AJKD

Kidney Biopsy Teaching Case

Hepatitis C–Associated Cryoglobulinemic Glomerulonephritis With Crystalline Deposits

Mazdak A. Khalighi, MD, and Charles R. Lassman, MD, PhD

Infection with hepatitis C virus has been associated with a number of extrahepatic manifestations, including kidney disease. Of the glomerular pathologic states described with hepatitis C virus infection, cryoglobulinemic glomerulonephritis is the most prevalent. On kidney biopsy, cryoglobulinemic glomerulonephritis has a variable appearance, with a membranoproliferative pattern of injury as the most common light microscopic finding. Ultrastructurally, curved and paired microtubules are the most characteristic finding, but these also can be variable. We present a case of cryoglobulinemic glomerulonephritis with distinct and highly unusual ultrastructural findings.

Am J Kidney Dis. xx(x):xxx.

INDEX WORDS: Cryoglobulinemia; cryoglobulinemic glomerulonephritis; membranoproliferative glomerulonephritis; organized deposits; crystalline deposits; hepatitis C.

INTRODUCTION

Infection with hepatitis C virus (HCV) has been associated with a number of extrahepatic manifestations, including kidney disease. The prevalence of HCV-infected patients in hemodialysis centers has been reported to be 6%-23%, and the contribution to chronic kidney disease worldwide has been well documented.[1] Cryoglobulinemic glomerulonephritis is the most prevalent HCV-associated glomerular disease. We present a case of cryoglobulinemic glomerulonephritis with distinct and unusual ultrastructural findings.

CASE REPORT

Clinical History and Initial Laboratory Data

A 66-year-old woman was evaluated for increasing proteinuria and edema. She had undergone partial orthotopic liver transplantation from a living donor in November 2000 for cirrhosis secondary to chronic hepatitis C (genotype 1b). Her history also included hypertension and diabetes mellitus. After transplantation, the patient developed recurrent hepatitis C with poor response to antiviral therapy, high viral load, and progressive liver disease. Physical examination showed blood pressure of 138-158/70-89 mm Hg and edema of the lower extremities. Laboratory evaluation in June 2011 showed decreased kidney function with a baseline serum creatinine level of 1.6 mg/dL, corresponding to estimated glomerular filtration rate (eGFR) of 32 mL/min/1.73 m^2 calculated by the 4-variable MDRD [Modification of Diet in Renal Disease] Study equation. Urinalysis in November 2011 showed proteinuria (3+), no red blood cells, and no casts. Spot urine protein-creatinine ratio was 3.03. Assays for circulating cryoglobulins were negative. Serum and urine electrophoresis with immunofixation were negative for monoclonal protein. In March 2012, creatinine level had increased to 3 mg/dL with eGFR of 16 mL/min/1.73 m^2, and proteinuria worsened. Urine protein quantification from that time is unavailable. C3 level was 80 (reference range, 71-141) mg/dL, and C4 level was 18 (reference range, 12-34) mg/dL. Hemoglobin A_{1c} level was 6.4%. Hepatitis C viral load ranged from 9,640,000-18,300,000 IU/mL. Quantitative DNA for hepatitis B virus was negative. A kidney biopsy was performed.

Kidney Biopsy

Of 25 glomeruli sampled, 10 were globally sclerosed, with many others showing segmental sclerosis. Nonsclerotic glomeruli showed moderate segmental to global mesangial expansion, primarily with increased matrix. Focal and segmental endocapillary hypercellularity was noted. Capillary loops showed segmental double contours, and one glomerulus demonstrated segmental intracapillary hyaline thrombi (Fig 1A and B). No fuchsinophilic deposits were identified on trichrome stain, and no spikes were seen on Jones methenamine silver stain. The tubulointerstitium showed moderate tubular atrophy and interstitial fibrosis involving 40% of the biopsy specimen. Tubular basement membrane thickening of nonatrophic tubules was apparent, typical of diabetic nephropathy. Arteries and arterioles showed moderate intimal fibrosis and hyalinosis.

Immunofluorescence microscopy was performed with antisera to human immunoglobulin G (IgG), IgM, IgA, C1q, C3, albumin, fibrinogen, and κ/λ light chains. IgG showed staining (2+) within the mesangium, as well as pseudolinear staining of capillary loops. IgM showed granular staining (3+) of the mesangium and capillary loops (Fig 2A and B). There was mesangial staining for C3 (3+) and staining of mesangial and capillary loop deposits with λ light chain (2+), but only trace staining with κ light chain (Fig 2C and D).

Ultrastructural examination showed near-complete foot-process effacement with focal microvillus transformation of podocytes. Basement membranes showed mild thickening characteristic of diabetic nephropathy. The most striking finding was large subendothelial and paramesangial electron-dense deposits that focally showed an organized grid-like crystalline substructure with period-

From the Department of Pathology and Laboratory Medicine, University of California, Los Angeles, Los Angeles, CA.

Received July 10, 2012. Accepted in revised form February 15, 2013.

