IgG4 梅原班フォースミーティング病理中央診断会議事録

症例１（筑波大前方視-2）47 歳、女性：両側涙腺腫脹、頸部・耳下腺内・左乳房内リンパ節腫大。血清 IgG 1363, IgG4 202。アレルギー性鼻炎、気管支喘息、蕁麻疹あり。涙腺生検組織では、比較的限局した病変ながら、胚中心の過形成が特徴的であり、IgG4+/IgG+=62%。導管は保たれている（LEL 無し）。IgG4 関連涙腺炎と診断し、前方視治療研究に登録の上で、PSL30mg/day より治療開始、経過良好。

症例２（長崎大前方視-1）67 歳、男性：右側眼窩腫大（眼窩偽腫瘍）、両耳下腺部腫脹、アレルギー性鼻炎あり。血清 IgG 2601, IgG4 539, IgE 759.3, WBC 6200 (Eos 15%), sIL2R 914, IL6 2.2。偏側性ではあるが、組織学的には典型例で IgG4+/IgG+は 50%以上。どこから発生して広がっていったかは議論があったが、涙腺から眼窩内へ波及していった可能性。

症例３（神戸海星病院非登録症例）81 歳、男性。13 年前左眼瞼腫瘍、病理未染やブロックが残存していないため現状ではこれ以上検索できないが、HE では IgG4 関連疾患の可能性が高い(サザンではオリゴの薄いバンドあり)。今回 2010 年右上眼瞼鼻側に腫瘍、IgG 2396, IgG4 691, 今回の組織は CD20 陽性の単調な細胞がびまん性に増殖しており、λ＞κで偏りも明確、サザンでも以前のものと別な濃いバンドがあり、MALT リンパ腫。リンパ腫細胞が IgG4 産生細胞から出てきたかどうかは、λと IgG4 の二重染色を行えば判定できる。

症例４（産業医大前方視-1）37 歳、男性。2010 年５月より蕁麻疹、炎症反応上昇（CRP 4.81)、高ガンマグロブリン血症、他院のリンパ節生検で idiopathic plasmacytic lymphadenopathy。IgG 2668, IgG4 171, IgE 925, IL6 6.5. sIL2R 729, 再度施行したリンパ節生検では IgG4+/IgG+細胞比率は最大でも 20%以下。胚中心は萎縮しており、IgG4 関連疾患は否定的。しかし、Multicentric Castleman disease (MCD)の典型例では形質細胞がシート上に増殖するが、本例では形質細胞はパラパラと存在し典型的ではない。病理組織からは何らかの自己免疫疾患に伴うリンパ節腫脹が最も疑わしい。しかし、臨床的には、二重鎖 DNA 抗体が陽性ではあるものの SLE その他典型的な膠原病／自己免疫性疾

患とは言い難い。本例は MCD の診断のもとでトシリズマブが投与され、治療効果良好との事。

症例５（金沢医大前方視-18）60 歳、女性。両側顎下部腫瘤で受診。他に両側涙腺腫脹、深頸部リンパ節腫大、両側下腿に網状皮斑。PET では両顎下腺（SUV8.0）と膵尾部腫瘤（SUV7.18）あり。IgG 1150, IgG4 110, IL6 1.1, sIL2R 649。病変分布は IgG4 関連疾患として典型的だが、血清 IgG4 が基準値を満たしていない例。顎下腺生検での病理診断は IgG4 関連疾患の典型像。下肢の皮膚生検は真皮の深い部位にフィブリノイド壊死を伴う血管炎であり、この病変は IgG4 と別であろう。膵臓は生検を拒否されたため、PSL 治療開始し顎下腺ならびに膵尾部腫瘤は著明に縮小。ステロイド反応が悪ければ、開腹での膵臓の手術も必要であったが、ステロイド反応良好であり、一元的に顎下腺と膵尾部腫瘤は IgG4 関連疾患と判断。

以上、典型例の診断は容易ですが、他の疾患を合併したり非典型的な所見が目立つ場合には、より慎重な診断が必要です。

X. 研究成果の刊行物・別刷

Review

IgG4-related Diseases Including Mikulicz's Disease and Sclerosing Pancreatitis: Diagnostic Insights

YASUFUMI MASAKI, SUSUMU SUGAI, and HISANORI UMEHARA

ABSTRACT. Since the first report of serum IgG4 elevation in sclerosing pancreatitis in 2001, various systemic disorders have been reported to elevate IgG4, and many names have been proposed from the perspective 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 2 entities. 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. Diagnosis of IgG4-related disease is defined by both elevated serum IgG4 (> 1.35 g/l) and histopathological features, including lymphocyte and IgG4+ plasma cell infiltration (IgG4+ plasma cells/IgG+ plasma cells > 50% on a highly magnified slide checked at 5 points). Differential diagnosis from other distinct disorders is necessary: these include sarcoidosis, Castleman's disease, Wegener's granulomatosis, lymphoma, cancer, and other existing conditions. The Japanese IgG4 research group has begun multicenter prospective studies to improve diagnostic criteria and treatment strategies. (First Release May 1 2010; J Rheumatol 2010;37:1380–5; doi:10.3899/jrheum.091153)

Key Indexing Terms:
MIKULICZ'S DISEASE SJÖGREN'S SYNDROME AUTOIMMUNE PANCREATITIS
GLUCOCORTICOID IgG4-RELATED DISEASES

Mikulicz's disease (MD) was first described in 1892 in a man with symmetrical swelling of the lacrimal, submandibular, and parotid glands[1]. Morgan, *et al* reported 18 cases of MD and concluded that it was not a distinct clinical and pathological disease entity but merely one manifestation of a more generalized symptom complex known as Sjögren's syndrome (SS)[2]. With the wide acceptance of the conclusions of Morgan, *et al* there have been few reports of MD in Western countries. However, many cases of MD have been reported in Japan, and there has been considerable discussion regarding the differences between MD and SS[3-7]. Patients with MD have been reported to have a point mutation in the *FasL* gene, which may account for their mild sicca symptoms despite massive lymphocytic infiltration[3]. Further, high IgG4 concentrations have been reported in the sera of patients with MD[4], suggesting that MD is an IgG4-related disease.

We describe the differences between MD (especially IgG4-related MD) and SS, and refer to other systemic complications of IgG4-related diseases.

Differences between IgG4+ MOLPS and SS. As so-called MD may include various conditions[3-6] and consist of IgG4-related or unrelated subtypes, the IgG4+ multiorgan lymphoproliferative syndrome (MOLPS)/MD research group has established tentative criteria for IgG4+ MD (Table 1).

MATERIALS AND METHODS

We collected data on 64 patients with IgG4+ MOLPS including MD and performed retrospective analysis to clarify the differences between IgG4+ MOLPS and definite SS (Table 2)[7]. Despite similarities in the involved organs, there are marked differences between IgG4+ MOLPS and SS. For example, their sex distributions were quite different. Men with SS were very rare (2 of 31), while almost half (31 of 64) the patients with IgG4+ MOLPS were men.

RESULTS

Significantly fewer patients with IgG4+ MOLPS than with SS showed symptoms of xerostomia, xerophthalmia, and arthralgia. Patients with IgG4+ MOLPS showed significantly lower incidences of rheumatoid factor (RF), antinuclear

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Supported by grants from Intractable Diseases, the Health and Labor Sciences Research Grants from the Ministry of Health, Labor, and Welfare, and the Japanese Ministry of Education, Culture, Sports, Science, and Technology (13557160, 15024236, 15390313, and 13877075 to H. Umehara and 17591060 to Y. Masaki), Umehara Memorial Foundation (to H. Umehara), The Vehicle Racing Commemorative Foundation, and the Kanazawa Medical University Research Foundation (C2009-4 to H. Umehara and S2004-16 and S2007-5 to Y. Masaki).

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Accepted for publication February 8, 2010.

Table 1. Diagnostic criteria of IgG4+ Mikulicz's disease (Japanese Sjögren's Syndrome Society, 2008). Differential diagnosis is necessary from other distinct disorders, including sarcoidosis, Castleman's disease, Wegener's granulomatosis, lymphoma, and cancer. The diagnostic criteria for Sjögren's syndrome (SS) may also include some patients with IgG4+ Mikulicz's disease; however, the clinicopathological conditions of patients with typical SS and IgG4+ Mikulicz's disease are different.

1. Symmetrical swelling of at least 2 pairs of the lacrimal, parotid, or submandibular glands continuing for more than 3 months.

AND

2. Elevated serum IgG4 (> 135 mg/dl), OR
3. Histopathological features including lymphocyte and IgG4+ plasma cell infiltration (IgG4+ plasma cells/IgG+ plasma cells > 50%) with typical tissue fibrosis or sclerosis.

Table 2. Comparison of symptoms, complaints, and laboratory findings in IgG4+ MOLPS and typical SS. Data are percentage (number) unless stated otherwise. Incidence rates (numbers of positive patients) are shown for xerophthalmia, xerostomia, arthralgia, allergic rhinitis, bronchial asthma, sclerosing pancreatitis, interstitial nephritis, interstitial pneumonitis, RF, ANA, A-SSA, A-SSB, and low CH50. Masaki Y, *et al*[7]. Ann Rheum Dis 2009; 68:1310-5. Adapted with permission.

