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Abstract

IgG4-related sclerosing disease (IRSD) is a steroid-responsive fibroinflammatory disorder characterized by increased IgG4+ cells. Nodal involvement usually lacks the dense sclerosis seen in extranodal sites, with histologic patterns overlapping with other reactive processes. Twenty-six lymph nodes showing IRSD-related histologic patterns were evaluated for IgG and IgG4 positive cells by immunohistochemistry and correlated with the clinical features. Cases included 7 Castleman disease–like cases (type I pattern), 10 follicular hyperplasia (type II), and 9 plasmacytosis (type III). The mean numbers of IgG4+ cells per high-power field (HPF) were 4.8 (I), 8.4 (II), and 26.6 (III), and the mean IgG4/IgG ratios were 0.05 (I), 0.04 (II), and 0.08 (III). Using >50 IgG4+ cells/HPF and IgG4/IgG ratio of >0.4 for absolute and relative increases, only 1 case fulfilled both criteria for increased IgG4+ cells, a patient with Hashimoto's thyroiditis without clinical evidence of IRSD. The results suggest that increased IgG4+ cells may rarely be seen in non-IRSD lymph nodes.

Keywords

IgG4-related sclerosing disease, IgG4, IgG, lymph nodes, immunohistochemistry

Introduction

IgG4-related sclerosing disease (IRSD) is a recently recognized systemic disease of possible autoimmune etiology with a characteristic clinicopathologic presentation. The prototypical disease affects 1 or more sites and presents as a mass lesion with dense sclerosis and increased IgG4-positive plasma cells.¹ The spectrum of disorders that may be part of IRSD continues to expand and includes autoimmune sclerosing pancreatitis, sclerosing cholangitis, chronic sclerosing sialadenitis, Riedel's thyroiditis, and fibroinflammatory lesions in other organs.^{1–9} It is becoming increasingly important for surgical pathologists to recognize the histopathologic features of IRSD given the dramatic response to steroid therapy.¹

IRSD may involve extranodal as well as nodal sites, and lymphadenopathy may sometimes be the presenting feature, causing clinical concern for lymphoma.^{10–12} However, histologic evaluation will typically show preservation of the overall architecture, which is more characteristic of a reactive process. Cheuk et al¹⁰ initially observed 3 major morphologic patterns: Castleman disease–like with

hyperplastic and/or regressed follicles, increased vascularity, and penetration of germinal centers by hyalinized blood vessels; follicular hyperplasia with variable numbers of interfollicular plasma cells; and interfollicular expansion by numerous plasma cells and immunoblasts. Two additional histologic patterns have been described, including patterns resembling progressive transformation of germinal centers, and nodal inflammatory pseudotumor, in which the lymph node is replaced by sclerotic tissue with variable numbers of lymphocytes, plasma cells, and eosinophils.^{1,11,13} However, the latter pattern is rare, and in contrast to extranodal lesions, dense sclerosis is not a prominent feature in IRSD-related lymphadenopathy.^{1,10}

It is unknown if a substantial portion of reactive lymph nodes showing histologic patterns overlapping with IRSD-related

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lymphadenopathy would have fulfilled the clinicopathologic criteria for IRSD, particularly prior to the era of widespread awareness of this entity and utilization of a IgG4 immunostain. The aim of this study was to investigate for increased IgG4-positive cells in lymph nodes showing IRSD-associated histologic patterns and to correlate with the clinical features to evaluate for occult involvement.

Materials and Methods

Cases

This study was exempt-approved by the institutional review board at the University of Pittsburgh. Lymph nodes showing 3 IRSD-related histologic patterns were identified, as previously described¹⁰: type I (Castleman disease/disease-like), type II (follicular hyperplasia), type III (interfollicular plasmacytosis). The histologic slides and paraffin-embedded tissue blocks from 26 lymph nodes were retrieved from the departmental archives, including 7 type I (4 hyaline vascular Castleman disease, 1 Castleman disease-like case, 1 Castleman disease-like case suggestive of POEMS, and 1 HHV8+ multicentric Castleman disease with focal Kaposi sarcoma); 10 type II (5 cases with histologic changes suggestive of toxoplasmosis, 2 cases with a history of systemic lupus erythematosus, 1 case with HIV, 1 case with HIV that was also Epstein-Barr virus (EBV) positive, and 1 case with dermatopathic changes); and 9 type III (3 cases with plasmacytosis and granulomatous inflammation, 2 cases with history of Hashimoto's disease, 1 case with Graves disease, and 3 cases without an identifiable etiology for the plasmacytosis). One lymph node from a patient with known IRSD was evaluated as a positive control. Clinical and follow-up information was obtained from review of the medical records.

