Renal Clinico-Pathology Teaching Case: Fibrillary Glomerulonephritis

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CASE REPORT

A 39-year-old Caucasian man with a history of hypertension for 5-8 years was referred to the renal clinic for evaluation of asymptomatic nephrotic-range proteinuria. At the time of his initial visit he had no specific complaints suggestive of a potential etiology. His past medical history was remarkable for chronic low back pain secondary to lumbar spine compression fracture in the 1980s, morbid obesity, obstructive sleep apnea, gastroesophageal reflux disease and depression. Social and family history were noncontributory. Prescription medications included tramadol, atenolol, klonopin and paroxetine.

On physical examination, he was an obese man in no apparent distress. Vital signs revealed BP of 120/74, a pulse rate of 100 beats per minute, and a temperature of 37.3 degrees Celsius. The rest of the physical examination was unremarkable. It

Table 1: Initial visit laboratory results

Na	142 (135-145	WBC	9.6 (4-11k/uL)
K	mmol/L)	Hg	15.4 (14-18 g/dL)
Cl	4.2 (3.5-4.5	Hct	45.4 (40-52%)
HCO3	mmol/L)	Platelets	236 (150-450
Bun	106 (97-107	Hep B Surf Ag	k/uL)
Cr	mmol/L)	Hep B Surf Ab	Negative
Calculated GFR	26 (22-29 mmol/L)	Hep C Ab	Negative
Uric acid	14 (9-20 mg/dL)	HIV	Negative
Total Protein	1.3 (0.7-1.2 mg/dL)	C3	Negative
Albumin	65 ml/min/1.73m2	C4	146 (83-156
Bilirubin	8.9 (3.5-7.2 mg/dL)	RF	mg/dL)
Alk phosphatase	7.4 (6-8.3 g/dL)	Cryoglobulin	19 (10-38 mg/dL)
AST	4.5 (3.5-5.7 g/dL)	ANA	<20 (<30 IU/ml)
ALT	0.7 (03-1.2 mg/dL)	Anti-DS-DNA	Negative
HgA1C	49 (40-150 U/L)	SPEP	Negative
LDL	25 (<35 U/L)		Negative
24 hour urine protein	43 (< 55 U/L)	UPEP	No anomalous immunoglobulins
Urinalysis	5.6 (< 6%)		No anomalous immunoglobulins

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showed no lower extremity edema, ascites, rash or synovitis. Results of the initial laboratory tests are listed in table 1.

Renal Biopsy Findings

On light microscopy, 15 glomeruli were identified, one of which was globally sclerotic. The other fourteen demonstrated mild to moderate mesangial matrix expansion and hypercellularity (Figure 1). There was

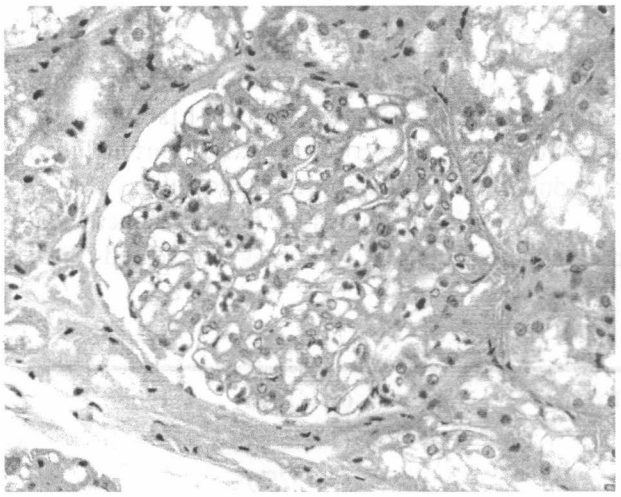

Figure 1: Light microscopy. Glomeruli demonstrate mild to moderate mesangial matrix expansion and hypercellularity (H&E, original magnification 200x).

minimal tubular atrophy and interstitial fibrosis. A scant lymphoplasmacytic infiltrate was primarily subcortical. Small arteries displayed medial hypertrophy. Congo red staining with and without potassium permanganate incubation was negative. Immunofluorescence (IF) with antisera specific for IgG, C3, and kappa and lambda light chains demonstrated 2+ positivity in the mesangium (on a scale of trace to 3+) (Figure 2).

