CASE REPORT

ANCA-Associated Renal Vasculitis Following Anti–Tumor Necrosis Factor α Therapy

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We report the case of a 62-year-old woman with rheumatoid arthritis treated with adalimumab, an anti–tumor necrosis factor α drug, who presented with 4 weeks of lethargy, upper respiratory tract symptoms, a vasculitic skin rash, and rapidly deteriorating renal function. She had cytoplasmic antineutrophil cytoplasmic antibodies and skin and renal biopsy specimens diagnostic of small vessel vasculitis and necrotizing crescentic glomerulonephritis, respectively. After immunosuppressive therapy and discontinuation of adalimumab therapy, vasculitis resolved and renal function recovered. This is the first report of antineutrophil cytoplasmic antibody associated necrotizing glomerulonephritis with adalimumab.

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INDEX WORDS: ANCA; renal vasculitis; glomerulonephritis; anti-TNF alpha therapy; adalimumab; rheumatoid arthritis.

Anti–tumor necrosis factor α (TNF-α) drugs have revolutionized the management of rheumatoid arthritis and generally are well tolerated. The most common side effects include injection-site reactions, headache, and nausea; more serious infections and hematological disorders are rare.[1] Patients are monitored closely during therapy, and it is now recognized that repeated treatment with anti–TNF-α therapy can lead to the development of autoantibodies (mainly immunoglobulin M), including antinuclear antibody, anti–double-stranded DNA, and anticardiolipin antibodies, in up to 10% of patients.[2] This de novo autoantibody synthesis is associated with a greater total dose of therapy. Although rare, there are reports of anti–TNF-α–induced systemic lupus erythematosus,[3-5] cutaneous leukocytoclastic vasculitis,[5-8] and antineutrophil cytoplasmic antibody (ANCA) associated systemic vasculitis (AASV).[3,6,7] Renal involvement is unusual, and such cases have implicated infliximab or etanercept.[5] We describe cytoplasmic ANCA (cANCA) associated necrotizing glomerulonephritis in a patient with long-standing rheumatoid arthritis receiving treatment with adalimumab. To our knowledge, this is the first such case report.

CASE REPORT

A 62-year-old woman presented with a 4-week history of malaise, weight loss, nasal stuffiness, visual blurring, and oliguria. She had a 15-year history of seropositive erosive rheumatoid arthritis which was symmetrically affecting the small joints of her hands and feet. She had no rheumatoid nodules, and her only extra-articular manifestation was mild keratoconjunctivitis. Previous disease-modifying antirheumatic drugs included hydroxychloroquine, sulfasalazine, and methotrexate (she never received auranofin or penicillamine). Current drug therapy included adalimumab (for 4 years, last received 1 month before presentation), ibuprofen or meloxicam, atorvastatin, and lansoprazole. She recently received trimethoprim for a urinary tract infection. Nine months before presentation, serum creatinine level was 0.92 mg/dL (81 μmol/L), estimated glomerular filtration rate (eGFR; estimated using the 4-variable isotope dilution mass spectroscopy–traceable Modification of Diet in Renal Disease Study equation) was 66 mL/min/1.73 m^2 (1.1 mL/s/1.73 m^2), and urinalysis results were negative. Autoantibody levels, including ANCA, were not checked before starting anti-TNF therapy. However, 2 years before presentation, antinuclear antibody titer was weakly positive (1/160), but anti–double-stranded DNA and extractable nuclear antigen test results were negative.

On examination, the patient was pale and afebrile, blood pressure was 160/80 mm Hg, and she had a small superficial ulcer on her tongue, bilateral pitting ankle edema, and a purpuric rash on her right ankle and the cleft of her buttocks.

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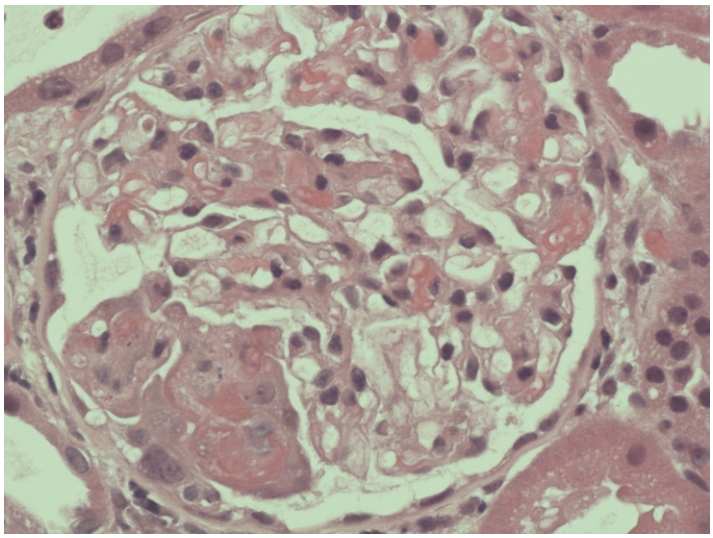

Figure 1. Glomerulus contains a segmental necrotizing lesion at 7 o'clock. Note fibrin and karyorrhectic nuclear debris. (Hematoxylin and eosin; high-power magnification).

