IgG4-related Disease of the Head and Neck

Rahat M. Bhatti, MD and Edward B. Stelow, MD

Abstract: IgG4-related disease is an uncommon sclerosing and inflammatory mass-forming disease that may affect a single organ or be systemic. The prototypical example of the disease is type 1 autoimmune pancreatitis. After the pancreatobiliary system, the head and neck is the next most common site for involvement by IgG4-related disease. Here, we describe the clinicopathologic features of the head and neck involvement by this disease process with particular attention to involvement of the major salivary glands, the lacrimal glands and periorbital tissues, the upper aerodigestive tract, the thyroid gland, lymph nodes, the ear, and the skin and soft tissues.

Key Words: IgG4, salivary gland, sialadenitis, sclerosing, dacryoadenitis, Kuttner, angiocentric eosinophilic fibrosis, submandibular, lacrimal, thyroid, lymph node

(Adv Anat Pathol 2013;20:10–16)

Hamano et al1 were the first to associate some cases of apparently autoimmune pancreatitis (AIP) with elevated serum levels of IgG4. They described patients who had tumofactive, sclerotic, chronically inflamed lesions of the pancreas with increased serum IgG4 concentrations and compared them to patients with other forms of pancreatic disease. Since that time, many studies have established the relationship of increased serum IgG4 concentrations and increased number of tissue IgG4 + plasma cells with chronically inflamed, sclerotic lesions in the pancreas (ie, AIP type 1).2–7

As our understanding of AIP has evolved, it has been shown that patients with type 1 disease often have similar sclerosing lesions in other organs and at other body sites.8–13 Described sites of involvement include salivary glands,14–19 lacrimal glands (and periorbital tissues),13,17,20–25 the thyroid gland,26–30 the upper aerodigestive tract (UADT),31–33 the aorta,13,34 extra and intrahepatic biliary tracts and the gallbladder,9,13,35 lungs,9,13 kidneys,11,36,37 the prostate,28 breasts,38 the mediastinum,39 meningies,9 lymph nodes,40,41 the retroperitoneum,13,27,35,39,42,43 and skin and soft tissues.44

Lesions at these sites share histologic features of type 1 AIP. The head and neck region is the second most common site overall, after the pancreatobiliary system, to be affected by IgG4-RD.12,13,27 As mentioned above, studies have indicated that salivary glands, lacrimal glands, and various other tissues in the head and neck region can be involved in patients with AIP and the histologic pattern seen with the lesions of the head and neck is similar to lesions seen in type 1 AIP (Table 1). Here, we review IgG4-RD of the head and neck.

Before we begin, however, we note that a plethora of nomenclature has been used to describe this disease, including IgG4-associated multifocal systemic fibrosis,45 IgG4-related systemic fibrosclerosis,46 IgG4-related autoimmune disease,4 IgG4-multiorgan lymphoproliferative syndrome,12 IgG4-related sclerosing disease,42 and IgG4-related disease (IgG4-RD).36,47 Among others, here, we will use the term IgG4-RD to describe this entity as decided in a recent consensus meeting regarding the disease.9

MAJOR SALIVARY GLANDS

Chronic sclerosing sialadenitis (CSS), or Kuttner tumor is the head and neck lesion most extensively associated with IgG4-RD. It is a benign chronic inflammatory disorder of the salivary glands that most commonly involves the submandibular glands.14–16,18,48,49 CSS has been associated with IgG4 sclerosing lesions in other tissues, as indicated above, especially type 1 AIP. In a recent study, 3 of 13 patients with CSS had other sites involved by apparent IgG4-RD.16

CSS usually presents as a mass lesion, and thus may clinically resemble carcinoma. These lesions may elicit local discomfort. Typically, the disease is unilateral, but bilateral lesions have been described. The lesions are found in middle-aged and older adults with a few patients noted to be in their 30s. Serum IgG4 levels have not been consistently reported; however, a wide range in concentrations has been noted, with levels often being several to more than 10-fold that of normal concentrations.18,48,50

CSS is characterized by a loss of acinar tissue with lymphoplasmacytic infiltrates, periductal fibrosis, sclerosis, and obliterative phlebitis (Fig. 1). The lobular architecture typically remains intact, however, with severe and chronic inflammation, the architecture may be lost or difficult to appreciate. In some cases, varying degrees of cosinophils and granulomatous inflammation have been noted. Germinal center formation within lymphoid follicles has been reported in some cases and may appear “geographic.”

