

IgG4-related Sclerosing Disease

A Potential New Etiology of Cutaneous Pseudolymphoma

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Abstract: IgG4-related sclerosing disease is a syndrome characterized by the involvement of a wide variety of tissues by lymphoplasmacytic infiltrates and sclerosis, elevated serum IgG4 titer, and increased IgG4+ plasma cells in tissues. This report describes 2 cases with skin involvement, a feature not well documented in the literature. The patients had plaques or nodules in the skin of the cheek, temporal or periauricular region. Histologically, there was dermal and subcutaneous involvement by a nodular lymphoid infiltration often interspersed with lymphoid follicles and sclerotic stroma. The infiltrate was rich in plasma cells, small lymphocytes, and sometimes plasmablasts. The IgG4+ cell count was high (342 to 425 per high power field), with an IgG4/IgG proportion from 68% to 100%. As the morphology was compatible with pseudolymphoma, 14 cases of cutaneous pseudolymphoma were retrieved from the archives for IgG4 and IgG immunostaining. Two cases exhibited marked increase in IgG4+ cells, and showed many similarities with cutaneous manifestation of IgG4-related sclerosing disease, but the limited available clinical information precluded a conclusion on their nosologic nature. In summary, IgG4-related sclerosing disease can manifest with skin lesions, and is also one of the potential etiologies of cutaneous pseudolymphomas.

Key Words: IgG4-related sclerosing disease, cutaneous pseudolymphoma, cutaneous lymphoid infiltrate

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IgG4-related sclerosing disease is a syndrome, probably autoimmune in nature, that has attracted increased attention in recent years.³⁷ It usually affects patients in late adulthood, with male predominance. It is characterized clinically by mass lesions which commonly involve exocrine glands, elevated serum IgG4 titer, frequent presence of circulating autoantibodies, and favorable clinical response to steroid therapy, and pathologically by lymphoplasmacytic infiltration, sclerosis, phlebitis,

and increased IgG4+ plasma cells.^{7,13,14,22,26} Although autoimmune pancreatitis is the prototypic form of the disease,^{7,19} increasing sites are recognized to be involved by the disease, such as hepatobiliary tree,¹⁸ lacrimal gland,^{8,9} salivary gland,²² lymph node,^{10,30} prostate,³⁴ lung,³³ kidney,³¹ soft tissue,^{20,36} retroperitoneum,^{17,25} mesentery,⁶ aorta,²⁰ mediastinum,³⁶ breast,^{11,35} pituitary,³² and central nervous system.⁵ Most patients have disease involving 2 or more sites, in various combinations, with or without pancreatic involvement, although the disease can rarely be confined to 1 organ-system.

Skin involvement has not been described in IgG4-related sclerosing disease, until the recent report on systemic IgG4-related lymphadenopathy by Sato et al,³⁰ who very briefly mentioned presence of skin lesions in 3 of 9 patients. In this study, we report the clinicopathologic features of 2 cases with long follow-up information, and also attempt to identify potential cases from a series of cutaneous pseudolymphomas.

MATERIALS AND METHODS

Two patients with IgG4-related sclerosing disease were diagnosed based on clinical and pathologic features (lacrimal gland and lymph node biopsies), and who had concomitant cutaneous lesions, were identified in the files of Department of Pathology, Queen Elizabeth Hospital, Hong Kong. To look for additional potential cases, 14 skin specimens diagnosed as pseudolymphoma or reactive lymphoid hyperplasia were retrieved from the archives for IgG4 and IgG immunostaining.

