A Subset of Rosai-Dorfman Disease Exhibits Features of IgG4-Related Disease

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Abstract

In this study we investigated the distribution of IgG4+ plasma cells and regulatory T (T_{REG}) cells, a major regulator of IgG4 production, in nodal and extranodal Rosai-Dorfman disease (RDD). Twenty-six specimens (15 nodal, 11 extranodal) were examined, with reactive lymph nodes and site-matched extranodal specimens as controls. Overall, 84.6% (22/26) of the specimens showed various degrees of sclerosis (7 mild, 8 moderate, and 7 severe). Nineteen cases (73.1%) exhibited more than 10 IgG4+ cells/0.060 mm^2 (photographed area at ×40), and 8 cases (30.8%) showed more than 40% of IgG+ cells being IgG4+. Only 1 control case exhibited more than 10 IgG4+ cells/0.060 mm^2 ($P < .05$). The number of T_{REG} cells was comparable between nodal RDD and controls, whereas extranodal RDD exhibited significantly higher numbers of T_{REG} cells than controls. These findings demonstrate that a subset of RDD shows features of IgG4-related disease and indicate an overlap between certain aspects of the 2 diseases.

Rosai-Dorfman disease (RDD) was established as a unique clinicopathologic entity based on 2 reports by Rosai and Dorfman in 1969[1] and 1972,[2] which were followed by numerous additional reports describing various aspects of this disorder. As a nodal-based disease, it typically presents as painless cervical adenopathy in young individuals. After the initial description in lymph nodes, RDD was subsequently found to occasionally involve extranodal sites (9% of RDD cases), most commonly skin, bone, and soft tissue, with a predilection for proximal limbs and trunk. However, involvement of almost every tissue/organ has been reported.

Although RDD typically presents as painless cervical lymphadenopathy in children and has a benign, self-limited course, recurrences do occur, and involvement of certain extranodal sites, including vital organs, has been associated with an aggressive course and, rarely, a fatal outcome.

The pathogenesis of RDD is not well understood. Emerging evidence suggests that RDD may be associated with an abnormal autoimmune response. Most cases of RDD demonstrate abundant plasma cells and sclerosis. Several case reports and 2 recent series of a limited number of cases have demonstrated that the plasma cells in extranodal RDD express IgG4.[3-6] IgG4+ plasma cells have been found in autoimmune pancreatitis (AIP) and in a variety of extrapancreatic sclerosing lesions. This group of diseases is now known as IgG4-related disease,[7-9] which is characterized by the presence of abundant IgG4+ plasma cells in the lesion, with tissue sclerosis and elevated serum IgG4 concentration. It has been proposed that type 2 T helper cells and regulatory T (T_{REG}) cells regulate IgG4 expression. The presence of many IgG4+ plasma cells and stromal fibrosis suggests that cutaneous RDD may be related to IgG4-related disease.[3] Whether and

to what extent nodal RDD and noncutaneous extranodal RDD demonstrate features of IgG4-related disease remains unclear.

In this study, we demonstrated that a proportion of both nodal and extranodal RDD exhibits a constellation of histologic features consistent with IgG4-related disease. In patients with recurrent diseases, a trend toward correlation between IgG4+ plasma cell/T_{REG} cell infiltration and degree of sclerosis was observed during disease progression.

Materials and Methods

Case Selection and Clinical Information

This study was approved by the Institutional Review Board of the University of Chicago Medical Center. We searched the pathology archive of the University of Chicago Medical Center from 1991 to 2009 and retrieved 26 specimens (15 nodal, 11 extranodal) of RDD from 15 patients. Outside consultation cases were not included in the study because of the lack of material for further studies. The patients' ages ranged from 1 to 69 years. Nine specimens were from 7 pediatric patients (1-14 years old), and 17 specimens were from 8 adult patients. Four patients had recurrent disease, and 3 patients had multicentric involvement by RDD. For all cases, the diagnosis was confirmed using the morphologic criteria published by Rosai and Dorfman[1,2] and further supported by characteristic immunohistochemical findings (S100+/CD68+/CD1a– histiocytes).[10] No initial diagnosis was changed after the review. Eight benign reactive lymph nodes from patients with early/in situ carcinoma served as controls for nodal RDD cases. For extranodal RDD, an age-, sex-, and anatomical site–matched tissue control was selected for each case. The control spleen was from a patient with papillary carcinoma of the fallopian tube undergoing debulking surgery. The patient had no prior treatment, and the spleen was not involved by carcinoma. The patient/specimen details are summarized in **Table 1**.

In addition to RDD, 1 patient had systemic lupus erythematosus, 1 patient had sarcoidosis, and 1 patient had positive antiphospholipid antibody. Serum IgG levels were tested in 4 patients, with 2 patients tested twice (more than 1 year apart). All the tested serum samples showed elevated IgG levels. Serum IgG4 levels were not available for any of the patients.

Immunohistochemistry

Immunohistochemistry was performed on 4-μm-thick paraffin tissue sections. Double labeling for IgG4/FOXP3 (a marker for T_{REG} cells) was performed on a BOND-MAX automated immunohistochemistry platform (Leica Microsystems, Buffalo Grove, IL) according to the manufacturer's sequential protocol. Antigen retrieval was performed in a high pH antigen epitope retrieval solution (Novocastra Bond Epitope Retrieval Solution 2, Leica Microsystems) for 20 minutes. Slides were incubated with anti–IgG4 antibody (1:500, clone HP6025; Invitrogen, Molecular Probes, Eugene, OR) for 25 minutes followed by the Bond Polymer Refine horseradish peroxidase detection system and subsequently with anti-FOXP3 (1:50, clone 236A/E7; Abcam, Cambridge, MA) for 25 minutes, followed by Bond Polymer Red detection (alkaline phosphatase; Leica Microsystems). Slides were counterstained with hematoxylin.

