

Ocular Adnexal Lymphoma Associated With IgG4+ Chronic Sclerosing Dacryoadenitis: A Previously Undescribed Complication of IgG4-related Sclerosing Disease

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Abstract: IgG4-related sclerosing disease is a recently recognized inflammatory lesion frequently involving pancreas, submandibular gland, lacrimal gland, and lymph node. We report 3 cases of ocular adnexal lymphoma arising in IgG4-related chronic sclerosing dacryoadenitis, a phenomenon that has not been previously reported. The patients presented with bilateral or unilateral ocular adnexal mass usually present for many years. One patient also had asymptomatic diffuse lymphadenopathy. Two patients had biopsy-proven IgG4-related chronic sclerosing dacryoadenitis before the current presentation, and 1 had systemic involvement by IgG4-related sclerosing disease as evidenced by increased IgG4+ cells in a prior nasopharyngeal biopsy. Two cases showed features of extranodal marginal zone lymphoma of mucosa-associated lymphoid-tissue type (1 with large cell transformation) and 1 follicular lymphoma. Thus, the lymphoid hyperplasia of IgG4-related sclerosing disease can provide a substrate for the emergence of lymphoma. In addition, we report 3 cases of ocular adnexal extranodal marginal zone B-cell lymphoma that show sclerosing inflammation in the background and numerous IgG4+ monotypic plasma cells. In the absence of prior biopsies or information on serum IgG4 titer, it is unclear whether these cases represent lymphoma complicating IgG4-related sclerosing disease or de novo lymphoma. Nonetheless, these cases are distinctive in that the neoplastic cells express IgG4 (light chain restricted), whereas unselected cases of ocular adnexal lymphomas do not show IgG4 expression.

Key Words: IgG4, IgG4-related sclerosing disease, chronic sclerosing dacryoadenitis, lymphoid hyperplasia, lymphoma, ocular adnexa, lacrimal gland

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IgG4-related sclerosing disease is a recently recognized syndrome, probably autoimmune in nature, characterized by tumorlike involvement of one or more exocrine glands or other extranodal sites by lymphoplasmacytic infiltrates and sclerosis, accompanied by increased IgG4+ plasma cells in the tissues and elevated IgG4 titer in the serum. The commonest components of this syndrome are autoimmune pancreatitis, chronic sclerosing sialadenitis of submandibular gland (Kuttner tumor) and chronic sclerosing dacryoadenitis.^{2,3,6,7,10,13} In this report, we describe 6 cases of lymphoma associated with or probably related to IgG4-related chronic sclerosing dacryoadenitis, a hitherto unreported phenomenon in IgG4-related sclerosing disease.

MATERIALS AND METHODS

The 6 cases of ocular adnexal lymphoma were retrieved from the consultation files (W.C., J.K.C.C., and A.C.L.C.) and surgical pathology archives of Queen Elizabeth Hospital, Hong Kong. The cases were divided into groups A and B for cases with or without prior histologically documented IgG4-related sclerosing disease respectively (Table 1). Cases in group B were prospectively identified after we recognized the phenomenon of lymphoma arising in IgG4-related chronic sclerosing dacryoadenitis, on the basis of morphologic similarities with group A and demonstration of increased IgG4+ plasma cells. Clinical information was obtained from the patient records, referring pathologists or clinicians. All available pathologic materials were retrieved for morphologic review and further workup. For comparison, 14 cases of uncomplicated IgG4-related chronic sclerosing

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dacryoadenitis, 16 consecutive cases of primary ocular adnexal lymphomas (including 14 extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) type and 2 diffuse large B-cell lymphomas), and 25 cases of gastric MALT lymphomas were studied.

Immunohistochemical staining was performed using the BOND-MAX automated immunostainer (Vision Biosystems, Australia), with a polymer-based detection system. The following antibodies were applied: anti-IgG (1:250, antiserum, Novocastra); anti-IgG4 (1:500, clone HP6025, Zymed); anti-IgM (1:5000, antiserum, Dako); anti-IgD (1:1000, antiserum, Dako); CD20 (1:1000, clone L26, Dako); CD3 (1:150, clone 56C6, NeoMarkers); CD5 (1:50, clone 4C7, Novocastra); CD10 (1:100, clone 56C6, Novocastra); bcl-2 (1:500, bcl-2-100, Zymed); bcl-6 (1:100, clone LN22, Novocastra); CD23 (1:60, clone 1B12, Novocastra); cyclin D1 (1:100, clone SP4, NeoMarkers); and immunoglobulin κ and λ -light chains (1:24,000, antiserum, Dako). Polymerase chain reaction (PCR) was performed using BIOMED-2 protocol (InvivoScribe Technologies) to assess clonality, with multiple primers being directed to the immunoglobulin heavy chain (IGH) gene and immunoglobulin- κ (IG κ) light chain gene.¹⁶

For enumeration of IgG4+ or IgG+ cells, the areas with the highest density of positive cells were evaluated. Three high power fields (HPF) in each section were counted, and an average number of positive cells per HPF was calculated. One HPF covered an area of 0.196 mm² (Nikon microscope, $\times 40$ objective, $\times 10$ eyepiece, 20-mm field of view). The proportion of IgG4+/IgG+ cells was considered significantly elevated when above 40%.⁴

RESULTS

Clinical Features

There were 4 male and 2 female patients, age ranging from 55 to 72 years (mean 65.7 y) (Table 1). The clinical presentation was bilateral ($n = 3$) or unilateral ($n = 3$) ocular adnexal masses for 1 to 6 years (mean duration 2 y). Asymptomatic generalized lymphadenopathy was detected in 2 patients (cases A3 and B1) by computed tomography, but lymph node biopsy was not available for examination in case B1. There was no known history of lymphoma. Orbital mass biopsy was obtained in all patients.

