AJKD

Kidney Biopsy Teaching Case

Glomerulonephritis With Masked Monotypic Immunoglobulin Deposits and Concurrent Lymphomatous Infiltration

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Kidney injury can be a complication of hematopoietic neoplasia by both direct and indirect mechanisms. Virtually all lymphomas and plasma cell dyscrasias can show kidney involvement, including parenchymal infiltration and by secondary injury. Recently, a unique form of glomerulonephritis with masked monotypic immunoglobulin deposits has been reported, which shows frequent association with hematopoietic neoplasia and a propensity for progressive kidney disease. In many instances, these cases are likely diagnosed as glomerulonephritis with dominant C3 due to the absence of immunoglobulin staining by routine immunofluorescence microscopy. The patient reported here showed lymphomatous infiltration on kidney biopsy and mesangial proliferative glomerulonephritis with dominant staining for C3 without immunoglobulins on initial immunofluorescence; however, monotypic immunoglobulin G κ light chain was revealed after additional immunofluorescence staining was performed on the paraffin-embedded tissue. This patient's case highlights the evolving state of kidney biopsy interpretation and the expanding spectrum of kidney disease in the setting of hematopoietic neoplasia.

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INDEX WORDS: Glomerulonephritis; masked deposits; IgGκ; lymphomatous infiltration; hematopoietic neoplasia; renal infiltration; proteinase predigestion; antigen retrieval; kidney biopsy.

INTRODUCTION

Kidney injury in the setting of hematopoietic neoplasia can be variable and may include mechanisms such as direct parenchymal infiltration by neoplastic cells, deposition of monotypic light chains within glomeruli, and more indirect mechanisms such as disruption of the alternative pathway of complement with glomerular deposition of complement components.[1-4] In some instances, these mechanisms can occur concurrently and result in a mixed clinical picture with multiple histologic findings.[5]

Recently, an unusual pattern of glomerular injury has been described in which routine immunofluorescence performed on frozen tissue shows dominant C3 staining; however, immunofluorescence performed on paraffin-embedded tissue following antigen retrieval demonstrates monotypic immunoglobulin staining. These patients have been shown to harbor a high incidence of underlying hematopoietic neoplasia, including plasma cell disorders and clonal B-cell neoplasms.[6]

We report a case of acute kidney injury in an elderly man who was found to have parenchymal infiltration by mantle cell lymphoma and concurrent glomerular injury with masked monotypic deposits. This case highlights the expanding spectrum of kidney injury seen in the setting of hematopoietic disease and the ever-evolving practice of nephropathology.

CASE REPORT

Clinical History and Initial Laboratory Data

A 66-year-old man with a history of hypertension presented with abdominal pain, nausea, and anorexia over a 6-week period, with an accompanying weight loss of 30 pounds. He reported normal urine output, but described an orange color without frank blood. His medications included lisinopril, hydrochlorothiazide, and a recent course of doxycycline for a sinus infection. Physical examination revealed blood pressure of 169/90 mm Hg and splenomegaly. There was no dependent edema or significant lymphadenopathy. Laboratory testing revealed anemia, with a hemoglobin level of 8 g/dL, and leukocytosis, with a white blood cell count of 18×10^9/L. Serum creatinine level was elevated at 10.2 mg/dL, corresponding to estimated glomerular filtration rate of 5 mL/min/1.73 m^2 as calculated by the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation. Urinalysis showed protein and blood, with more than 400 red blood cells per high-power field and spot urine protein-creatinine ratio of 1.5 g/g. Results of serologic studies were reportedly negative, but they were not available. Serum protein electrophoresis results were not available at the time of presentation. A kidney biopsy was performed.

Kidney Biopsy

The light microscopy sample contained up to 14 glomeruli, of which 2 were globally sclerosed. The other glomeruli demonstrated minimal increase in mesangial matrix with segmental and mild increase in mesangial cellularity (Fig 1A). There was no significant endocapillary hypercellularity or glomerular basement membrane duplication. Crescents were not observed. An atypical lymphoid infiltrate was seen in the cortex with infiltration into the

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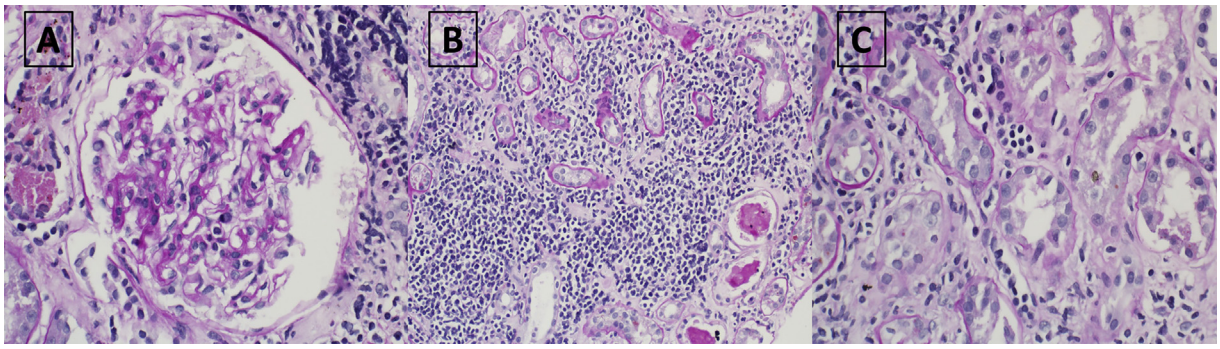

