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Proposal for a new clinical entity, IgG₄-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG₄-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 IgG₄-related disorder.

Objective: To determine the differences between IgG₄-related disorders including MD and SS.

Methods: A study was undertaken to investigate patients with MD and IgG₄-related disorders registered in Japan and to set up provisional criteria for the new clinical entity IgG₄-positive multiorgan lymphoproliferative syndrome (IgG₄+MOLPS). The preliminary diagnostic criteria include raised serum levels of IgG₄ (>135 mg/dl) and infiltration of IgG₄⁺ plasma cells in the tissue (IgG₄⁺/IgG⁺ plasma cells >50%) with fibrosis or sclerosis. The clinical features, laboratory data and pathologies of 64 patients with IgG₄+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 IgG₄+MOLPS than in those with typical SS. Allergic rhinitis and autoimmune pancreatitis were significantly more frequent and total IgG, IgG₂, IgG₄ and IgE levels were significantly increased in IgG₄+MOLPS. Histological specimens from patients with IgG₄+MOLPS revealed marked IgG₄⁺ plasma cell infiltration. Many patients with IgG₄+MOLPS had lymphocytic follicle formation, but lymphoepithelial lesions were rare. Few IgG₄⁺ cells were seen in the tissue of patients with typical SS. Thirty-eight patients with IgG₄+MOLPS treated with glucocorticoids showed marked clinical improvement.

Conclusion: Despite similarities in the involved organs, there are considerable clinical and pathological differences between IgG₄+MOLPS and SS. Based on the clinical features and good response to glucocorticoids, we propose a new clinical entity: IgG₄+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 IgG₄ and IgG₄⁺ 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 IgG₄-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: IgG₄-positive multiorgan lymphoproliferative syndrome (IgG₄+MOLPS).

METHODS

Case reports of MD involving two or three sets of swollen lacrimal, parotid or submandibular glands on physical examination and IgG₄-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 IgG₄+MOLPS was defined as both raised serum IgG₄ levels (>135 mg/dl)¹¹ and histopathological features including lymphocyte and IgG₄⁺ plasma cell infiltration (IgG₄⁺ 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 IgG₄+MOLPS. Of these 64 patients with IgG₄+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

Table 1 Comparison of frequencies of symptoms and complications in patients with IgG₄-positive multiorgan lymphoproliferative syndrome (IgG₄+MOLPS) and those with typical Sjögren's syndrome (SS)

	IgG ₄ +MOLPS			Typical SS		Japanese*	p Value†	p Value‡	p Value§
	All (n = 64)	Women (n = 33)	Men (n = 31)	All (n = 31)	Women (n = 29)				
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 IgG₄+MOLPS vs all typical SS.

‡Female IgG₄+MOLPS vs female typical SS.

§Female vs male IgG₄+MOLPS.

2:29; mean age 52.0 years; median age 49.0 years; range 34–76). Typical patients with SS fulfilled both Japanese¹⁴ and European¹⁵ 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-IgG₄ 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 IgG₄ 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. IgG₄+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 IgG₄+MOLPS patients and only female patients with IgG₄+MOLPS with those of typical SS patients. We also compared female vs male patients with IgG₄+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 IgG₄-positive multiorgan lymphoproliferative syndrome (IgG₄+MOLPS) and those with typical Sjögren's syndrome (SS)

	IgG ₄ +MOLPS			Typical SS		Normal range	p Value†	p Value‡	p Value§
	All (n = 64)	Women (n = 33)	Men (n = 31)	All (n = 31)	Women (n = 29)				
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, IgG₁, IgG₂, IgG₃, IgG₄, 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 IgG₄+MOLPS. IgG₁, IgG₂ and IgG₃ were examined in 58 patients (not all) with IgG₄+MOLPS.

†All IgG₄+MOLPS vs typical SS.