Clinical information was obtained from the patient records, referring pathologists, or clinicians. Serum IgG4 was assayed by radial immunodiffusion. All available pathologic materials were retrieved for morphologic review. Immunostaining was performed on the BOND-MAX automated immunostainer (Vision Biosystems, Australia) by using a polymer-based detection system. The following antibodies were applied: anti-IgG (1:250, clone IgGp, Novocastra), anti-IgG4 (1:500, clone HP6025, Zymed), CD20 (1:1000, clone L26, Dako), CD3 (1:150, clone PS1, Novocastra), CD21 (1:15, clone 2G9, Novocastra), CD10 (1:10, clone 56C6, Neomarkers), CD5 (1:50, clone 4C7, Novocastra), cyclin D1 (1:100, clone SP4, Neomarkers), CD43 (1:300, clone MT1, Clonab), BCL2 (1:500, clone Bcl-2-100, Zymed),

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and immunoglobulin κ and λ -light chains (1:48,000, antiserum, Dako).

Plasma cells showing moderate or strong cytoplasmic staining for IgG4 or IgG were considered to be positive. A multitissue control mounted on each test slide served as the positive and negative controls—the tonsillar tissue should show scanty scattered IgG4+ plasma cells and many more IgG+ plasma cells, whereas other tissues should be devoid of staining except in plasma cells. IgG4+ or IgG+ cells were enumerated in areas with the highest density of positive cells. Three high power fields (HPFs) were counted, and an average number of positive cells per HPF was calculated. One HPF covered an area of 0.196 mm² (Nikon microscope, 40 $\times$ objective, 10 $\times$ eyepiece, 20 mm field of view). An absolute IgG4+ cell count > 50 cells/HPF, together with a proportion of IgG4+/IgG+ cells > 40%, was considered significant.¹⁰

RESULTS

Clinical Features

The patients were aged between 74 and 76 years, including 1 male and 1 female (Table 1). They had ill-defined, indurated plaque or nodule in the skin of the face, noted to be present for 3 to 3.5 years (Fig. 1A). One patient (case A1) had concomitant bilateral lacrimal gland swelling, and 1 (case A2) had a right orbital mass, left parotid swelling, right renal mass, and diffuse

lymphadenopathy. The serum IgG4 levels were markedly elevated (1060 mg/dL to 1320 mg/dL). One tested patient had circulating autoantibodies (rheumatoid factor). Systemic steroid therapy effected rapid decrease in the size of the various mass lesions and resolution of lymphadenopathy in case A2.

Pathologic Features

The skin showed involvement of both the dermis and subcutaneous tissue, whereas the overlying epidermis was spared (Fig. 1). There were perivascular and periadnexal lymphoid aggregates, with or without coalescence to form compact nodules (Figs. 1B, E). The infiltrate comprised plasma cells and small lymphocytes, admixed with small numbers of eosinophils and histiocytes (Figs. 1D, G). In case A2, many plasma cells were immature-looking, and were intermingled with plasma-blasts with distinct nucleoli (Fig. 1D). There were interspersed lymphoid follicles of variable sizes, with mantles ranging from thick to thin, and sometimes with irregular-shaped germinal centers. Hyalinized collagen bundles were present within the lesions (Fig. 1F). Obliterative phlebitis was not found.

The lymphoid infiltrate comprised mixed populations of CD20⁺ B cells in nodular aggregates and CD3⁺ T cells. CD21 highlighted the follicular dendritic cell meshworks of the lymphoid follicles. The follicle centers expressed CD10, but not BCL2. There was no aberrant

TABLE 1. Clinicopathologic Features of Patients With Cutaneous IgG4-related Sclerosing Disease

