

Lymphadenopathy of IgG4-related Sclerosing Disease

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Abstract: IgG4-related sclerosing disease is a recently recognized syndrome characterized by mass-forming lesions in exocrine glands or extranodal tissues due to lymphoplasmacytic infiltrates and sclerosis, a raised serum IgG4 level and increased IgG4+ plasma cells in the involved tissues. We report the morphologic features of the enlarged regional (n = 3) and nonregional lymph nodes (n = 3) in patients with this syndrome. The patients presented with autoimmune pancreatitis, lymphoplasmacytic sclerosing cholangitis, chronic sclerosing dacryoadenitis, or chronic sclerosing sialadenitis. The histologic features of the lymph nodes could be categorized into 3 patterns: Castleman diseaselike, follicular hyperplasia, and interfollicular expansion by immunoblasts and plasma cells. The percentage of IgG4+/IgG+ plasma cells was markedly elevated (mean 62% vs. 9.9% in 54 control lymph nodes comprising a wide variety of reactive conditions). We also report 6 cases of primary lymphadenopathy characterized by increased IgG4+/IgG+ plasma cells (mean 58%). These cases share many clinical and pathologic similarities with IgG4-related sclerosing disease. In fact, 2 of these patients developed lymphoplasmacytic sclerosing cholangitis or lacrimal and submandibular gland involvement during the clinical course. These cases therefore probably represent primary lymph node manifestation of the disease. The importance of recognition of the lymphadenopathic form of IgG4-related sclerosing disease lies in the remarkable response to steroid therapy, and the potential of mistaking the disease for lymphoma either clinically or histologically.

Key Words: IgG4-related sclerosing disease, IgG4-related autoimmune disease, autoimmune pancreatitis, lymph node, lymphadenopathy, lymphoma, immunohistochemistry

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IgG4 is the least common subclass of IgG, normally accounting for only 3% to 6% of the total IgG in the serum. IgG4-related sclerosing disease (IgG4-related

autoimmune disease) is a recently recognized syndrome characterized clinically by tumorlike enlargement of one or more exocrine glands or extranodal tissues (most commonly pancreas, biliary tract, submandibular gland, and lacrimal gland) and raised serum IgG4 level, and pathologically by lymphoplasmacytic infiltration and sclerosis, as well as increased IgG4-secreting plasma cells.^{5–7,9,10,12} It is probably autoimmune in nature as autoantibodies against lactoferrin, carbonic anhydrase, rheumatoid factor, smooth muscle antigens, and nuclear antigens are frequently found, and there is often favorable response to steroid therapy.²³ Concomitant lymphadenopathy is common in IgG4-related sclerosing disease,^{3,13,25} but the morphologic features have not been described in detail. In this study, we analyze the clinicopathologic features of lymphadenopathy associated with IgG4-related sclerosing disease. We also describe 6 cases of primary lymphadenopathy that share many clinicopathologic features with IgG4-related sclerosing disease, suggesting that they may represent primary lymph node manifestation of this disease.

MATERIALS AND METHODS

We searched the archives of the Department of Pathology, Queen Elizabeth Hospital, Hong Kong, and the consultation files of the authors (W.C. and J.K.C.C.) for all cases with a diagnosis of IgG4-related sclerosing disease. Cases in which lymph node specimens were available for histologic examination were selected. Six cases with enlarged regional (group A, n = 3) or nonregional (group B, n = 3) lymph nodes of the organs affected by IgG4-related sclerosing disease were identified. Six cases of unexplained lymphadenopathy, designated as group C, with significantly increased IgG4+ plasma cells were also studied. These cases were prospectively identified since we became aware of possible involvement of lymph node by IgG4-related sclerosing disease in 2004. To establish an appropriate threshold for an increase in IgG4+ cells, 54 reactive lymph nodes of various types (Table 1) were immunostained for IgG4 and IgG. On the basis of these results (see results), we adopted “> 40% of IgG4+ cells among IgG+ cells” as the definition for a significant increase of IgG4+ cells in this study.

Clinical information was obtained from the patient records, referring pathologists, or clinicians. All available pathologic materials were retrieved for morphologic

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TABLE 1. Results of Immunostaining of Control Lymph Nodes

Diagnosis	No. Cases	IgG4+ /IgG+ Plasma Cells per HPF
Reactive follicular hyperplasia	10	29/145 (20%), 4/83 (4.8%), 100/669 (14.9%), 79/649 (12.2%), 30/228 (13.2%), 7/86 (8.1%), 3/165 (1.8%), 178/595 (29.9%), 3/196 (1.5%), 55/290 (19%)
Nonspecific lymphoid hyperplasia	8	4/415 (1%), 10/71 (14%), 4/664 (0.6%), 2/291 (0.7%), 12/68 (17.6%), 3/284 (1.1%), 50/281 (17.8%), 4/581 (6.9%)
Rheumatoid arthritis	3	192/730 (26.3%), 4/191 (2.1%), 144/747 (19.3%)
Progressive transformation of germinal center	3	22/257 (8.6%), 120/498 (24.1%), 68/398 (17.1%)
Castleman disease (hyaline-vascular n = 2, plasma cell n = 1, and multicentric n = 2)	5	34/130 (26.2%), 0/24 (0%), 42/706 (5.9%), 51/181 (28.2%), 8/60 (13.3%)
AIDS-related lymphadenopathy	1	7/158 (4.4%)
Infectious mononucleosis	2	1/106 (0.9%), 20/130 (15.4%)
Rosai-Dorfman disease	2	73/423 (17.3%), 83/282 (29.4%)
Dermatopathic lymphadenopathy	5	15/310 (4.8%), 51/448 (11.4%), 12/257 (4.7%), 12/168 (7.1%), 60/540 (11.1%)
Kikuchi lymphadenitis	5	3/102 (2.9%), 1/61 (1.6%), 2/197 (1.0%), 7/10 (7%), 3/87 (3.4%)
Kawasaki disease	1	1/256 (0.4%)
Systemic lupus erythematosus	2	5/145 (3.4%), 12/154 (7.8%)
Cat scratch disease	1	4/353 (1.1%)
Regional lymph nodes of breast carcinoma	4	7/76 (9.2%), 3/179 (1.7%), 2/98 (2.0%), 15/223 (6.7%)
Regional lymph nodes of colonic carcinoma	2	18/84 (21.4%), 1/269 (0.4%)

review. 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, clone NCL-IgGp-S, Novacastra); anti-IgG4 (1:500, clone HP6025, Zymed); CD20 (1:1,000, clone L26, Dako), CD3 (1:150, clone PS1, Novacastra), CD21 (1:15, clone NCL-CD21-2G, Novacastra), CD10 (1:10, clone 56C6, NeoMarkers), HHV-8 LNA-1 (1:20, 13B10, Novacastra), and immunoglobulin κ and λ -light chains (1:24,000, antiserum, Dako).

