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Teaching Point
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When the finding of glomerular fibrils in patients with nephrotic syndrome leads to an erroneous diagnosis

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Background

The finding of fibrils in the examination of renal biopsies by electron microscopy represents a very important clue for establishing a precise diagnosis [1–5]. This assertion is particularly important in patients with nephrotic syndrome (NS) or severe proteinuria, because most renal diseases characterized by the glomerular deposition of fibrils have proteinuria, generally in the nephrotic range, as the commonest clinical presentation. In this context, nephrologists and pathologists tend to automatically establish a causative link between the finding of fibrils in a particular patient with proteinuria and the aetiology of his/her renal disease. Nevertheless, some isolated studies have suggested that glomerular fibril deposition may be a nonspecific finding of unknown significance in some cases. Here we report on two cases that illustrate well how the finding of fibrils on electron microscopy can induce an erroneous diagnosis that only the final outcome of the patients (spontaneous resolution of the NS) helped to elucidate.

Case reports

Case 1

A 78-year-old woman presented with oedema and asthenia for 1 month. She had no previous medical problems with the exception of a transitory ischaemic attack some years ago. On examination, she was afebrile, her blood pressure was 125/80 mmHg and no remarkable findings were observed with the exception of important bilateral lower extremity oedema. In addition to a normal haemogram, the most important laboratory findings were as follows: serum creatinine 0.8 mg/dl (70.4 μmol/l), GFR (estimated by MDRD-4) 72 ml/min/1.73 m^2, total proteins 5.2 g/dl (52 g/l), serum albumin 1.8 g/dl (18 g/l), total cholesterol 550 mg/dl (14.2 mmol/l) and triglycerides 310 mg/dl (3.5 mmol/l). A massive proteinuria, ranging from 8 to 15 g/24 h, was detected. Serum and urine immunoelectrophoresis were normal, and tests for HCV, HBV and HIV were negative. Complement fractions were normal, and tests for antinuclear antibodies, anti-DNA antibodies and cryoglobulins negative. Both kidneys were normal on echographic examination. A percutaneous renal biopsy was performed, obtaining two small samples of renal tissue. Three out of 15 glomeruli (20%) were globally sclerotic. In the remainder, a mild expansion of extracellular mesangial matrix was observed. Isolated strips of inflammation and fibrosis were found in the interstitial tissue, and the vessels showed a moderate degree of nephrosclerosis. All these findings were considered as changes compatible with the patient's age and of no diagnostic significance. No material was available for immunofluorescence studies. On electron microscopy, a diffuse effacement of podocyte foot processes was found as well as a mild expansion of mesangial matrix. The glomerular basement membrane (GBM) had a normal thickness, and no electrondense deposits were found. A nonbranching fibrillar material, randomly arranged, was irregularly deposited in the mesangial matrix (Figure 1). The fibrils had a diameter of 10 nm. No fibrils were detected out of mesangial area. Congo red stain was negative.

On the basis of the finding of fibrillar deposits, a diagnosis of NS due to nonamyloid fibrillar glomerulopathy was made and the relatives were informed about the unfavourable prognosis of these diseases. Considering the patient's age, her relatives asked for a conservative management of the NS, avoiding a bone marrow biopsy and any other invasive procedure. The patient was treated with diuretics, statins and enalapril at low doses (2.5–5 mg/day), and her clinical condition, with lower limb oedema and nephrotic proteinuria, persisted for 3 months. Thereafter, proteinuria showed a slow but continuous decrease. Three