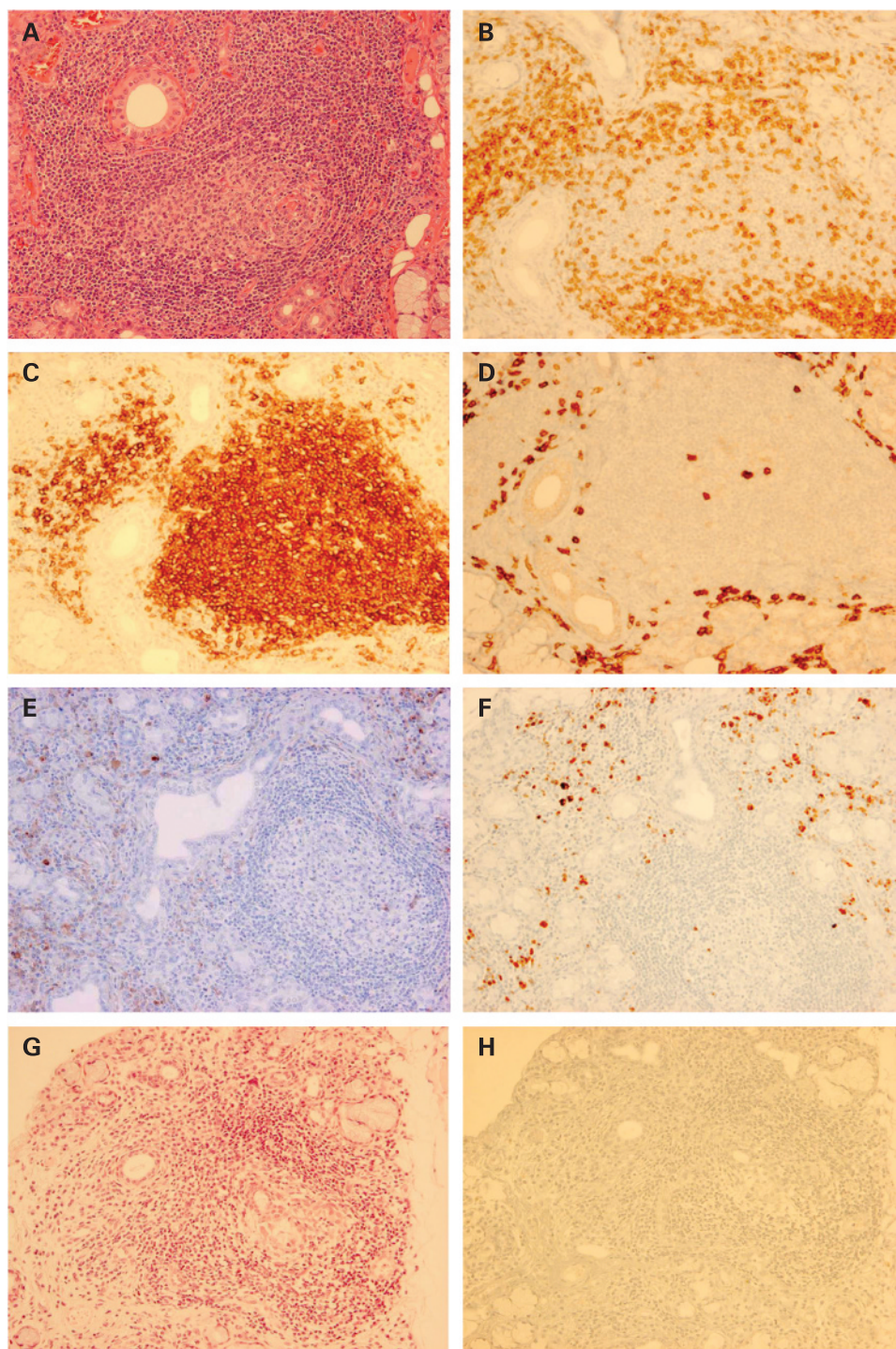
‡Female IgG₄+MOLPS vs typical SS.

§Female vs male IgG₄+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.

Extended report

Figure 1 Histopathological findings of labial minor salivary gland biopsy in (A–F) patients with IgG₄+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) IgG₄ immunostaining. Massive lymphocyte and plasmacyte infiltration and lymphoid follicle formation were seen in IgG₄+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 IgG₄+ plasma cells were scattered in the periphery of the follicle. The ratio of IgG₄+ plasma cells/IgG+ plasma cells was > 50%. On the other hand, there were few or no IgG₄+ 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, IgG₁, IgG₂, IgG₃, IgG₄, IgA, IgM and IgE) were performed using the Mann-Whitney U test. All analyses were performed using SPSS V.11 (SPSS, Chicago, Illinois, USA).

