A case of comma-shaped fibrillary glomerulonephritis

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Abstract

We present a case of a 77-year-old male with multiple co-morbidities who underwent a renal biopsy for progressive loss of renal function. Examination by electron microscopy revealed glomerular deposits within which were numerous randomly orientated 22 nanometre mean diameter curvilinear fibrils, consistent with a rare form of fibrillary glomerulonephritis. Review of the literature has revealed just one similar case. The investigative work up and histological findings are discussed along with the clinical implications of making a diagnosis of fibrillary glomerulonephritis.

Keywords Chronic kidney disease; electron microscopy; fibrillary deposits; medical renal; membranoproliferative glomerulonephritis

Case report

A 77-year old white male presented with a bilateral lower limb purpuric rash, hypertension, and haematoproteinuria. His past medical history included type two diabetes mellitus, chronic kidney disease, interstitial lung disease, and raised body mass index. He had numerous cardiovascular co-morbidities including: atrial fibrillation, previous myocardial infarction with subsequent coronary stents and congestive cardiac failure. He was a retired school caretaker and an ex-smoker of 100 pack years.

At presentation, blood tests showed a creatinine of 280 μm/L from a baseline of 140 μm/L. His medication included furosemide 40 milligram od, bisoprolol 5 milligram od, simvastatin 10 milligram od and omeprazole 20 milligram od.

Screening blood tests revealed a polyclonal raised serum IgG, type three cryoglobulinaemia, raised rheumatoid factor of 478 IU/ml (0–15) and low complement (C3 0.35 g/L (0.75–1.65), C4 <0.04 (0.14–0.54). Serum ANA, anti-dsDNA and ANCA were negative. Viral serology was negative including HIV, hepatitis B, C and syphilis. CMV IgG was detected with high avidity in keeping with infection within the previous three months. A renal tract ultrasound scan showed bilateral simple renal cysts with no calculi or hydronephrosis. A urine culture was positive for *Klebsiella* and was treated with a course of pivmecillinam. His urine was negative for Bence-Jones protein.

A renal biopsy was performed which included cores for routine light microscopy (LM), direct immunofluorescence (IF) and electron microscopy (EM); placed in 10 % phosphate buffered formalin, Michel's medium and 3% phosphate buffered glutaraldehyde respectively.

For histology, a 10 millimetre core of renal cortex was obtained. On LM there were four glomeruli present for examination. Some displayed lobular accentuation of their architecture along with mesangial proliferation and endocapillary hypercellularity in keeping with a focal membranoproliferative pattern (Figure 1). There were large numbers of neutrophil polymorphs within the glomeruli, with no hyaline or pseudo thrombi. On examination with a silver stain, there were no membranous spikes nor double contouring of the basement membrane. No amyloid deposition was identified on Sirius Red staining. The interstitium showed moderate patchy fibrosis with oedema and inflammation. The inflammatory infiltrate consisted of plasma cells, lymphocytes and occasional eosinophils. There was mild to moderate tubular atrophy within the scarred areas. There was a marked degree of tubular injury with occasional dilated profiles (Figure 2). The arteries had thickened walls with reduplication of the internal elastic lamina.

IF revealed deposition of IgG (+) IgM (+), C3 (++), Kappa (+) and Lamba (++) within the two examined glomeruli. There was no deposition of C1q or IgA.

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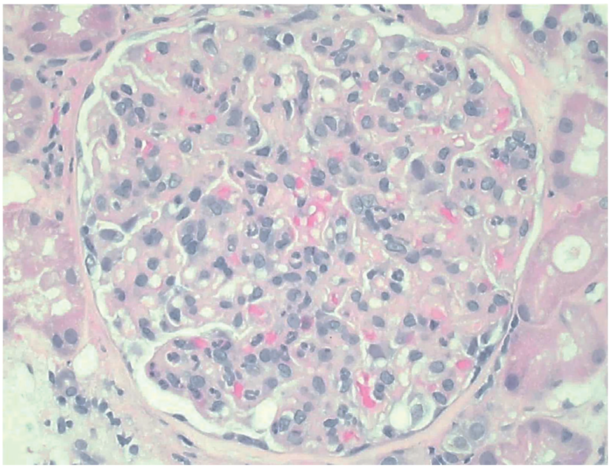

Figure 1 H&E of a representative glomerulus showing mild mesangial matrix expansion and membranoproliferative change with a mild acute proliferative infiltrate and mild accentuation of the lobular architecture.

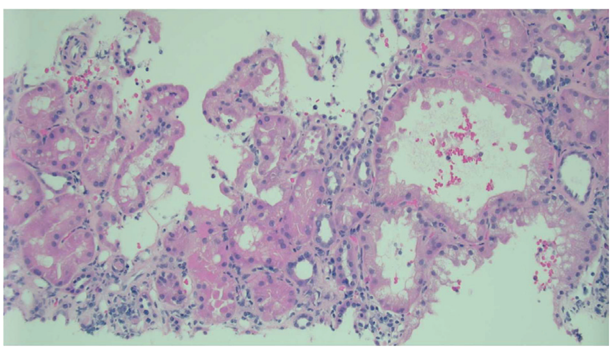

Figure 2 H&E of occasional convoluted tubule showing apical shedding and dilation.

For EM, a 4 millimetre core was obtained, the sections of which contained two glomeruli. These showed mild acute proliferative changes. The podocyte foot processes were moderately to severely effaced. The glomerular basement membrane was unremarkable (insofar as there were no epimembranous spikes, diabetic thickening, or collagen IV pathology related changes). Moderate numbers of small mesangial, small to large subendothelial and scattered medium sized subepithelial deposits were demonstrated (Figures 3–6). The substructure of the deposits were similar to those seen in fibrillary glomerulonephritis (mean 22 nanometre diameter fibrils, range 15–30 nanometre), measuring 22 nanometre in diameter and were curved/comma shaped. There were no endothelial tubuloreticular inclusions.

Discussion

There are a range of glomerular diseases characterised by non-amyloid organised deposits including: fibrillary glomerulonephritis, immunotactoid glomerulonephropathy, cryoglobulinaemic glomerulonephritis, collagenofibrotic glomerulopathy and fibronectin glomerulopathy.[1] The diagnosis of such glomerulopathies requires assessment by LM with Sirius/Congo red staining and IF studies. However, EM plays a vital role in identifying and categorising fibrils and microtubules based on their ultrastructure. Fibrillary glomerulonephritis is relatively

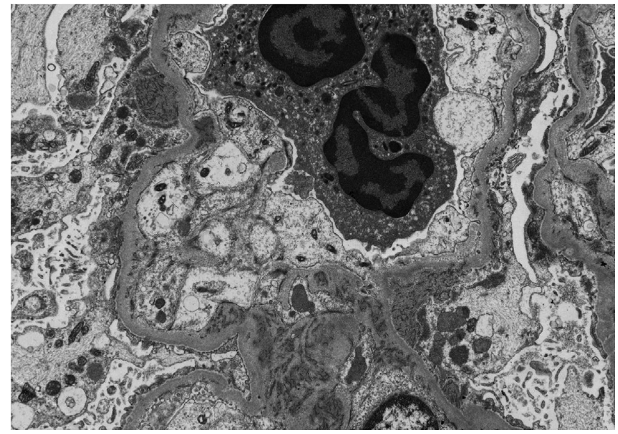

Figure 3 TEM of part of a capillary loop and mesangial area showing a neutrophil interacting with an endothelial cell showing loss of fenestration. There is a small subendothelial deposit at 9 o'clock with a closely associated mesangial cytoplasmic process. The GBM is normal thickness. There are 2 medium-sized subepithelial deposits at 4 and 11 o'clock and there are moderate numbers of small mesangial deposits at 6 o'clock. The podocyte foot processes are severely effaced.

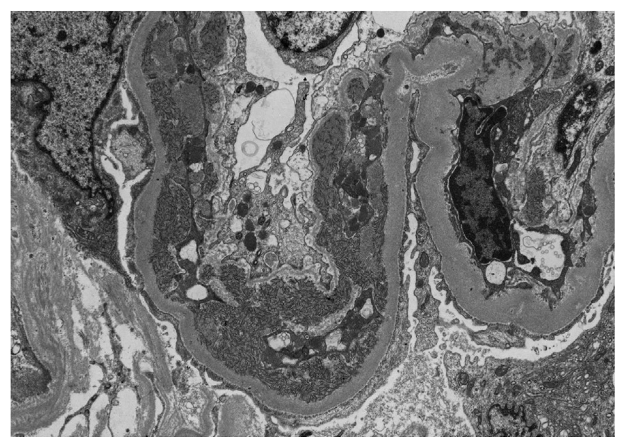

Figure 4 Large subendothelial deposits with interacting mesangial cell cytoplasmic processes and endothelial cells showing loss of fenestration. The podocyte foot processes are severely effaced.

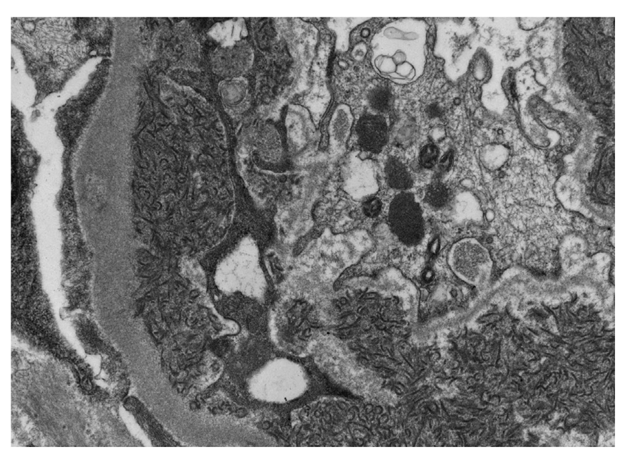

Figure 5 Higher magnification of figure 4 demonstrating the large number of curvilinear or comma shaped fibrils embedded within large subendothelial deposits.

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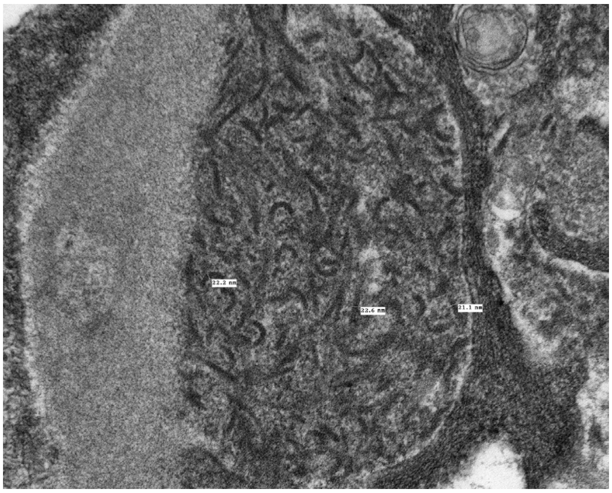

Figure 6 Higher magnification of figure 5 demonstrating diameter of the comma shaped fibrils.

rare, being diagnosed in 0.5%–1% of native kidney biopsies.[2] It is characterised by deposits of randomly distributed fibrils, larger in diameter than amyloid (mean 10 nanometre), that are IgG positive on IF. There are a spectrum of associated patterns including membranoproliferative, focal segmental sclerosing and crescentic.[2–4] Studies have shown an association with autoimmune disease, infection and malignancy.[3] Demonstration of coma-shaped fibrillary deposits has only been described in one case in the literature to the best of our knowledge,[5] where the patient was found to have a uterine malignancy.

The overall LM pattern of injury in our presented case was membranoproliferative, the most common change seen in glomeruli in fibrillary glomerulonephritis.[4] There was no evidence of cryoglobulinaemic glomerulonephritis in the biopsy despite detecting type three cryoglobulinaemia. This is a similar finding to that observed in the previously published case.[5] Changes typically associated with diabetic glomerulopathy were not identified.

In light of the association with malignancy, the clinical team went on to perform imaging investigations, however, to date no unifying diagnosis has been identified. ◆

REFERENCES

1. DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995. Record No. T921649, Glomerular Diseases Due to Nonamyloid Organized Deposits; [updated 2018 Dec 04].
2. Andeen NK, Troxell ML, Riazy M, et al. Fibrillary glomerulonephritis: clinicopathologic features and atypical cases from a multi-institutional cohort. *Clin J Am Soc Nephrol* 2019 Dec 6; **14:** 1741–50.
3. Payan Schober F, Jobson MA, Poulton CJ, et al. Clinical features and outcomes of a racially diverse population with fibrillary glomerulonephritis. *Am J Nephrol* 2017; **45:** 248–56.
4. Nasr SH, Valeri AM, Cornell LD, et al. Fibrillary glomerulonephritis: a report of 66 cases from a single institution. *Clin J Am Soc Nephrol* 2011 Apr; **6:** 775–84.
5. Stabellini N, Fabbian F, Sartori S, Tombesi P, Aleotti A. Fibrillary comma-shaped electron-dense organized glomerular deposits associated with cryoglobulinaemia. *NDT Plus* 2008 Jun; **1:** 182–3.
6. Nasr SH, Vrana JA, Dasari S, et al. DNAJB9 is a specific immunohistochemical marker for fibrillary glomerulonephritis. *Kidney Int Rep* 2017 Aug 8; **3:** 56–64.

Practice points

- A comprehensive examination of medical renal biopsies requires examination by light microscopy, immunofluorescence studies and electron microscopy
- Fibrillary glomerulonephritis is relatively rare and is characterised by the finding of fibrillary deposits on electron microscopy with a mean diameter of 22 nm
- Immunofluorescence typically shows IgG positivity and glomerular injury on light microscopy most commonly shows a membranoproliferative pattern
- Underlying malignancy, autoimmune disease or infection should be considered when a diagnosis of fibrillary glomerulonephritis is reached
- Fibrillary glomerulonephritis can be diagnosed immunohistochemically using DNAJB9 in cases whereby immunofluorescence shows IgG staining, but not if light chain staining is absent.[6] However, given the relative rarity of fibrillary GN, staining with DNAJB9 is not routinely applied. In many centres, electron microscopy is applied to all medical renal biopsies as it is a good catch-all technique.

Self-assessment questions

1. Which type diagnosis best fits with the following electron microscopy description: *there are large amounts of mesangial and subepithelial deposits of randomly arranged, straight 7–13 nanometre diameter filaments*

a. Diabetic glomerulonephropathy
b. Amyloidosis
c. Fibrillary glomerulonephritis
d. Membranous glomerulonephritis

Answer: B.

2. Which of the following diagnoses is NOT associated with a membranoproliferative pattern of glomerulonephritis

a. Dense deposit disease
b. Fibrillary glomerulonephritis
c. Lupus nephritis
d. Minimal change disease

Answer: D.

3. A patient presents with heavy proteinuria, hypoalbuminaemia and hyperlipidaemia. What glomerular clinical syndrome best characterises this presentation?

a. Nephritic syndrome
b. Nephrotic syndrome
c. Rapidly progressive glomerulonephritis

Answer: B.

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