Table I. Criteria for Mikulicz disease

Essential requirements:
1. Bilateral persistent swelling during more than three months in at least one of the lacrimal, parotid, and submandibular glands.
2. Lymphocyte infiltration pattern shows that of benign lymphoepithelial lesion on histopathologic studies.

IgG4 requirements:
1. Increased level of IgG4 in the serum.
2. Infiltration of IgG4-positive plasmacytes on histopathologic studies.

Other conditions:
1. Mild decrease in saliva secretion.
2. Low positive rates of antiSS-A and/or antiSS-B antibody in the serum.
3. No punctuate or globular pattern on sialograms.
4. High steroid sensitivity.

Ig, Immunoglobulin.

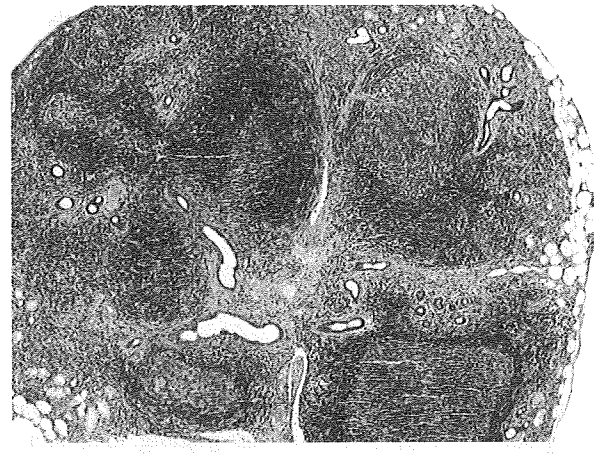

Fig. 1. Histopathological section (HE stain) of a labial gland of Case 7 (under low magnification). The section shows extensive replacement of gland parenchyma by lymphoid follicles. Periductal lymphocytic infiltration is relatively modest compared with Sjögren syndrome.

entity independent of SS. They also gave a brief description of diagnostic imaging of MD; however, details of the imaging characteristics of this disease have not yet been reported.

The purpose of the present study was to investigate the diagnostic imaging characteristics of MD, especially the sonographic ones, and to clarify the differences between those characteristics and those of SS, based on the new criteria of MD.

MATERIALS AND METHODS

Criteria of MD

Although unanimous criteria for MD have not been defined so far, they are being discussed in the working group for MD of the Japanese Medical Society for SS. Our institution's criteria are listed in Table I. There are 2 conditions that are essential for an ailment to be considered as MD. The first is persistent bilateral swelling in ≥1 of the lacrimal, parotid, and submandibular glands for >3 months. SS shows repeated swelling or swelling that disappears in due course. The second condition is that the lymphocyte infiltration pattern should show that of benign lymphoepithelial lesion on histopathologic studies. Benign lymphoepithelial lesion is characterized by lymphocytic infiltration of the salivary glands, similar to the germinal center, and is further characterized by destruction or replacement of the acini with the persistence of islands of epithelial cells (Fig. 1). In contrast, SS shows mainly periductal infiltration of lymphocytes. Regarding IgG4, MD generally shows: 1) increased level of IgG4 in the serum; and 2) Infiltration of IgG4-positive plasmacytes with immunostaining on the histopathologic studies. Other characteristics of MD include the following conditions:

1. Mild decrease in saliva secretion.
2. Low positive rates of antiSS-A and/or antiSS-B antibody in the serum.
3. No punctuate or globular pattern on sialograms.
4. High steroid sensitivity.

In the present study, when a case satisfied the 2 essential conditions, it was considered to be MD, even if it did not satisfy other supplemental conditions.

Patients

We retrospectively analyzed patients who visited our hospital from January 1999 to July 2007 with suspected MD or complaints of salivary gland swelling. In this study the patients who satisfied the 2 essential requirements mentioned in the preceding section were analyzed. The subjects comprised 9 patients: 7 women and 2 men, with a mean age of 56.9 years (range 31 to 68 years).

Clinical findings

We checked the location and duration of persistent bilateral swelling (essential requirement 1), general problems, complications, and the presence of dryness of mouth and eyes. All the patients underwent gum tests and/or Saxon tests for objective assessment of mouth dryness. When the patients had dryness of eyes, the Schirmer test was added for objective assessment. Normal values for the gum test and the Saxon test are >10 mL/10 min, and >2 g/2 min, respectively. Normal values for the Schirmer test are >10 mm/5 min, and a value of ≤5 mm is diagnosed as dry eyes. MD shows a mild decrease in saliva secretion (other condition 1),

whereas SS generally shows below-normal levels in objective assessment value of dryness.

Histopathologic examinations

Materials by labial gland biopsy were stained with hematoxylin and eosin, and were evaluated based on the scores reported by Chisholm and Mason.[15] They defined a focus as an aggregate of >50 lymphocytes and histiocytes, and 5-level grading was performed according to the number of foci seen on labial gland biopsy material per 4 mm^2 as follows: grade 0: lymphocytes were absent; grade 1: slight infiltration; grade 2: moderate infiltration or <1 focus; grade 3: 1 focus; and grade 4: >1 focus. Besides this grading, the pattern of lymphocytes infiltration, whether intralobular (pattern of benign lymphoepithelial lesion) or periductal (pattern of SS), was evaluated (essential requirement 2).

Serologic examinations

Serologic analysis was performed on rheumatoid factor (RF), antinuclear antibody (ANA), IgG, IgG4, IgA, IgM, and antiSS-A and antiSS-B antibodies. Normal values were as follows: RF: <20 immunizing units (IU)/mL; IgG: 872-1,815 mg/dL; IgG4: 4.8-135 mg/dL; IgA: 95-405 mg/dL; and IgM: 59-269 mg/dL. Levels of ANA were divided into 4 grades: negative: <40; 1+: 40-160; 2+: 160-640; and 3+: >640. AntiSS-A and antiSS-B antibodies were evaluated as positive when minute amounts of them were detected. Although MD shows high values in IgG and IgG4 (IgG4 requirement 1), it shows low positive rates in antiSS-A and/or antiSS-B antibodies (other condition 2).

Sonographic examinations

Sonographic examinations were performed and evaluated by 6 certified oral and maxillofacial radiologists, with more than 10 years of sonographic experience each, using an Acuson Sequoia 512 (Mochida Siemens Medical Systems, Tokyo, Japan). B-Mode multifoci images were taken with a center frequency of 8 MHz. Doppler-mode images were taken with a center frequency of 7 MHz and a flow range of 0.023 m/s. The bilateral parotid glands of each patient were scanned in 2 planes: parallel to the Frankfort-horizontal plane at the infra-auricular level and parallel to the retromandibular plane. The bilateral submandibular glands of each patient were scanned in 2 planes: one parallel and the other perpendicular to the submandibular plane. These are the standardized planes for salivary glands.[16]

We analyzed sonograms to determine whether there were findings compatible with SS on B-mode or other characteristic features. The findings compatible with SS on B-mode sonograms are stated in detail in our previous study,[17] which analyzes 79 suspected SS cases (including 43 actual cases). Compatible findings include multiple hypoechoic areas in the parotid gland and/or submandibular gland. These areas are often surrounded with hyperechoic lines and/or spots in typical SS cases. Obscuration of the gland configuration in the submandibular gland is also observed.