Table 1
Summary of Demographic and Clinical Information

Patient No.	Age, y	Sex	Location	Note
1	9	M	Lymph node, cervical	
2	14	F	Lymph node, cervical	
3	1	M	Lymph node, cervical	
4	14	M	Lymph node, retroperitoneal	
5	12	M	Lymph node, cervical	
6	61	M	Lymph node, intraparotid	
7	2	F	Lymph node, cervical	
			Lymph node, cervical	Recurrence 3 y later
8[a]	46	M	Lymph node, periumbilical, supraclavicular, and axillary	
			Lymph node, cervical	Other node involvement 7 mo later
			Testis and lymph node, femoral	Testis and other node involvement 1 y later
9	14	F	Skin, right breast	Biopsied and excised 18 mo later
10	41	F	Bone	
11	69	F	Breast (involving parenchyma)	
12[a]	29	F	Left atrium, periaortic lymph node	
13	63	F	Soft tissue, abdominal wall	
14	30	F	Soft tissue, left arm	
			Soft tissue, left arm	Recurrence 9 mo later
15[a]	51	F	Colon and pericolonic lymph node	
			Spleen	Splenic involvement 2 y later

[a] Patient with multicentric disease.

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Immunohistochemistry for IgG was performed using the BenchMark XT automated slide preparation system (Ventana Medical Systems, Tucson, AZ). Following antigen retrieval in a Target Retrieval Solution (DakoCytomation, Carpinteria, CA) at 95°C for 40 minutes, a 1:10,000 dilution of polyclonal rabbit anti–human IgG antibody (DakoCytomation) was applied for 20 minutes at room temperature, and the anti-IgG antibody was detected using ultraView Universal DAB Detection Kit (Ventana Medical Systems).

Data Analysis

The degree of sclerosis was scored on a scale of 0 to 3, corresponding to no, mild (increased amount of scattered, delicate collagen fibers), moderate (delicate collagen fibers forming loose bundles or meshwork), and severe (thick collagen bands or large confluent fibrotic areas), respectively. Since fibrotic/sclerotic bands are frequently seen surrounding lesions of RDD, only sclerosis within the lesions was scored. Analysis of immunohistochemical stains was performed as described by Shrestha et al.[4] Three areas rich in positively stained cells (IgG4+ plasma cells or FOXP3+ T_{REG} cells) in each specimen were photographed under a ×40 objective (0.060 mm^2). For all cases, the number of positively stained cells was counted on a computer screen by the same pathologist (X.Z.). IgG+ and IgG4+ plasma cells were identified based on morphology and their immunoreactivity. Rare cells that exhibited cytoplasmic reactivity but did not have typical plasma cell morphology were excluded. Average positive cell count in the 3 photographed areas was calculated. For each photographed area of IgG4 stain, the same field on an adjacent section stained for IgG was also photographed, and the ratio of IgG4+ to IgG+ cells was calculated. Data were expressed as mean ± SE. Standard and paired Student *t* test and χ^2 test were used for statistical analysis.

Results

Overall, 84.6% of RDD cases showed various degrees of sclerosis, which was moderate to severe in 50.0% of the cases **Table 2**. Extranodal and adult cases tended to be more sclerotic than their nodal or pediatric counterparts, but the difference was not statistically significant.

Both nodal and extranodal RDD showed a statistically significant increase in the number of IgG4+ plasma cells compared with controls. Of all RDD cases, 73.1% (19/26; nodal 11/15, extranodal 8/11) exhibited more than 10 IgG4+ plasma cells/0.060 mm^2, and 46.2% (12/26; nodal 6/15, extranodal 6/11) showed more than 30 IgG4+ cells/0.060 mm^2. Nodal RDD cases showed 39.7 ± 11.0 IgG4+ plasma cells/0.060 mm^2; in contrast, control reactive lymph nodes showed 6.6 ± 2.3 IgG4+ cells/0.060 mm^2 ($P = .04$) **Figure 1A**. In extranodal RDD, mean IgG4+ plasma cells were 22.5 ± 4.6/0.060 mm^2, whereas controls only exhibited rare IgG4+ plasma cells (1.0 ± 0.4/0.060 mm^2, $P = .0002$) **Figure 1B**.

The ratio of IgG4+ plasma cells to IgG+ cells showed a statistically significant increase in RDD. Overall, 30.8% of RDD cases (8/26; nodal 5/15, extranodal 3/11) exhibited an IgG4/IgG ratio of more than 40%. The mean IgG4/IgG ratio was 30.1% in RDD cases. Nodal RDD cases exhibited a mean IgG4/IgG ratio of 27.9%, higher than that of the reactive lymph nodes (6%; $P = .01$) **Figure 1C**. The mean IgG4/IgG ratio was 33.7% in extranodal RDD cases **Figure 1D**. However, it is not possible to calculate the ratio in extranodal controls because of the scarcity of plasma cells in most types of normal tissue.

The number and percentage of IgG4+ plasma cells were similar between nodal and extranodal RDD cases ($P > .40$) **Figure 2A** and **Figure 2C**. The number of IgG4+ cells was comparable between adult and pediatric cases ($P = .50$) **Figure 2B**. The IgG4/IgG ratio was higher in adult cases compared with pediatric cases, but the difference did not reach statistical significance ($P = .056$) **Figure 2D**.

