Fibrillary glomerulopathy: report of a case and review of the literature

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ABSTRACT
Fibrillary or immunotactoid glomerulopathy is a glomerular disease due to nonamyloid fibrillary deposits. It belongs to a category of glomerular diseases that is defined by ultrastructural features of organized deposits of extracellular nonbranching microfibrils within the mesangium and capillary walls of renal glomeruli. Light microscopy findings are so diverse and nondiagnostic that fibrillary glomerulonephritis has been nicknamed the "great mimicker". Since its first description in 1977, there have been marked controversies regarding diagnostic criteria. We here report a case of fibrillary glomerulonephritis in a 65-year-old patient presenting with nephrotic syndrome and progressive renal impairment. He did not respond to corticosteroid treatment.

Key words: Fibrillary/immunotactoid glomerulonephropathy

CASE REPORT

A 65-year-old Chinese gentleman presented to our unit in 1998 with shortness of breath. He had been enjoying good health apart from hypertension. Upon admission, he had marked ankle edema. Blood pressure was 170/90 mmHg. Percussion of the chest revealed dullness over both lung bases. Examination of other systems was unremarkable. Complete blood count was normal. Erythrocyte sedimentation rate was 15 mm/hour. Renal function was impaired. Serum urea and creatinine (Cr) were 15.2 mmol/L and 275 µmol/L, respectively. Spot glucose was 6.0 mmol/L. Serum albumin depressed to 22 g/L. Serum globulin was not elevated. Liver function tests were otherwise normal. Cholesterol was 8.4 mmol/L. Twenty-four hour urine protein excretion was 7.9 g. Creatinine clearance was 22 ml/min. Chest radiograph confirmed bilateral pleural effusion. Heart size was normal. Ultrasonographic examination of kidneys was normal. Kidney sizes were within normal limits. Antinuclear factor was negative. C3 complement level depressed to 0.60 g/L (normal range 0.7-1.5 g/L). He was put on calcium channel blocker and diuretics. His blood pressure was normalized and fluid retention improved. Renal biopsy was performed about a week after admission.

Under light microscopy, 15 glomeruli were included. The glomeruli were enlarged and showed enhanced lobulation. Focal neutrophilic infiltration was seen within many of the glomeruli. There was diffuse mesangial proliferation. Endocapillary proliferation was prominent with capillary walls having a focal double contour. One partial fibrocellular crescent was present. Mild tubular atrophy and interstitial fibrosis were noticed. Congo-red stain of the specimen was negative. Under
immunofluorescence, there was moderate patchy deposition of IgG. IgM and C3 deposition was mild and diffuse. C1q deposition was moderate and the pattern was similar to that of IgM. IgA was negative. The working differential diagnoses were either some form of post-infective glomerulopathy or membrano-proliferative glomerulonephritis.

Hepatitis B surface antigen, anti-HCV and VDRL were all negative. Repeated blood cultures showed no growth. Blood smear for malaria was negative. Streptozyme test was negative. Serum protein electrophoresis was negative for paraprotein. Test for serum cryoglobulin was negative. Stool for microscopy revealed clonorchis ova. A course of praziquantel was given. However, his renal function continued to deteriorate. His serum Cr level climbed up to 320 µmol/L 4 weeks after his first presentation. He was then started on aspirin 300 mg and dipyridamole 225 mg per day. After initiation of antiplatelet therapy, his hemoglobin level dropped progressively. Upper gastrointestinal endoscopy revealed moderate antral gastritis and duodenitis with superficial erosions. Antral biopsy showed chronic gastritis with colonization by Helicobacter heilmannii. A course of triple eradication therapy comprising omeprazole, amoxicillin and clarithromycin was given. Repeated antral biopsy confirmed clearance of Helicobacter. Eight weeks after the first presentation, serum Cr level rose to 450 µmol/L. Prednisolone at 1 mg/kg/day was introduced. Unfortunately, his renal function continued to run a downhill course. Twelve weeks after his first presentation, serum Cr level was 550 µmol/L.

Electron microscopy of the renal biopsy specimen revealed numerous subendothelial deposits. Many of the subendothelial deposits were composed of tightly packed tubular structures having a diameter of about 33 nm to 43 nm (Fig. 1). Immunofluorescence study was repeated, demonstrating positive staining for both kappa and lambda light chains, corresponding to the subendothelial deposits. The ultrastructural diagnosis was fibrillary/immunotactoid glomerulopathy.

DISCUSSION
Fibrillary or immunotactoid glomerulopathy is a relatively new disease entity. It was first described in 1977. Rosenmann and Eliakim, reported an unusual glomerular lesion in a 45-year-old lady presenting with nephrotic syndrome and renal insufficiency (1). Light microscopy showed increased mesangium and thickening of the capillary wall. Congo-red stain of the specimen was negative. Electron microscopy revealed electron dense deposits in the mesangium, which demonstrated a high degree of organization in the form of fibrils measuring about 10 nm in diameter. There was no evidence of a systemic process, like myeloma, cryoglobulinemia or lymphoma. The authors were not certain of the nature of the disease. They postulated that this might represent a preamyloid process. In 1980, Schwartz and Lewis reported a similar lesion with immune aggregates associated with highly organized electron dense deposits composed of microtubules (2). The patient was observed for 7 years, during which he developed progressive renal insufficiency. There was never clinical or serological evidence of a systemic disease. This was the first time when the term immunotactoid glomerulopathy was introduced. In Hong Kong, the first case of fibrillary glomerulonephritis was described in 1995 (3).

