

Case Report:

Fibrillary Glomerulopathy Secondary to Light Chain Deposition Disease in a Patient with Monoclonal Gammopathy

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Abstract. The pathologic manifestations of renal diseases related to monoclonal plasma cell dyscrasia include light chain deposition disease, the AL type of amyloidosis, and myeloma cast nephropathy. Light chain deposit disease (LCDD) is an uncommon condition in which monoclonal light chains are deposited in the glomeruli, tubules, and vessels causing varying degree of damage. We report a case of LCDD coincident with fibrillary glomerulonephropathy (FGN) in a 73-yr-old man with a diagnosis of monoclonal gammopathy of undetermined significance who presented with progressive renal insufficiency and mild proteinuria. The serum kappa light chain level was markedly raised. Immunofluorescent stains showed IgG along with C3 and kappa staining in glomeruli, but lambda staining was negative. Electron microscopic studies revealed diffuse punctuate-type deposits along the subendothelial areas. There were also scattered randomly oriented fibrils with a mean fibril thickness of 15-25 nm seen mainly in the glomerular mesangium, consistent with FGN. The congo red stain was negative on the histologic section. The present case illustrates that LCDD can progress to develop FGN in a patient with monoclonal gammopathy.

Keywords: light chain deposit disease, fibrillary glomerulopathy, monoclonal gammopathy

Introduction

Renal disease associated with plasma cell disorders results from the deposition of monoclonal light chains in the renal parenchyma, including the glomeruli, tubulointerstitium, and vessels. Depending on the physicochemical characteristics of the individual light chain, the renal manifestations include light chain deposit disease (LCCD), the AL type of amyloidosis, and myeloma cast nephropathy [1]. Light chains are normally filtered by the glomeruli and metabolized by the proximal tubules. When an excess of light chains overwhelms the capacity of the proximal tubules, light chains can reach the distal tubules and precipitate as casts

and sometimes as fibrils. In 1983, Duffy and colleagues [2] described fibrillary renal deposits that were distinct from amyloid and cryoglobulins. The fibrils measured approximately 20 nm in diameter and were arranged haphazardly within the glomerulus, a condition that was termed fibrillary glomerulonephropathy (FGN) [2]. Fibrillary glomerulonephritis usually presents clinically as proteinuria, hematuria, renal insufficiency, and hypertension. Treatments with corticosteroids, cytotoxic agents, and plasma exchange have proven to have little benefit and the affected patients generally follow a rapid downhill course and require chronic hemodialysis.

We present an unusual case of FGN associated with evidence of LCDD in a patient with monoclonal gammopathy of undetermined significance (MGUS). In this paper, we also review the literature concerning this disease.

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Case Report

A 73-yr-old man presented to the nephrology clinic for a consultation regarding chronic renal insufficiency of >1 yr duration and a history of recurrent renal stones. He was asymptomatic at the time of the consultation. He had a history of hypertension for the past 25 yr and controlled type 2 diabetes without retinopathy for 15 yr. His blood pressure was 142/62 mmHg. Physical examination did not reveal any noteworthy findings.

The results of routine laboratory tests at the time of initial consultation were: platelet count, 242,000/mm³; hematocrit, 34%; hemoglobin, 11.9 gm/dl; white blood count, 7630/mm³ with 61% neutrophils, 30% lymphocytes, 7% monocytes, and 2% eosinophils. Serum test results were: urea nitrogen, 35 mg/dl; creatinine, 1.8 mg/dl; sodium 144 mmol/L; potassium, 4.9 mmol/L; chloride, 109 mmol/L; bicarbonate, 25 mmol/L; calcium, 9.7 mg/dl; glucose, 103 mg/dl; and albumin, 4.5 gm/dl. Urinalysis showed slight microscopic hematuria, 1+ proteinuria, 1-4 RBC/high power field, and 1-4 WBC/high power field. No casts were seen. In a random urine specimen, the proteinuria was 740 mg/g of creatinine. The estimated glomerular filtration rate was 39.4 ml/min.

