A Case of Minimal Change Disease in a Patient with Rheumatoid Arthritis Treated with Certolizumab

To the Editor:

Manifestations of renal disease have been reported to develop after tumor necrosis factor-α (TNF-α) inhibition, and they should be considered as a possible complication as TNF-α inhibitors become more prevalent in the treatment of autoimmune inflammatory diseases. We report a case of minimal change disease (MCD) that developed in a woman receiving the TNF-α inhibitor certolizumab and was resolved with high-dose steroids and discontinuation of TNF-α blockade. Ethics approval was waived by the Mayo Clinic Institutional Review Board; the patient's written informed consent was obtained.

A 49-year-old woman with a background history of rheumatoid arthritis (RA) and Sjögren syndrome presented with a 1-week history of foamy urine, peripheral edema, and 15-kg weight gain. For her RA, she was taking prednisone 5 mg daily and certolizumab 400 mg monthly; the latter had been started 6 months prior to presentation. Physical examination findings demonstrated 2+ pitting edema to the knees bilaterally, abdominal distension, and facial edema. Laboratory examination was significant for creatinine 2.4 (baseline 1.0) and serum albumin 1.7. Urinalysis showed markedly elevated protein and 3–10 red blood cells/high power field. A 24-h urine collection revealed a total protein of 17.5 g. Renal ultrasound showed mildly echogenic renal parenchyma bilaterally, consistent with intrarenal disease. A renal biopsy was performed, and electron microscopy revealed slightly thickened glomerular basement membranes and evidence of diffuse (100%) podocyte foot process effacement consistent with MCD. The patient's certolizumab was discontinued and she was initiated on high-dose prednisone, resulting in complete resolution of her edema and proteinuria.

MCD accounts for about 10% of cases of nephrotic syndrome in adults[1]. Most cases of MCD are idiopathic, but there are reported cases in the setting of medications, including sulfasalazine, antimicrobials, and nonsteroidal antiinflammatory drugs[2]. TNF-α inhibitors are effective in treating autoimmune inflammatory diseases, but the side effect profile has not yet been fully elucidated. To our knowledge, we are reporting the first case of MCD in a patient treated with certolizumab.

There are a few reports describing associations between TNF-α inhibitors and nephrotic syndrome in the literature. Den Broeder, *et al* reported a case of membranous glomerulopathy 12 months after starting adalimumab for the treatment of RA[3]. Takeuchi, *et al* similarly described a case of biopsy-proven MCD 3 months after initiating etanercept for the treatment of RA[4]. Both these patients demonstrated resolution of clinical symptoms of nephrotic syndrome shortly after discontinuation of TNF-α inhibition, suggesting a medication-induced etiology for their renal disease. In addition, there have been a couple of reports specifically noting the development of nephrotic syndrome following initiation of certolizumab. Leong and Fung-liu reported the case of a patient treated with certolizumab for Crohn disease who subsequently developed focal segmental glomerulosclerosis[5]. Most recently, Butendieck, *et al* published a case of a patient treated with certolizumab for RA who subsequently developed membranous glomerulonephropathy[6]. Both these patients demonstrated gradual resolution of their renal disease after discontinuation of certolizumab. We hypothesize that our patient may have similarly developed a nephropathy associated with certolizumab therapy.

There is biological plausibility for the relationship between certolizumab and MCD. First, prior reports demonstrated similar timing of TNF-α inhibitor initiation and the development of nephrotic syndrome 3–12 months after initiation[3,4,5,6]. Second, TNF-α blockade has been shown to shift the Th cell response toward Th2 and the promotion of humoral immunity[7,8] and MCD has been associated with elevated levels of various Th2 cytokines[9,10]. This suggests that TNF-α inhibition may have made our patient more susceptible to the development of MCD. However, we acknowledge that it is equally likely that this was a case of idiopathic MCD unrelated to the use of TNF-α blockade. Notably, our patient was started on high-dose prednisone concurrently with the discontinuation of certolizumab, given the severity of her presenting symptoms. Although we were unable to clearly delineate a temporal relationship upon discontinuation, physicians should be aware of a possible link between TNF-α inhibition and nephropathies.

As TNF-α inhibitors become more commonly used to treat RA and other autoimmune inflammatory diseases, we may gain a better understanding of potential rare side effects. Drug-induced nephrotic syndrome is an important diagnosis to keep on the differential, because a key component of management is the discontinuation of the offending agent. Renal manifestations as a result of TNF-α inhibition should be considered as potential rare complications when treating autoimmune inflammatory diseases.

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