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).

RESULTS

Clinical Features and Outcome

The clinical features, salient laboratory findings, and clinical outcome of the patients are listed in Table 2.

Group A (n = 3)

There were 2 male and 1 female patients aged 59 to 68 years, with a mean of 63.3 years. Two patients had autoimmune pancreatitis (A1 and A2) and 1 had lymphoplasmacytic sclerosing cholangitis (A3). These patients underwent Whipple's operation or right hepatectomy with provisional diagnoses of pancreatic carcinoma or cholangiocarcinoma, respectively. All patients had mild anemia (Hb 10.2 to 12.9 g/dL) and erythrocyte sedimentation rate (ESR) was raised in 2 tested patients.

The serum IgG level was raised (2290 to 2887 mg/dL, normal < 1600 mg/dL). One tested patient showed mildly elevated serum IgG4 (180 mg/dL, normal < 135 mg/dL). All patients were well at follow-up 1 to 4 years after the operation.

Group B (n = 3)

All 3 patients were men, aged 67 to 77 years, with a mean of 71.7 years. They had IgG4-related chronic sclerosing dacryoadenitis affecting the right or bilateral lacrimal glands. Diffuse or localized axillary lymphadenopathy developed simultaneously with the lacrimal gland enlargement or after 4 to 8 years. One patient also had eosinophilic gastroenteritis on long-term steroid therapy. Common findings included anemia, raised ESR, raised lactate dehydrogenase, and positive autoimmune markers. Serum IgG level ranged from 1660 to 2830 mg/dL (normal < 1600 mg/dL). Serum IgG4 was markedly raised in 1 tested patient (580 mg/dL, normal < 135 mg/dL). The orbital masses were relatively static in size in response to steroid therapy with or without cytotoxic drugs such as azathioprine and chlorambucil or radiotherapy. Two patients were well at 1 to 2 years, and 1 died of acute myocardial infarction.

Group C (n = 6)

All patients were men ranging in age from 37 to 74 years (mean 61.7 y, median 69.5 y). They presented with multiple lymphadenopathy accompanied by the following symptoms in 1 patient each: diarrhea and abdominal discomfort, dry cough and lung shadows, dysphagia, and lower limb swelling. One patient was asymptomatic, with the lymphadenopathy being incidentally found during investigation for aortic stenosis. One patient had autoimmune thyroiditis receiving thyroxine replacement.

TABLE 2. Clinical Features

Case No.	Sex/ Age	Presentation	Serum IgG4/IgG Level (mg/dL)	Other Laboratory Findings	Treatment and Clinical Outcome
A1	M/63	History of transitional cell carcinoma of bladder treated by cystectomy. Presented with obstructive jaundice; Whipple's operation performed because of clinical and radiologic diagnosis of pancreatic carcinoma	IgG4 180	Anemia, raised ESR	Well at 1 y
A2	M/59	Presented with obstructive jaundice, epigastric discomfort and weight loss. Ultrasound showed pancreatic head mass with dilated common bile duct. Whipple's operation carried out with clinical impression of pancreatic cancer	IgG 2290	Decreased C3, raised ESR	Well at 4 y
A3	F/68	Presented with obstructive jaundice. USG showed prominent intrahepatic duct and common bile duct tumor was suspected. CT showed narrowing of intrahepatic ducts near hilum with regional lymphadenopathy. Right hepatectomy performed for suspected cholangiocarcinoma	IgG 2887	Anemia	Well at 2 y
B1	M/77	Right lacrimal gland swelling. Developed bilateral submandibular gland swelling and diffuse lymphadenopathy (mediastinal, axillary, paraaortic and groin, up to 3 cm) at 4 y	IgG 2830	RF positive, ANA positive, raised ESR, anemia, decreased C3 and C4, hypergammaglobulinemia	Well at 1 y. No steroid therapy
B2	M/67	Bilateral orbital swelling and peripheral lymphadenopathy (periauricular, cervical, axillary, 1 cm)	IgG4/IgG 580/1660 (34.9%)	Anemia, raised ESR, LDH raised	Well at 2 y. Steroid-dependent. Mild decrease in orbital swelling after addition of azathioprine
B3	M/71	Known history of eosinophilic gastroenteritis on long-term steroid therapy. Presented with proptosis of right eye 8 y ago. Recently developed enlargement of right lacrimal gland, soft tissue infiltration of cavernous sinuses on both sides, and axillary lymph node (2 cm)	IgG 2533	RF positive, hemolytic anemia, LDH raised	Steroid therapy all along. Chlorambucil and local radiotherapy given for the mass in the orbit and cavernous sinuses. Died of acute myocardial infarct
C1	M/47	Diarrhea, abdominal discomfort and poor appetite, hepatosplenomegaly, CT revealed diffuse lymphadenopathy involving axilla, retroperitoneum and groin (up to 5.1 cm), inflammatory changes in the wall of the small bowel, and small amount of ascites	IgG4/IgG 1383/5940 (23.2%)	RF positive, ANA positive, hemolytic anemia, raised ESR, hypergammaglobulinemia, amylase normal	Steroid therapy with marked clinical improvement. Liver biopsy showed lymphoplasmacytic sclerosing cholangitis
C2	M/74	Incidental finding of generalized lymphadenopathy for 10 y (cervical, mediastinal, axillary, pancreatic and paraaortic, up to 2 cm)	NA	ANA positive, anticardiolipin positive, C-ANCA weakly positive, decreased C3 and C4, anemia, thrombocytopenia, raised ESR, LDH raised	Refused steroid therapy
C3	M/73	Dry cough, CT revealed miliary shadows and bronchial wall thickening especially in the lower lobes of the lungs, diffuse lymphadenopathy (supraclavicular, mediastinal, hilar, axillary, and abdominal), right hydronephrosis	IgG4/IgG 3200/5620 (57.1%)	RF negative, ANA negative	Developed bilateral lacrimal and submandibular glands swelling 9 mo later. Steroid therapy with significant clinical improvement
C4	M/70	Left lower limb swelling with large left groin lymph node and diffuse lymphadenopathy (supraclavicular, mediastinal, abdominal, pelvic, up to 2 cm). CT revealed lymph node compression on the left ureter causing hydronephrosis and hydronephrosis. Impaired renal function	IgG4/IgG 2150/3667 58.6%	ANA positive, raised ESR, hemolytic anemia	After steroid therapy, groin lymph node disappeared, and renal function improved (creatinine dropped from 188 to 129 μ mol/L)
C5	M/69	Known history of autoimmune thyroiditis on thyroxine replacement. Presented with diffuse lymphadenopathy (cervical, mediastinal, axillary and groin, up to 1 cm)	IgG4/IgG 260/2606 (10%)	Antithyroglobulin antibody positive, antimicrosomal antibody positive, anemia, raised ESR	Lymph nodes diminished in size without steroid therapy
C6	M/37	Presented with dysphagia of unknown cause. Endoscopy showed thickening of esophageal wall and biopsies were negative for malignancy. CT scan showed paraesophageal and right hilar lymphadenopathy as well as multiple small nodules (1 cm) in both lungs. Two years later, developed submandibular, axillary, and groin lymph node enlargement up to 2.2 cm. Groin lymph node biopsy performed	IgG 5790 mg/dL	Anemia, lymphocytosis, raised platelet count, C-reactive protein increased	Lymph nodes decreased in size with steroid therapy