As shown in IgG4/FOXP3 double-stained slides, the distribution of FOXP3+ T_{REG} cells showed a different pattern from that of IgG4+ plasma cells. Although areas of intermingled FOXP3+ T_{REG} cells and IgG4+ plasma cells were seen, surprisingly in most cases, T_{REG} cells and IgG4+ plasma cells were localized to different areas of the tissue sections. Because reactive lymph nodes feature abundant FOXP3+ T_{REG} cells (119.0 ± 18.1/0.060 mm^2), there was no statistical difference in the number of T_{REG} cells between reactive lymph nodes and nodal RDD cases (87.2 ± 13.8; $P = .18$) **Figure 3A**. Similar to nodal RDD cases, extranodal RDD exhibited 110.5 ± 23.8 T_{REG} cells/0.060 mm^2, higher than

Table 2
Sclerosis in Rosai-Dorfman Disease

Sclerosis	Nodal, No. (%)	Extranodal, No. (%)	Pediatric, No. (%)	Adult, No. (%)	Total, No. (%)
0	4 (26.7)	0 (0.0)	2 (22.2)	2 (11.8)	4 (15.4)
1	4 (26.7)	5 (45.5)	3 (33.3)	6 (35.3)	9 (34.6)
2	4 (26.7)	2 (18.2)	3 (33.3)	3 (17.6)	6 (23.1)
3	3 (20.0)	4 (36.4)	1 (11.1)	6 (35.3)	7 (26.9)
Total	15 (100.0)	11 (100.0)	9 (100.0)	17 (100.0)	26 (100.0)

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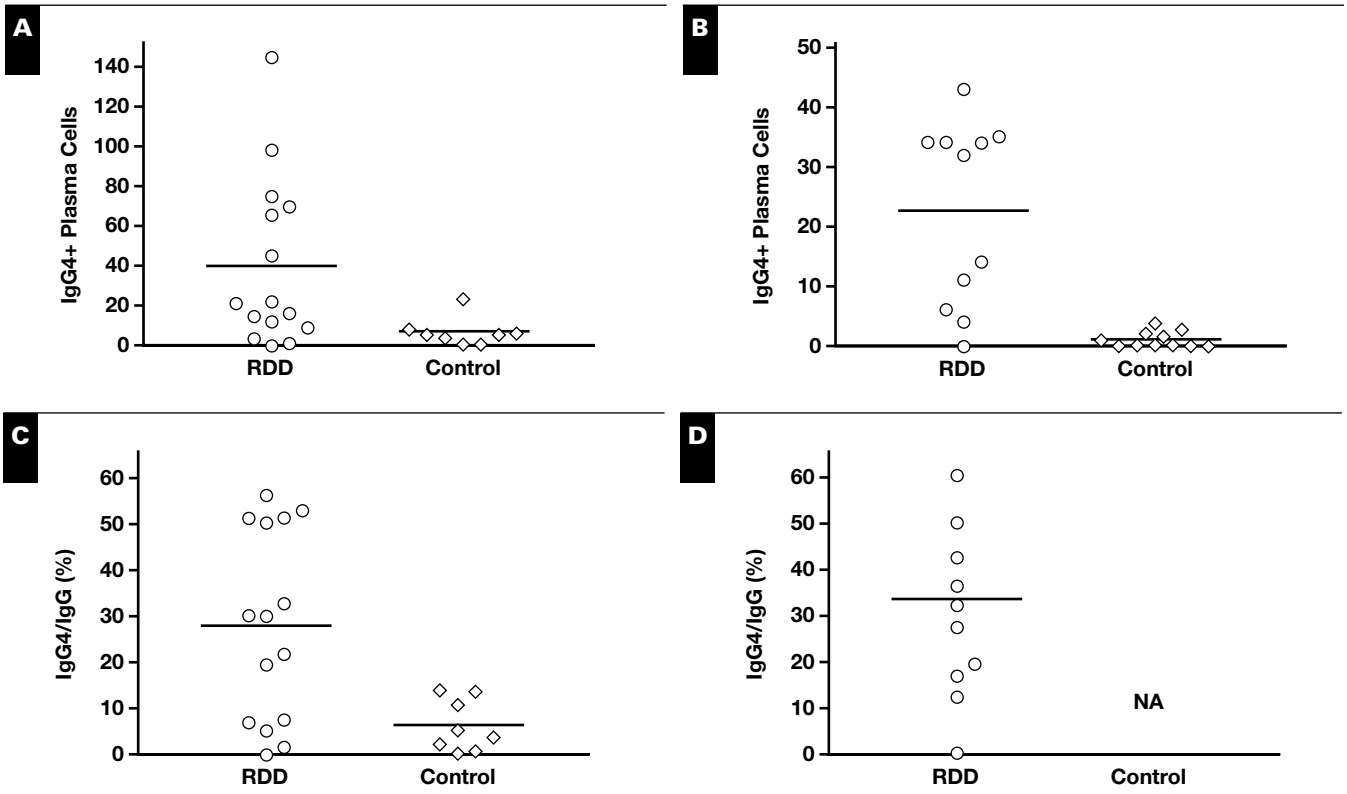

Figure 1 Both nodal (**A**, **C**) and extranodal (**B**, **D**) Rosai-Dorfman disease (RDD) showed a significant increase in the number of IgG4+ plasma cells per photographed area (0.060 mm^2; **A**, **B**) and IgG4+ to IgG+ cells ratio (**C**, **D**) compared with the controls. The IgG4/IgG ratio cannot be calculated in extranodal control (normal tissue) because of the scarcity of plasma cells (**D**). **A**, $P = .04$; **B**, $P = .0002$; **C**, $P = .01$; **D**, NA, not applicable.

that of extranodal controls, where T_{REG} cells were rarely seen (12.9 ± 8.3; $P = .0015$) **Figure 3B**.

