Case Report

Proliferative Lupus Nephritis and Leukocytoclastic Vasculitis During Treatment with Etanercept

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ABSTRACT. Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine. Agents that neutralize TNF-α are effective in the treatment of disorders such as rheumatoid arthritis, juvenile rheumatoid arthritis (JRA), spondyloarthropathies, and inflammatory bowel disease. TNF-α antagonist therapy has been associated with the development of antinuclear antibodies (ANA) and double-stranded DNA (dsDNA) antibodies, as well as the infrequent development of systemic lupus erythematosus (SLE)-like disease. We describe the first case of biopsy-confirmed proliferative lupus nephritis and leukocytoclastic vasculitis in a patient treated with etanercept for JRA. (J Rheumatol 2005; 32:740–3)

Key Indexing Terms:
TUMOR NECROSIS FACTOR SYSTEMIC LUPUS ERYTHEMATOSUS
NEPHRITIS VASCULITIS ETANERCEPT

Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine involved in the pathogenesis of several inflammatory and autoimmune diseases[1]. Agents that neutralize TNF are effective in the treatment of disorders such as rheumatoid arthritis, juvenile rheumatoid arthritis (JRA), spondyloarthropathies, and inflammatory bowel disease. One TNF antagonist is etanercept, a soluble type II TNF receptor (p75) fused to the Fc portion of human immunoglobulin (Ig) G1. TNF antagonist therapy has been associated with the development of antinuclear antibodies (ANA) and anti-double-stranded DNA (dsDNA) antibodies, as well as the infrequent development of systemic lupus erythematosus (SLE)-like disease[2]. Other phenomena that have been reported in association with TNF antagonist therapies include discoid lupus, necrotizing vasculitis, leukocytoclastic vasculitis, accelerated nodulosis, demyelinating lesions of the central nervous system, and development of anticardiolipin antibodies[3].

We describe the first case of biopsy-confirmed proliferative lupus nephritis and leukocytoclastic vasculitis in a patient treated with etanercept for JRA. Other autoimmune aspects associated with etanercept are discussed.

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CASE REPORT

A 22-year-old woman presented with a purpuric rash and lower extremity edema. At 14 years of age she was diagnosed with polyarticular JRA after presenting with symmetric arthritis of hands, shoulders, ankles, and knees. C-reactive protein (CRP) and erythrocyte sedimentation rate were elevated, while both ANA and rheumatoid factor (RF) were negative. During her disease course she did not experience any extraarticular manifestations. She was treated with multiple disease modifying antirheumatic drugs [e.g, plaquenil, sulfasalazine, and methotrexate (MTX)] without achieving complete remission. Four years prior to current admission, she was started on etanercept and responded immediately.

Six weeks before admission to our hospital, she started to have oral pain due to erupting wisdom teeth. She was treated with 4 days of oral penicillin for possible gingivitis. Three weeks later she gradually developed ankle edema and a purpuric rash over her legs. A week prior to admission she noticed darkening urine. Because of additional diffuse joint pain (known manifestation of her JRA) she decided to seek medical attention.

Her family history was remarkable for maternal grandmother's sister who died of complicated lupus nephritis. The patient's medications on admission included etanercept (25 mg/2 times per week), MTX (10 mg/week), folic acid (1 mg/day), and rofecoxib (25 mg/day as needed).

Examination on admission revealed a weight of 88 kg, blood pressure 140/90 mm Hg, pulse 84/min, and temperature 37°C. She had enlarged cervical lymph nodes and bilateral bucal ulcers adjacent to her wisdom teeth. No heart murmurs were auscultated; however, the second heart sound (S_2) was prominent. She had bilateral ulnar deviation and synovitis of both wrists and second to third metacarpophalangeal joints. On her lower extremities she had 3+ bilateral pitting edema and multiple palpable purpuric plaques with scattered nonblanching petechiae. The rest of the physical examination was normal.

