Netherlands
The Journal of Medicine

CASE REPORT

# Fibrillary glomerulonephritis in a patient with type 2 diabetes mellitus

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## ABSTRACT

**We report a 62-year-old man with documented type 2 diabetes mellitus and hypertension, who presented with a rapid deterioration in renal function. The sudden decrease in renal function in this well-controlled diabetic patient prompted us to consider a nondiabetic and nonhypertensive cause. The urinary sediment showed a glomerular haematuria suggestive of glomerulonephritis. A diagnosis of fibrillary glomerulonephritis was made on renal biopsy. Fibrillary glomerulonephritis is a rarely diagnosed disease with clinical manifestations such as proteinuria, microscopic haematuria, nephrotic syndrome and impairment of renal function. A diagnosis of fibrillary glomerulonephritis can only be made by electronmicroscopy of the renal tissue. In this case report the spectrum of this disease is reviewed.**

## KEYWORDS

Fibrillary glomerulonephritis, diabetes mellitus, fibrillary glomerulopathy

## INTRODUCTION

The development of proteinuria and deterioration in renal function in a patient with diabetes mellitus and hypertension usually suggests diabetic nephropathy. However, other causes of renal failure should also be considered. In this report we present a case of fibrillary glomerulonephritis, a rare form of immunoglobulin deposit glomerulopathy, in a patient with diabetes. Our patient illustrates that other causes of proteinuria must be carefully considered, also in patients with diabetes. Furthermore, we discuss the entity of-fibrillary glomerulonephritis.

## CASE REPORT

A 62-year-old male appeared at his scheduled six-monthly outpatient visit for monitoring of his diabetes mellitus and hypertension. He reported nonspecific tiredness for about three weeks. There was no gross haematuria, no dysuria and no fever. The relevant medical history revealed diabetes mellitus type 2 since 1979, necessitating insulin treatment since 1998; a coronary artery bypass graft in 1986; a nephrectomy in 1992 because of a complicated pyelonephritis; hypertension diagnosed in 1992 and treated since then. There was no evidence of microvascular complications of the diabetes, specifically there was no diabetic retinopathy. The patient was treated with a basal/prandial insulin regimen. Additional medical treatment consisted of phenprocoumon, bisoprolol, quinapril, pravastatin, ranitidine and transdermal nitroglycerine. Over the past years his blood pressure had been well controlled, values averaging 150/70 mmHg, and renal function had been stable with serum creatinine values ranging from 110 to 130 μmol/l. On presentation, the physical examination was unremarkable, except for a blood pressure of 174/98 mmHg. Laboratory testing revealed renal insufficiency, with a serum creatinine amounting to 284 μmol/l, implicating a creatinine clearance of 27 ml/min. The HbA1c was 7.2%. Proteinuria averaged 2.2 g/24 hours. Because of the rapid deterioration in the renal function, the sudden increase in proteinuria (*figure 1*) and the absence of microvascular complications (retinopathy), diabetic nephropathy was considered an unlikely cause. The presentation was not compatible with secondary focal glomerulosclerosis either, due to hyperfiltration injury in a single kidney. Therefore, other causes were considered. Microscopic examination of the urine sediment showed red cells (84% dysmorphic, 16% monomorphic), granular casts and red cell casts. This finding is suggestive of a glomerular disease. Tests for antinuclear antibodies,

antibodies to extractable nuclear antigens, antineutrophil cytoplasmic antibodies, cryoglobulins, antiglomerular basement membrane antibodies, antistreptolysin-O titre and complement consumption were all negative. Immunofixation did not reveal an M-protein in the serum and there were no immunoglobulin light chains in the urine. Because of the fact that the patient had a single kidney, a renal biopsy was initially not performed and the patient was treated with a short course of high-dose prednisone. However, because of further deterioration in renal function a renal biopsy was done to obtain a diagnosis.

