CASE REPORT

Rare diagnosis in a patient with diabetes with nephrotic proteinuria

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SUMMARY

We report a 63-year-old man with well-controlled type 2 diabetes mellitus and hypertension, who presented with new onset nephrotic proteinuria and rapid deterioration in renal function. The atypical clinical presentation prompted us to consider a non-diabetic and non-hypertensive cause and to perform a renal biopsy. A diagnosis of fibrillarglomerulonephritis (FGn) was made based on electronic microscopy. Proteinuria remained in nephrotic range despite treatment with prednisolone, and renal function deteriorated. We suggest that other causes of proteinuria should be considered in patients with diabetes who present with the nephrotic syndrome when there is no other evidence of microvascular disease. We review the spectrum of fibrillar glomerulopathies including FGn, primary and secondary amyloidosis and immunotactoid glomerulonephritis.

BACKGROUND

The development of proteinuria and renal function deterioration in a patient with diabetes usually suggests diabetic nephropathy. Nevertheless, other causes should be considered when clinical or laboratory findings are atypical. We report a rare case of fibrillar glomerulonephritis (FGn) in a patient with diabetes without diabetic retinopathy, who presented with new onset proteinuria and rapid renal function deterioration.

FGn is a rare primary glomerular disease found in 1% of native kidney biopsies.[1] It usually develops at middle or older age and clinical findings include proteinuria, which often reaches the nephrotic range. It is characterised by the presence of ultrastructural randomly arranged fibrils measuring approximately 10–30 nm in diameter by electron microscopy (EM). These fibrils are Congo red negative, which distinguishes it from amyloid. Although most cases are idiopathic, the association with underlying malignancy, dysproteinaemia or autoimmune diseases is increasingly recognised and must be excluded. Prognosis is poor, often progressing to end-stage renal disease within a few years.

CASE PRESENTATION

A 63-year-old man attended to his scheduled 6 monthly outpatient visit for renal function monitoring on December 2016. Besides peripheral oedema and non-controlled hypertension (160/80 mm Hg), physical examination was unremarkable and the patient was asymptomatic. He was first referred to our department 3 years before for renal dysfunction with serum creatinine (Scr) of 2.2 mg/dL (glomerular filtration rate (GFR) of 32.3 mL/min/1.73 m^2, using the modification of diet in renal disease equation (MDRD)). His medical history was relevant for type 2 diabetes mellitus diagnosed in 2013, without microvascular complications, especially no diabetic retinopathy; arterial hypertension diagnosed in 2012 and treated since then; left carotid endarterectomy in 2010; and Wolff-Parkinson-White syndrome submitted to ablation in 2006. The initial laboratory workout showed normal urinalysis with 24 hours protein excretion <1 g and normal renal ultrasound. Over the next years, his glycaemia and blood pressure were well controlled, and renal function remained stable. Current medication included atorvastatin, allopurinol, rilmenidine, telmisartan, lercanidipine, furosemide, aspirin and insulin (started in 2016).

INVESTIGATIONS

Laboratorial findings were remarkable for new onset of nephrotic proteinuria (10 g/24 hours), microscopic haematuria with erythrocyte casts in urinalysis and decreased renal function (Scr 3.2 mg/dL, GFR 20 mL/min/1.73 m^2 according to MDRD). Haemoglobin (140 g/L), white blood cell and platelet count were normal. Serum albumin was normal (3.7 g/dL). Mixed dyslipidaemia was founded, with elevated total cholesterol (300 mg/dL), low high density lipoprotein (36 mg/dL) and elevated triglycerides (394 mg/dL). Hemoglobin A1c test was 7.7%. Both serum and urinary protein electrophoresis were normal and no monoclonal component was detected. Serum-free light chains, complement compounds (C3 and C4), ANA, anti-ds DNA, rheumatoid factor, cryoglobulins, soluble urokinase plasminogen activator receptor and antibody antiphospholipase A2 receptor were all normal. Blood and urine cultures were negative. Hepatitis B surface antigen, anti-hepatitis C virus and anti-HIV 1/2 antibodies were negative.

The clinical condition of a sudden increase in proteinuria, renal function deterioration and absence of microvascular complications (retinopathy), turns diabetic nephropathy an unlikely cause of renal disease. Therefore, a kidney biopsy was performed. A total of nine glomeruli were obtained: three showed global sclerosis and one had ischaemic appearance; five glomeruli showed increased mesangial matrix with an amorphous 'fibrillar-like aspect' material in the mesangium that was negative for silver stain. No cell proliferation was seen, and capillary walls were not thickened (figure 1).

