

Cutaneous Immunoglobulin G4-Related Systemic Disease

Immunoglobulin G4-related systemic disease is a fibro-inflammatory condition that has distinctive clinical findings, involves multiple organs, and has unique histopathology.¹ Regardless of which organ(s) is involved, patients with immunoglobulin G4-related systemic disease have similar histopathologic features: a lymphoplasmacytic infiltrate, obliterative phlebitis, fibrosis, and modest tissue eosinophilia.¹ The presence of immunoglobulin G4-positive plasma cells within an affected organ is the feature most critical to diagnosis.

We report a patient who was diagnosed with Sjögren's syndrome on the basis of lacrimal gland enlargement and parotid hypertrophy. The correct diagnosis was rendered after biopsies of lacrimal gland and skin lesions that had a relatively innocuous appearance. We review this patient's clinical and histopathologic findings in the skin and discuss them in the context of emerging knowledge about immunoglobulin G4-related systemic disease. We also describe the patient's precise immunologic response and dramatic clinical improvement after the administration of a targeted B-cell depletion strategy.

CASE REPORT

A 72-year-old woman was referred for evaluation of a nodular facial rash accompanied by periorbital swelling and parotid gland enlargement. A magnetic resonance imaging study of her head and neck showed marked lacrimal, parotid, and submandibular gland swelling bilaterally. A lacrimal gland biopsy showed reactive lymphoid hyperplasia with an abundance of immunoglobulin G4+ plasma cells. Biopsy of the rash revealed perivascular and interstitial lymphohistiocytic infiltrates that stained positively for immunoglobulin G4. The patient began treatment with prednisone 40 mg/d. Her glandular swelling improved, but the nodular rash never resolved completely, even with prednisone 20 mg/d.

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Physical examination revealed nontender lacrimal and parotid gland swelling bilaterally and several flesh-colored, faintly erythematous nodules on her left cheek (Figure 1A). An antinuclear antibody assay was positive (1:320), but test results for rheumatoid factor and anti-precipitin, anti-double-stranded DNA, and anti-mitochondrial antibodies were negative. Serum complement levels were normal. The total immunoglobulin G was 1170 mg/dL (normal 600-1500 mg/dL), but the immunoglobulin G4 concentration was 429 mg/dL (8-140 mg/dL).

Review of the patient's skin biopsy revealed a dense, deep dermal infiltrate with focal involvement of the subcutaneous fat (Figure 1B). There was sparing of the Grenz zone and relative sparing of the periadnexal zones. The infiltrate was composed predominantly of lymphocytes, plasma cells, and a few eosinophils. There were 210 immunoglobulin G4 positive plasma cells per high-power field, and the immunoglobulin G4 to immunoglobulin G ratio was 0.95 (Figure 1C).

The patient tolerated glucocorticoids poorly, but her lacrimal and parotid enlargement increased and the rash worsened during prednisone tapering. The total immunoglobulin G and immunoglobulin G4 serum concentrations increased to 1790 mg/dL (600-1500 mg/dL) and 1140 mg/dL (8-140 mg/dL), respectively. She was treated with 2 doses of rituximab 1000 mg intravenously. One month after completing rituximab, her serum immunoglobulin G4 concentration decreased to 31 mg/dL, but the total immunoglobulin G and other individual immunoglobulin G subclasses remained stable. Two months after her first rituximab infusion, her nodular skin rash had resolved (Figure 1D).

DISCUSSION

Immunoglobulin G4-related systemic disease is an emerging fibroinflammatory illness that can involve multiple organs, but little has been written about its cutaneous manifestations. The erythematous plaques and papules found in our patient are consistent with findings reported in one previous communication. Cheuk et al² described 2 patients with immunoglobulin G4-related systemic disease who had had ill-defined, indurated plaques or nodules on the facial skin for more than 3 years. The histopathologic findings in our patient's skin biopsy were highly characteristic of immunoglobulin G4-related systemic disease: a lymphoplasmacytic infiltrate, fibrosis, and modest tissue eosinophilia, with intense im-