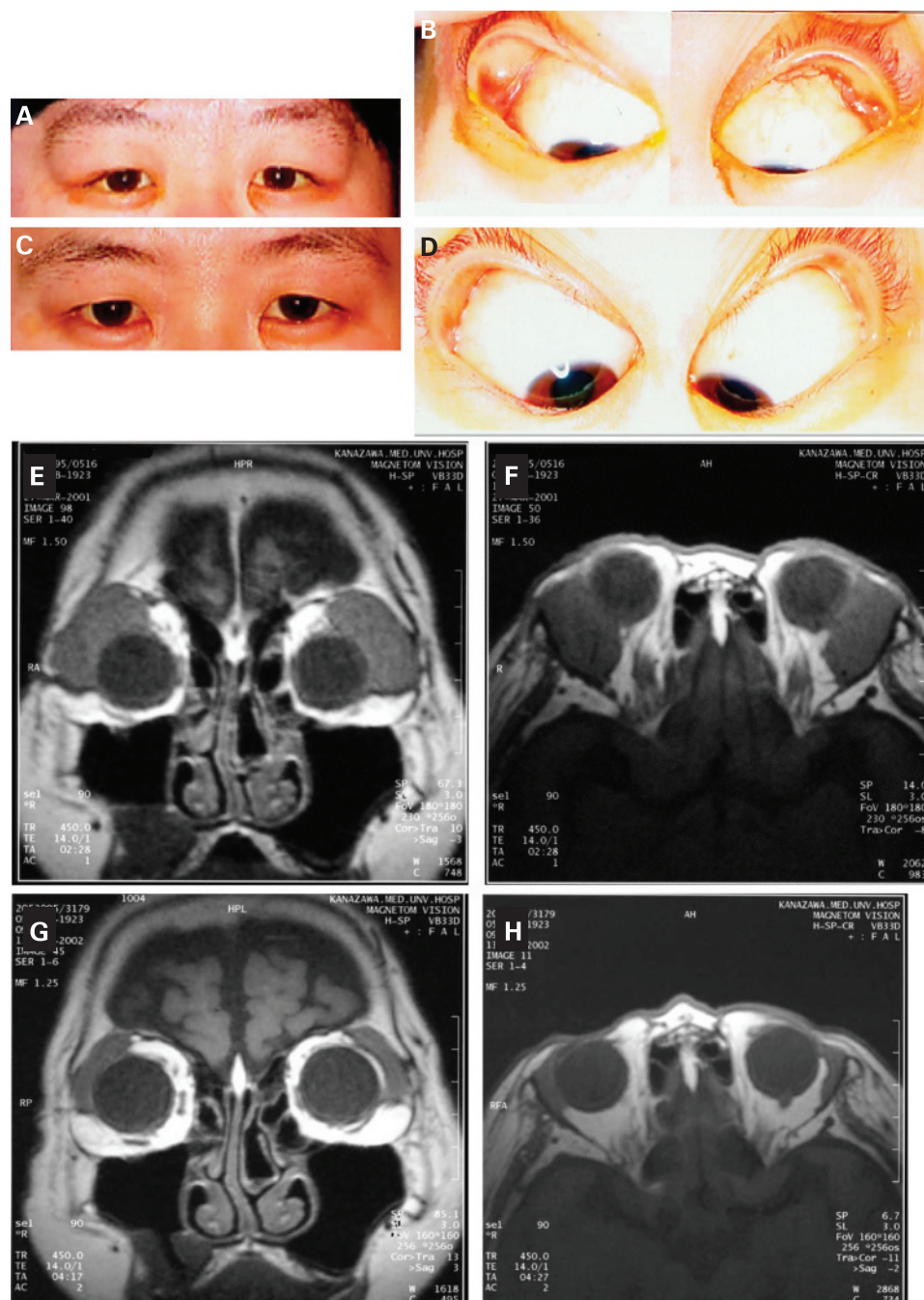
RESULTS

As shown in table 1, the numbers of patients with symptoms of xerostomia, xerophthalmia and arthralgia were significantly lower in all cases of IgG₄+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 IgG₄+AMOLPS compared with patients with typical SS. Allergic rhinitis and autoimmune pancreatitis were significantly more common in IgG₄+MOLPS than in typical SS (40.6% vs 6.5%, 17.2% vs 0%, respectively). Interstitial pneumonitis was significantly rarer in all patients with IgG₄+MOLPS than in patients with typical SS (9.4% vs 32.3%). We compared gender differences among IgG₄+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 IgG₄+MOLPS than in those

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 IgG₄+MOLPS were compared with patients with typical SS. We compared immunoglobulin classes and subclasses and found that not only IgG₄ but also total IgG, IgG₂ and IgE levels were significantly higher in IgG₄+MOLPS than in typical SS. In contrast, IgG₁, IgG₃, IgA and IgM levels were significantly lower in IgG₄+MOLPS than in typical SS.

Patients with IgG₄+MOLPS showed marked lymphocyte and IgG₄+ 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 IgG₄+ 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 IgG₄+ 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 IgG₄+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