Renal ultrasonogram showed bilaterally echogenic kidneys with normal size and a few simple cysts in the renal cortex. As a part of an evaluation for renal insufficiency in the elderly, a urine assay for Bence-Jones protein and a serum immunofixation test were ordered. The patient had monoclonal IgG kappa in his serum and he excreted IgG kappa light chains into the urine. Serum IgG, IgA, and IgM levels were all normal. Free kappa light chains in serum were elevated at 157 mg/dl and free lambda light chains were normal at 22.4 mg/dl; thus the kappa/lambda ratio was elevated at 7.01. The patient excreted intact monoclonal kappa light chains in the urine. The urine concentration of Bence-Jones protein was 78 mg/dl. Fat pad biopsy did not show amyloidosis. There were no skeletal abnormalities. Examinations of bone marrow biopsy and aspirate showed normocellular marrow with trilineage hematopoiesis and mild plasmacytosis (4%).

Based on these findings, the differential diagnosis was in favor of a monoclonal gammopathy of undetermined significance (MGUS) that did not warrant further treatment, but a possibility of multiple myeloma with the potential for chemotherapy was also considered. A renal biopsy was done to resolve this diagnostic and therapeutic dilemma.

Methods

Frozen sections of the renal biopsy were cut for direct immunofluorescent stains of IgG, IgA, IgM, C3, C1q, kappa, lambda, and albumin, using a Dako Autostainer (Carpinteria, CA). The remaining renal tissue was divided into 2 parts and fixed with 10% formalin and 3% glutaraldehyde, respectively. Formalin-fixed tissue was routinely embedded, sectioned, and examined using H&E, PAS, and Masson's trichrome stains for light microscopy. After fixation, tissue for electron microscopy was routinely postfixated in osmium tetroxide, embedded in resin, sectioned, and stained with uranyl acetate and lead citrate. Grids for electron microscopy were examined using a transmission electron microscope (JEM-1200EX electron microscope, JEOL, Tokyo, Japan).

Results

Light microscopy revealed 10 glomeruli, 3 of which were globally sclerosed. The viable glomeruli showed varying degrees of mesangial expansion accompanied by nodule formation and segmental thickening of peripheral capillary loops (Fig. 1A). Moderate thickening of the walls of the arterioles and of the small and medium-sized arteries was noted. A few casts in tubules did not show features of myeloma casts. There were no obvious features of diabetic nephropathy. Thioflavine T-stained sections were negative, ruling out amyloidosis. Trichrome-stained sections revealed moderate interstitial fibrosis and tubular atrophy, along with thickening of tubular walls and chronic inflammation.

Immunofluorescent examinations revealed fine granular to pseudo-linear staining along the glomerular capillary loops for kappa light chains (3+) (Fig. 1B), but staining for lambda light chains was negative. Faint staining for kappa light chains was seen along the tubular basement membrane. Granular staining for IgG (3+) and C3 (2+) was also seen along the capillary walls. The glomeruli were negative for IgA, IgM, C1q, and fibrinogen.

