表1 自己免疫性膵炎臨床診断基準2006
(厚生労働省難治性膵疾患調査研究班・日本膵臓学会)

Ⅰ．臨床診断基準
1．膵画像検査にて特徴的な主膵管狭細像と膵腫大を認める．
2．血液検査で高γグロブリン血症，高IgG血症，高IgG4血症，自己抗体のいずれかを認める．
3．病理組織学的所見として膵にリンパ球，形質細胞を主とする著明な細胞浸潤と線維化を認める．
上記の1を含め2項目以上を満たす症例を，自己免疫性膵炎と診断する．
ただし，膵癌・胆管癌などの悪性疾患を除外することが必要である．

と考えられる．

3. 鑑別すべき疾患

1)膵　　癌

限局性に腫瘤を形成する場合にとくに鑑別が困難で，過去に膵癌として切除された病変組織を検討し，2～3％が自己免疫性膵炎の病理組織像，lymphoplasmacyticsclerosing pancreatitis(LPSP)であったと報告されている．臨床所見，血液・画像所見,生検病理所見などを総合的に検討して両者を鑑別する．血清IgG4高値，組織でIgG4陽性形質細胞浸潤が鑑別に有用であるが，膵癌でも認められるので膵癌の存在を否定できるわけではない．画像所見で上記の特徴的な所見以外に，腫瘤内を主膵管が貫いて認められるduct-penetrating signが鑑別に有用である．膵生検で自己免疫性膵炎を積極的に診断することは困難であるが，癌細胞の存在は本症を否定できる．

2)idiopathic duct-centric chronic pancreatitis (IDCP)

本邦の自己免疫性膵炎の病理所見はリンパ球，形質細胞を主体とした著明な炎症細胞浸潤と線維化を伴った膵炎像，LPSPである．閉塞性静脈炎，IgG4陽性形質細胞の著明な浸潤も特徴的である．一方，膵管周囲にリンパ球・形質細胞浸潤を伴う特発性膵炎組織を病理組織学的に検討すると，LPSP以外に好中球浸潤を伴い膵管上皮の破壊を認める病変があり，idiopathic duct-centric chronic pancreatitis(IDCP)と呼称された．IDCPの臨床像は，40歳を中心に幅広い年齢層に分布し，男女差はなく，強度の腹痛発作を呈する場合もあり，炎症性腸疾患の合併例が多いなど，LPSPの臨床像とは異なっている．欧米の自己免疫性膵炎にはIDCPも含まれていると考えられている．

4. 治　　療

自己免疫性膵炎の治療は経口プレドニゾロン投与が基本である．ステロイド治療に際し，黄疸例ではドレナージを考慮し，糖尿病合併例では血糖のコントロールを行う．寛解導入には経口プレドニゾロン30～40mg/日から投与を開始し，2～4週間投与した後，臨床徴候の改善をみながら，2～3ヵ月を目安に維持量まで減量する．6～12ヵ月間程度維持療法を施行し，臨床徴候の改善をみて中止し，再燃を念頭においた経過観察を行う．

ステロイド治療なしでも自然軽快する例が報告されているが，活動性の高い症例にはステロイド治療が必要であり，胆管狭窄による閉塞性黄疸例，腹痛・背部痛を有する例，膵外病変合併例などがステロイド治療の適応と考えられる．維持療法中にIgG4が正常に低下した例は，活動性が低下したと考えられ，ステロイド中止も可能と考えられる．

経口ステロイド剤投与で下部胆管狭窄などに対して十分な効果が得られない場合，手術などが予定されていて長期のステロイド経口投与が困難な場合，患者が長期のステロイド内服を拒否する場合，ステロイド・ミニパルス療法が試みられる．また，海外では難治例に対して免疫抑制剤の使用が報告されているが，その有効性については今後の検討課題である．

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

Y Masaki, L Dong, N Kurose, K Kitagawa, Y Morikawa, M Yamamoto, H Takahashi, Y Shinomura, K Imai, T Saeki, A Azumi, S Nakada, E Sugiyama, S Matsui, T Origuchi, S Nishiyama, I Nishimori, T Nojima, K Yamada, M Kawano, Y Zen, M Kaneko, K Miyazaki, K Tsubota, K Eguchi, K Tomoda, T Sawaki, T Kawanami, M Tanaka, T Fukushima, S Sugai and H Umehara

Ann Rheum Dis 2009;68;1310-1315; originally published online 13 Aug 2008; doi:10.1136/ard.2008.089169

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

Y Masaki,[1] L Dong,[1,2] N Kurose,[3] K Kitagawa,[4] Y Morikawa,[5] M Yamamoto,[7] H Takahashi,[7] Y Shinomura,[7] K Imai,[8] T Saeki,[9] A Azumi,[10] S Nakada,[11] E Sugiyama,[12] S Matsui,[12] T Origuchi,[13] S Nishiyama,[14] I Nishimori,[15] T Nojima,[3] K Yamada,[16] M Kawano,[16] Y Zen,[17] M Kaneko,[18] K Miyazaki,[19] K Tsubota,[20] K Eguchi,[21] K Tomoda,[6] T Sawaki,[1] T Kawanami,[1] M Tanaka,[1] T Fukushima,[1] S Sugai,[1] H Umehara[1]

► Additional data are published online only at http://ard.bmj.com/content/vol68/issue8

For numbered affiliations see end of article

Correspondence to:
Dr Y Masaki, Department of Hematology and Immunology, Kanazawa Medical University, 1-1 Daigaku, Uchinada, Kahoku-gun, Ishikawa, 920-0293, Japan; yasum@kanazawa-med.ac.jp

The first two authors contributed equally to this work.

Accepted 26 July 2008
Published Online First 13 August 2008

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 15] 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

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.