Laboratory studies were notable for the following values: white blood cell count 4700/mm^3, hemoglobin 9.0 g/dl, platelet count 163,000/mm^3, creatinine 2.1 mg/dl (normal 0.1–1.1), blood urea nitrogen 21 mg/dl (normal 15–45), albumin 2.6 g/dl (normal 3.5–4.5), CRP 7.6 mg/l (normal < 3 mg/l). Urinalysis revealed 3+ protein, packed white blood cells, 3+ red blood cells with dysmorphic appearance, and granular casts. Urinalysis and creatinine 2 months earlier were normal. Chest radiograph showed a borderline enlarged cardiac silhouette. Hand and wrist radiographs were notable for marked periarticular osteopenia, ulnar deviation, and severe

narrowing of the intercarpal, radiocarpal and carpal metacarpal spaces with marginal erosive changes, compatible with JRA.

The etanercept was stopped and a diagnostic investigation was obtained. Additional laboratory studies revealed negative RF, cryoglobulins, antineutrophil cytoplasmic antibodies, anti-RNP antibody, anticardiolipin antibodies, and hepatitis C antibodies. Blood and throat cultures were sterile. Anti-streptolysin-O titer was within normal limits. Laboratory studies also indicated positive ANA titer at 1:320 (homogenous pattern, ≤ 1:40 negative), anti-dsDNA > 200 units/ml (0–30 negative; ELISA, Quest Diagnostics, Teterboro, NJ, USA), anti-Ro/SSA > 6 units (positive > 1.0), with negative anti-La/SSB, anti-Sm 1.54 units (positive > 1.0), antihistone 10.1 units (positive > 1.0), C4 1.3 mg/dl (normal 10–34), C3 35 mg/dl (normal 75–140), and circulating immune complexes > 31 UG eq/ml (C1Q binding assay; Quest; normal < 4.0); 24 h urine collection revealed 3.6 g of proteinuria (normal < 0.3 g). HLA typing showed: A2, A-, B18(BW6), B58(BW4), CW7, CW-, DR17, DR10, DQ5, and DQ2, lacking markers classically associated with genetic predisposition for lupus.

Skin biopsy revealed leukocytoclastic vasculitis (Figure 1). A renal biopsy revealed lupus nephritis, World Health Organization classification Type IV (Figure 2). Glomeruli showed severe hypercellularity and lobulation of the tufts. Endocapillary proliferation, extensive double contours with interposition of mesangial cells, and subendothelial (wire loops) and intraluminal deposits were noted. Areas of interstitial fibrosis and tubular atrophy occupied less than 5% of the parenchyma. Immunofluorescence showed a "full house" pattern of positive staining for IgG, IgA, IgM, C3, C1q, kappa and lambda light chains, with global granular mesangial and segmental granular semilinear staining in the capillary loops (Figure 3). Ultrastructural studies revealed extensive electron-dense deposits in the mesangium, subendothelium and intracapillary. Double contours of the capillary walls with interposition of mesangial cells were seen on electron microscopy (Figure 4).

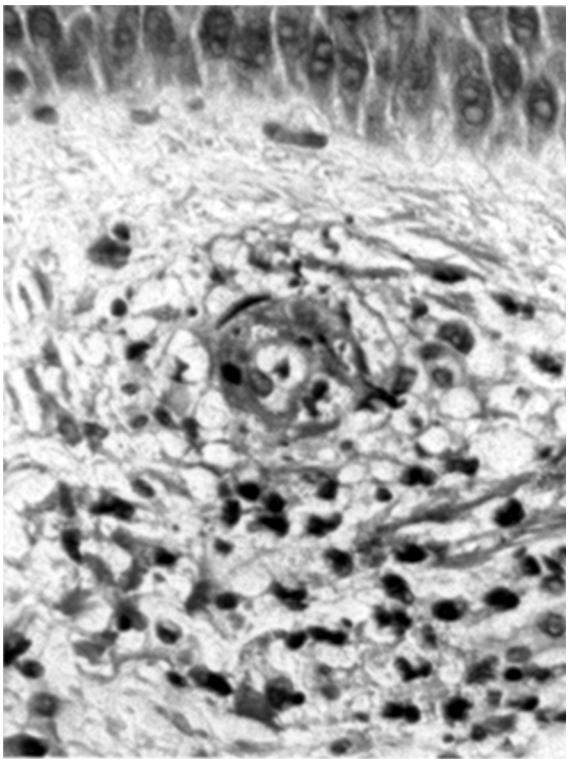

Figure 1. Hematoxylin-eosin stain of skin biopsy from right leg, high magnification, reveals perivascular and focal interstitial infiltrate of predominantly neutrophils with eosinophils, lymphocytes, and mural fibrin in small vessel.