Feature	IgG4+ MOLPS	Typical SS	Japanese, %	p
No. of Patients	64	31		
Xerophthalmia	32.8 (21)	93.5 (29)		< 0.001
Xerostomia	37.5 (24)	87.1 (27)		< 0.001
Arthralgia	15.6 (10)	48.4 (15)		0.001
Allergic rhinitis	40.6 (26)	6.5 (2)	5–10	0.001
Bronchial asthma	14.1 (9)	3.2 (1)	3–5	0.158
Sclerosing pancreatitis	17.2 (11)	0 (0)	< 0.001	0.014
Interstitial nephritis	17.2 (11)	6.5 (2)	< 0.005	0.210
Interstitial pneumonitis	9.4 (6)	32.3 (10)	< 0.005	0.008
RF	26.6 (17)	87.1 (27)		< 0.001
ANA	23.4 (15)	90.3 (28)		< 0.001
A-SSA	1.6 (1)	100 (31)		< 0.001
A-SSB	0 (0)	100 (31)		< 0.001
Low CH50	57.8 (37)	48.4 (15)		0.510
IgG, mg/dl	2960.1 (1.7)	2473.4 (1.4)	870–1700	0.042
IgG1, mg/dl	1155.3 (1.6)	1437.1 (1.5)	320–748	0.039
IgG2, mg/dl	786.5 (1.5)	566.6 (1.6)	208–754	0.001
IgG3, mg/dl	57.6 (2.8)	81.9 (1.8)	6.6–88.3	0.047
IgG4, mg/dl	697.7 (2.6)	23.5 (2.1)	4.8–105	< 0.001
IgA, mg/dl	194.7 (1.80)	389.7 (1.7)	110–410	< 0.001
IgM, mg/dl	63.0 (2.0)	147.3 (1.7)	35–220	< 0.001
IgE, IU/ml	307.4 (4.0)	15.3 (1.4)	< 173	0.005

P values are for comparisons of all IgG4+ MOLPS with typical SS. MOLPS: multiorgan lymphoproliferative syndrome; SS: Sjögren's syndrome; RF: rheumatoid factor; ANA: antinuclear antibody. Japanese: Incidence rates of the entire Japanese study population for allergic rhinitis, bronchial asthma, sclerosing pancreatitis, interstitial nephritis, interstitial pneumonitis, and ranges of normal laboratory values of total IgG, IgG1, IgG2, IgG3, IgG4, IgA, IgM, and IgE. IgE was measured in 50 patients (not all), and IgG1, IgG2, and IgG3 were measured in 58 patients (not all), with IgG4+ MOLPS. Geometric means (geometric SD) are shown for IgG, IgG1, IgG2, IgG3, IgG4, IgE, IgA, and IgM concentrations. Patients with typical SS fulfilled both Japanese[8] and European[9] SS criteria, and were positive for both anti-SSA/Ro and anti-SSB/La antibodies.

antibody (ANA), anti-SSA/Ro antibody, and anti-SSB/La antibody than patients with SS. We found that not only IgG4 but also total IgG, IgG2, and IgE concentrations were significantly higher in patients with IgG4+ MOLPS than in patients with SS[7]. Almost half of patients with IgG4+ MOLPS demonstrated low CH50, which apparently correlated with hyper-IgG (especially IgG1 and IgG2).

Histological specimens from patients with IgG4+ MOLPS showed marked IgG4+ plasma cell infiltration with occasional lymphocyte follicular formation, but without lymphoepithelial lesions (Figure 1)[7]. This may explain the marked glandular swelling without severe dryness in patients with IgG4+ MOLPS. Importantly, treatment with glucocorticoids resulted in marked clinical improvements in almost all patients with IgG4+ MOLPS, while the effects of glucocorticoids on SS were not so dramatic[10].

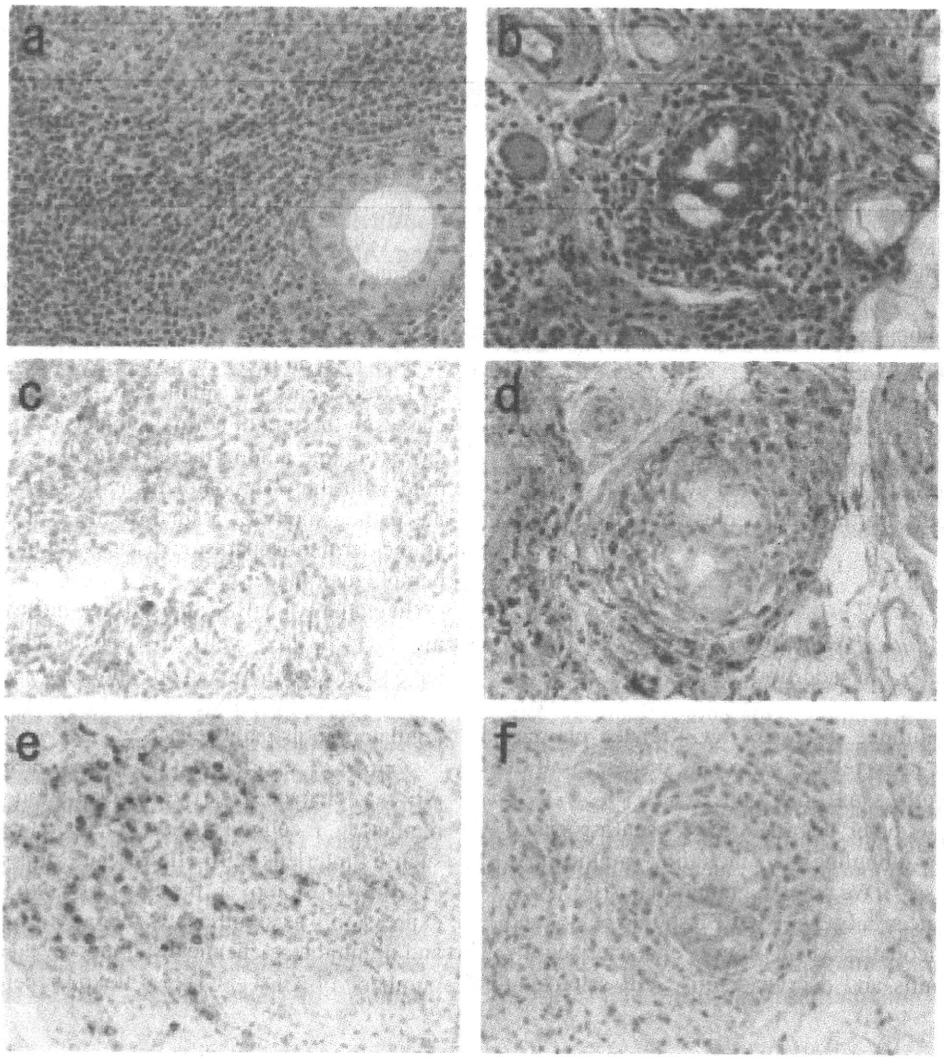

Figure 1. Histopathological findings of labial minor salivary gland biopsy in patients with IgG4+ MOLPS/Mikulicz's disease (a, c, e) and Sjögren's syndrome (b, d, f). (a, b) Hematoxylin and eosin staining; (c, d) IgG immunostaining; (e, f) IgG4 immunostaining. (a) Massive lymphocyte and plasmacyte infiltration and lymphoid follicle formation were seen in IgG4+ MOLPS. The ducts remained clear without lymphocytic infiltration. Both IgG+ and IgG4+ plasma cells were scattered in the periphery of the follicles (c, e). In contrast, there were few or no IgG4+ cells in typical SS (d, f), not even in patients with severe lymphocytic infiltration (b).

Autoimmune pancreatitis and IgG4. Autoimmune pancreatitis (AIP) is a unique form of chronic pancreatitis, first described by Sarles, *et al* in 1961[11] and characterized by infrequent attacks of abdominal pain, jaundice, irregular narrowing of the pancreatic duct, and swelling of the pancreatic parenchyma[11-22]. Kawaguchi, *et al* described cases complicated with similar pathological features in the common bile duct, gall bladder, and minor salivary glands, suggesting a systemic disorder[12]. Yoshida, *et al* described the typical features of AIP as hyper-γ-globulinemia, the presence of autoantibodies (RF and ANA), lymphocytic infiltration of pancreas tissue, coexistence of other manifestations such as sicca complex, and good responsiveness to glucocorticoids[13]. AIP is now known to be associated with types of sialadenitis and cholangitis distinct from SS and primary sclerosing cholangitis.

In 2001, Hamano, *et al* first reported high serum IgG4 concentrations in patients with sclerosing pancreatitis[14]. Further, massive IgG4+ plasmacytic infiltration in the pancreatic tissue was reported[15]. There have been many recent reports of AIP in Asia[12-19] and in Western countries[20,21].

Various diagnostic criteria for AIP have been proposed in Japan[23], Korea[17], and the United States (Mayo Clinic)[21]. In 2008, the Japan-Korea Symposium on AIP proposed Asian diagnostic criteria[19]. Further international criteria are currently under discussion.

IgG4 and other clinical conditions (Figure 2). Hyper-IgG4-γ-globulinemia and IgG4+ plasma cell infiltration with sclerotic lesions, although first reported in patients with sclerosing pancreatitis, have also been reported in patients with many other disorders, including sclerosing cholangitis[15,16]; inflammatory pseudotumors of the lung[24], liver[16], and breast[16,25]; retroperitoneal or mediastinal fibrosis[26]; interstitial nephritis[27]; hypophysitis[5]; sclerosing dacryoadenitis[28]; sialadenitis (MD and Küttner's tumor)[4,5,29]; inflammatory aortic aneurysm[30,31]; tumorous lesions of the coronary artery[31]; lymphadenopathy[32]; and many other inflammatory conditions in multiple organs.

In addition, various systemic involvements have been reported in each disorder. Kawaguchi, *et al*[12] noted the same etiology between autoimmune pancreatitis and multifocal idiopathic fibrosclerosis (MIF) reported by Comings, *et al*[33] because both conditions include occlusive phlebitis and sclerotic lesions.

DISCUSSION

Proposal of a new clinical entity, IgG4+ MOLPS, as a more generalized disorder. In addition to the term "IgG4+ MOLPS," there are many synonyms, such as MIF, IgG4-related autoimmune disease[15], IgG4-related plasmacytic disease[6], and IgG4-related sclerosing disease[18], all of which may refer to the same conditions.

Although various other disorders have been associated with hyper-IgG4-γ-globulinemia, including multicentric Castleman's disease[34], Wegener's granulomatosis[35], lymphoma[36,37], and cancer[38], IgG4+ MOLPS should be defined as a distinct clinicopathological entity, characterized by sclerosing sialadenitis and dacryoadenitis, AIP, sclerosing cholangitis, and other clinical conditions with good response to glucocorticoids.

Hypothetical mechanism of IgG4+ MOLPS. At present, the pathogenesis of IgG4+ MOLPS is not clear. Although some patients are positive for RF and ANA, these incidences are significantly lower than in SS, suggesting that RF and ANA positivity may be due to nonspecific immunoglobulin binding. Although IgG4+ MOLPS is accompanied by various immunological disorders, including AIP, there is little evidence that IgG4+ MOLPS is an autoimmune disorder because of the lack of disease-specific autoantibodies.

The role of IgG4 in IgG4+ MOLPS is still unknown. IgG4 represents the smallest population among IgG subclasses in the sera of normal subjects (3%–6% of total IgG), and is unique among the IgG subclasses in its inability to bind with the C1q complement[39]. IgG4 is associated with the pathogenicity of a small number of disorders, such as atopic dermatitis, parasitic disease, pemphigus vulgaris, and pemphigus foliaceus.