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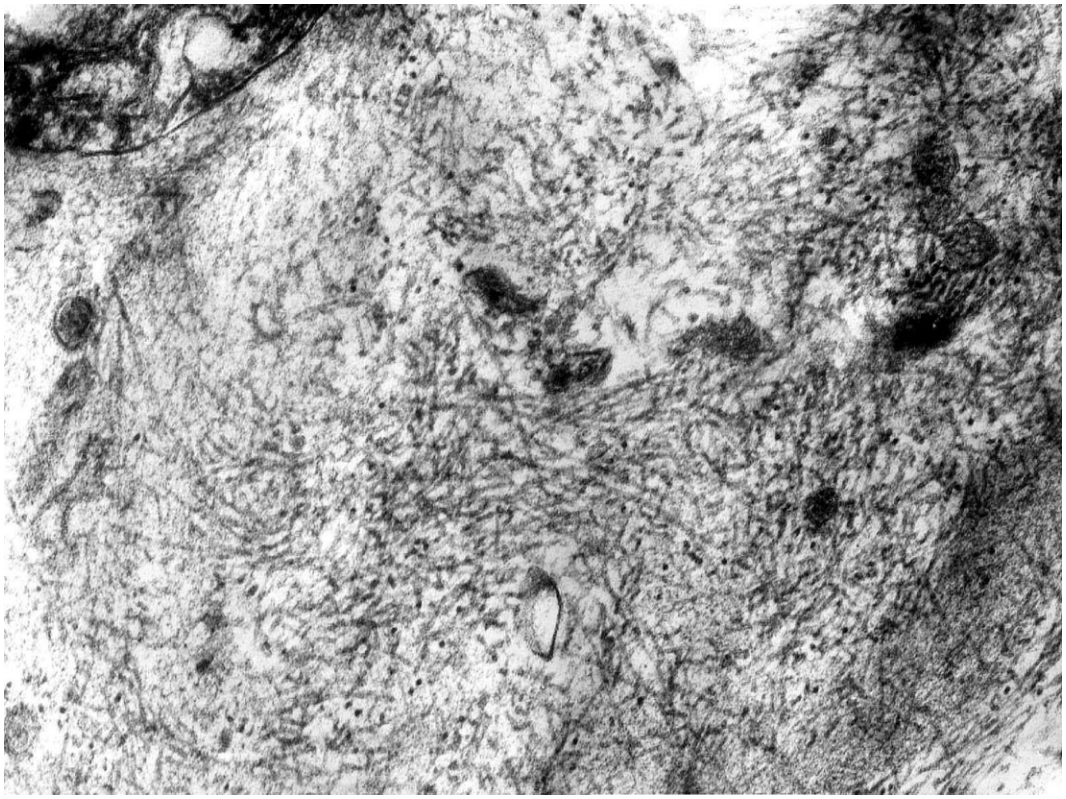

Fig. 1. First patient. Randomly arranged mesangial fibrils, 10 nm diameter, in the ultrastructural study of a renal biopsy.

months later proteinuria was <3.5 g/24 h, and 9 months after the performance of renal biopsy proteinuria ranged between 0.1 and 0.4 g/24 h, with a stable renal function. Treatment with statins and enalapril was maintained, and the patient remained asymptomatic, performing a visit to our outpatient clinic every 6 months.

Six years after the first episode, she noted again massive bilateral leg oedema. Laboratory evaluation showed nephrotic-range proteinuria ranging between 6 and 10 g/24 h, with serum creatinine of 0.9 mg/dl (79.2 μmol/l), hypoalbuminaemia, hypoproteinaemia and hypercholesterolaemia. Oral prednisone was started at a dose of 1 mg/kg/day. After 15 days of treatment, proteinuria started to decrease and a complete response (proteinuria <0.5 g/24 h) was obtained 3 weeks later. Prednisone was tapered off for 3 months. Proteinuria remained <0.5 g/24 h throughout the follow-up (1 year).

Case 2

A 75-year-old woman was admitted to our hospital because of progressive oedema for 3 months. Blood pressure was 115/68 mmHg, and physical examination showed bilateral lower extremity oedema as the only abnormal finding. Blood tests showed a normal haemogram, serum creatinine 0.9 mg/dl (79.2 2 μmol/l), GFR (MDRD-4) 86 ml/min/1.73 m^2, total proteins 4.9 g/dl (49 g/l), albumin 2 g/dl (20 g/l) and total cholesterol 351 mg/dl (9 mmol/l). Proteinuria ranged between 5 and 7.5 g/24 h. Serum and urine immunoelectrophoresis were normal as well as serum complement values. Tests for HCV, HBV, HIV, antinuclear and anti-DNA-antibodies and cryoglobulins were negative. Ultrasound examination showed that both kidneys had a normal morphology.

A renal biopsy revealed a mild expansion of mesangial matrix, and 4 out of 21 glomeruli (19%) were globally sclerosed. Mild tubulointerstitial fibrosis and vascular nephrosclerosis were found. No material was available for immunofluorescence studies. Electron microscopy demonstrated a diffuse effacement of podocyte foots and the presence of fibrillar deposits within extracellular mesangial matrix. Some isolated fibrillar deposits were also observed in the GBM. Fibrils were randomly arranged and nonbranching, with a diameter of 12 nm. Congo red stain was negative.

A tentative diagnosis of fibrillar glomerulopathy was considered, and the patient was discharged with diuretics, statins and low doses of an ACE inhibitor.