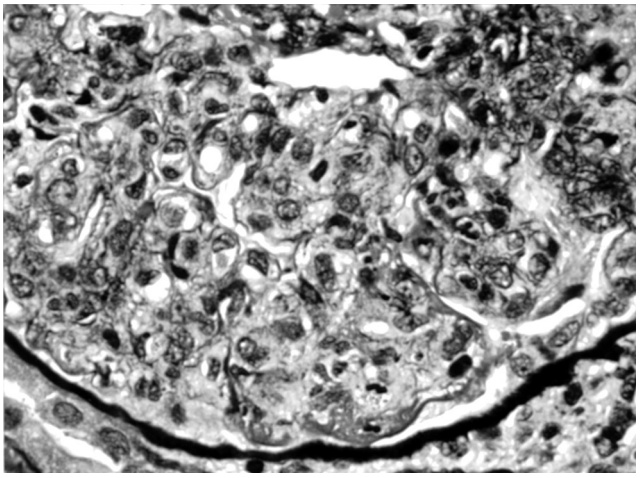

Figure 2. Light microscopy: silver staining shows a hypercellular glomerulus with double contours and subendothelial deposits (wire loops). Inflammatory cells are also noted within the glomerular tuft.

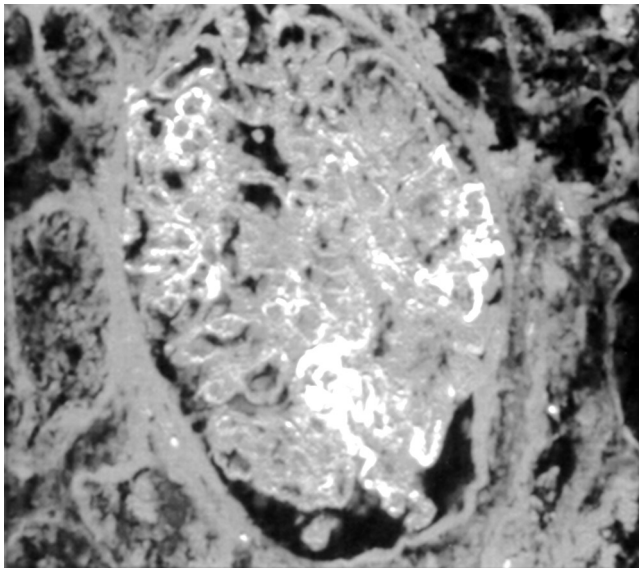

Figure 3. Immunofluorescence: C1q is strongly positive in the mesangium (granular) and in the capillary loops (granular and semilinear).

A week after the withdrawal of etanercept, in the absence of antihypertensive drug, the patient's blood pressure improved from 140/90 to 120/80 mm Hg, the skin lesions disappeared, and improvement was observed in some laboratory values (Table 1). Parenteral solumedrol (1 mg/kg/day) was instituted on the 8th hospital day. Two months later, her blood pressure normalized, the creatinine returned to 1.1 mg/dl, and all other laboratory indicators were significantly improved (Table 1). When last seen 6 months after onset of lupus-like syndrome, no longer taking steroids, she had normal renal function and no other evidence of active inflammatory disease.

