AJKD

Kidney Biopsy Teaching Case

Sjögren Syndrome and Cryoglobulinemic Glomerulonephritis

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We report the case of a 53-year-old woman with Sjögren syndrome and cryoglobulinemia. The patient presented with nephrotic syndrome, hematuria, and reduced estimated glomerular filtration rate. The kidney biopsy revealed diffuse endocapillary proliferation and leukocyte exudation with focal intraluminal hyaline thrombi, prominent tubulointerstitial inflammation, and vasculitis. Diffuse granular mesangial and segmental to global capillary wall staining was observed on immunofluorescence with antisera to C3 and immunoglobulin M (IgM), with less intense staining indicative of IgG and κ and λ light chains. A biopsy diagnosis of Sjögren syndrome–related cryoglobulinemic membranoproliferative glomerulonephritis and vasculitis was rendered. Subsequent investigations revealed the presence of circulating type II cryoglobulins with cryocrit of 9%. Although rare, Sjögren syndrome is the most common cause of non–hepatitis C virus–related mixed cryoglobulinemia. We discuss the possible pathogenic mechanisms involved in the development of mixed cryoglobulinemia and its evolution to lymphoma, as best described in the setting of hepatitis C virus infection. Although the specific antigen involved is unknown, it is likely that the mixed cryoglobulinemia in Sjögren syndrome is triggered by the long-term B-cell stimulation, resulting in clonal proliferation of B cells. Additional chromosomal aberrations and cytokine milieu alterations, as seen in hepatitis C virus infection, may result in prolonged B-cell survival and progression to non-Hodgkin lymphoma.
Am J Kidney Dis. ■(■):■-■.

INDEX WORDS: Sjögren's syndrome; cryoglobulinemia; glomerulonephritis; lymphoma; membranoproliferative; kidney biopsy; vasculitis; tubulointerstitial nephritis (TIN).

Sjögren syndrome is a chronic inflammatory disease marked by lymphoplasmacytic infiltration of the exocrine glands. It also is a systemic disease, affecting multiple organs including lungs, kidneys, skin, blood vessels, and muscles. The most common kidney lesion seen in Sjögren syndrome is tubulointerstitial nephritis (TIN). Glomerular disease is rare and when present, often is associated with the presence of mixed cryoglobulinemia.

CASE REPORT

Clinical History and Initial Laboratory Data

A 53-year-old woman with a history of Sjögren syndrome for several decades presented with anasarca and acute kidney injury. She had undergone contrast computed tomography of the neck a week prior for evaluation of diffuse thyroid goiter; it showed enlarged benign-appearing submandibular lymph nodes as well. Two days following the procedure, the patient developed nausea, vomiting, and reduced urine output. Her medical history was otherwise unremarkable, and medication history included only pilocarpine eye drops.

Physical examination showed facial and pedal edema along with enlarged thyroid and parotid glands. Breath sounds at lung bases were diminished bilaterally. Laboratory studies showed the following values: serum sodium, 118 mEq/L (likely due to excess water intake); serum urea nitrogen, 35 mg/dL; serum creatinine, 1.5 mg/dL (corresponding to estimated glomerular filtration rate [eGFR] of 39 mL/min/1.73 m^2 as calculated by the CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] creatine equation)[1]; hemoglobin, 8.8 g/dL; hematocrit, 25.8%; serum albumin, 2.5 g/dL; thyroid-stimulating hormone, 5.3 U/mL, and urine osmolality, 362 mOsm/L. Urinalysis showed proteinuria (3+), 25-50 red blood cells per high-power field, and a few granular casts. Urine protein was quantified as 8,790 mg per gram of creatinine. Subsequently, serum creatinine level peaked at 5 mg/dL (eGFR, 5 mL/min/1.73 m^2), requiring intermittent hemodialysis. Thoracentesis revealed a transudate.

