

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 Japanese⁸ and European⁹ 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 SS⁷. 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 dramatic¹⁰.

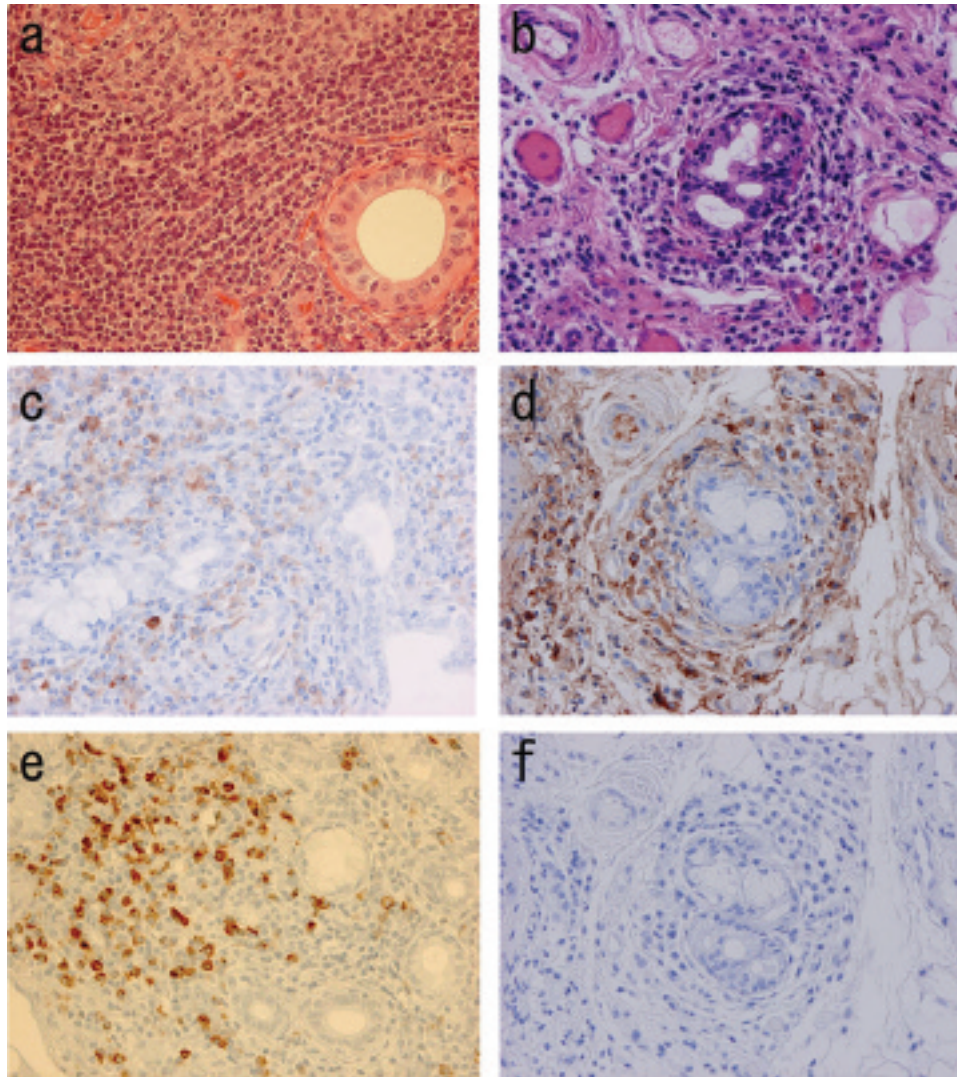


Figure 1. Histopathological findings of labial minor salivary gland biopsy in patients with IgG4+ MOLPS/Mikulicz's disease (a, c, e) and Sjögren's syndrome (b, d, f). (a, b) Hematoxylin and eosin staining; (c, d) IgG immunostaining; (e, f) IgG4 immunostaining. (a) Massive lymphocyte and plasmacyte infiltration 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 1961¹¹ and characterized by infrequent attacks of abdominal pain, jaundice, irregular narrowing of the pancreatic duct, and swelling of the pancreatic parenchyma¹¹⁻²². Kawaguchi, *et al* described cases complicated with similar pathological features in the common bile duct, gall bladder, and minor salivary glands, suggesting a systemic disorder¹². 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 gluco-

corticoids¹³. 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 pancreatitis¹⁴. Further, massive IgG4+ plasmacytic infiltration in the pancreatic tissue was reported¹⁵. There have been many recent reports of AIP in Asia¹²⁻¹⁹ and in Western countries^{20,21}.

Various diagnostic criteria for AIP have been proposed in Japan²³, Korea¹⁷, and the United States (Mayo Clinic)²¹. In 2008, the Japan-Korea Symposium on AIP proposed Asian diagnostic criteria¹⁹. 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 lung²⁴, liver¹⁶, and breast^{16,25}; retroperitoneal or mediastinal fibrosis²⁶; interstitial nephritis²⁷; hypophysitis⁵; sclerosing dacryoadenitis²⁸; sialadenitis (MD and Küttner's tumor)^{4,5,29}; inflammatory aortic aneurysm^{30,31}; tumorous lesions of the coronary artery³¹; lymphadenopathy³²; 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 disease¹⁵, IgG4-related plasmacytic disease⁶, and IgG4-related sclerosing disease¹⁸, 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 disease³⁴, Wegener's granulomatosis³⁵, lymphoma^{36,37}, and cancer³⁸, 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 complement³⁹. 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 polyclonal⁴⁰. 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- β (TGF- β)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

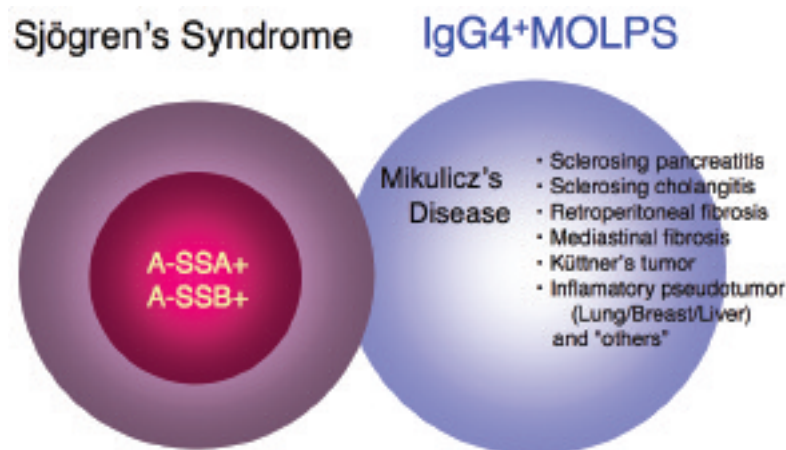


Figure 2. IgG4+ MOLPS should be defined as a distinct clinicopathological entity that includes Mikulicz's disease (MD), autoimmune pancreatitis (AIP), sclerosing cholangitis, and other clinical conditions with good response to glucocorticoids. Although the diagnostic criteria of SS may include some patients 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- β , which could be followed by IgG4 class switching and fibroplasia⁴¹.

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+ MOLPS⁷. The immunoglobulin gene fragments C μ , C δ , C γ 3, C γ 1, C α 1, C γ 2, C γ 4, C ϵ , and C α 2, 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 Clinic²¹ 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.Festschr.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 immunoglobulin 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.