Tissue IgG4 + plasma cell counts typically range from greater than 60 cells per high power field (HPF) to a few hundred cells/HPF (Fig. 1). However, a wide range exists, and cases with counts ranging from 20 cells/HPF and over 600 cells/HPF have been reported. Tissue IgG4:IgG + plasma cell ratios have ranged from approximately 50% to over 90% in reported cases. Of note, IgG4:IgG + plasma cell ratios <40% have also been reported in some cases.

The literature is confused regarding the association of IgG4-RD and Mikulicz disease (an entity frequently associated with Sjogren syndrome).15,25,42,47,51–53 Reports have shown increased numbers of tissue IgG4 + plasma cells and elevated serum levels of IgG4 in some cases of patients with enlarged salivary glands and/or lacrimal glands. In our opinion, the term “Mikulicz disease” is a nonspecific term...
most often used today to describe parotid disease associated with Sjogren syndrome and lymphoepithelial sialadenitis. Such cases represent a distinct condition from IgG4-RD with little clinical or histomorphologic overlap. Confusion has arisen because of the nonspecific nature of the term “Miculicz disease,” used sometimes to describe the simple clinical presence of enlarged salivary glands and/or lacrimal glands, and nonspecific increases of serum IgG4 levels and IgG4 + plasma cells in tissues from inflamed but nonsclerosing diseases.

**LACRIMAL GLANDS AND PERIOCULAR TISSUES**

Chronic sclerosing dacryoadenitis of the lacrimal glands and similar disease seen in the extraocular muscles, periorbital soft tissues, and nasolacrimal ducts, have been associated with elevated serum IgG4 levels and numbers of tissue IgG4 + plasma cells. Patients are typically in their sixth to eighth decade of life with occasional patients noted to be in their 30s to 40s. Patients present with a variety of symptoms including swollen lacrimal glands (often bilateral). Swollen eyelids, extraocular muscle swelling, pain, diplopia, and proptosis may also be seen. Blindness due to entrapment of the optic nerve has even been reported. Serum levels of IgG4 have varied, ranging from several fold to 20-fold above normal ranges. As with CSS, this disease may be seen in patients with other IgG4-RD, including CSS.

Histologic sections of sclerosing dacryoadenitis show dense lymphoplasmacytic infiltrates, loss of acinar tissue,
periductal fibrosis, and lymphoid follicles with germinal center formation, similar to changes seen with CSS (Fig. 2). Some cases have a predominance of fibrocollagenous tissue with scattered lymphoid aggregates. Obliterative phlebitis may or may not be seen (Fig. 2). A wide range of tissue IgG4 + plasma cell numbers has been reported, from as low as 10 IgG4 + plasma cells/HPF to nearly 800 cells/HPF. Tissue IgG4: IgG + plasma cell ratios range from approximately 40% to over 90%.

UPPER AERODIGESTIVE TRACT

Eosinophilic angiocentric fibrosis (EAF) is a process of unknown etiology that typically involves the upper respiratory tract.31–33 Recently, it has been proposed that this disease may represent UADT involvement by IgG4-RD. The disease typically presents as an obstructing mass, and nearly 3 quarters of the cases have involved the sinonasal tract, although oral, pharyngeal, and laryngeal disease has also been reported. Interestingly, the disease has been described in the periorbital tissues as well, although the histologic features certainly overlap with chronic sclerosing dacryoadenitis, described above. Patients vary widely in age from those in their 20s to the elderly. With nasal involvement, patients may also present with congestion, facial pain, or epistaxis.