On the following months, a slow improvement of oedema and proteinuria reduction was observed. Six months after renal biopsy performance, proteinuria was <3.5 g/24 h and it continued to decrease very slowly during the following months. Twenty-four months after the renal biopsy, a complete remission of proteinuria (<0.2 g/24 h) was detected. The patient maintained a stable clinical condition, and 10 years after the onset of NS her serum creatinine is 0.66 mg/dl (58 μmol/l) and proteinuria 0.1 g/24 h.

Discussion

Amyloidosis, either primary (AL) or secondary (AA), is the most frequently diagnosed cause of fibrillar

Table 1. Differential diagnosis of fibrillary glomerulopathies

	Amyloidosis	Fibrillary GN	Immunotactoid GN	Collagenofibrotic GN	Fibronectin GN	Nonspecific fibrils
Fibril size	8–12 nm	12–20 nm	>30 nm	80–100 nm	10–20 nm	5–20 nm
Arrangement of fibrils	Random	Random	In bundles	In bundles	Random	Random or in bundles
Distribution of fibrils	Mesangium, GBM, subendothelium	Mesangium, GBM, subendothelium	Mesangium, GBM, subendothelium	Mesangium, subendothelium	Mesangium, Subendothelium	Mesangium (rarely in GBM)
Congo red and Thioflavine T	(+)	(−)	(−)	(−)	(−)	(−)
Immunoglobulin immunofluorescence	Primary forms, AL (+); secondary forms, AA (+)	IgG	IgG	(−)	(−)	(−)

glomerulopathy. NS is the commonest clinical presentation of renal amyloidosis and the prognosis unfavourable, with the exception of some patients with secondary amyloidosis in whom the inflammatory stimulus for AA fibril deposition can be removed [6]. Among fibrillary glomerulopathies other than amyloidosis, fibrillary and immunotactoid glomerulonephritis are the most commonly reported and investigated entities [1–5]. As in amyloidosis, severe proteinuria and NS are common and the prognosis is adverse, most of patients dying or starting chronic dialysis in a few months or years.

In addition to these entities, some rare hereditary renal diseases characterized by massive glomerular fibrillar deposits have been described, such as fibronectin and collagenofibrotic glomerulopathies [7,8]. In some patients with lupus nephritis and cryoglobulinaemia isolated fibrillar, deposits can be detected on ultrastructural studies.

The finding of fibrils in the ultrastructural studies of renal biopsies of patients with NS generally orientates the diagnosis to one of the above-referred diseases. A positive stain for Congo red and Thioflavine T is characteristic of amyloidosis, whereas the presence of glomerular deposits of IgG on immunofluorescence studies is the rule in fibrillary and immunotactoid glomerulopathies. On the other hand, the size and arrangement of fibrils show significant differences among these entities that are useful to establish a correct diagnosis (Table 1).

Our patients were very similar in their clinical presentation and histologic findings: two aged woman showing a complete NS with preserved renal function; unspecific age-related changes (sclerosed glomeruli, tubulointerstitial fibrosis, arteriolar sclerosis) and a mild mesangial matrix expansion were detected in both renal biopsies. The most striking and significative findings were obtained on ultrastructural studies: a diffuse effacement of podocyte foot processes accompanied by randomly arranged fibrillar deposits within the mesangial matrix and (in the second case) also within the GBM. No immunofluorescence studies were available. The size of fibrils (diameter 10–12 nm) was more compatible with amyloidosis than with other fibrillary diseases (Table 1). However, considering the Congo red negative stains, as well as the absence of either monoclonal paraproteins (very common in primary amyloidosis) or chronic infectious or inflammatory diseases as precipitating disorders for secondary amyloidosis, a tentative diagnosis of atypical fibrillar glomerulopathy was considered in both cases.