Sialographic examinations

Sialography was performed with a water-soluble contrast medium, amidotrizoate 76% (Urografin 76%; Schering-Japan, Osaka, Japan). Sialographic images were evaluated by a single observer (M.S.), based on the classifications by Rubin and Holt[18]: normal: no abnormal dilatation of the peripheral ducts; punctate: diffuse punctate dilatation of the peripheral ducts <1 mm; globular: the globules of contrast material increase to 1-2 mm; cavitary: the globules become irregular in size and distribution, cystic dilatation; and destructive: destruction of the gland parenchyma. MD shows generally normal sialograms (other condition 3), whereas SS shows an abnormal sialographic pattern in the classifications by Rubin and Holt at high rates.

Other imaging modalities

All of the patients underwent at least one of computerized tomography (CT), magnetic resonance imaging (MRI), and gallium scintigraphy under suspicion of, or to rule out, malignant lymphoma. When these images included salivary glands, we compared the findings with those of sonography.

Follow-up examinations

A follow-up CT or MRI was performed mainly for complications. When the patients showed persistent swelling of salivary glands, sonography was performed to assess the salivary gland condition.

RESULTS

Clinical findings

Table II shows the clinical findings of 9 cases. All cases showed bilateral swelling over the course of >3 months in ≥1 of the lacrimal, parotid, or submandibular glands (essential requirement 1). One case showed the swelling of lacrimal glands only, and 2 cases showed solely submandibular gland swelling. Five of the 9 cases showed swelling in lacrimal glands. Only 2 cases showed swelling in parotid glands, whereas in almost all (8 cases), submandibular glands showed swelling.

Six cases suffered from dryness of mouth; however, only one-half of them showed an objective decrease of saliva flow in both gum and Saxon tests. The average values of the gum and Saxon tests of 9 cases were 9.6 mL/10 min and 2.97 g/2 min, respectively. This result

Table II. Clinical findings

Case no.	Location of swelling					Duration (mo)	General problems	Complications	Dryness		Gum test (mL/10 min)	Saxon test (g/2 min)	Schirmer test (right/left, mm/5 min)
	LG	PG	SMG	SLG	PLG				Mouth	Eyes			
1	+					3	Fatigue	Asthma	+	+	4.0	3.76	8/4
2	+		+	+		18	Weight loss	AIP, DM	+		8.0	3.05	
3	+		+	+		3	Joint pain	—	+		13.0	2.73	
4	+		+	+	+	36	Weight loss	AIP, DM	+		7.8	1.03	
5		+	+	+		24	—	Prostate hypertrophy			16.0	5.80	
6			+			5	—	Hydronephrosis			12.0	4.26	
7	+		+			6	Anemia	AIP, PSC			9.8	4.33	
8			+			3	Weight loss	AIP, PSC	+	+	6.3	1.20	3/1
9		+	+			12	—	AIP, PSC	+		ND	0.60	

LG, Lacrimal glands; *PG*, parotid glands; *SMG*, submandibular glands; *SLG*, sublingual glands; *PLG*, palatal glands; *AIP*, autoimmune pancreatitis; *DM*, diabetes; *PSC*, primary sclerosing cholangitis; *ND*, not done.

Table III. Histopathologic and serologic findings

Case no.	Histopathologic findings		Serologic findings							
	Grade	Pattern	RF	ANA	IgG	IgG4	IgA	IgM	AntiSS-A	AntiSS-B
1	4	BLEL	−	+	high	ND	WNL	WNL	−	−
2	4	BLEL	−	+	high	ND	WNL	WNL	−	−
3	2	BLEL	−	−	high	ND	WNL	WNL	−	−
4	4	BLEL	−	2+	high	ND	WNL	WNL	−	−
5	4	BLEL	ND	−	ND	ND	ND	ND	−	−
6	4	BLEL	−	−	high	high	WNL	WNL	−	−
7	4	BLEL	−	−	high	high	WNL	WNL	−	−
8	4	BLEL	−	−	high	high	WNL	WNL	−	−
9	3	BLEL	+	2+	high	high	WNL	WNL	−	−

BLEL, Benign lymphoepithelial lesion; *RF*, rheumatoid factor; *ANA*, antinuclear antibody; *Ig*, immunoglobulin; *ND*, not done; *WNL*, within normal limits.

shows that the decrease of saliva flow was relatively mild in MD (other condition 1).

Frequent complications of MD were autoimmune pancreatitis (5 cases), primary sclerosing cholangitis (3 cases), and diabetes (2 cases).

Histopathologic and serologic findings

Table III shows the histopathologic and serologic findings of 9 cases. The histopathologic grades showed varying degrees; however, lymphocytes infiltrated mainly around acinar cells and showed a pattern of benign lymphoepithelial lesion (essential requirement 2). This infiltration pattern of lymphocytes was different from SS, which shows mainly periductal infiltration.

The IgG test was available in 8 cases, and all of them showed high IgG levels. The IgG4 test could be performed only 4 cases; however, they also all showed high IgG4 levels (IgG4 requirement 1). On the other hand, all cases were negative for antiSS-A and antiSS-B antibodies (other condition 2). The results of the IgA and IgM tests were all within normal limits.

Sonographic findings

Six of 9 cases showed normal parotid glands on the sonograms (Table IV; Fig. 2, *A*). Three other cases showed a slight change in parotid glands, which showed multiple hypoechoic areas, either unilaterally or bilaterally; however, they were not necessarily related to the swelling of the glands (Fig. 2, *B*). These hypoechoic areas were observed in normal parotid parenchyma without reduction of echo intensity level and heterogeneity.

On the other hand, all submandibular glands with swelling (8 cases) showed nodal areas on the sonograms (Table IV). They were hypoechoic areas with relatively high vascularization, and bulged from the normal surface of the submandibular glands (Fig. 3, *A* and *B*). Parenchyma of the submandibular glands around nodal areas showed homogeneity and a normal echo intensity level. Such areas were observed bilaterally on 7 of these 8 cases, although the degree of bulge varied from one case to the next (Fig. 3, *C*). In the remaining case, the nodal area was seen unilaterally, because the submandibular gland on the other side had

Table IV. Sonographic findings

	Parotid glands		*Submandibular glands*	
Case no.	*Swelling*	*Sonographic findings*	*Swelling*	*Sonographic findings*
1	−	WNL	−	Bi-SC
2	−	WNL	+	Bi-NA
3	−	WNL	+	Bi-NA
4	−	WNL	+	Uni-NA*
5	+	Uni-SC	+	Bi-NA
6	−	Uni-SC	+	Bi-NA
7	−	Bi-SC	+	Bi-NA
8	−	WNL	+	Bi-NA
9	+	WNL	+	Bi-NA

WNL, Within normal limits; *Uni*, unilateral; *Bi*, bilateral; *SC*, slight change; *NA*, nodal area(s).
*The submandibular gland on the other side had been removed on suspicion of a tumor.