Histologically, lesions typically display a concentric fibrosis surrounding small vessels with a mixed inflammatory infiltrate (Fig. 3). The majority of the infiltrate is composed of eosinophils, but also includes plasma cells, lymphocytes, and neutrophils. In some cases, the inflammatory infiltrate has a periductal component. When looked for with this disease, obliterative phlebitis has not been seen. A single series linking EAF with IgG4-RD described elevated serum IgG4 levels, tissue IgG4 + plasma cells ranging from 0 to 118 cells/HPF, and IgG4: IgG + plasma cell ratios ranging from 0% to 97%. Further work will be necessary to examine the relationship between EAF and IgG4-RD.

Other reports of possible IgG4-RD involvement with mucosal surfaces in the head and neck are uncommon. Ishida et al60 reported on a 73-year-old man with mass lesions in the maxillary sinus, nasal septum, and parotid gland. Biopsies from the effected tissues revealed typical IgG4-RD histology with lymphoplasmacytic infiltration, fibroelastic changes, acinar structure loss, and occasional obliterative phlebitis. Lymphoid follicles and germinal centers were also seen in the parotid and nasal septum lesions. The IgG4: IgG + plasma cell ratio was 86%, 75%, and 72% in lesions of the nasal septum, parotid gland, and maxillary sinus, respectively. Although uncommon, other fibroelastic mass lesions of the UADT may also someday be categorized within the spectrum of this disease.

THYROID

Some forms of sclerosing thyroiditis have been proposed to be associated with IgG4-RD.26,28–30,61–64 Typical Hashimoto thyroiditis almost certainly does not fall into this category of disease, but more poorly understood sclerosing lesions such as Reidel thyroiditis and some cases previously diagnosed as “Hashimoto thyroiditis” may.
Indeed, a subtype of Hashimoto thyroiditis, tentatively named “IgG4 thyroiditis” has been proposed. Patients with this disease present with subclinical hypothyroidism, rapid progress, and diffuse low echogenicity throughout their glands on ultrasound. Here, it is interesting to note that patients with AIP have been found to have greater rates of hypothyroidism. Patients described as having thyroid lesions that may be associated with IgG4-RD are more often women and are typically middle aged with some in their 30s to 40s.

Histologic findings have included a densely fibrotic stroma (described as interfollicular), degenerating follicular thyroid tissue, and dense lymphoplasmacytic inflammation. The presence of phlebitis has been inconsistent, with most reports of thyroid disease lacking it. Some cases are reported to have an eosinophilic infiltrate as well. Tissue IgG4 + plasma cell numbers are variable in reported cases, ranging from none to over 50 cells/HPF. Similarly, in reported cases, IgG4:IgG + plasma cell ratios have varied from 0% to 90%.

**EAR**

Although uncommon, there are descriptions of apparent IgG4-RD involving the ears. Cho et al described a 66-year-old woman with bilateral progressive hearing loss. The patient also had chronic cough and pain in and around 1 eye. Otoscopic examination showed turbidity of both the eardrums and computed tomography showed thickening of the tympanic membrane and middle ear mucosa. Further imaging revealed bilateral lung nodules and a renal mass. Serum IgG4 concentration was increased to approximately 240 mg/dL. The authors reported dense lymphoplasmacytic infiltration with numerous IgG4 + plasma cells in tissue sampled from the lacrimal gland, renal mass, and pulmonary nodules. Histology from the actual ear lesion was not obtained, however.

**LYMPH NODES**

Lymphadenopathy is a common finding in IgG4-RD. Regional and nonregional lymph nodes can be involved. Among cases of IgG4-RD of the head and neck, sites of lymphadenopathy have included submandibular, cervical, periauricular, axillary, mediastinal, para-aortic, and groin. The lymphadenopathy tends to be asymptomatic but localized effects have been described.

