Fibrillary Glomerulonephritis in a Patient with Longstanding SLE

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Abstract
We report the case of a 56 year old woman with a 36-year-history of systemic lupus erythematosus (SLE) and recurrent episodes of active membranous lupus nephritis. She developed recurrent proteinuria in December 2015 and on repeat biopsy was found to have electron microscopy findings notable for membranous nephritis with subepithelial deposits meeting criteria for fibrillary glomerulonephritis (FGN). FGN is a rare condition and is usually a primary disorder. It can occur in association with malignancy and autoimmune conditions including SLE.

Abbreviations
FGN: For Fibrillary Glomerulonephritis; SLE: Systemic Lupus Erythematosus

Case Presentation
The patient is a 56-year-old Afro-American woman who was first diagnosed with SLE 36 years ago. At that time she presented with arthralgia, malar rash, pedal edema, lymphadenopathy, positive ANA and proteinuria (3.5 gram/24 hours). Kidney biopsy at that time revealed equivocal glomerular capillary wall thickening on light microscopy. Immunofluorescence revealed granular deposition of C3, IgG, IgE and IgM. Electron microscopy showed extensive mesangial, paramesangial, subepithelial, and a few subendothelial deposits. The patient was determined to have WHO class V lupus nephritis. She was treated with prednisone however upon discharge the patient was not compliant with regular follow up.

In February of 1997 she presented to clinic with worsening periorbital edema, proteinuria and an increase in serum creatinine from 0.8 mg/dl to 1.4 mg/dl. Repeat kidney biopsy again revealed membranous lupus nephritis. She was treated with high dose steroids and captopril. Her creatinine returned to normal and proteinuria resolved over the next four months; and she was tapered off prednisone.

In February of 1998 she developed progressive cognitive impairment. Neurologic work up was negative. Lupus cerebritis was diagnosed, and the patient was treated with high dose steroids. One month later she presented with arthralgia, worsening memory, vasculitic rash of the hands and worsening proteinuria (777 mg /24 hours). At that time she was treated with cyclophosphamide IV every three months. SLE disease became relatively quiescent. Cyclophosphamide treatment was discontinued in August 2002, and mycophenolatemofetil was added for maintenance treatment.

In December of 2015 the patient developed worsening proteinuria. At that time her regimen included mycophenolate mofetil 2 gram daily, hydroxychloroquine 200 mg twice daily and prednisone 5 mg once daily. Her urine spot protein to creatinine ratio was 1.2 mg /mg; a creatinine 0.87 mg/dl (normal 0.7 – 1.3 mg/dl), albumin 3.75 g/dl (3.5 – 5.7 g/dl), anti-ds DNA antibodies negative, C3 -126 ( 83 -200 mg/gl ), C4 -40.4 ( 16 -47.0 mg/dl). Urinalysis revealed 12 WBC/hpf, 2 RBC/hpf, with no casts. She had many bacteria though no symptoms of a urinary tract infection. Repeat kidney biopsy was performed. There were 27 glomeruli, of which 4 were globally sclerotic. Light microscopy revealed no hypercellularity, segmental sclerosis, glomerular basement membrane thickening or spikes. There was minimal focal tubular atrophy and interstitial fibrosis with moderate arteriosclerosis (Figure 1). Immunofluorescence revealed sparse segmental possibly mesangial deposits of IgG, IgM, kappa and lambda (Figure 2). Tests for C1q, C3, C4, IgA, fibrin and albumin were negative. Two glomeruli were examined by electron microscopy. In one of these there was segmental, subepithelial and paramesangial deposits with organized para crystalline appearance. They consisted of amorphous material, notably fibrils measuring 20 nm in diameter with a suggestion...
of tubular structure in some (Figure 3-7). Foot processes were effaced in relation to the deposits and elsewhere in both glomeruli. There were no subendothelial or mesangial deposits seen. Biopsy was thought to favor membranous lupus nephritis however the presence of the microfibrils raised concern for possible fibrillary glomerulonephritis. A second opinion was sought from the glomerulonephritis team at Columbia University Medical Center. The absence of endothelial cell or tubuloreticular inclusions and the lack of “finger print” substructure were thought to suggest a diagnosis other than SLE. Based on the presence of the 20 nm fibrils the patient was felt to have fibrillary glomerulonephritis with membranous nephropathy phenotype.