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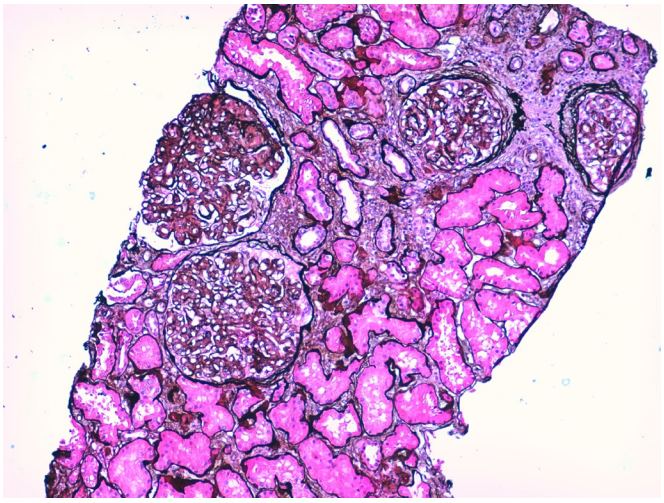

Figure 1 Hypertrophic glomeruli with diffuse mesangial expansion by an amorphous material negative for silver stain; no cell proliferation; normal capillary walls; tubular atrophy and interstitial fibrosis are present. Jones silver staining (x100).

Tubular atrophy and interstitial fibrosis were presented in 40 per cent of renal parenchyma. No vascular lesions were documented. Congo red staining was negative. Immunofluorescence in frozen section demonstrated mesangial and capillary staining with C3 (+), IgG (+++), kappa (+++) and lambda (+/+++). EM revealed electron-dense deposits of bundles of non-branching, randomly arranged fibrils (figure 2). The histological findings on EM confirmed the diagnosis of FGn. To exclude secondary causes associated with FGn, namely malignancies, a thoracoabdominopelvic CT was performed showing no alterations. Serum prostate-specific antigen and thyroid function were normal.

TREATMENT

Angiotensin II receptor blocker dose was titrated to the maximum tolerated dose. Supposing a primary cause for FGn, immunosuppressive therapy with prednisolone (1 mg/kg/day) was started. However, steroids were tapered 1 month later because proteinuria remained in nephrotic range (13 g/24 hours) and renal function degraded (Scr 4 mg/dL, GFR 11 mL/min/1.73 m^2 according to MDRD).

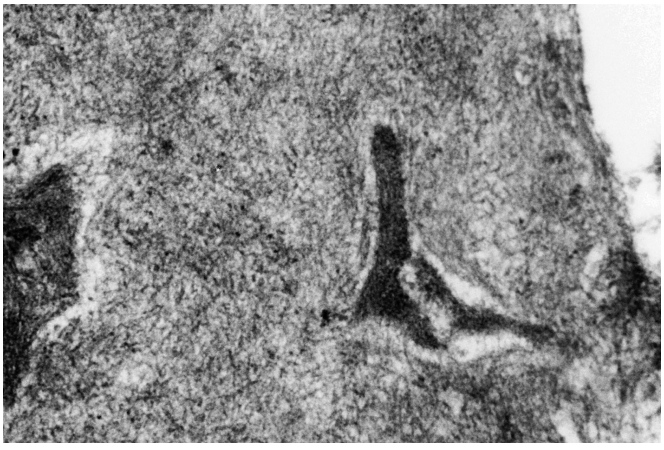

Figure 2 Electron microscopy showing randomly arranged fibrils deposited in mesangial areas and along glomerular basal membrane (x20 000).

OUTCOME AND FOLLOW-UP

He was referred to vascular access creation and renal transplant evaluation.

DISCUSSION

The development of diabetic nephropathy is usually a gradual and progressive process that takes years. Diagnosis is based in a composite of clinical criteria: persistently high urinary-albumin excretion in a patient with diabetes duration >7–10 years with evidence of microvascular complications such as diabetic retinopathy.[2]

In our patient, the sudden increase in proteinuria, rapid decrease in renal function and absence of diabetic retinopathy rendered diabetic nephropathy less likely. While haematuria may be present in diabetic nephropathy, the identification of red cell casts is suggestive of glomerulonephritis. A negative serological and immunological workup prompted the performance of a renal biopsy, confirming the diagnoses.

FGn is a rare glomerular disease, more common in Caucasians, with a peak incidence between the fifth and sixth decades of life and with a male-to-female ratio of 1:1.2–1.8.[1]

The clinical presentation does not distinguish FGn from other causes of proteinuria and nephrotic syndrome. Symptoms are usually non-specific and most patients present with nephrotic-range proteinuria with or without renal insufficiency, hypertension and haematuria.[3 4] Nephrotic syndrome can be seen in one-third of cases.[4]

The pathogenesis of FGn is not clearly understood. A recent single-centre retrospective study of 66 patients with FGn found an association with malignancy, dysproteinaemia or autoimmune disease in 23, 17% and 15% of cases, respectively.[4] Interestingly, the same study showed that diabetes mellitus was a coexistent condition found in 20% of patients. In our patient, both serum and urinary protein electrophoresis were normal and no monoclonal component was detected. Laboratorial studies for autoimmune diseases were negative and no solid malignancy was found.

FGn belongs to a heterogeneous group of glomerular diseases characterised by organised deposits with structural appearance of fibrils or microtubules in glomeruli.[5–8] These disorders have similar morphological features by light microscopy but differ in their clinical and ultrastructural characteristics.