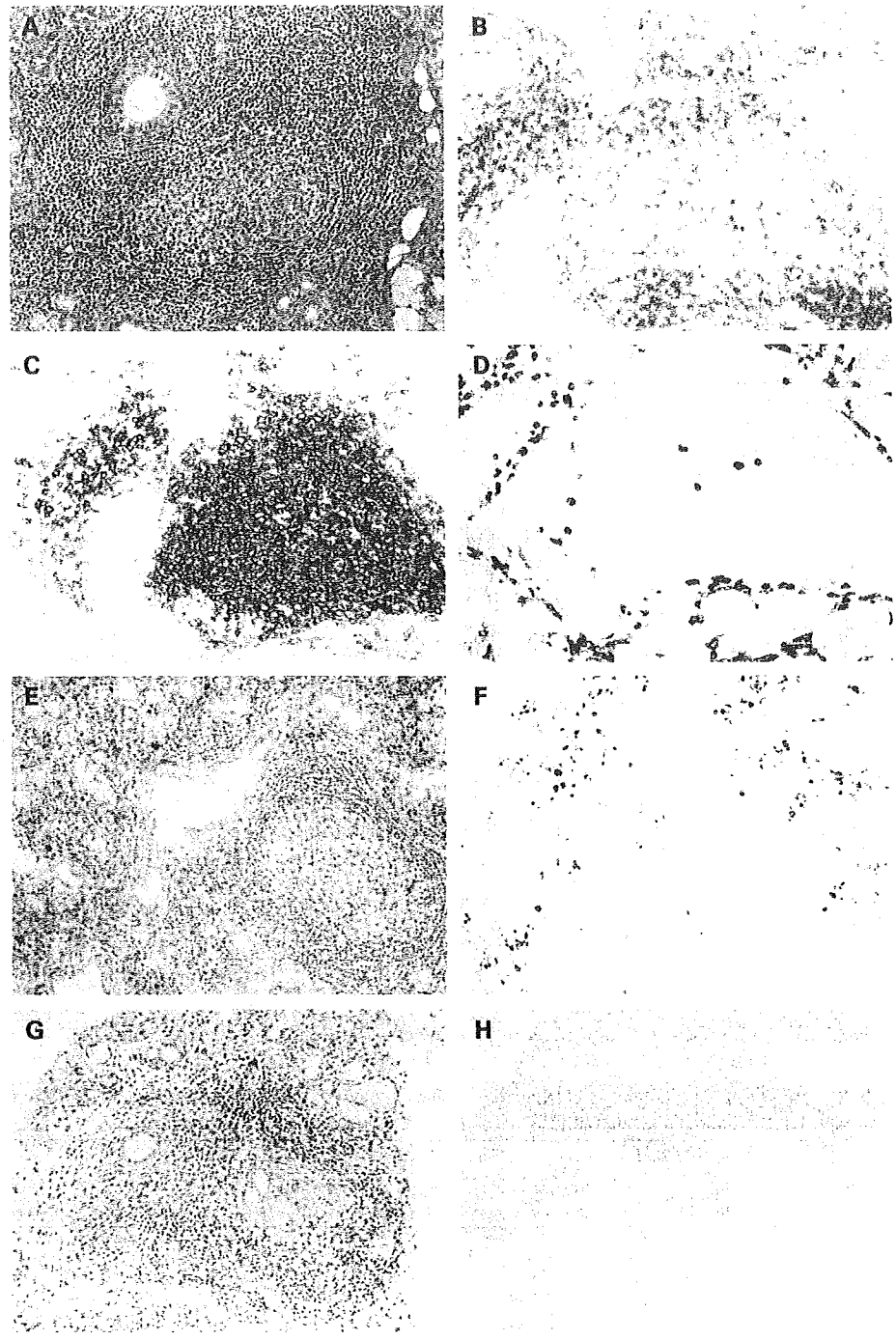

Figure 1 Histopathological findings of labial minor salivary gland biopsy in (A–F) patients with IgG_4+MOLPS/Mikulicz's disease and (G, H) patients with Sjögren's syndrome. (A, G) H&E staining; (B) CD3; (C) CD20; (D) CD38; (E) IgG; (F, H) IgG_4 immunostaining. Massive lymphocyte and plasmacyte infiltration 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

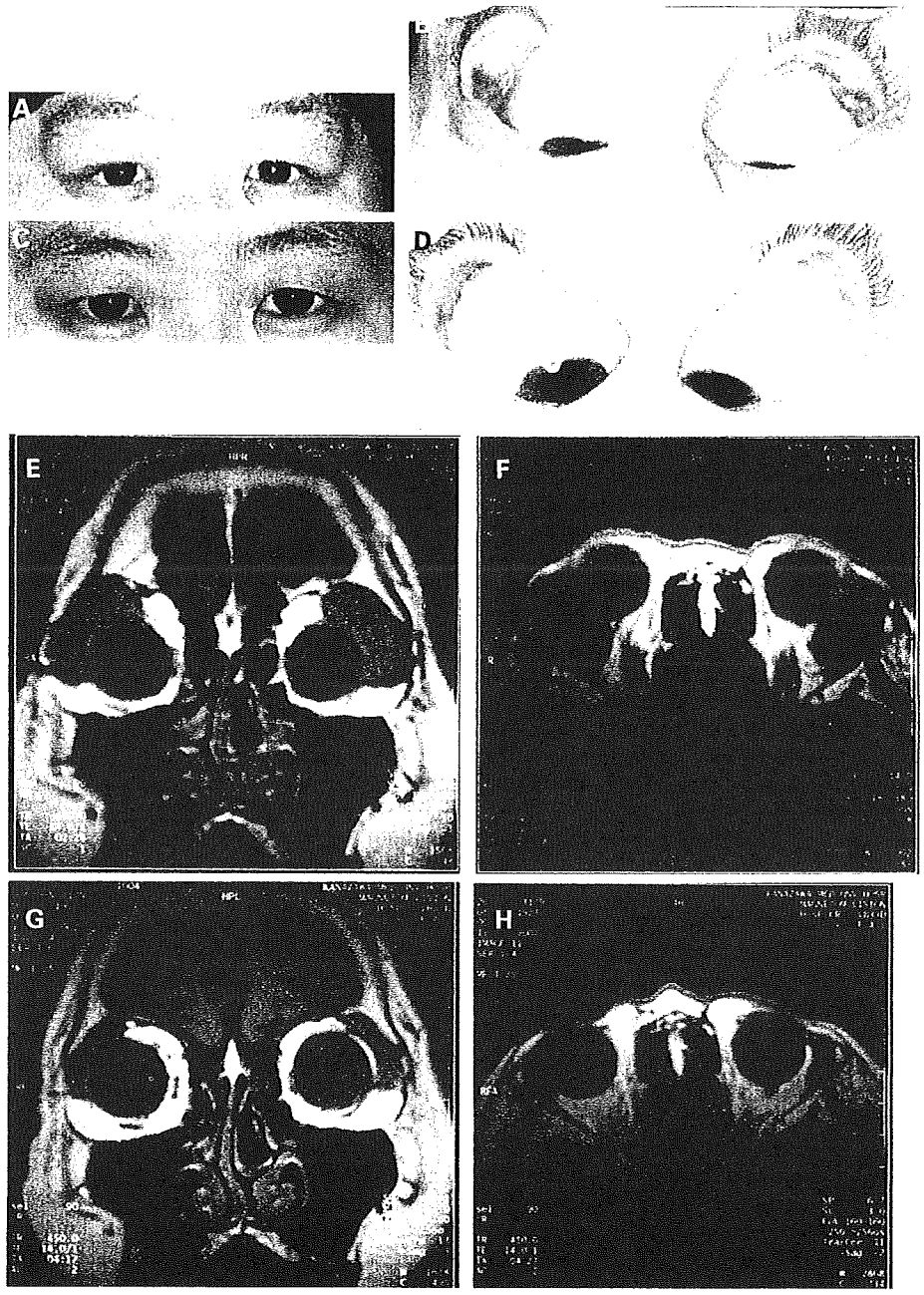

Figure 2 Effect of glucocorticoid therapy on swollen lacrimal glands. (A–D) Photographs of face and eyes. (E–H) MRCT T1 imaging of another patient. (E, G) Frontal cross-section. (F, H) Coronal cross-section. (A, B, E, F) Before treatment, markedly swollen lacrimal glands were seen. (C, D, G, H) After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

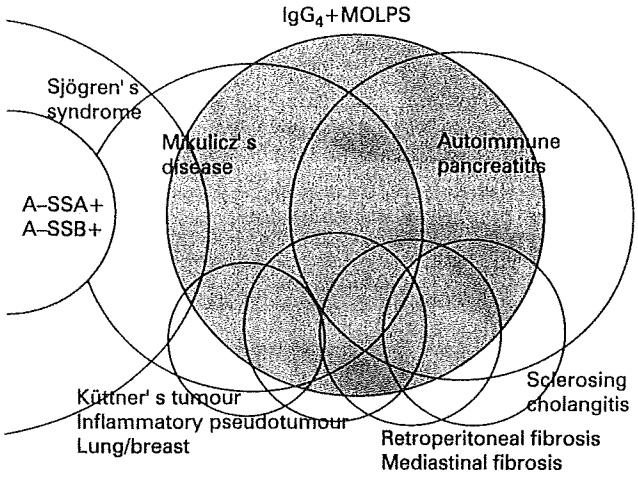

Figure 3 Spectrum of IgG_4+MOLPS. IgG_4+MOLPS included Mikulicz's disease, autoimmune pancreatitis and many other inflammatory conditions. A-SSA, anti-SS-A/Ro antibody; A-SSB, anti-SS-B/La antibody.

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.