The biopsy (*figures 2 to 4*) contained on average 12 glomeruli per cross section, of which approximately 30% showed abnormalities. There was segmental endocapillary hypercellularity with both mononuclear cells and neutrophils. Mesangial areas and the glomerular basement membrane mostly appeared unremarkable, although at high magnification a 'moth eaten' appearance of the mesangium and glomerular basement membrane was seen. Immunofluorescence (IF) revealed deposits of IgG, C3, C1q, kappa and lambda light chains, mostly in the mesangium with some involvement of the peripheral capillary walls as well. The depositions were homogeneous rather than granular in nature. Electron microscopy revealed the presence of straight fibrils measuring approximately 20 nm in diameter in mesangial areas, subendothelially and within the glomerular basement membrane. On the basis of these findings we diagnosed a focal segmental endocapillary proliferative glomerulonephritis with deposition of polyclonal IgG in the form of 20 nm wide fibrils, consistent with fibrillary glomerulonephritis.

Because of further deterioration in the renal function, the patient became dependent on haemodialysis and is currently awaiting renal transplantation.

**Figure 1.** *Course of renal function (expressed as 1000/serum creatinine) and urinary albumin excretion (expressed as mg albumin/mmol creatinine) in the patient*

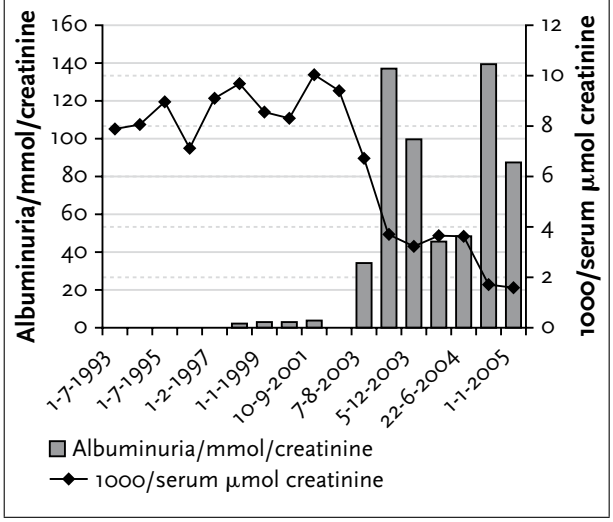
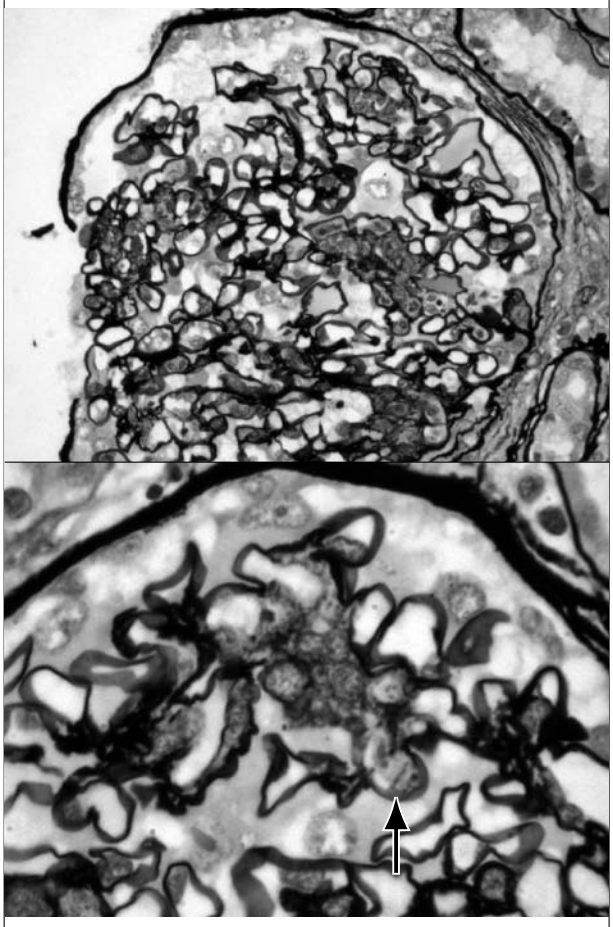