All patients presumably had stage I_E disease based on the limited available workup findings; staging

TABLE 1. Clinicopathologic Features

Case No.	Sex/Age	Presentation	Investigation Findings	Available Specimens	Treatment and Outcome
A1	F/69	Asymptomatic bilateral lacrimal gland swelling for 6 y	IgG κ paraproteinemia discovered on lymphoma workup	Right lacrimal gland biopsy 3 y ago (IgG4-related chronic sclerosing dacryoadenitis) Right lacrimal gland biopsy*	Treated with chemotherapy; well at 6 mo
A2	M/69	Bilateral proptosis for several years	CT showed diffuse bilateral orbital soft tissue infiltrate; antinuclear antibodies +, rheumatoid factor –	Nasopharyngeal biopsy performed 1 y ago (reactive lymphoid hyperplasia with increased IgG4+ cells) Left orbital mass biopsy*	No treatment; alive at 2 mo
A3	M/60	Right lacrimal gland swelling for 1 y	CT revealed bilateral orbital infiltrative soft tissue masses, systemic lymphadenopathy (cervical, axillary, mediastinal and paraaortic, up to 1 cm); decreased serum complement 3 and complement 4	Right lacrimal gland biopsy performed 1 y ago (IgG4-related chronic sclerosing dacryoadenitis) Right lacrimal gland biopsy* Right axillary lymph node excision (IgG4-related lymphadenopathy)	Treated with chemotherapy; well at 6 mo, with decrease in orbital swelling
B1	M/69	History of explosion injury resulting in blindness of both eyes 40 y ago; presented with right eye swelling for 1 y. CT revealed bilateral soft tissue masses in both orbits, most prominent in the lacrimal region of the right orbit, measuring 4.8 cm	Staging CT revealed systemic lymphadenopathy involving mediastinum, intra-abdominal and left renal hilum	Right orbital mass biopsy*	NA
B2	M/72	Right lacrimal gland swelling	NA	Right orbital mass biopsy*	NA
B3	F/55	Progressively enlarging right orbital mass for 2 mo	NA	Right orbital mass biopsy*	Treated with radiotherapy; well at 8 mo

*Current specimens showing lymphoma.

CT indicates computed tomography; F, female; M, male; NA, not available.

information was limited by a lack of biopsy materials from the contralateral orbit or enlarged lymph nodes.

Pathologic Findings of Ocular Adnexal Lesions

In cases A2, A3, B1, B2, and B3, the tissue showed diffuse and dense infiltration by small lymphoid cells, with many being centrocytelike and some showing clear cytoplasm, reminiscent of monocytoid B cells (Figs. 1–3). Aggregates of mature plasma cells were also present (Fig. 1B). There were interspersed reactive lymphoid follicles and sclerotic bands. Lymphoepithelial lesions were not found. The lymphoid cells were positive for CD20, and negative for CD3, CD5, CD10, CD23, and cyclin D1 (Fig. 4). The features were those of extranodal marginal zone B-cell lymphoma of MALT type (Table 2). In case A3, there were, in addition, solid sheets of CD20-positive large cells with vesicular nuclei, distinct nucleoli and frequent mitoses, consistent with large cell transformation (Fig. 2B). In case A1, aggregates of large lymphoid follicles were separated by broad sclerotic

septa. The germinal centers of most follicles were populated by abnormal large cells with oval, convoluted, or lobated nuclei, vesicular chromatin and distinct nucleoli (Fig. 5). These atypical cells were much larger than normal centroblasts and were not observed outside the follicles. They expressed CD20, bcl-2, bcl-6, and CD10, and furthermore exhibited κ light chain restriction, consistent with grade 3b follicular lymphoma (Fig. 5C).

Residual lacrimal gland tissue was identified in 4 cases, with marked loss of acini, periductal fibrosis, lymphoplasmacytic infiltrate, and sclerosis. The proportion of IgG4+/IgG+ cells ranged from 68% to 94% for cases from group A, and these plasma cells were polytypic. For cases from group B, the proportion ranged from 53% to 209%. In case B3, the number of IgG4+ plasma cells outnumbered IgG+ plasma cells, suggesting that the IgG4+ cells might have alterations in the antigenic determinant, resulting in failure of binding by the anti-IgG antibody being used. All 3 cases from group B showed light chain restriction of the IgG4+ cells (κ in 1 case, and λ in 2 cases) (Fig. 6).