Immunohistochemistry

Paraffin-section immunohistochemistry was performed for IgG4 (clone HP6025, mouse monoclonal, 1:1000 [Invitrogen, Camarillo, CA]) and IgG [n/a, rabbit polyclonal, prediluted [Ventana, Tucson, AZ]] using the Ventana Benchmark automated system. The areas with the highest density of positive cells were evaluated. Three high-power fields (HPFs) in each section were counted at 400× magnification, and mean numbers of positive cells per HPF was calculated. One HPF covered an area of 0.238 mm² (×40 objective, ×10 ocular, 22 mm field of view).

Results

Cases showed a wide range in the numbers of IgG4-positive cells (Tables 1-3). One IRSD lymph node served

Table 1. Absolute and Relative Numbers of IgG4+ Cells in Pattern I Lymph Nodes

Case	Number of IgG+ Cells/HPF	Number of IgG4+ Cells/HPF	IgG4/IgG Ratio
1	35.3	0.7	0.02
2	29.7	1.7	0.06
3	342.0	13.0	0.04
4	60.7	11.7	0.19
5	195.7	2.3	0.01
6	178.0	2.7	0.01
7	77.3	1.7	0.02
Mean	131.2	4.8	0.05

Abbreviation: HPF, high-power field.

Table 2. Absolute and Relative Numbers of IgG4+ Cells in Pattern II Lymph Nodes

Case	Number of IgG+ Cells/HPF	Number of IgG4+ Cells/HPF	IgG4/IgG Ratio
1	182.0	0.0	0.00
2	169.0	0.7	0.00
3	37.3	4.3	0.12
4	135.3	0.3	0.00
5	263.0	16.3	0.06
6	64.7	1.7	0.03
7	123.3	1.3	0.01
8	95.3	1.0	0.01
9	86.3	1.0	0.01
10	434.0	57.3	0.13
Mean	159.0	8.4	0.04

Abbreviation: HPF, high-power field.

Table 3. Absolute and Relative Numbers of IgG4+ Cells in Pattern III Lymph Nodes

Case	Number of IgG+ Cells/HPF	Number of IgG4+ Cells/HPF	IgG4/IgG Ratio
1	262.7	12.3	0.05
2	629.7	29.0	0.05
3	174.0	0.0	0.00
4	234.0	3.0	0.01
5	342.3	185.0	0.54
6	125.0	7.0	0.06
7	155.7	2.7	0.02
8	68.7	0.0	0.00
9	282.7	0.0	0.00
Mean	252.7	26.6	0.08

Abbreviation: HPF, high-power field.