In clonality analysis, most tissue-infiltrating and circulating IgG4-positive cells are polyclonal[40]. These findings have suggested that IgG4 does not play a major pathological role in IgG4+ MOLPS, and that there may be other upstream regulators in its pathogenesis.

Zen, *et al* reported that the pathogenesis of IgG4-related AIP was characterized by the infiltration of T helper 2 and regulatory T cells (Treg), which secrete various cytokines such as interleukin 10 (IL-10) and tumor growth factor-ß (TGF-ß)[41]. Moreover, the level of Foxp3 messenger RNA expression was significantly increased in patients with AIP, and immunohistochemical staining revealed increases in the numbers of CD4+ CD25+ Foxp3+ cells. Treg may be

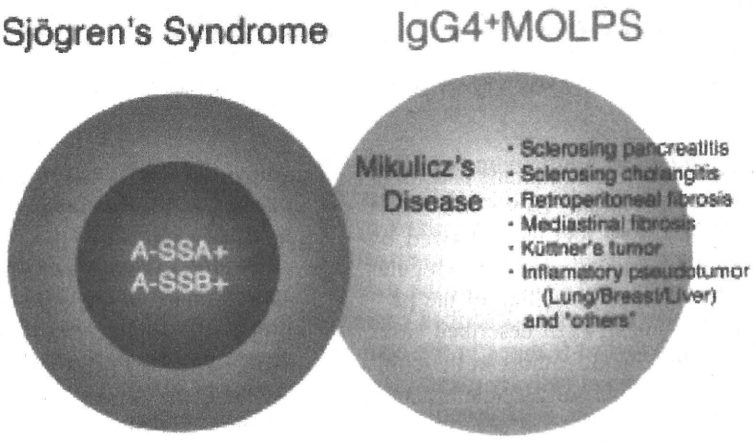

Figure 2. IgG4+ MOLPS should be defined as a distinct clinicopathological entity that includes Mikulicz's disease (MD), autoimmune pancreatitis (AIP), sclerosing cholangitis, and other clinical conditions with good response to glucocorticoids. Although the diagnostic criteria of SS may include some patients with IgG4+ MOLPS/MD, typical SS and IgG4+ MOLPS/MD are different clinical conditions.

involved in the *in situ* production of IL-10 and TGF-ß, which could be followed by IgG4 class switching and fibroplasia[41].

The concentrations of IgG2, IgG4, and IgE have been shown to be significantly higher in patients with IgG4+ MOLPS than in those with typical SS, while the concentrations of IgG1, IgG3, IgA, and IgM were significantly higher in patients with typical SS than in those with IgG4+ MOLPS[7]. The immunoglobulin gene fragments Cμ, Cδ, Cγ3, Cγ1, Cα1, Cγ2, Cγ4, Cε, and Cα2, which encode IgM, IgD, IgG3, IgG1, IgA1, IgG2, IgG4, IgE, and IgA2, respectively, are arranged linearly in this order from upstream to downstream. Gene linkage and different class-switch mechanisms may cause the hyperproduction of the different immunoglobulin subclasses observed in these 2 diseases, which may contribute to the pathophysiology of IgG4+ MOLPS.

Future perspectives. Although IgG4+ MOLPS may be distributed worldwide, this disease entity has not been well recognized to date. Most reports on IgG4-related diseases have been from Japan, while many reports on AIP have come from Western countries, especially the Mayo Clinic[21] in the United States. Therefore, we believe that an international consensus regarding IgG4-related diseases as new clinical entities is required.

In this regard, the Japanese IgG4 research group (Research Committee of Intractable Diseases, Health and Labor Sciences Research Grants, Ministry of Health, Labor and Welfare, Japan) has begun multicenter prospective clinical studies (UMIN: R000002820, R000002823) to formulate better diagnostic criteria, to identify novel diagnostic and prognostic factors, and to design better treatment strategies.

ACKNOWLEDGMENT

We thank all participants in the IgG4+ MOLPS/Mikulicz's Disease Research Group and the researchers of the Autoimmune Pancreatitis Group for critical discussion.

REFERENCES

1. Mikulicz J. Über eine eigenartige symmetrische erkrankung der tränen und mundspeicheldrüsen. Stuttgart: Beitr.z.Chir.Fesrschr.f. 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. 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.
4. 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 Rheumatol 2004;33:432-3.
5. Yamamoto M, Ohara M, Suzuki C, Naishiro Y, Yamamoto H, Takahashi H, et al. A case of Mikulicz's disease (IgG4-related plasmacytic disease) complicated by autoimmune hypophysitis. Scand J Rheumatol 2006;35:410-1.
6. 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.
7. Masaki Y, Dong L, Kurose N, Kitagawa K, Morikawa Y, Yamamoto M, et al. Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: Analysis of 64 cases of IgG4-related disorders. Ann Rheum Dis 2009;68:1310-5.
8. 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.
9. 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.
10. Miyawaki S, Nishiyama S, Matoba K. Efficacy of low-dose prednisolone maintenance for saliva production and serological abnormalities in patients with primary Sjögren's syndrome. Intern Med 1999;38:938-43.
11. Sarles H, Sarles JC, Muratore R, Guien C. Chronic inflammatory sclerosis of the pancreas — an autonomous pancreatic disease? Am J Dig Dis 1961;6:688-98.
12. 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.
13. Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. Dig Dis Sci 1995;40:1561-8.
14. 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.
15. 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.
16. 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: do they belong to a spectrum of sclerosing pancreatitis? Am J Surg Pathol 2004;28:1193-203.
17. Kim KP, Kim MH, Kim JC, Lee SS, Seo DW, Lee SK. Diagnostic criteria for autoimmune chronic pancreatitis revisited. World J Gastroenterol 2006;12:2487-96.
18. Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. J Gastroenterol 2006;41:613-25.
19. Otsuki M, Chung JB, Okazaki K, Kim MH, Kamisawa T, Kawa S, et al. Research Committee of Intractable Pancreatic Diseases provided by the Ministry of Health, Labor and Welfare of Japan and the Korean Society of Pancreatobiliary Diseases. Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis. J Gastroenterol 2008;43:403-8.
20. Notohara K, Burgart LJ, Yadav D, Chari S, Smyrk TC. Idiopathic chronic pancreatitis with periductal lymphoplasmacytic infiltration: clinicopathologic features of 35 cases. Am J Surg Pathol 2003;27:1119-27.
21. Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Zhang L, et al. Diagnosis of autoimmune pancreatitis: The Mayo Clinic experience. Clin Gastroenterol Hepatol 2006;4:1010-6.
22. Okazaki K, Kawa S, Kamisawa T, Ito T, Inui K, Irie H, et al. Japanese clinical guidelines for autoimmune pancreatitis. Pancreas 2009;38:849-66.

23. Okazaki K, Kawa S, Kamisawa T, Naruse S, Tanaka S, Nishimori I, et al. Research Committee of Intractable Diseases of the Pancreas. Clinical diagnostic criteria of autoimmune pancreatitis: revised proposal. J Gastroenterol 2006;41:626-31.
24. 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.
25. Zen Y, Kasahara Y, Horita K, Miyayama S, Miura S, Kitagawa S, et al. Inflammatory pseudotumor of the breast in a patient with a high serum IgG4 level: histologic similarity to sclerosing pancreatitis. Am J Surg Pathol 2005;29:275-8.
26. 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.
27. Saeki T, Saito A, Yamazaki H, Emura I, Imai N, Ueno M, et al. Tubulointerstitial nephritis associated with IgG4-related systemic disease. Clin Exp Nephrol 2007;11:168-73.
28. Cheuk W, Yuen HK, Chan JK. Chronic sclerosing dacryoadenitis: part of the spectrum of IgG4-related sclerosing disease? Am J Surg Pathol 2007;31:643-5.
29. 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.
30. Kasashima S, Zen Y, Kawashima A, Konishi K, Sasaki H, Endo M, et al. Inflammatory abdominal aortic aneurysm: close relationship to IgG4-related periaortitis. Am J Surg Pathol 2008;32:197-204.
31. Matsumoto Y, Kasashima S, Kawashima A, Sasaki H, Endo M, Kawakami K, et al. A case of multiple immunogloblin G4-related periarteritis: a tumorous lesion of the coronary artery and abdominal aortic aneurysm. Hum Pathol 2008;39:975-80.
32. Cheuk W, Yuen HK, Chu SY, Chiu EK, Lam LK, Chan JK. Lymphadenopathy of IgG4-related sclerosing disease. Am J Surg Pathol 2008;32:671-81.
33. Comings DE, Skubi KB, Van Eyes J, Motulsky AG. 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 1967;66:884-92.
34. 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.
35. Brouwer E, Tervaert JW, Horst G, Huitema MG, van der Giessen M, Limburg PC, 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 1991;83:379-86.
36. Cheuk W, Yuen HK, Chan AC, Shih LY, Kuo TT, Ma MW, et al. Ocular adnexal lymphoma associated with IgG4+ chronic sclerosing dacryoadenitis: a previously undescribed complication of IgG4-related sclerosing disease. Am J Surg Pathol 2008;32:1159-67.
37. Sato Y, Ohshima K, Ichimura K, Sato M, Yamadori I, Tanaka T, et al. Ocular adnexal IgG4-related disease has uniform clinicopathology. Pathol Int 2008;58:465-70.
38. Oh HC, Kim JG, Kim JW, Lee KS, Kim MK, Chi KC, et al. Early bile duct cancer in a background of sclerosing cholangitis and autoimmune pancreatitis. Intern Med 2008;47:2025-8.
39. van der Zee JS, van Swieten P, Aalberse RC. Inhibition of complement activation by IgG4 antibodies. Clin Exp Immunol 1986;64:415-22.
40. Yamada K, Kawano M, Inoue R, Hamano R, Kakuchi Y, Fujii H, 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 2008;152:432-9.
41. Zen Y, Fujii T, Harada K, Kawano M, Yamada K, Takahira M, et al. Th2 and regulatory immune reactions are increased in immunoglobulin G4-related sclerosing pancreatitis and cholangitis. Hepatology 2007;45:1538-46.

Med Mol Morphol (2010) 43:■■–■■
DOI 10.1007/s00795-010-0525-0

ORIGINAL PAPER

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Immunoglobulin G4-related lymphadenopathy with inflammatory pseudotumor-like features

Received: June 2, 2010 / Accepted: July 20, 2010

Abstract Immunoglobulin (Ig) G4-related disease has been recently described. This disease affects various organs, including lymph nodes. We describe the case of a 52-year-old Japanese man with IgG4-related lymphadenopathy with inflammatory pseudotumor (IPT)-like features. Five years ago, the patient noticed a painless mass in the mandible but did not consult a doctor. Recently, he noted that the mass had increased in size and consulted an oral surgeon in the hospital. Excisional biopsy was performed for diagnosis. Histopathological examination revealed that most of the enlarged lymph node was occupied by the hyalinized tissue. A few residual lymphoid follicles with hyperplastic germinal centers and infiltration of plasma cells and eosinophils were observed. Most of the plasma cells expressed IgG4, and the ratio of IgG4-positive cells to IgG-positive cells was 57.1%. These findings suggested IgG4-related disease, and therefore a diagnosis of IgG4-related lymphadenopathy was established. In conclusion, pathologists should consider IgG4-related lymphadenopathy when diagnosing a lesion with IPT-like features.

Key words IgG4-related disease · Lymph node · Lymphadenopathy · Inflammatory pseudotumor · Histopathology

Introduction

Recently, autoimmune pancreatitis and its related disorders, such as sclerosing cholangitis, sclerosing sialadenitis (Küttner tumor), retroperitoneal fibrosis, and Mikulicz's disease, have been shown to be associated with immunoglobulin (Ig) G4-related abnormalities.[1–6] Such abnormalities include the elevation of serum IgG4 levels and the infiltration of the affected tissue with numerous IgG4-positive plasma cells. These autoimmune pancreatitis-related disorders, therefore, are classified as IgG4-related disease.[3–6] Interestingly, patients with IgG4-related disease respond well to steroid therapy, and many cases have been reported in Western countries and Japan.[1–6]

Here, we report a case of inflammatory pseudotumor (IPT)-like IgG4-related lymphadenopathy and have described its clinical and pathological findings. This disease sometimes involves regional and/or systemic lymph nodes.[6,7] Hyalinized fibrosis is one of the specific findings of IgG4-related disease; in addition, some inflammatory pseudotumors (IPTs) are recognized as IgG4-related disease.[6] However, no detailed reports on IgG4-related lymphadenopathy with features of IPT are available.

Case report

A 52-year-old Japanese man noticed a painless mass in the mandible 5 years ago, but he did not consult a doctor. He recently noted that the mass had increased in size, and he consulted an oral surgeon in the hospital. A computed tomography (CT) scan identified that the mass as a single lymph node swelling 4 × 2 cm in size. No other peripheral lymphadenopathy and no exocrine organ swelling were detected, and the patient did not have any B symptoms such as fever, fatigue, and night sweats. Lymph node excisional biopsy was performed for diagnosis.

The biopsied specimens of the lymph node were fixed in 10% formaldehyde and embedded in paraffin. Serial sections (4 μm) were cut and stained with hematoxylin and eosin and immunohistochemical stains.

Immunohistochemical staining was carried out using the BenchMark XT automated slide stainer (Ventana Medical Systems, Tucson, AZ, USA). Before the immunohistochemical

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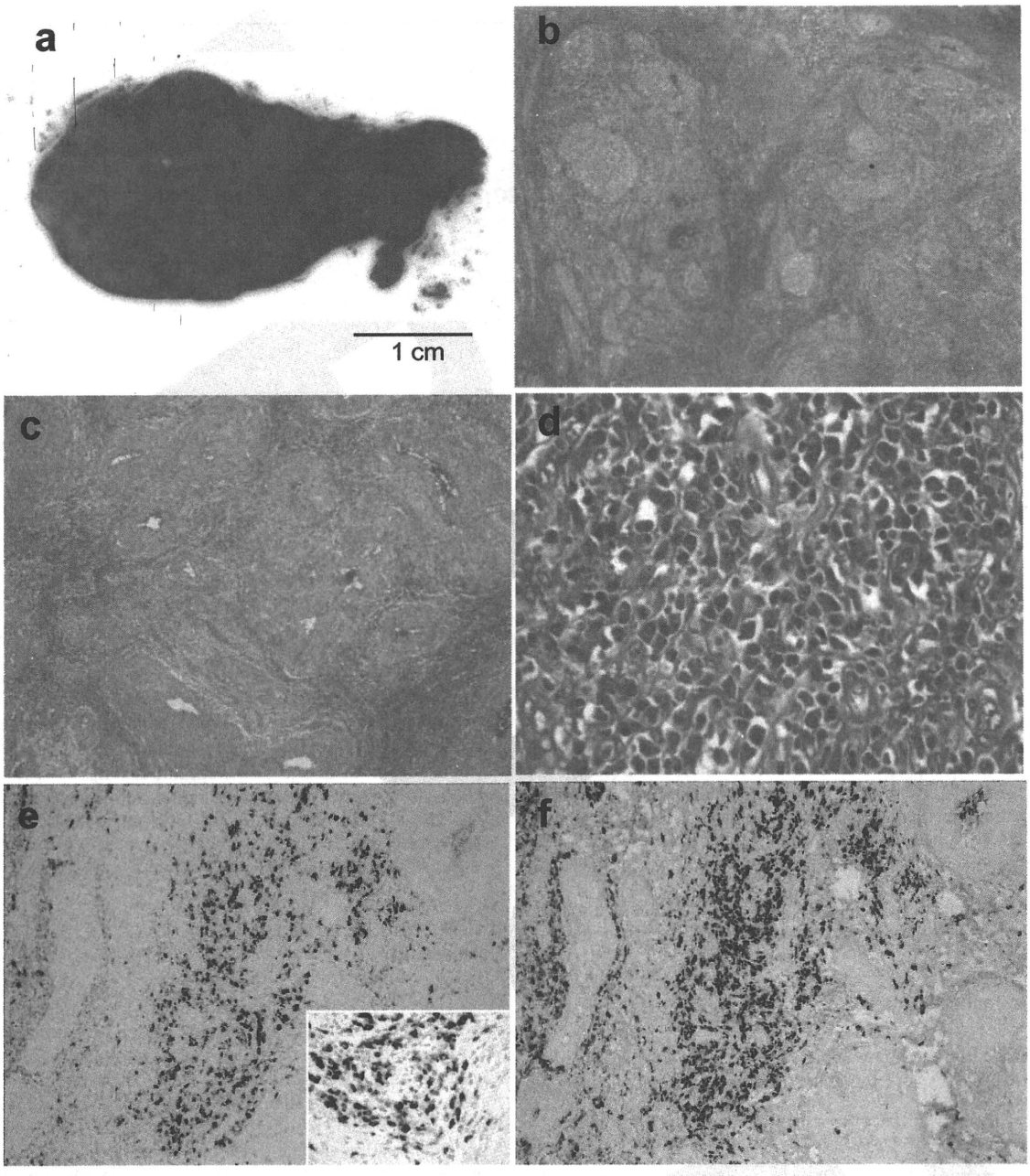

Fig. 1. **a** Most of the enlarged lymph node comprised hyalinized tissue [hematoxylin and eosin (H&E) stain, gross finding]. **b** A few residual lymphoid follicles with hyperplastic germinal centers and focally dense lymphoid infiltrate were observed (H&E stain). **c** Increased vascularity that predominantly comprised thickened vessels with perivascular fibrosis and hyalinization (H&E stain). **d** Infiltration of plasma cells, plasmacytoid cells, small lymphocytes, and eosinophils (H&E stain). Immunostaining for IgG4 (**e**) and IgG (**f**). Infiltration of many IgG4-positive cells was observed. **b** ×20; **c** ×40; **d** ×400; **e**, **f** ×100 (inset in **e**, ×400)

procedures, the tissue sections were subjected to standardized heating pretreatment for antigen retrieval. The following primary antibodies were used: cluster of differentiation (CD) 20 (L26, 1:200; Novocastra, Newcastle, UK), CD3 epsilon (PS1, 1:50; Novocastra), CD10 (56C6, 1:50; Novocastra), B-cell lymphoma (Bcl)-2 (3.1, 1:200; Novocastra), IgG (polyclonal, 1:20,000; Dako), IgG4 (HP6025, 1:400; Binding Site, Birmingham, UK), kappa light chain (kp-53, 1:100; Novocastra), lambda light chain (HP-6054, 1:200; Novocastra), and alpha-smooth muscle actin (1A4, 1:50; Dako).

The number of IgG4- or IgG-positive cells was estimated in areas with the highest density of these cells. In each section, five different high-power fields (HPFs; eyepiece, 10×; lens, 40×) were examined, and the average number of IgG4- or IgG-positive cells per HPF was calculated.[7]

Pathological findings

Microscopic findings

The enlarged lymph node was 3.8 × 2.8 cm in size (Fig. 1a). The histological findings revealed that most of the lymph node was occupied by hyalinized tissue and had increased vascularity that predominantly comprised thickened vessels with perivascular fibrosis and hyalinization (Fig. 1a–c). A few residual lymphoid follicles with hyperplastic germinal centers and focally dense lymphoid infiltrate were observed in the lymph node (Fig. 1b). Plasmacytoid cells, small lymphocytes, plasma cells, and eosinophils infiltrated the dense sclerotic tissue, with the latter two being particularly predominant (Fig. 1d).

Immunohistochemical findings

The cells that contained germinal centers and mantle zones were found to express CD20. The germinal centers expressed CD10 but not Bcl-2. CD20-positive B cells were scattered among CD3-positive T cells in the interfollicular areas. The B-cell population in both the follicles and the interfollicular areas exhibited polytypic expression of Ig light chains. The hyalinized connective tissue in the interfollicular area was negative for alpha-smooth muscle actin. The plasma cells and plasmacytoid cells predominantly expressed IgG4, and the ratio of IgG4-positive cells to IgG-positive cells was 57.1% (Fig. 1e,f). This IgG4-/IgG-positive cell ratio is consistent with IgG4-related lymphadenopathy.[6–8]

Discussion

The term IPT has been used to describe inflammatory/fibrosing tumoral processes of an undetermined cause that may involve a variety of organ systems, including the lungs, spleen, liver, skin, and soft tissues.[9–11] IPTs are clinicopathologically similar to inflammatory myofibroblastic tumors. However, recent evidence shows that inflammatory myofibroblastic tumors are actually neoplastic processes that often harbor balanced chromosomal translocations involving the anaplastic lymphoma kinase (*ALK*) gene.[11]

Concomitant lymphadenopathy is common in IgG4-related diseases. In recent times, several studies on the morphology and immunohistology of lymph node lesions have been reported.[6,7] These studies show that IgG4-related lymphadenopathy exhibits histological diversity. In addition, IgG4-related lymphadenopathy is frequently associated with clinical features of systemic lymphadenopathy such as hypergammaglobulinemia, especially elevated levels of IgG and IgE, and expression of various autoantibodies.[6,7]

The pathogenesis of IgG4-related disease remains unclear. A recent study reported that T helper (Th)-2 cytokines [interleukin (IL)-4, IL-5, and IL-13] and regulatory cytokines [IL-10 and transforming growth factor (TGF)-β] were upregulated in the affected tissue of the patients with IgG4-related diseases.[12] Th2 cytokines activate eosinophil infiltration and IgE production. Moreover, IL-4 and IL-10 induce B-cell differentiation into IgG4-positive cells, and TGF-β is a powerful fibrogenic cytokine. Although the presence of IgG subclasses in the serum was not examined in our patient, we considered that the pathological findings were consistent with IgG4-related lymphadenopathy.