Extended report

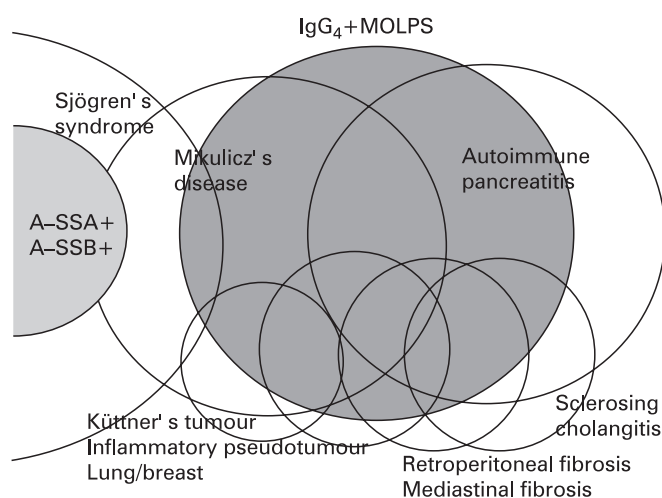


Figure 3 Spectrum of IgG₄+MOLPS. IgG₄+MOLPS included Mikulicz's disease, autoimmune pancreatitis and many other inflammatory conditions. A-SSA, anti-SS-A/Ro antibody; A-SSB, anti-SS-B/La antibody.

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, IgG₄+MOLPS, a syndrome characterised by hyper-IgG₄ gammaglobulinaemia and IgG₄+ plasma cell infiltration in the tissue (lymphoproliferative disorder). IgG₄+MOLPS includes MD, autoimmune pancreatitis,^{11 16–21} sclerosing cholangitis,¹⁸ Küttner's tumour,¹⁵ inflammatory pseudotumour of the lung,¹⁹ liver¹⁸ and breast,^{16 22} retroperitoneal and mediastinal fibrosis,²⁰ interstitial nephritis,^{8 23} autoimmune hypophysitis⁹ and many other inflammatory conditions in multiple organs (fig 3). The distribution of involved organs in IgG₄+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 IgG₄+MOLPS with 31 cases of typical SS.

The age range of patients with IgG₄+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 IgG₄+MOLPS were men. These results suggest that the differential diagnosis of IgG₄+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 IgG₄+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 IgG₄+MOLPS, even in cases showing severe lymphocyte and plasma cell expansion. This may explain the marked swelling of the glands without severe dryness in IgG₄+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 IgG₄+MOLPS than in typical SS. This tendency towards an

increased incidence of these allergic conditions may be related to the observation that IgG₄ and IgE levels were significantly higher in IgG₄+MOLPS than in SS. With regard to gender differences, autoimmune pancreatitis and interstitial nephritis were more common in men with IgG₄+MOLPS than in women. Thus, the clinical picture was more severe in men with IgG₄+MOLPS.

The incidence of rheumatoid factor, antinuclear antibody, anti-SSA/Ro antibody and anti-SSB/La antibody was significantly lower in IgG₄+MOLPS than in SS. IgG₄+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, IgG₂, IgG₄ and IgE were significantly higher and IgG₁, IgG₃, IgA and IgM were significantly lower in patients with IgG₄+MOLPS than in patients with typical SS. The amount of immunoglobulin protein differed markedly between IgG₄+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 IgG₂, IgG₄ and IgE, respectively—line up side by side and therefore gene linkage may explain the observed association.

Histopathological differences are important to differentiate IgG₄+MOLPS from SS. IgG₄+ plasma cell infiltration in tissue was seen in patients with IgG₄+MOLPS but not in those with SS. Expansion of IgG₄+ plasma cells with fibrosis or sclerosis is an important histopathological finding in IgG₄+MOLPS which is not usually seen in SS. Furthermore, lymphocytic follicle formation is commonly observed in IgG₄+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 IgG₄/IgG+ immunostaining of tissue should be examined.

A good response to glucocorticoid therapy is usually seen in IgG₄+MOLPS, and this is the most important reason for separating IgG₄+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 IgG₄+MOLPS from multicentric Castleman's disease (MCD) or idiopathic plasmacytic lymphadenopathy (IPL) is important. Hyper-IgG₄ gammaglobulinaemia and IgG₄ 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 IgG₄+MOLPS. IgG₄+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 IgG₄+MOLPS. An IgG₄/IgG+ cell ratio of >50% is usually not seen in MCD or IPL.

In Wegener's granulomatosis, hyper-IgG₄ gammaglobulinaemia and IgG₄ plasma cell infiltration of tissue may be present.²⁵ However, it is not difficult to discriminate between Wegener's granulomatosis and IgG₄+MOLPS based on the histological differences between these two conditions. IgG₄+ plasma cells are also seen in other inflammatory or neoplastic conditions, and it is necessary to determine the IgG₄/IgG+ cell ratio to make a definite diagnosis of IgG₄+MOLPS.

In conclusion, we propose a new clinical entity, IgG₄+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 IgG₄⁺ cells) differences. Owing to the good response to glucocorticoid treatment, IgG₄+MOLPS should be excluded from the SS criteria. However, these conditions are still rare, and the aetiology and mechanism of development of IgG₄⁺ cells are still unknown. It is therefore necessary to collect and analyse more of data from patients worldwide.

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