We also analyzed whether there were any statistical correlations of the degree of sclerosis with the number/percentage of IgG4+ plasma cells and the number of T_{REG} cells. Although no statistical correlations were seen in the entire patient population, a trend toward correlation between the degree of sclerosis and the number of IgG4+ plasma cells/T_{REG} cells was observed in patients with recurrent or persistent disease. Three representative cases are shown in **Image 1**, **Image 2**, and **Image 3**. The first patient (Image 1) presented with RDD involving the soft tissue of the left arm that recurred 9 months later. In the recurrent specimen, there was decreased sclerosis, decreased IgG4+ plasma cells, and decreased T_{REG} cells, suggesting the disease might evolve to a less sclerotic form, with decreased IgG4+ plasma cells and T_{REG} cells. There was no medical treatment between the 2 surgeries in this case. The second patient (Image 2) had colonic RDD and recurrent disease in the spleen 2 years later. There was no radiographic evidence of splenic involvement when the colonic RDD was diagnosed. The recurrent RDD in the spleen exhibited an increased level of sclerosis, as well as higher numbers of IgG4+ cells and T_{REG} cells. Because no other superimposed conditions may cause splenic fibrosis, the findings indicated that the disease might evolve to the sclerotic end of the spectrum. The third patient (Image 3) is unique because the lesion was initially biopsied but was not excised until 18 months later without any interval therapy. In the later resection specimen, the degree of sclerosis and the number of IgG4+ plasma cells and T_{REG} cells were all increased as compared with the initial biopsy specimen.

Discussion

In this study, about 30% of RDD cases showed various degrees of sclerosis and increased number/percentage of IgG4+ plasma cells, features characteristic for IgG4-related disease. In view of the fact that both the morphology and the distribution of IgG4+ plasma cells in RDD exhibit a wide spectrum, it is possible that only a subset of RDD overlaps with IgG4-related disease, or it is only during certain phases of the disease when RDD may demonstrate features

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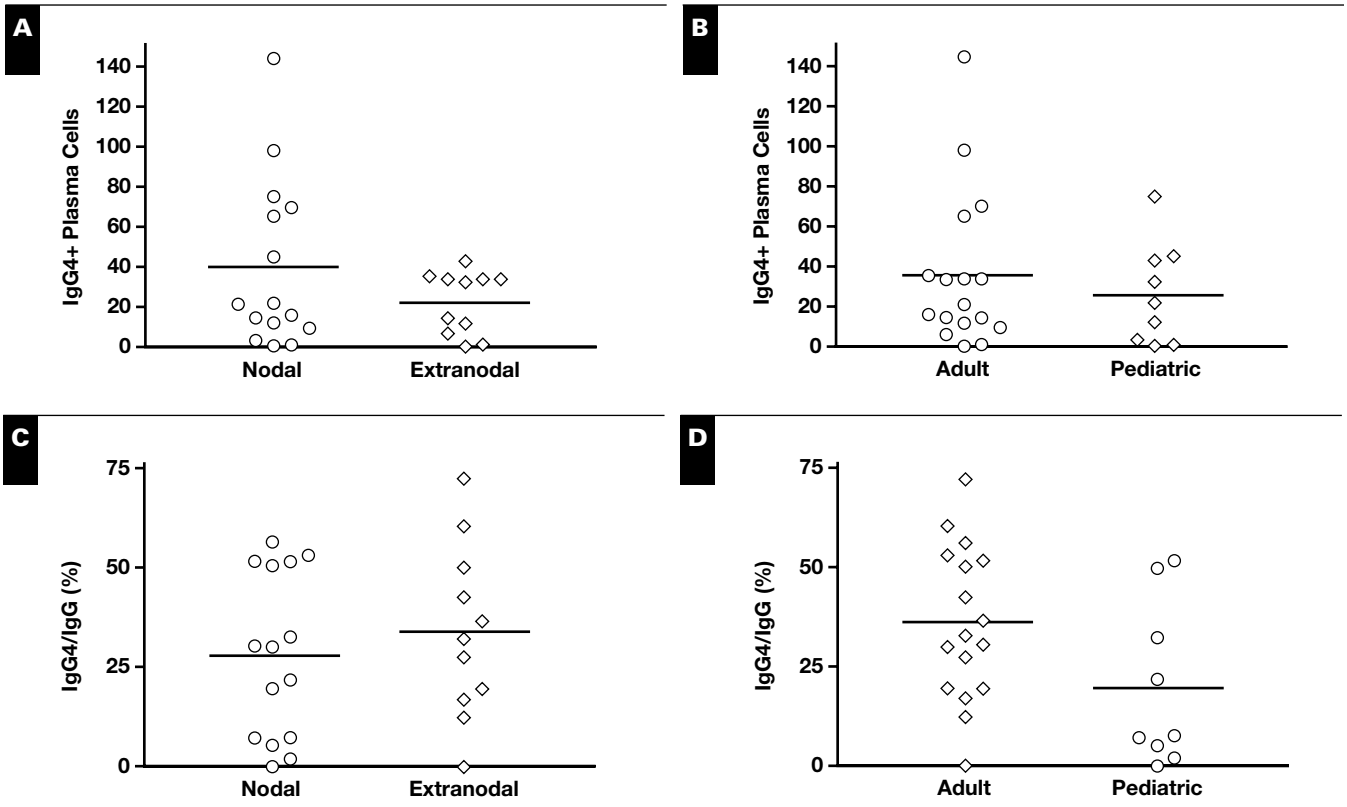

Figure 2 The number of IgG4+ plasma cells per photographed area (0.060 mm^2) and IgG4+ to IgG+ cells ratio were comparable between nodal and extranodal cases (**A**, **C**). Adult and pediatric cases exhibited a similar number of IgG4+ cells per photographed area (**B**), but the IgG4/IgG ratio tended to be higher in adult cases compared with pediatric cases, leading toward a statistical difference (**D**). **A**, $P = .48$; **B**, $P = .50$; **C**, $P = .50$; **D**, $P = .056$.