DISCUSSION

Our patient presented with lupus nephritis (diffuse proliferative glomerulonephritis, DPGN) and leukocytoclastic vasculitis while being treated with etanercept. Although the onset of symptoms did not coincide with the initiation of etanercept treatment, rapid resolution of the clinical features

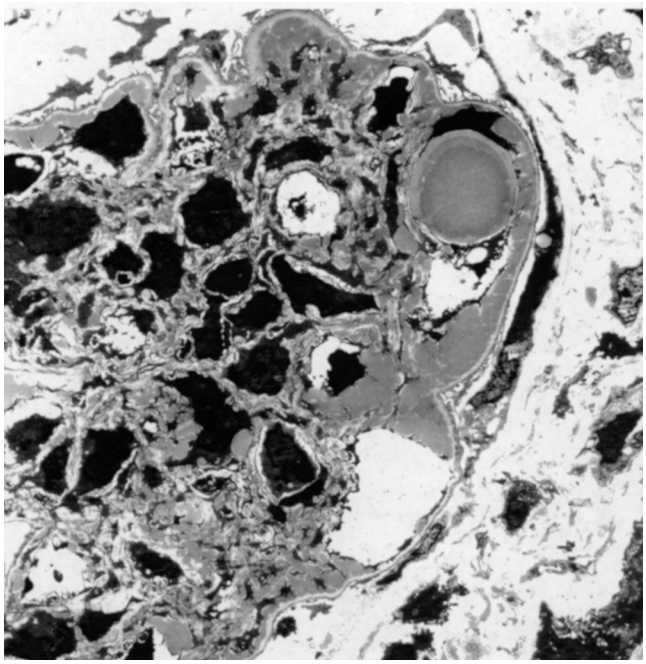

Figure 4. Electron microscopy: large subendothelial (wire loops) and intraluminal deposits (pseudo-thrombi). Occasional mesangial deposits are also present.

and accompanying laboratory improvement following discontinuation of the drug implicates etanercept as either unmasking or inducing her disease. Also, the absence of autoantibodies at initial presentation that converted later to positive (i.e., ANA, anti-dsDNA, anti-Ro, anti-Sm, anti-histone, hypocomplementemia) further suggests etanercept, and not penicillin, as the possible offending agent for development of lupus-like syndrome. Unfortunately, assessments for these antibodies were not routinely performed immediately preceding or during etanercept treatment, although 3 months prior to starting treatment the results were negative for ANA, anti-dsDNA, and RF. Serum creatinine and urinalysis were monitored during the treatment period and found to be in normal limits. It is unlikely that the patient had lupus prior to the treatment due to lack of clinical symptoms, repeated negative ANA, and articular erosions typical of JRA.

The superiority of cyclophosphamide plus prednisone compared to prednisone alone in the treatment of lupus nephritis has been established only in controlled trials of patients that failed prior steroid treatment. Therefore, it may be appropriate to use only steroids as initial management of even DPGN and reserve cytotoxics as rescue therapy for unresponsive or remitted diseases[4,5].

Development of autoantibodies has been well described in association with all available TNF antagonists including etanercept. Weinblatt, *et al* found that 14% of patients with RA treated with a combination of etanercept and MTX for 24 weeks had positive anti-dsDNA compared with 7% at baseline[6]. Moreland, *et al* followed 234 RA patients treated with etanercept as monotherapy[7]. Before treatment 5% were positive for anti-dsDNA compared to 12% after 6 months. In the placebo group, 5% were positive before the treatment compared to 6% after the study period. Genovese, *et al* studied patients with early RA and were not able to find consistent differences in the number of patients testing positive for autoantibodies[8]. Aggregate clinical trial datasets for etanercept in RA compared to placebo have reported an incidence of 15% positive anti-dsDNA and 11% positive ANA after treatment with etanercept compared to 4% and 5%, respectively, in a placebo group[9].

Several explanations have been suggested to explain the relationship between TNF antagonist therapies and anti-dsDNA formation. The balance between CD4+ T-helper cell subsets (Th1 vs Th2) is felt to play an important role in the pathogenesis of RA and SLE. RA is believed to be a Th1-mediated disease with TNF as a prominent downstream cytokine, while SLE is characterized by a predominant Th2 cytokine profile with B cell activation[10,11]. Heine, *et al* showed that a decline in the Th1/Th2 ratio accompanies clinical remission in SLE in patients with nephritis[12]. Inhibition of TNF by etanercept also induced a reduction of Th1 responses in an *in vitro* system[13]. By reducing the level of free TNF, TNF inhibition may shift toward a Th2 bias, thus contributing to the development of autoantibodies and lupus-like manifestations.