Enlarged lymph nodes are not routinely sampled with IgG4-RD. However, when lymph node tissue is taken, the characteristic findings of IgG4-RD are usually lacking. Instead, dense infiltrates of IgG4 + plasma cells are observed, whereas sclerosis and obliterator phlebitis are usually not. Cheuk et al examined lymph nodes from patients with various forms of IgG4-RD, including lesions of the head and neck. They found that IgG4 + plasma cell numbers ranged from 17 to 877 cells/HPF (mean 416 cells/HPF) and IgG4:IgG + plasma cell ratios ranged from 43% to 99% (mean 60%). In their study, control nodes had a mean tissue IgG4 + plasma cell count of 31.1 cells/HPF and a mean IgG4:IgG + plasma cell ratio of 9.9%. They categorized IgG4-RD lymph node histologic patterns into the following groups: Castleman disease-like features (type I), follicular hyperplasia (type II), interfollicular expansion (type III), progressive transformation of germinal center-like (type IV) (Fig. 4), and nodal inflammatory pseudotumor-like (type V). Some have likened the overall reactive-appearing picture of lymph nodes associated with IgG4-RD to lymphadenopathy in rheumatic disease.

In general, the lymph node pathology of IgG4-RD has been described by using enlarged nodes from patients with known extranodal sclerotic, mass lesions. A recent study looked only at lymph nodes from the neck of patients diagnosed with progressively transformed germinal centers. The authors found increased IgG4 + plasma cells localized to the germinal centers and nearly 90% of patients tested were found to have increased serum IgG4 concentrations. Interestingly, more than half the patients with follow-up went on to develop extranodal lesions typical of IgG4-RD, most often involving the submandibular and/or lacrimal glands.

**SOFT TISSUES AND SKIN**

Soft-tissue sclerotic lesions of the head and neck with increased numbers of IgG4 + plasma cell infiltrates have not been commonly reported. As with other IgG4-RD lesions, patients are middle aged to elderly. They present with indurated nodules in various locations including the neck, cheek, temporal area, or periauricular region. Some patients presented with synchronous masses in other tissues such as lacrimal glands, and some had a prior history of submandibular CSS.

Histologically, there was a lymphoplasmacytic infiltrate with follicle formation, sclerotic changes, and hyalinized collagen bundles. Phlebitis was seen in some cases but not others. Serum concentrations of IgG4 were up to 10-fold higher than normal. Tissue IgG4 + plasma cells/HPF are reported in a few patients and averaged approximately 400 cells/HPF. IgG4:IgG + plasma cell ratios range from approximately 68% to nearly 100%.

**TREATMENT AND PROGNOSIS**

Clinically, IgG4-RD lesions from the head and neck have shown improvement with glucocorticoid therapy. As with AIP, glucocorticoid therapy
leads to both a clinical response and a decrease in serum IgG4 levels and tissue IgG4 + plasma cell numbers. Lymphadenopathy has also been seen to resolve with glucocorticoid therapy. 40 Relapse following cessation of glucocorticoid therapy has been noted. 43 Some cases that have shown suboptimal response to glucocorticoids, have responded to rituximab. 70

In general, prognosis is favorable. Although IgG4-RD is benign, locally destructive effects of chronic inflammation and sclerosis may be avoided with prompt glucocorticoid or other treatment. The relationship between IgG4-RD and malignancy is less clear. There have been a number of case reports and small series of lymphoma, usually extranodal marginal zone lymphoma, associated with the disease, sometimes diagnosed after a previous diagnosis of IgG4-RD. 20,22,55 This suggests that the IgG4-RD may provide for a chronic inflammatory stimulus that then predisposes to the development of lymphoma. Epithelial malignancies have also been described and possibly associated with IgG4-RD including sclerosing mucopidermoid carcinoma and salivary duct carcinoma, as well as papillary thyroid carcinoma. 71–73 The relationships here seem more tenuous, but it may be that epithelial damage caused by IgG4-RD increases the risk for the development of malignancy.