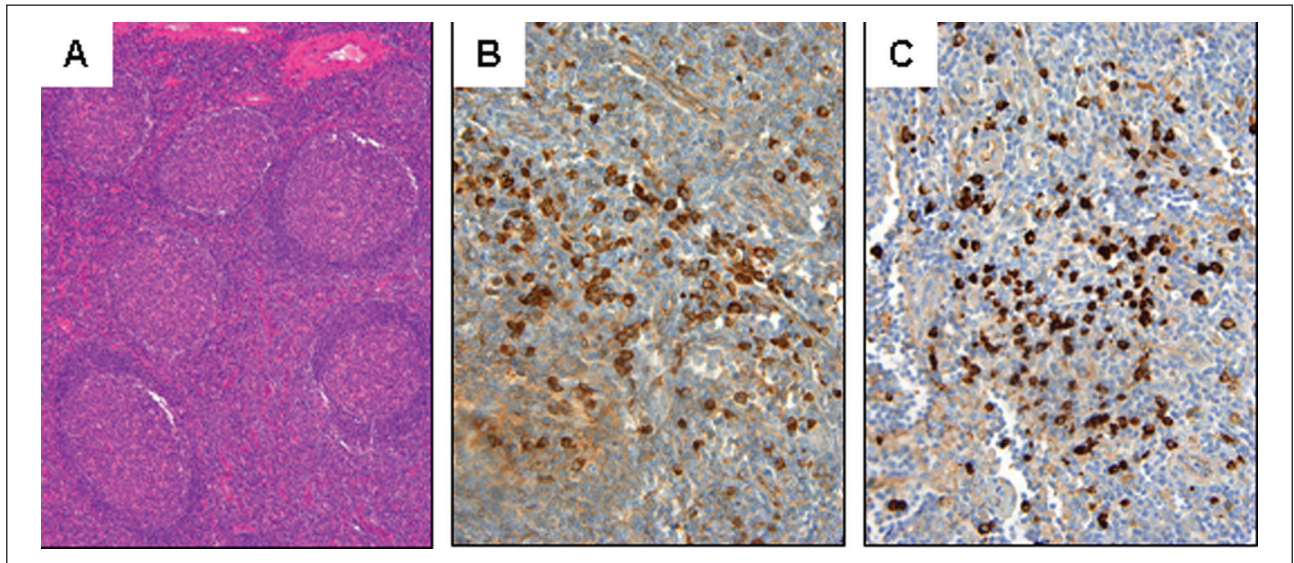


Figure 1. (A) IgG4-related lymphadenopathy showing follicular hyperplasia and increased interfollicular plasma cells (hematoxylin–eosin staining, original magnification 100×). (B) IgG immunohistochemical staining highlights many positive plasma cells (immunoperoxidase staining, original magnification 400×). (C) IgG4 immunohistochemical staining shows an increased proportion of this plasma cell subtype (immunoperoxidase staining, original magnification 400×)

as a positive control case, which showed a type II histologic pattern (follicular hyperplasia) and demonstrated 164 IgG4-positive cells/HPF and a IgG4/IgG ratio of 0.71 (Figure 1). The highest number of IgG4-positive cells per HPF was seen with the type III histologic pattern (interfollicular plasmacytosis) with a mean of 26.6 IgG4-positive cells/HPF (Figure 2). The mean numbers of IgG4-positive cells/HPF seen with the type I (Castleman's disease/Castleman's disease–like) and type II (follicular hyperplasia) histologic patterns were less than 10/HPF. The type III pattern also showed the widest range of 0 to 185 when compared with types I and II (Figure 3). The mean IgG4/IgG ratio ranged from 0.04–0.05 (types II and I) to 0.08 (type III), with the widest range again seen in type III cases (0–0.54; Figure 4).

Using the criteria of Cheuk and Chan,¹ greater than 50 IgG4-positive cells per high-power field was considered an absolute increase in IgG4 positive cells, and a ratio of greater than 0.4 IgG4/IgG-positive cells was considered a relative increase. An absolute increase was only identified in 2 cases (8%), and a relative increase was only identified in 1 case (4%). Only 1 case fulfilled both criteria for an absolute and relative increase of IgG4-positive cells, as detailed below.

None of the lymph nodes with type I or II histologic patterns demonstrated increased IgG4/IgG ratios. Although 1 case from the type II group, a patient with HIV and EBV, showed an average of 57 IgG4-positive cells/HPF, the IgG4/IgG ratio was 0.13. One case with

a type III pattern (interfollicular plasmacytosis) showed both an absolute (185/HPF) and relative (IgG4/IgG ratio of 0.54) increase in IgG4-positive cells (Figure 5). This patient had a long-standing history of Hashimoto's thyroiditis, has been followed for more than 11 years at our institution, and has no clinical evidence for IRSD or pancreatitis.