Figure 1. Light microscopic evaluation shows: (A) glomeruli with an essentially normal appearance with only minimal mesangial expansion (periodic acid–Schiff; original magnification, ×40); (B) atypical lymphoid infiltrate within the superficial cortex with monotonous appearance and cells with irregular nuclear contours (periodic acid–Schiff; original magnification, ×20); and (C) peritubular capillaries with congestion by atypical lymphocytes (periodic acid–Schiff; original magnification, ×40).

overlying capsule. These lymphocytes were monotonous in appearance with small size and irregular nuclear contours (Fig 1B). The infiltrate involved 10% to 15% of the sample, and many peritubular capillaries showed congestion by these lymphocytes (Fig 1C). A full immunohistochemical workup was unable to be performed on the infiltrate due to tissue constraints; however, staining for CD20 showed diffuse positivity, consistent with B-cell proliferation. Proximal tubules showed features of injury, including loss of brush borders and sloughing of epithelial cells into tubular lumina. Scattered intratubular red blood cell casts were present. The degree of interstitial fibrosis and tubular atrophy was mild, involving ~20% of the sample.

Immunofluorescence microscopy (scale, 0-4+) of one glomerulus showed granular mesangial staining for C3 (3+; Fig 2A) without glomerular staining for immunoglobulin G (IgG; Figure 2B), IgA, IgM, C1q, κ light chain (Fig 2C), λ light chain (Fig 2D), fibrinogen, or albumin. Retrospectively, additional immunofluorescence staining on the paraffin-embedded tissue following predigestion with proteinase K (Dako) demonstrated granular mesangial staining for IgG and κ light chain without staining for λ light chain. Repeat paraffin immunofluorescence following digestion with proteinase type XXIV (Sigma-Aldrich) also revealed IgG κ light chain deposits within mesangial areas (Fig 2E-G). There was no tubular basement membrane or interstitial staining. An immunohistochemical study for C4d showed strong mesangial staining (Fig 2H).

Ultrastructural evaluation revealed scattered mesangial immune-type electron-dense deposits without substructural organization. Deposits were not identified within the capillary loops, and duplication of the glomerular basement membrane was not seen. Podocyte foot processes showed focal effacement, but were mostly intact. Endothelial tubuloreticular inclusions were absent.

Diagnosis

The final diagnosis was atypical lymphoid infiltrate suspicious for lymphoproliferative disorder and mesangial proliferative glomerulonephritis (GN) with masked monotypic IgG κ light chain deposits.

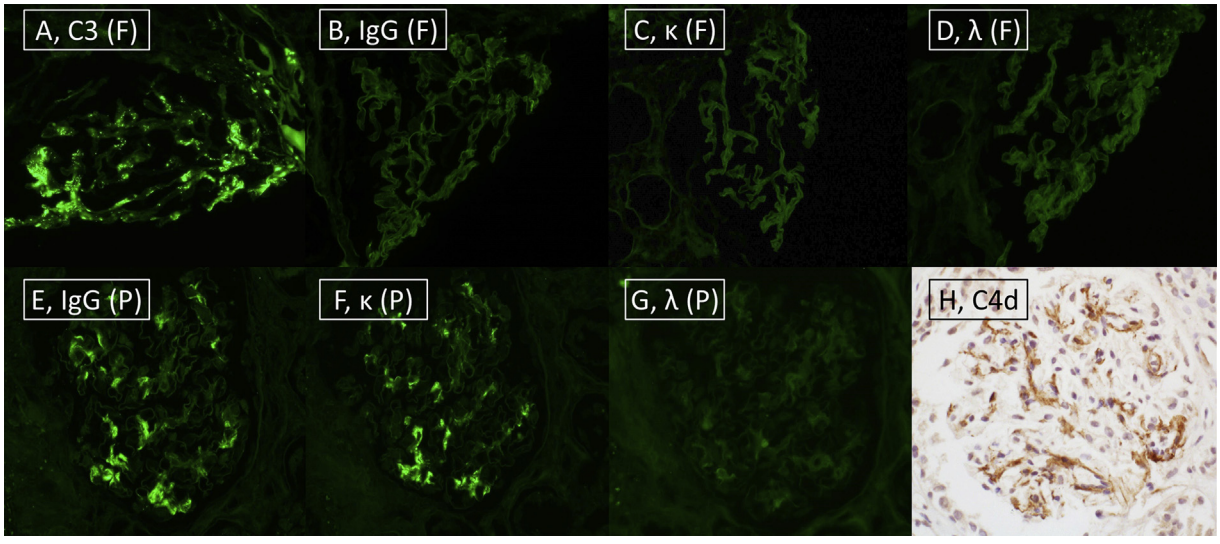

Figure 2. Routine immunofluorescence microscopy on frozen (F) tissue shows primarily mesangial staining for: (A) C3 only (3+ [scale, 0-4+]), without staining for (B) immunoglobulin G (IgG), (C) κ light chain, or (D) λ light chain. Immunofluorescence microscopy on the paraffin (P)-embedded tissue following digestion with proteinase type XXIV (Sigma-Aldrich) reveals mesangial deposits staining for (E) IgG and (F) κ light chain, (G) without staining for λ light chain. (H) Staining for C4d by immunohistochemistry shows strong mesangial staining.