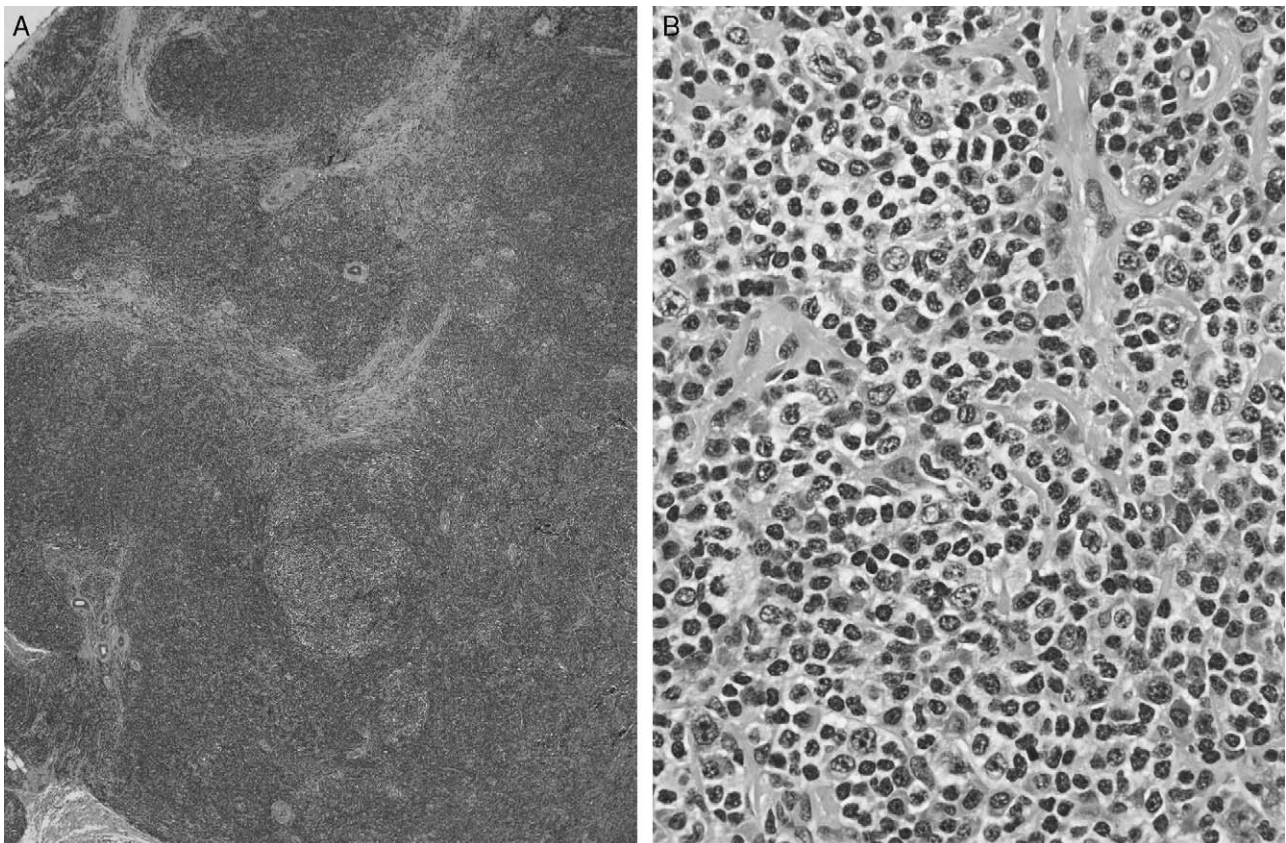


FIGURE 1. MALT lymphoma, case A2. A, The lacrimal gland parenchyma is effaced by a diffuse dense infiltrate of lymphoid cells. The pale areas (lower central field) represent foci rich in cells resembling monocytoid B cells. Sclerotic bands and a few residual small ducts are seen. B, The infiltrate comprises small lymphoid cells with round to irregularly folded nuclei and scanty to moderate amounts of clear cytoplasm. There are admixed mature plasma cells.