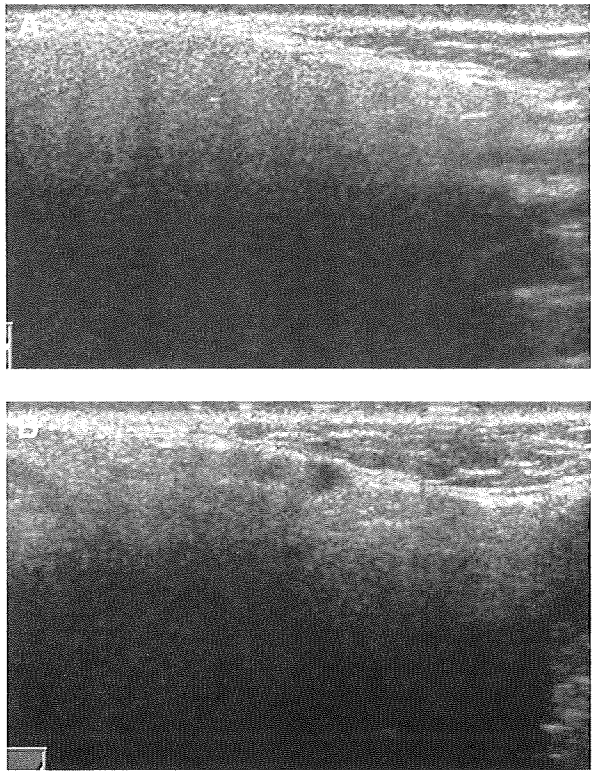

Fig. 2. **(A)** Normal parotid gland sonogram seen in Mikulicz disease (scanned parallel to the retromandibular plane, left: superior, right: inferior). Internal echoes are homogeneous. **(B)** Parotid gland sonogram shows slight change in some cases. Multiple hypoechoic areas are observed in parotid parenchyma with normal echo intensity level.

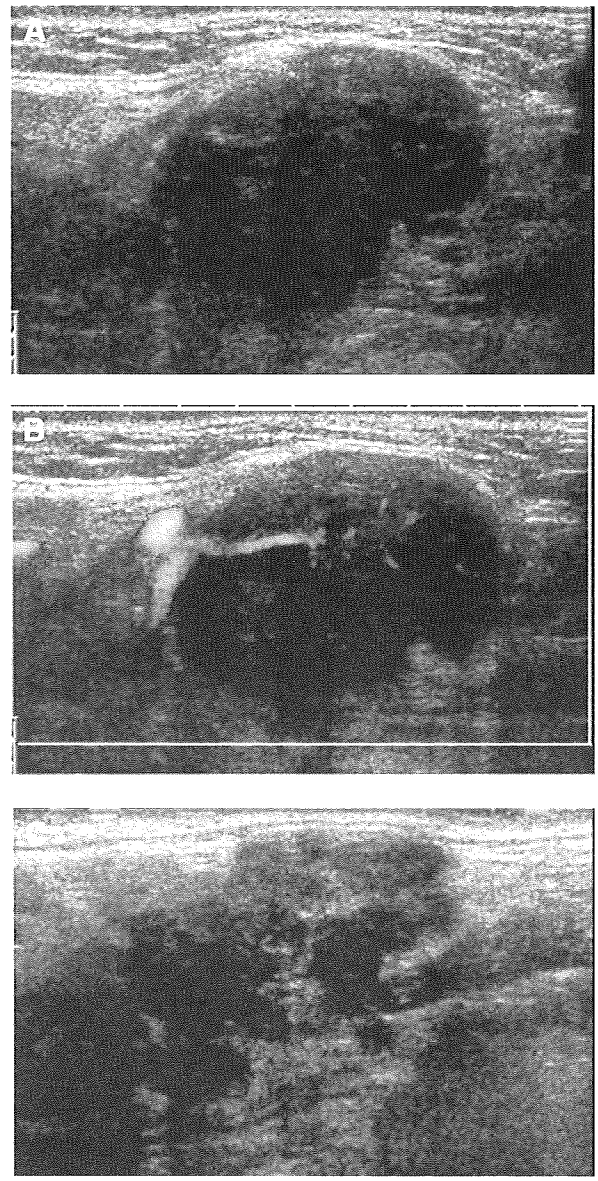

Fig. 3. **(A)** Nodal area in submandibular gland (scanned parallel to the submandibular plane, left: posterior, right: anterior). It is a hypoechoic area bulging from normal surface of the submandibular gland. Note the adjacent submandibular gland parenchyma show normal echo intensity level and homogeneity. **(B)** Doppler mode of the same case as Fig. 3A. The nodal area shows relatively high vascularization. **(C)** Nodal areas show a variety in size and in degree of bulge from case to the next. This case shows smaller nodal area than the case seen in Fig. 3A, 3B (scanned same as Fig. 3A).

been removed owing to suspicion of a tumor. Thus, all submandibular glands with swelling showed bilateral nodal areas on the sonograms. Even 1 case without submandibular gland swelling showed slight change bilaterally on the sonograms.

When we defined the cases with decreased saliva flow in both gum and Saxon tests as cases of objective dryness of mouth, cases 4, 8, and 9 fell into the defi-

Table V. Sialographic findings

	Parotid glands		*Submandibular glands*	
Case no.	*Swelling*	*Sialographic findings*	*Swelling*	*Sialographic findings*
1	–	WNL	–	ND
2	–	WNL	+	GD
3	–	DD	+	ND
4	–	WNL	+	ND
5	+	WNL	+	GD
6	–	WNL	+	GD
7	–	WNL	+	ND
8	–	WNL	+	GD
9	+	WNL	+	GD

WNL, Within normal limits; *DD*, ductal dilation; *ND*, not done; *GD*, glandular defect.

nition. Sonograms of these cases showed findings similar to those cases without objective dryness.

Sialographic findings

Excepting 1 case of ductal dilation, 8 of 9 cases showed normal parotid gland sialograms (Table V). No cases showed punctate or globular patterns, which is in contrast to SS (other condition 3; Fig. 4). Two cases with swelling of the glands showed also normal sialograms.

On the other hand, defects in glandular images were observed on all submandibular gland sialograms in accordance with the nodal areas on the sonograms, although submandibular gland sialography could be performed on only 5 of 9 cases (Fig. 5).

