

Case Report

Membranous Glomerulopathy and Massive Cervical Lymphadenopathy Due to Immunoglobulin G4-disease

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ABSTRACT. A 32-year-old male presented with acute and severe nephrotic syndrome as well as massive right cervical lymphadenopathy for <2 years. Computed tomography scan of the chest, abdomen, and pelvis did not reveal any lymphadenopathy. Histopathology and immunohistochemical testing of his lymph node biopsy showed infiltrate enriched with immunoglobulin G4 (IgG4)-positive plasma cells. His kidney biopsy showed granular membranous deposits of IgG4 in the basement membrane without interstitial infiltrate. Antiphospholipid 2 receptor antibodies were absent excluding its “idiopathic” nature. Since he was allergic to rituximab, he was treated with corticosteroids for two months and a combination of tacrolimus and mycophenolate. His lymphadenopathy disappeared, and his proteinuria abated. The dose of the latter two medications was reduced to half after four months and will be maintained for a minimum of two years to prevent relapse of his disease.

Introduction

Immunoglobulin G4 (IgG4)-related disease is a systemic syndrome of unknown etiology characterized by tumor-like swelling of the involved organs and/or a lymphoplasmacytic infiltrate enriched with IgG4-positive plasma cells. If untreated, fibrosis of the involved organs with a characteristic “storiform” pattern may result in end-organ failure.¹ The prototype

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is IgG4-related sclerosing pancreatitis (also known as autoimmune pancreatitis), most commonly presenting as painless obstructive jaundice with or without a pancreatic mass. Other sites of involvement are the hepatobiliary tract, salivary gland, orbit, and lymph nodes. In a large study, 41% of the 114 patients, with varied organ involvement, had lymphadenopathy.² Multiple groups of lymph nodes were involved, especially the mediastinal, hilar, intra-abdominal, and axillary ones. Individual nodes are typically no more than 2 cm in diameter.³ Massive isolated cervical lymphadenopathy for <2 years associated with membranous glomerulopathy without tubulointerstitial infiltrate is rarely reported with this disease.⁴

Case Report

A 32-year-old male presented with progressive lower limbs edema for two weeks. He denied fever, skin rash, joint disease, weight loss, shortness of breath, or localized body ache. Past history included a persistent right cervical lymphadenopathy for the past two years. Their previous biopsy was labeled as reactive hyperplasia. He did not have past history of other significant medical illness, surgery, allergy, or chronic intake of medications. On his initial examination, he was conscious, oriented X3, and without distress of shortness of breath or pain. Blood pressure was 120/80 mm Hg. He was afebrile with a body weight of 77 kg. He had multiple 8 cm cervical lymph nodes on the right side. They were firm in consistency, freely mobile, and with normal overlying skin (Figure 1a). Systemic examination did not show abnormality except for massive lower limbs and sacral edema as well as ascites. Laboratory investigations showed normal peripheral leukocytic and platelets counts. Hemoglobin was normal. Serum glucose, urea, creatinine, electrolytes, amylase, and liver functions were normal except for albumin at 9 g/L. Serum cholesterol was 8 mmol/L. Thyroid-stimulating hormone was normal. Urine routine and microscopy showed 4+ proteinuria without hematuria or pyuria. Serum complements (C3

and C4) were normal. Serum protein electrophoresis showed polyclonal hypergammaglobulinemia and hypoalbuminemia. antinuclear antibody, antineutrophil cytoplasmic antibody, and hepatitis B and C serology were negative. Chest X-ray and plain X-ray of abdomen and pelvis were normal. Abdominal and pelvic ultrasound was normal except for ascites. Computed tomography scan of the chest, abdomen, and pelvis did not show abnormal lymphadenopathy or organomegaly. Biopsy of the lymph node showed follicular hyperplasia with diffuse lymphoplasmacytic infiltrate enriched with IgG4-positive plasma cells. The interfollicular areas were slightly expanded and contained lymphocytes, few macrophages, eosinophils, and plasma cells. Plasma cells were dense and stained positive with anti-IgG (Figure 2). Their counts averaged 120 plasma cells/HPF. Those areas were also stained by anti-IgG4, and the counts averaged 90 plasma cells/HPF, and hence the ratio IgG4/IgG was $\frac{3}{4}$. Serum IgG4 was elevated at 750 mg/dL (normal 9-89). On the other hand, his kidney biopsy showed diffuse thickening of glomerular basement membrane without interstitial, tubular, or vascular disease. Immunofluorescent stains showed deposition of IgG on glomerular basement membrane. There were no "spikes" on Jones' (silver) stain. Immunoperoxidase stains showed diffuse staining of the glomerular basement membrane with IgG4 without