Author affiliations: [1] Hematology and Immunology, Kanazawa Medical University, Ishikawa, Japan; [2] Department of Hematology and Immunology, Tongji Hospital, Huazhong University of Science and Technology, Wuhan, Hubei, China; [3] Department of Pathology and Laboratory Medicine, Kanazawa Medical University, Ishikawa, Japan; [4] Department of Ophthalmology, Kanazawa Medical University, Ishikawa, Japan; [5] Department of Epidemiology and Public Health (School of Nursing), Kanazawa Medical University, Ishikawa, Japan; [6] Department of Otolaryngology, Kanazawa Medical University, Ishikawa, Japan; [7] First Department of Internal Medicine, Sapporo Medical University School of Medicine, Hokkaido, Japan; [8] Sapporo Medical University, Hokkaido, Japan; [9] Department of Internal Medicine, Nagaoka Red-Cross Hospital, Niigata, Japan; [10] Department of Ophthalmology, Department of Surgery Related, Kobe University Graduate School of Medicine, Hyogo, Japan; [11] Department of Japanese Oriental Medicine, University of Toyama, Toyama, Japan; [12] First Department of Internal Medicine, University of Toyama, Toyama, Japan; [13] Nagasaki Graduate School of Health Sciences, Nagasaki, Japan; [14] Department of Internal Medicine, Kurashiki Medical Center, Okayama, Japan; [15] Department of Gastroenterology and Hepatology, Kochi Medical School, Kochi, Japan; [16] Division of Rheumatology, Department of Internal Medicine, Kanazawa University, Ishikawa, Japan; [17] Department of Human Pathology, Kanazawa University, Ishikawa, Japan; [18] Department of Internal Medicine, Uwajima Hospital, Ehime, Japan; [19] Department of Hematology and Oncology, Mie University Graduate School of Medicine, Mie, Japan; [20] Department of Ophthalmology, Keio University, Tokyo, Japan; [21] First Department of Internal Medicine, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan

Acknowledgements: We thank the members of the MOLPS/Mikulicz's Disease Society of Japan as follows: T Itho (Nagaoka Red-Cross Hospital); S Ideta (Keio University); Y Sasaki (Tokyo Dental University); K Fujibayashi (Dokkyo Medical University); Y Yamanishi (Hiroshima Citizen Hospital); A Kawakami, H Wada (Nagasaki University); M Uchida (Khochi University); K Nagasawa (Saga University); N Ogawa, K Shimoyama (Hamamatus Medical University); Y Hirose, H Minato, E Kinoshita, H Karasawa, M Miki, H Iwao, A Nakajima, Z-X Jin, C-R Huang, X-P Tong, Y Sun, K Fujimoto (Kanazawa Medical University). This work was supported by grants from the Japanese Ministry of Education, Culture, Sports, Science and Technology (13557160, 15024236, 15390313, 13877075, to Umehara and 17591060 to Masaki), Uehara Memorial Foundation (to Umehara) and Kanazawa Medical University Research Foundation (C2006-1 to Umehara and S2004-16, S2007-5 to Masaki).

Competing interests: None.

Ethics approval: 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.

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 multicentric 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.

総　説

IgG4関連疾患～その診断の混沌，および混沌から抜け出すための提言～

正木康史，梅原久範

IgG4-related disease—the diagnostic confusion and how to avoid it.

Yasufumi MASAKI M.D. and Ph.D. and Hisanori UMEHARA M.D. and Ph.D.

Kanazawa Medical University

(Received November 4, 2009)

summary

Since Hamano *et al.* have first reported serum IgG4 elevation in sclerosing pancreatitis in 2001, various systemic disorders have been reported to be related to elavated IgG4, and many names have been proposed from the point of view of the systemic condition. Despite similarities in the organs damaged in IgG4-related Mikulicz's disease and Sjögren's syndrome, there are marked clinical and pathological differences between the two entities. IgG4-related Mikulicz's disease and Küttner's tumor are related diseases and complete differentiation is very difficult. The majority of cases diagnosed with autoimmune pancreatitis in Japan are IgG4-related sclerosing pancreatitis, and it should be recognized that this is distinct from the western type. There is a likelihood that cases once diagnose as Castleman's disease that showed good responsiveness to glucocorticoid treatment may have been IgG4-related lymphadenopathy, and should be re-assessed in light of recent findings. Diagnosis of IgG4-related disease is defined by both 1) Elevated serum IgG4 (> 135 mg/dl) and 2) Histopathological features including lymphocyte and IgG4$^+$ plasma cell infiltration (IgG4$^+$ plasma cells/IgG$^+$ plasma cells > 50% on a highly-magnified slide checked in five points), however differential diagnosis from other distinct disorders, such as sarcoidosis, Castleman's disease, Wegener's granulomatosis, lymphoma, cancer, and other existing conditions is necessary. To avoid diagnostic confusion, simpler and more scientific names should be used where disease-specific pathogenesis or markers have been ascertained.

Key words——Mikulicz's disease; Küttner's tumor; autoimmune pancreatitis; Castleman's disease; Sjögren's syndrome

抄　録

IgG4関連疾患は，2001年にHamanoらにより硬化性膵炎における高IgG4血症が報告されてから，全身の多彩な病変におけるIgG4の関与が報告され，全身性疾患であるとの観点から様々な呼称が提案されている．傷害される臓器は類似しているが，Sjögren症候群とIgG4関連Mikulicz病とは異なった疾患概念である．一方，IgG4関連Mikulicz病とKüttner腫瘍とは連続性の病態であり厳密な区別は困難である．本邦の自己免疫性膵炎は多くの症例がIgG4関連硬化性膵炎の病像を呈しており，欧米型のものとは区別して理解する必要がある．かつてCastleman病と診断され，ステロイド治療の反応性が良好であった症例は，IgG4関連のリンパ節症であった可能性も大きい．IgG4関連疾患の診断は，1）高IgG4血症（135 mg/dl以上）と，2）組織のIgG4陽性形質細胞浸潤（強拡大5視野でIgG4$^+$/IgG$^+$が50%以上）に基づくが，ステロイド治療の反応性や臨床経過の異なるCastleman病，Wegener肉芽腫，Sarcoidosis，悪性リンパ腫，がん，その他既知の疾患を除外鑑別する必要がある．今後，疾患概念の確立のために，より一層の症例の集積と解析，および病因に迫る研究が必要である．

I. はじめに

2001年にHamanoらにより硬化性膵炎における高IgG4血症が，New England Journal of Medicine誌に報告されて以来[1]，全身の様々な疾患においてIgG4の関与が報告されている．それらは単独よりも幾つか合併し存在する事が多いため，全身性疾患であるとの観点から様々な呼称が提案されている．1967年にComingsらにより提唱された，multifocal idiopathic fibrosclerosis (MIF) という概念が最も古典的なものである（ただしこの時代にIgG4の関与は勿論知られていない）[2]．その後，KamisawaらによるIgG4-related autoimmune disease[3]あるい

金沢医科大学血液免疫制御学（血液・リウマチ膠原病科）

はIgG4-related sclerosing disease[4]，Yamamotoらによる IgG4-related plasmacytic disease[5] あるいは Systemic IgG4 plasmacytic syndrome（SIPS）[6]，そして我々の提案した IgG4+ multiorgan lymphoproliferative syndrome（IgG4+MOLPS）[7]という呼称がある．しかし，これらは全て同一疾患（あるいは同じ病態）を見ている可能性が高い．

このように様々な疾患名が使われている事がIgG4関連疾患の解明を妨げている一つの原因であろう．現在，厚生労働省科学研究費によるIgG4関連疾患研究班として，診断確立のための研究班（班長；金沢医科大学　梅原久範）と病因病態解明のための研究班（班長；関西医科大学　岡崎和一）の2班による検討が進行中である．将来的には，病名の統一を含めて，IgG4関連疾患の概念，病態把握，診断基準，治療法などについて合同の見解を世界にむけて発信すべきであろう．

II. Sjögren症候群とMikulicz病およびKüttner腫瘍

1892年にJohann Mikuliczにより対称性の涙腺・耳下腺・顎下腺腫脹を来した男性例が報告され[8]，以後このような病態はMikulicz病と呼ばれるようになった．しかし，1953年にMorganとCastlemanにより，18例のMikulicz病症例の検討が行われ，彼らがMikulicz病はSjögren症候群の一亜型にすぎないと結論し[9]，以後は欧米からの英語論文は報告されなくなった．一方，日本ではMikulicz病に対する検討が続けられ，Tsubotaらにより Mikulicz 病では FasL 遺伝子に変異がある事[10]，更にその後 Yamamoto らにより，Mikulicz病も IgG4 関連疾患の一つである事が報告された[11]．単一施設で経験できる症例には限界があるため，2004年9月に「IgG4+MOLPS/Mikulicz病検討会」http://www.kanazawa-med.ac.jp/~hematol/topics4.html を，日本シェーグレン症候群研究会（2009年より日本シェーグレン症候群学会へ名称変更）の一分化会として設立した．

Mikulicz病という病名は，研究者によって様々な使われ方をしており混乱を招いていたため，IgG4関連Mikulicz病については診断基準を提案し，2008年9月の第17回日本シェーグレン症候群研究会で合意を得て承認された（表1）．

