An Unusual Cause of Nephrotic Syndrome

CLINICAL PRESENTATION
A 53-year-old man presented with pedal edema and facial puffiness of 6 months’ duration. Nephrotic-range proteinuria was diagnosed 3 months earlier and empirically treated with prednisolone, 50 mg/d, without a response. Physical examination was notable for blood pressure of 140/86 mm Hg while on treatment with losartan, 25 mg/d, and pitting pedal edema (2+) up to the knees. Urine dipstick showed protein (3+), and urine microscopy revealed 6 to 7 red blood cells/high-power field. Other test results included the following values: serum creatinine, 2.62 mg/dL (corresponding to estimated glomerular filtration rate [GFR] of 26 mL/min/1.73 m² as calculated by the 4-variable MDRD [Modification of Diet in Renal Disease] Study equation); hemoglobin, 8.3 g/dL; serum albumin, 2.9 mg/dL; cholesterol, 210 mg/dL; and 24-hour urinary protein excretion, 6.5 g. Antinuclear antibody was undetectable in serologic testing, and serum C3 and C4 levels were normal. Serum protein electrophoresis identified a faint band in the γ region, but immunofixation, free light chain assay, urine Bence Jones protein, and bone marrow examination were negative for monoclonal gammopathy. Markers for hepatitis B virus, hepatitis C virus, and HIV (human immunodeficiency virus) were undetectable. Imaging revealed kidneys of normal size with preserved corticomedullary differentiation, and a kidney biopsy was performed (Figs 1 and 2). Direct immunofluorescence did not detect immunoglobulin or complement components (immunoglobulin G [IgG], IgA, IgM, C3, and C1q) along the capillary walls or mesangium.

- Describe the kidney biopsy findings.
- What is the pathologic diagnosis, and what additional investigations are recommended?
- What are the clinical manifestations of this disease?
- What are the treatment options?

Figure 1. Kidney biopsy with light microscopy: (A) hematoxylin-eosin stain, (B) periodic acid–Schiff stain, (C) Masson trichrome stain, (D) Congo Red stain, (A-D) original magnification, ×400.
Figure 2. Kidney biopsy by transmission electron microscopy: (A) capillary wall and mesangium; original magnification, ×4,200; (B) ultrastructural characteristic of the extracellular material; original magnification, ×43,000. Abbreviations: GBM, glomerular basement membrane; M, mesangium; P, podocyte; U, urinary space, *Extracellular material with typical ultrastructural appearance.
DISCUSSION

Describe the kidney biopsy findings

Light microscopy shows lobulated to nodular glomeruli without increased cellularity, but marked mesangial expansion and thickening of capillary walls by accumulation of pale eosinophilic homogenous material (Fig 1A). This material was not stained with periodic acid–Schiff (Fig 1B), methenamine silver, Congo Red (Fig 1D), and thioflavin T, but stained blue with Masson trichrome (Fig 1C).

Electron microscopy (EM) demonstrates the presence of banded collagen fibers in the mesangium and subendothelial regions (Fig 2A), arranged in irregular curvilinear bundles exhibiting characteristic cross-striations with a periodicity of 50 to 60 nm (Fig 2B). There is prominent expansion of the lamina rara interna, but no fibrils or motting in the lamina densa. There are no electron-dense immune complex–type deposits. Podocyte foot processes are extensively effaced.

What is the pathologic diagnosis, and what additional investigations are recommended?

The histology is suggestive of a glomerulopathy due to accumulation of extracellular fibers in the mesangium and capillary walls. In this patient, lobulated to nodular glomeruli prompt consideration of membranoproliferative glomerulonephritis type I, chronic thrombotic microangiopathy (TMA), amyloidosis, diabetic glomerulosclerosis, and light chain deposition disease. A paucity of double contours and the absence of hypercellularity and immune complex/complement deposits by immunofluorescence and EM rule out membranoproliferative glomerulonephritis type I. The lack of extraglomerular vascular changes excludes chronic TMA, and the absence of periodic acid–Schiff staining eliminates light chain deposition disease and diabetic glomerulopathy. The lack of Congo Red and thioflavin T staining rules out amyloidosis. The EM feature of frayed curvilinear collagen fibers with typical cross-striations in glomeruli is pathognomonic of collagen type III glomerulopathy, or collagenofibrotic glomerulopathy. Immunostaining with fluorescein-conjugated antibodies to collagen type III in the mesangium and capillary walls can confirm the diagnosis, but it was not performed in this case.

Nail-patella syndrome, an inherited collagen type III glomerulopathy caused by mutations in the LMX1B gene, is a related diagnosis with banded collagen fibers in the lamina densa, giving a “moth-eaten” appearance. In this case, the spared lamina densa and absence of extrarenal manifestations rule out nail-patella syndrome.

While levels of procollagen type-III peptide (PIIINP), a post-translational cleavage product of type III collagen, are elevated in serum and urine of patients with fibrotic conditions, in collagenofibrotic glomerulopathy, they are increased markedly (10-100 times normal). Although such high levels of serum and urinary PIIINP can support the diagnosis, they were not measured in this patient.

What are the clinical manifestations of this disease?

Collagenofibrotic glomerulopathy often occurs sporadically in adults, with no age or sex predilection. A few cases have been reported in siblings whose parents had no kidney disease, supporting the possibility of a genetic disease with autosomal recessive inheritance.1 Patients commonly present with nephrotic-range proteinuria (>50%), hypertension (60%), occasional microscopic hematuria, and a normal or mildly reduced GFR. The disease can progress to end-stage renal disease, but anemia predates.2 A few pediatric patients have been reported to have TMA with additional inherited factor H deficiency.3,4 Extrarenal manifestations are typically absent, except for a rare case with associated hepatic perisinusoidal fibrosis.5

What are the treatment options?

There is no specific treatment. Supportive therapy to control edema and hypertension may be useful. There are few reports of improved GFR, proteinuria, and anemia with prednisolone (40 mg/d),6 but this response seems time limited. After kidney failure, a few patients have received kidney transplants with no reports of disease recurrence.7

FINAL Diagnosis

Collagenofibrotic glomerulopathy.
REFERENCES


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