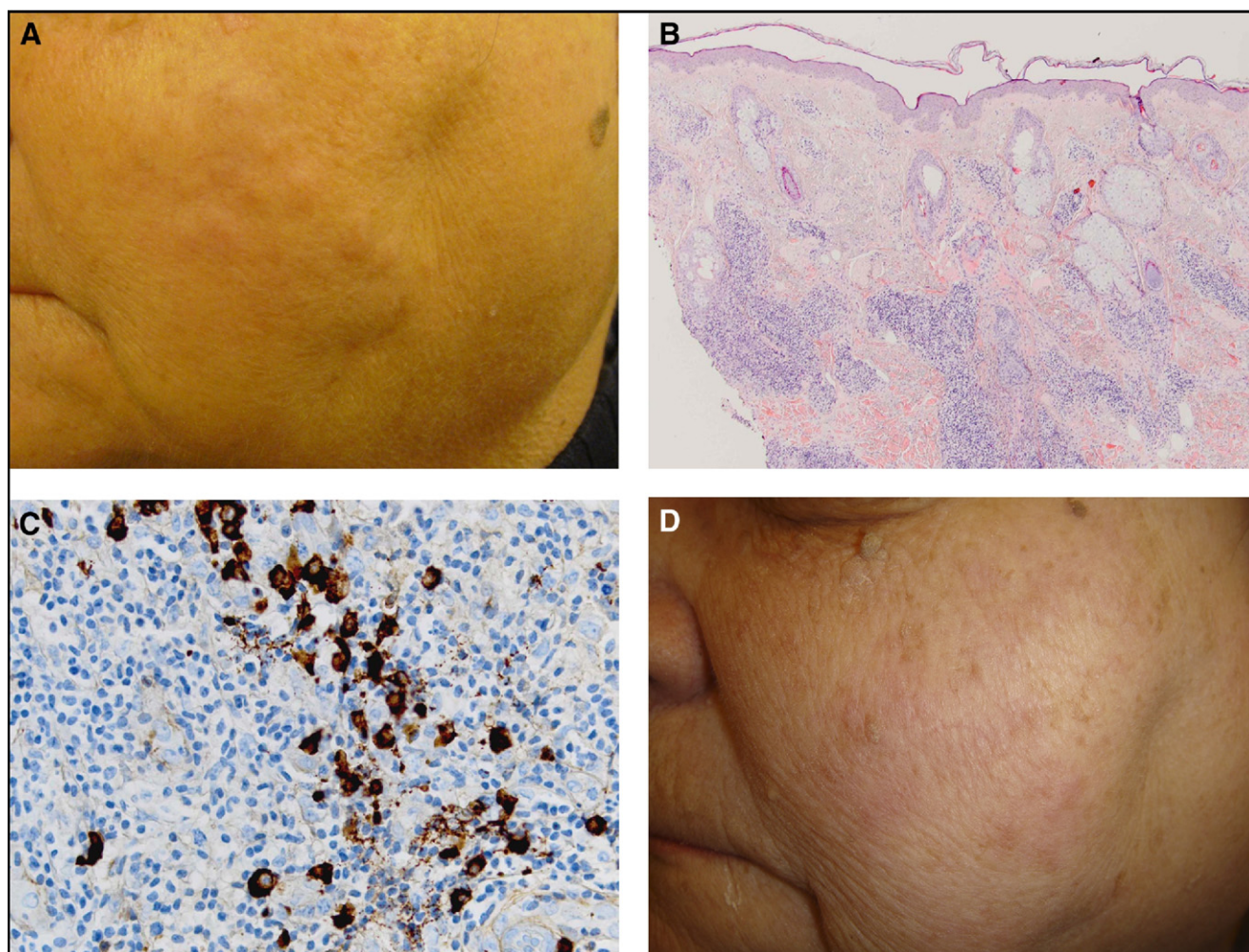


Figure 1 Clinical, pathologic, and immunohistochemical findings in cutaneous immunoglobulin G4-related systemic disease. **A**, Nodular facial rash. **B**, Dense inflammatory infiltrate involving the deep dermal tissue and subcutaneous fat, composed of lymphocytes, plasma cells, and occasional eosinophils (hematoxylin–eosin stain). **C**, Virtually all plasma cells stain for immunoglobulin G4 (immunoglobulin G4 immunoperoxidase stain). **D**, Resolution of the nodular skin rash after treatment with rituximab.

munostaining for immunoglobulin G4 and an elevated immunoglobulin G4:immunoglobulin G ratio. Immunoglobulin G4-related systemic disease must be distinguished from a variety of disorders, including Sjögren's syndrome, sarcoidosis, Wegener's granulomatosis, and lymphoma.

CONCLUSIONS

Our patient's prompt response to rituximab underscores the potential utility of B-cell depletion in glucocorticoid-refractory immunoglobulin G4-related systemic disease.³ Contrary to the dramatic decline in immunoglobulin G4 levels observed in our patient after rituximab treatment, the concentrations of the immunoglobulin G1, immunoglobulin G2, and immunoglobulin G3 subclasses remained stable.

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