Spontaneous Resolution of Lupus Nephritis Following Withdrawal of Etanercept

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Abstract. Introduction. Etanercept, a systemic inhibitor of α-TNF, is used for treatment of various autoimmune disorders. We report a case of spontaneous resolution of etanercept-induced lupus nephritis.

Case description. A 57-year-old female patient taking etanercept for psoriasis presented with laboratory- and histology-confirmed lupus nephritis. After stopping etanercept, there was normalization of proteinuria, hematuria, serum complement, anti-dsDNA antibody, and resolution of the acute glomerular inflammatory process on repeat kidney biopsy. Conclusion. This case demonstrates serology- and biopsy-confirmed resolution of active lupus nephritis upon withdrawal of etanercept.

Key words: etanercept, glomerulonephritis, lupus nephritis, kidney biopsy.

Introduction

Tumor necrosis factor alpha (α-TNF) plays a central role in the pathophysiology of psoriasis and psoriatic arthritis. The use of TNF inhibitors in the treatment of psoriasis is well established. There is significant improvement in the cutaneous and arthritic symptoms, as well as amelioration of the progression of the disease with the use of TNF inhibitors such as etanercept [1].

Induction of autoantibodies following treatment with anti-TNF alpha therapies has been widely reported. These autoantibodies include antinuclear antibodies (ANA), anti-dsDNA Ab, p-ANCA, and anti-cardiolipin antibodies. The induction of ANA is reported in 50-100% of patients, anti-DNA antibodies in 50-75%, and anti-cardiolipin Ab in about 25% [1,2,3,4].

Case Report

A 57-year-old female with a past medical history of Sjögrens, Psoriasis, hepatitis C virus, and cryoglobulinemia had been on a prolonged course of etanercept for moderately severe psoriasis. Treatment had to be discontinued following the development of palpable purpura on her lower extremities. Skin biopsy confirmed leukocytoclastic vasculitis. The lesions disappeared a few weeks after stopping the etanercept.

A few months after withdrawal of the medication, the patient had a relapse of psoriasis and etanercept was reintroduced. Eight months following re-introduction of etanercept she developed hypertension, new onset microscopic hematuria, non-nephrotic range proteinuria, and mild elevation of serum creatinine. Vital signs at that time were blood pressure 142/74 mmHg, pulse 68/min. Physical exam was also significant for synovitis of both wrists, but was otherwise unremarkable.

Laboratory studies showed white blood cell count 4.66 k/uL, hemoglobin 11g/dl, platelet count 131 K/uL, creatinine 1.1mg/dl (normal 0.7-1.5). Urinalysis revealed 2+ protein, 50 red blood cells/hpf with dysmorphic appearance and few white blood cells. The random urine protein/creatinine ratio was 0.75.

Additional laboratory studies showed a positive ANA titer 1:320 (homogenous pattern, ≤1:40 negative), anti-dsDNA >160 units/ml (<10 negative), C3 56mg/dl (normal 90-180), positive type II mixed cryoglobulins, positive RF 1070 IU/ml (normal <14 IU/ml), anti-SSB 22.5U/ml (normal <10U/ml). Antineutrophil cytoplasmic antibodies, anti-RNP antibody, and anticardiolipin antibodies were negative, and C4 was normal.

Etanercept was stopped and a kidney biopsy performed. The tissue submitted contained 40 glomeruli. There was an increase in intracapillary and mesangial cellularity, mesangial matrix, and thickening of the glomerular basement membrane. Vasculitis and intravascular thrombi were not seen. Immunofluorescent (IF) microscopy revealed granular 3+ staining for IgG, IgM, C3, C1q, kappa, and lambda in both glomerular capillary loops and mesangium. Electron microscopy (EM) showed large electron-dense deposits in the...
subendothelial and mesangial locations, consistent with Class IV lupus nephritis (Figures 1A, B, and C). Seven months after stopping etanercept there was progressive resolution of the proteinuria, normalization of the C3 level and ANA, and reduction of the anti-dsDNA Ab titer (Figures 3A and B). A repeat kidney biopsy was performed eight months after withdrawal of etanercept. The biopsy showed a decrease in intracapillary and mesangial cellularity as well as near resolution of the subendothelial dense deposits (Figures 2A, B and C).

**Discussion**

We describe the case of a 57-year-old female who, while on etanercept developed biopsy confirmed leukocytoclastic vasculitis, and serologic and histopathologic findings consistent with diffuse proliferative lupus nephritis. Etanercept was withdrawn, and there was complete resolution of the proteinuria, normalization of the serum complement C3, reduction of the anti-DNA antibody titer, and a significant improvement in the histopathologic findings on repeat kidney biopsy. The patient did not receive any immunosuppressive treatment, including steroids, for the lupus nephritis.

There are no recognized criteria for drug-induced lupus, but the clear temporal relationship of the clinical and laboratory manifestations with exposure, and subsequent resolution after withdrawal, leads us to believe that this patient had etanercept-induced lupus nephritis. We believe this report is unique in that we demonstrate significant resolution of the glomerular inflammatory process without specific immunosuppressive therapy for lupus nephritis. Notably, in all previous reports of lupus nephritis, immunosuppressive therapy was administered after withdrawal of etanercept. We cannot answer with clarity as to whether SLE was induced by etanercept, or whether the drug exacerbated a pre-existent SLE. Our patient had no evidence of prior kidney disease, and no prior serologic evidence of SLE. Spontaneous resolution would have been unlikely if this patient had pre-existing underlying SLE or if the biopsy findings were due to cryoglobulinemia.

In a French National Survey in 2005, the incidence of SLE induced by anti-TNF alpha therapy was reported as 0.18% [5]. Other investigators report a figure closer to 0.5 – 1.6% [3].
Ramos-Casals reported the occurrence of 233 cases of autoimmune diseases among 226 patients receiving TNF-targeted therapies [4]. There were 113 patients with vasculitis, 92 with lupus (including lupus-like syndrome, systemic lupus erythematosus, and isolated cutaneous lupus), and 24 with lung disease, and other diseases in four. Of the 92 patient with lupus, 44% were treated with infliximab and 40% with etanercept. Of the patients who fulfilled 4 or more SLE criteria, 51% received infliximab versus 37% with etanercept. The patients were predominantly female; the average duration of anti-TNF therapy was 41.2 weeks. Cutaneous features were found in 67%, arthritis in 31%, nephropathy in 7%, and CNS involvement in 3%. Anti-TNF therapy was stopped in 94% of the patients; 40% received corticosteroid therapy, and 12% immunosuppressive agents. Almost all patients improved. Costa [6] similarly drew attention to the increased prevalence of cutaneous manifestations, anti-DNA Ab, and hypocomplementemia and lupus nephritis in anti-TNF-alpha-related drug-induced lupus erythematosus.

P-ANCA positive pauci-immune necrotizing and crescentic glomerulonephritis (PiNCGN) [7, 8] have also been reported in the context of TNF therapies. There has also been a report of a patient with concurrent leukocytoclastic vasculitis and lupus nephritis [9], and a patient with p-ANCA associated PiNCGN and pulmonary vasculitis.

We concur with the recommendation to explore the possibility of an underlying autoimmune disease both clinically and serologically in patients considered for TNF-targeted therapy, as well as to closely monitor renal function at initiation and at regular intervals during therapy. Our report raises the possibility that, in the appropriate clinical scenario, withdrawal of etanercept may be sufficient to ameliorate autoimmune disease induced by TNF therapy.

References