

Nephroquiz 3: Nephrotic Syndrome in Adult Patients With Skin Lesions

Mojgan Asgari,¹ Yoosef Ataiipoor²

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¹Department of Pathology, Hasheminejad Kidney Center, Iran University of Medical Sciences, Tehran, Iran
²Division of Nephrology, Department of Medicine, Hasheminejad Kidney Center, Iran University of Medical Sciences, Tehran, Iran

CASE

A 52-year-old man presented with malaise and weakness associated with edema and nephrotic range proteinuria. He also had arthralgia and myalgia. Serum creatinine level was between 2 mg/dL and 2.5 mg/dL. Physical examination revealed purpura on the extremities and also on the abdominal skin. Laboratory studies revealed high serum cholesterol and triglyceride levels. He also was anemic (haemoglobin level, 8 g/dL to 10g/dL). Serum complements including C3 and C4 and also CH50 had decreased. Serum antinuclear antibody, anti-double-stranded-DNA, and antineutrophil cytoplasmic antibody were negative. A percutaneous kidney biopsy containing 17 glomeruli showed marked endocapillary hypercellularity with lobular accentuation characterized by mesangial cell proliferation and leukocytes infiltration (Figure 1). Thickening of the glomerular basement membrane was evident with double contour appearance in silver-stained sections (Figure 2). Most of the glomeruli contained amorphous, eosinophilic, fuschinophilic positive deposits, totally filling the capillary lumina (intraluminal thrombi; Figure 3). A few glomeruli showed karyorrhexis and features suggestive of fibrinoid necrosis. The interstitium was edematous with tubular atrophy in about 10% to 20% of the specimen and lymphocytic infiltration in the scarred area. Immunofluorescent evaluation showed intense massive staining of immunoglobulin G (IgG), immunoglobulin M (IgM), and C3 with huge deposits filling the capillary lumen (Figure 4). Considering above findings a diffuse proliferative glomerulonephritis suggestive of a cryoglobulinemic glomerulonephritis was diagnosed. The patient underwent plasma exchange together with cyclophosphamide and corticosteroid therapy. Serum creatinine decreased to about 1.6 mg/dL and urine protein to about 1.5 g/24 hours after 4 weeks. Viral markers, including antihepatitis C virus antibody, were evaluated and were negative.

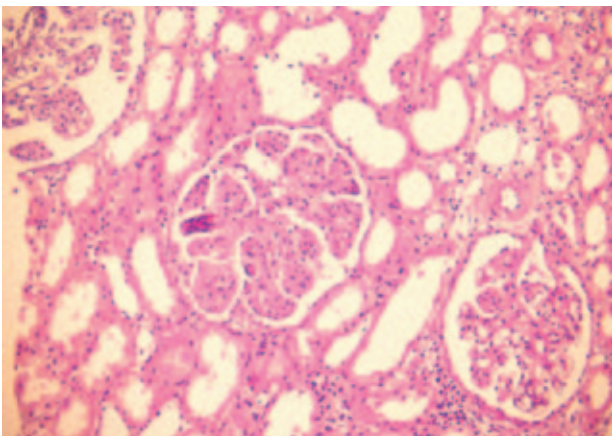


Figure 1. Marked endocapillary hypercellularity with lobular accentuation characterized by mesangial cell proliferation and leukocytes infiltration.

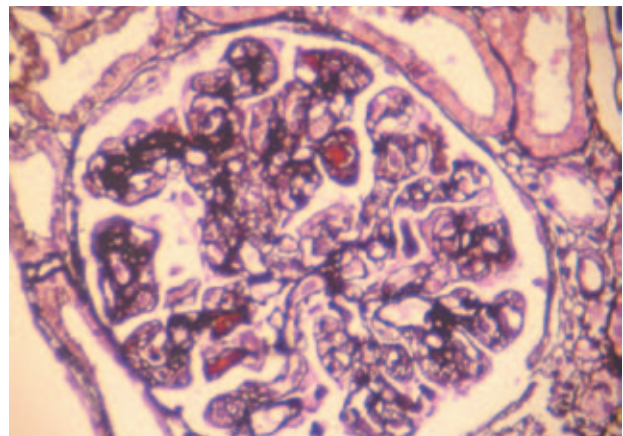


Figure 2. Thickening of the glomerular basement membrane with double contour appearance in silver stained sections. Intraluminal plugs are also present.