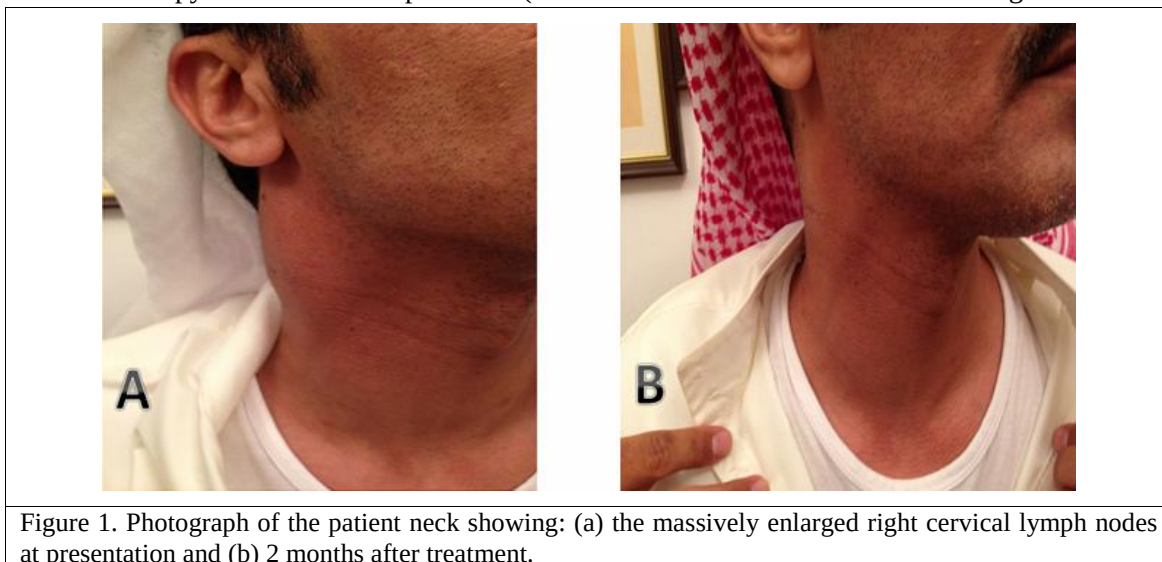


Figure 1. Photograph of the patient neck showing: (a) the massively enlarged right cervical lymph nodes at presentation and (b) 2 months after treatment.