Serologic studies gave positive results for rheumatoid factor (RF; level, 970 IU/mL; reference range, <14), SS-A (>8 U), and antinuclear antibody (ANA; signal at a dilution of 1:320; present in a speckled pattern), low levels of complement (C3, 37; C4, <4), and negative results for anti–double-stranded DNA antibody, anti-SS-B antibody, hepatitis C virus (HCV), hepatitis B virus, human immunodeficiency virus (HIV), antinuclear cytoplasmic antibody (antibodies to proteinase 3 [PR3] and myeloperoxidase [MPO] also were undetectable), and anti–glomerular basement membrane antibody. Serum protein electrophoresis showed no protein spike; urine protein electrophoresis and immunofixation testing were not performed.

Kidney Biopsy

Light microscopy showed 20 glomeruli, with one globally sclerosed. The other glomeruli had segmental to global endocapillary proliferation with variable mononuclear cell and macrophage infiltration; 3 glomeruli also contained intracapillary hyaline thrombi (Fig 1A,B). Occasional afferent arterioles and terminal interlobular arteries showed hyaline deposits and focal necrosis. An interlobular artery had prominent subendothelial exudation of lymphocytes and

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Received October 16, 2014. Accepted in revised form November 23, 2014.

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0272-6386

http://dx.doi.org/10.1053/j.ajkd.2014.11.032

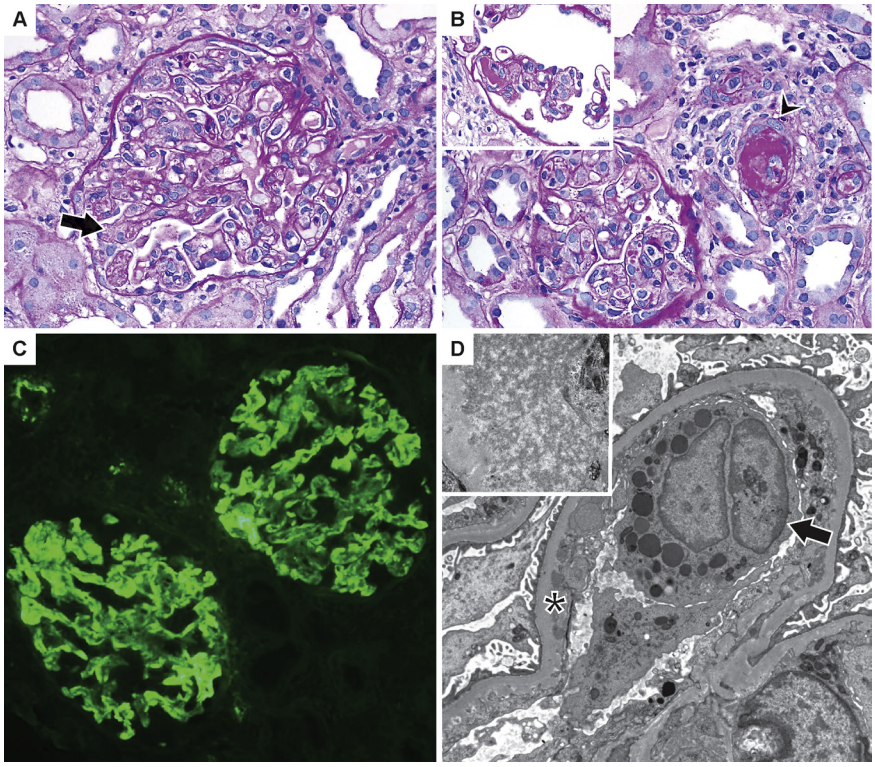

Figure 1. Cryoglobulinemic glomerulonephritis and vasculitis in Sjögren syndrome. (A) The glomerulus shows endocapillary proliferation and a few infiltrating macrophages with intracytoplasmic granules (arrow) (periodic acid–Schiff (PAS); original magnification, ×400). (B) Arteriolar deposits and perivascular inflammation (arrowhead) (PAS; original magnification, ×400); hyaline thrombus in a glomerular capillary loop (inset: PAS; original magnification, ×600). (C) Immunofluorescence microscopy with antiserum to C3 shows diffuse granular mesangial and capillary wall deposits (4+ staining; original magnification, ×200). (D) Electron microscopy shows an infiltrating macrophage phagocytized granular material (arrow) in the capillary lumen (original magnification, ×7,000). Subendothelial deposits are seen (*), which focally have substructure (inset: original magnification, ×25,000).