Fibrillary or immunotactoid glomerulopathy is a glomerular disease due to nonamyloid fibrillary deposits. It belongs to a category of glomerular diseases that is defined by ultrastructural features of organized deposits of extracellular nonbranching microfibrils within the mesangium and capillary walls of renal glomeruli. These fibrils are different from those in amyloidosis in two ways. First, they are larger in diameter. Fibrils in
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Amyloidosis are in general less than 10 nm in diameter whereas those in fibrillary/immunotactoid glomerulopathy are usually larger. Second, fibrils in fibrillary/immunotactoid glomerulopathy do not form the characteristic beta-pleated sheet tertiary structure so that they do not take up Congo-red stain (4). Light microscopy findings are diverse and nondiagnostic. Changes may include mesangial hypercellularity, mesangial expansion with an amorphous PAS-positive material, a membranoproliferative pattern and, in some cases, crescent formation. Under immunofluorescence, positive staining for IgG, C3 and both kappa and lambda light chains is usual. On the other hand, IgM and IgA staining is less common and characteristically weak. Under electron microscopy, there are two major patterns. Majority of patients have smaller-sized fibrils, around from 15 nm to 25 nm in diameter, arranged randomly. The remaining patients have larger fibrils arranged in a more organized manner (5).

Since its first description in 1977, there have been marked controversies and disagreement in terms of diagnostic criteria and histologic classification. The conventional classification is etiology-based (6). Under this classification, the term fibrillary glomerulopathy encompasses all those glomerulopathies which have nonamyloid fibrillar deposits. Most of these deposits are derived from immunoglobulins. Many of these patients have an underlying cause for immunoglobulin deposition, including cryoglobulinemia, lymphoma, monoclonal gamopathy and systemic lupus erythematosus. The term immunotactoid glomerulopathy is thereby reserved for those fibrillary glomerulonephritis without clinical or serological evidence of a systemic disease that may give rise to immunoglobulin deposition. Some investigators, however, suggested to classify them according to their ultrastructural patterns (7,8). Under this classification, fibrillary glomerulonephritis refers to those with smaller fibrils (<30 nm in diameter) arranged in a random fashion, while immunotactoid glomerulopathy refers to those with larger fibrils (>30 nm in diameter) arranged in a more organized manner. To address the need for such distinction, Fogo analyzed 26 cases with fibrillary pattern and compared to six cases with immunotactoid pattern (9). They found that patients with the immunotactoid pattern were older, had a worse renal survival and had a higher chance of harboring an underlying malignancy. However, the validity of the results of this study was hampered by the fact that they had included patients with underlying hematological diseases, which by definition, should be first excluded. Pronovost analyzed 186 patients with fibrillary and immunotactoid patterns (10). They found that patients with the two patterns behaved rather similarly. The disagreement in diagnostic criteria has hampered understanding of the pathophysiology of the disease in the past two decades. It is probably prudent to adhere to a broader terminology until that future studies demonstrate clear clinical differences among variants or define distinct mechanism of fibrillation (5).

Fibrillary glomerulonephritis accounts for about 1% of all nontransplant renal biopsy diagnoses. In general, it is a disease of adults with a mean age of onset of 49 years (7). The youngest patient reported in the literature was a 9-year-old girl (11). There is a female preponderance with a female to male ratio of 1.8 to 1. Whites are more commonly affected than Blacks. Patients usually present with heavy proteinuria. Microscopic hematuria is common. Renal insufficiency is common at the time of presentation and tends to progress with time. After an average follow-up of 24 months, mean renal survival was only 48% (7).

Fibrillary glomerulonephritis has been reported to occur in association with a multitude of diseases. These include hematological diseases like monoclonal gammopathy, chronic lymphocytic leukemia and lymphoma. In fact, these diseases should be excluded first before the diagnosis of fibrillary glomerulonephritis is made. Other malignancies include adenocarcinoma of stomach and metastatic adenocarcinoma of liver. Nonneoplastic diseases that have been reported include mixed connective tissue disorder, Sjögren's syndrome, hepatitis C infection, tuberculosis and leukocytoclastic vasculitis (5).

There is no proven effective therapy. Published data on the influence of conventional immunosuppressive therapy on this process is scanty. An uncontrolled report suggested that corticosteroid offered little benefit (7). Renal transplantation had been successfully performed in affected patients with end-staged renal failure. Recurrence is common, up to 75% in one series. However, the rate of progression is slow (10).

To our knowledge, this patient is the fourth reported case of fibrillary glomerulopathy in Hong Kong. Whether this reflects a lower incidence of the disease in our local population remains to be established. Alternatively, the lower observed incidence of this important disease entity here may be related to the fact that not all renal biopsy specimens were sent for electron microscopy examination, so that this “great mimicker” was left undetected.

REFERENCES
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