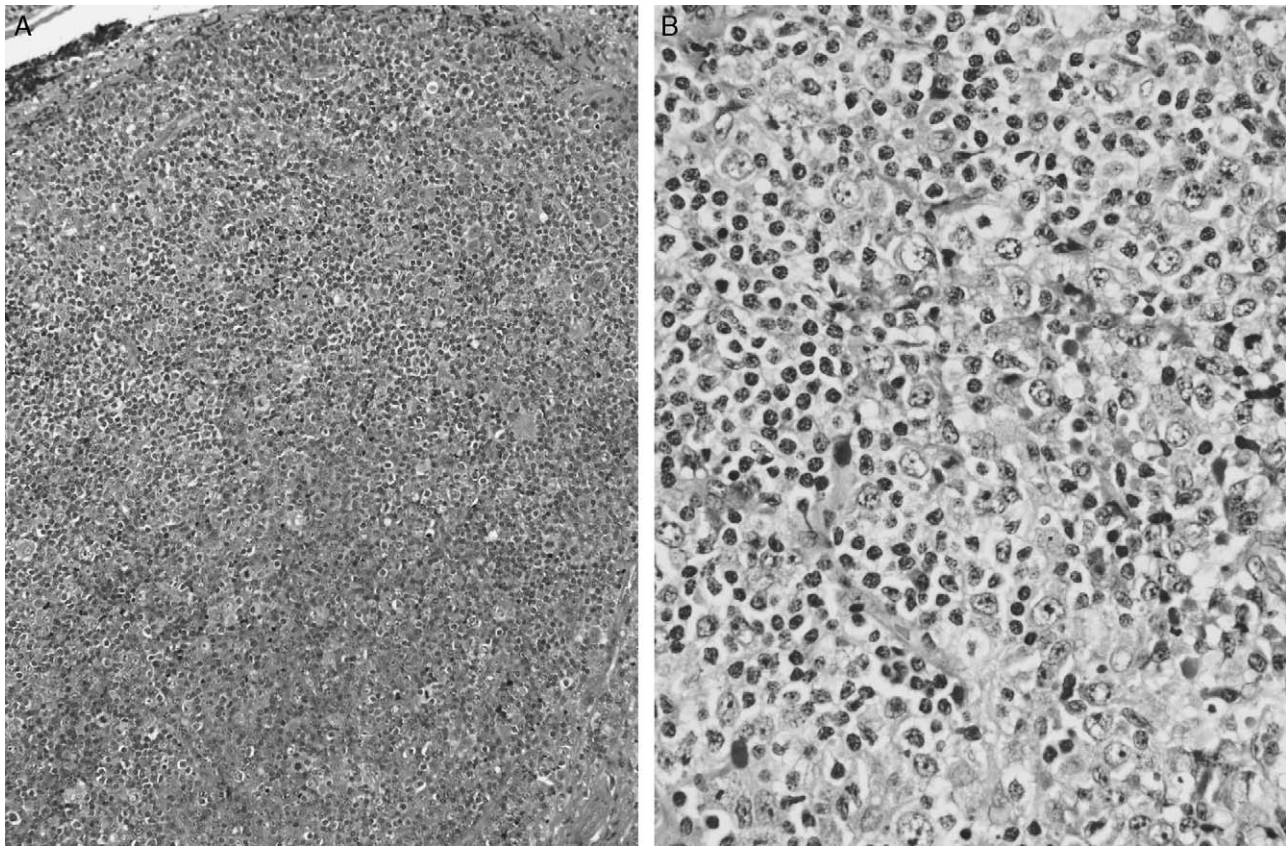


FIGURE 2. MALT lymphoma, with a component of large B-cell lymphoma, case A3. A, In this diffuse infiltrate of lymphoid cells, the proportion of large cells increases from the upper toward the lower field. B, Higher magnification shows MALT lymphoma (rich in clear cells) in the left field and large B-cell lymphoma in the right field.

All cases except case A1 and B3 showed clonal immunoglobulin gene rearrangement on PCR (Table 2). Clonal band was demonstrable using primers to IGH in 3 cases and was demonstrable only with primers to IGκ in 1 case.

Previous and Other Biopsies

In cases A1 and A3, ipsilateral orbitotomy had been performed 3 years and 1 year before current presentation, respectively. Both specimens revealed features of IgG4-related chronic sclerosing dacryoadenitis, featuring atrophic lacrimal acini, periductal fibrosis, dense lymphoplasmacytic infiltrate, reactive lymphoid follicles, and septal sclerosis (Fig. 7). On immunostaining, B cells (CD20⁺) were organized in nodules separated by zones rich in T cells (CD3⁺). The proportions of IgG4⁺/IgG⁺ plasma cells were 68% and 92%, respectively (Fig. 7A). The plasma cells were polytypic with no light chain restriction.

In case A3, who also had diffuse lymphadenopathy, an excised axillary lymph node showed reactive follicular hyperplasia and increased plasma cells (Fig. 8). There was no evidence of lymphomatous involvement, light chain

restriction or immunoglobulin gene rearrangement. The proportion of IgG4⁺/IgG⁺ cells was markedly elevated (91%), consistent with lymphadenopathy of IgG4-related sclerosing disease.⁴

In case A2, a nasopharyngeal biopsy obtained 1 year before current presentation during investigation for anosmia (subsequently found to be due to sinusitis) exhibited reactive lymphoid hyperplasia with polytypic plasmacytosis. The proportion of IgG4⁺/IgG⁺ plasma cells was markedly elevated (84%). The features were consistent with systemic involvement by IgG4-related sclerosing disease.³

Control Cases

The 14 cases of IgG4-related chronic sclerosing dacryoadenitis did not show light chain restriction on immunohistochemical staining, or clonal immunoglobulin gene (IGH and IGκ) rearrangement on PCR. IgG4⁺ cells were absent or sparse in 16 cases of ocular adnexal lymphoma (14 MALT lymphomas and 2 diffuse large B-cell lymphomas) and 25 cases of gastric MALT lymphomas.