Mikulicz病を含むIgG4関連疾患症例を広く全国より後方視的に募り，典型的Sjögren症候群（SS群）との異同を検討した．これまでに，140例を越す症例が登録され，そのうちの110例以上をIgG4+MOLPSと診断した（表2）．その結果，1）IgG4+MOLPSにおいてはアレルギー性鼻炎，硬化性膵炎の合併が典型的SS群に比べ有意に高率に認められた．2）IgG4+MOLPSの殆どが抗SS-A抗体および抗SS-B抗体が陰性であった．RFおよびANA陽性率は典型的SS群に比べ有意に低率であった．3）IgG4+MOLPS群では血清IgG, IgE, IgG2およびIgG4が有意に典型的SS群より高値．血清IgA, IgM, IgG1, IgG3は典型的SS群に比べ有意に低値であった．4）IgG4+MOLPSの組織では著明なリンパ球とIgG4陽性形質細胞浸潤が認められ，リンパ濾胞形成も高率に認めたが，リンパ球に

表1　IgG4関連Mikulicz病診断基準（日本シェーグレン症候群研究会，2008年9月）

（1）涙腺・耳下腺・顎下腺の持続性（3ヶ月以上），対称性に2ペア以上の腫脹を認める．
（2）血清学的に高IgG4血症（135 mg/dl以上）を認める．
（3）涙腺・唾液腺組織に著明なIgG4陽性形質細胞浸潤（強拡大5視野でIgG4+/IgG+が50%以上）を認める．

（1）と，（2）または（3）を満たすものをIgG4関連Mikulicz病とする．全身性IgG4関連疾患の部分症であり，多臓器の病変を伴う事も多い．
鑑別疾患：
Sarcoidosis，Castleman病，Wegener肉芽腫，悪性リンパ腫，癌，その他既知の疾患

表2　IgG4関連多臓器リンパ増殖性症候群（IgG4+MOLPS）の診断基準（案）
（厚生労働科学研究難治性疾患克服研究事業研究奨励分野「新規疾患，IgG4関連多臓器リンパ増殖性疾患（IgG4+MOLPS）の確立のための研究」班（梅原班）

（1）血清学的に高IgG4血症（135 mg/dl以上）を認める．
（2）組織に著明なIgG4陽性形質細胞浸潤（強拡大5視野でIgG4+/IgG+が50%以上）を認める．

- 以上の（1）（2）両方を満たすもので，下記の除外すべき疾患群を除外出来るもの；Castleman病，Wegener肉芽腫，Sarcoidosis，悪性リンパ腫，がん，その他既知の疾患（明らかな自己免疫疾患・膠原病；SLE，ANCA関連血管炎，抗SS-A，抗SS-B抗体陽性のシェーグレン症候群，など）

- （1）（2）片方しか満たさないものは，IgG4+MOLPS疑い症例と表記する．
- （1）（2）を満たし，鑑別疾患を有するものはIgG4+MOLPSとの関連が疑われる○○と表記する．
- IgG4陽性形質細胞の増殖を主体とした多臓器に及ぶリンパ増殖性疾患であり，今までに多くの疾患が報告されている．
例；自己免疫性膵炎，硬化性胆管炎，Mikulicz病，炎症性偽腫瘍（肺，肝，乳腺など），後腹膜線維症，縦隔線維症，Küttner腫瘍，Riedel甲状腺炎，間質性腎炎，自己免疫性下垂体炎，その他（ただし，これらの疾患の全てがIgG4関連ではない）

よる導管への浸潤破壊（リンパ上皮性病変：Lymphepithelial lesion：LEL）は認められなかった．一方，典型的SS群ではリンパ球・形質細胞浸潤が著明な症例でも，IgG4陽性形質細胞は殆ど認められなかった．5）典型的SS群でも，ステロイド治療で若干の治療効果が認められる場合もあるが，その効果は限定的である．一方，IgG4⁺MOLPSは，ステロイド投与が初期には著効するのが特徴である．しかし，漸減すると再燃する傾向もあり，prednisolone 5～10 mg/dayの維持量が必要な症例が多かった．以上より傷害する臓器は類似しているものの，典型的Sjögren症候群とIgG4⁺MOLPSとは異なった疾患であると結論した[7]．

また，片側性の硬化性顎下腺炎であるKüttner腫瘍もIgG4関連疾患である事が判明している[12]．Mikulicz病とKüttner腫瘍の異同に関し，両者はIgG4関連疾患としての唾液腺炎であるという点で共通している．Küttner腫瘍の組織は非常に強い線維性・硬化性病変の中にIgG4陽性形質細胞が認められる．一方，Mikulicz病ではそれほど線維化が強くない事も多いが，両者に厳密な境界を設ける事は出来ず，一連の病態と捉えた方が分かりやすい（図1）．Mikulicz病の組織でも，大唾液腺と口唇小唾液腺では線維化の程度に差があるため，一般に口唇小唾液腺生検で代用し診断されるMikulicz病では線維化が軽く評価されている可能性がある．

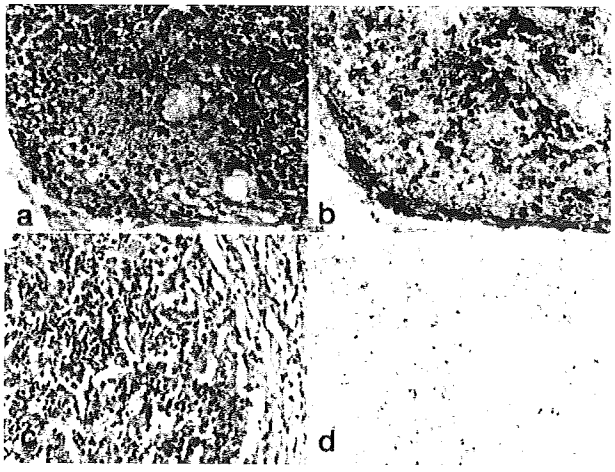

図1 IgG4関連Mikulicz病とKüttner腫瘍
IgG4関連Mikulicz病症例の口唇小唾液腺生検組織（a；HE染色，b；IgG4免疫染色）とIgG4関連Küttner腫瘍症例の顎下腺生検組織（c；HE染色，d；IgG4免疫染色）．Mikulicz病の口唇小唾液腺では線維化よりリンパ球・形質細胞浸潤が目立ち，一方Küttner腫瘍の顎下腺組織では線維化が著明である．しかしこれらは，各々別の疾患というよりは，一連の病態と考えられる．大唾液腺に比べ，口唇小唾液腺では線維化が目立ちづらいだけかもしれない．

さて，Sjögren症候群とIgG4関連疾患の最も根本的な違いは何であろうか．前述のデータの差に加え，Sjögren症候群ではサブクリニカルな症状が前面に出ている症例でも必ず涙腺炎・唾液腺炎が基盤として存在するのに対して，IgG4関連疾患では必ずしも全例が涙腺・唾液腺に病変を有する訳ではなく，一部の涙腺・唾液腺病変を呈した症例がMikulicz病，Küttner腫瘍と診断される事である．

III. 自己免疫性膵炎とIgG4

自己免疫性膵炎の最初の報告例は1961年のフランスのSarlesらによる自己免疫機序によると推測された慢性膵炎10例の報告であるが[13]，全てが今日の自己免疫性膵炎と同じ病態であるかは定かでなく，多様な病態が含まれていたと考えられている．確実な自己免疫性膵炎の報告例は1978年にNakanoらにより報告された症例で，涙腺・唾液腺腫大，膵腫大を呈し，Sjögren症候群に合併した腫瘤形成性膵炎と診断され，ステロイド治療により改善したとされている[14]．自己免疫性膵炎に特徴的な病理所見は1991年にKawaguchiらによりLymphoplasmacytic sclerosing pancreatitis（LPSP）と提唱されている[15]．更に，1995年にYoshidaらによって，高γグロブリン血症，各種自己抗体の存在，膵組織へのリンパ球浸潤，他の自己免疫性疾患の合併，良好なステロイド反応性等より，MacKayの自己免疫性疾患の基準を満たすことから，自己免疫性膵炎の疾患概念が提唱された[16]．その後，2001年にHamanoらによるIgG4上昇の発見があり[1]，本邦の自己免疫性膵炎はIgG4関連疾患と考えられるようになった．