Case	Sex/Age	Presentation	Treatment and Outcome	Blood Tests	Skin biopsy IgG4+/IgG+ Cell Counts per HPF
A1	Male/76	Itchy, erythematous, indurated and ill-defined plaque over left cheek (3 cm) and left temporal area (2 cm) for 3.5 y, with slow increase in size; bilateral lacrimal swelling (with biopsy) for 1 y. History of chronic obstructive airway disease, hypertension, hyperlipidemia, stroke, ischemic heart disease and gout	Lesion persisted despite topical steroid therapy. Alive with disease at 5 y	IgG4 1060 mg/dL. IgG 2340 mg/dL. Rheumatoid factor 32 IU/mL. Antinuclear antibody 1:40. Anti-double stranded DNA < 5 IU/mL. – Antineutrophil cytoplasmic antibody	342/285 (100%)
A2	Female/74	Ill-defined right periauricular indurated subcutaneous lesion for 3 y, accompanied by right retrobulbar orbital mass, left parotid swelling, diffuse lymphadenopathy (with biopsy) involving submandibular, cervical, axillary and para-aortic regions, and a heterogeneous mass in lower pole of right kidney (2.5 cm). History of chronic hepatitis B infection, asthma, and pulmonary tuberculosis	Initially treated empirically as for low-grade lymphoma with chlorambucil, but without response. The subcutaneous lesion, orbital mass, lymph nodes and right kidney mass decreased in size after oral steroid therapy (0.5 mg/kg daily). Currently on maintenance steroid therapy; well at 4 y	IgG4 1320 mg/dL, which decreased to 525 mg/dL after steroid therapy. IgG 4540 mg/dL, which decreased to 1880 mg/dL after therapy	425/630 (68%)

Normal range: serum IgG4 (0 to 135 mg/dL), IgG (700 to 1600 mg/dL), rheumatoid factor (< 15 IU/mL), antinuclear antibody (< 1:80), anti-double stranded DNA (0 to 35 IU/mL).

HPF indicates high power field; Ig, immunoglobulin.