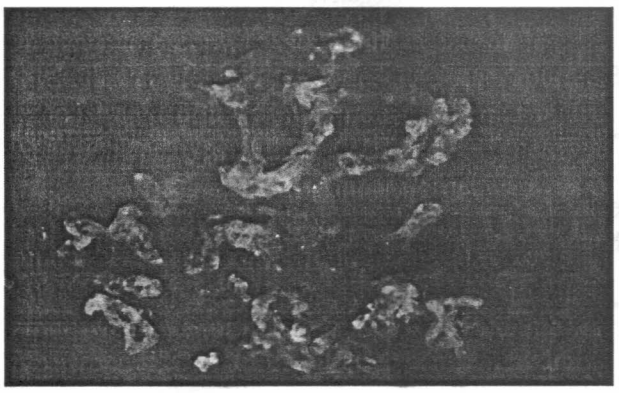

Figure 2: Immunofluorescence microscopy. Staining with antiserum to kappa light chain demonstrates 2+ smudgy mesangial positivity. Similar staining for IgG, C3, and lambda light chain was observed. IgA was negative. (anti-kappa light chain, 400x).

There was 1+ positivity with anti-sera specific to IgM and C1q. Immunofluorescence with anti-sera specific for IgA and fibrin was negative. Electron microscopy (EM) revealed deposition of randomly arranged, non-branching 15 nm fibrils, predominantly in the mesangium and focally in the glomerular basement membrane (Figure 3).

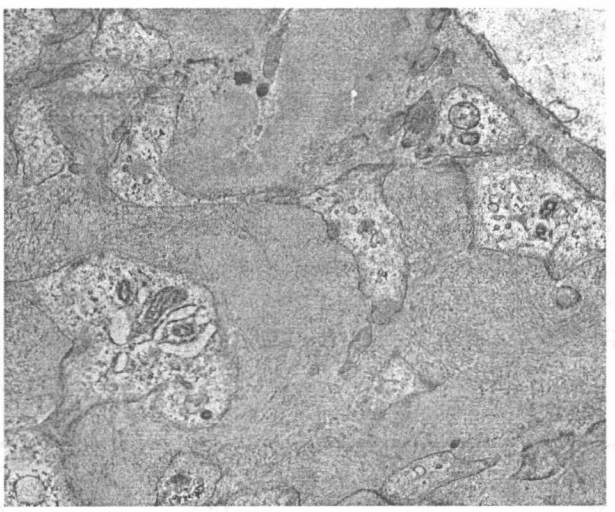

Figure 3: Electron microscopy. Randomly arranged fibrils are deposited predominantly in the mesangium. For orientation, a glomerular basement membrane is included in the top right (uranyl acetate and lead citrate, 12000x).

No immune complexes or tubuloreticular inclusions were identified. Based principally on the ultrastructural findings, a diagnosis of fibrillary glomerulonephritis was made.

DISCUSSION

Fibrillary glomerulonephritis (GN) is an uncommon form of glomerular disease found in approximately 0.5-1% of native kidney biopsies. It was originally described as "Congo-red negative amyloidosis" by Rosenmann and Eliakim in 1977 [1]. Usually an idiopathic disorder, it has been linked to chronic hepatitis C infection in one study [2]. The average age at presentation is 45 years. Main clinical features include proteinuria (virtually 100%), often nephrotic range (50-70%), hematuria (60-70%), renal insufficiency (55-70%), and hypertension (65%) [3-5]. Fibrillary GN is a primary renal disorder and serologic tests for complement levels, lupus antibodies, rheumatoid factor, anti-neutrophil cytoplasmic antibodies and anti-glomerular basement membrane antibodies are usually negative or within the normal range.

Renal biopsy with ultrastructural examination of the specimen is required for a definitive diagnosis

of fibrillary GN. Light microscopic findings are nonspecific, as the lesion manifests a variety of histologic patterns, including mesangioproliferative (as in the patient discussed above), diffuse proliferative, membranoproliferative, crescentic, membranous, and diffuse sclerosing. Rosenstock *et al* described IF findings in 61 patients with fibrillary GN. Ninety six percent displayed positivity for IgG, 52% for IgM, 30% for IgA, 83% for C3, 41% for C1q, and 96% for both kappa and lambda light chains [4]. The ultrastructural appearance is pathognomonic, showing randomly oriented fibrils in the mesangium (in 98% of cases) and/or the glomerular basement membrane (in 90% of cases). The fibrils are usually 15-25 nm in diameter, larger than those seen in amyloidosis, which are typically 6-10 nm. Although overlap in fibril size in fibrillary GN and amyloidosis may occur, staining with Congo red reagent readily distinguishes these two conditions [7]. Subendothelial or subepithelial distribution of fibrils is seen in < 15% of cases [4].