Moran et al.[10] reported that IPTs of the lymph node can be histologically classified into three different stages: stage I, small nodules with partial involvement of the lymph node; stage II, infiltration of inflammatory cells and fibroblastic proliferation causing marked distortion of the lymph node connective tissue framework, including the hilum, trabeculae, and capsules, with secondary spread into the lymph node parenchyma and extranodal adipose tissue; and stage III, almost complete sclerosis of the lymph node with scant residual inflammatory elements. The histological findings in our case were similar to those of patients with stage III IPT; however, the clinical findings differed. Patients with IPT of the lymph node usually exhibit symptoms that are suggestive of lymphoid malignancy such as fever, fatigue, and night sweats.[9,10]

In conclusion, if the relationship between IPTs of the lymph node and IgG4 is examined in detail, it is possible that the lesions previously identified as IPTs of the lymph node are actually IgG4-related lymphadenopathies. Therefore, a misdiagnosis of IgG4-related lymphadenopathy as IPT should be avoided, especially in stage III, because the two diseases are clinically different.

References

1. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, Fukushima M, Nikaido T, Nakayama K, Usuda N, Kiyosawa K (2001) High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med 344:732–738
2. Hamano H, Kawa S, Ochi Y, Unno H, Shiba N, Wajiki M, Nakazawa K, Shimojo H, Kiyosawa K (2002) Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. Lancet 359:1403–1404

3. Sato Y, Ohshima K, Ichimura K, Sato M, Yamadori I, Tanaka T, Takata K, Morito T, Kondo E, Yoshino T (2008) Occular adnexal IgG4-related disease has uniform clinicopathology. Pathol Int 58:465–470
4. Masaki Y, Dong L, Kurose N, Kitagawa K, Morikawa Y, Yamamoto M, Takahashi H, Shinomura Y, Imai K, Saeki T, Azumi A, Nakada S, Sugiyama E, Matsui S, Origuchi T, Nishiyama S, Nishimori I, Nojima T, Yamada K, Kawano M, Zen Y, Kaneko M, Miyazaki K, Tsubota K, Eguchi K, Tomoda K, Sawaki T, Kawanami T, Tanaka M, Fukushima T, Sugai S, Umehara H (2009) Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. Ann Rheum Dis 68:1310–1315
5. Kuroda N, Nakamura S, Miyazaki K, Inoue K, Ohara M, Mizuno K, Sato Y, Yoshino T (2009) Chronic sclerosing pyelitis with an increased number of IgG4-positive plasma cells. Med Mol Morphol 42:236–238
6. Sato Y, Notohara K, Kojima M, Takata K, Masaki Y, Yoshino T (2010) IgG4-related disease: historical overview and pathology of hematological disorders. Pathol Int 60:247–258
7. Sato Y, Kojima M, Takata K, Morito T, Asaoku H, Takeuchi T, Mizobuchi K, Fujihara M, Kuraoka K, Nakai T, Ichimura K, Tanaka T, Tamura M, Nishikawa Y, Yoshino T (2009) Systemic IgG4-related lymphadenopathy: a clinical and pathologic comparison to multicentric Castleman's disease. Mod Pathol 22:589–599
8. Kojima M, Nakamura N, Motoori T, Shimizu K, Otuski Y, Haratake J, Ogawa A, Igarashi T, Masawa N, Kobayashi H, Nakamura S (2010) Castleman's disease of the retroperitoneum: with special reference to IgG4-related disorder. J Clin Exp Hematopathol 50:39–44
9. Kojima M, Nakamura S, Shimizu K, Hosomura Y, Ohno Y, Itoh H, Yamane N, Yoshida K, Masawa N (2001) Inflammatory pseudotumor of lymph node. Clinicopathologic and immunohistological study of 11 Japanese cases. Int J Surg Pathol 9:207–214
10. Moran CA, Suster S, Abbondanzo SL (1997) Inflammatory pseudotumor of lymph nodes: a study of 25 cases with emphasis on morphological heterogeneity. Hum Pathol 28:332–338
11. Oshiro H, Nomura M, Yamanaka S, Watanabe S, Inayama Y (2007) Splenic inflammatory pseudotumor (inflammatory myofibroblastic tumor). J Clin Exp Hematopathol 47:83–88
12. Zen Y, Fujii T, Harada Kawano M, Yamada K, Takahira M, Nakanuma Y (2007) Th2 and regulatory immune reactions are increased in immunoglobulin G4-related sclerosing pancreatitis and cholangitis. Hepatology 45:1538–1546

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Pathology International

Pathology International 2010; **60**: 247–258 doi:10.1111/j.1440-1827.2010.02524.x

Review Article

IgG4-related disease: Historical overview and pathology of hematological disorders

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IgG4-related diseases comprise a recently recognized systemic syndrome characterized by mass-forming lesions in mainly exocrine tissue that consist of lymphoplasmacytic infiltrates and sclerosis. There are numerous IgG4-positive plasma cells in the affected tissues, and the serum IgG4 level is increased in these patients. The present study describes the history, autoimmune pancreatitis (AIP), IgG4-related lymphadenopathy and lymphomagenesis based upon ocular adnexal IgG4-related disease. Lymphoplasmacytic sclerosing pancreatitis, a prototypal histological type of AIP, is now recognized as a systemic IgG4-related disease. Lymph node lesions can be subdivided into at least five histological subtypes, and systemic IgG4-related lymphadenopathy should be distinguished from multicentric Castleman's disease. Interleukin-6 and CRP levels are abnormally high in multicentric Castleman's disease, but are normal in the majority of systemic IgG4-related lymphadenopathy. Ocular adnexal IgG4-related disease frequently involves bilateral lacrimal glands swelling, and obliterative phlebitis is rare. Moreover, some malignant lymphomas, especially mucosa-associated lymphoid tissue lymphoma, arise from ocular adnexal IgG4-related disease. In addition, IgG4-producing lymphoma also exists.

Key words: autoimmune pancreatitis, IgG4, lymph node, mucosa-associated lymphoid tissue lymphoma, ocular adnexa

IgG4 is a minor component of the four subclasses of IgG in serum. Sporadic examples, such as IgG4 autoantibodies present in patients with autoimmune bullous skin diseases[1–3] and deposition of IgG4 seen in membranous nephropathy,[4] had indicated that IgG4 might be pathogenetically related to some diseases. But little attention has been paid to this minor component of IgG since Hamano *et al.* found elevated serum IgG4 level in patients with autoimmune pancreatitis (AIP).[5] This was the beginning of the use of IgG4 as a serological marker for a specific disease, and nowadays serum IgG4 is acknowledged as an important serological test for making a diagnosis of AIP and other related diseases. The same group also reported that numerous IgG4-positive plasma cells were characteristically observed in pancreatic tissues with AIP.[6] This perception facilitated the identification of numerous extrapancreatic diseases that were potentially related to AIP pathogenetically, and more importantly triggered a reclassification of pre-existing entities. These diseases are now grouped together and called IgG4-related diseases, and the number of constituents in this category is still increasing.

This review article first focuses on how the concept of IgG4-related diseases emerged by reviewing the history, and debates the pathology of AIP, with special references to the lymph nodal lesion and lymphomagenesis of the ocular adnexal region.

HISTORICAL PERSPECTIVES OF AUTOIMMUNE PANCREATITIS AND IgG4-RELATED DISEASES

Pathology of AIP and its relationship to IgG4

The concept of AIP was proposed by Yoshida *et al.* in 1995.[7] According to their description and other reports mainly from Japan, AIP is common in elderly men. The chief complaint is usually mild abdominal symptoms or obstructive jaundice. Diabetes mellitus is commonly associated with this. Some patients are asymptomatic. Severe abdominal pain is exceptional. Radiologically, the affected pancreas has diffuse or focal swelling and irregular narrowing of the main pancreatic

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Received 28 October 2009. Accepted for publication 20 December 2009.

duct. Thus from the clinical standpoint, it is difficult to distinguish AIP from pancreatic carcinoma, and many resections had been performed for suspected carcinoma before this entity was recognized. Serology often indicated hypergammaglobulinemia, elevated IgG level and the presence of various autoantibodies, such as antinuclear antibody and rheumatoid factor. Characteristically, serum IgG4 level is often elevated. Notably, corticosteroid treatment is effective, and its effect is usually evident in a few weeks. From these observations, autoimmune mechanism has been considered to play a role in this condition, which led to the term AIP.