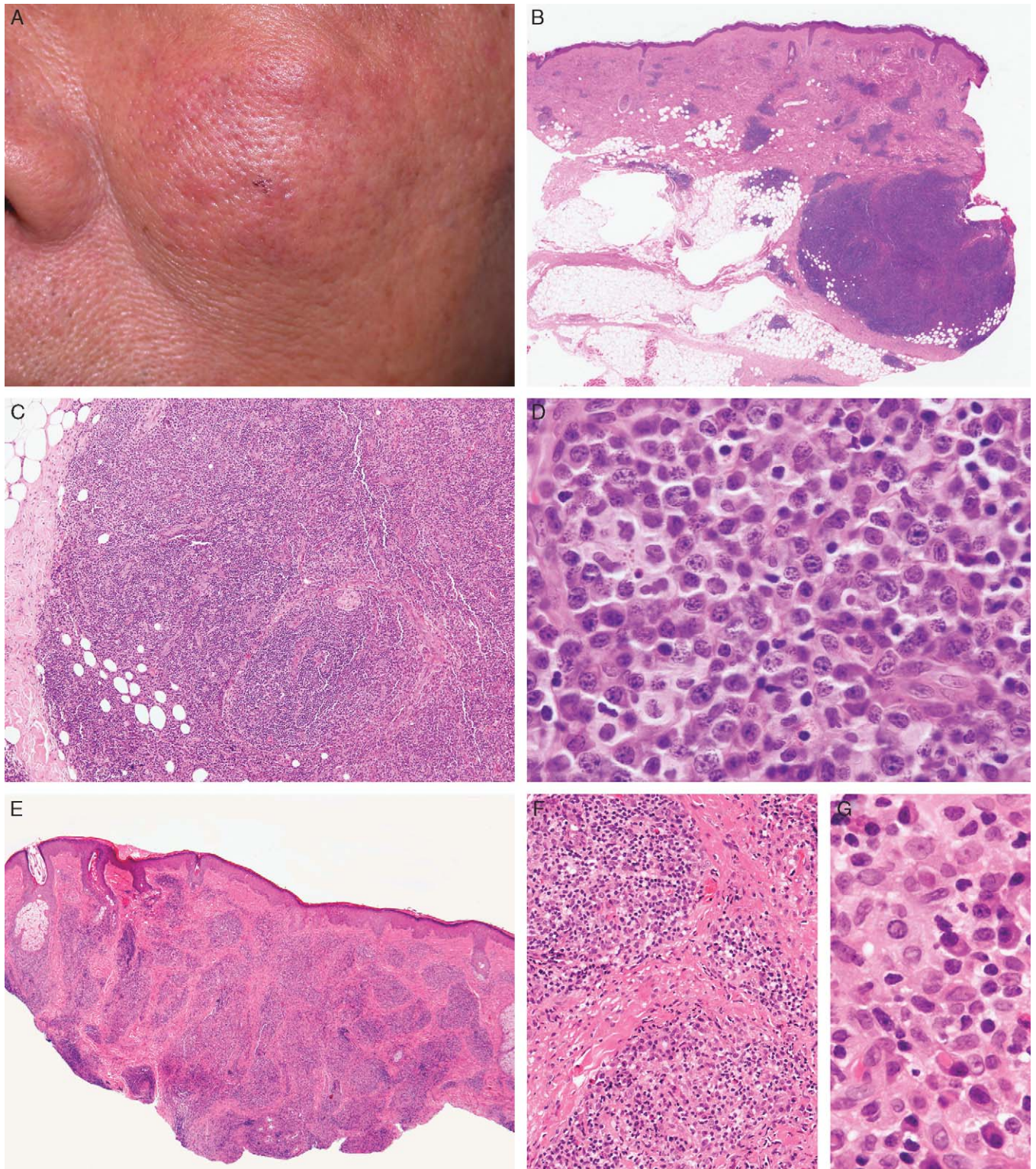


FIGURE 1. A, Case A1. Erythematous plaque over the left cheek. B, Case A2. A predominantly subcutaneous lymphoid nodule accompanied by smaller perivascular lymphoid aggregates in the dermis and subcutis. C, Case A2. The subcutaneous lymphoid nodule is surrounded by a sclerotic band. Within the diffuse infiltrate, a reactive lymphoid follicle is seen in the lower field. D, Case A2. The infiltrate comprises mature plasma cells, immature plasma cells, plasmablasts, and small lymphocytes. E, Case A1. The skin shows confluent perivascular and periadnexal lymphoid infiltrates. F, Case A1. The lymphoplasmacytic infiltrate is accompanied by deposition of sclerotic collagen in the dermis. G, Case A1. The infiltrate comprises small lymphocytes, plasma cells, histiocytes, and rare eosinophils.

staining for CD5, CD43 or cyclin D1, and the plasma cells showed polytypic light chains. The number of IgG4+ cells ranged from 342 to 425 per HPF, constituting of 68% to 100% of IgG+ cells (Table 1) (Fig. 2).

Cutaneous Pseudolymphomas

Among 14 cases of cutaneous pseudolymphoma, IgG4+ cells were markedly elevated in 2 cases (cases B1 and B2): 144 and 328 per HPF, respectively, with IgG4+/IgG+ proportion being 93% and 69% (Table 2). Both patients were males, aged 74 to 76 years, who had skin lesions in the head and neck region. Unfortunately, further clinical details were not available to determine if they had other known features of IgG4-related sclerosing disease. The histologic findings were similar to those described above, except that the lymphoid infiltrate in case B2 was confined to the dermis (Fig. 3).

The other 12 cases had low numbers of IgG4+ cells (2 to 30 per HPF), with IgG4+/IgG+ cells ranging from 7.4% to 44.8% (Table 2). These cases differed from cases B1 and B2 in showing less significant male predominance (M: F = 7: 5), a wider age range (5 to 81 y, mean 53.3 y) and more varied anatomic distribution (head and neck 75%, other sites 25%).

DISCUSSION

Cutaneous pseudolymphoma, also known variably as cutaneous lymphoid hyperplasia and lymphocytoma cutis, refers to a group of benign lymphoid proliferations in the skin morphologically mimicking lymphoma.³ This is a descriptive diagnosis encompassing entities of diverse etiologies such as pseudolymphomatous folliculitis,^{1,2} *Borrelia burgdorferi* infection,²⁸ and aberrant response to a wide variety of foreign antigens such as tattooing,¹⁵ vaccination,⁴ arthropod reaction,²⁷ acupuncture,²¹ hypersensitization antigen injection,¹² and metal contact.¹⁶ However, frustratingly, in routine practice, an etiology cannot be identified in most cases.