ANA indicates antinuclear antibody; C-ANCA, cytoplasmic-antineutrophil cytoplasmic antibodies; CT, computed tomography; C3, complement 3; C4, complement 4; LDH, lactate dehydrogenase; RF, rheumatoid factor; USG, ultrasonography.

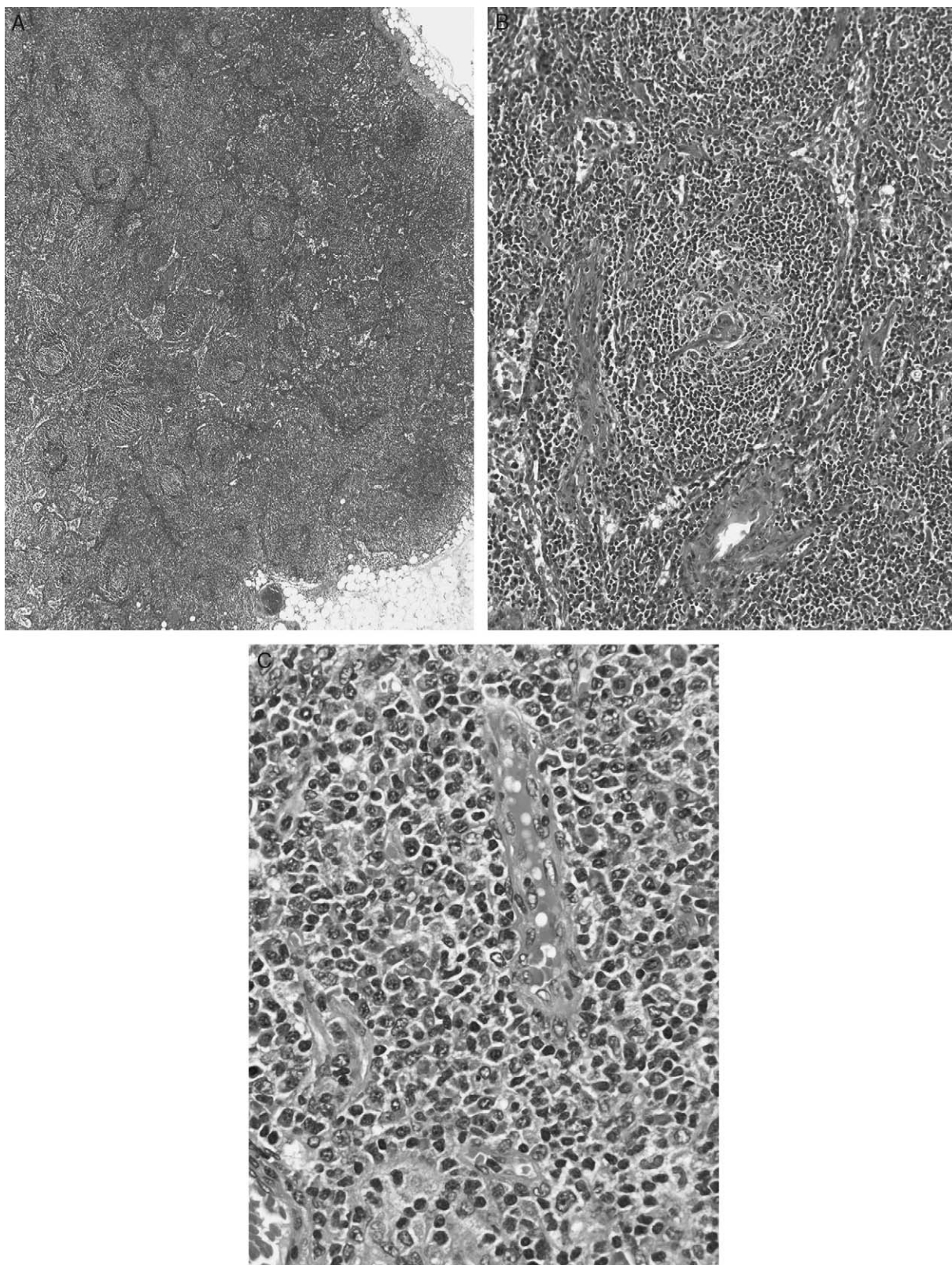


FIGURE 1. Lymph node showing multicentric Castleman disease-like features (type I pattern). A, The nodal architecture is intact with patent sinuses. Many reactive follicles are present. B, The follicles commonly show hyaline-vascular changes, and the background is rich in plasma cells. C, The interfollicular zone is densely populated by mature plasma cells.