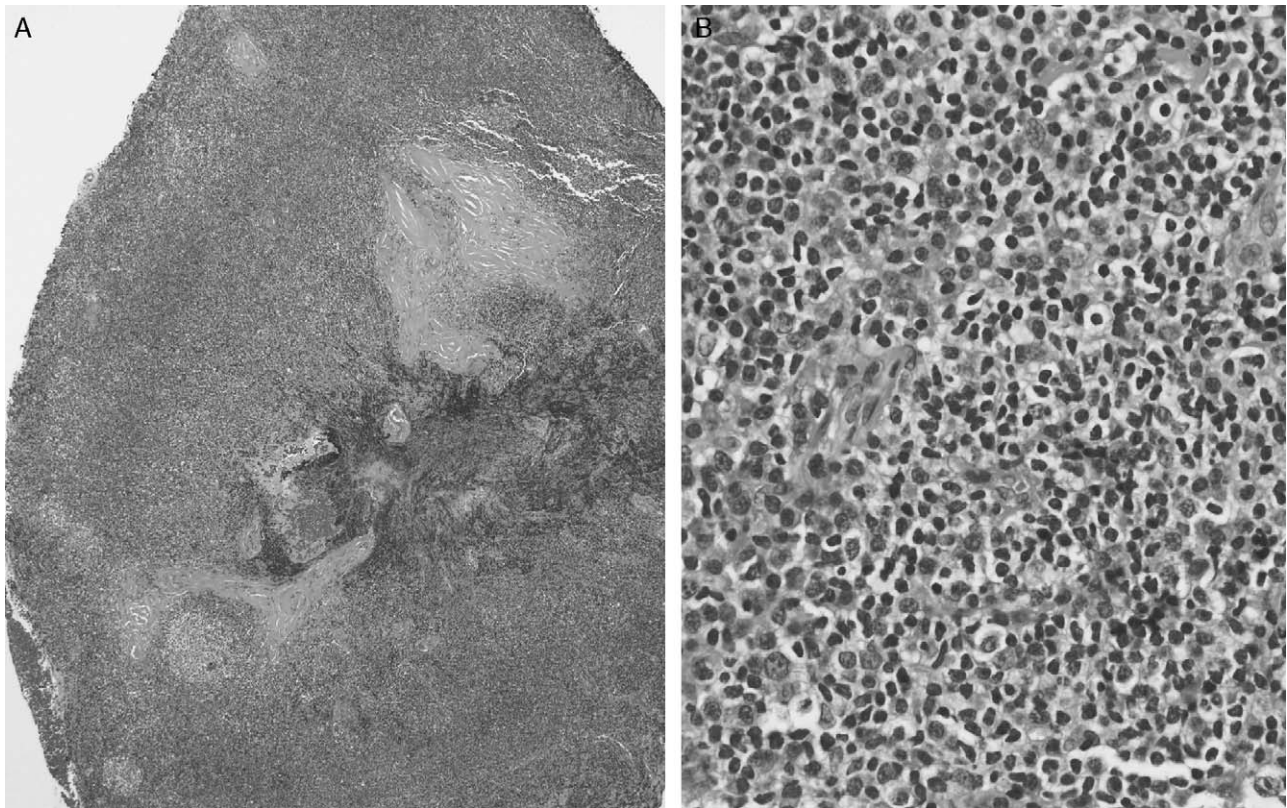


FIGURE 3. MALT lymphoma, case B1. A, Within this diffuse lymphoid infiltrate, a few reactive lymphoid follicles are present. Note the presence of sclerotic bands. B, The infiltrate comprises small lymphoid cells and mature plasma cells. Some lymphoid cells have clear cytoplasm.

DISCUSSION

This report describes 6 cases of ocular adnexal lymphoma arising in or probably related to IgG4-related sclerosing disease. The diagnosis of lymphoma is based on a combination of morphology, immunoglobulin light chain restriction (cases A1, B1, B2, B3) and clonal immunoglobulin gene rearrangement (cases A2, A3, B1, B2). Failure to demonstrate immunoglobulin gene rearrangement in cases A1 and B3 does not rule out lymphoma, because false negative results are known to occur in a proportion of cases of B-cell lymphomas, despite use of multiple primers for PCR.¹⁶ For comparison, no light chain restriction or immunoglobulin gene rearrangement is found in 14 cases of uncomplicated IgG4-related chronic sclerosing dacryoadenitis. The morphology and immunophenotype in 5 cases are compatible with extranodal marginal zone B-cell lymphoma of MALT type. In contrast to MALT lymphoma of other sites, lymphoepithelial lesions are not found, which is in keeping with a low frequency of lymphoepithelial lesions in ocular adnexal MALT lymphomas.^{5,14}

The presence of preexisting IgG4-related chronic sclerosing dacryoadenitis is histologically confirmed in 2 cases (cases A1 and A3) by previous biopsies from the

same site, and can be inferred in 1 case (case A2) by a previous nasopharyngeal biopsy showing a high proportion of IgG4/IgG+ cells, coupled with a long history of orbital lesion (not biopsied).³

For the 3 cases from group B, no previous biopsy or serum IgG4 level is available to unequivocally document presence of IgG4-related sclerosing disease. Nonetheless, case B1 has slightly enlarged lymph nodes, predominantly mediastinal and intra-abdominal, quite reminiscent of the lymphadenopathy pattern of IgG4-related sclerosing disease, although the possibility of lymphoma involvement cannot be totally excluded.⁴ These cases were selected because of morphologic similarities to group A, in particular the presence of sclerosis and periductal fibrosis, raising the consideration of IgG4-related sclerosing disease and prompting performance of IgG4 immunostaining. Indeed, all 3 cases show sheets of IgG4+ plasma cells, but because these cells are light chain restricted, we cannot ascertain if there is a significant population of admixed polytypic IgG4+ cells in the background to support a diagnosis of preexisting IgG4-related sclerosing disease. On the other hand, it can be argued that the sclerosing inflammation seen in the residual lacrimal gland may merely represent changes secondary to the space occupying lesion (lymphoma).

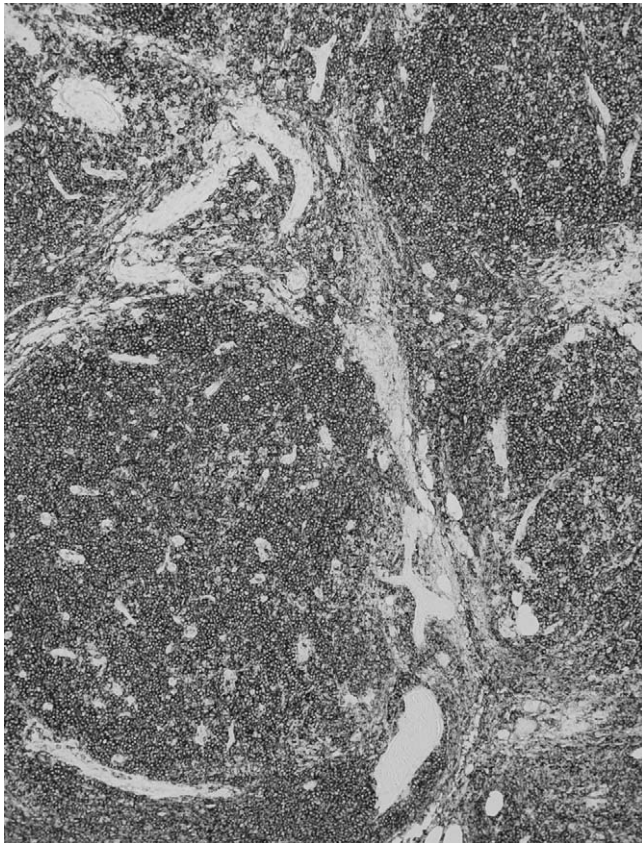


FIGURE 4. MALT lymphoma, case A2. On immunostaining, there are diffuse sheets of CD20⁺ cells, supporting a B-lineage cellular proliferation.