The prevalence of bacterial infections can increase with

Table 1. Clinical progress of this patient.

Variable	Upon Admission	1 Week After Admission	2 Weeks After Admission*	4 Weeks After Admission	2 Months After Admission	6 Months After Admission**
Blood pressure, mm Hg	140/90	120/80	110/70	110/65	110/70	110/65
ANA titer (≤ 1:40 negative)	1:320	NA	NA	1:80	NA	1:640
dsDNA units (0–30 negative)	> 200	200	160	143	61	Negative
C3 mg/dl (75–140)	35	48	37	64	108	134
C4 mg/dl (10–34)	1.3	1.6	3.3	6.4	14.4	17.5
Creatinine mg/dl (0.1–1.1)	2.1	1.6	1.4	1.2	1.1	0.7
Urine Protein, g/day (< 0.3)	3.6	2.4	2	1.2	0.134	0.250

* On steroid treatment. ** Not on steroid treatment. NA: Not available.

TNF blockade. Bacterial infection is a powerful immunostimulant that may lead indirectly to anti-dsDNA positivity by inducing polyclonal B cell activation. In one study, bacterial infections were documented in 3 patients treated with etanercept who became anti-dsDNA positive; antibiotic treatment produced a return to normal of the anti-dsDNA titer[14].

The binding of TNF antagonists to target cells may induce apoptosis and secondary release of nuclear antigens into the circulation. While apoptosis of target cells has been observed *in vitro* with monoclonal antibody therapies against TNF, this has not been reported to date for etanercept. Whether apoptosis occurs at low levels *in vivo* has not been determined. Furthermore, CRP, a molecule that clears apoptotic cells, is rapidly downregulated by anti-TNF therapy, possibly yielding higher immunogenic DNA load.

Ten cases of biopsy-proven autoimmune rashes associated with etanercept have been described[15-18]. In most cases ANA were negative, and in all 10 cases anti-dsDNA were negative. In all cases the rash resolved after discontinuation of treatment. A literature search revealed 6 cases of lupus-like symptoms developing after etanercept therapy[19,20]. All patients were women, with an average age of 43 years. The duration between the initiation of treatment and the onset of symptoms was between 6 weeks and 14 months. The symptoms consisted of arthritis, pleuritis, and rash. ANA were positive in all cases and anti-dsDNA were positive only in 4. The symptoms resolved 2 to 4 weeks after drug withdrawal. Several cases of SLE-like disease associated with other TNF antagonists have also been reported. In most cases no major organ involvement was reported and preexisting positive ANA was found to be a risk factor[18-21].

Carlson, *et al* reported a case of etanercept-associated renal disease. This patient developed positive anti-Ro, anti-La, anti-Sm, and anti-RNP and active urine sediment after etanercept treatment. A renal biopsy was not performed in this case; however, drug discontinuation and prednisone treatment led to reversal of the clinical findings[21].

To our knowledge, our case is the first description of coexistent leukocytoclastic vasculitis and biopsy-proven lupus DPGN occurring in a patient treated with etanercept. This case does not prove causality, but illustrates the importance of continued monitoring for lupus-like disease in patients undergoing longterm etanercept treatment. Based on this case and the literature review, we recommend baseline ANA test, and when positive, anti-dsDNA, anti-Ro, anti-La, anti-Sm, and C3 and C4 before instituting TNF antagonist therapy. This case also suggests that patients who have family members affected by clinical SLE may be especially at risk. Periodic serologic surveillance, including ANA, dsDNA, C3 and C4, creatinine, and urinalysis and clinical surveillance for development of lupus-like symptoms is indicated to determine the true incidence of SLE-like syndromes in patients treated with TNF antagonists in clinical practice.

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Mor A, Bingham C 3rd, Barisoni L, Lydon E, Belmont HM. Proliferative lupus nephritis and leukocytoclastic vasculitis during treatment with etanercept. J Rheumatol 2005;32: 740-3. For indexing purposes, the name of the second author should read Clifton O. Bingham 3rd.

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