Findings on other imaging modalities

Table VI shows the findings of nodal areas on submandibular gland sonography on other imaging modalities. A CT examination was performed in 6 cases. Nodal areas on the sonograms could not be differentiated from adjacent normal glandular tissues. Those areas were demonstrated as low-signal-intensity masses on a T2-weighted MRI in 2 cases. In the other 3 cases, however, they could not be differentiated from adjacent normal glandular tissues, even on MRI. On gallium scintigraphy, 2 cases showed abnormal uptake in accordance with those areas, and 1 case did not show particular findings.

Follow-up examinations

One case was mainly followed up by MRI, and CT was performed in 2 other cases, because these cases were complicated by autoimmune pancreatitis. Sonography was performed in 4 of the 9 cases as a follow-up examination of the persistent salivary gland swelling. Submandibular gland nodal areas in 2 cases showed reduction in size, and 1 case showed no interval change. One case, in which glucocorticoid administration was refused, showed deterioration in the condition of the salivary gland. The bilateral parotid gland showed multiple hypoechoic areas in this case at the time of fol-

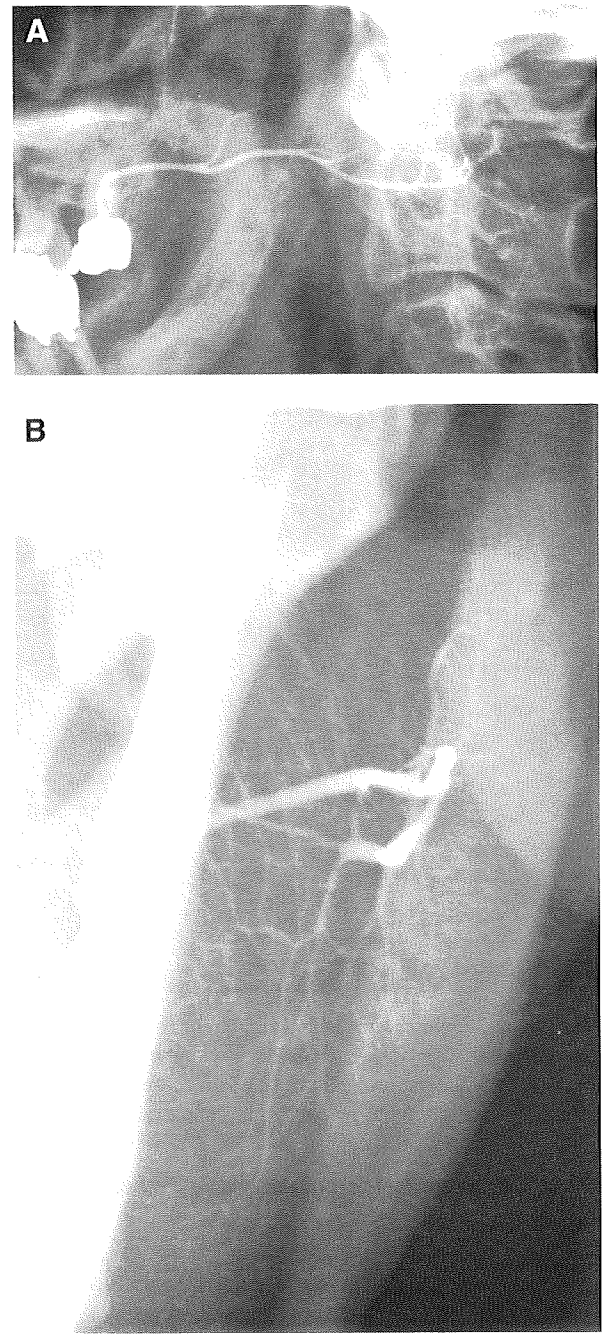

Fig. 4. **(A)** Parotid gland sialogram shows normal findings without punctate or globular pattern seen in Sjögren syndrome (lateral projection). **(B)** Same case as Fig. 4A in postero-anterior projection.

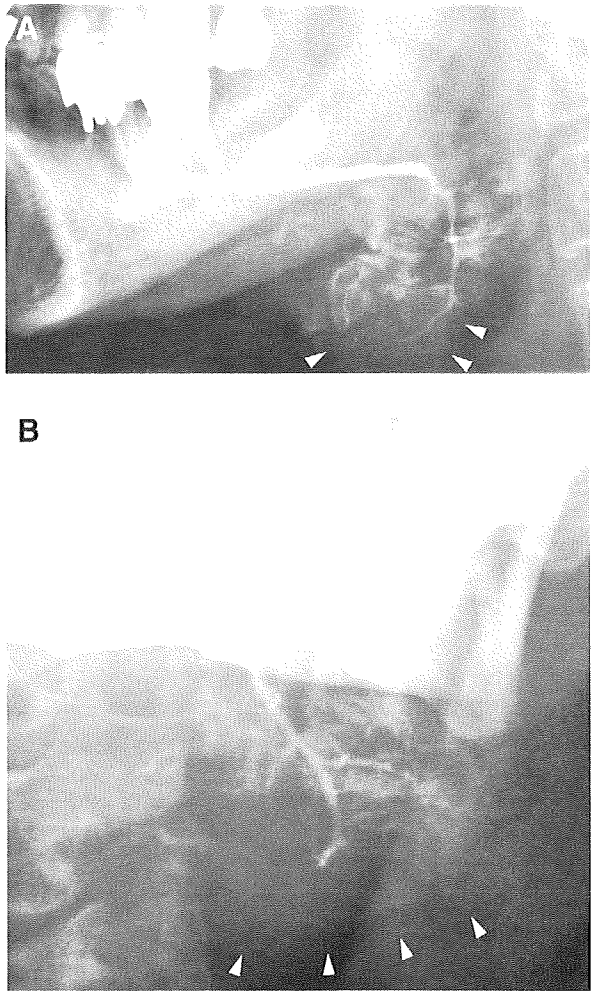

Fig. 5. **(A)** Submandibular gland sialogram shows parenchymal defect (arrowheads) in accordance with the nodal area on the sonogram (lateral projection). **(B)** Same case as Fig. 5A in oblique projection. Note parenchymal defect (arrowheads).