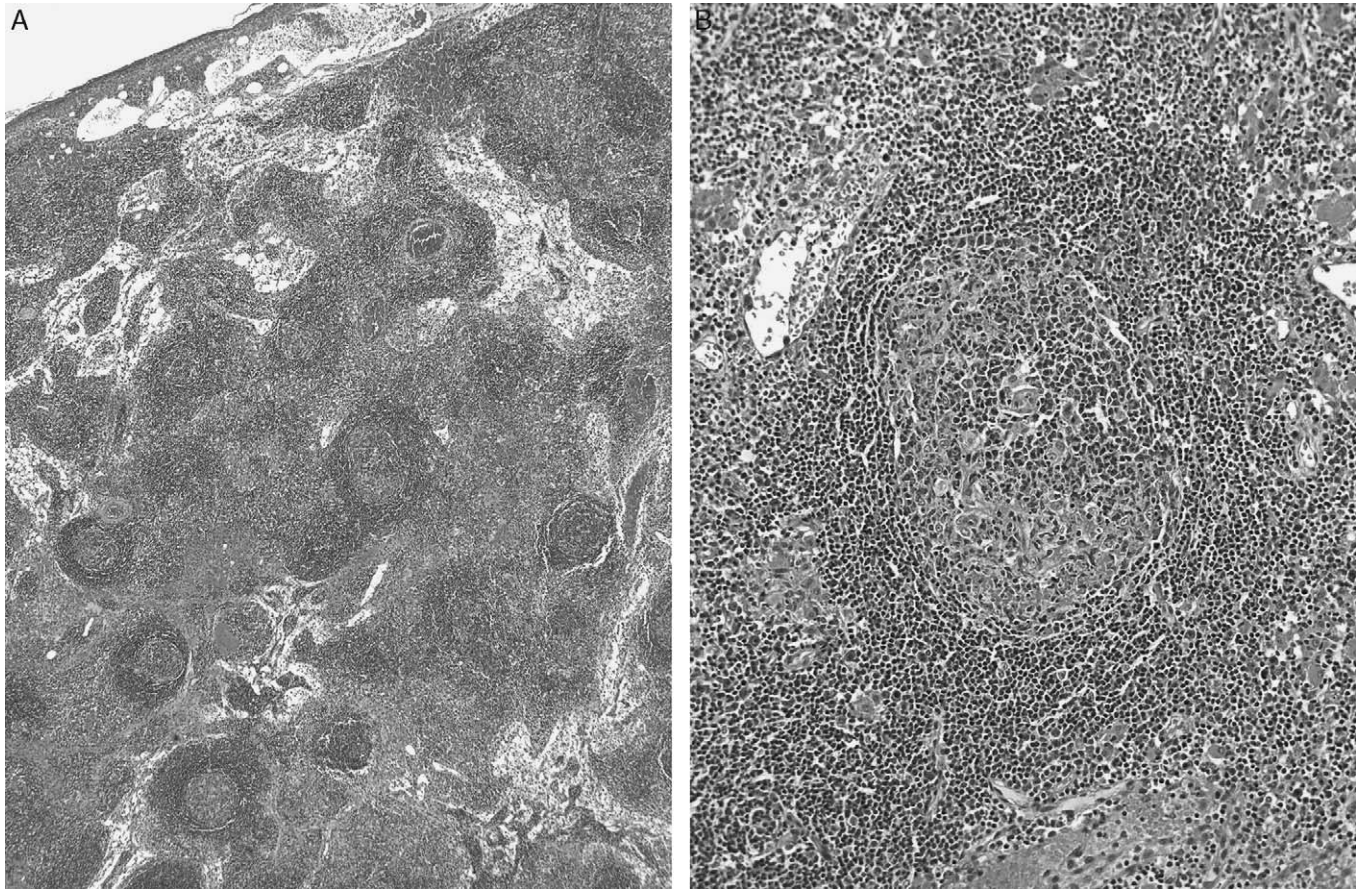


FIGURE 2. Lymph node showing usual reactive follicular hyperplasia (type II pattern). A, The nodal architecture is intact with patent sinuses. Reactive lymphoid follicles are evident. B, The reactive follicle comprises germinal center surrounded by a discrete mantle. The interfollicular zone is populated by small lymphocytes mixed with variable numbers of plasma cells.

All except 1 patient had anemia, which was autoimmune hemolytic type in 2. ESR was raised in 4 patients and autoimmune markers were positive in 4 patients. Serum IgG ranged from 3667 to 5940 mg/dL (normal < 1600 mg/dL) and IgG4 ranged from 260 to 3200 mg/dL (normal < 135 mg/dL). The enlarged lymph nodes showed increased uptake of Gallium-67 or fluorodeoxy-D-glucose (SUV 3-6.2) on positron emission tomography. There was significant clinical response to steroid therapy with shrinkage of lymph nodes (C1, C3, C4, C5, and C6), symptomatic improvement (C1, C3, and C6), and improvement of renal function (C4). One patient (C2) refused steroid therapy.

Pathologic Findings

The size of the lymph nodes ranged from 1 to 5.1 cm, with a mean of 2 cm (group A: 1.3 to 1.8 cm, mean 1.5 cm; group B: 1 to 3 cm, mean 2 cm; and group C: 1 to 5.1 cm, mean 2.5 cm). Three morphologic patterns could be identified, namely Castleman diseaselike (type I), follicular hyperplasia (type II), and interfollicular expan-

sion (type III). The lymph nodes did not exhibit sclerosis or phlebitis.

Lymph nodes of cases B1, C1, C2, C5, and C6 demonstrated Castleman diseaselike features (type I). The lymph node architecture was preserved. The lymphoid follicles showed variable degrees of regressive changes in the germinal centers, with decreased centroblasts, tingible-body macrophages, and mitotic counts (Fig. 1). Hyalinized blood vessels frequently penetrated the germinal centers. In some follicles, concentric files of small lymphocytes produced an onionskin pattern in the mantle zone. The interfollicular region showed mild to moderate increase in vascularity, and moderate to large numbers of mature plasma cells. On immunostaining, CD20-positive B cells were largely confined to the follicles, and the CD3-positive T cells resided mainly in the interfollicular areas. The plasma cells did not show immunoglobulin light chain restriction, and HHV-8 was negative in all cases.

In cases A1, A2, A3, B2, and C3, the lymph nodes showed usual reactive follicular hyperplasia (type II) (Fig. 2). Small to moderate numbers of mature plasma cells were present in the interfollicular areas.

