

Development of Nephrotic Syndrome in a Patient with Rheumatoid Arthritis Treated with Certolizumab

To the Editor:

Tumor necrosis factor- α (TNF- α) inhibitors have become widely accepted and are vital in the treatment of rheumatoid arthritis (RA) and other autoimmune inflammatory diseases¹. Their target, TNF- α , promotes inflammation through a variety of mechanisms, including cytokine and chemokine expression, and suppression of regulatory T cells². Although an important therapy for many inflammatory diseases, TNF- α inhibitors may contribute to serious adverse effects, including infection, heart failure, and hematologic and nervous system disorders¹.

Here we describe the first documented case, to our knowledge, of nephrotic syndrome with biopsy-proven membranous glomerulonephritis (GN) due to certolizumab in an individual with RA.

A 63-year-old female with nodular, erosive, seropositive RA for over 15 years with suboptimal control with hydroxychloroquine (HCQ) monotherapy and previous intolerance to methotrexate presented to the clinic for a second opinion. Her rheumatoid factor was 95 IU/ml and anti-citrullinated protein antibody was > 250. Given her active inflammatory disease with a 28-joint Disease Activity Score (DAS28) of 5.89, we began treatment with adalimumab (ADA). She responded well initially, but effectiveness waned over 12 months with intermittent discontinuation of therapy for successive orthopedic surgeries. Upon discontinuation of ADA, DAS28 was 6.15, and certolizumab was initiated about 1 month later. At her 3-month follow up, DAS28 had improved to 2.13. However, about 6 months into treatment, she developed progressive bilateral lower extremity pitting edema with hypoalbuminemia and 4+ proteinuria. A 24-h urine study revealed

14 g total protein. Urinalysis prior to certolizumab therapy was negative for proteinuria. A mildly elevated antinuclear antibody (ANA) of 1.2 was noted; however, her ANA had been 1.4 prior to TNF- α inhibition. Additional examination was unrevealing, including dsDNA, cryoglobulins, testing for extractable nuclear antigens, and hepatitis serologies. Renal function was stable with a creatinine < 1 mg/dl. She did not develop any cutaneous eruption, vasculitic lesions, mucocutaneous aphthosis, or serositis. Certolizumab therapy was discontinued after a total of 12 months once renal biopsy results demonstrated membranous GN with segmental sclerosis, focal mesangial proliferative features, and rare crescents (Figure 1). No necrosis or significant features of diabetic nephropathy were noted. Electron microscopy (EM) showed diffuse irregularity of glomerular basement membranes with many medium to large subepithelial immune complex deposits without substructure with basement membrane reaction, scattered intramembranous deposits, and occasional mesangial deposits (Figure 2). Extensive foot process fusion and podocyte microvillous transformation was noted. Features of vasculitis were not seen. On immunofluorescence, there was diffuse global coarse granular capillary loop staining of 3+ IgG, 2-3+ κ and λ , 2+ IgM, and 1+ C3. No staining for IgA or C1q was identified.

Discontinuation of certolizumab and medical management with torsemide and losartan resulted in gradual improvement of the membranous GN. Steroids were not used for treatment. Using rituximab for both her RA and membranous GN was discussed, but she was reluctant because of cost factors. Since discontinuation of certolizumab 25 months ago, the patient has only trace proteinuria and mild peripheral edema. Surprisingly, her RA disease activity has improved and she has received HCQ monotherapy for the past 22 months without significant RA symptoms. Her DAS28 at last visit was 1.9.