CONCLUSIONS

In summary, IgG4-RD is a sclerosing, chronic inflammatory disorder that affects various tissues, mainly occurring in middle-aged to elderly individuals. A male predominance has been reported by some. Clinically, affected organs typically appear to be involved by a malignant process. Early diagnosis (before resection) is the key as many lesions will have a favorable response to steroids or other immunosuppressive agents. According to a new consensus statement, histologic diagnosis rests on specific cutoff values for serum IgG4 levels and tissue IgG4 + plasma cell counts do not exist although various numbers have been used.

Several other important points should be appreciated. Elevated serum IgG4 levels or numbers of IgG4 + plasma cells in tissue are not specific to IgG4-RD. The disease has distinct histologic features necessary for a diagnosis. In addition, our understanding of the disease process in general is incomplete. Although the process seems to be “related” to elevated serum concentration of IgG4 and increased numbers of IgG4 + plasma cells in affected tissues, the nature of the relationship is unclear.

REFERENCES

1. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med. 2001;344:732–738.
2. Choi EK, Kim MH, Lee TY, et al. The sensitivity and specificity of serum immunoglobulin G and immunoglobulin G4 levels in the diagnosis of autoimmune chronic pancreatitis: Korean experience. Pancreas. 2007;35:156–161.
3. Deshpande V, Chicanco S, Finkelberg D, et al. Autoimmune pancreatitis: a systemic immune complex mediated disease. Am J Surg Pathol. 2006;30:1537–1545.
4. Kamisawa T, Funata N, Hayashi Y, et al. A new clinicopathological entity of IgG4-related autoimmune disease. J Gastroenterol. 2003;38:982–984.
5. Kojima M, Sipos B, Krapper W, et al. Autoimmune pancreatitis: frequency, IgG4 expression, and clonality of T and B cells. Am J Surg Pathol. 2007;31:521–529.
6. Morselli-Labate AM, Pizzilli R. Usefulness of serum IgG4 in the diagnosis and follow up of autoimmune pancreatitis: a systematic literature review and meta-analysis. J Gastroenterol Hepatol. 2009;24:15–36.
7. Sepehr A, Mino-Kenudson M, Ogawa F, et al. IgG4 + to IgG + plasma cells ratio of ampulla can help differentiate autoimmune pancreatitis from other “mass forming” pancreatic lesions. Am J Surg Pathol. 2008;32:1770–1779.
8. Bateman AC, Deheragoda MG. IgG4-related systemic sclerosing disease - an emerging and under-diagnosed condition. Histopathology. 2009;55:373–383.
9. Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol. 2012;25:1181–1192.
10. Kamisawa T, Funata N, Hayashi Y, et al. Close relationship between autoimmune pancreatitis and multifocal fibrosclerosis. Gut. 2003;52:683–687.
11. Kamisawa T, Okamoto A. IgG4-related sclerosing disease. World J Gastroenterol. 2008;14:3948–3955.
12. Masaki Y, Dong L, Kurose N, 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;68:1310–1315.
13. Zen Y, Nakamura Y. IgG4-related disease: a cross-sectional study of 114 cases. Am J Surg Pathol. 2010;34:1812–1819.
14. Cheuk W, Chan JK. Kuttner tumor of the submandibular gland: fine-needle aspiration cytologic findings of seven cases. Am J Clin Pathol. 2002;117:103–108.
15. Geyer JT, Deshpande V. IgG4-associated sialadenitis. Curr Opin Ophthalmol. 2011;22:95–101.
16. Geyer JT, Ferry JA, Harris NL, et al. Chronic sclerosing sialadenitis (Kuttner tumor) is an IgG4-associated disease. Am J Surg Pathol. 2010;34:202–210.
17. Jakobiec FA, Stacy RC, Mehta M, et al. IgG4-positive dacyroadenitis and Kuttner submandibular sclerosing inflammatory tumor. Arch Ophthalmol. 2010;128:942–944.
18. Kitagawa S, Zen Y, Harada K, et al. Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Kuttner’s tumor). Am J Surg Pathol. 2005;29:783–791.
19. Tsuneyama K, Saito K, Ruebner BH, et al. Immunological similarities between primary sclerosing cholangitis and chronic sclerosing sialadenitis: report of the overlapping of these two autoimmune diseases. Dig Dis Sci. 2000;45:366–372.
20. Cheuk W, Yuen HK, Chan AC, et al. Ocular adnexal lymphoma associated with IgG4 + chronic sclerosing dacyroadenitis: a previously undescribed complication of IgG4-related sclerosing disease. Am J Surg Pathol. 2008;32:1159–1167.
21. Cheuk W, Yuen HK, Chan JK. Chronic sclerosing dacyroadenitis: part of the spectrum of IgG4-related Sclerosing disease? Am J Surg Pathol. 2007;31:643–645.
22. Lee LY, Chen TC, Kuo TT. Simultaneous occurrence of IgG4-related chronic sclerosing dacyroadenitis and chronic sclerosing sialadenitis associated with lymph node involvement and Warthin’s tumor. Int J Surg Pathol. 2011;19:369–372.
23. Oshitari T, Yotsukura J, Asahagi K, et al. Relationship between chronic sclerosing dacyroadenitis with high level of IgG4 and Castleman disease. Clin Ophthalmol. 2010;5:23–25.
24. Sato Y, Ohshima K, Ichimura K, et al. Ocular adnexal IgG4-related disease has uniform clinicopathology. Pathol Int. 2008;58:465–470.
25. Suzuki K, Tamaru J, Okuyama A, et al. IgG4-positive multi-organ lymphoproliferative syndrome manifesting as chronic symmetrical sclerosing dacyro-sialadenitis with subsequent secondary portal hypertension and remarkable
IgG4-linked IL-4 elevation. *Rheumatology (Oxford).* 2010; 49:1789–1791.