**Figure 2.** *Light microscopy, methenamine silver staining*



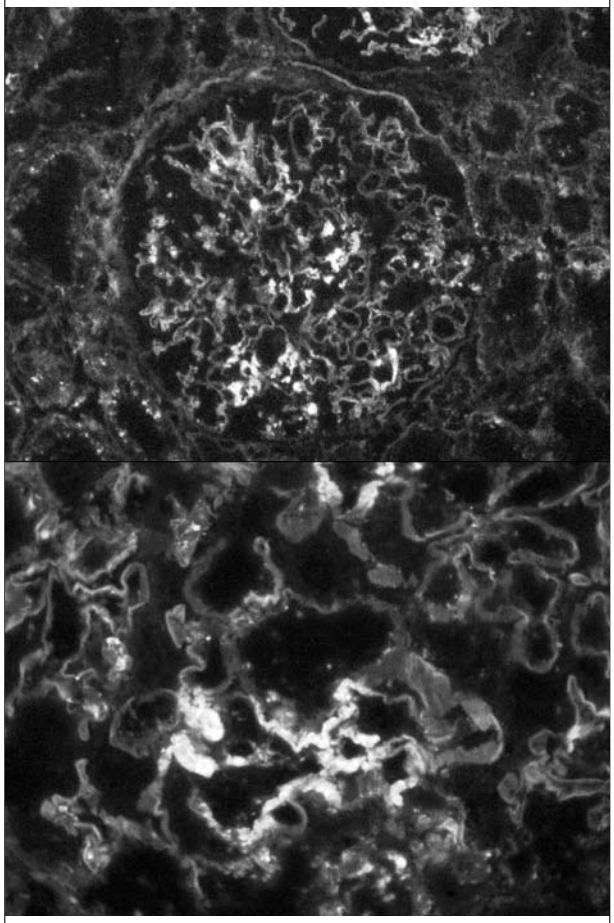
**There is segmental endocapillary hypercellularity with mononuclear cells and neutrophils and some mesangiolysis. At high magnification a lucent ('moth eaten') appearance of the mesangium can be appreciated. Also the glomerular basement membrane appears locally thickened and structurally altered (arrow).**

## DISCUSSION

Progression from microalbuminuria to overt nephropathy occurs in 20 to 40% of Caucasian patients with type 2 diabetes within a ten-year period.[1-3] Diabetic nephropathy typically begins with the urinary excretion of small amounts of protein (microalbuminuria). Although microalbuminuria may sometimes be temporary,[4] it often heralds the development of overt diabetic nephropathy, characterised by a slowly increasing proteinuria and a gradual deterioration of renal function. This process may take many years. Most patients with diabetic nephropathy have evidence of other microvascular complications such as diabetic retinopathy.

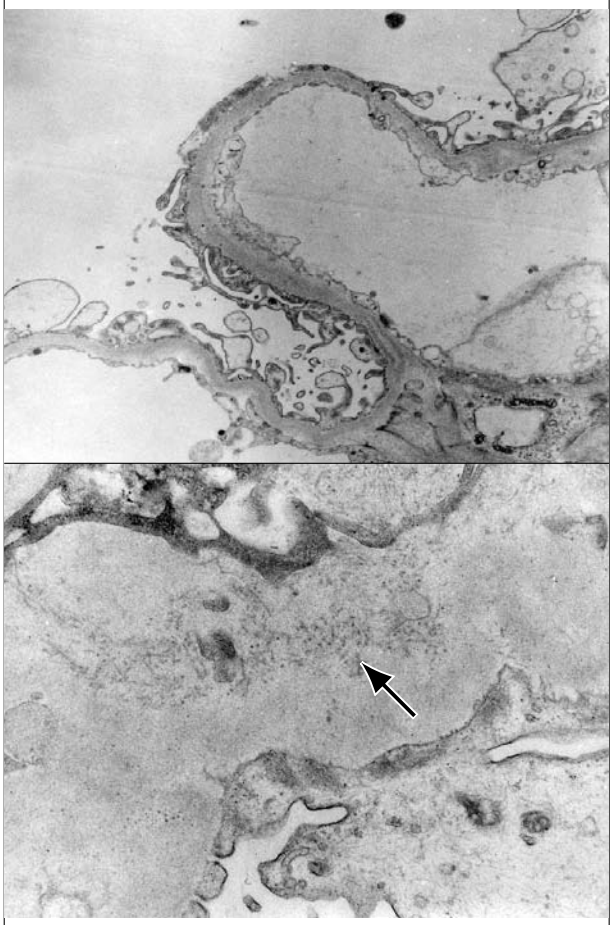
In our patient several points argued against a diagnosis of diabetic nephropathy, specifically the rapid deterioration in renal function, the sudden increase in proteinuria