The clinical outcome, however, fortunately contradicted the dismal prognosis that patient's relatives received in both cases. A progressive and spontaneous resolution of the NS was observed, and proteinuria had almost completely disappeared 9 and 24 months, respectively, after the onset of NS. This unexpected outcome forced us to reconsider the diagnosis and, taking into account the diffuse fusion of podocyte foot processes observed in both cases, the possibility of a minimal change NS started to be seriously considered. Old clinical studies from the pre-steroid era had shown that children suffering from 'lipoid nephrosis' could attain a complete and spontaneous resolution after several months of oedema, although complications such as infections and thrombosis were common and the mortality rate was considerable [9,10]. To further confirm the possibility of minimal change disease, our first patient showed a second bout of NS 6 years after the first one and steroid therapy led to a rapid and complete resolution of NS. These clinical characteristics, both the relapse of NS and the rapid response to steroids, are typical of minimal change disease. Elderly patients presenting with NS due to minimal change disease frequently exhibit a slower response to steroids, and a higher rate of steroid resistance and of acute renal function worsening than the children suffering the disease [11]; otherwise, their clinical picture is very similar, including the possibility of spontaneous remission in the absence of steroid treatment. An important concept to keep in mind is that the histological diagnosis of minimal change disease (which is defined by a normal renal parenchyma on optical microscopy, negative immunofluorescence and effacement of podocyte foot processes on electron microscopy) can be hindered in elderly patients by the constant finding of arteriosclerosis, sclerosed glomeruli and tubulointerstitial fibrosis related with aging. In these cases, the presence of diffuse fusion of podocyte foot processes, although not specific for minimal change disease, represents a strong support for this diagnosis.

What interpretation could be given to the finding of glomerular fibrils in our patients?

In the absence of a second renal biopsy performed after the resolution of NS, the possibility of a NS pathogenically

related to glomerular fibrillar deposition cannot be completely ruled out. However, no spontaneous remissions have been reported in NS caused by amyloidosis, fibrillary or immunotactoid glomerulopathies and this possibility appears thus very unlikely. Another way of interpretation offers a more attractive explanation for our cases: some studies have reported that glomerular fibrils of 5–20 nm may be seen in renal biopsies of patients affected by different types of glomerulopathies, including diabetic nephropathy, crescentic and membranoproliferative glomerulonephritis, focal and segmental glomerulosclerosis, IgA nephropathy, transplant glomerulopathy, preeclampsia and malignant hypertension [12–14]. In one of these studies, Kronz and collaborators [14] showed that the finding of these nonspecific fibrils might be relatively frequent (3% of renal biopsies examined by electron microscopy in the experience of these authors). In comparison with true fibrillary glomerulopathy (Table 1), localization of nonspecific fibrils was restricted to the mesangium (only rarely GBM was involved) and fibrils were thinner and arranged in bundles or in a random disposition. Other important differences were the number and distribution of fibrils (diffuse in fibrillary glomerulonephritis and segmentally distributed in nonspecific cases) and the immunofluorescence studies (strongly positive for IgG in the former and usually negative in the later). However, as the authors remark, to differentiate nonspecific fibrillar deposits from true fibrillar glomerulopathies may be difficult [14].

The finding of nonspecific fibrils in the renal biopsies of diabetic patients has been termed 'diabetic fibrillosis' [12]. A recent study [15] has reported the presence of fibrils in the ultrastructural studies of 72 out of 149 renal biopsies obtained in diabetic patients. These fibrils were composed of islet amyloid polypeptide, also known as amylin, a type of fibrillar deposits that are also found in pancreatic islets. The fibrils were located in the expanded mesangial matrix of some glomeruli and their pathological characteristics were very similar to the nonspecific fibrils described by Kronz *et al*. [14,15]. Interestingly, in this study amylin fibrils were also found in 12.5% of renal biopsies of patients with obesity-related glomerulopathy [15]. As far as we know, no studies have investigated if aging-related pathological changes in renal parenchyma are accompanied by fibrillar deposits, composed by amylin or other constituents.

To summarize, we believe that our patients had a NS due to minimal change disease. The finding of nonspecific fibrils induced an erroneous diagnostic of fibrillary glomerulopathy, and the patients were not treated with steroids. However, as reported in patients with minimal change NS in the pre-steroid era, our patients developed a spontaneous remission of NS after several months of follow-up. More investigation is needed about the presence, composition and significance of nonspecific fibrillar deposits in patients with glomerular diseases and in the elderly.

Teaching points

These cases highlights the following important teaching points:

(1) The presence of fibrillar deposits in ultrastructural studies of renal biopsies may be a nonspecific finding of unknown significance.
(2) The finding of such nonspecific fibrillar deposits in patients with NS may induce an erroneous diagnosis of fibrillary glomerulopathy. A careful differential diagnosis between true fibrillary glomerulopathies and nonspecific fibrillar deposits should be performed in every case.
(3) The diagnosis of minimal change disease in the elderly may be hinder by the constant presence of age-related pathological findings (sclerosed glomeruli, tubulointerstitial fibrosis, vessel atherosclerotic changes).
(4) Patients with minimal change disease not treated with steroids may exhibit a complete resolution of NS within a variable period of time.

Conflict of interest statement. None declared.

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