Table VI. Sonographic nodal areas on other imaging modalities

Case no.	*CT*	*MRI*	*RI (gallium)*
2	Unclear	Unclear	ND
3	ND	Low in T2	ND
4	ND	Low in T2	ND
5	Unclear	Unclear	ND
6	Unclear	ND	Abnormal uptake
7	Unclear	ND	Abnormal uptake
8	Unclear	Unclear	ND
9	Unclear	ND	Unclear

CT, Computerized tomography; *MRI*, magnetic resonance imaging; *RI*, radionuclide imaging (scintigraphy); *ND*, not done.

low-up (Fig. 6), although nodal change in the submandibular gland showed no interval change. Unlike SS, these multiple hypoechoic areas were surrounded by

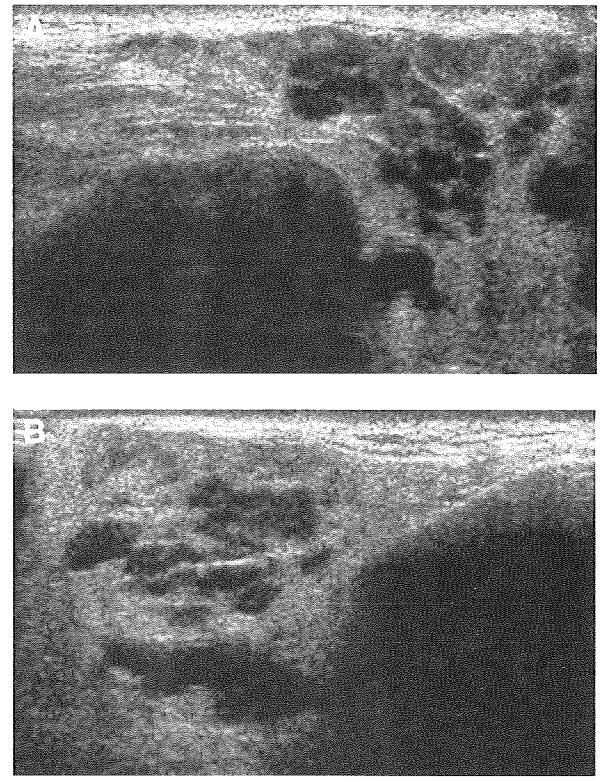

Fig. 6. **(A)** Parotid gland sonogram which shows deterioration in the condition in a follow-up period. Multiple hypoechoic areas are distinct, however, adjacent parotid parenchyma are still within normal echo intensity level (scanned parallel to the Frankfort-Horizonral plane, left: anterior, right: posterior). **(B)** Same case as Fig. 6A (scanned parallel to the retromandibular plane, left: superior, right: inferior).

normal parotid gland parenchyma. Parotid gland parenchyma in SS are generally heterogeneous and show decrease in echo intensity level.[17]

DISCUSSION

Unanimous criteria of MD have not been defined so far, although a new concept of MD has been recently discussed. In the present criteria, we emphasized a histopathologic pattern of lymphocytes different from SS. Lymphocytes infiltrate mainly around acinar cells in MD, whereas SS shows mainly periductal infiltration. Yamamoto et al.[14] showed figures in which the difference in the amount of plasmacytes with IgG4 between MD and SS could be seen. These figures also showed the difference of lymphocyte infiltration patterns. These infiltration patterns can explain why cases of MD respond well to glucocorticoid administration. Ducts in MD are not severely affected; therefore, regeneration of the acinar cells can be easily induced.

In other reports, persistent bilateral swelling in >2 of the lacrimal, parotid, or submandibular glands was the

requirement for an ailment to be considered to be MD. However, we considered an ailment to be MD if only 1 of these glands experienced persistent bilateral swelling. Although 3 of the 9 cases showed only 1 pair of swollen glands, they showed typical findings of MD such as high IgG and IgG4 values and negative results on both antiSS-A and antiSS-B antibody tests.[19]

It is still controversial whether or not cases showing features of both MD and SS should be classified as MD. For example, Yamamoto et al.[20] reported a case of MD with autoimmune pancreatitis, which also met the criteria of SS. To clarify the imaging characteristics of MD more clearly, we excluded the cases showing punctuate or globular pattern on sialograms from this study.

We could not find enough references which showed change dominant in submandibular glands rather than in parotid glands. Tsubota et al.[11] used both lacrimal and parotid gland swelling as criteria of MD, whereas the case reported by Miyake et al.[19] showed only submandibular gland swelling. A case of Yamamoto et al.[20] and a case of Shimoyama et al.[21] suffered from lacrimal and submandibular gland swelling. Lee et al.[22] showed 2 cases: In 1 case lacrimal and parotid gland swelling were observed, and in the other case lacrimal, parotid, and submandibular glands were swollen. Thus, dominance in change in submandibular glands was not clearly demonstrated. However, a nodal area in submandibular glands was removed by an operation in 1 of the 2 cases of Lee et al.[22] and in 1 of the present 9 cases. One case in the present study, in which glucocorticoid administration was refused, showed deterioration of the condition of the salivary glands. The bilateral submandibular glands in this case showed nodal change with no interval change. Whereas the parotid glands showed deterioration and no nodal formation could be seen. These facts suggested that the change in submandibular glands was more dominant than that in parotid glands.

Nodal areas on sonograms in MD resembled Küttner tumor (chronic sclerosing sialadenitis) and other salivary gland tumors; however, they appeared bilaterally in MD. Furthermore, the areas in MD showed relatively high vascularization compared with Küttner tumor and other salivary gland tumors.

Salivary glands affected with SS show characteristic sonographic findings with hypoechoic areas delineated by hyperechoic lines or spots.[17] The change involves the whole gland; therefore, parenchyma are heterogeneous and show a decrease in echo intensity level. Submandibular glands show obscuration of gland configuration but no nodal areas.[17] Parotid glands rarely reveal nodal areas. When parotid glands show nodal areas, however, they are always accompanied by typical sonographic findings of SS.[23] These sonographic features are completely different from those of MD.

Sarcoidosis should be differentiated from MD, because the sonographic findings of both diseases can be very similar in parotid glands.[24,25] However, sarcoidosis tends to involve mostly parotid glands, and if no bilateral nodal areas have been reported,[26,27] these 2 diseases can be differentiated by sonography. Therefore, sonographic examination is recommended in making an imaging diagnosis.

These nodal areas on sonograms were not clearly demonstrated on other modalities. CT[14,21,22] and MRI[20,21] could show only glandular swelling. Some of the present cases showed slightly low signal intensity on T2-weighted images on MRI; however, they were not significant. The reasons these nodal areas were not clearly demonstrated on other modalities can be given as follows: 1) The change in MD was not neoplastic; and/or 2) lymphocytes infiltration was not accompanied by fibrosis or edema. Besides sonography, gallium scintigraphy seemed sensitive to the change in MD.[19-21]

Sonography can also be recommended as a follow-up examination of persistent swelling in salivary glands. Change in salivary glands can be easily examined by sonography without using ionizing radiation. In the present study, because the objective dryness was not related to the swelling, and because the other imaging modalities were not sensitive to the nodal areas, we could conclude that it is effective to observe the glands by sonography to see if they are back on the recovery track or not.

In conclusion, salivary glands affected by MD showed bilateral nodal change in submandibular glands at high rates. Nodal changes were detected as hypoechoic areas with relatively high vascularization by sonography and a parenchymal defect on sialograms. Those changes were completely different from previously reported sonographic characteristics of SS. To detect and also as a follow-up examination of these changes, sonography is indicated as the best imaging modality.