The histological feature of AIP is diffuse lymphoplasmacytic infiltration and fibrosis. It is pathologically so peculiar among inflammatory conditions of the pancreas that, indeed, there had been some sporadic reports on pathology dealing with this topic even before the concept of AIP was proposed, such as chronic inflammatory sclerosis of the pancreas,[8] lymphoplasmacytic sclerosing pancreatitis (LPSP),[9] non-alcoholic duct destructive chronic pancreatitis[10] and inflammatory pseudotumor.[11] As the concept of AIP had been gradually accepted among clinicians, and it has become recognized that lymphoplasmacytic infiltration with fibrosis was a histological characteristic of AIP, these pathological concepts were regarded as equivalent to AIP. It should be noted, however, that there are some differences among these reports. For example, patients with chronic inflammatory sclerosis complained of severe abdominal pain and died of cachexia, which is unusual for the current concept of AIP.[8] According to studies of non-alcoholic duct destructive chronic pancreatitis, neutrophilic infiltration in interlobular ducts was common, although this is not a feature of LPSP.[5,10]

After 2000, some groups argued that what was clinically diagnosed as AIP was not pathologically a single entity, but consisted of at least two different groups. A group from Mayo Clinic conducted a retrospective study with resected pancreata with a diagnosis of pancreatitis, and concluded that, in addition to a group that corresponded to LPSP, there was a group designated as idiopathic duct-centric chronic pancreatitis (IDCP).[12] A similar observation was also reported from Europe and Massachusetts General Hospital.[13–15]

LPSP is a histologically unique lesion that was proposed by Kawaguchi *et al.* in 1991.[9] It consists of diffuse lymphoplasmacytic infiltration and fibrosis that focally gives rise to a swirling pattern (storiform fibrosis; Fig. 1a). Eosinophils can be observed, but neutrophils are absent. Pancreatic lobules are relatively well preserved compared to alcoholic chronic pancreatitis, but focal destruction of pancreatic acini and replacement with fibrosis are commonly seen. The same inflammatory process is characteristically observed around the main and interlobular ducts, leaving the duct epithelium and lumen intact (Fig. 1b). It appears as if the duct wall is thickened with inflammation. Veins are almost always obliterated by the same inflammatory process (obliterative phlebitis; Fig. 1c). Splenic vein and even portal vein may be involved, which makes surgeons suspect that they are dealing with an inoperative carcinoma. The common bile duct is also often inflamed. This is the main cause of jaundice seen in patients with AIP. Numerous IgG4-positive plasma cells are identified in LPSP (Fig. 1d).[16,17]

Another group, designated as IDCP, is characterized by inflammation centered on the duct epithelium.[12,13,15] Neutrophilic infiltration in the main and/or interlobular ducts is characteristic, and is seen within the epithelium and lumen (Fig. 2). This finding is called 'granulocytic epithelial lesion' by the European group.[13] Duct epithelium shows destructive and regenerative changes, and, due to the inflammation, the lumen looks stenotic or tortuous. A band of lymphocytes and plasma cells surrounds the lumen but, in contrast to LPSP, the ductal lesion lacks the appearance of a thickened wall. Sometimes the entire duct appears to be entrapped within an aggregate of inflammatory cells (Fig. 2a). When the inflammation is severe, pancreatic lobules are also inflamed with neutrophils, lymphocytes and plasma cells. Microabscesses may be encountered. Although there is fibrosis around pancreatic lobules, inflammatory cells are scarce within fibrosis itself, in contrast to LPSP, in which inflammatory cells are numerous within fibrosis. Obliterative phlebitis is rare, and inflammation of the common bile duct is less common compared to LPSP. IgG4-positive plasma cells are usually few in IDCP.[17]

The clinical features of LPSP are concordant with those of AIP reported from Japan, described previously.[12] Serum IgG4 is elevated in 80% of AIP patients in Japan, which correlates well with numerous IgG4-positive plasma cells seen in LPSP. In contrast, patients with IDCP are younger than LPSP patients, and many of them are younger than 40 years.[12] There is no gender preponderance. Obstructive jaundice is less common in IDCP than in LPSP. The association of inflammatory bowel disease (IBD) is found in IDCP, but extrapancreatic manifestations seen in LPSP, which are described in the following section, are rare. Notably, IDCP is rare in Japan.[18]

Both LPSP and IDCP share some clinicopathological features. There has been a debate therefore on whether these two pathological groups are different manifestations of a single entity of AIP, or whether they are different clinicopathological entities. The controversy is due to the variety of AIP diagnostic criteria proposed by different groups. The diagnostic criteria from Japan,[19] Korea,[20] Asia[21] and Mayo Clinic[22] define LPSP as the pathological entity of AIP, but other groups include both LPSP and IDCP in AIP.[13,15,23] Considering the demographic and clinical differences as well as different immunoreactivity for IgG4, however, the idea that LPSP and IDCP are different is gradually gaining acceptance. Recently, new terms, type 1 and type 2 AIP, which correspond to LPSP and IDCP, respectively, have been proposed from the West.[24] It is important to note that, among these two groups, only

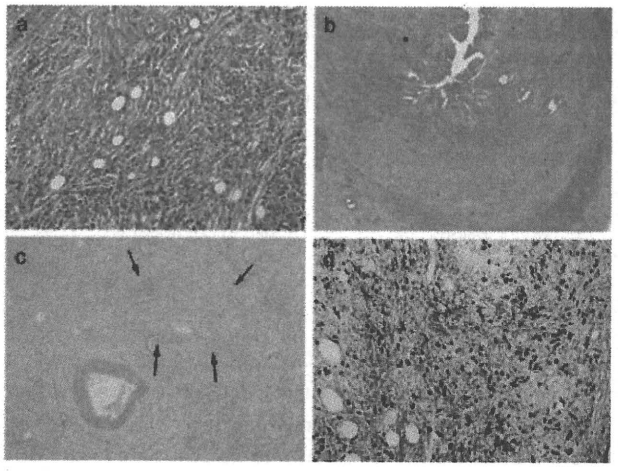

Figure 1 Lymphoplasmacytic sclerosing pancreatitis. (**a**) Lymphoplasmacytic infiltration and fibrosis giving rise to storiform fibrosis. (**b**) Ductal inflammation around the intact epithelium. The duct wall appears to be thickened with the inflammation. (**c**) Obliterative phlebitis (arrow). (**d**) Numerous IgG4-positive plasma cells are identified on immunostaining.

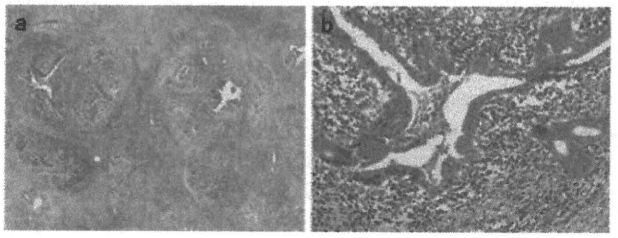

Figure 2 Idiopathic duct-centric chronic pancreatitis. (**a**) Duct-centric inflammation. Two ducts shown here are entrapped within an aggregate of inflammatory cells. (**b**) Neutrophilic infiltration in the duct lumen.

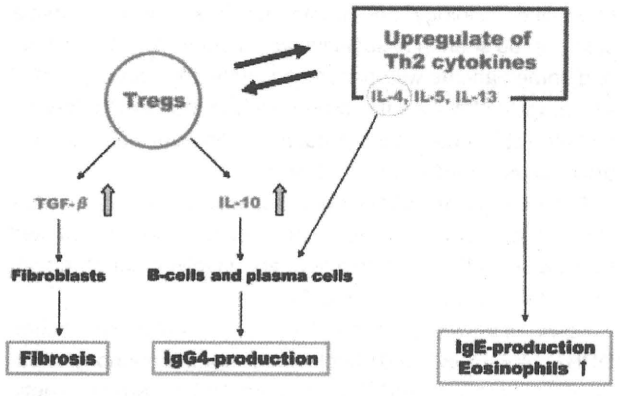

Figure 3 IgG4-related disease: hypothesis of the pathogenesis. The expression of T-helper cell 2 (Th2) cytokines (interleukin (IL)-4, IL-5, and IL-13) and regulatory cytokines (IL-10 and transforming growth factor (TGF)-β) was upregulated in the affected tissues of patients with IgG4-related diseases, suggesting that this disease might reflect an allergic mechanism in its pathogenesis. Tregs, regulatory T cell.

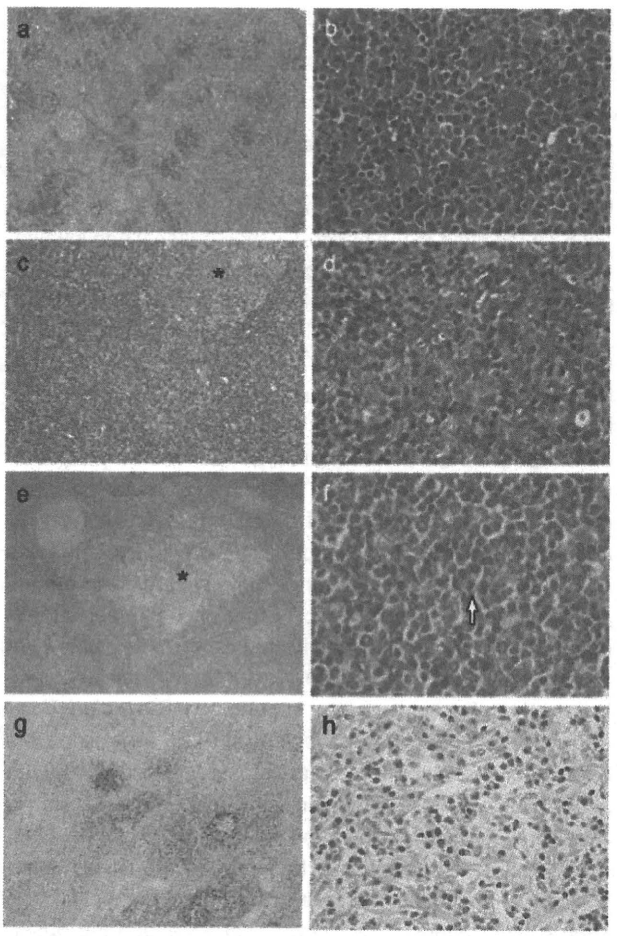

Figure 4 (**a**) Type I lesion. On low-power field, the lymph node demonstrated numerous lymphoid follicles with active germinal centers and distinct mantle zone and expansion of the interfollicular area. The interfollicular area contained a moderate number of capillaries. (**b**) Type I lesion. On high-power field, the interfollicular area was heavily infiltrated by mature plasma cells, plasmacytoid cells and small lymphocytes. Scattered medium-sized lymphocytes, transformed lymphocytes including immunoblasts and eosinophils were also present. (**c**) Type III lesion. On medium-power field, the lymph node demonstrated an active germinal center (*) with a distinct mantle zone, and expansion of the interfollicular area containing moderate vascularization. (**d**) Type III lesion. On high-power field, the paracortical area contained numerous mature plasma cells, plasmacytoid cells, immunoblasts, small and medium-sized lymphocytes and histiocytes. Note an eosinophil. (**e**) Type IV lesion. On low-power field a large early stage progressive transformation of germinal center (*) is surrounded by secondary lymphoid follicles. (**f**) Type IV lesion. On high-power field, a relatively large number of residual centrocytes, centroblasts and immunoblasts are present, in addition to the small mantle zone lymphocytes. Note a few mature plasma cells (arrow). (**g**) Type V lesion. On low-power field, the majority of the lymph nodes were occupied by the hyalinized tissue, and a few residual lymphoid follicles and a focally dense lymphoid infiltrate were observed. (**h**) Type V lesion. On high-power field, mature plasma cells, small lymphocytes and eosinophils focally infiltrated in the sclerosing tissue.