Urinalysis showed blood (3+) and protein (3+), with urine protein to creatinine ratio of 5,923 mg/g. Kidney function on initial evaluation included a serum creatinine level of 1.9 mg/dL (164 μmol/L) and eGFR of 29 mL/min/1.73 m^2 (0.48 mL/s/1.73 m^2), which peaked a week later with a creatinine level of 6.7 mg/dL (590 μmol/L) and eGFR of 6 mL/min/1.73 m^2 (0.1 mL/s/1.73 m^2). cANCA was strongly positive with proteinase 3 levels of 57.2 U/L. Myeloperoxidase was negative at less than 1.2 U/L. Serum albumin level was 1.9 g/dL (19 g/L), hemoglobin level was 7.4 g/dL (74 g/L), C-reactive protein level was 257 mg/L, complement (normal) C3 level was 136 mg/mL (1.36 g/L), C4 level was 37 mg/mL (0.37 g/L), antinuclear antibody was positive at 1/640, and extractable nuclear antigen screen and double-stranded DNA antibodies were negative. Anti–glomerular basement membrane and anticardiolipin antibodies were negative.

An echocardiogram showed structurally normal valves with no vegetation. A computed tomographic chest scan showed no evidence of pulmonary vasculitis. Renal ultrasound identified 2 normal-sized kidneys. Renal and skin biopsies were performed.

Light microscopy showed 8 glomeruli: 1 was globally sclerosed and 5 contained segmental necrotizing lesions (Fig 1) with 4 active cellular crescents and 2 segmental glomerular sclerosing lesions. Fifteen percent of tubules were atrophic. There were red blood cell casts and a few intraluminal neutrophils, and 35% of the interstitium showed mild to moderate fibrosis and lymphocytic infiltrate. There was focal interstitial hemorrhage. There were no arteries in the biopsy specimen; however, arterioles were normal. Congo red and Sirius red stains for amyloid were negative. There were no glomeruli in the sample processed for immunofluorescence. Electron microscopy showed mild segmental sclerosis with no immune complex type deposits and no tubuloreticular lesions.

Light microscopy (Fig 2) showed a small to medium vessel vasculitic process with leukocytoclasis and prominent thrombosis. No organisms were identified on gram staining.

The diagnosis was ANCA-associated necrotizing glomerulonephritis and cutaneous vasculitis, possibly caused by long-term administration of adalimumab.

Treatment included intravenous methylprednisolone, 8 plasma exchanges, 1 hemodialysis treatment, oral prednisolone, and cyclophosphamide. The skin lesions resolved, and renal function improved to a creatinine level of 2.6 mg/dL (229 μmol/L) and eGFR of 19 mL/min/1.73 m^2 (0.32 mL/s/1.73 m^2) 4 weeks later. At outpatient review at 2 months, creatinine level was stable at 3 mg/dL (230 μmol/L) and eGFR was 19 mL/min/1.73 m^2 (0.32 mL/s/1.73 m^2), urine protein to creatinine ratio decreased to 1,786 mg/g, and cANCA was negative.

DISCUSSION

Anti–TNF-α drugs are now established therapy in the management of rheumatoid arthritis and several other chronic inflammatory diseases.[1] The proinflammatory cytokine TNF-α has a key role in the pathogenesis of rheumatoid arthritis and is the target for biological disease-modifying antirheumatic drugs. There currently are 3 anti–TNF-α agents: adalimumab, infliximab, and etanercept. All these were evaluated in clinical trials for the treatment of patients with rheumatoid arthritis.[1,9] Adalimumab is a fully human monoclonal antibody to TNF-α that binds both soluble and membrane-bound TNF-α.[10] Infliximab is a chimeric anti–TNF-α monoclonal antibody that binds to both soluble TNF-α and cells expressing TNF-α on their surface. These drugs mediate apoptosis through complement and antibody-dependent cytotoxicity.[10] Etanercept is a synthetic human TNF receptor–Fc fusion protein