ところが，海外からも自己免疫性膵炎が報告されるようになり，欧米（特にヨーロッパ）の報告例は本邦のものとは臨床像・組織像が異なる事が明らかとなってきた．欧米の自己免疫性膵炎の組織像は，idiopathic duct-centric chronic pancreatitis（IDCP）[17]あるいはautoimmune pancreatitis with granulocytic epithelial lesion（GEL）[18]と呼ばれる，好中球浸潤による病態であり，IgG4関連ではないものが多い．自己免疫性膵炎の診断基準を巡って，世界的な議論が行われているが，IgG4関連のもの（LPSP）と好中球関連のもの（GEL）とを同じ土俵で議論する事には無理があるようにも思われる．

IgG4関連硬化性膵炎の病因について，前述のMacKayの自己免疫性疾患の基準項目に当てはめて

みると，1）高γグロブリン血症，2）組織へのリンパ球浸潤，3）良好なステロイド反応性，の3項目は満たすものの，4）各種自己抗体の存在に関しては，リウマトイド因子や抗核抗体が時に陽性に出ることはあるが頻度は低く，特異的自己抗体も確立されておらず，多クローン性高γグロブリン血症による非特異的陽性の可能性がある，5）他の自己免疫性疾患の合併についても，合併していた疾患はSjögren症候群ではなくMikulicz病である，との根拠より，現時点ではIgG4関連硬化性膵炎が自己免疫性疾患であるとは断定できない．

IV. IgG4関連疾患とCastleman病，Crow-Fukase症候群，Wegener肉芽腫症，Sarcoidosisなど

IgG4関連疾患とMikulicz病，自己免疫性膵炎との関連が議論されつつある中で，リンパ節腫脹を主徴とするIgG4関連疾患の存在[19]が分かり，特に病理医の中で多発性Castleman病との異同が議論されている．欧米の多発性Castleman病症例は，AIDS（HIV感染）に関連して発症する．さらに，HIV陽性Castleman病ではhuman herpesvirus-8（HHV-8）が陽性であり，HIV陰性例でも4割程度にHHV-8が陽性とされている[20]．ところが，本邦で多発性Castleman病として報告されてきた症例の大部分は，HIVもHHV-8も陰性であり，欧米と本邦で報告される多発性Castleman病は異なった疾患の可能性が推察されていた．本邦でCastleman病と診断されていた症例で，ステロイド治療が著効した症例は，今日的な診断としてはIgG4関連疾患の可能性が高く，その目で臨床データおよび病理組織を見直す必要がある．Castleman病ではステロイド治療を行ってもその効果は限定的であり，抗IL-6レセプター抗体tocilizumab（アクテムラ®）の適応であり[21]，両疾患は臨床像として似通った部分はあるものの治療戦略が大きく異なり鑑別診断が重要である．両者とも多クローン性高γグロブリン血症を来し，全身に腫瘤を形成する事が共通している．鑑別点としては，IgG4関連疾患では高IgG4血症と組織IgG4陽性形質細胞増多が主体であり，IL-6も正常値よりは若干上昇している例があるものの[22]，著明上昇例はなく，炎症反応（CRP上昇）や貧血は殆ど目立たない．一方，多発性Castleman病では血清IL-6上昇が著明で，それに伴い著明な炎症反応（CRP上昇，フィブリノーゲン増加），貧血，血小板増多，低アルブミン血症を呈する．ただし，多発性Castleman病でも高IgG4血症や組織IgG4陽性形質細胞増加を認める例も存在するため注意が必要で[23]，上記のIL-6著増に伴う強い炎症性生体反応を呈する例はIgG4関連疾患よりも多発性Castleman病と判断するべきである．

臨床的・病理組織学的に最も鑑別が困難であるのが多発性Castleman病であるが，その他の多クローン性～オリゴクローン性高γグロブリン血症を来す疾患（Crow-Fukase症候群など），Wegener肉芽腫症[24]，Sarcoidosis等においても，高IgG4血症や組織IgG4陽性形質細胞増加を認める報告があり，鑑別が重要である．

V. IgG4関連疾患と悪性リンパ腫および癌

Sjögren症候群では悪性リンパ腫の合併が多い事が知られている．最近の解析によると，6.56倍～18.8倍の標準化発生率があるとされており[25,26]，リンパ球の活性化状態の強い症例にリンパ腫が発症しやすいとされている．一方，IgG4関連疾患における悪性リンパ腫の発症リスクに関しては未だデータがない．しかし，IgG4関連疾患を基盤に悪性リンパ腫を発症したという報告も相次いでおり[27,28]，特に眼窩領域のリンパ腫では，IgG4関連疾患との関連を調べる必要がある．大多数のIgG4関連疾患症例のBリンパ球のクロナリティは多クローン性であるが[29]，Sjögren症候群と同様に病態の遷延および活性化により単クローン性を獲得しうるか否か，興味の持たれるところである．

また，腫瘍細胞の産生するサイトカインにより，多クローン性高γグロブリン血症を呈するタイプのリンパ腫，特に血管免疫芽球性T細胞リンパ腫（angioimmunoblastic T-cell lymphoma；AITL）においても，高IgG4血症や組織IgG4陽性形質細胞増加を呈しうるため，鑑別が重要である．診断困難な症例においてはT細胞レセプターの再構成の有無を確認する必要がある．

IgG4関連疾患における癌の発症リスクに関しては未だデータはない．一方，特に硬化性膵炎の診断においては常に膵臓癌との鑑別が問題となる．近年，固形癌症例でも高IgG4血症や組織IgG4陽性形質細胞増加を認めたとする報告があり[30,31]，IgG4関連疾患の診断とステロイド治療に拘泥し，癌の診断と治療が遅れるというような事態に陥らないようにすべきである．

VI. 人名を冠した病名の功罪～分かりやすい科学的な名称を！～

本稿中には，「Mikulicz 病」「Küttner 腫瘍」「Sjögren 症候群」「Castleman 病」「Crow-Fukase 症候群」「Wegener 肉芽腫症」など過去の偉人の人命を冠した病名が多く登場する．実はこの事が，IgG4 関連疾患およびその周辺疾患との異同を混沌とさせた大きな要因では無かろうか．過去の偉人を敬う気持ちは大切ではあるが，人名を病名として冠すると，後に様々な解釈を生み出し不要な混沌を引き起こす種となる．何故ならば，各々の病名の診断根拠や基準が必ずしも明確ではなく，個々の疾患概念（思い入れ）が研究者毎に異なるためである．論文投稿時にも，著者と査読者間での病名の解釈の差により，互いに余分な労力を浪費する結果となる．

病態が不明な症候群としてしか捉えられない時期には，そのような病名を用いる事も仕方ないが，疾患特異的な病因やマーカーが判明した場合は，それらを組み込んだ病像や病態を表す病名を使用すべきであろう．IgG4 関連疾患の解明に取り組んでいる現在，そのことを切実に感じている．その意味でも，厚生労働科学研究費による 2 つの IgG4 関連疾患研究班が，合同で日本からの統一見解を世界にむけて発信することは，大きな意味をもつと信じている．