Cryoglobulinemia, hepatitis C, hepatitis B, HIV and monoclonal gammopathy were ruled out. The dose of mycophenolate mofetil was tapered from 3 grams to 1 gram daily, and cyclosporine was started at 100 mg twice daily with gradual dose escalation to 200 mg twice daily. Enalapril was discontinued due to angioedema. Pedal edema resolved with hydrochlorothiazide therapy. The patient continues to have proteinuria with urine protein to creatinine ratio of 1.9 mg/mg. Her serum creatinine remains normal, however albumin has decreased to 2.63 g/dl (normal 3.5-5.7 gm/dl).

**DISCUSSION**

A 56 year old woman with SLE and recurrent membranous glomerulonephritis presented with worsening proteinuria.
Kidney biopsy revealed microfibrils on electron microscopy consistent with FGN, rather than active SLE (figure 3-7). FGN is characterized by the presence of randomly arranged non branching fibrillary deposits in the mesangium and the glomerular basement membrane which correspond with the immunofluorescence pattern and stain negative with Congo red staining. The fibril diameter is 12 – 22 nm [1]. The most common light microscopy findings associated with FGN include mesangioproliferative (71 %) membrano proliferative (15%) and membranous (2%) [2]. Immuno fluorescence is always positive for IgG which may show predominance of IgG4 [3]. C3 was positive in 88% and 92% of patients in two large studies [2,3]. FGN has an incidence of 0.5-1% in native kidney biopsies and usually presents with proteinuria, renal insufficiency and hypertension [1,4]. Samih et al [2] found in a recent case series involving 66 FGN patients from one institution that 71% of patients had hypertension, the mean 24 hour protein excretion was 5.62 grams, 62% had hypoalbuminemia, 38% had nephrotic syndrome and the mean serum creatinine was 2.1 mg/dl [2]. In another study involving 27 patients with FGN Javague et al [3] found that 70% of patients had hypertension, 56% had lower limb edema, the median protein excretion was 3.2 grams per day and 56% of patients had a GFR < 60 mL/min/1.73 m² [3].

SLE has been shown to be associated with organized deposits known as fingerprint deposits. These organized semicircular deposits have a diameter of 10 -15 nm and in a study involving 227 kidney biopsies from 185 patients Hvala et al showed these deposits to be present in 17.3% of kidney biopsies of patients with SLE [5]. Notably in the same study fibrils resembling those seen in FGN were seen in only 1% of patients with SLE. Additional cases of FGN occurring in SLE have been reported. One case involved a 12 year old boy with class IV nephritis who was subsequently diagnosed with FGN on repeat biopsy [6]. He progressed to end stage renal disease and required renal replacement therapy despite aggressive immune suppression. Another case involved a 28 year old male with SLE who developed rapidly progressive glomerulonephritis and was found to have FGN [7]. He too progressed to end stage renal disease and required renal replacement despite immunosuppression.

The pathogenesis of FGN has not been clearly elucidated. Ig G, C3 and amyloid P have been localized to individual fibril deposits by immunoelectron microscopy. However labels for the glomerular basement membrane proteins type IV collagen, heparin sulfate proteoglycan, fibronectin, or fibrillin have not been detected in the fibrils. This suggests that the fibrils are protein deposits from circulation modified by polymerization as opposed to collections of endogenous membranous fibrils proliferating in response to injury [8]. This does not conclusively prove, however, that the fibrils are made of IgG as they may be bound to a fibrillar protein unrecognized by the anti sera [9].

There is no established treatment for FGN. Immunosuppression has been shown not to affect renal outcome [2]. One approach is to treat the patients according to the light microscopy pattern as we have done [10]. In one retrospective case series, rituximab was associated with non-progression of decline in kidney function and it has been suggested that it may be effective in patients with relatively preserved kidney function [11]. Despite treatment with cyclosporine our patient continues to have proteinuria with hypoalbuminemia.

The importance of distinguishing between FGN with membranous phenotype and membranous nephropathy due to systemic lupus nephritis is based on the poor renal prognosis of FGN. Samih et al [2] found that 44% percent of the patients with FGN progressed to renal failure [2]. Of these 52% received a kidney transplant; of which 36% had recurrence of the disease in the transplanted allograft.

In summary, we describe another patient with SLE who developed the nephrotic syndrome with biopsy findings of membranous nephropathy, but showed typical fibrils associated with FGN. This case provides support for the association of SLE with FGN.

REFERENCES