Discussion

In this study evaluating lymph nodes with IRSD-related histologic patterns, we found rare cases with elevated relative and/or absolute numbers of IgG4-positive cells but no clinical evidence of IRSD. One limitation is the lack of availability of serum IgG4 levels, a useful diagnostic adjunct to establish the diagnosis of IRSD.^{1,4} However, a raised IgG4 level (greater than 135 mg/dL) is not essential for the diagnosis, due to the fact that although serum levels generally correlate with disease activity, false negatives may occur.^{8,14–16} Based on review of the clinical records available, none of the patients showed clinical manifestations of IRSD. Our findings show that absolute and relative increases in IgG4-positive cells are only rarely observed in non-IRSD lymphadenitis (1/26, 4%) and further suggest that increased IgG4-positive cells are not entirely specific for IRSD. It is also our view that these immunohistochemical results should not be used alone to establish an IRSD diagnosis, but could suggest this possibility if the clinical impression is also suspicious for IRSD.

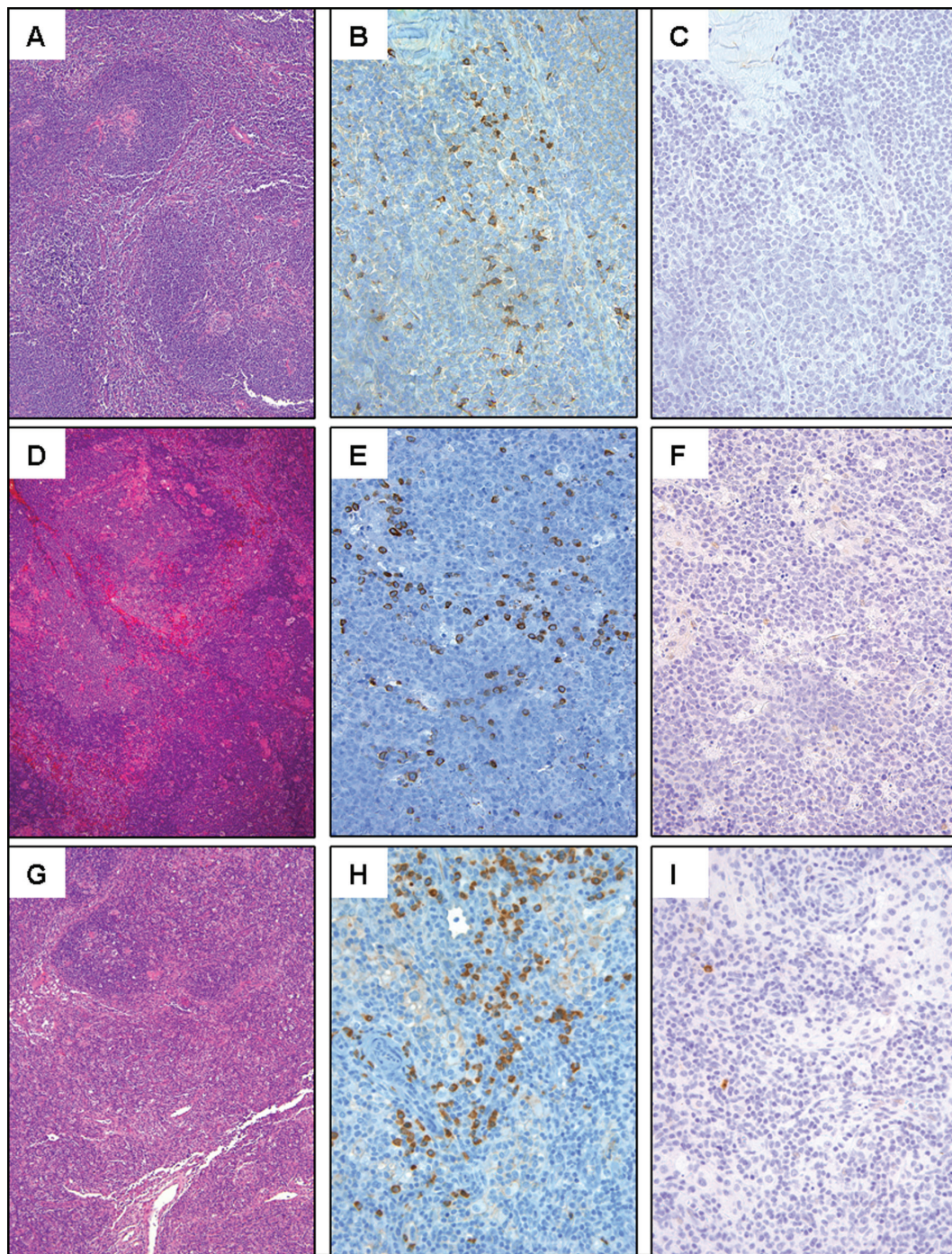


Figure 2. (A) Type I (Castleman's disease/disease-like) histologic pattern (hematoxylin–eosin staining, original magnification 100×). (B) IgG immunohistochemical staining highlights very few positive plasma cells (immunoperoxidase staining, original magnification 400×). (C) IgG4 immunohistochemical staining shows absence of positive cells (immunoperoxidase staining, original magnification 400×). (D) Type II (follicular hyperplasia) histologic pattern (hematoxylin–eosin staining, original magnification 100×). (E) IgG immunohistochemical staining highlights few positive plasma cells (immunoperoxidase staining, original magnification 400×). (F) IgG4 immunohistochemical staining shows only very rare positive cells (immunoperoxidase staining, original magnification 400×). (G) Type III (interfollicular plasmacytosis) histologic pattern (hematoxylin–eosin