文　献

1) Hamano H, et al. : High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med.* **344** : 732–738, 2001.
2) Comings DE, et al. : Familial multifocal fibrosclerosis. Findings suggesting that retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, Riedel's thyroiditis, and pseudotumor of the orbit may be different manifestations of a single disease. *Ann Intern Med.* **66** : 884–892, 1967.
3) Kamisawa T, et al. : A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol.* **38** : 982–984, 2003.
4) Kamisawa T, Okamoto A. : Autoimmune pancreatitis : proposal of IgG4-related sclerosing disease. *J Gastroenterol.* **41** : 613–625, 2006.
5) Yamamoto M, et al. : A case of Mikulicz's disease (IgG4-related plasmacytic disease) complicated by autoimmune hypophysitis. *Scand J Rheumatol.* **35** : 410–411, 2006.
6) 山本元久，ほか：ミクリッツ病と全身性 IgG4 関連疾患—当科における systemic IgG4-related plasmacytic syndrome (SIPS) 40 例の臨床的検討から—日本臨床免疫学会誌 **31** : 1–8, 2008.
7) Masaki Y, et al. : Proposal for a new clinical entity, IgG4-positive multi-organ lymphoproliferative syndrome : Analysis of 64 cases of IgG4-related disorders. *Ann Rheum Dis.* **68** : 1310–1315, 2009 ; published online 13 Aug 2008 doi : 10.1136/ard.2008.089169.
8) Mikulicz J. : Uber Eine Eigenartige Symmetrishe Erkrankung Der Tranen Und Mundspeicheldrusen. Stuttgart : Beitr.z.Chir. Fesrschr.f. Theodor Billroth, pp. 610–30, 1892. in German.
9) Morgan WS, Castleman B. : A clinicopathologic study of Mikulicz's disease. *Am J Pathol.* **29** : 471–503, 1953.
10) Tsubota K, et al. : 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.* **129** : 177–182, 2002.
11) Yamamoto M, et al. : Elevated IgG4 concentrations in serum of patients with Mikulicz's disease. *Scand J Rhumatol.* **33** : 432–433, 2004.
12) Kitagawa S, et al. : Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Küttner's tumor). *Am J Surg Pathol.* **29** : 783–791, 2005.
13) Sarles H, et al. : Chronic inflammatory sclerosis of the pancreas—an autonomous pancreatic disease? *Am J Dig Dis.* **6** : 688–698, 1961.
14) Nakano S, et al. : Vanishing tumor of the abdomen in patient with Sjoegren's syndrome. *Digestive Disease.* 23 : 75–79, 1978 (Supplement).
15) Kawaguchi K, et al. : Lymphoplasmacytic sclerosing pancreatitis with cholangitis : a variant of primary sclerosing cholangitis extensively involving pancreas. *Hum Pathol.* **22** : 387–395, 1991.
16) Yoshida K, et al. : Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. *Dig Dis Sci.* **40** : 1561–1568, 1995.
17) Notohara K, et al. : Idiopathhic chronic pancreatitis with periductal lymphoplasmacytic infiltration : clinicopathologic features of 35

cases. *Am J Surg Pathol.* **27** : 1119–1127, 2003.
18) Zamboni G, et al. : Histopathological features of diagnostic and clinical relevance in autoimmune pancreatitis : a study on 53 resection specimens and 9 biopsy specimens. *Virchows Arch.* **445** : 552–563, 2004.
19) Cheuk W, et al. : Lymphadenopathy of IgG4–related sclerosing disease. *Am J Surg Pathol.* **32** : 671–681, 2008.
20) Soulier J, et al. : Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's dsease. *Blood.* **86** : 1276–1280, 1995.
21) Nishimoto N, et al. : Humamized anti-interleukin–6 receptor antibody treatment of multicentric Castleman disease. *Blood.* **106** : 2627–2632, 2005.
22) Yamamoto M, et al. : The analysis of interleukin–6 in patients with systemic IgG4–related plasmacytic syndrome-expansion of SIPS to the territory of Castleman's disease. *Rheumatology (Oxford).* **48** : 860–2,2009.
23) Ishida F, et al. : Elevated IgG4 levels in a case with mlticentric Castleman's disease. *Br J Haematol.* **99** : 981–982, 1997.
24) Brouwer E, et al. : Predominance of IgG1 and IgG4 subclass of anti-neutrophil cytoplasmic autoantibodies (ANCA) in patients with Wegener's granulomatosis and clinically related disorders. *Clin Exp Immunol.* **83** : 379–386, 1991.
25) Ekström Smedby K, et al. : Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes : a pooled analysis within the InterLymph Consortium. *Blood.* **111** : 4029–4038, 2008.
26) Zintzaras E, et al. : The risk of lymphoma development in autoimmune diseases : a meta-analysis. *Arch Intern Med.* **165** : 2337–2344, 2005.
27) Cheuk W, et al. : Ocular adnexal lymphoma associated with IgG4$^+$ chronic sclerosing dacryoadenitis : a previously underscribed complication of IgG4–related sclerosing disease. *Am J Surg Pathol.* **32** : 1159–1167, 2008.
28) Sato Y, et al. : Ocular adnexal IgG4–related disease has uniform clinicopathology. *Pathol Int.* **58** : 465–470, 2008.
29) Yamada K, et al. : Clonal relationship between infiltrating immunoglobulin G4 (IgG4)–positive plasma cells in lacrimal glands and circulating IgG4–positive lymphocytes in Mikulicz's disease. *Clin Exp Immunol.* **152** : 432–439, 2008.
30) Oh HC, et al. : Early bile duct cancer in a background of sclerosing cholangitis and autoimmune pancreatitis. *Intern Med.* **47** : 2025–2028, 2008.
31) Kamisawa T, et al. : Pancreatic cancer with a serum IgG4 concentration. *World J Gastroenterol.* **12** : 6225–6228, 2006.

Mod Rheumatol (2009) 19:87–90
DOI 10.1007/s10165-008-0127-z

CASE REPORT

A case of immunoglobulin G4-related chronic sclerosing sialadenitis and dacryoadenitis associated with tuberculosis

Mitsuhiro Kawano · Kazunori Yamada · Yasushi Kakuchi · Kiyoaki Ito · Ryoko Hamano · Hiroshi Fujii · Ryo Inoue · Masami Matsumura · Masayuki Takahira · Yoh Zen · Akihiro Yachie · Akikatsu Nakashima · Masakazu Yamagishi

Received: 9 May 2008 / Accepted: 11 August 2008 / Published online: 15 October 2008

Abstract We describe a 64-year-old woman with chronic sclerosing sialadenitis and dacryoadenitis, which developed during treatment for cervical lymph node tuberculosis. Anti-tuberculosis treatment did not improve the swelling in the lacrimal and submandibular glands, and a biopsy specimen of the lacrimal gland showed inflammation, with abundant lymphoid follicles with fibrosis and granuloma without caseous necrosis. Immunohistological examination of a repeat biopsy specimen showed abundant immunoglobulin (Ig) G4-positive plasma cell infiltration. Corticosteroid therapy improved the salivary gland swelling without reactivation of the tuberculosis. This case suggests that an abnormal immunological reaction to tuberculosis may be one of the etiological candidates for IgG4-related disease.

Keywords Immunoglobulin G4 (IgG4) · Mikulicz's syndrome · Sclerosing dacryoadenitis · Sclerosing sialadenitis · Tuberculosis

M. Kawano (✉) · K. Yamada · Y. Kakuchi · K. Ito · R. Hamano · H. Fujii · R. Inoue · M. Matsumura · M. Yamagishi
Division of Rheumatology, Department of Internal Medicine, Graduate School of Medical Science, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan
e-mail: mk0920@mac.com

M. Takahira
Department of Ophthalmology, Graduate School of Medical Science, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan

Y. Zen
Department of Human Pathology, Graduate School of Medical Science, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan

A. Yachie
Department of Pediatrics, Graduate School of Medical Science, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan

A. Nakashima
Department of Internal Medicine, Saiseikai Kanazawa Hospital, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan

Introduction

Mikulicz's disease (MD) is a chronic inflammatory disorder of unknown etiology [1]. For many years, MD and Sjögren's syndrome had been considered to be the same clinical entity [2]. However, recent advances have revealed that these two disorders are histopathologically extremely different with respect to immunoglobulin G4 (IgG4) involvement [3].

Mikulicz's original patient had symmetrical swelling of the lacrimal, parotid, and submandibular glands [1], and recently proposed diagnostic criteria for MD include bilateral swelling of the lacrimal and salivary glands [3]. However, Morgan reported that more MD cases were confined to the salivary glands in the absence of lacrimal gland swelling, and slightly more than half of cases showed unilateral involvement [4]. In this respect, IgG4-related chronic sclerosing sialadenitis [5] and/or dacryoadenitis [6] encompasses a wider disease spectrum than Yamamoto's criteria for MD, with the former including the latter.

Recently, many inflammatory conditions have been reported to have common histological features of abundant IgG4-positive plasma cell infiltration with fibrosis, and the concept of IgG4-related disease was proposed [5–8].

In this report, we describe a case of IgG4-related chronic sclerosing sialadenitis and dacryoadenitis possibly

associated with latent or reactivated tuberculosis infection, and we discuss the possible etiological involvement of tuberculosis infection in IgG4-related disease.