26. Dahlgren M, Khosroshahi A, Nielsen GP, et al. Riedel’s thyroiditis and multifocal fibrosclerosis are part of the IgG4-related systemic disease spectrum. *Arthritis Care Res (Hoboken).* 2010;62:1312–1318.

27. Hamano H, Arakura N, Muraki T, et al. Prevalence and distribution of extrapancreatic lesions complicating autoimmune pancreatitis. *J Gastroenterol.* 2006;41:1197–1205.

28. Kakudo K, Li Y, Hirokawa M, et al. Diagnosis of Hashimoto’s thyroiditis and IgG4-related sclerosing disease. *Pathol Int.* 2011;61:175–183.

29. Komatsu K, Hamano H, Ochi Y, et al. High prevalence of hypothyroidism in patients with autoimmune pancreatitis. *Dig Dis Sci.* 2005;50:1052–1057.

30. Li Y, Bai Y, Liu Z, et al. Immunohistochemistry of IgG4 can help subclassify Hashimoto’s autoimmune thyroiditis. *Pathol Int.* 2009;59:636–641.

31. Deshpande V, Khosroshahi A, Nielsen GP, et al. Eosinophilic angiocentric fibrosis is a form of IgG4-related systemic disease. *Am J Surg Pathol.* 2011;35:701–706.

32. Kosarac O, Luna MA, Ro JY, et al. Eosinophilic angiocentric fibrosis of the sinonasal tract. *Ann Diag Pathol.* 2008;12: 267–270.

33. Sunde J, Alexander KA, Reddy VV, et al. Intranasal eosinophilic angiocentric fibrosis: a case report and review. *Head Neck Pathol.* 2010;4:246–248.

34. Kasashima S, Zen Y, Kawashima A, et al. Inflammatory abdominal aortic aneurysm: close relationship to IgG4-related periarteritis. *Am J Surg Pathol.* 2008;32:197–204.

35. Kamisawa T, Nakajima H, Egawa N, et al. IgG4-related sclerosing disease incorporating sclerosing pancreatitis, cholangitis, sialadenitis and retroperitoneal fibrosis with lymphadenopathy. *Pancreatology.* 2006;6:132–137.