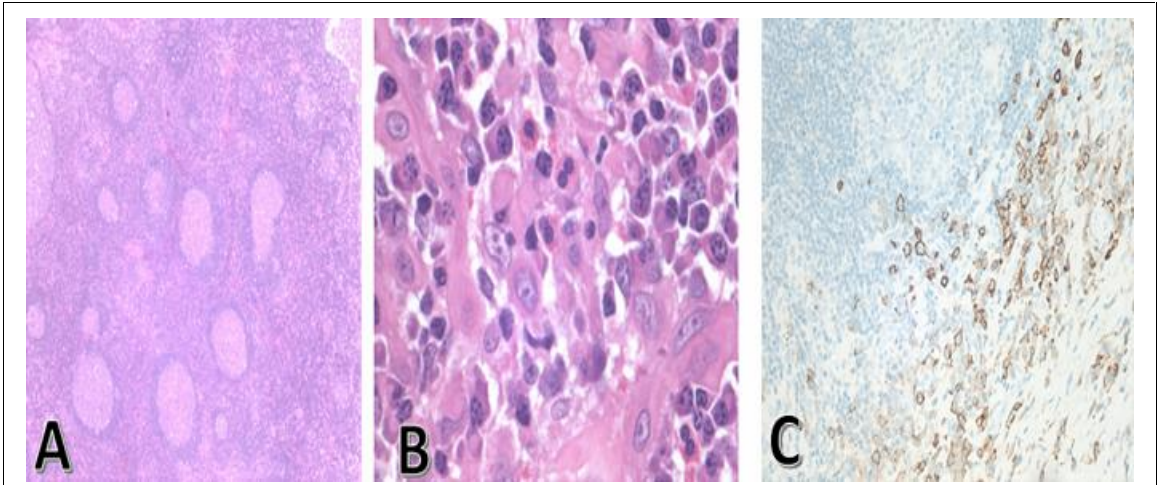


Figure 2. Photomicrograph of the lymph node biopsy showing (a) follicular hyperplasia with a rim of small lymphocytes (H and E, $\times 100$), (b) Expanded interfollicular area with lymphocytes, macrophages, and plasma cells without malignant cells (H and E, $\times 200$), (c) predominant staining of lymphocytes with anti-IgG4stain (Immunoperoxidase IgG4, $\times 200$).

interstitial involvement (Figure 3). Antiphospholipase 2 receptor antibodies were absent. The patient was treated with 1 g of Solumedrol intravenous for three consecutive days, followed by prednisone 1 mg/kg/day for one month which was tapered down gradually till discontinuation after two months. His lymphadenopathy disappeared, and his proteinuria abated (Figure 1b). Since he was allergic to rituximab, he received tacrolimus (2 mg twice daily) and mycophenolate (1 g twice daily). The dose of the latter two medications was

reduced to half four months later and he remains well. The later dose of medications will be maintained for two years to prevent future relapse of his disease.

Discussion

The hallmark of IgG4-related disease is lymphoplasmacytic tissue infiltration with a predominance of IgG4-positive plasma cells and T-lymphocytes. The etiology of this disease remains elusive, yet its rapid response to

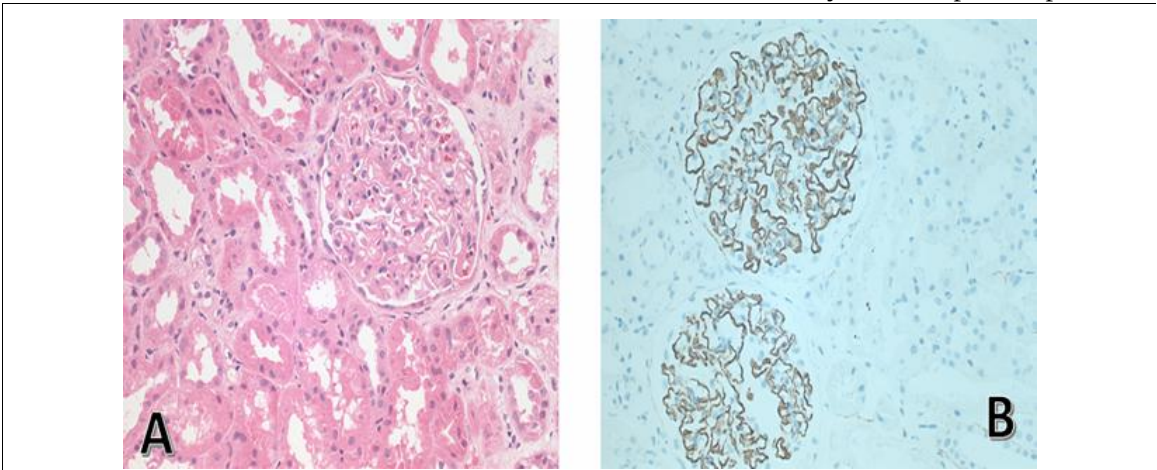


Figure 3. Photomicrograph of kidney biopsy showing: (a) Diffuse thickening of glomerular basement membrane on (H and E, $\times 100$), (b) Diffuse granular membranous staining with IgG4 (Immunoperoxidase IgG4, $\times 100$).