Case report

Patient

A 64-year-old woman was admitted to our hospital because of a swelling in her right lacrimal gland. Three years before admission, she had noticed swelling of her right cervical lymph nodes. Cervical ultrasound showed swelling in the right cervical and right supraclavicular lymph nodes and bilateral swelling in the submandibular lymph nodes. In addition, a small swelling in the left cervical lymph nodes was detected. A computed tomography (CT) scan of her chest showed neither lung lesions suggestive of tuberculosis nor hilar or mediastinal lymph node swelling. Histological examination of the right cervical lymph node revealed epitheloid granuloma with multinucleated giant cells and caseation necrosis compatible with tuberculosis. Although *Mycobacterium* spp. were not detected in the lymph nodes, reactivation of latent primary tuberculosis was highly suggested, and anti-tuberculosis therapy with isoniazid, 300 mg/day, rifampicin, 450 mg/day, and ethambutol, 750 mg/day, was started and continued for 8 months. One month after she had started the anti-tuberculosis therapy, the swelling in her right supraclavicular lymph nodes disappeared. Two months later, swelling in the right lacrimal gland appeared. Three months after the initiation of triple therapy for tuberculosis, the size of the left cervical lymph node had increased, in spite of continuing anti-tuberculosis therapy. Nineteen months before entry, a mass in her right lacrimal gland had been resected because of a gradual increase in size. Histological examination revealed that it was not lymphoma but inflammation with abundant lymphoid follicles with fibrosis. There were scattered eosinophils and obliterative phlebitis. Granuloma without caseous necrosis was also noted (Fig. 1). Despite the surgical removal of this mass, the swelling in the right lacrimal gland gradually recurred, and she consulted our hospital for further examination. At the time of her admission, the bilateral submandibular glands were also swollen. Laboratory study revealed a white blood cell count of 4,500/mm^3, with a slightly increased percentage of eosinophils (7.9%), a platelet count of 189,000/mm^3, and a hemoglobin value of 13.9 g/dl. C-reactive protein (CRP) level was 0.1 mg/dl, and erythrocyte sedimentation rate was 8 mm/h. Findings for rheumatoid factor, anti-nuclear antibodies, anti-Sjögren's syndrome A (anti-SSA) antibodies and anti-Sjögren's syndrome B (anti-SSB) antibodies were all negative. Serum IgG level was 1,820 mg/dl, including 486 mg/dl of IgG4 (26.7% of IgG), IgA 221 mg/dl, IgM 59 mg/dl, and IgE 90 U/ml. Tuberculin skin test result was positive, and result of QuantiFERON®-TB gold test (Cellestis Ltd., Australia) was also positive, with 8 IU/ml of interferon gamma (IFN-γ) response to the early secreted antigenic target 6 kDa (ESAT-6) protein. However, findings from repeated smears and cultures for *Mycobacterium* spp. and the polymerase chain reaction (PCR) test for tuberculosis were all negative. To clarify whether the lacrimal gland swelling was related to tuberculosis, we repeated the biopsy of the right lacrimal gland. Histological examination showed severe lymphoplasmacytic infiltrates with fibrosis composed of abundant IgG4-positive plasma cells (Fig. 2). No granuloma was detected. These findings were compatible with IgG4-related chronic sclerosing sialadenitis and dacryoadenitis, and administration of 30 mg/day of corticosteroid was started.

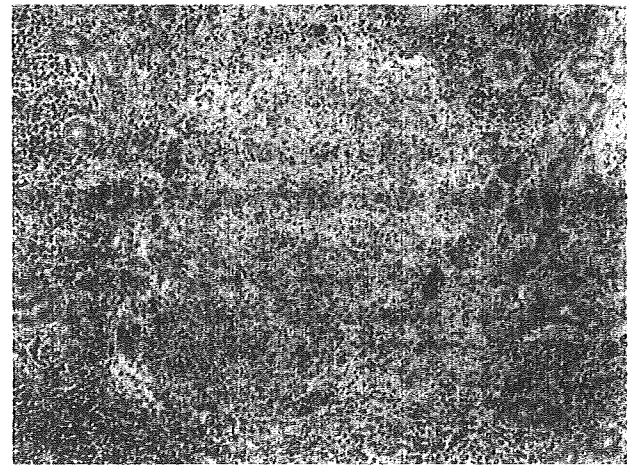

Fig. 1 A biopsy specimen from the right lacrimal gland. Granuloma without caseous necrosis is noted. Hematoxylin and eosin (H&E) ×100

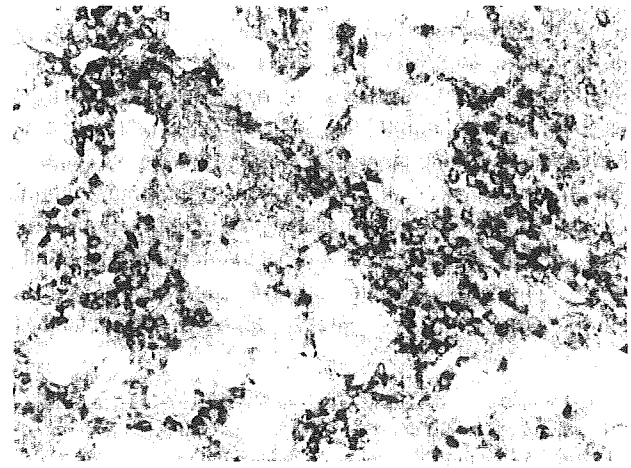

Fig. 2 IgG4 Immunostaining of biopsy specimen from right lacrimal gland. Abundant IgG4-positive plasma cells have infiltrated around the lacrimal glands. ×200

Isoniazid was also administered, for tuberculosis prophylaxis, and the bilateral swelling in the submandibular gland decreased without reactivation of tuberculosis.

Discussion

In this report we have described a case of IgG4-related chronic sclerosing sialadenitis and dacryoadenitis with increased serum IgG4 levels, in which latent or reactivated tuberculosis infection was highly suggested.

Our case did not fulfill the criteria for MD, proposed by Yamamoto et al., i.e., (1) persistent (for more than 3 months) symmetrical swelling of more than two lacrimal and major salivary glands; (2) prominent mononuclear infiltration of lacrimal and salivary glands; and (3) exclusion of other diseases presenting glandular swelling, such as sarcoidosis and lymphoproliferative disease [3], because our patient had only unilateral swelling in the lacrimal gland and bilateral swelling of the submandibular glands. However, Morgan reported that more MD cases were confined to the salivary glands in the absence of lacrimal gland swelling, and slightly more than half of cases showed unilateral involvement [4]. Thus, although our case did not strictly fulfill the diagnostic criteria of Yamamoto et al., it did meet those of Morgan.

Histological analysis of a lacrimal gland revealed IgG4 producing plasma cell infiltration with fibrosis and partial granuloma formation with giant cells. In addition, reactivation of latent tuberculosis infection was highly suggested, because histological analysis of the cervical lymph node had revealed granuloma with caseation necrosis. Decreased size of the supraclavicular lymph node after anti-tuberculosis therapy also supported reactivation of tuberculosis. Several reports are available about lacrimal gland granuloma in patients with sarcoidosis [9] or Crohn's disease [10]. Tuberculous dacryoadenitis is also known as a disease with lacrimal gland granuloma, though it is a very rare condition [11]. However, granuloma has not been reported in MD. In our case, neither sarcoidosis nor Crohn's disease was detected. These findings suggest that some relationship might have existed between lacrimal gland inflammation with IgG4-positive plasma cell infiltration and tuberculosis in this patient.

After the original description of MD, many cases of enlargement of the lacrimal or salivary glands resembling MD were accumulated. However, while the etiology of MD remains unknown, it had been recognized that many systemic diseases such as leukemia, lymphoma, sarcoidosis, and tuberculosis can also induce similar bilateral swelling of the lacrimal and salivary glands, and systemic disease associated with MD-like symptoms were separated as 'Mikulicz's syndrome' [12]. In this respect, our case might be considered as Mikulicz's syndrome associated with tuberculosis. The relationship between Mikulicz's syndrome associated with tuberculosis and tuberculous dacryoadenitis is not well recognized, and tuberculous dacryoadenitis is usually unilateral [11]. Although no report is available about the relationship between Mikulicz's syndrome associated with tuberculosis and IgG4, our case suggests that tuberculosis-associated Mikulicz's syndrome shares the same immunopathological findings with MD.

