Human Pathology (2014) **45**, 875–879

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Case Study

Combined crystalline podocytopathy and tubulopathy associated with multiple myeloma☆

Shreeram Akilesh MD, PhD[a,*], Astier Alem MD[b], Roberto F. Nicosia MD, PhD[a,c]

[a]*Department of Pathology, University of Washington, Seattle, WA 98195*
[b]*Eastside Nephrology and Hypertension, PLLC, Kirkland, WA 98034*
[c]*Pathology and Laboratory Medicine Services, Veterans Administration Puget Sound Health Care System, Seattle, WA 98108*

Received 20 August 2013; revised 27 September 2013; accepted 2 October 2013

Keywords:
Podocyte;
Collapsing glomerulopathy;
Crystalline inclusions;
Multiple myeloma

Summary Lymphoplasmacytic neoplasms cause a wide range of injuries to the kidney exemplified by light chain cast nephropathy and amyloidosis. Filtered paraproteins can also accumulate within kidney cells and cause direct cytotoxic injury. Rarely, paraproteins that are resistant to proteolysis can crystallize within proximal tubules and cause acute tubular injury. In contrast, accumulation of crystallized paraproteins in other kidney cells, especially podocytes, is exceptional. Here, we report the finding of crystalline inclusions within podocytes and proximal tubules in a patient who presented with a combined nephrotic syndrome and Fanconi syndrome. Further workup revealed previously unsuspected multiple myeloma and elevated serum free light chains, highlighting the protean presentation of paraprotein-mediated injuries to the kidney.

1. Introduction

Lymphoplasmacytic disorders can cause renal dysfunction in numerous ways. Common pathologic findings associated with circulating (and filtered) paraproteins include cast nephropathy, amyloidosis, and monoclonal immunoglobulin deposition disease. These pathologies are unified by aberrant properties of the monoclonal immunoglobulin proteins that cause them to aggregate extracellularly and/or resist proteolytic clearance mechanisms [1]. Paraproteins can also accumulate within the cell and cause injury. This is best understood in the context of light chain proximal tubulopathy in which paraproteins can aggregate as crystalline inclusions within proximal tubular epithelial cells causing acute tubular injury and dysfunction [2]. Only a handful of cases have reported paraprotein crystalline inclusions in other kidney cells such as podocytes, and the direct cytotoxic effects of these inclusions on these specialized epithelial cells is unclear [3–11]. Here, we report a case of a combined crystalline podocytopathy and tubulopathy presenting clinically as a combined nephrotic and Fanconi syndrome. Uniquely, the crystalline inclusions within podocytes were associated with a severe histologic manifestation of podocyte injury and collapsing glomerulopathy, thereby implicating the crystalline inclusions in direct toxic injury to the podocyte.

2. Materials and methods

Routine processing pipelines for kidney biopsies at our institution were utilized for specimen preparation. For light microscopy, formalin-fixed, paraffin-embedded kidney

☆ Financial Disclosure: The authors declare that they have no relevant financial interests.

* Corresponding author. University of Washington, Department of Pathology, Box 356100, 1959 NE Pacific Avenue, Seattle, WA 98195.
E-mail address: shreeram@uw.edu (S. Akilesh).

0046-8177/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.humpath.2013.10.007

biopsy tissue was cut at 2-μm thickness (10-μm thickness for Congo red), deparaffinized and stained with hematoxylin and eosin, periodic acid–Schiff reagent, Jones methenamine silver, trichrome and Congo red stains. For direct immunofluorescence studies, 3-μm cryostat sections were stained with fluorescein isothiocyanate–conjugated anti-human IgG, IgM, IgA, C3, C1q, κ and λ light chain, fibrinogen, and albumin (Dako, Carpinteria, CA) following standard protocols. Tissue for electron microscopy was fixed in 1/2 strength Karnovsky solution, postfixed in 2% osmium tetroxide, dehydrated in a graded ethanol series, and embedded in Polybed 812 (Polysciences, Inc, Warrington, PA). Sections measuring 100 nm were stained with uranyl acetate and lead citrate and examined with a Philips 410 electron microscope (Philips Export BV, Eindhoven, the Netherlands).

3. Case report

The patient was a 45-year-old man who was found to have acute kidney injury (serum creatinine 1.85 mg/dL), glycosuria, proteinuria (7.925 g/24 h) and dyslipidemia on a routine annual physical exam. The patient was also hypertensive (138/95 mmHg). Serologic evaluation for viral infections (hepatitis B and C, human immunodeficiency virus) was negative. An ultrasound-guided kidney biopsy was performed.

Examination of all the material submitted revealed renal cortex with approximately 27 to 50 glomeruli per level section, of which approximately 2 to 6 glomeruli were completely sclerosed. Up to 3 glomeruli showed segmental or global collapse of the capillary tufts associated with marked hypertrophy of overlying podocytes, many of which were engorged with eosinophilic protein droplets (Fig. 1A). In these glomeruli, some podocytes demonstrated poorly staining needle-like material within their cell body, which was surrounded by eosinophilic cytoplasmic condensation. One glomerulus showed segmental sclerosis characterized by accumulation of matrix, obliteration of capillary lumina and fibrous adhesions to the adjacent Bowman's capsule. The tubules diffusely showed acute injurious changes characterized by epithelial attenuation, loss of brush borders, cytoplasmic vacuolization and shedding of cells and/or cytoplasm into the tubular lumens (Fig. 1B). Some tubular epithelial cells also contained poorly staining needle-like material within their cytoplasm, similar to that seen in podocytes. This material was fuschinophilic in trichrome-stained sections. There was mild patchy tubular atrophy, interstitial fibrosis and associated nonspecific interstitial chronic inflammation. Some arteries showed mild to focally moderate intimal sclerosis and some arterioles showed mild hyalinosis.

Immunofluorescence microscopy revealed a diffuse, dull interstitial staining for IgG and κ light chains, but not λ light chains (Fig. 1C and D). This immunofluorescence signal

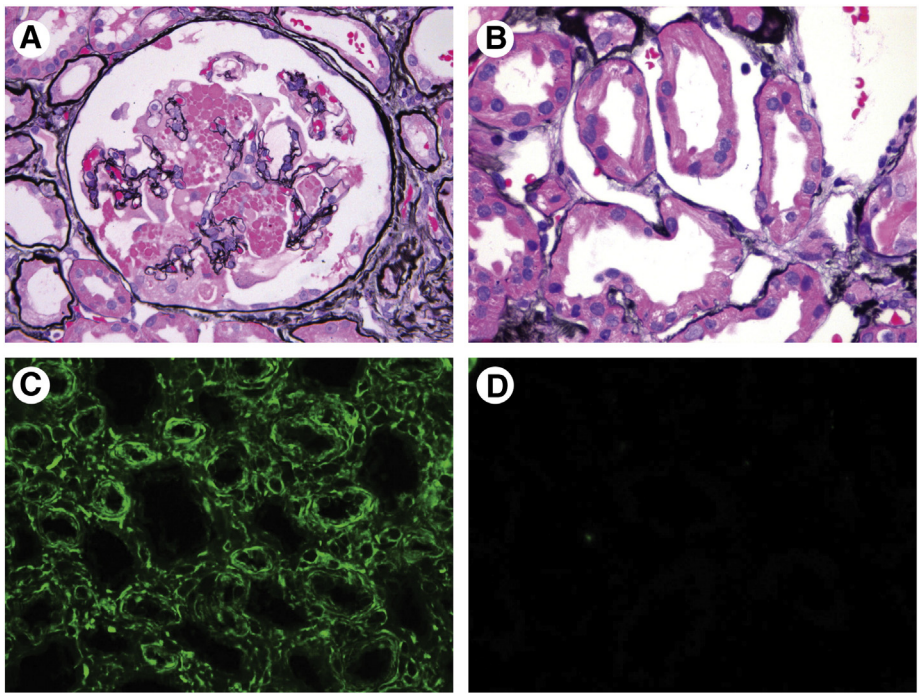

Fig. 1 A, Some glomeruli exhibited features of collapsing glomerulopathy. B, Tubules diffusely exhibited acute injurious changes characterized by epithelial attenuation and loss of brush borders. Some tubular epithelial cells demonstrated pale staining intracellular clefts surrounded by eosinophilic cytoplasmic material. Immunofluorescence staining revealed diffuse interstitial/intracellular staining for κ (C) but not λ (D) light chains. The immunohistochemistry studies for κ and λ light chains produced similar results (not shown). A and B, Jones methenamine silver (original magnification ×400). C and D, Direct immunofluorescence (original magnification ×200).