corticosteroids indicates an autoimmune or allergic disorder.¹ High serum IgG4 was detected in 70% of the reported cases, yet it is not pathognomonic nor the pathogenic of the disease since it was also found in disorders such as multicentric Castleman disease, allergic disorders, Churg-Strauss syndrome, sarcoidosis, and a large number of other conditions.⁵ The disease affects middle-aged and older men. Manifestations of the disease include autoimmune pancreatitis and IgG4-related sclerosing cholangitis, Mikulicz's disease and sclerosing sialadenitis (Küttner's tumor), inflammatory orbital pseudotumor, and chronic sclerosing dacryoadenitis, idiopathic retroperitoneal fibrosis, chronic sclerosing aortitis and periaortitis, Riedel's thyroiditis, and a subset of Hashimoto's thyroiditis, interstitial pneumonitis, and pulmonary inflammatory pseudotumors. The natural history is characterized by the development of multiple sites of involvement with time, sometimes after many years. If untreated, the initial lymphoplasmacytic infiltrate can progress to obliterative phlebitis and fibrosis. The fibrosis associated with IgG4-related disease has a characteristic "storiform" pattern, typified by a cartwheel appearance of the arranged fibroblasts and inflammatory cells, termed the "nuclear streaming artifact."¹ Progressive fibrosis can lead to end-organ damage which is poorly responsive to corticosteroids. Moreover, the disease may herald the development of malignant lymphoma and possibly carcinoma.¹

Asymptomatic IgG4-related lymphadenopathy has been reported.^{2,3} However, isolated, massive, and persistent IgG4-cervical lymphadenopathy for <2 years, as described in our patient, has not been reported to the best of our knowledge. Large and localized lymphadenopathy can be seen with tuberculosis, lymphoma, Castleman disease, or malignancy. However, histopathological examination and immunohistochemical testing are diagnostic for each disorder. The presence of 11–30 IgG4 cells/40 IgG cells/HPF is essential to distinguish IgG4-disease, as in our patient, from other forms of inflammations.⁶ On the other hand, IgG4-renal disease is rare. Most of the

reported cases describe tubulointerstitial nephritis with IgG4-positive plasma cells and T-lymphocytes. However, in a large study, five of their nine patients had isolated membranous glomerulonephritis (MG).⁴ Those patients as our patient did not have antiphospholipid 2 receptor antibodies akin to "idiopathic" MG.⁷ However, their patients had visceral evidence of IgG4-related disease elsewhere rather than isolated MG and massive lymphadenopathy as in our case. Moreover, the lack of "typical spikes on glomerular basement membrane" on Jones' (silver) stain indicates the absence of the immune deposits usually seen in idiopathic MG and should be a clue to suspect the nonidiopathic one.⁸ The optimal treatment for IgG4-related disease has not been established, and there are no randomized trials that have evaluated the different approaches including its corticosteroid therapy. Most patients respond to glucocorticoids within several weeks, and the duration of treatment is uncertain. Those who respond less well may have included patients with more advanced fibrotic changes. Moreover, even in those who exhibited an initial response, relapses were common following discontinuation of therapy. Corticosteroid-sparing drugs, for example, azathioprine and mycophenolate have been used as a maintenance therapy to avoid relapses, and rituximab has been used to treat the refractory ones.^{9,10} The latter drug would have been an ideal one with its ease of administration as once yearly and its lack of significant side effects. Unfortunately, he was allergic to it. Hence, after his initial response to corticosteroids, mycophenolate, and tacrolimus, we elected to keep him on 1/2 of the initial dose of the latter two drugs for a minimum period of two years to prevent future relapse.

Conflict of interest: None declared.

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