CLINICAL VIGNETTE

Fibrillary Glomerulonephritis

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A 75-year-old female with mixed connective tissue disorder (MCTD) and CKD stage 3a with baseline serum creatinine of 1.1-1.3mg/dl presented to nephrology clinic to re-establish care. Her MCTD was a mixture of over-lapping features of SLE, scleroderma, and rheumatoid arthritis and she was maintained on azathioprine. She also had interstitial lung disease, hypertension, and anemia. She previously had been diagnosed with interstitial nephritis due to sterile pyuria on urinanalysis, but this had not been confirmed with a kidney biopsy. Upon re-evaluation her serum creatinine increased to 1.7mg/dl, previously 1.3mg/dl two years earlier. Her urinanalysis showed 2+ protein, 40 WBCs/ul, 4 RBCs/ul, 2 granular casts per LPF, and a urine total protein to creatinine ratio of 0.6 mg/dl. Her Double Stranded DNA was positive at 312 IU/ml, with negative serum hepatitis B and C panels and negative serum ANCA level. Serum immunofixation did not show any monoclonal protein bands. A kidney biopsy obtained showed fibrillary and immune complex mediated nephritis, with severe arteriosclerosis and arteriolosclerosis and mild chronic tubulointerstitial changes. On electron microscopy, the subepithelial space was markedly expanded by randomly arranged fibrils which measured 10.0 to 13.9 nm in width. The mesangial matrix was also extensively involved by fibrils. Congo red was negative for amyloid. She was started on low dose of lisinopril 5mg daily and rituximab two doses of 1000mg IV, two weeks apart. She had a good response with this treatment and her serum creatinine returned back to her baseline of 1.1-1.3 mg/dl, and decrease in urine protein-to-creatinine to 0.3 or less. The two doses of Rituximab were repeated every 6 months for 3 years and then withheld 18 months ago. She continues to have stable kidney function and minimal proteinuria.

Discussion

Fibrillary Glomerulonephritis (FGN) is a form of glomerulonephritis seen in less than 1% of kidney biopsies.[1-3] The hallmark of the disease is the finding of organized, randomly oriented, non-branching fibrils of 16-24 nm in diameter in the mesangium and glomerular capillary walls. The findings can only be observed on electron microscopy. They are typically Congo red negative, distinguishing them from amyloid fibrils.[2,3] On immunofluorescence (IF) microscopy, 85-90% of cases will stain for Dnaj heat shock protein family member B9 (DNAJB9).[4-6] However, this staining technique was not available at the time of our patient's kidney biopsy. On IF microscopy, the fibrils are shown to be composed of immunoglobulin G(IgG) and polyclonal light chains.[1] Around 50% of cases are thought to be idiopathic. The other half are associated with malignancies, monoclonal gammapathies, chronic hepatitis C, and auto-immune diseases such as lupus.[7,8]

There is a scarcity of good treatment data for FGN. Most treatment has focused on prednisone and an additional agent such as cyclophosphamide and rituximab. Most of the available treatment data is from retrospective case series. Most cases of FGN reach ESRD within a median of 13 to 25 months.[3,9] Optimum treatment has not been defined. If FGN can be attributable as secondary, treatment should be aimed at the primary disorder. This is particularly true regarding chronic hepatitis C and lymphomas. In a case series by Javaugue et el, the majority of patients treated with rituximab, 5 of 7, achieved a partial remission. This was defined as at least a 50% decline in urine protein excretion and by <15% decline in eGFR.[8] In another case series, treatment with rituximab led the clinical response of preserved kidney function in only 33% of patients.[10] Another study found, only 1 in 9 of patients treated with rituximab had stable kidney function.[9] In most of the studies, the patients that gained the most benefit had higher initial GFRs. Non-immune suppressive medications used to preserve kidney function in proteinuric kidney disease, such as serum Ace Inhibitors and ARBs, should be standard therapy for all patients that can tolerate them.

This case of FGN is notable for a few select reasons. First, FGN has rarely been described in patients with mixed connective tissue disease. A search of the literature reveals only one other case in a patient with un-differentiated connective tissue disease (UCTD).[11] Second, as noted above, FGN has a poor renal prognosis, with most patients continuing to have a decline in kidney function. Our patient had a favorable response to treatment with rituximab, with a decline in urine protein excretion and improvement in GFR. She continues to maintain these parameters, five years after diagnosis. Lastly, her proteinuria was not massive and was always sub-nephrotic, unlike most patients who have protein excretion greater than 3.5 grams daily. This may contribute to her favorable response.

In summary, FGN is a rare form of glomerulonephritis that presents with worsening renal parameters of decreasing GFR and increasing serum protein. It is of outmost importance to obtain a kidney biopsy for diagnosis is based on classic electron microscopy findings of organized, randomly oriented, non-branching fibrils with a mean diameter of 20 nm, that usually stain negative for Congo red. Treatment is usually prednisone,

with rituximab or cyclophosphamide. However, most do not respond to treatment and progression to ESRD.