36. Umehara H, Okazaki K, Masaki Y, et al. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. *Mod Rheumatol.* 2012;22:1–14.

37. Cornell LD, Chicanco SL, Deshpande V, et al. Pseudotumors due to IgG4 immune-complex tubulointerstitial nephritis associated with autoimmune pancreateocentric disease. *Am J Surg Pathol.* 2007;31:1586–1597.

38. Zen Y, Kasahara Y, Horita K, 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;29:275–278.

39. Zen Y, Sawazaki A, Miyayama S, et al. A case of retroperitoneal and mediastinal fibrosis exhibiting elevated levels of IgG4 in the absence of sclerosing pancreatitis (autoimmune pancreatitis). *Hum Pathol.* 2006;37:239–243.

40. Cheuk W, Yuen HK, Chu SY, et al. Lymphadenopathy of IgG4-related sclerosing disease. *Am J Surg Pathol.* 2008;32:671–681.

41. Kojima M, Miyawaki S, Takada S, et al. Lymphoplasmacytic infiltrate of regional lymph nodes in Kuttner’s tumor (chronic sclerosing sialadenitis): a report of 3 cases. *Int J Surg Pathol.* 2008;16:263–268.

42. Cheuk W, Chan JK. IgG4-related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity. *Adv Anat Pathol.* 2010;17:303–332.

43. Divatia M, Kim SA, Ro JY. IgG4-related sclerosing disease, an emerging entity: a review of a multi-system disease. *Yonsei Med J.* 2013;54:15–34.

44. Cheuk W, Tam FK, Chan AN, et al. Idiopathic cervical fibrosis—a new member of IgG4-related sclerosing diseases: report of 4 cases, 1 complicated by composite lymphoma. *Am J Surg Pathol.* 2010;34:1678–1685.

45. van der Vliet HJ, Penerboom RM. Multiple pseudotumors in IgG4-associated multifocal surgical fibrosis. *Am Intern Med.* 2009;141:889–897.

46. Strehl JD, Hartmann A, Agaimy A. Numerous IgG4-positive plasma cells are ubiquitous in diverse localised non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. *J Clin Pathol.* 2011;64: 237–243.

47. Masaki Y, Kurose N, Umehara H. IgG4-related disease: a novel lymphoproliferative disorder discovered and established in Japan in the 21st century. *J Clin Exp Hematop.* 2011;51: 13–20.

48. Kamisawa T, Nakajima H, Hishima T. Close relationship between chronic sclerosing sialadenitis and immunoglobulin G4. *Intern Med J.* 2006;36:527–529.

49. Laco J, Ryska A, Celakovsky P, et al. Chronic sclerosing sialadenitis as one of the immunoglobulin G4-related diseases: a clinicopathological study of six cases from Central Europe. *Histopathology.* 2011;58:1157–1163.

50. Abe T, Sato T, Tomaru Y, et al. Immunoglobulin G4-related sclerosing sialadenitis: report of two cases and review of the literature. *Oral Surg Oral Med Oral Path Oral Radiol Endod.* 2009;108:544–550.

51. Kuriyama T, Takano K, Yamamoto M, et al. A novel concept of Mikulicz’s disease as IgG4-related disease. *Auris Nasus Larynx.* 2012;39:9–17.

52. Takano K, Yamamoto M, Takahashi H, et al. Clinicopathologic similarities between Mikulicz disease and Kuttner tumor. *Am J Otolaryngol.* 2010;31:429–434.

53. Yamamoto M, Takahashi H, Ohara M, et al. A novel conceptualization for Mikulicz’s disease as an IgG4-related plasmacytic disease. *Mod Rheumatol.* 2006;16:335–340.

54. Kubota K, Moritani S, Katayama M, et al. Ocular adnexal IgG4-related lymphoplasmacytic infiltrative disorder. *Arch Ophthalmol.* 2010;128:577–584.