**Figure 3.** *Immunofluorescence, staining for IgG*



**There are discontinuous areas with homogeneous staining for IgG. On higher magnifications IgG is located mainly in mesangial areas with some extension into the peripheral capillary walls as well.**

**Figure 4.** *Electronmicroscopy*



**A glomerular segment with variation in the thickness of the glomerular basement membrane is shown. The glomerular basement membrane appears structurally abnormal and high magnification shows the presence of 20 nm wide straight fibrils located within the glomerular basement membrane (arrow). These fibrils were also seen in the mesangium. There is podocyte swelling with focal foot process effacement. There also is mild endothelial swelling with some subendothelial lucency.**

and the absence of diabetic retinopathy. Secondary focal glomerulosclerosis in a hyperfiltrating single kidney must be considered; however, in such cases patients develop proteinuria well before the onset of renal function deterioration.

Although a significant haematuria with red cell casts may be a clinical feature of diabetic nephropathy,[5] the active urinary sediment with dysmorphic erythrocytes and erythrocyte casts in this case suggested the presence of a second, unrelated form of glomerulonephritis.[6] In the diagnostic work-up positive autoimmune serology may help to narrow the differential diagnosis prior to renal biopsy. In our patient the serological findings were negative and the suspicion of a glomerular disease was ultimately confirmed by renal biopsy, which showed fibrillary glomerulonephritis. Performing a renal biopsy in a patient with a solitary kidney is not routinely done and deserves some comments. The presence of a single kidney is still a relative contraindication for performing a renal biopsy, even though the number of serious complications from renal biopsy has decreased in recent years with the use of ultrasound guidance and an automated biopsy gun. Therefore, we first attempted to induce remission with a short course of prednisone. Since the patient did not respond the necessity of a diagnostic procedure was discussed. Important aspects were the risks of a biopsy, the risks of prolonged and more intensive immunosuppressive therapy, and the likelihood of diagnosing a treatable disease such as membranous nephropathy, focal glomerulosclerosis or amyloidosis. In this diabetic patient the balance in our view was in favour of the renal biopsy.

Fibrillary glomerulonephritis is a glomerular disease that belongs to the class of the fibrillary glomerulopathies, a heterogeneous group of glomerular diseases characterised by the presence in the glomeruli of organised deposits with the structural appearance of fibrils or microtubules.[7-10]

The deposits in fibrillary glomerulonephritis are immunoglobulin derived, either polyclonal or monoclonal. These organised structures cannot be recognised by light microscopy, thus a diagnosis of fibrillary glomerulopathy can only be made with certainty if renal tissue is appropriately examined by electron microscopy. The light microscopic findings associated with fibrillary glomerulonephritis are quite diverse.[11] The most frequently encountered is a membranoproliferative pattern of injury (44%), less frequently observed are mesangial proliferative (21%), diffuse endocapillary proliferative (15%), membranous (7%) and sclerosing patterns of injury (13%). Most patients present with haematuria (60%), renal insufficiency (72%) and proteinuria (in all patients, with 52 % in the nephrotic range).

The literature has proposed various classifications or algorithms for the diagnosis of the fibrillary glomerulopathies.[9] Often, these schemes seem rather confusing, because they incorporate clinical and laboratory data. We provide an overview of the fibrillary glomerulopathies in *table 1*, and discern three major classes: deposition in the form of amyloid, the immunoglobulin derived nonamyloid fibrillary glomerulopathies and the nonimmunoglobulin derived fibrillary glomerulopathies. A diagnosis of fibrillary glomerulonephritis is thus made if Congo-Red negative immunoglobulin-derived deposits are present in the glomerulus in the absence of evidence of systemic diseases such as SLE, multiple myeloma or cryoglobulinaemia. Immunotactoid glomerulopathy is a special form of fibrillary glomerulonephritis, characterised