The light microscopic findings associated with FGn are diverse and non-diagnostic, showing patterns similar to those seen in other glomerulopathies.[9] The most frequently encountered pattern is membranoproliferative (44%), and the less frequently observed are mesangial proliferative (21%), diffuse endocapillary proliferative (15%), membranous (7%) and sclerosing patterns of injury (13%).[9 10] Crescents are a relatively uncommon finding, seen in 20% of cases.[1] Likewise, immunofluorescence is non-specific and is usually positive for IgG, C3 and both kappa and lambda chains.[11] Definitive diagnosis is based on EM, which reveals the nature of the glomerular deposits: they consist of randomly arranged fibrils, measuring approximately 10–30 nm in diameter, deposited in the mesangium, glomerular membrane basement or both.[4] These fibrils are Congo red negative which, along with fibrils size, distinguishes FGn from amyloid.

Immunotactoid glomerulopathy is characterised by the presence of microtubules, often measuring >30 nm in diameter that are arranged in parallel. Some authors consider FGn and immunotactoid glomerulopathy as a single entity with differences in morphological spectrum, whereas others

Table 1 Immunological and clinical features of amyloidosis, fibrillar and immunotactoid glomerulopathies

	Amyloidosis			
	Primary (amyloid light-chain (AL))	Secondary (amyloid A protein (AA))	Fibrillar glomerulonephritis (FGn)	Immunotactoid glomerulopathy
Composition	Fibrils	Fibrils	Fibrils	Microtubules
Fibril or microtubule size (nm)	8–12 nm	8–12 nm	12–24 (most often 18–20)	Typically>30
Arrangement of fibrils or microtubules in tissue	Random	Random	Random	Organised in parallel arrays
Congo red staining	+	+	–	–
Ig deposition	Monoclonal light chains	–	Usually polyclonal; occasionally oligoclonal or monoclonal IgG; 3%–5% have light chain restriction	Usually monoclonal or oligoclonal IgG; 60%–70% have light chain restriction, usually kappa
AA deposition	–	+	–	–
Association with lymphoplasmatic disorders	Yes	No	Uncommon	Common
Treatment	Chemotherapy±bone marrow transplantation	Variable (dependent of the cause)	No known established therapeutic regimens; various immunosupressive drugs tried with variable results	No known established therapeutic regimens; treatment of the associated lymphoproliferative disorder if present
Prognosis	Patient and renal prognosis are variable but generally poor	Variable (dependent of the cause)	40%–50% progression to end-stage renal disease within 2–4 years	Probably better than FGn
Recurrence after renal transplantation	10%–20%; graft failure in 33%	Variable (dependent of the cause)	35%–50%, but usually with a more benign course	~50%, but usually with a more benign course
Incidence	Most commom renal amyloidosis in USA/western hemisphere	Higher in non- developed countries (chronic infections)	Rare (found in <1% of native renal biopsies)	Very rare (found in <0.1% of native renal biopsies)

consider them to be a separated disease. More important than this classification issue is to recognise that both entities should be morphologically distinguished from amyloidosis and these morphological patterns have important clinical considerations that should be evaluated in affected patients.[12] Table 1 summarises the main clinicopathological features that distinguish FGn from amyloidosis and immunotactoid glomerulonephritis.

In our patient, light microscopy showed mesangial expansion with an amorphous Congo red negative material and immunofluorescence demonstrated mesangial staining with C3, IgG and both kappa and lambda. Although these features are according to the diagnosis of FGn, the definitive diagnosis was only possible with EM findings of electron-dense deposits organised in bundles of non-branching randomly arranged fibrils.

To date, there is no proven effective therapy for FGn and most patients are treated with renin–angiotensin system blockers, alone or in combination with steroids or other immunosuppressive agents, such as rituximab. However, results are generally unsatisfactory with 50% of patients progressing to end-stage renal disease within a few years after diagnosis despite therapy.[4 9] In our patient, treatment with steroids was attempted with unsatisfactory results. Nasr *et al* identified older age, degree of proteinuria, Scr at diagnosis and higher percentage of globally sclerotic glomeruli as independent markers for rapid disease progression.[4] Our patient presented a high degree of proteinuria, an elevated Scr at biopsy and global sclerosis of 1/3 of sampled glomeruli.

Patients with FGn and end-stage renal disease may be offered renal transplantation. Recurrence rate in allograft may be as high as 50%, although recurring disease seems to have a relatively more benign course after transplantation.[13 14]

Learning points

- Fibrillar glomerulonephritis is a rare primary glomerular disease with poor prognosis. It belongs to a group of fibrillar glomerular diseases that includes amyloidosis and immunotactoid glomerulopathy.
- Most patients present with nephrotic-range proteinuria with or without renal insufficiency, hypertension and haematuria.
- Definitive diagnosis is based on electron microscopy findings of randomly arranged fibrils measuring approximately 10–30 nm in diameter.
- Causes other than diabetic nephropathy should be considered in patients with diabetes with new onset of nephrotic proteinuria when there is no evidence of microvascular disease.

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