55. Kubota K, Moritani S, Yoshino T, et al. Ocular adnexal marginal zone B cell lymphoma infiltrated by IgG4-positive plasma cells. *J Clin Pathol.* 2010;63:1059–1065.

56. Suzuki M, Mizumachi T, Morita S, et al. A case of immunoglobulin G4-related disease with bilateral mass-forming lesions in the nasolacrimal ducts. *J Clin Rheumatol.* 2011;17: 207–210.

57. Higashiyama T, Nishida Y, Ugi S, et al. A case of extraocular muscle swelling due to IgG4-related sclerosing disease. *Jpn J Ophthalmol.* 2011;55:315–317.

58. Nagai K, Andoh K, Nakamura N, et al. Suspected idiopathic sclerosing orbital inflammation presenting as immunoglobulin G4-related disease: a case report. *J Med Case Rep.* 2011;5:427.

59. Wallace ZS, Khosroshahi A, Jakobiec FA, et al. IgG4-related systemic disease as a cause of “idiopathic” orbital inflammation, including orbital myositis, and trigeminal nerve involvement. *Surv Ophthalmol.* 2012;57:26–33.

60. Ishida M, Hotta M, Kushima R, et al. Multiple IgG4-related sclerosing lesions in the maxillary sinus, parotid gland and nasal septum. *Pathol Int.* 2009;59:670–675.

61. Hennessey JV. Clinical review: Riedel’s thyroiditis: a clinical review. *J Clin Endocrinol Metab.* 2011;96:3031–3041.

62. Kakudo K, Li Y, Taniguchi E, et al. IgG4-related disease of the thyroid glands. *Endocr J.* 2012;59:273–281.

63. Li Y, Nishihara E, Hirokawa M, et al. Distinct clinical, serological, and sonographic characteristics of hashimoto’s thyroiditis based with and without IgG4-positive plasma cells. *J Clin Endocrinol Metab.* 2010;95:1309–1317.

64. Li Y, Zhou G, Ozaki T, et al. Distinct histopathological features of Hashimoto’s thyroiditis with respect to IgG4-related disease. *Mod Pathol.* 2012;25:1086–1097.

65. Cho HK, Lee YJ, Chung JH, et al. Otolagic manifestation in IgG4-related systemic disease. *Clin Exp Otorhinolaryngol.* 2011;4:52–54.

66. Sato Y, Inoue D, Asano N, et al. Association between IgG4-related disease and progressively transformed germinal centers of lymph nodes. *Mod Pathol.* 2012;25:956–967.

67. Cheuk W, Lee KC, Chong LY, et al. IgG4-related sclerosing disease: a potential new etiology of cutaneous pseudolymphoma. *Am J Surg Pathol.* 2009;33:1713–1719.

68. Seki N, Yamazaki N, Kondo A, et al. Spontaneous regression of lung lesions after excision of the submandibular gland in a...
patient with chronic sclerosing sialadenitis. *Auris Nasus Larynx*. 2012;39:212–215.

69. Takahashi H, Yamamoto M, Suzuki C, et al. The birthday of a new syndrome: IgG4-related diseases constitute a clinical entity. *Autoimmun Rev*. 2010;9:591–594.

70. Khoroshahi A, Bloch DB, Deshpande V, et al. Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. *Arthritis Rheum*. 2010;62:1755–1762.

71. Gill J, Angelo N, Yeong ML, et al. Salivary duct carcinoma arising in IgG4-related autoimmune disease of the parotid gland. *Hum Pathol*. 2009;40:881–886.

72. Ito M, Naruke Y, Mihara Y, et al. Thyroid papillary carcinoma with solid sclerosing change in IgG4-related sclerosing disease. *Pathol Int*. 2011;61:589–592.

73. Tian W, Yakirevich E, Matoso A, et al. IgG4(+) plasma cells in sclerosing variant of mucoepidermoid carcinoma. *Am J Surg Pathol*. 2012;36:973–979.