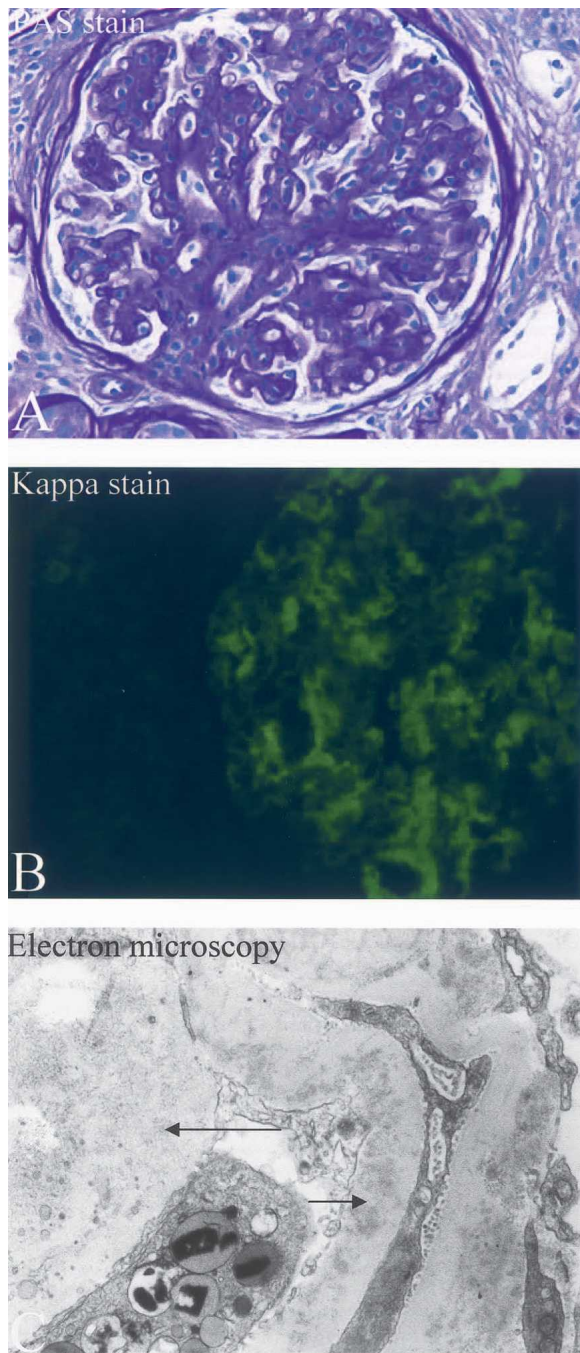


Fig. 1. A. Light microscopy revealed lobulated glomerular loops with proliferative features and thickened capillary loops (PAS, x600). B. Immunofluorescent staining of kappa showed confluent positive staining along loops and in mesangial areas of a glomerulus (x600). C. Electron microscopy revealed large amounts of subendothelial deposits (short arrow) with punctate features (characteristic of light chain deposits) in contrast to mesangial deposits (long arrow) with long fibrils (a feature of FGN) (EM, x18,000).

Electron microscopy showed effacement of foot processes in the visceral epithelial cells. Diffuse punctuate-type electron-dense deposits were noted along the subendothelial areas and focally in the mesangial areas, which were consistent with light chain material. Scattered randomly disposed nonbranching elongated fibrils of 15-25 nm thickness were noted in the mesangial areas and along some peripheral capillary loops. In some areas, the two patterns of light chain deposits and long fibrils were present (Fig. 1C).

Overall, these findings were consistent with LCDD, kappa type, with features of FGN. Six months later, the patient's test results remained similar to the previous ones; these included serum kappa/lambda ratio, 7.82; urine Bence-Jones protein, 83 mg/dl; serum creatinine, 1.7 mg/dl; serum urea nitrogen, 38 mg/dl; and estimated glomerular filtration rate, 42.1 ml/min.

Discussion

Immunoglobulin-mediated kidney disorders can be divided into those that result from deposition into the kidney of intact immunoglobulin molecules or of components of immunoglobulin molecules. In the latter, the pathogenic protein is usually produced by a clonal population of plasma cells or B-lymphocytes and is therefore monoclonal. Monoclonal light chains can impair renal function in a variety of ways. These include (a) deposition in the glomerular or tubular basement membrane as in light chain deposit disease (LCCD), (b) forming casts within distal tubular lumen as in myeloma cast nephropathy, (c) directly injuring tubular epithelial cells as in Fanconi's syndrome, or (d) forming beta-pleated sheets as in light chain amyloidosis [3].

We describe a patient with monoclonal gammopathy who had the simultaneous presence of both light chain deposit disease (LCCD) and fibrillary glomerulopathy (FGN). In 1977, Rosenmann and Eliakim [4] described a form of glomerulonephritis characterized by fibrillary deposition seen by electron microscope that failed to stain with congo red. In 1983, Duffy et al [2] introduced the term "fibrillary renal deposits and nephritis," which came to be known as fibrillary

glomerulonephropathy. FGN is characterized by the widespread deposition of randomly arranged, elongated, non-branching microfibrils in the mesangium and glomerular basement membrane, with a focal admixture of finely granular dense unorganized material. In a small percentage of these patients, the deposition of fibrils also involves the tubular basement membranes. The diameters of the fibrils are approximately twice those of amyloid fibrils and range from 12 to 30 nm, with the majority 20 nm [5]. Immunofluorescence in most cases reveals polyclonal IgG and C3. The deposits appear to have a somewhat smudgy texture in the mesangium and confluent granular or pseudoliner patterns along the glomerular basement membrane. Light microscopy shows diverse histological patterns such as membranoproliferative glomerulonephritis (GN), mesangial proliferative GN, diffuse proliferative GN with endocapillary exudation, sclerosing GN, or membranous thickening of the capillary tufts. Crescents may be present and on occasion crescentic FGN is encountered [6]. The congo red and thioflavin T stains are negative.

Clinically, these patients were observed to have severe proteinuria, hematuria, hypertension, and renal insufficiency or nephrotic syndrome that progressed over months to years. The majority of these cases were idiopathic and occurred in the absence of other systemic disease, but some cases were reported in association with systemic diseases, including lymphoproliferative malignancy, gastric adenocarcinoma, metastatic adenocarcinoma of the liver, mixed connective tissue disease, and leukocytoclastic vasculitis [7]. Occasional association with infections such as hepatitis C also was noted [5]. Serum complement levels (C3 and C4) typically were normal and assays for anti-nuclear antibodies, antineutrophil cytoplasmic antibody, anti-glomerular basement membrane antibodies, and rheumatic factor were negative, with occasional exceptions [8].