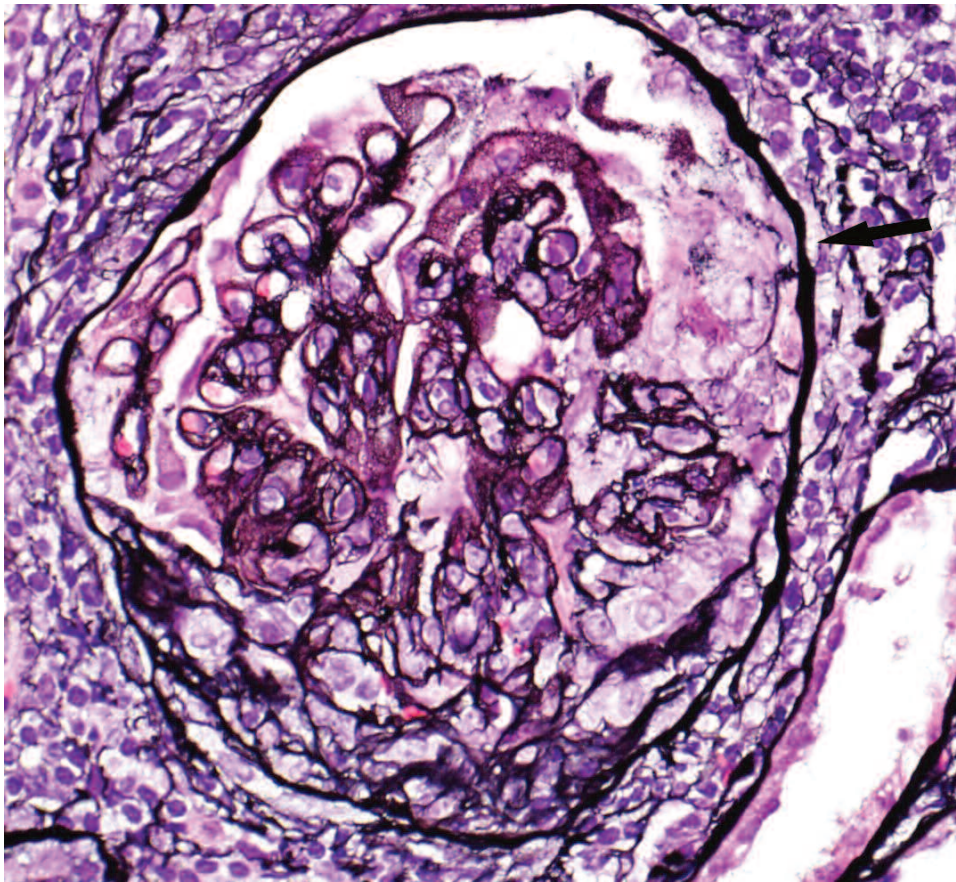


Figure 1. Glomerulus with segmental sclerosis and early cellular crescent (arrow). Jones' silver stain, original magnification 400 \times .