**Table 1.** *Overview of glomerular diseases characterised by the presence of organised glomerular deposits (fibrillary glomerulopathies)*[a]

| | Congo red staining | IF (IgG)[b] | IF light chain restriction | Electronmicroscopy | Remarks |
|---|---|---|---|---|---|
| *Amyloidosis* | | | | | |
| AL amyloidosis | + | - | + (not always)[c] | Nonbranching fibrils 8-10 nm | Localisation: mesangial, subendothelial, in the GBM |
| AA amyloidosis | + | - | - | Idem | Idem |
| Other | + | - | - | Idem | Idem |
| *Immunoglobulin derived* | | | | | |
| SLE | - | + | - | Organised deposits, with substructures with the appearance of curvilinear fibrils 8-15 nm | Deposits give impression of 'fingerprint', deposits can also be localised subepithelially; SLE is a clinical diagnosis based on ARA criteria |
| Cryoglobulinaemia | - | + | + or - | Organised deposits with variable structural organisation, fibrils, tubules, grid-like, 6-62 nm | Typical is presence of cryoglobulin thrombi in the capillary lumina; cryoglobulinaemia is not always detected |
| Fibrillary gn | - | + | 3-5% + | Nonbranching fibrils 12-24 nm | Localisation: see amyloid |
| Immunotactoid gn | - | + | 60-70% + | Microtubules > 30 nm | Localisation: see amyloid |
| M-protein related to clinical evidence of systemic disease | - | + | + | Variable structures as described for cryoglobulins LCDD is characterised by electron-dense granular deposits | Often classified based on clinical diagnosis (CLL, MM). Difficult to differentiate from cryoglobulinaemia and immunotactoid gn. M-protein related glomerular disease better description? |
| *Non-immunoglobulin derived* | | | | | |
| Fibronectin gn | - | - | - | Mostly amorphous deposits, with sometimes irregular fibrils 10-12 nm | Fibronectin + |
| Collagen III gn | - | - | - | Striated bundles with periodicity of 60 nm, giving striped appearance | Typical collagen bundles easily recognised by electron microscopy. Collagen III + |
| Diabetes mellitus | - | - | - | 10-120 nm | Localised in mesangium |

**[a]There is no uniform definition of fibrils in the literature. Most authors include diseases characterised by organised deposits that do not contain fibrils. [b]In M-protein related diseases the heavy chain is predominantly IgG, but it may be of another class (IgA, IgM) and in SLE there is usually a 'full house'. [c]Amyloid is composed of the variable part of the light chains, which does not contain the antigens recognised by the commercial antibodies. SLE = systemic lupus erythematosus; IF = immunofluorescence; LCDD = light chain deposition disease; gn = glomerulonephritis; CLL = chronic lymphatic leukaemia; MM = multiple myeloma; GBM = glomerular basement membrane; ARA = American Rheumatoid Association.**

by the presence of microtubules that are arranged in parallel, with a hollow centre at high-power magnification, and a diameter of more than 30 nm. Overlap, however, does occur. Some authors consider fibrillary glomerulonephritis and immunotactoid glomerulopathy as a single entity with differences in the morphological spectrum, whereas others consider them to be a separate disease characterised by the size and organisation of the fibrils.

The presence of a monoclonal protein (M-protein) in the kidney as detected by IF should be used as an important criterion for further classification of fibrillary glomerulopathies. It is well known that in up to 20% of patients with M-protein associated renal diseases (such as light chain deposition disease or AL amyloidosis) a M-protein is found in the kidney but not in the serum or in the urine. Since the characteristics of the glomerular fibrils are dependent on the physicochemical properties of the immunoglobulins it is not surprising that M-proteins more often form well-organised deposits with a periodical structure in contrast to polyclonal immune globulin derived fibrils which are more randomly arranged. Indeed, M-proteins are more often detected in immunotactoid glomerulopathy (66%) than in fibrillary glomerulonephritis (3%). Detection of a monoclonal protein in IF should lead to an intensive search for associated conditions, since the incidence of lymphoproliferative malignancies is markedly higher in patients with the immunotactoid as compared with the fibrillary variant.[12-14]

To date there is no proven effective therapy for fibrillary glomerulonephritis.[7,11] The results of treatment with prednisone or cytotoxic agents are disappointing. Intensified treatment of hypertension and proteinuria preferably with ACE inhibitors may improve the outcome. We advocate a trial of immunosuppressive treatment only in patients with evidence of M-protein related deposits.[15] Of the affected patients, 45% develop end-stage renal failure (ESRD) within 24 months.[11] The prognosis is determined by serum creatinine and the presence of tubulo-interstitial fibrosis at presentation. Patients with ESRD may be offered renal transplantation. Unfortunately, the disease often recurs after transplantation (50% recurrence rate), although the course of disease after transplantation is often more protracted.[16]

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