Thus, it remains unclear whether these cases represent lymphoma arising from preexisting IgG4-related chronic sclerosing dacryoadenitis, or de novo IgG4⁺ MALT lymphoma. In 16 cases of ocular adnexal lymphomas we have retrieved for comparison, there is no periductal fibrosis or septal sclerosis in the background, and there are very rare IgG4⁺ cells. Similarly, gastric MALT lymphomas, the prototype of MALT lymphoma, also show few IgG4⁺ cells. Hence, even if these 3 cases (group B) represent de novo MALT lymphoma, the expression of IgG4 indicates their uniqueness or a possible relationship with IgG4-related sclerosing disease.

Lymphoma has so far not been documented to arise in IgG4-related sclerosing disease. In a recent study of autoimmune pancreatitis, the prototype of IgG4-related sclerosing disease, only 1 of 11 informative cases exhibits an oligoclonal pattern on PCR for immunoglobulin gene.¹¹ In 2001, Ochoa et al¹² reported a case of MALT lymphoma supervening on chronic sclerosing sialadenitis of the submandibular gland. However, it is unclear whether this case represented IgG4-related sclerosing disease, because not all cases of chronic sclerosing sialadenitis are IgG4-related.

Lymphomas can arise in a background of chronic inflammation or autoimmune-related lymphoid hyperplasia, the best known examples being MALT lymphoma arising in *Helicobacter*-associated gastritis,⁹ lymphoepithelial sialadenitis,⁸ and Hashimoto thyroiditis.¹ The pathogenesis may be related to chronic antigenic stimulation, be the antigen self or nonself, driving proliferation of lymphoid cells, and the lymphoma is often a low grade B-cell lymphoma of MALT type. The documentation of

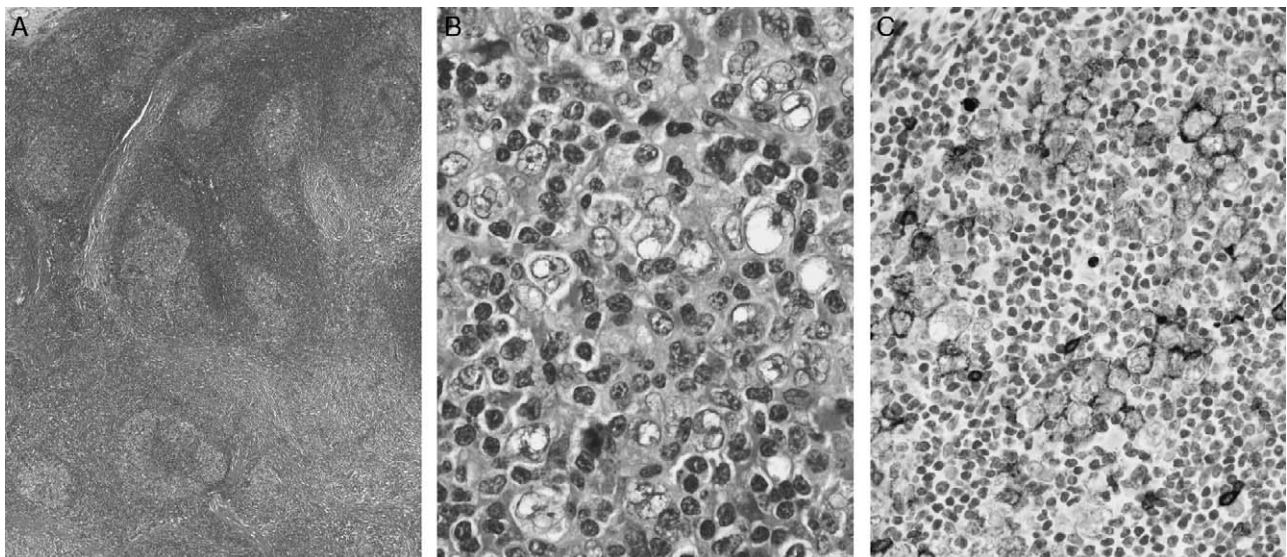


FIGURE 5. Follicular lymphoma, case A1. A, Abnormal lymphoid follicles with well-defined mantles are accompanied by a sclerotic stroma. B, Within the germinal centers, very large cells with multilobated or convoluted vesicular nuclei are present in a background of small lymphoid cells. C, These atypical large cells are immunoreactive for CD10, whereas the admixed small cells are mostly reactive T cells that are CD3⁺, CD10[−] and bcl6[−] (not shown).