REFERENCES

1. Daniels TE. Benign lymphoepithelial lesion and Sjogren's syndrome. In: Ellis GL, Auclair PL, Gnepp DR, editors. Surgical pathology of the salivary glands, Philadelphia: Saunders; 1991. p. 83-106.
2. Schaffer AJ, Jacobsen AW. Mikulicz's syndrome: a report of ten cases. Am J Dis Child 1927;34:327-46.
3. Morgan WS, Castleman B. A clinicopathologic study of Mikulicz's disease. Am J Pathol 1953;29:471-503.
4. Sprinkle PM, Yarington CT Jr. Disease of the salivary glands and benign lymphoepithelial lesion. South Med J 1968;61:971-4.
5. Leban SG, Stratigos GT. Benign lymphoepithelial sialoadenopathies. The Mikulicz/Sjögren controversy. Oral Surg Oral Med Oral Pathol 1974;38:735-48.

6. Zhaoju Z, Yuntang W, Guangxi S, Xuanpen Z, Fengming Y, Qiguang W, et al. Roentgenologic analysis of 62 cases of Mikulicz-Sjögren's syndrome. Chin Med J 1979;92:379-97.
7. Som PM, Shugar JM, Train JS, Biller HF. Manifestations of parotid gland enlargement: radiographic, pathologic, and clinical correlations. Part II: The diseases of Mikulicz syndrome. Radiology 1981;141:421-6.
8. Cvetinovic M, Jovic N, Mijatovic D. Evaluation of ultrasound in the diagnosis of pathologic processes in the parotid gland. J Oral Maxillofac Surg 1991;49:147-50.
9. Yousem DM, Kraut MA, Chalian AA. Major salivary gland imaging. Radiology 2000;216;19-29.
10. Yamazaki M, Ohmori K, Takinami S, Iizuka T, Fukuda H. [Sialography IV—Sjögren syndrome and Mikulicz disease.] Rinsho Hoshasen 1984;29:79-84 [in Japanese].
11. Tsubota K, Fujita H, Tsuzaka K, Takeuchi T. Mikulicz's disease and Sjögren's syndrome. Invest Ophthalmol Vis Sci 2000;41: 1666-73.
12. Yamamoto M, Harada S, Ohara M, Suzuki C, Naishiro Y, Yamamoto H, et al. Clinical and pathological differences between Mikulicz's disease and Sjögren's syndrome. Rheumatology 2005;44:227-34.
13. Yamamoto M, Takahashi H, Sugai S, Imai K. Clinical and pathological characteristics of Mikulicz's disease (IgG4-related plasmacytic exocrinopathy). Autoimmunity Rev 2005;4: 195-200.
14. Yamamoto M, Takahashi H, Ohara M, Suzuki C, Naishiro Y, Yamamoto H, et al. A new conceptualization for Mikulicz's disease as an IgG4-related plasmacytic disease. Mod Rheumatol 2006;16:335-40.
15. Chisholm DM, Mason DK. Labial salivary gland biopsy in Sjögren's syndrome. J Clin Pathol 1968;21:656-60.
16. Wittich GR, Scheible WF, Hajek PC. Ultrasonography of the salivary glands. Radiol Clin North Am 1985;23:29-37.
17. Shimizu M, Okamura K, Yoshiura K, Ohyama Y, Nakamura S, Kinukawa N. Sonographic diagnostic criteria for screening Sjögren's syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;102:85-93.
18. Rubin P, Holt FJ. Secretory sialography in disease of the major salivary gland. AJR Am J Roentgenol 1957;77:575-98.
19. Miyake K, Moriyama M, Aizawa K, Nagano S, Inoue Y, Sadanaga A, et al. Peripheral CD4+ T cells showing a Th2 phenotype in a patient with Mikulicz's disease associated with lymphadenopathy and pleural effusion. Mod Rheumatol 2008;18:86-90.
20. Yamamoto M, Ohara M, Suzuki C, Oka T, Naishiro Y, Yamamoto H, et al. A case of Mikulicz's disease complicated by autoimmune pancreatitis, in which impaired glucose tolerance was improved by glucocorticoid treatment. Jpn J Clin Immunol 2005;28:349-56 (in Japanese).
21. Shimoyama K, Ogawa N, Sawaki T, Karasawa H, Masaki Y, Kawabata H, et al. A case of Mikulicz's disease complicated with interstitial nephritis successfully treated by high-dose corticosteroid. Mod Rheumatol 2006;16:176-82.
22. Lee S, Tsirbas A, McCann JD, Goldberg RA. Mikulicz's disease: A new perspective and literature review. Eur J Ophtalmol 2006;16:199-203.
23. Goto TK, Shimizu M, Kobayashi I, Chikui T, Kanda S, Toshitani K, et al. Lymphoepithelial lesion of the parotid gland. Dentomaxillofac Radiol 2002;31:198-203.
24. Kelly IM, Lees WR, Watts RW. Case report: grey scale and colour Doppler ultrasound appearance of acute sarcoidosis of the parotid gland. Clin Radiol 1994;49:425-6.
25. Fischer T, Filimonow S, Petersein J, Zimmer C, Beyersdorff D, Guski H. Diagnosis of Heerfordt's syndrome by state-of-the-art ultrasound in combination with parotid biopsy: a case report. Eur Radiol 2002;12:134-7.
26. Iko BO, Chinwuba CE, Myers EM, Teal JS. Sarcoidosis of the parotid gland. Br J Radiol 1986;59:547-52.
27. Alyas F, Lewis K, Williams M, Moody AB, Wong KT, Ahuja AT, et al. Diseases of the submandibular gland as demonstrated using high resolution ultrasound. Br J Radiol 2005;78:362-9.

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Advance Publication

REVIEW

Pituitary and Stalk Lesions (Infundibulo-hypophysitis) Associated with Immunoglobulin G4-related Systemic Disease: an Emerging Clinical Entity

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Abstract. Inflammatory lesions of the pituitary gland are rarely encountered. Recently, the concept of immunoglobulin G4 (IgG4)-related systemic disease was proposed in Japan, and more than 20 cases have been reported as possibly associated with infundibulo-hypophysitis since 2000. We herein review such case reports in the published literature and in the abstracts of scientific meetings. Almost all cases involved middle-aged to elderly men presenting with various degrees of hypopituitarism and diabetes insipidus and demonstrating a thickened pituitary stalk and/or pituitary mass. These structures shrank remarkably in response to glucocorticoid therapy, even in a lower dose range similar to that prescribed as a replacement for adrenocortical insufficiency. Some of the anterior pituitary insufficiencies were also resolved by glucocorticoid administration. The presence of IgG4-related systemic disease and an elevated serum IgG4 level before glucocorticoid therapy were the main clues to a correct diagnosis of IgG4-related infundibulo-hypophysitis. Autoimmunity is suggested but not yet established to play a role in the pathogenesis for IgG4-related systemic disease. The fact that hypertrophic pachymeningitis and para-sinusitis accompanied some cases suggested that both sellar and parasellar structures are involved in the chronic inflammation. We therefore classify this disorder not as a variant form of primary autoimmune hypophysitis but as a secondary form of infundibulo-hypophysitis associated with IgG4-related systemic disease.