The morphologic features of cutaneous involvement by IgG4-related sclerosing disease are similar to those seen in the various tissues affected by the disease, and are also compatible with cutaneous pseudolymphoma. There is a nodular lymphoid infiltrate including lymphocytes and plasma cells, accompanied by lymphoid follicle formation and sclerosis. The recent publication of Sato et al³⁰ alluded to the presence of skin lesions in 3 patients with IgG4-related sclerosing disease, but the anatomic distribution was not stated. The illustrations and brief description “the skin lesions showed lymphoplasmacytic infiltration with abundant IgG4+ cells and eosinophils” are broadly similar to our cases, except that we have

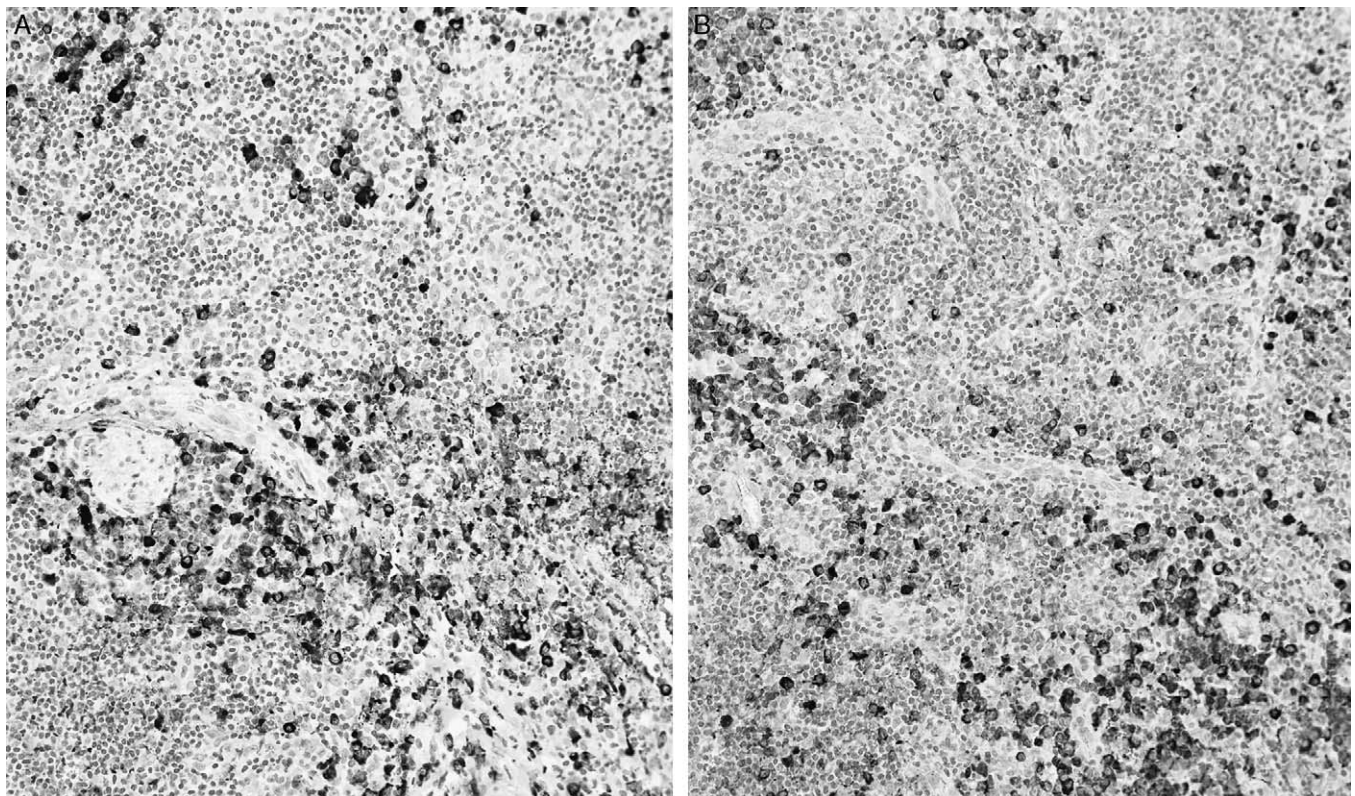


FIGURE 2. Case A2, immunohistochemical staining for IgG4 and IgG. A, Many IgG4+ plasma cells are present (approximately 300 positive cells in this field). B, In a corresponding field stained for IgG, approximately 380 positive cells are seen. Thus the proportion of IgG4+/IgG+ cells is 79% in this field.

TABLE 2. Clinicopathologic Features of Patients With Cutaneous Pseudolymphoma

Case	Sex/Age	Sites of Involvement	Skin Biopsy IgG4+ /IgG+ Cell Counts per HPF
B1	M/74	Left preauricular region	144/155 (93 %)
B2	M/76	Right clavicular region	328/478 (69 %)
B3	F/53	Nasal skin	9/106 (9 %)
B4	M/76	Face	8/35 (23 %)
B5	M/81	Back	22/210 (11 %)
B6	M/35	Left upper arm	12/29 (41 %)
B7	M/13	Left ear lobe	3/24 (13 %)
B8	F/28	Back	4/54 (7 %)
B9	F/82	Face	9/45 (20 %)
B10	M/5	Face	6/69 (9 %)
B11	F/59	Nasal skin	30/323 (9 %)
B12	M/56	Face	19/100 (19 %)
B13	F/73	Forehead	22/68 (32 %)
B14	M/78	Eyelid	13/29 (45 %)

F indicates female; HPF, high power field; Ig, immunoglobulin; M, male.

found subcutaneous in addition to dermal involvement, and eosinophils not to be a prominent feature.

Among the 14 cases of cutaneous pseudolymphoma studied, the 2 with abundant IgG4+ cells showed features quite compatible with IgG4-related sclerosing disease, including old age, male predominance, head and neck location of skin lesions, and histologic features. Unfortunately, further information is not available on the laboratory findings and whether there is concomitant or subsequent development of other features of IgG4-related sclerosing disease. Nonetheless, the existence of a “solitary” cutaneous counterpart of the syndrome cannot be excluded.

Recently, Miyagawa-Hayashino et al²⁴ reported an increase of IgG4+ plasma cells in cutaneous plasmacy-

tosis, and proposed a possible relationship to IgG4-related sclerosing disease. Despite some similarities, we believe cutaneous plasmacytosis represents a different disease, for the following reasons: (1) many patients have fever and hepatosplenomegaly, features practically never found in IgG4-related sclerosing disease; (2) presence of numerous skin lesions widely distributed over the body, differing from the limited regional skin lesions in the latter syndrome; (3) generally no response to steroid therapy; (4) cutaneous infiltrate consisting almost entirely of mature plasma cells in a perivascular or periadnexal distribution, without formation of large lymphoid aggregates, admixed small lymphocytes or interspersed lymphoid follicles; (5) absence of sclerosis, a cardinal feature of IgG4-related sclerosing disease; and (6) the elevated