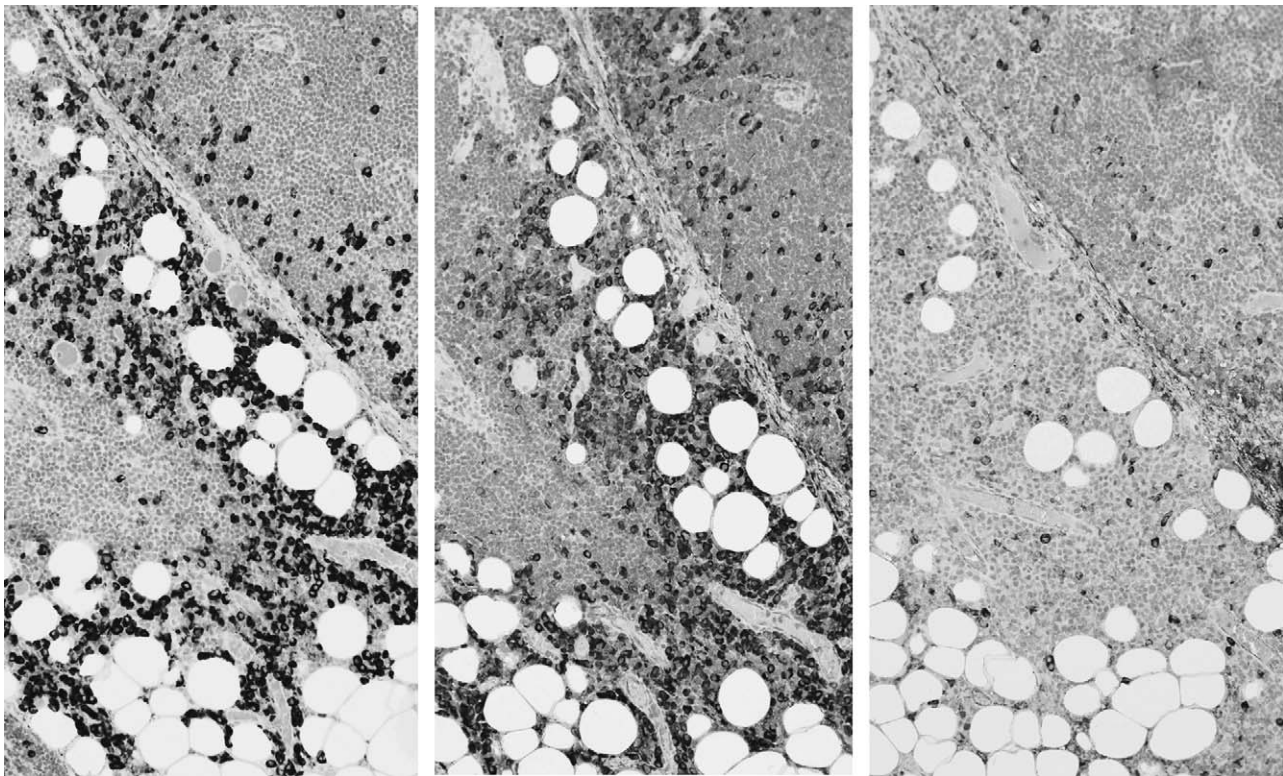


FIGURE 6. MALT lymphoma, case B2, immunostained for IgG4 (left), κ light chain (middle) and λ light chain (right). Most of the plasma cells are positive for IgG4, and exhibit κ light chain restriction.

lymphoma in the setting of IgG4-related chronic sclerosing dacryoadenitis in this study suggests that the latter may represent another predisposing factor for the emergence of lymphoma. Although the etiology and pathogenesis of IgG4-related sclerosing disease is not known, the chronic hyperplasia of the acquired lymphoid tissue in this condition appears to provide the substrate for the emergence of autonomous B-cell clones and eventually malignant lymphoma.

In conclusion, IgG4-related chronic sclerosing dacryoadenitis can be complicated by lymphoma. The frequency is 10% (counting only group A) among 30 cases of IgG4-related chronic sclerosing dacryoadenitis in our files, but this figure may be overestimated because a high proportion of the latter represent consultation cases. Nevertheless, this percentage is still very remarkable in comparison with the other sites involved by IgG4-related sclerosing disease such as the pancreas and salivary gland,

TABLE 2. Summary of Pathologic, Immunohistochemical, and Molecular Findings

Case No.	Pathologic Diagnosis	IgG4+/IgG+ Cells/HPF	Immunostaining for Immunoglobulin in Lymphoma Cells	Immunoglobulin Gene Rearrangement by PCR
A1	Follicular lymphoma grade 3b	722/1060 (68%)	κ light chain restriction IgM–, IgD–, IgG–	Not demonstrated (IGH–, IG κ –*)
A2	MALT lymphoma	718/762 (94%)	No demonstrable light-chain restriction IgM+, IgD–, IgG–	Monoclonal (IGH+)
A3	MALT lymphoma with large cell transformation	666/730 (91%)	No demonstrable light-chain restriction IgM+, IgD–, IgG–	Monoclonal (IGH–, IG κ +))
B1	MALT lymphoma	703/1325 (53%)	λ light-chain restriction IgM–, IgD–, IgG4+, IgG+	Monoclonal (IGH+)
B2	MALT lymphoma	691/831 (83%)	κ light-chain restriction IgM–, IgD–, IgG4+, IgG+	Monoclonal (IGH+)
B3	MALT lymphoma	1408/674 (209%)	λ light-chain restriction IgM–, IgD–, IgG4+, IgG–	Not demonstrated (IGH–, IG κ –*)

*There was a band of 150-bp size in the tube A PCR reaction, which was also detected in 5 control cases of chronic sclerosing dacryoadenitis. This pseudoclonal band was considered to result from the limited heterogeneity of V κ -J κ junctional region.¹⁶