Our patient had a history of MGUS and diabetes mellitus. The patient developed proteinuria and renal dysfunction. His serum kappa/lamda ratio was about 7 and free kappa level was 157 mg/dl. The overall findings suggest a light chain deposition disease in the glomeruli. Several lines of evidence support this diagnosis. First, the patient

had a high kappa/lamda ratio. Second, there was only kappa light chain staining in the glomeruli by immunofluorescent study without the presence of lamda. There was also the concurrent presence of IgG and C3 staining with additional long fibrils present ultrastructurally, which are typically seen in fibrillary glomerulopathy. It is known that FGN, myeloma kidney, and immunotactoid glomerulopathy are in a spectrum of renal diseases somewhat related to immunoglobulin disorders. Most cases of fibrillary glomerulopathy are associated with an underlying immune complex disease. However a minority has been shown to have an underlying plasma cell dyscrasia, but no large studies have been reported. One study in the literature reported the presence of a combination of light chain disease and fibrillary glomerulonephritis in 3 patients with monoclonal gammopathy [9].

The differential diagnosis in our case could be membranoproliferative glomerulopathy; however the finding of kappa-positive and lambda-negative staining, the lack of a proliferative pattern, and the presence of punctuate/fluffy type of dense deposits are against this diagnosis. In conclusion, the findings were consistent with a light chain deposit disease, kappa type, with features of fibrillary glomerulopathy.

FGN and LCCD lack distinctive features in clinical manifestations and laboratory findings, and these diagnoses are generally made by renal biopsy. Despite the fact that light chains are found in both conditions, abnormalities in serum and urine protein analysis are inconsistent. From a morphologic viewpoint, in a typical case of LCCD the histologic picture is one of severe mesangial expansion with multinodularity with glomerular and peritubular deposits of usually kappa light chains, while nodules are not usually found in fibrillary glomerulonephritis. The most striking difference between LCCD and FGN lies at an ultrastructural level in the prominently fibrillary nature of deposits in FGN. One further difference is the systemic involvement in LCCD [10], a phenomenon not well documented in FGN. Clinically, the coincident presence of fibrillary glomerulonephritis indicates a poorer renal prognosis, and treatment using corticosteroids, cytotoxic drugs, or plasma exchange is of little

benefit [5]; the condition can recur in the allograft even after renal transplantation [11].

The pathogenesis of fibrillogenesis in FGN has not been elucidated. Deposition of this type of long fibrils is generally limited to the kidney, although there have been occasional reports of extra-renal involvement [12]. The predominantly renal involvement suggests that the specific glomerular environment and the physicochemical properties of the deposited immunoglobulins are factors that favor fibrillogenesis. In a series of FGN, the fibrils were shown to co-localize with the amyloid P component, but not with fibronectin or fibrillin [13]. In a study of a crescentic case of FGN, fibronectin was detected both in the deposits and in a cryoprecipitate that formed after prolonged storage of the patient's serum, but it appeared that fibronectin was not an essential component of the fibrils [14].

In our case, the combination of kappa light chain deposition and fibrillary glomerulopathy is unusual and interesting. There is evidence of tubular damage probably due to deposition of light chains. Most cases of fibrillary glomerulopathy are associated with an underlying immune complex-mediated disease. However, a few of these patients have been shown to have plasma cell disorders but are not well documented in the literature. In view of the ultrastructural and immunopathologic finding of kappa light chains, it seems reasonable to surmise that the deposits in FGN are derived from these light chains, perhaps secreted abnormally by a dispersed population of plasma cells. In our case, light chain deposits were mainly located along subendothelial spaces with punctate (dots) appearance, whereas long fibrils were chiefly located in mesangial areas.

Since AL amyloid fibrils are intermediate products of light chains and since mesangial cells can function as both macrophages and smooth muscle cells, we speculate that the long fibrils might represent a type of intermediate product of light chains partially metabolized by mesangial cells. Based on the location of the long fibrils, mentioned previously, and the presence of kappa but not lambda in the renal biopsy, it seems likely that the FGN was secondary to LCDD rather than an coincidental occurrence with LCDD in this case.

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