The clinical course of fibrillary GN is that of subacute progression to end stage renal disease (ESRD). Approximately 50% of patients will require renal replacement therapy within 2-6 years. The prognosis appears to be somewhat dependent on the histologic pattern found on light microscopy with the worst prognosis observed in patients with a diffuse sclerosing pattern on initial biopsy (~7 months to ESRD) and the best prognosis seen in those with membranous lesions (~87 months to ESRD) (4). There is no proven treatment for fibrillary GN. Cytotoxic agents and/or steroids, chlorambucil, plasmapheresis and NSAIDS have been tried with limited success. Response to therapy may again depend on the histologic appearance, and patients with glomerular crescents on light microscopy may respond better to immunosuppressants. Dickenmann *et al* reported successful clinical remission in 3 patients with normal renal function and nephrotic range proteinuria at the time of diagnosis, when they treated with high dose prednisone and nonspecific therapy with an angiotensin converting enzyme inhibitor [6].

Renal transplantation is an option for fibrillary GN patients who progress to ESRD. Recurrence was 50% in one small study [3], however, the rate of disease progression appears to be slower than in the native kidney.

Immunotactoid Glomerulopathy

In contrast to fibrillary GN, immunotactoid glomerulopathy (ITG) is morphologically characterized by parallel arrangement of microtubular deposits in the mesangium and in the glomerular basement membrane [8]. The size of microtubules in ITG is in general larger than in fibrillary GN, usually > 30nm and can be up to 90nm. As in fibrillary GN staining with Congo red reagent is negative and ultrastructural examination of the glomerular tissue is essential for diagnosis.

Clinical features of ITG largely overlap with those of fibrillary GN and almost universally include proteinuria (nephrotic range 80%) with hematuria (75%), hypertension (85%) and renal insufficiency (45%) being frequently present. Association of ITG with several systemic diseases including monoclonal gammopathies, lymphoproliferative disorders, autoimmune conditions and chronic hepatitis C infection has been described in several case series [4, 5], therefore diagnosis of ITG should prompt a search for these conditions. While it has been suggested that prognosis may be better in patients with ITG [9], this was not confirmed in later publications [3, 4].

Whether fibrillary GN and immunotactoid glomerulopathy (ITG) are separate entitities is still a subject of significant debate. Brady [5] and Pronovost *et al* [3] suggest that it is too early to make a clinical distinction as the two conditions have a significant overlap in clinical presentation, fibril size and prognosis. On the other hand, Alpers *et al* [7, 10] and Rosenstock *et al* [4] contend that fibrillary GN and ITG should be separated since the latter has a higher coexistence with serious systemic illnesses.

Teaching Points

- Fibrillary glomerulonephritis (GN) is an uncommon form of glomerular disease found in approximately 0.5-1% of native kidney biopsies.
- Presentation is usually with proteinuria, often nephrotic range. Hematuria and renal failure also occur but less often.
- Diagnosis is made by ultrastructural appearance of randomly oriented fibrils in the mesangium . The fibrils are usually 15-25 nm in diameter, larger than those seen in amyloidosis, which are typically 6-10 nm. Congo red staining is negative.

- Clinical course of subacute progression to end stage renal disease, approximately 50% of patients will require renal replacement therapy within 2-6 years.
- No proven effective treatment. Cytotoxic agents and/or steroids, chlorambucil, plasmapheresis and NSAIDS have been tried with limited success. Renal transplantation is an option.

REFERENCES

1. Rosenmann E and Eliakim M. Nephrotic syndrome associated with amyloid-like deposits. Nephron 1977; 18: 301-308.

2. Markowitz GS, Cheng JT and Colvin RB. Hepatitis C viral infection is associated with fibrillary glomerulonephritis and immunotactoid glomerulopathy. J Am Soc Nephrol 1998; 9: 2244.

3. Pronovost PH, Brady HR *et al.* Clinical features, predictors of disease progression and results of renal transplantation in fibrillary/immunotactoid glomerulopathy. Nephrol Dial Transplant 1996; 11: 837-842.

4. Rosenstock JL, Markowitz GS *et al*. Fibrillary and immunotactoid glomerulonephritis: Distinct entities with different clinical and pathologic features. Kidney International 2003; 63:1450-1461.

5. Brady HR. Fibrillary glomerulopathy. Kidney International 1998; 53: 1421-1429

6. Dickenmann M, Schaub S *et al.* Fibrillary Glomerulonephritis: early diagnosis associated with steroid responsiveness. AJKD 2002; 40(3): 1-5.

7. Alpers C and Kowalewska J. Fibrillary Glomerulonephritis and Immunotactoid Glomerulopathy. JASN 2008; 19: 34-37.

8. Ivanyi B and Degrell P. Fibrillary Glomerulonephritis and Immunotactoid Glomerulopathy. Nephrol Dial Transplant 2004; 19: 2166-2170.

9. Fogo A, Quereshi N and Horn RG: Morphological and clinical features of fibrillary glomerulonephritis versus immunotactoid glomerulopathy. Am J Kidney Dis 1993; 22: 367–377.