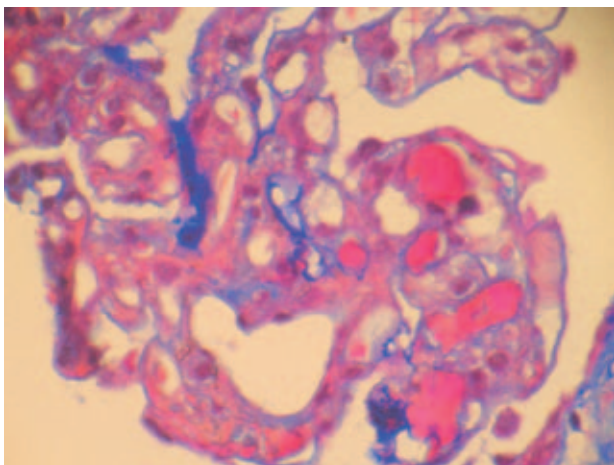


Figure 3. Amorphous, eosinophilic, fuschinophilic positive deposits totally filling the capillary lumina (intraluminal thrombi or cryoplug).

QUIZ

What Are the common Histopathologic Changes of renal Involvement in Cryoglobulinemia?

Mixed cryoglobulins are proteins that reversibly precipitate from human serum cooled to 4°C.¹⁻⁵ Two types of mixed cryoglobulins exist: type II and III, and in both of them, a polyclonal IgG is bound to another immunoglobulin, which is an antiglobulin and acts as an anti-IgG rheumatoid factor (RF). The main difference between these 2 types of mixed cryoglobulins is that in type II, the antiglobulin RF, usually of the IgM class, is monoclonal, whereas in type III, it is polyclonal. Mixed cryoglobulins may be found in association with infections, systemic autoimmune diseases, and lymphoproliferative disorders (secondary mixed cryoglobulinemias), or without any identifiable underlying disease. The latter condition, occurring in 30% to 50% of mixed cryoglobulinemia, has been referred to as essential mixed cryoglobulinemia. Most of the patients (up to 90%) with essential mixed cryoglobulinemia of either type have been shown to have hepatitis C virus (HCV) infection.⁶⁻⁸ The majority of cryoglobulinemic HCV-infected patients are either asymptomatic or have nonspecific findings. The triad of purpura, asthenia, and arthralgia was first described by Meltzer and colleagues⁹ and is currently evident at disease onset in a variable percentage of cases (27.5% of patients in 1 multicenter study).¹⁰

Cryoglobulinemic vasculitis involving small and medium-sized arteries, capillaries, and venules is

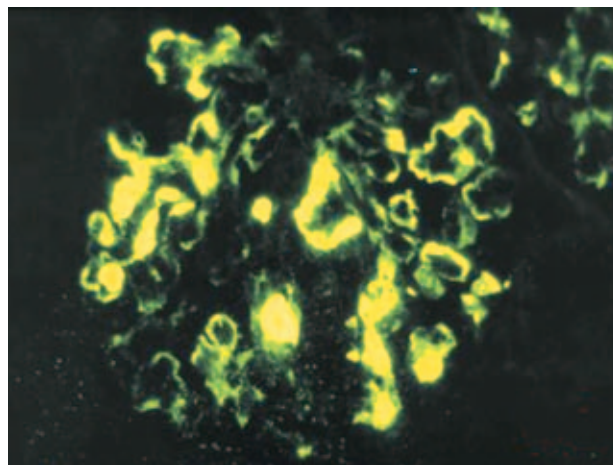


Figure 4. Intense, massive staining of immunoglobulin M with huge deposits filling the capillary lumen.

observed in less than 10% of patients. The most frequently affected organs are the skin (purpura and leg ulcers), nerves (peripheral neuropathy), and kidneys (glomerulonephritis). The vessel wall deposition of circulating cryoglobulins leads to complement activation and is responsible for the vasculitic lesions and organ damage.

Renal involvement is reported in one-third of cryoglobulinemic patients and almost exclusively occurs in association with type II mixed cryoglobulinemia.⁵⁻⁷ The most frequent histologic findings of cryoglobulinemic glomerulonephritis is membranoproliferative glomerulonephritis with subendothelial deposits. In patients with HCV infection cryoprecipitable immune complexes are composed of HCV, anti-HCV polyclonal IgG, and monoclonal IgM-sharing rheumatoid activity. Renal histology of cryoglobulinemic glomerulonephritis includes a diffuse endocapillary, proliferative, or mesangiocapillary lesion with crescents in a few glomeruli and numerous subendothelial deposits. Large eosinophilic intracapillary thrombi may be seen in the acute phases. Interstitial infiltration by mononuclear cells is usually found. Necrotizing vasculitis of the small- and medium-sized arteries is observed in one-third of kidney biopsy specimens. Immunofluorescence microscopy reveals deposits of C3, IgM, and IgG on the capillary wall and mesangium, intraluminal and subendothelial deposits. Electronic microscopy study reveals fibrillary pattern of the deposits, suggesting cryoglobulin deposition.¹

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Correspondence to:

Mojgan Asgari, MD

Department of Pathology, Hasheminejad Kidney Center, Vanak Sq, Tehran, Iran

Tel: +98 912 193 0279

E-mail: