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On the Cover

What is the Diagnosis?

An 85-year-old man with type 2 diabetes and hypertension was initially evaluated for proteinuria (1 g/day), of which only 200 mg was albuminuria. Serum protein electrophoresis showed an IgA-lambda monoclonal protein and an elevated serum kappa/lambda ratio at 5.71. Urine protein electrophoresis showed free kappa monoclonal protein (8% of total urine protein). A bone marrow biopsy workup revealed chronic myelomonocytic leukemia (CMML). His plasma lysozyme level taken shortly after was greater than 10.8 μg/ml (reference range: 2.6–6.0 μg/ml) with concurrent monocytosis (7.2 billion/L). His serum creatinine increased to 2.25 mg/dl from a baseline serum creatinine at 1.70 mg/dl. A kidney biopsy was then performed.

Image Description:
Light microscopy (left image) showed an unremarkable glomerulus (G) but dilated proximal tubules (blue arrows) with granular and strongly eosinophilic cytoplasm on hematoxylin and eosin-stained sections. Immunohistochemical staining for lysozyme (prediluted polyclonal antibody, Cell Marque, Rocklin, CA) was strongly positive (green arrows) in the cytoplasm and nuclei of the proximal tubules (middle image). Lysozyme staining was negative in the glomerulus (G), serving as an internal control. Electron microscopy (right image) showed expanded lysosomes in the proximal tubular cytoplasm with rounded, dense dots in a chocolate chip cookie pattern indicated with orange arrows (scale bar =1.5 μm), as demonstrated previously (1). No monoclonal protein was detected by immunofluorescent stains in the kidney biopsy.

Teaching Points:
Lysozyme nephropathy is a rare etiology of AKI in patients with chronic myelomonocytic leukemia (1,2). Lysozymes are small cationic proteins produced by monocytes that can be freely filtered through glomerular basement membranes and reabsorbed by proximal tubules. Overproduction of lysozyme in patients with CMML leads to over-reabsorption and retention within the proximal tubule lysosomes, which can be confirmed ultra-structurally and immunohistochemically. After the kidney biopsy, our patient was treated with azacitidine for 1 week and his serum creatinine improved to 1.67 mg/dl after a 1-month follow-up. Further work with larger patient cohorts will be needed to better understand the pathophysiology and outcomes of lysozyme nephropathy, in addition to investigating whether serum creatinine and proteinuria in patients with CMML should be closely monitored for early targeted therapy, as with monoclonal gammopathy of renal significance (3).

References:

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