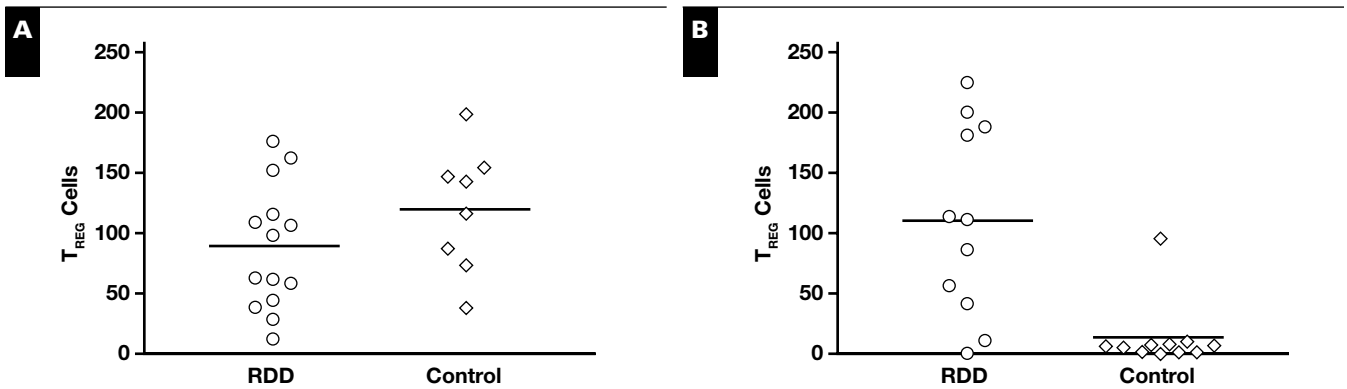

Figure 3 The number of regulatory T (T_{REG}) cells per photographed area (0.060 mm^2) was similar in nodal Rosai-Dorfman disease (RDD) cases and reactive lymph node controls (**A**). In contrast, extranodal RDD cases showed a significantly higher number of T_{REG} cells per photographed area compared with their age-, sex-, and anatomical site–matched normal tissue controls (**B**). **A**, $P = .18$; **B**, $P = .0015$.

of IgG4-related disease. Generally, IgG4-related disease involves multiple organ systems. Similarly, multiple organ system involvement is sometimes seen in RDD. In this study, 3 of 15 patients had multicentric RDD involving multiple organs. Three patients in this study had other autoimmune diseases in addition to RDD, including systemic lupus erythematosus, sarcoidosis, and positive antiphospholipid antibody. Although diseases within the IgG4-related disease spectrum were not present in any patients in this study, 1 patient with concurrent RDD and AIP has been reported.[11]

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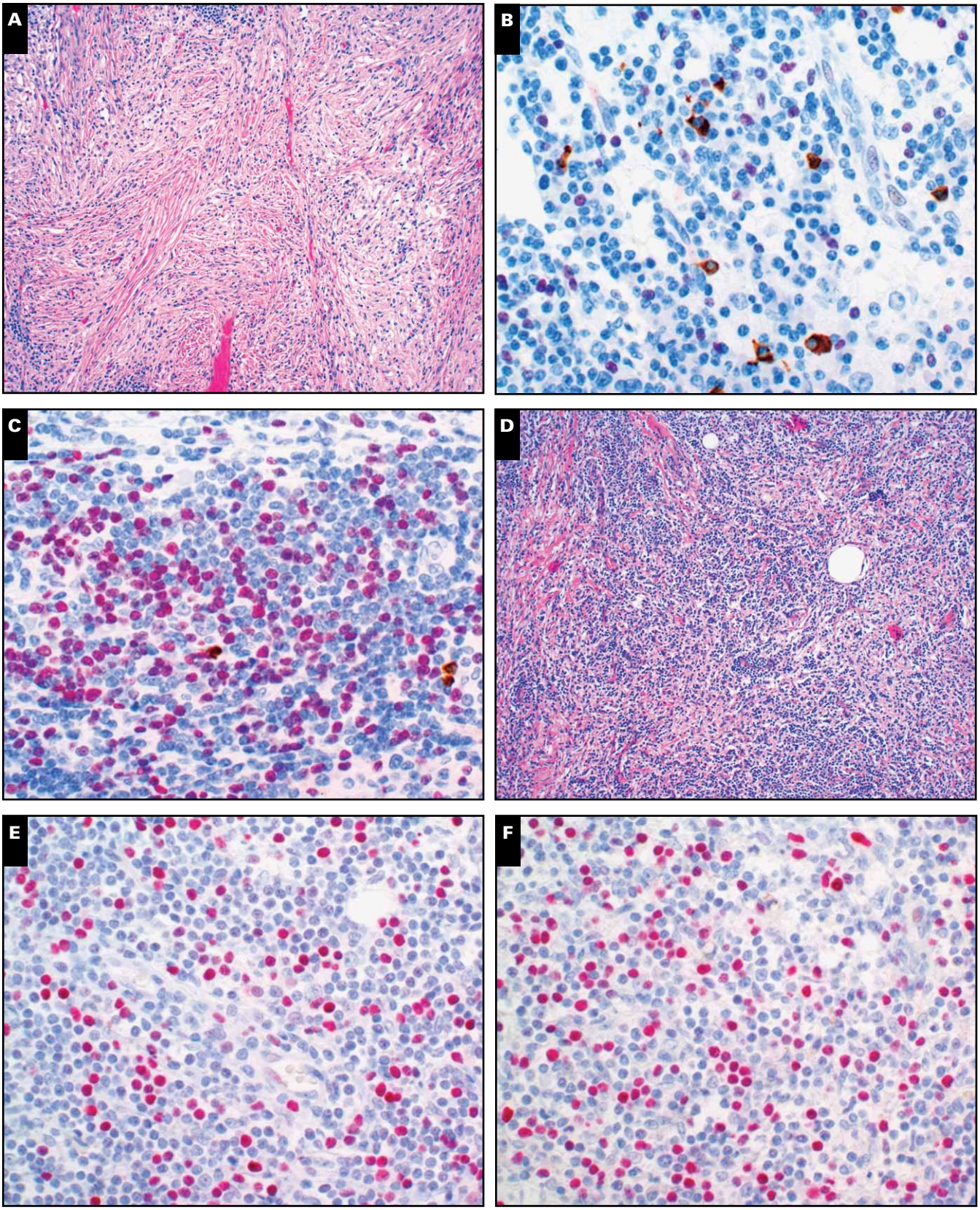