Key words: Secondary hypophysitis, Immunoglobulin G4, Multifocal fibrosclerosis, Hypopituitarism, Diabetes insipidus

INFLAMMATORY LESIONS of the pituitary and pituitary stalk are rarely encountered. However, due to the availability of magnetic resonance (MR) imaging, so-called lymphocytic hypophysitis has been reported more frequently in Japan than in Western countries [1]. Infundibulo-hypophysitis may be categorized into three groups according to the involved tissues: adenohypophysitis, infundibulo-neurohypophysitis and panhypophysitis [2]. An autoimmune mechanism is thought to be involved in adenohypophysitis and infundibulo-hypophysitis. However, panhypophysitis may be heterogeneous; that is, it may be primary or secondary as a direct result of systemic infectious or inflammatory processes or as a result of local processes such as a ruptured Rathke cleft cyst, craniopharyngioma, or germinoma. Chronic inflammation of parasellar structures such as seen in hypertrophic pachymeningitis or Tolosa-Hunt syndrome may spread into the pituitary gland. Rare cases associated with multifocal fibrosclerosis have been reported [3, 4].

Recently, the new concept of immunoglobulin G4 (IgG4)-related systemic disease was proposed from the close observation of autoimmune pancreatitis (AIP) and lymphoproliferative diseases [5, 6]. Involvement of the pituitary gland may be recognized as a possible extra-pancreatic manifestation of AIP. More than 20 cases have been reported since 2000. In the present article, we review these case reports and summarize the clinical features of IgG4-related infundibulo-hypophysitis. We also discuss

the relationship to autoimmune hypophysitis and the possible pathogenesis of IgG-4 related disease.

1. IgG4-related systemic disease

IgG4-related sclerosing disease is a systemic disease characterized by extensive infiltration of IgG4-positive plasma cells and T-lymphocyte into various organs [5]. Clinical manifestations are apparent in the pancreas, bile duct, gallbladder, salivary gland, retroperitoneum, kidney, lung, and prostate, in which organ tissue fibrosis with occlusive phlebitis is pathologically induced. Most IgG4-related sclerosing diseases have been found to be associated with AIP, but IgG4-related diseases without pancreatic involvement have been reported. Some inflammatory pseudotumors may be involved in this disease. The disease occurs predominantly in elder men, is frequently associated with lymph node swelling, and responds well to glucocorticoid therapy. Serum IgG4 levels and immunostaining with anti-IgG4 antibody are useful for making a diagnosis.

Multifocal fibrosclerosis is an uncommon fibroproliferative systemic disorder with multiple manifestations, including sclerosing cholangitis, salivary gland fibrosis, retroperitoneal fibrosis, Riedel's thyroiditis, and fibrotic orbital pseudotumor [7]. As the histopathological findings of these disorders are similar - i.e., fibrotic changes with lymphoplasmacytic infiltration and occasional phlebitis - it is suggested that they are all interrelated and probably different manifestations of a common disorder of fibroblastic proliferation. The histopathology of the extrapancreatic lesions associated with AIP strongly suggests that multifocal fibrosclerosis is an IgG4-related sclerosing disease [8].

2. Pituitary and stalk lesions (infundibulo-hypophysitis) associated with IgG4-related systemic disease

Chronic inflammatory diseases of the pituitary gland, inflammatory pseudotumor [9] or plasma cell granuloma [10] have been described, and several cases of pituitary lesion associated with retroperitoneal fibrosis have been reported [3, 4]. More recently, a new disease entity consisting of hypophysitis associated with IgG4-related systemic disease has been described [11-14]. We surveyed the case reports involving this entity both in the published literature and in the abstracts of scientific meetings since 2000. Inclusion criteria for the survey were the presence of pituitary and stalk lesions associated with at least one IgG4-related systemic disease or multifocal fibrosclerosis, and/or the biopsy-proven inflammatory pseudotumor of the pituitary mass infiltrated with IgG4-positive plasma cells.

There were 22 such cases (Table 1: [11-34]). Twenty-one cases were male and only one was female. The age distribution was as followed; 2 patients were in their 40s, 4 in their 50s, 8 in their 60s, and 8 in their 70s. The median age was 64 years. Whether the observed extreme male predominance is the characteristics for the IgG4-related hypophysitis or not remains to be determined, since the male: female ratio of AIP was reported as 2.77:1 [35].

1) Clinical manifestations

Symptoms related to the hypothalamic-hypophyseal system were general malaise (11 cases), headache (6 cases), visual disturbances including impaired eye movement (6 cases), fever (5 cases), polyuria (6 cases), appetite loss (4 cases), weight loss (4 cases), and decreased libido (3 cases). General malaise, loss of appetite and weight loss was closely related with ACTH deficiency.

2) Pituitary function

Various degrees of anterior pituitary hormone deficiency were observed in 19 cases, and central diabetes insipidus was observed in 12 cases. Eleven cases had both hypopituitarism and diabetes insipidus. Masked diabetes insipidus was diagnosed in 3 cases. Diabetes insipidus may have preceded the development of hypopituitarism in 4 cases.

Isolated hypogonadism, isolated central hypothyroidism, and isolated ACTH deficiency were observed in 2 patients, one patient and one patient, respectively. Another 15 cases had combined anterior pituitary hormone deficiencies. Decreased secretion of LH/FSH (15 cases), ACTH (14 cases), TSH (12 cases), GH (8 cases) were documented. It is unclear whether specific combinations of pituitary hormone deficiencies may exist, since provocative tests to examine the pituitary hormone reserve were not used in every patient. Three cases with hyperprolactinemia were reported. Altered hypothalamic regulation of pituitary hormone secretion was demonstrated in one case [22].

3) MR imaging of the pituitary

A thickened pituitary stalk or mass formation on the stalk was observed in 18 cases, and some of the thickening took place at the level of infundibulum or the proximal end of the stalk. On the other hand, a swelling of the pituitary gland or mass formation in the pituitary was present in 10 cases. Among these 10 cases, 2 showed a pituitary mass alone, and 3 showed both a thickened stalk and pituitary mass occurring simultaneously. The other 5 cases showed a united large mass formation involving both the pituitary and stalk (Fig. 1).

The "bright" signal seen in the posterior portion of the pituitary on T1-weighed imaging was absent in the cases involving central diabetes insipidus and in several cases without clinical diabetes insipidus.

Hypertrophic pachymeningitis was found in 5 patients and orbital lesion including pseudotumor formation was in 2 cases. Para-sinusitis was observed in 3 cases.

4) Laboratory findings

Seven of the 9 patients who were tested for C-reactive protein were found to be positive. Elevated levels of serum immunoglobulin G and serum IgG4 were observed in 7 of 9 cases and in 12 of 13 cases in which they were assessed, respectively. A normal serum level of IgG4 was observed only in patients receiving steroid therapy [29]. Serum levels of IgG4 promptly decreased to reference range after initiation of steroid therapy [21]. Clinical manifestations and laboratory findings did not seem to differ between the cases with and without IgG4 measurement.