staining, original magnification 100×). (H) IgG immunohistochemical staining highlights a moderate number of positive plasma cells (immunoperoxidase staining, original magnification 400×). (I) IgG4 immunohistochemical staining shows only very few positive cells (immunoperoxidase staining, original magnification 400×)

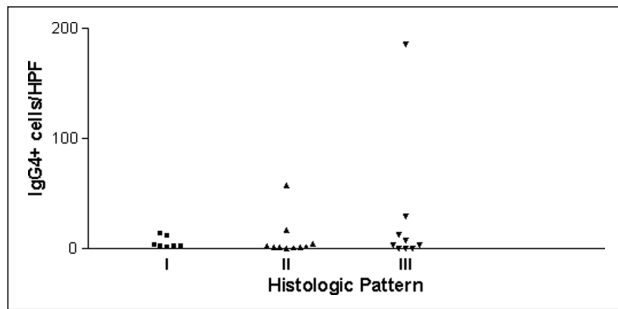


Figure 3. IgG4-positive cells per high power field by histologic pattern

Type I, Castleman's disease/Castleman's disease-like; type II, follicular hyperplasia; type III, interfollicular plasmacytosis.

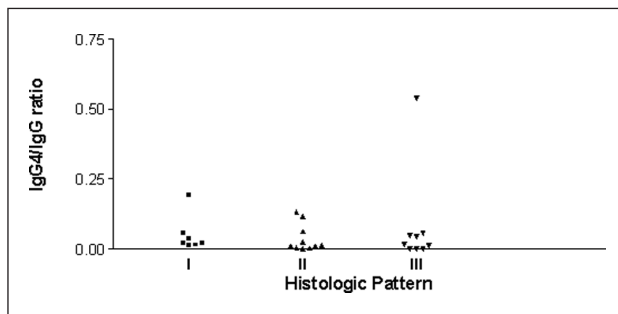


Figure 4. IgG4/IgG ratio by histologic pattern

Type I, Castleman's disease/Castleman's disease-like; type II, follicular hyperplasia; type III, interfollicular plasmacytosis.

Two histologic patterns rarely showed an absolute increase in IgG4-positive cells within the range associated with IRSD lymphadenopathy. One case with follicular hyperplasia (type II histologic pattern) related to viral infection (HIV, EBV) showed an increased number of IgG4-positive cells/HPF but no increase in the IgG4/IgG ratio. This case underscores the importance of evaluating both the absolute number of IgG4-positive cells/HPF as well as the relative number (ie, the IgG4/IgG ratio) in lymph nodes. It is also important to be aware that the thresholds differ based on nodal versus extranodal locations and that the IgG4/IgG ratio may be more informative in lymph nodes. Although greater than 10 IgG4 positive plasma cells per HPF has been proposed as a criteria for IgG4-related sclerosing pancreatitis, we and others show that non-IRSD lymph nodes may exceed this threshold.^{1,4} Our average of 26.6 IgG4-positive cells/HPF (range 0-185) seen in cases with the type III histologic pattern (interfollicular plasmacytosis) may seem high, but the mean IgG4/IgG ratio was not elevated (0.08). Our findings are in line with the control lymph nodes studied in Cheuk et al's initial report,¹⁰ which showed an average number of