Image 1 Specimen from a 30-year-old woman with Rosai-Dorfman disease involving the soft tissue of the left arm, which showed moderate sclerosis (score 2; **A**). There were 11 IgG4+ plasma cells per photographed area, with an IgG4/IgG ratio of 12.3% (**B**). Regulatory T (T_{REG}) cell count was 188 per photographed area (**C**). The patient developed recurrence 9 months later, with decreased sclerosis (mild, score 1; **D**). There were no IgG4+ plasma cells (IgG4/IgG ratio 0%; **E**). T_{REG} cell count decreased to 112 per photographed area (**F**).

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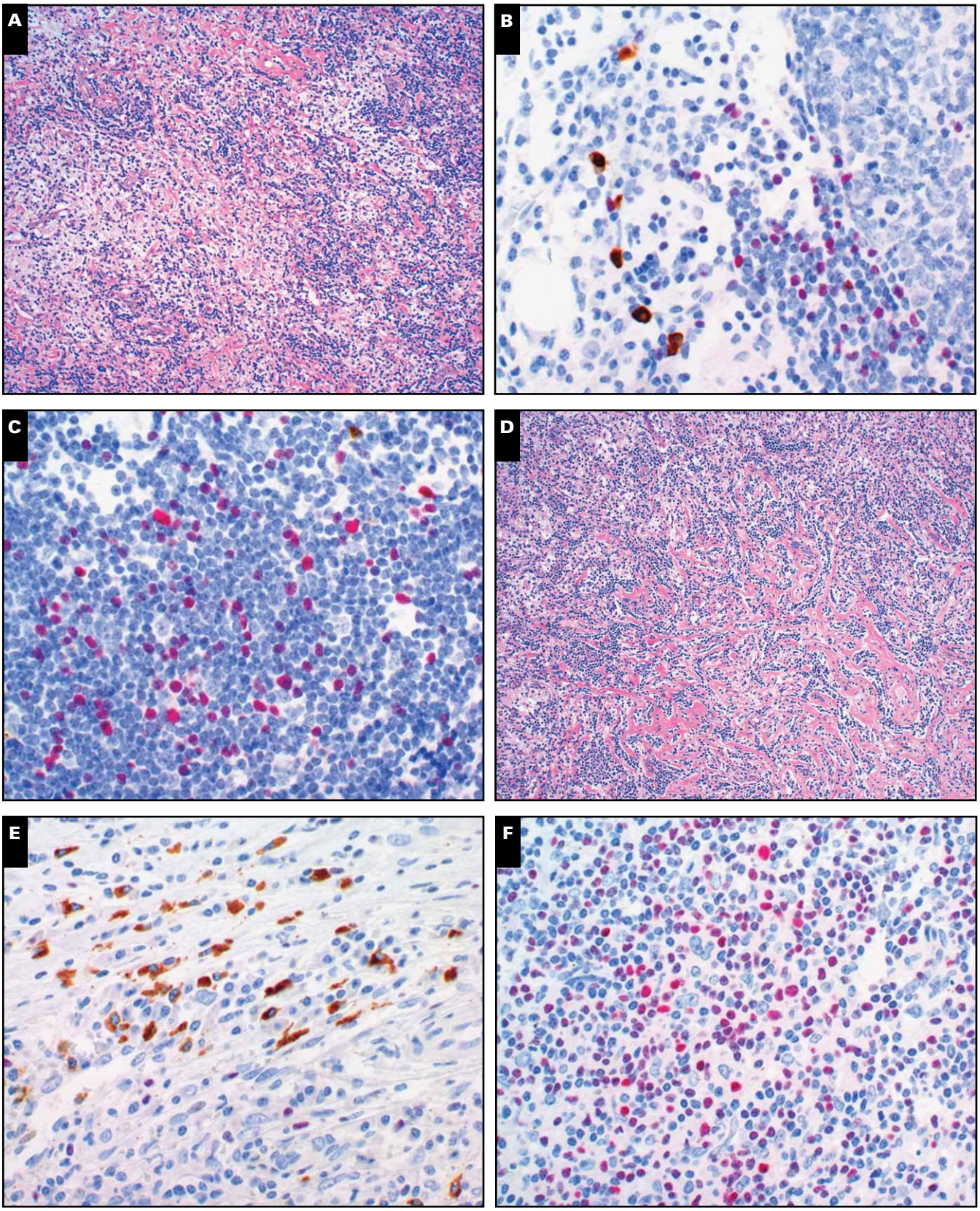

Image 2 Specimen from a 51-year-old woman with Rosai-Dorfman disease (RDD) involving the colon, showing mild sclerosis (score 1; **A**). There were 4 IgG4+ cells per photographed area, with an IgG4/IgG ratio of 17.1% (**B**). Regulatory T (T_{REG}) cell count was 86 per photographed area (**C**). The patient had recurrent RDD involving the spleen 2 years later. The spleen showed severe sclerosis (score 3; **D**). The IgG4+ plasma cell count increased to 34 per photographed area (IgG4/IgG ratio 43.6%; **E**). T_{REG} cell count increased to 181 per photographed area (**F**).