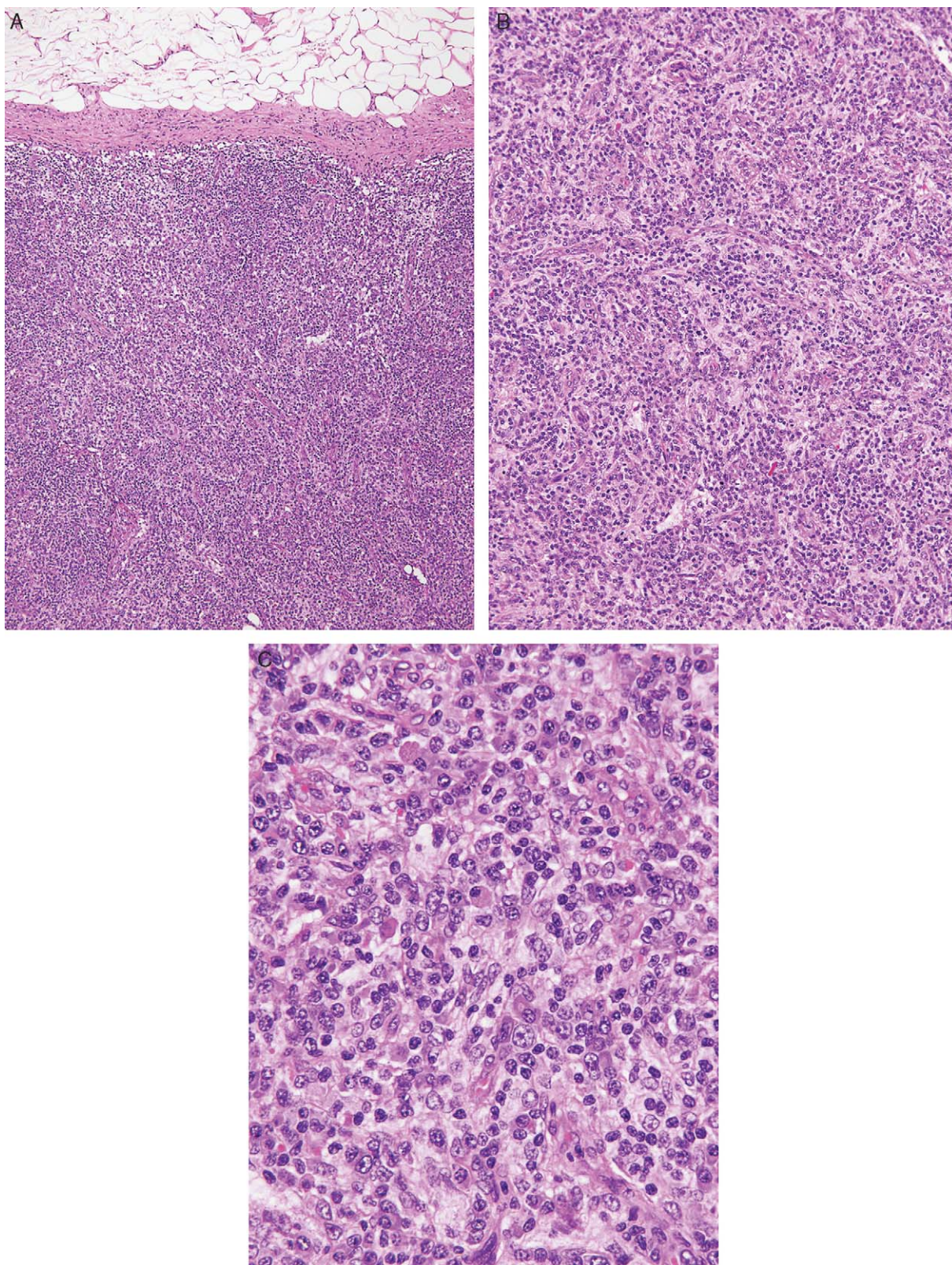


FIGURE 3. Lymph node showing interfollicular expansion (type III pattern). A, The sinuses are patent, but the interfollicular zone is markedly expanded. B, High endothelial venules are prominent, and there is a polymorphous cellular infiltrate. C, The infiltrate comprises lymphocytes, activated lymphoid cells, mature plasma cells, and immature plasma cells.

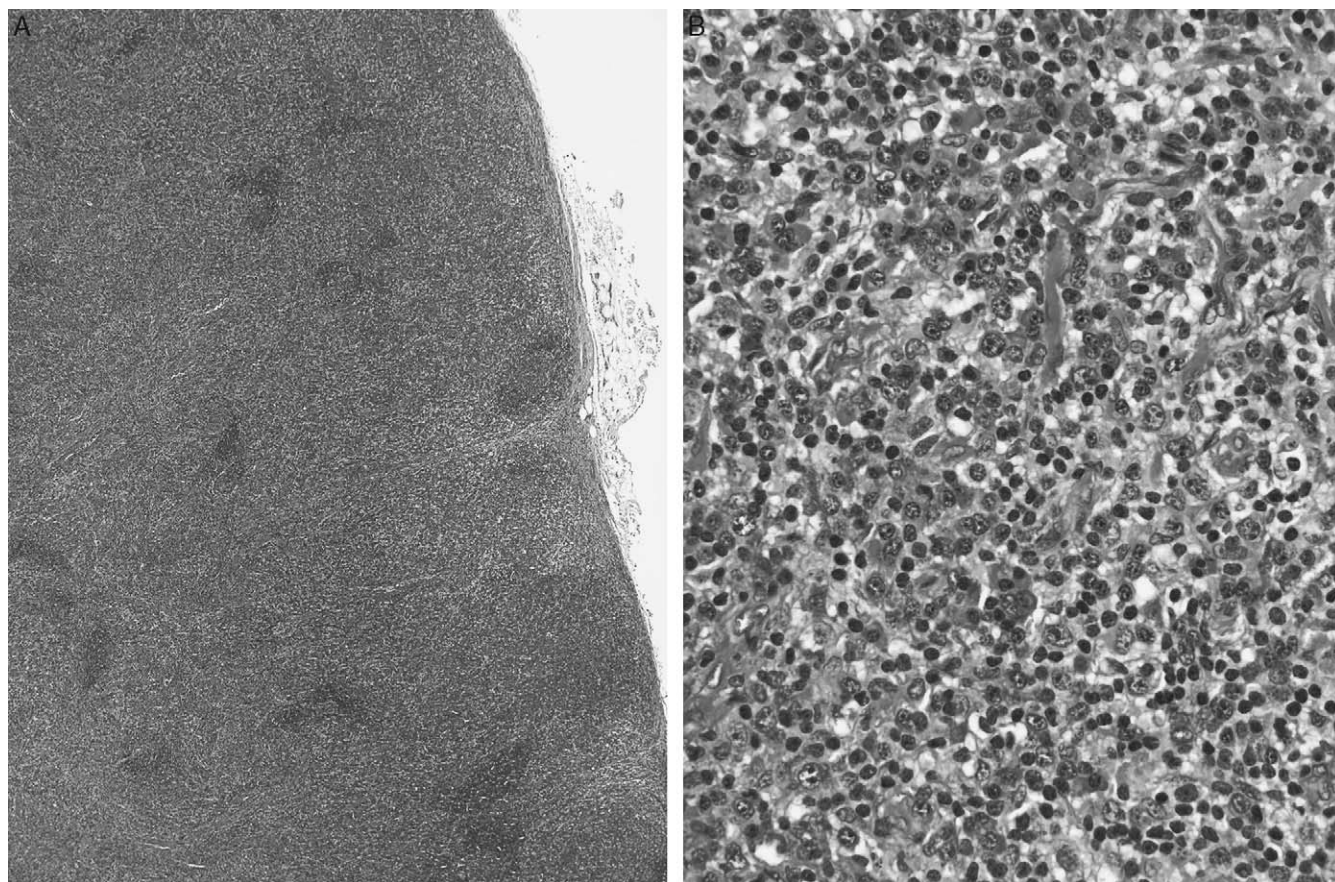


FIGURE 4. Lymph node showing interfollicular expansion (type III pattern). A, The interfollicular zone is markedly expanded, and there are only scattered atrophic lymphoid follicles in the cortex. B, There is a mixed infiltrate of lymphocytes, immunoblasts, and plasma cells, accompanied by prominent high endothelial venules.