31.1 IgG4-positive cells/HPF (range 0-192) but IgG4/IgG ratios below 0.30. A higher percentage of Cheuk et al's control lymph nodes (26%, 14/54) showed greater than 50 IgG4-positive cells/HPF when compared with our study (8%, 2/26). The reason for this difference is not clear; however, it may in part be related to the larger sample size and inclusion of some plasma cell-rich diseases (such as Rosai-Dorfman disease) in the prior study, which would not have been identified by our search criteria, which focused on cases signed out descriptively by their histologic patterns.¹⁰ Our findings support the more stringent criteria for IRSD-related lymphadenopathy, including evaluation of both absolute and relative IgG4-positive plasma cells.

One case within the type III histologic category (interfollicular plasmacytosis) showed an absolute and relative increase in IgG4-positive cells (185 IgG4-positive cells/HPF and 0.54 IgG4/IgG ratio). It is interesting that this patient had a history of an autoimmune disorder (Hashimoto's thyroiditis). An autoimmune etiology has been suggested for IRSD, with several lines of evidence supporting this, including the characteristic responsiveness to steroid therapy and the circulating autoantibodies detected in many patients.¹⁷ Interestingly, 26.8% of patients with autoimmune pancreatitis show hypothyroidism, with 63.6% demonstrating elevated antithyroglobulin antibodies.¹⁸ In fact, one group separated Hashimoto's thyroiditis into IgG4-positive plasma cell rich and plasma cell poor subgroups on the basis of immunohistochemistry, with the IgG4-positive plasma cell rich groups exceeding 20 IgG4-positive cells/HPF and a IgG4/IgG ratio of 0.3.^{19,20} The IgG4-positive plasma cell rich group showed some differences in the clinical features, including a greater proportion of males and shorter disease duration.²⁰ However, it is unclear if these should be viewed as a variant of IRSD, as other autoimmune diseases such as rheumatoid arthritis may show absolute and relative increases in IgG4-positive cells but would not be reclassified as IRSD.^{10,21} Therefore, we cannot entirely exclude the possibility that our one case with increased IgG4+ cells represents the IgG4-rich subtype of Hashimoto's thyroiditis, especially if future studies confirm distinctive clinicopathologic features and support separating this putative subtype into a distinctive IRSD-related entity. It is also not clear if IRSD is truly autoimmune in nature, as an alternative allergic mechanism has been proposed, supported by the fact that some cases show an elevated serum IgE level and eosinophil infiltration.¹¹ Further studies are required to understand the pathologic basis for IRSD.

None of the Castleman disease/disease-like (type I histologic pattern) lymph nodes showed an absolute or relative increase in IgG4-positive plasma cells. However, one limitation of our study is that most (4/6 cases, 67%) were