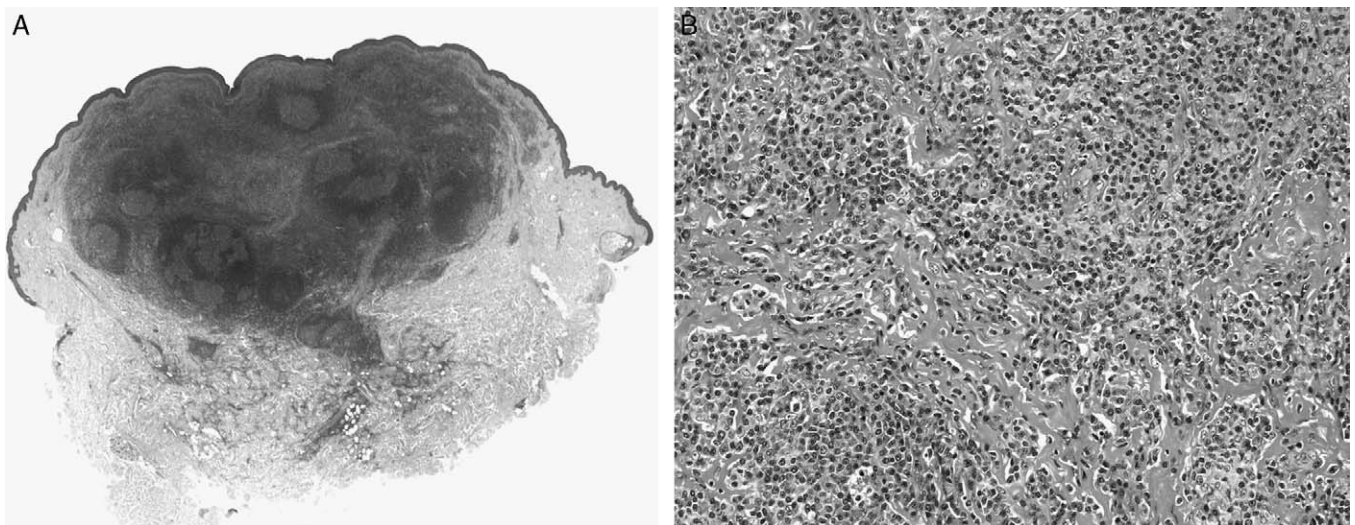


FIGURE 3. Case B2. A, There is a nodular lymphoid infiltrate involving the upper and mid dermis. Many reactive follicles are present, and some show irregular-shaped germinal centers. B, Between the follicles, there is an infiltrate of small lymphocytes and plasma cells, accompanied by sclerosis.

IgG4+ cell count is generally on the low side, often only slightly over 50 per HPF, contrasting with counts that are often much above 100 per HPF in the latter syndrome.

Similarly, although cutaneous Rosai-Dorfman disease has been suggested to be related to IgG4-related sclerosing disease because of the presence of increased IgG4+ plasma cells,²³ we believe these are completely different diseases on clinical and pathologic grounds. Rosai-Dorfman disease is predominantly a disease of young rather than middle-aged or elderly patients, and the diagnostic S100-positive histiocytes with round vesicular nuclei and voluminous cytoplasm are never found in IgG4-related sclerosing disease.

The histologic features of cutaneous IgG4-related sclerosing disease are rather non-specific, being indistinguishable from conventional cases of cutaneous pseudolymphoma,³ but this diagnosis may have to be considered in particular for lesions rich in plasma cells or showing significant sclerosis, especially if there are accompanying mass lesions in sites commonly involved by IgG4-related sclerosing disease (such as orbit, salivary gland and pancreas). The diagnosis is clinched on the demonstration of large numbers of IgG4+ plasma cells together with a high proportion of IgG4+/IgG+ cells. One caveat is that the mere abundance of IgG4+ cells is not necessarily synonymous with this diagnosis, as rare cases of malignant lymphoma can be IgG4-positive.^{9,29} In contrast, presence of sheets of plasma cells, some with immature appearance, admixed with plasmablasts (such as case A2), in cutaneous IgG4-related sclerosing disease can be worrisome for lymphoma. Thus, the morphology has to be considered in context, further substantiated by the polytypic nature of the plasma cells (by immunostaining or in situ hybridization for immunoglobulin light chain protein or mRNA, respectively) and absence of diffuse sheets of CD20+ B cells.

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