LPSP should be regarded as the pancreatic manifestation of IgG4-related diseases.

Concept of IgG4-related disease

Kawaguchi *et al.* suggested that LPSP was a systemic disease.[9] In addition to the pancreas, their patients had involvements in the extrahepatic bile duct, gallbladder and labial gland, and all lesions showed histological similarity to LPSP. They further noted that LPSP histologically resembled multifocal fibrosclerosis. Multifocal fibrosclerosis is an entity that includes systemic diseases, such as 'primary sclerosing cholangitis' (PSC), retroperitoneal fibrosis, Riedel thyroiditis and orbital pseudotumor. Association of 'pancreatic pseudotumors' has also been reported.[25] Notably, obliterative phlebitis, one of the unique features of LPSP, has been reported to occur in multifocal fibrosclerosis.[26–29] Ever since AIP was recognized as an entity, it has become well realized among clinicians that extrapancreatic lesions are common in AIP patients. According to a recent report, pulmonary hilar lymphadenopathy, bile duct lesions, lacrymal and salivary gland lesions, hypothyroidism and retroperitoneal fibrosis are commonly seen in Japanese patients with AIP,[30] suggesting the analogy of LPSP and multifocal fibrosclerosis. Curiously, an association with Riedel thyroiditis has been rarely reported in AIP, but the reason is not known.

On immunohistochemistry, Hamano *et al.* identified numerous IgG4-positive plasma cells in the retroperitoneal fibrosis seen in AIP patients.[6] Kamisawa *et al.* extended the observation, and reported that IgG4-positive plasma cells are increased systemically in patients with AIP.[31] They concluded that AIP patients have a systemic disease, and proposed the entity 'IgG4-related sclerosing disease'.[32] More recent entities, such as IgG4-related plasmacytic exorinopathy[33] and IgG4-positive multiorgan lymphoproliferative syndrome,[34] are synonymous.

The histological features and numerous IgG4-positive cells are unique to LPSP. Using these morphological and immunohistochemical features as a hallmark, Zen *et al.* proposed new concepts of IgG4-related diseases in various organs.[35–40] This is not merely a proposal of new concepts, but a reclassification of pre-existing entities. In addition, the recognition of these new entities is important from the clinical standpoint as well, because many of these lesions involve a mass that is clinically suspicious for malignant diseases, and nevertheless they are responsive to corticosteroid therapy. For example, IgG4-related sclerosing cholangitis had been diagnosed as PSC before this entity was recognized,[35] but the histological finding is different from classic PSC.[35] IgG4-related sclerosing cholangitis produces changes that are histologically similar to LPSP including numerous IgG4-positive plasma cells, while in classic PSC, the inflammation is centered on the bile duct epithelium, and IgG4-positive plasma cells are usually few. Importantly, IgG4-related sclerosing cholangitis is common in elderly men, in a similar fashion to LPSP. Classic PSC is well known to be associated with IBD, but such an association is rare in IgG4-related sclerosing cholangitis. The radiological features of the two are also different.[41] Corticosteroid treatment is effective for patients with IgG4-related sclerosing cholangitis, while there is no such indication for classic PSC, for which the only treatment option is liver transplantation.

Table 1 Previous reports of IgG4-related diseases

• Pachymeningitis	• Autoimmune pancreatitis
• Hypophysitis	• Hepatitis
• Lacrimal gland lesion (Mikulicz's disease)	• Sclerosing cholangitis
	• Retroperitoneal fibrosis
• Sclerosing sialadenitis (Küttner tumor)	• Prostatitis
	• Inflammatory aortic aneurysm
• Thyroid gland	• Tubulointerstitial nephritis
• Pulmonary lesions	• Lymphadenopathy
• Mastitis	• Skin Lesion

Since then, many entities that are related to IgG4 have been described from all over the world (Table 1), especially in Western countries, as well as in Japan.[36–57] They include sclerosing sialadenitis,[36] pulmonary plasma cell granuloma and other pulmonary lesions,[38,47,48] mastitis,[37,49] hepatitis,[39] tubulointerstitial nephritis,[50] prostatitis,[51]inflammatory aortic aneurysm,[40,43,44,52] lymphadenopathy,[53,54] pachymeningitis[55] and skin lesion.[54,56] Each of these diseases could occur separately, or in various combinations. It should be stressed, however, that the occurrence of numerous IgG4-positive plasma cells is not entirely specific for IgG4-related diseases. Suppurative granulation tissue, for example, may contain numerous IgG4-positive cells.[57] It is also well known that LPSP-like histology and numerous IgG4-positive plasma cells can be seen in association with pancreatic carcinomas, and some patients with pancreatic carcinoma have elevated serum IgG4.[58–60] A cautious approach is thus mandatory for pathologists to determine if each condition or each case is truly related to IgG4-related diseases.

The etiology of IgG4-related diseases is not well understood. The overall immune response seems to be mediated by T-helper cell 2 (Th2) reaction, and involvement of regulatory T cells is suggested (Fig. 3)[61]

Kawa *et al.* reported that the human leukocyte antigen DRB1*0405-DQB1*0401 haplotype is common among Japanese patients with AIP,[62] suggesting that a certain genetic preponderance is involved in the disease. IgG4 autoantibodies to various tissues have been found in the patients' sera,[63] and dense deposits have been identified ultrastructurally.[15] But IgG4 cannot activate the classic complement pathway, and it is unclear how IgG4 deposition can lead to tissue damage. Another unique feature of IgG4 is its ability to bind

other immunoglobulins through its Fc (Fragment, crystallizable),[64] but its relationship to IgG4-related diseases is still unknown.

IgG4-RELATED LYMPHADENOPATHY

Pathology and clinical findings of IgG4-related lymphadenopathy.

Concomitant lymphadenopathy is common in IgG4-related diseases.[39,53] Recently, several reports dealing with the morphological and immunohistological findings of the lymph nodal lesion have been published.[53,54,65,66] It appears that histomorphological findings of IgG4-related lymphadenopathy showed histological diversity.[53,54,65,66] Moreover, clinically, IgG4-related lymphadenopathy occasionally showed systemic lymphadenopathy, polyclonal hyperimmunoglobulinemia, especially elevation of IgG and IgE, and positivity of various autoantibodies.[53,54,65] Although some cases of lymphadenopathy were previously designated as atypical lymphoproliferative disorders,[67] mimicking malignant lymphomas, these cases lack immunoglobulin gene monoclonality, and are thought to be non-neoplastic.

We considered that there are five histological subtypes in IgG4-related lymphadenopathy (Table 2).

Type I: Castleman's disease- like morphology

The lymph node architecture is preserved. The lesion contains numerous lymphoid follicles (Fig. 4a). Cheuk *et al.* noted that the lymphoid follicles had a variable degree of regressive changes in the germinal centers, with decreased centroblasts, tingible body macrophages, and mitotic figures in some cases.[53] Hyalinized blood vessels frequently penetrate into the germinal centers. In some lymphoid follicles concentric files of small lymphocytes produced an onion skin pattern in the mantle zone. Other authors, however, reported that the lymphoid follicles had normal germinal centers with distinct mantle zone (Fig. 4a).[54,65,66] The interfollicular area contained mild–moderate increased vascular proliferation and moderate–large numbers of mature plasma cells with a few plasmacytoid cells and large transformed cells (immunoblasts) (Fig. 4b).[54,65,66] Occasionally, eosinophilic infiltration is observed in the interfollicular area (Fig. 4b). Immunohistology showed polytypic immunoglobulin in the plasma cells, and there was no human herpes virus type-8 (HHV-8) positive cells in 11 cases examined.[53,54,66]

Table 2 Histological subtypes and distribution pattern of IgG4-positive cells in IgG4-related lymphadenopathy

	Histological subtype	Distribution pattern of IgG4-positive cells
Pattern I	Castleman's disease-like morphology	Interfollicular
Pattern II	Reactive follicular hyperplasia	Interfollicular
Pattern III	Interfollicular plasmacytosis and immunoblastosis	Interfollicular
Pattern IV	Progressive transformation of germinal center-like	Intra-germinal center
Pattern V	Inflammatory pseudotumor-like morphology	Interfollicular

Type II: Reactive follicular hyperplasia

The lymph node shows reactive follicular hyperplasia, and small–moderate numbers of mature plasma cells in the interfollicular area.[53]

Type III: Interfollicular plasmacytosis and immunoblastosis

On low-power field, the lesion has paracortical hyperplasia with small vessel proliferation, and various numbers of lymphoid follicles with minimal sinuses (Fig. 4c).[53,54] The germinal centers were usually hyperplastic, although a few were atrophic. On high-power field, the paracortical area was diffusely infiltrated by a polymorphous population consisting of numerous mature plasma cells, plasmacytoid cells, large basophilic transformed lymphocytes (immunoblasts), eosinophils, small to medium-sized lymphocytes and histiocytes (Fig. 4d).[53,54] Immunostain demonstrates the mixed T- and B-cell nature of immunoblasts. The T cells in the interfollicular area were negative for CD10 and there was no extrafollicular proliferation of follicular dendritic cells using the anti-follicular dendritic cell antibodies, which are usually observed in angioimmunoblastic T-cell lymphomas (AITL). On immunohistochemistry, light chain immunoglobulin of the interfollicular plasma cells, plasmacytoid cells and B-immunoblasts is bi-modal and non-neoplastic.

Type IV: Progressive transformation of germinal center like

Progressive transformation of germinal center (PTGC) is characterized by the presence of large nodules of lymphocytes, often threefold to fourfold the size of other normal reactive germinal centers (Fig. 4e).[68] In PTGC, small lymphocytes migrate into the germinal center in a multifocal fashion, progressively accumulate and expand there, and then disrupt germinal centers.[68] In the early stage, germinal centers develop an unusual shape or break up without clear demarcation of the germinal center and mantle zone (Fig. 4e). These germinal center cell clusters contain centroblasts and centrocytes. Mitotic figures and tingible body macrophages are usually evident in the germinal center. In the late stage, PTGC are composed of large nodules with numerous small lymphocytes and centroblasts and centrocytes. In IgG4-related lymphadenopathy, early PTGC and normal

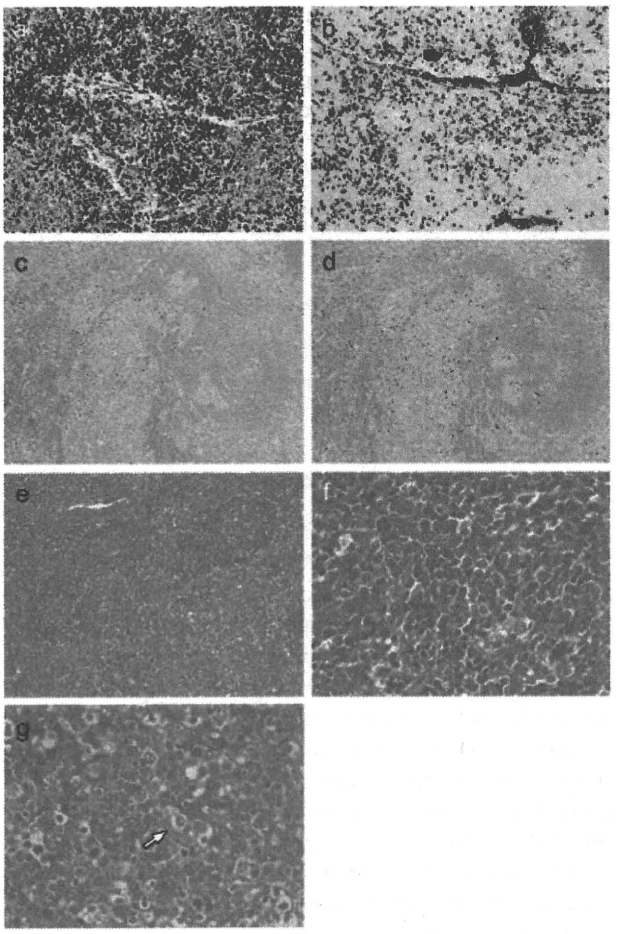

Figure 5 (**a**) Immunostaining for IgG and (**b**) IgG4. A large number of IgG4-positive cells infiltrated the type III lesion. (**c**) Immunostaining for IgG and (**d**) IgG4. IgG4-positive cells mainly infiltrated the type IV lesion of PTGC. (**e**) ALPIB. On low-power field, the lesion contained diffuse paracortical hyperplasia with small vessel proliferation and two small germinal centers. (**f**) ALPIB. On high-power field, the paracortical area contained numerous mature plasma cells, plasmacytoid cells, immunoblasts, small and medium-sized lymphocytes and histiocytes. (**g**) Angioimmunoblastic T-cell lymphoma. On high-power field, the lesion contained numerous plasma cells. Note scattered clear cells (arrow).

reactive germinal centers had scattered mature plasma cells (Fig. 4f) in the germinal centers.[54]

Type V: Inflammatory pseudotumor like

Inflammatory pseudotumor (IPT) of the lymph node develops in stages:[68,69] stage I, small nodules with partial involvement of the lymph node; stage II, inflammatory infiltrate and fibroblastic proliferation cause marked distortion of the connective tissue framework of the lymph node including hilum, trabeculae and capsule with secondary spread into the lymph node parenchyma and extranodal adipose tissue; and stage

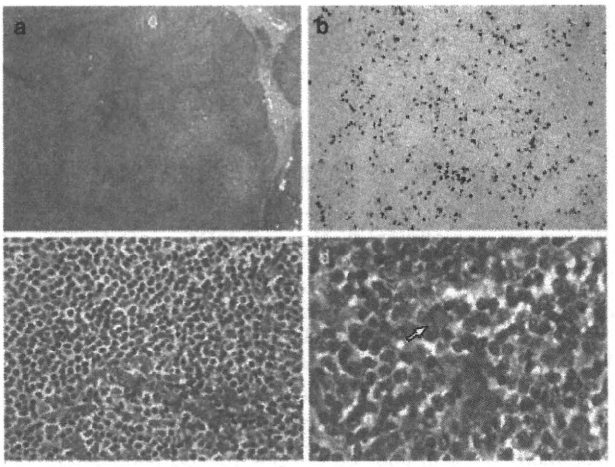

Figure 6 Ocular adnexal IgG4-related mucosa-associated lymphoid tissue lymphoma. (**a**) Diffuse dense infiltrate of lymphoid cells with lymphoid follicles and fibrosis band in lacrimal gland. (**b**) Numerous IgG4-positive plasma cells are identified (IgG4/IgG-positive cell ratio ≥ 50%). (**c**) The infiltrate consists of monocytoid B-cell-like cells, centrocytic cells and eosinophils. (**d**) Eosinophil infiltration and a few lymphoid cells exhibit Dutcher body (arrow).

III, areas of dense sclerosis of the lymph node with minimal inflammation. IgG4-related lymphadenopathy has similar histological findings to those of stage III of IPT (YS and MK, pers. comm., 2009). Histologically, the majority of the lymph nodes were occupied by the hyalinized tissue, and a few residual lymphoid follicles and focally dense lymphoid infiltrate were observed in the lymph node (Fig. 4g). Mature plasma cells, small lymphocytes and eosinophils focally infiltrate the sclerosing tissue (Fig. 4h).

The proportion of IgG4/IgG-positive plasma cells ranged from 40% to 99% in the literature.[53,54,66] We recognized two types of distribution pattern of IgG4-positive plasma cells, namely interfollicular and intra-germinal center type (Table 2).[54] In the interfollicular pattern, the majority of IgG4-positive plasma cells are located in the interfollicular area (Fig. 5a,b), whereas IgG4-positive plasma cells were observed more frequently in the lymphoid follicles in the intragerminal center type (Fig. 5c,d). Patterns I, II, III and V usually involved an interfollicular distribution, but pattern IV involved an intragerminal center distribution.

Clinically, three types of lymphadenopathy are recognized.[53] Group A involves enlarged regional and group B involves non-regional lymph node of organs affected by IgG4-related disease. Cases of unexplained lymphadenopathy were designated as group C. The characteristic clinical presentation of group B and C patients can be summarized as follows (Table 3):[53,54] (i) the patients are middle-aged to elderly with marked male predominance; (ii) usually systemic lymphadenopathy; (iii) the lymph nodes are not very large (usually up to 2 cm); (iv) the exocrine or extranodal lesions

Table 3 Clinical characters of systemic IgG4-related lymphadenopathy

Clinical presentation	(i)	Patients are middle-aged–elderly with marked male predominance
	(ii)	Systemic lymphadenopathy
	(iii)	Lymph node are not very large (usually up to 2 cm)
	(iv)	Exocrine or extranodal lesions may precede, follow, or present together with the lymph node swelling
	(iv)	Absence of fever
Abnormal laboratory findings	(i)	Polyclonal hyperimmunoglobulinemia
	(ii)	Raised serum IgG and IgE levels
	(iii)	Elevation of serum soluble interleukin-2 receptor
	(iv)	Presence of autoantibodies
Normal laboratory findings	(i)	Interleukin-6 level
	(ii)	Negativity of C-reactive protein
	(iii)	Lactate dehydrogenase level

may precede, follow, or present together with the lymph node swelling; and (v) despite the systemic nature of the disease, there is no fever or other B symptoms. The diagnostic laboratory clues to diagnosis are polyclonal hyperimmunoglobulinemia, raised serum IgG and IgE levels, elevation of serum soluble interleukin-2 (IL-2) receptor and presence of autoantibodies, whereas the IL-6, CRP and lactate dehydrogenase level were within normal limits in the majority of cases.

Differential diagnostic problems of IgG4-related lymphadenopathy

The present review demonstrates the histological variety of IgG4-related lymphadenopathy. Clinically, this disease frequently affected middle-aged and elderly patients, producing systemic lymphadenopathy associated with various immunological abnormalities.[53,54]

IgG4-related lymphadenopathy should be differentiated from various atypical and malignant LPD containing numerous and plasma cells.

Type I lesions had similar clinicopathological findings to multicentric Castleman's disease (MCD), including idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia (IPL).[67,70] In Japan, HHV-8 appears to be unrelated to the etiology of MCD except for HIV type-1 infection as well as IgG4-related lymphadenopathy.[70,71] We (YS and MK) have seen numerous IgG4-positive plasma cells in the lymph nodal lesion of IPL, although the serum IL-6 level was within normal limits in the majority of type I lesions.[54,66] The abnormal clinical findings, such as general fatigue, anemia and polyclonal hypergammaglobulinemia, elevated CRP and thrombocytosis may be related to a high level of IL-6 in the MCD,[72–74] but there were no clinical characteristics of MCD in any of the IgG4-related lymphadenopathies.

Type I lesions also should be differentiated from lymph node lesions of autoimmune disease-associated lymphadenopathy, in particular rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).[75,76] The characteristic histological finding of lymph nodal lesion of RA is both reactive follicular hyperplasia and interfollicular plasmacytosis.[75] The lymph nodal lesion of SLE occasionally has similar histological findings to Castleman's disease,[76] but there is no evidence of definite autoimmune disease in any of the IgG4-related lymphadenopathies.

One of the most important differential diagnostic problems is atypical lymphoplasmacytic and immunoblastic proliferation (autoimmune-disease-associated lymphadenopathy).[77] Koo *et al.* reported an unusual lymph node lesion, namely 'ALPIB',[77] which is associated with various autoimmune disease including RA and SLE.[77,78] Histologically, the lesion is characterized by prominent polyclonal lymphoplasmacytic infiltration with various numbers of immunoblasts.[77] There is no evidence, however, of definite autoimmune disease in any of the IgG4-related lymphadenopathies.

When AITL contains a few tumor cells (clear cells) with numerous plasma cells and B-immunoblasts, it can be confused with type III lesions. In contrast to AITL, there are no cytologically atypical CD10+ T-cells and there is no extrafollicular follicular dendritic proliferation in type III lesions.[79] Moreover, AITL usually involves systemic symptoms such as fever.[79]

Type IV lesion has histological findings of early stage PTGC.[68] A portion of PTGC containing numerous plasma cells in the germinal center may be an IgG4-related lymphadenopathy.

Type V lesions have similar histological findings to those of the IPT of the lymph node. IPT of the lymph node, however, mainly affects the lymph node framework such as hilum, trabeculae and capsule,[68,69] whereas lesions of IgG4-related disease are usually located in the lymph node parenchyma.

The importance of recognition of this entity lies in the remarkable response to steroid therapy. The diagnosis requires awareness and a high index of suspicion for this entity, which could present as unexplained lymphadenopathy with numerous plasma cells and scattered eosinophils, or lymphadenopathy in patients with known pancreatitis, lacrimal gland lesion or salivary gland lesion.

OCULAR ADNEXAL IgG4-RELATED DISEASE

Clinical and pathological findings of ocular adnexal IgG4-related disease

IgG4-related diseases frequently involve the ocular adnexal region.[80,81] Ocular adnexal IgG4-related disease is also