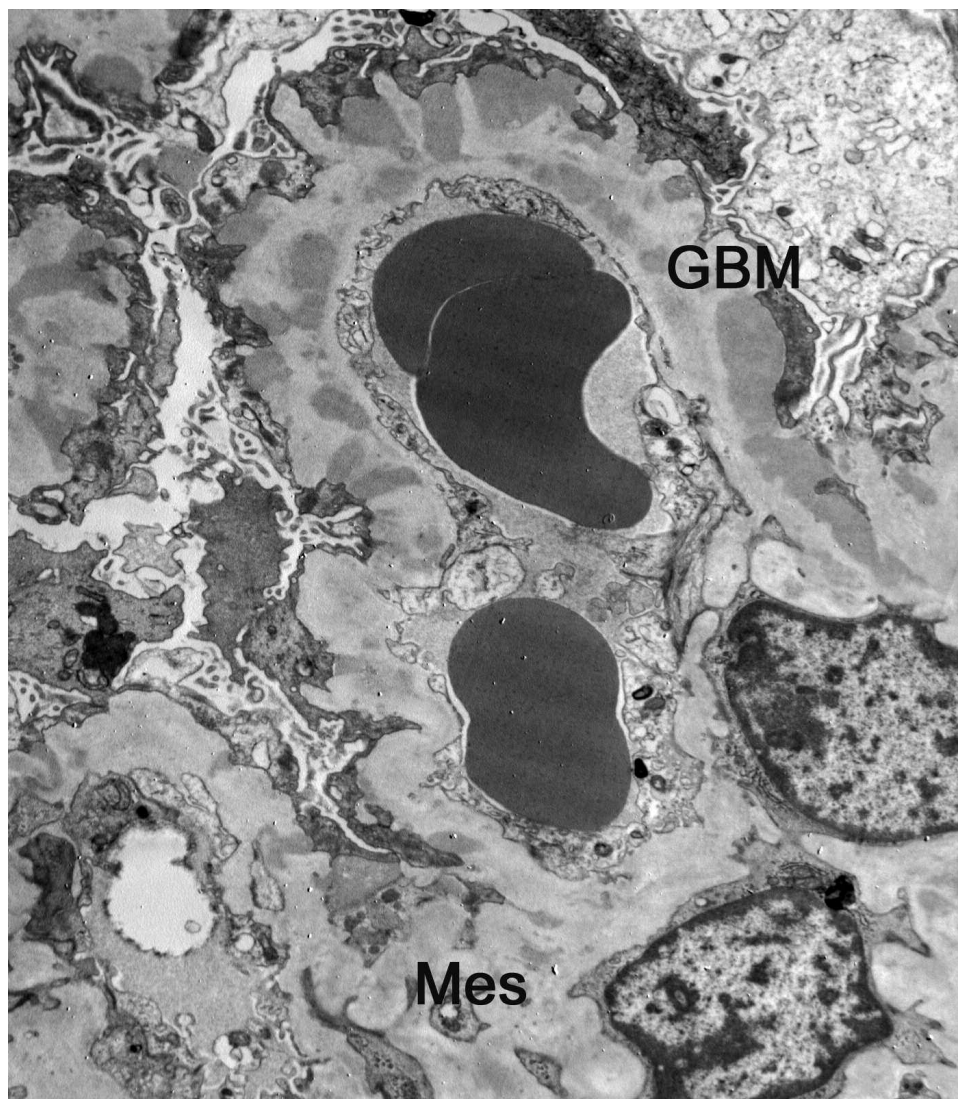


Figure 2. There are many large subepithelial and intramembranous basement membrane (GBM) electron-dense immune complex deposits with surrounding basement membrane reaction. Similar scattered deposits are also present in the mesangium (Mes). Electron microscopy, original magnification 4800 \times .

Renal disorders, while rare, have been documented in the literature as potential adverse effects of TNF- α inhibitors³. Their pathogenesis is suspected to be related to a paradoxical, drug-induced autoimmune process^{3,4}. A 2014 systematic literature review and cohort analysis found 29 reports of renal disorder secondary to TNF- α inhibitors in patients with rheumatologic disease, 22 of whom had RA³. The agents responsible were etanercept, ADA, and infliximab. The renal disorders were a systemic vasculitis-associated GN, lupus-like syndrome-associated GN, or an isolated renal glomerulonephropathy. The nephrotic syndrome in our patient, owing to its lack of vasculitis or lupus-like features or symptoms, was likely an isolated renal glomerulonephropathy secondary to certolizumab. There has been only 1 published case to date of certolizumab causing nephrotic syndrome, and this was in an individual with Crohn disease, whose renal biopsy showed focal and segmental glomerulosclerosis⁵.

We determined that our patient's nephrotic syndrome and membranous GN were likely associated with certolizumab therapy, because symptoms coincided with treatment and discontinuation led to gradual improvement.

Glomerulonephropathy in the setting of RA may be related to medications [e.g., TNF- α inhibitor, gold, penicillamine, nonsteroidal antiinflammatory drug (NSAID)], secondary amyloidosis, or RA itself⁶. Our patient never used gold or penicillamine and only rarely used low-dose NSAID. Her renal biopsy did not show features of amyloidosis. When RA itself causes glomerulonephropathy, biopsy typically shows a mesangial rather than membranous GN, the latter of which is more closely associated with medication-induced glomerulonephropathy^{6,7,8}. Hepatitis and cryoglobulinemia were ruled out as potential etiologies of her membranous GN because of negative serologic investigations and lack of typical EM deposit substructure for the latter. We also considered malignancy as an infrequent cause of membranous GN, but she had a mammogram, colonoscopy, and PAP smear within 1 year of nephrotic symptoms, and all were negative.

As biologic therapy for inflammatory diseases continues to expand, and newer TNF- α inhibitors such as certolizumab gain more popularity, it is important for providers to be aware of the potential for renal toxicity and nephrotic syndrome with these agents.

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