In the two cases in which FDG-PET was performed, uptake was observed in both the pituitary gland and other involved lesions [11, 23].

5) Histopathology of pituitary lesion

Pituitary biopsy was performed in only 5 cases via a transsphenoidal approach or transcranial approach. The inflammatory pseudotumor of the pituitary was densely infiltrated with both lymphocyte and plasma cells and fibrous changes were demonstrated in all cases. The plasma cells were stained positive by IgG4 immunostaining (Fig. 2).

6) Associated IgG4-related systemic disease

Various IgG4-related systemic diseases are associated with pituitary and stalk lesion. Among these, retroperitoneal fibrosis was the most prevalent disease (n=10), followed by Mikulicz disease and salivary gland lesions (n=8), pulmonary lesions (m=8), pancreatic lesion (n=6), and lymph node swelling (n=5).

Systemic diseases preceded the pituitary lesions in 11 patients, the two occurred simultaneously in 8 cases, and the pituitary lesion preceded the systemic disease in 2 cases. An isolated pituitary lesion not associated with any systemic IgG-4 related disease was described in one patient [33].

7) Effect of glucocorticoid therapy

Various kinds and doses of glucocorticoid were used for replacing adrenocortical insufficiencies or actively treating the pituitary mass and/or accompanying hypertrophic pachymeningitis, AIP or other lesions. Some of the anterior pituitary insufficiencies were resolved by glucocorticoid even in a lower dose range similar to that prescribed as a replacement for adrenocortical insufficiency. In most cases of diabetes insipidus, glucocorticoid therapy did not lead to remission.

As for the pituitary mass and the stalk thickening, almost all lesions shrank during glucocorticoid therapy. However, several cases showed a relapse of the pituitary mass when the doses of glucocorticoid were decreased. Serum levels of IgG and IgG4 promptly decreased to normal ranges after glucocorticoid therapy.

8) Summary of clinical features

Table 2 provides a summary of the clinical features of the IgG4-related pituitary and stalk lesion. Almost all cases involved middle-aged to elderly men presenting with various degrees of hypopituitarism and diabetes insipidus and demonstrating a thickened pituitary stalk and/or pituitary mass. These structures shrank remarkably in response to glucocorticoid therapy. Some of the anterior pituitary insufficiencies were also resolved by glucocorticoid administration. The presence of IgG4-related sys-

temic diseases and the elevated serum IgG4 levels before glucocorticoid therapy were the main clues to a correct diagnosis of IgG4-related infundibulo-hypophysitis. Several cases were accompanied with pachymeningitis and para-sinusitis, suggesting that both sellar and parasellar structures were involved in chronic inflammation.

3. Relationship to other forms of hypophysitis (Fig.3)

Primary hypophysitis is of unknown etiology and is classified on a histopathological basis as lymphocytic, granulomatous, or xanthogranulomatous hypophysitis [36-38], whereas secondary hypophysitis occurs as a direct result of systemic infectious or inflammatory processes or as a result of local processes such as a ruptured Rathke cleft cyst, craniopharyngioma, adenoma, or germinoma.

Primary hypophysitis may also be categorized into adenohypophysitis, infundibulo-neurohypophysitis, and panhypophysitis based on the tissues involved. Adenohypophysitis typically affects females during the puerperal period and presents a pituitary mass and hypopituitarism, whereas patients with infundibulo-neurophysitis typically show diabetes insipidus with a posterior pituitary mass or thickened pituitary stalk. Both entities are regarded as autoimmune-mediated. On the other hand, panhypophysitis involves both lobes of the pituitary gland, which has a different developmental origin, suggesting that it may not arise solely from an autoimmune mechanism. Inflammation of the anterior or posterior lobe of the pituitary may spread out over the whole pituitary [37]. There are several case reports of panhypophysitis showing an aggressive behavior and invading into the cavernous sinus or hypothalamus and causing cranial nerve paralyses [39]. Whether these types of lymphocytic hypophysitis belong to the same category as other types of hypophysitis is currently unknown.

Chronic parasellar inflammation such as those in hypertrophic pachymeningitis, cavernous sinusitis or Tolosa-Hunt syndrome have been reported to be accompanied by hypopituitarism and/or diabetes insipidus [40]. We have previously reported three such cases but did not measure the subjects' IgG or IgG4 levels [41]. Both sellar and parasellar structures were involved in the chronic inflammation in the cases of IgG4-related hypophysitis with pachymeningitis, para-sinusitis, and/or orbital pseudotumor. The previously reported cases of pituitary lesion associated with multifocal fibrosclerosis were considered to belong the same category as the currently reviewed cases of IgG4-related pituitary diseases.

Cases of isolated pituitary lesions or cases in which onset of diabetes insipidus preceded the other lesions by several years present a challenge for diagnosis. It is recommended that the measurement of serum IgG4 levels be included in the panel during the initial workup for investigating hypopituitarism and/or diabetes insipidus.

4. Pathogenesis

The pathogenesis of IgG4-related systemic disease is currently under intensive investigation [5]. Elevated serum IgG4 and dense infiltration of IgG4-positive plasma cells in various organs suggest that IgG4 plays a major role in the pathogenesis, although the trigger for IgG4 elevation has not been clearly established.

There are increased numbers of activated CD4+ and CD8+ T cells bearing HLA-DR in the pancreas of AIP patients. An inhibitory molecule, cytotoxic T-lymphocyte antigen 4 (CTLA-4), which is expressed on activated memory T cells and CD4+CD25+ regulatory T cells (Tregs), acts as a negative regulator of T cell responses [42]. The soluble isoform of CTLA-4 is reported to be elevated in patients with AIP, enhancing immune responses by blocking the interaction of CD80 on antigen-presenting cells and CTLA-4 on T cells. Tregs are thought to be associated with various autoimmune diseases [43]. Miyoshi *et al.* [44] have observed that the number of circulating naïve Tregs is decreased in the peripheral blood of the patients with AIP, whereas the number of memory Tregs is significantly increased. Prominent infiltration of Tregs has been observed in the liver of patients with sclerosing cholangitis. These finding suggest that regulatory functions of T cells, such as CTLA-4 and Tregs, are involved in the development and pathophysiology of AIP [45].

Given the preponderance of the disease amongst elderly males and the dramatic responses to oral steroid therapy, the pathogenesis may not involve an autoimmune mechanism but rather other mechanisms, such as an allergic reaction. Zen *et al.* [46] have reported that the expression of T helper 2 (Th2) cytokines and regulatory cytokines (IL-10 and transforming growth factor-beta) was up-regulated in the affected tissues of patients with IgG4-related pancreatitis and cholangitis. They have suggested that the