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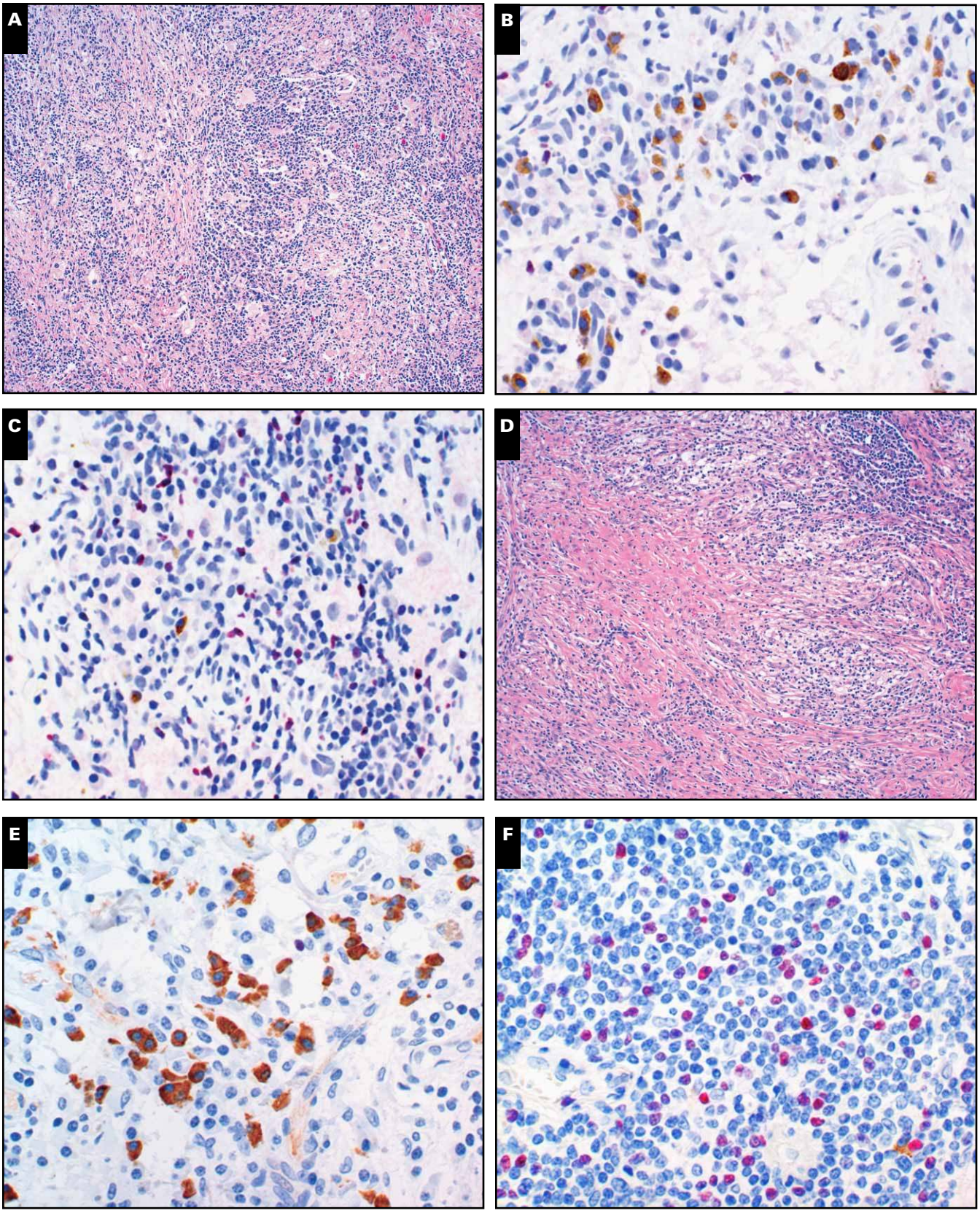

Image 3 Specimen from a 14-year-old girl with Rosai-Dorfman disease of the breast. The initial biopsy specimen exhibited no sclerosis (score 0; **A**). There were 32 IgG4+ cells per photographed area, with an IgG4/IgG ratio of 32.3% (**B**). Regulatory T (T_{REG}) cell count was 42 per photographed area (**C**). The lesion, excised 18 months later, became moderately sclerotic (score 2; **D**). The IgG4+ plasma cell count increased to 43 per photographed area (IgG4/IgG ratio 50.0%; **E**). T_{REG} cell count increased to 56 per photographed area (**F**).

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Currently, there is no general consensus on the cutoff of IgG4+ plasma cells for the diagnosis of IgG4-related disease. The recently published International Consensus Diagnostic Criteria for Autoimmune Pancreatitis by Shimosegawa et al[12] proposed a cutoff of 10 IgG4+ plasma cells per high-power field (hpf) as a diagnostic criterion. Similarly, the comprehensive diagnostic criteria for IgG4-related disease published by Umehara et al[9] include (1) serum IgG4 concentration less than 135 mg/dL and (2) more than 40% of IgG+ plasma cells being IgG4+ and more than 10 IgG4+ cells/hpf. Other authors have suggested higher numbers to increase the specificity of the diagnosis.[13] The more recently published consensus statement on the pathology of IgG4-related disease by Deshpande et al[14] proposed a set of cutoff points specific to each organ and required an IgG4+/IgG+ plasma cell ratio of more than 40%. Because the area actually examined in a ×40 hpf may vary depending on the size of the field of view of the ocular, it would be difficult to compare the results of different studies. Furthermore, some studies,[4] including the current study, count IgG4+ cells in areas photographed at ×40 (0.060 mm^2), but the photograph may not capture the entire area of a ×40 field. For future studies, it would be practical to report IgG4+ plasma cells per square millimeter, so that interstudy comparison would be more feasible. Many publications, including the recent comprehensive diagnostic criteria for IgG4-related disease[9] and consensus statement,[14] used the ratio of IgG4+ cells to IgG+ plasma cells as a criterion. The combination of an IgG4/IgG ratio greater than 40% and more than 10 IgG4+ cells/hpf, as proposed by Umehara et al,[9] provides a reasonable solution, but such stringent criteria may decrease the diagnostic sensitivity. Despite the heterogeneity of the organ being involved, over 30% of the RDD cases in this study do show more than 10 IgG4+ cells/hpf and an IgG4/IgG ratio greater than 40%. Because of the retrospective nature of the study, the serum IgG4 levels of these patients are unavailable. However, it is worth noting that 4 patients in this study did have elevated serum IgG levels.

The pathologic role of IgG4 in IgG4-related disease remains unknown. In humans, IgG4 is related to the pathogenesis of limited diseases, including IgE-related allergies, pemphigus, and IgG4-related disease.[15] Although the pathogenic role of IgG4 in pemphigus has been well characterized, whether IgG4 is pathogenic or an epiphenomenon for IgG4-related disease remains unknown. The production of IgG4 is regulated by T helper 2 cells and T_{REG} cells.[15,16] In patients with AIP, circulatory T_{REG} cells are significantly increased, and naive T_{REG} cells are significantly decreased.[8] In the affected tissues of patients with IgG4-related sclerosing pancreatitis and cholangitis, the expression of T helper 2 cytokines (interleukin [IL]–4, IL-5, and IL-13) and T_{REG} cytokines (IL-10 and transforming growth factor–β) was upregulated.[16] Infiltration of the major duodenal papilla by IgG4+ plasma cells (≥10/hpf) and FOXP3+ T_{REG} cells (≥14/hpf) was also recognized in patients with AIP.[17] The increased number of T_{REG} cells in the disease sites suggests that T_{REG} cells might be involved in the in situ production of IL-10, which induces IgG4 class switching, and transforming growth factor–β, which induces collagen production and fibrosis.[16] In this study, we observed abundant FOXP3+ T_{REG} cells in RDD, of both nodal and extranodal location. The number of T_{REG} cells in extranodal cases was significantly higher than that of anatomical site–matched controls, where T_{REG} cells are rarely seen. Therefore, it is possible that T_{REG} cells play a similar role in extranodal RDD as they do in IgG4-related disease by inducing both fibrosis and IgG4 subclass switch. Because of the abundance of T_{REG} cells in reactive lymph nodes, the number of T_{REG} cells is similar in nodal RDD compared with reactive lymph nodes. However, the functional status of those T_{REG} cells in reactive lymph nodes remains unclear. In contrast to reactive lymph nodes, nodal RDD cases do show increased sclerosis and IgG4+ plasma cell infiltration. Theoretically, the possibility that T_{REG} cells exert similar function in both extranodal and nodal RDD cannot be ruled out. An important aspect that remains unclear is the relationship between IgG4+ plasma cells, T_{REG} cells, and histiocytes. Since extensive histiocytosis is a defining feature of RDD, whereas increased numbers of IgG4+ plasma cells and T_{REG} cells are present in only a subset of the disease, it is unlikely that there is a pathologic link between the 2 phenomena.

Because T_{REG} cells may induce both IgG4 production and fibrosis in RDD, we analyzed the correlation of the degree of sclerosis with the number of IgG4+ plasma cells and T_{REG} cells. The number/percentage of IgG4+ plasma cells, number of T_{REG} cells, and extent of sclerosis did not show any statistical correlation in the overall patient population, which may reflect the variation of these parameters in different patients, in different anatomical sites, and during the progression of the disease. For example, an increased number of T_{REG} cells and an increased number of IgG4+ plasma cells, which are theoretically induced by T_{REG} cells, might represent 2 phases of the disease. This might explain the lack of geographic correlation between the 2 cell types. Interestingly, in patients with recurrent diseases, the degree of IgG4+ plasma cell infiltration, the number of T_{REG} cells, and levels of sclerosis do correlate during the disease progress.

It is well known that AIP typically responds dramatically to corticosteroid treatment.[7] Since RDD frequently presents a self-limited clinical course, with 80% of cases having spontaneous remission without receiving any therapy,[18] corticosteroids are not routinely used for the treatment of RDD. As a result, whether RDD responds to steroid treatment is not well documented in the literature. An increasing

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number of case reports have shown quick and dramatic response to steroids in patients with RDD, most of whom received steroid treatment because of respiratory obstruction, disfiguration, or surgically inaccessible locations.[19-27] In 2 case reports, patients did not respond to steroid treatment.[28,29] It is likely that authors tend to publish RDD cases successfully treated with corticosteroids rather than those cases that failed to respond, resulting in the predominance of steroid-responsive RDD case reports in the literature. In keeping with our observation, we hypothesize that only a portion of RDD may respond to steroid treatment, including those who have features of IgG4-related disease. Unfortunately, no information on the serum IgG4 levels or IgG4+ plasma cells infiltration was available in the published case reports. In our series, 1 patient was treated with steroids. The patient, who presented with RDD diffusely involving multiple lymph nodes and the colonic wall, developed recurrence involving the spleen 2 years after initial surgery. The patient received steroid treatment because of sarcoidosis, and there was no recurrent RDD during the 9-year follow-up. Further prospective studies will be helpful to verify the therapeutic effects of corticosteroids for patients with RDD who require medical intervention and whether IgG4 may be a marker for response to steroids.

In conclusion, a significant portion of RDD shows features characteristic of IgG4-related disease, indicating these cases of RDD may overlap with IgG4-related disease. We believe it is of clinical importance to increase the awareness of this observation for pathologists who make the diagnosis of RDD and clinicians who treat such patients.

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