macrophages, compatible with vasculitis (Fig 1B). The cortex had prominent tubulointerstitial inflammation, with patchy lymphocytic tubulitis, interstitial edema, and acute tubular injury. The interstitial infiltrate was composed of lymphocytes, plasma cells, macrophages, and rare eosinophils. Focal dense collections of CD20-positive small B lymphocytes were admixed with fewer CD3-positive T lymphocytes. T Cells also were seen in the interstitium and tubules. Although lymphoid aggregates had a monomorphic appearance, there was no histologic or immunohistochemical support for lymphoma (aggregates were negative for CD43, CD5, and CD23).

Immunofluorescence microscopy for immunoglobulin G [IgG], IgA, IgM, κ light chain, λ light chain, C3, C1q, fibrinogen, and albumin showed diffuse granular mesangial and segmental to global capillary wall staining for C3 (4+), IgM (2+), IgG (1+), κ (1+), and λ (1+), supporting an immune complex–mediated glomerulonephritis (GN) (Fig 1C). Several small arterioles contained hyaline thrombi highlighted by IgM and κ and λ light chains.

Ultrastructural examination confirmed prominent glomerular exudation of monocytes and macrophages. Scattered electron-dense deposits were seen within the mesangium and subendothelium and in capillary lumens. Most deposits were granular, but a few had an organized microtubular substructure (27 nm thick) (Fig 1D). Glomerular basement membranes were normal in thickness, and podocyte foot processes were largely intact.

Additional Studies

Subsequent to the biopsy results, tests for serum cryoglobulins were positive, with cryocrit of 9%. Immunofixation of the cryoprecipitate revealed IgM and κ light chain monoclonal proteins in the gamma region. Immunodiffusion of cryoprecipitate showed polyclonal IgG, IgA, IgM, and C3.

Diagnosis

A biopsy diagnosis of Sjögren syndrome–related cryoglobulinemic GN and vasculitis with active TIN was rendered.

Clinical Follow-up

No extrarenal manifestations of cryoglobulinemia were apparent in our patient during follow-up. She was treated with prednisone and intravenous cyclophosphamide, with rapid resolution of kidney failure. Prednisone dosage was tapered over 3 months, and the patient elected not to continue with cyclophosphamide therapy after 2 doses. On last follow-up a year later, the patient was doing well, with blood pressure of 130/70 mm Hg, serum creatinine level of 0.8 mg/dL (eGFR, 84 mL/min/1.73 m^2), and urine protein-creatinine ratio of 150 mg/g.

DISCUSSION

The diagnosis of cryoglobulinemic GN is supported by characteristic features of diffuse endocapillary proliferation with monocyte/macrophage-rich infiltrate, intraluminal hyaline thrombi, and electron-dense deposit substructure seen in the biopsy specimen. Other features not seen in our case include mesangial interposition and crescents. The immune-mediated small-vessel vasculitis as seen in our biopsy specimen has been reported in 20% to 25% of cryoglobulinemic GN cases. The prominent active TIN most likely is related to Sjögren syndrome. The dominant C3 staining along with IgM (and weaker IgG) staining is compatible with the presence of mixed cryoglobulinemia, particularly type II. The typical complement profile is normal to low levels of C3 and extremely low to undetectable levels of C4.[2]

The differential diagnosis includes proliferative/membranoproliferative GN without cryoglobulinemia, but it usually lacks intraluminal thrombi, vasculitis,