Address correspondence to Mazdak A. Khalighi, MD, 10833 Le Conte Blvd, CHS: Rm 13-145, Los Angeles, CA 90095. E-mail: mkhalighi@mednet.ucla.edu

0272-6386/$36.00

http://dx.doi.org/10.1053/j.ajkd.2013.02.354

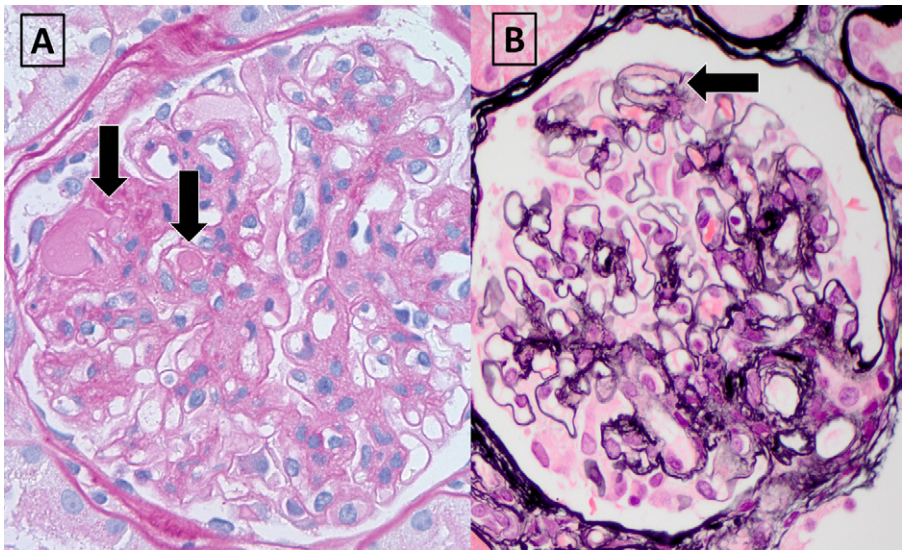

Figure 1. (A) A nonsclerotic glomerulus with intracapillary "hyaline" thrombi (arrow) (periodic acid–Schiff; original magnification, ×400). (B) Segmental duplication of glomerular basement membranes in a nonsclerotic glomerulus (arrow) (Jones methenamine silver; original magnification, ×400).

icity of 12 nm (Fig 3A-C). No other organized ultrastructural patterns were identified.

Diagnosis

The biopsy specimen was read as immune complex–mediated glomerulonephritis suggestive of cryoglobulinemic glomerulonephritis, moderate diabetic nephropathy, and moderate interstitial fibrosis and tubular atrophy. Given the clinical and histopathologic findings, a diagnostic comment suggested a repeated assay for cryoglobulins.

Clinical Follow-up

After kidney biopsy, a cryocrit was repeated and returned positive for circulating cryoglobulins with precipitation at 4°C

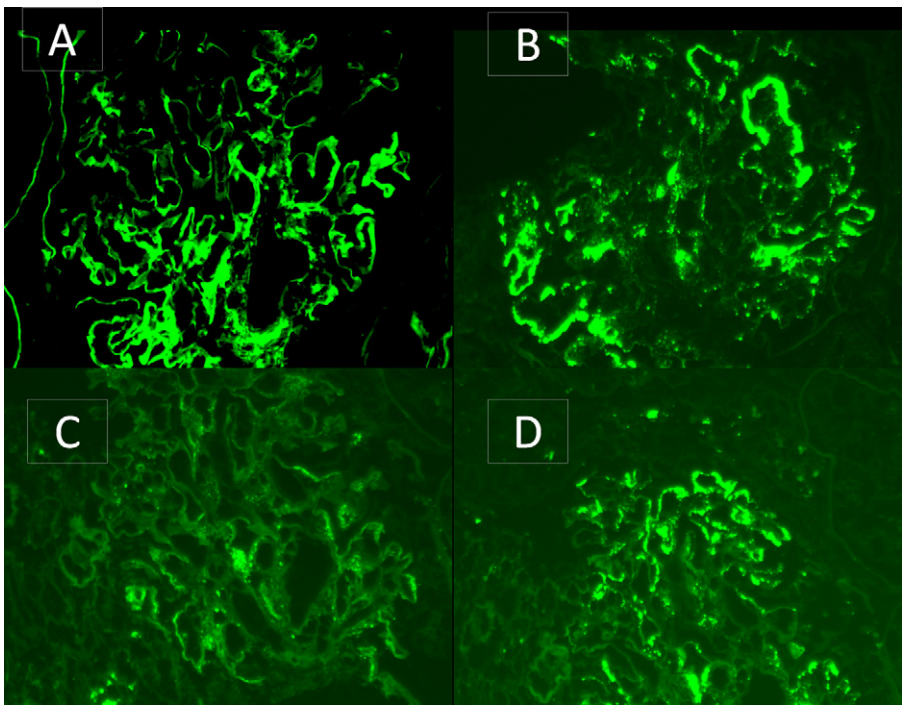

Figure 2. Kidney biopsy specimen evaluation with immunofluorescence microscopy shows (A) segmental granular mesangial immunoglobulin G (IgG) deposits with capillary loop "pseudolinear" appearance. (B) Strong mesangial and capillary loop IgM deposits also are seen. Staining for light chains shows (C) a light chain bias with trace κ light chain and (D) λ light chain staining (2+) (A-D: original magnification, ×400).