Lymph nodes of cases B3 and C4 were characterized by marked interfollicular expansion (type III). The lymph node architecture was distorted by an expanded interfollicular zone, with only a few small follicles scattered in the cortex (Figs. 3, 4). The interfollicular zone was

densely populated by immature and mature plasma cells and also by immunoblasts accompanied by arborizing high endothelial venules. Focally, there were small numbers of admixed lymphoid cells with clear cytoplasm. On immunostaining, the large cells in the interfollicular areas consisted of mixed populations of CD20-positive B cells and CD3-positive T cells. The T cells were negative for CD10 and there was no extrafollicular proliferation of CD21-positive follicular dendritic cells. There was no immunoglobulin light chain restriction.

In all lymph nodes, the number of IgG4-positive plasma cells was increased, ranging from 17 to 877 per HPF (mean 416, median 383). The proportion of IgG4+/IgG+ plasma cells ranged from 43% to 99% (mean 60%, median 58%) (Table 3) (Fig. 5). The mean number of IgG4+/IgG+ plasma cells per HPF and the proportion of IgG4+/IgG+ plasma cell for the 3 morphologic patterns were as follows: type I, 521, 50%; type II, 266, 67%; and type III, 527, 67%.

Immunostaining of Control Reactive Lymph Nodes

The results of IgG4 and IgG staining in control lymph nodes are listed in Table 1 (Figs. 6, 7). The mean number of IgG4+ plasma cells per HPF and the

TABLE 3. IgG4+/IgG+ Plasma Cell Count and Ratio, and Corresponding Morphologic Patterns

Case	Sites	IgG4/IgG-positive Plasma Cells per HPF (0.196 mm ²)	Morphologic Pattern
A1	Peripancreatic lymph node	103/214 (48%)	II
A2	Peripancreatic lymph node	178/180 (99%)	II
A3	Hepatic hilar lymph node	17/40 (43%)	II
B1	Groin lymph node	531/1150 (46%)	I
B2	Parotid lymph node	353/391 (72%)	II
B3	Axillary lymph node	413/649 (64%)	III
C1	Mesenteric lymph node	553/922 (60%)	I
C2	Supraclavicular lymph node	877/1592 (55%)	I
C3	Axillary lymph node	678/899 (75%)	II
C4	Groin lymph node	641/914 (70%)	III
C5	Groin lymph node	307/706 (43%)	I
C6	Groin lymph node	335/725 (46%)	I

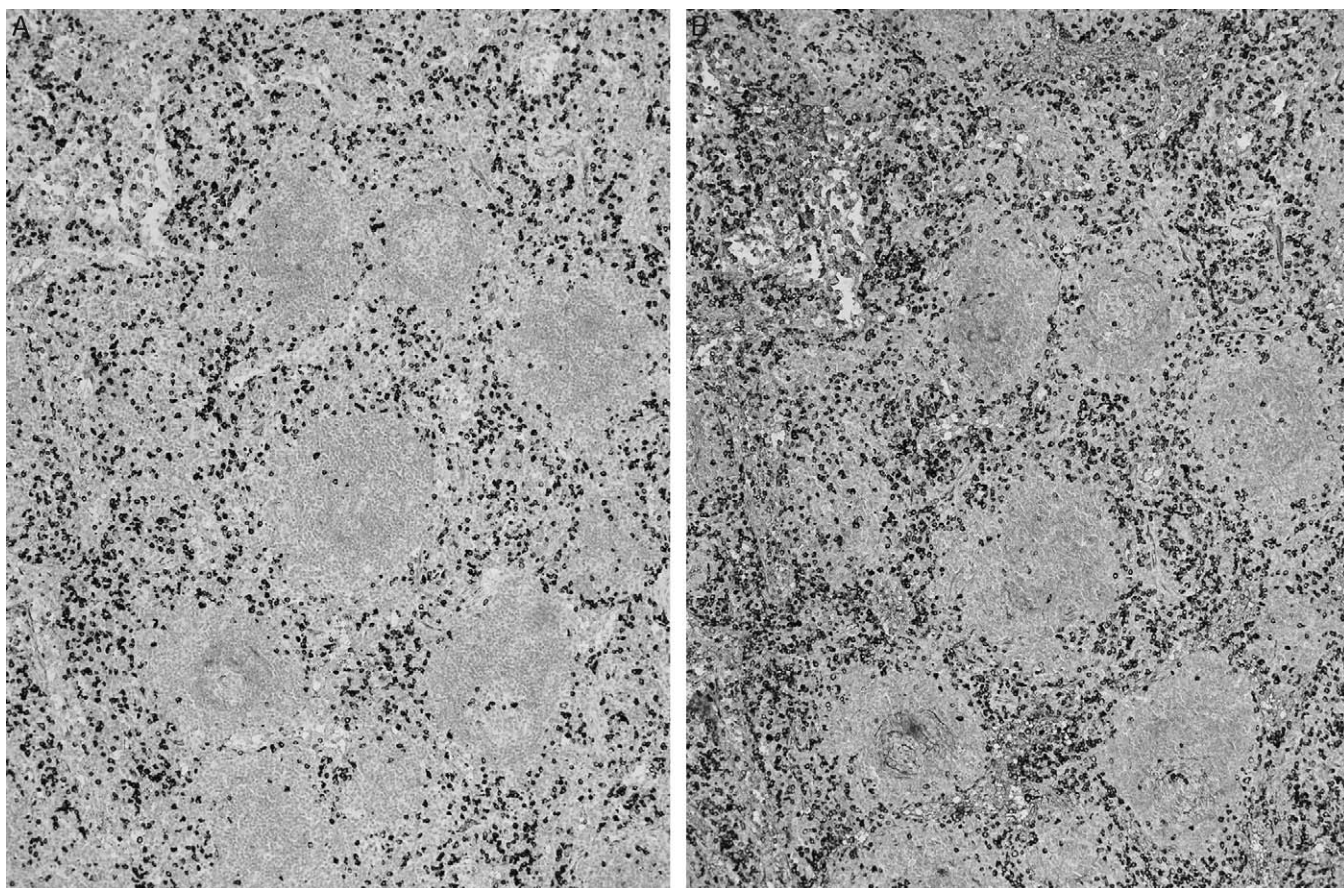


FIGURE 5. Lymph node showing type I pattern immunostained for IgG4 and IgG. A, Numerous IgG4+ cells are present between the follicles. B, The number of IgG+ cells is only slightly higher than that of IgG4+ cells in a corresponding field. Thus the IgG4+/IgG+ cell proportion is over 50%.

proportion of IgG4+/IgG+ plasma cells were 31.1 (range, 0 to 192) and 9.9% (range, 0% to 29.9%), respectively.

DISCUSSION

Autoimmune pancreatitis is a newly recognized clinicopathologic entity with an uncertain etiology and favorable clinical outcome.⁹ The diagnosis is based on a combination of imaging (computed tomography or endoscopic retrograde cholangiopancreatography), histologic (lymphoplasmacytic infiltrate, sclerosis, and obliterative phlebitis), and serologic criteria (elevated serum IgG4 level),⁹ although the Japan Pancreas Society does not require histologic proof.²⁸ As patients with autoimmune pancreatitis are recognized to have lesions involving an ever-growing number of extrapancreatic sites,^{5,6,11} and patients with primary extrapancreatic disease with otherwise typical clinical and morphologic features can have no pancreatic lesion,^{4,13,14,22} autoimmune pancreatitis is now recognized to represent merely a component of a systemic disease known as “IgG-related sclerosing disease,” “IgG4-autoimmune disease,” or

“hyper-IgG4 disease.”^{13,14,22} The finding of an increased number of IgG4-positive plasma cells in otherwise normal bone marrow, gastric mucosa, and lymph nodes of affected patients also testifies to the systemic nature of this disease.¹³ The extrapancreatic lesions may precede or follow the pancreatitis for as long as 15 years, such that the presence of pancreatic lesion, or “autoimmune pancreatitis,” is no longer considered essential for the diagnosis.¹³ Currently, the most characteristic feature of this disease is a high serum IgG4 level or abundant IgG4+ plasma cells in the involved tissues.^{2,6,11,25,29}

Lymphadenopathy, as defined by elevated uptake of Gallium-67 or significant decrease in Gallium-67 uptake after 4 weeks of steroid therapy, can be found in 80% of patients with IgG4-related sclerosing disease.¹¹ These lymph nodes have been described in the literature to show follicular hyperplasia with many IgG4-positive plasma cells but without further characterization.^{3,4,14-17}

In this study, we document that the morphologic features of regional and nonregional lymph nodes in patients with known IgG4-related sclerosing disease are rather nonspecific, but can be broadly divided into 3 patterns characterized by Castleman disease-like, follicular

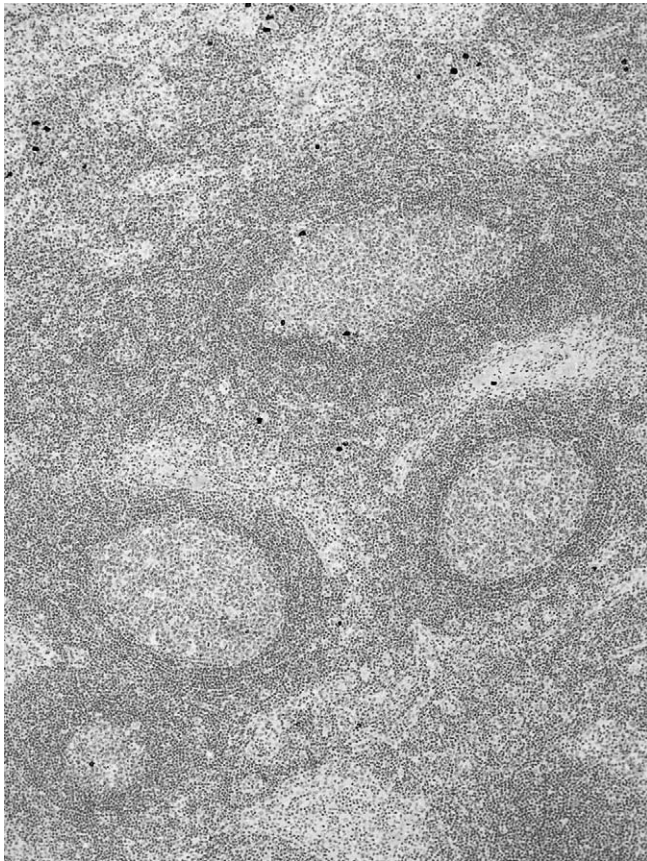


FIGURE 6. Lymph node from a patient with rheumatoid arthritis immunostained for IgG4. Like most reactive lymph nodes studied as controls, IgG4+ cells are sparse and occur singly.

hyperplasia, and interfollicular expansion. In the first pattern (type I), there are follicles with variable degrees of regressive changes, hyalinized blood vessels, increased high endothelial venules, and many plasma cells in the interfollicular region. Taken together with the clinical findings of multifocal lesions, hypergammaglobulinemia, and raised ESR, the features are highly reminiscent of multicentric Castleman disease. However, in contrast to the latter, the patients do not have fever, HHV-8 is negative, some patients show lacrimal gland involvement, and the clinical course is much more benign. Type I morphologic pattern also overlaps with autoimmune disease-associated lymphadenopathy as seen in rheumatoid arthritis,^{21,26} and so-called idiopathic plasmacytic lymphadenopathy with polyclonal hypergammaglobulinemia.¹⁹

Cases with marked interfollicular expansion, plasmacytic and immunoblastic proliferation, and arborizing high endothelial venules (type III) can be confused with angioimmunoblastic T-cell lymphoma. In contrast to the latter, there are no definite cytologically atypical T cells, CD10 is negative, and there is no extrafollicular follicular dendritic cell proliferation. The 2 cases in this series were

originally given the diagnostic label of “atypical lymphoid hyperplasia,” prompting repeat biopsies to ascertain the diagnosis.

In this study, we also studied 6 cases of unexplained lymphadenopathy associated with raised serum IgG4/IgG and/or increased IgG4+ plasma cells in the lymph node. We believe that these cases belong to the IgG4-related sclerosing disease spectrum because (1) the serum IgG4 was raised in all tested patients, (2) all showed increased IgG4+ plasma cells in lymph nodes, (3) the morphologic features are similar to those found in patients with typical IgG4-related sclerosing disease, (4) the age group and male predilection are similar, (5) autoimmune antibodies are frequently present, and (6) there is favorable clinical response to steroid therapy, accompanied by a decrease in serum IgG4. In fact, 2 of these patients developed features of classical IgG4-related sclerosing disease (lymphoplasmacytic sclerosing cholangitis in 1 and bilateral lacrimal/submandibular gland disease in 1) during the clinical course (Fig. 8). Further studies are required to confirm that these cases truly represent the lymphadenopathic form of the syndrome.

The salient clinical features of IgG4-related lymphadenopathy (groups B and C in this study) can be summarized as follow. The patients are middle-aged to elderly with marked male predominance. Usually multiple lymph node groups are involved, the commonest being mediastinal, intra-abdominal, and axillary. The lymph nodes are generally not very large (usually 1 to 2 cm). The exocrine or extranodal lesions may precede, follow, or present together with the lymphadenopathy. Despite the systemic nature of the disease, there is usually no fever. The laboratory clues to diagnosis are anemia (sometime Coombs’ positive), raised ESR, or C-reactive protein, raised globulin, raised IgG, and presence of autoantibodies, whereas lactate dehydrogenase is often normal or only slightly elevated.

In extranodal sites, different investigators have used different criteria in defining IgG4-related sclerosing disease, such as > 10, > 20, > 30, > 50 IgG4+ plasma cells per HPF.^{8,13,20,29} However, the exact field size is often not stated in these studies, and such a range can be observed in other reactive lesions, especially in conditions rich in plasma cells. For these reasons, we established our criteria based on a study of a variety of control lymph nodes. We adopted > 40% IgG4+/IgG+ cells as a cutoff because all reactive lymph nodes show a percentage below 30%.¹⁸ Although an increased proportion of IgG4+/IgG+ plasma cells can occasionally be observed in various reactive lymphadenopathies, this strict criterion can help sort out cases which demonstrate clinicopathologic features of IgG4-related sclerosing disease. The occasional finding of increased IgG4+ cells in other reactive lymph nodes is by no means surprising as IgG4 is merely a surrogate marker of this evolving entity, and elevated serum IgG4 levels can be found in other immune-mediated or related diseases such as atopic dermatitis, asthma, some parasitic diseases, and bullous skin diseases.^{1,24,27}

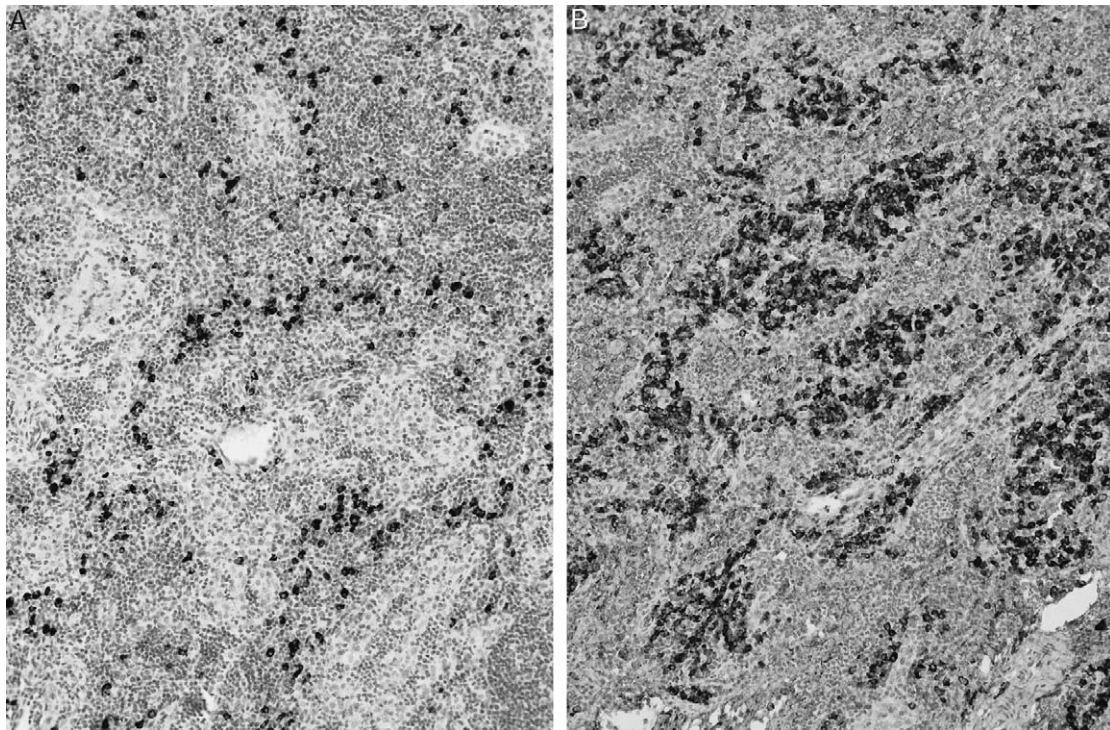


FIGURE 7. Another lymph node from a patient with rheumatoid arthritis immunostained for IgG4 and IgG. A, A moderate number of IgG4+ plasma cells is present. B, There are however many more IgG+ plasma cells. The IgG4+/IgG+ cell proportion in this case is 26%.

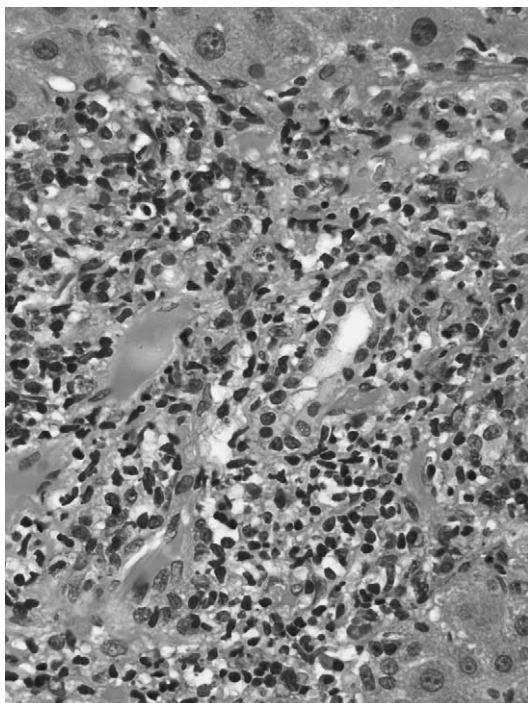


FIGURE 8. Liver biopsy from case C1. The portal tracts are heavily infiltrated by lymphocytes and plasma cells, accompanied by bile duct damage.

In summary, we report the morphologic features of lymph nodes in a series of IgG4-related sclerosing disease and the primary lymph node manifestations of this disease. The importance of recognition of this disease lies in the remarkable response to steroid therapy. The diagnosis requires awareness and a high index of suspicion for this entity—unexplained lymphadenopathy with increased plasma cells, lymph node with features suggestive of multicentric Castleman disease, or lymphadenopathy in patients with known pancreatitis, lacrimal gland lesion, or salivary gland lesion. Liberal use of immunostaining for IgG4 and IgG may help in identifying these cases.

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