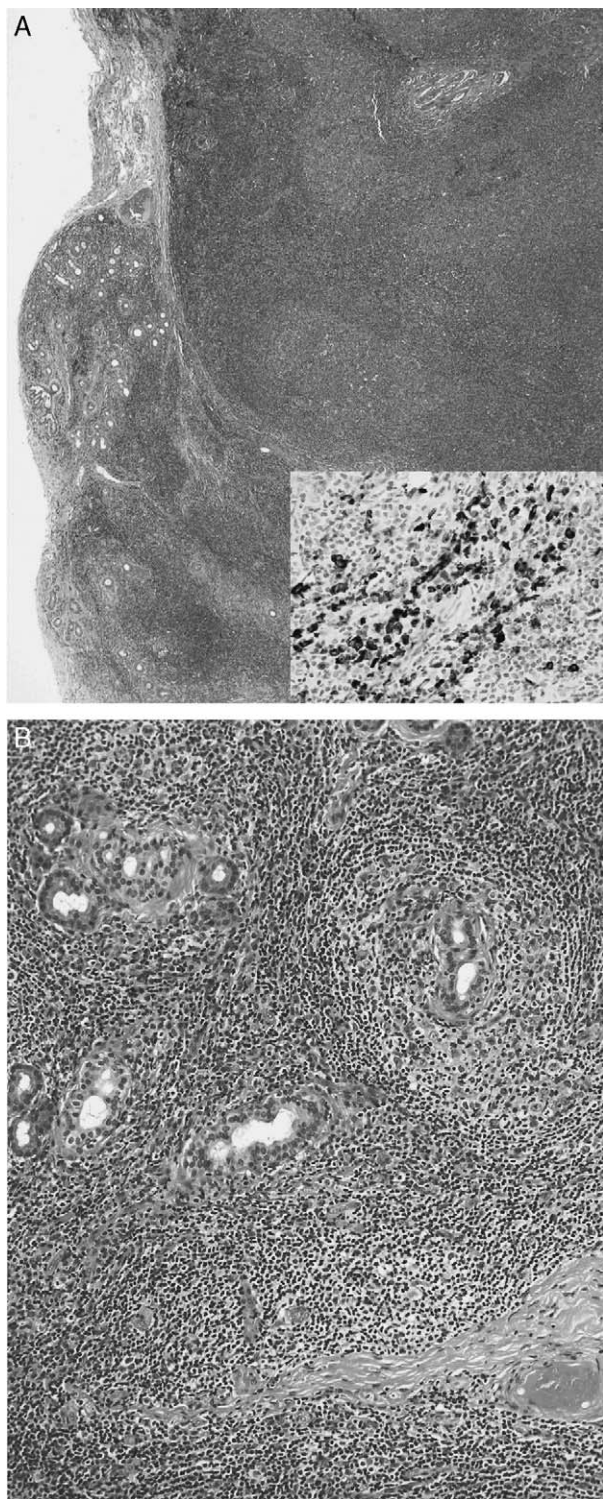


FIGURE 7. Prior biopsies of lacrimal gland. A, The lacrimal gland shows a heavy lymphoid infiltrate predominated by reactive lymphoid follicles are present (which lack atypical large cells in the germinal centers as depicted in Fig. 5B). Sclerotic septa. The inset shows numerous IgG4+ cells on immunostaining (case A1). B, The lacrimal gland shows loss of acini, periductal fibrosis, lymphoid cell infiltration, lymphoid follicle formation, and septal sclerosis (case A3).

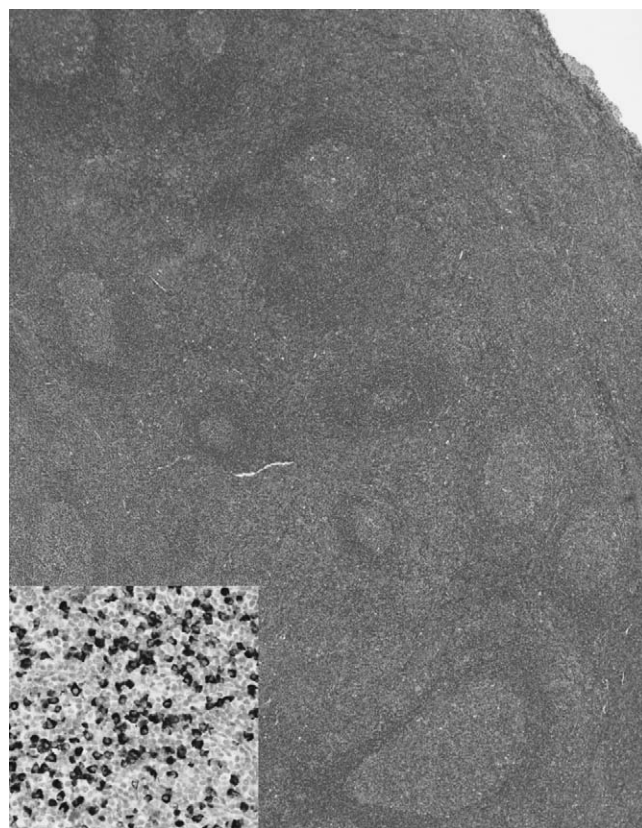


FIGURE 8. Axillary lymph node biopsy, case A3. The lymph node shows usual reactive follicular hyperplasia. The inset shows abundant IgG4+ plasma cells in the interfollicular zone on immunostaining.

where not a single case of lymphoma has been convincingly reported in the literature,^{11,15} and we have observed only 1 convincing example of lymphoma among a large collection of cases of chronic sclerosing sialadenitis (unpublished) and no cases of lymphoma in the setting of autoimmune pancreatitis. Further investigations are needed to ascertain whether the differences in the propensity of lymphoma development in IgG4-related sclerosing disease is related to site.

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