REFERENCES

1. **Alpers CE, Rennke HG, Hopper J Jr, Biava CG.** Fibrillary glomerulonephritis: an entity with unusual immunofluorescence features. *Kidney Int*. 1987 Mar;31(3):781-9. doi: 10.1038/ki.1987.66. PMID: 3106698.
2. **Iskandar SS, Falk RJ, Jennette JC**. Clinical and pathologic features of fibrillary glomerulonephritis. *Kidney Int*. 1992 Dec;42(6):1401-7. doi: 10.1038/ki.1992.433. PMID: 1474772.
3. **Rosenstock JL, Markowitz GS, Valeri AM, Sacchi G, Appel GB, D'Agati VD**. Fibrillary and immunotactoid glomerulonephritis: Distinct entities with different clinical and pathologic features. *Kidney Int*. 2003 Apr;63(4):1450-61. doi: 10.1046/j.1523-1755.2003.00853.x. PMID: 12631361.
4. **Dasari S, Alexander MP, Vrana JA, Theis JD, Mills JR, Negron V, Sethi S, Dispenzieri A, Highsmith WE Jr, Nasr SH, Kurtin PJ**. DnaJ Heat Shock Protein Family B Member 9 Is a Novel Biomarker for Fibrillary GN. *J Am Soc Nephrol*. 2018 Jan;29(1):51-56. doi: 10.1681/ASN.2017030306. Epub 2017 Nov 2. PMID: 29097623; PMCID: PMC5748911.
5. **Andeen NK, Yang HY, Dai DF, MacCoss MJ, Smith KD**. DnaJ Homolog Subfamily B Member 9 Is a Putative Autoantigen in Fibrillary GN. *J Am Soc Nephrol*. 2018 Jan;29(1):231-239. doi: 10.1681/ASN.2017050566. Epub 2017 Nov 2. PMID: 29097624; PMCID: PMC5748922.
6. **Nasr SH, Vrana JA, Dasari S, Bridoux F, Fidler ME, Kaaki S, Quellard N, Rinsant A, Goujon JM, Sethi S, Fervenza FC, Cornell LD, Said SM, McPhail ED, Herrera Hernandez LP, Grande JP, Hogan MC, Lieske JC, Leung N, Kurtin PJ, Alexander MP**. DNAJB9 Is a Specific Immunohistochemical Marker for Fibrillary Glomerulonephritis. *Kidney Int Rep*. 2017 Aug 8;3(1):56-64. doi: 10.1016/j.ekir.2017.07.017. PMID: 29340314; PMCID: PMC5762944.
7. **Nasr SH, Valeri AM, Cornell LD, Fidler ME, Sethi S, Leung N, Fervenza FC**. Fibrillary glomerulonephritis: a report of 66 cases from a single institution. *Clin J Am Soc Nephrol*. 2011 Apr;6(4):775-84. doi: 10.2215/CJN.08300910. Epub 2011 Mar 24. PMID: 21441134; PMCID: PMC3069369.
8. **Javaugue V, Karras A, Glowacki F, McGregor B, Lacombe C, Goujon JM, Ragot S, Aucouturier P, Touchard G, Bridoux F**. Long-term kidney disease outcomes in fibrillary glomerulonephritis: a case series of 27 patients. *Am J Kidney Dis*. 2013 Oct;62(4):679-90. doi: 10.1053/j.ajkd.2013.03.031. Epub 2013 Jun 4. PMID: 23759297.
9. **Payan Schober F, Jobson MA, Poulton CJ, Singh HK, Nickeleit V, Falk RJ, Jennette JC, Nachman PH, Pendergraft Iii WF**. Clinical Features and Outcomes of a Racially Diverse Population with Fibrillary Glomerulonephritis. *Am J Nephrol*. 2017;45(3):248-256. doi: 10.1159/000455390. Epub 2017 Feb 4. PMID: 28161700; PMCID: PMC5482172.
10. **Hogan J, Restivo M, Canetta PA, Herlitz LC, Radhakrishnan J, Appel GB, Bomback AS**. Rituximab treatment for fibrillary glomerulonephritis. *Nephrol Dial Transplant*. 2014 Oct;29(10):1925-31. doi: 10.1093/ndt/gfu189. Epub 2014 May 27. PMID: 24867652.
11. **Nebuloni M, Genderini A, Tosoni A, Caruso S, di Belgiojoso GB**. Fibrillary glomerulonephritis with prevalent IgA deposition associated with undifferentiated connective tissue disease: A case report. *NDT Plus*. 2010 Feb;3(1):57-9. doi: 10.1093/ndtplus/sfp125. Epub 2009 Sep 19. PMID: 25949407; PMCID: PMC4421553.