In association with host defenses against tuberculosis, activation of T helper (Th)1 cells and production of Th1-associated cytokines, such as IFN-γ and interleukin-12 (IL-12), are critical [13]. However, recent reports suggest that Th2 activation may also be elicited by tuberculosis, resulting in increased IgE production [14]. In particular, the fact that successful treatment for tuberculosis reduces serum IgE concentration [15] supports this hypothesis. IgG4 is also produced under the condition of Th2 activation [16]. The underlying mechanism in our case can be explained by latent or reactivated tuberculosis inducing Th2 activation, resulting in IgG4-related MD.

Although the clinical entity of IgG4-related disease is widely accepted now, and many cases have been accumulated [5–8], the etiology of IgG4-related disease is still unknown. In our case, the clinical and histological features were those of typical IgG4-related disease, while the strong T cell response to the mycobacterial antigen, ESAT-6, shows that this patient was in an immunologically active state against *M. tuberculosis*. In addition, granuloma was not only detected in the cervical lymph node but also in the lacrimal gland, where IgG4-positive plasma cell infiltration was noted. These findings suggest a causal link between IgG4-related disease and tuberculosis as a possible pathogen that can induce IgG4-related disease through an allergic mechanism. Further analyses of a larger number of cases are needed to clarify whether tuberculosis plays a significant pathogenetic role in IgG4-related disease.

Acknowledgments We would like to thank John Gelblum for his critical reading of the manuscript. This article does not contributes to any conflict of interest.

References

1. Mikulicz. Uber eine eigenartige symmetrische erkrankung der tranen und mundspeicheldrusen. Beitr Chir Fortsch Gewidmet Theodor Billroth. 1892; 610–30.
2. Morgan WS, Castleman B. A clinicopathologic study of Mikulicz's disease. Am J Pathol. 1953;29:471–503.
3. Yamamoto M, Harada S, Ohara M, Suzuki C, Naishiro Y, Yamamoto H, et al. Clinical and pathological differences between Mikulicz's disease and Sjögren's syndrome. Rheumatology (Oxford). 2005;44:227–34.
4. Morgan WS. The probable systemic nature of Mikulicz's disease and its relation to Sjögren's syndrome. New Engl J Med. 1954; 251:5–10.

5. Kitagawa S, Zen Y, Harada K, Sasaki M, Sato Y, Minato H, et al. Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Kuttner's tumor). Am J Surg Pathol. 2005;29:783–91.
6. Takahira M, Kawano M, Zen Y, Minato H, Yamada K, Sugiyama K. IgG4-related chronic sclerosing dacryoadenitis. Arch Ophthalmol. 2007;125:1572–4.
7. Hamano H, Kawa S, Ochi Y, Unno H, Shiba N, Wajiki M, et al. Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. Lancet. 2002;359:1403–4.
8. 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.
9. Nowinski T, Flanagan J, Ruchman M. Lacrimal gland enlargement in familial sarcoidosis. Ophthalmology. 1983;90:909–13.
10. Hwang IP, Jordan DR, Acharya V. Lacrimal gland inflammation as the presenting sign of Crohn's disease. Can J Ophthalmol. 2001;36:212–3.
11. van Assen S, Lutterman JA. Tuberculous dacryoadenitis: a rare manifestation of tuberculosis. Neth J Med. 2002;60:327–9.
12. Schaffer J. Mikulicz's syndrome: a report of ten cases. Am J Dis Child. 1927;34:327–46.
13. Dieli F, Singh M, Spallek R, Romano A, Titone L, Sireci G, et al. Change of Th0 to Th1 cell-cytokine profile following tuberculosis chemotherapy. Scand J Immunol. 2000;52:96–102.
14. Ohrui T, Zayasu K, Sato E, Matsui T, Sekizawa K, Sasaki H. Pulmonary tuberculosis and serum IgE. Clin Exp Immunol. 2000;122:13–5.
15. Adams JF, Scholvinck EH, Gie RP, Potter PC, Beyers N, Beyers AD. Decline in total serum IgE after treatment for tuberculosis. Lancet. 1999;353:2030–3.
16. Zen Y, Fujii T, Harada K, Kawano M, Yamada K, Takahira M, et al. Th2 and regulatory immune reactions are increased in immunoglobin G4-related sclerosing pancreatitis and cholangitis. Hepatology. 2007;45:1538–46.

病気のはなし

全身性IgG4関連疾患

山本元久　鈴木知佐子　高橋裕樹　篠村恭久

検査と技術
第37巻　第7号　別刷
2009年7月1日　発行

医学書院

病気のはなし

全身性 IgG4 関連疾患

山本元久(やまもともとひさ)*1・鈴木知佐子(すずきちさこ)*2・高橋裕樹(たかはしひろき)*3・篠村恭久(しのむらやすひさ)*4

サマリー

全身性 IgG4 関連疾患(systemic IgG4-related plasmacytic syndrome, SIPS)は，高 IgG4 血症と病変腺組織中の著明な IgG4 陽性形質細胞浸潤を特徴とする全身性の慢性疾患である(図 1)．涙腺，唾液腺，甲状腺，肺，膵臓，腎臓，前立腺などが炎症の標的とされうる．硬化性病変・腫瘤形成性病変による機能障害を呈することがあり，多くはステロイド剤が奏効する．従来のミクリッツ病(Mikulicz's disease)，キュットナー腫瘍(Küttner's tumor)，自己免疫性膵炎，間質性腎炎の一部などがこれに包括されると考えられ，各領域において疾患の定義およびカテゴリーの見直しが始まっている．

用語解説

IgG4(immunoglobulin G4)

IgG には IgG1～4 の四つのサブクラスが存在し，IgG4 はその分画の一つである．分子量は 146 kDa，半減期は約 21 日とほかの分画と差はないが，通常 IgG4 は補体活性化能をもたない．健常人における IgG4 の全 IgG に占める割合は 4%前後であり，血清中の IgG 分画のなかでは最も少ない．これまでに IgG4 が高値をとる疾患として知られているのは，一部のアレルギー疾患や寄生虫感染，尋常性天疱瘡や水疱性類天疱瘡などに限られている．IgG4 の生理的役割に関してはまだ不明な点が多いが，アレルギー性疾患では遮断抗体として作用することがいわれており，抗炎症的な機能を有すると推測される．

リンパ増殖性疾患

自己免疫疾患の一つであるシェーグレン症候群(Sjögren's syndrome)や，ヘリコバクター・ピロリ菌感染時に発生するリンパ腫のように，慢性の抗原刺激により B リンパ球が増殖している病態を指す．最初は，多クローン性の増殖(良性)にとどまっているが，さらになんらかの要因が加わると，その一部が単クローン性増殖(悪性)に変わり，リンパ腫が発生する．炎症性偽腫瘍や反応性リンパ球増殖症といった偽リンパ腫は，この多クローン性増殖の段階である．

シェーグレン症候群

1933 年にスウェーデンの眼科医 Henrik Sjögren が報告した原因不明の慢性に経過する自己免疫性外分泌腺炎である．自己免疫機序による涙腺と唾液腺の組織破壊によって各分泌能の低下をきたし，臨床的に乾燥性角結膜炎と口腔乾燥症状を呈する．一過性の涙腺や唾液腺腫脹を認めることがあるが自然に軽快する．間質性肺炎や腎炎などの臓器障害を伴うことがあるため全身性疾患として認識されている．血液検査では高ガンマグロブリン血症，抗核抗体陽性を示し，なかでも疾患特異的な抗 SS-A 抗体が約 7 割で陽性となる．近年，SIPS の涙腺・唾液腺病変であるミクリッツ病との鑑別が問題となっている．

病　因

全身性 IgG4 関連疾患(SIPS)は，高 IgG4 血症と病変腺組織中の著明な IgG4 陽性形質細胞浸潤を特徴とする慢性疾患である．ミクリッツ病(涙腺・唾液腺病変)，リーデル甲状腺炎(Riedel thyroiditis)，間質性肺炎，自己免疫性膵炎，一部の間質性腎炎および糸球体腎炎，慢性前立腺炎などがこの疾患群に包括されると考えられているが，病因については現時点では不明である．気管支喘息，アレルギー性鼻炎，アレルギー性結膜炎などの既往を有する症例が多く，かつ IgG4 自体がアレルギーの病態に関与していることが推察されていることから，この疾患群ではアレルギー性

*1 札幌医科大学医学部内科学第一講座・助教　〒060-8543 札幌市中央区南 1 条西 16-291
*2 同・診療医　*3 同・准教授　*4 同・教授