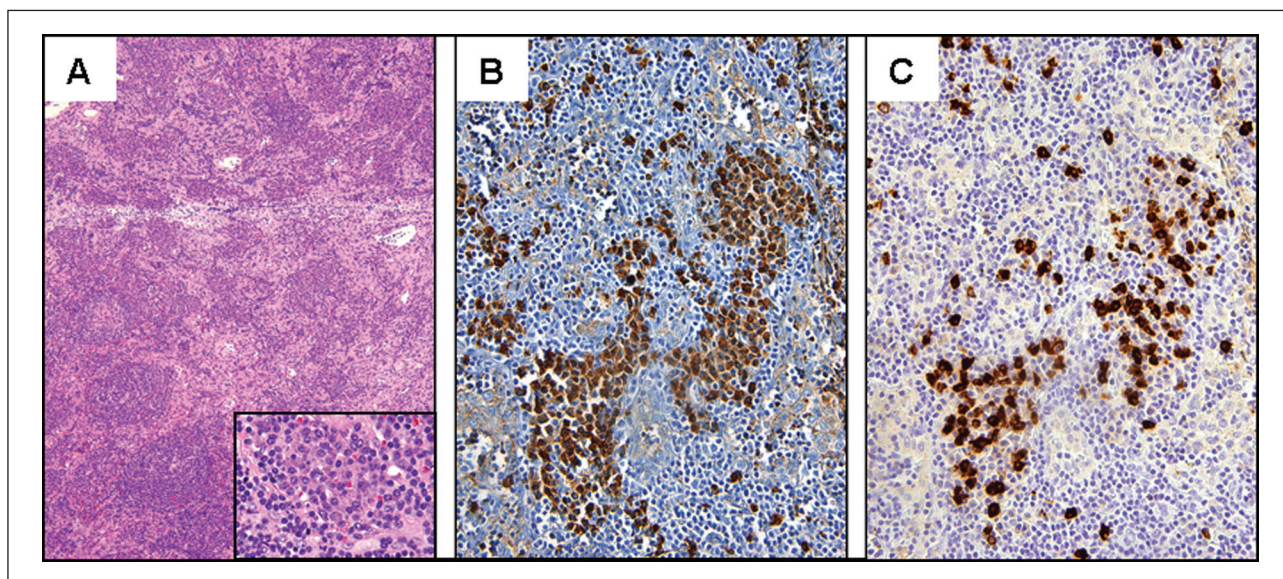


Figure 5. (A) Type III histologic pattern and increased interfollicular plasma cells in a lymph node from a patient with Hashimoto's thyroiditis (hematoxylin–eosin staining, original magnification 100 $\times$, inset 400 $\times$). (B) IgG immunohistochemical staining highlights many positive plasma cells (immunoperoxidase staining, original magnification 400 $\times$). (C) IgG4 immunohistochemical staining shows many positive cells, overlapping with IRSD (immunoperoxidase staining, original magnification 400 $\times$)

hyaline-vascular type rather than the multicentric/plasma cell variant; the latter has been more frequently described to show histologic overlap with IRSD. Multicentric Castleman's disease may sometimes show abundant IgG4-positive cells and elevated IgG4 levels. However, in contrast to IRSD, multicentric Castleman's disease is considered a hyper IL-6 syndrome that results in elevated C-reactive protein levels and thrombocytosis.²² Ancillary laboratory findings (such as the IL-6 level) are important in distinguishing between the 2 processes. Therefore, it is uncertain if our negative findings relating to this category can be generalized, and future studies with larger numbers of cases may assist in clarification.

Increased IgG4-positive cells may be seen in other reactive, mass-forming processes that clinically can mimic lymphoma. Cases of Rosai–Dorfman disease bearing increased IgG4-positive cells have been reported involving the skin²³ and the lung.^{21,24} The significance of this subgroup of Rosai–Dorfman disease with increased IgG4-positive cells and its relationship with IRSD is uncertain. A recent study that evaluated the IgG4-expressing plasma cell subtype in 36 inflammatory myofibroblastic tumors (IMTs) showed that 5 cases fell within an IgG4 to IgG ratio of 0.4 to 1, with IgG4 positive plasma cell counts that ranged from 19 to 33 per HPF.²⁵ These patients did not differ in age or ALK expression when compared with IMTs lacking significant numbers of IgG4-positive cells. Given the overlap between IMT and IRSD in a subset of cases, the authors did not feel that the IgG4/IgG ratio was

diagnostically useful in cases fulfilling the histologic criteria for an ALK-negative IMT. Although these observations come from extranodal-based lesions, the emphasis on caution in interpreting the significance of an increase in IgG4-positive plasma cells also has relevance for nodal-based lesions. Further studies are necessary to clarify the diagnostic significance of increased IgG4-positive cells, especially given the therapeutic ramifications.

In summary, increased IgG4-positive cells may rarely be seen in non-IRSD lymph nodes. If IRSD is clinically suspected, both absolute (IgG4-positive cells/HPF) and relative (IgG4/IgG ratio) numbers of IgG4-positive cells should be evaluated, with awareness that the range is particularly wide in non-IRSD cases showing interfollicular plasmacytosis, necessitating stringent criteria to establish the diagnosis.

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Declaration of Conflicting Interests

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