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Accelerated Nodulosis and Vasculitis Following Etanercept Therapy for Rheumatoid Arthritis

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Introduction

Cytokine networks play an important role in the clinical manifestations of inflammatory diseases such as rheumatoid arthritis (RA). Tumor necrosis factor α (TNFα) is a proinflammatory cytokine that influences a number of immunologic events. It increases other proinflammatory mediators, induces expression of cell adhesion molecules, and stimulates production of proteolytic enzymes (1). Elevated levels of TNFα have been demonstrated in the synovial fluid and synovial membranes of patients with RA (2). TNFα is, therefore, an important target in disease control.

Etanercept is a recombinant human TNF receptor fusion protein, consisting of the extracellular portion of 2 p75 receptors bound to the Fc component of human IgG1. It competitively inhibits the binding of both TNFα and TNFβ to cell surface TNF receptors, thus preventing the biologic consequences of TNF activity. Several randomized clinical trials have demonstrated the remarkable benefits of anti-TNFα treatment. It has been shown to induce a rapid and significant clinical response and decrease radiographic progression with apparent minimal toxicity in patients with RA (1,3,4). Injection site reactions are the most commonly cited adverse events. However, reports of more serious side effects have been published (5–7). Herein, we describe 3 patients with longstanding, refractory, seropositive erosive RA who, despite clinical improvement with etanercept, developed new nodulosis and, in 2 cases, an associated vasculitis shortly after the initiation of treatment with this biologic medication. Possible mechanisms underlying these pathologic events are discussed.

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Case reports

Patient 1 is a 52-year-old Hispanic man with a 25-year history of nodular, erosive, seropositive RA. His disease has been poorly responsive to intramuscular gold, methotrexate, azathioprine, and cyclosporine. In April 1999, he developed a polyarticular flare (erythrocyte sedimentation rate [ESR] 37 mm/hour) despite therapy with prednisone (20 mg/day), naproxen (500 mg twice daily), and cyclosporine (250 mg/day). Etanercept (25 mg twice weekly) was started in place of cyclosporine. Within a month, there was a remarkable decrease in joint pain and swelling, a reduction in ESR to 12 mm/hour, and an improvement in well being. The patient had never noted such a dramatic response to previous disease-modifying medications. The dosage of prednisone was slowly tapered, but approximately 8 weeks after starting etanercept he noted new nodules on his fingers and left elbow. Although the ESR had risen to 31 mm/hour, his joint symptoms remained quiescent. Thus, despite this extraarticular development, etanercept was continued and the prednisone dosage was slowly reduced to 8 mg/day. In July 2000, the patient noted increasing joint pain and stiffness, but no change in his nodular disease. His ESR was 37 mm/hour. Leflunomide was added to his regimen, resulting in good symptomatic improvement. He remains stable taking leflunomide (20 mg/day), etanercept (25 mg twice weekly), and prednisone (8 mg/day). He has had no further progression of his nodulosis, and his acute phase response is within normal limits (ESR 7 mm/hour).

Patient 2 is a 50-year-old Caucasian man with a 20-year history of nodular, erosive, seropositive RA. He had incomplete clinical responses to several disease-modifying medications including hydroxychloroquine, methotrexate, and azathioprine. Accelerated nodulosis had been observed while taking methotrexate. In January 2000, because of active disease (polyarticular involvement, ESR 70 mm/hour), he began taking etanercept (25 mg twice weekly). When examined in the clinic 1 month later, a dramatic symptomatic improvement was noted, with decreased pain and swelling of all joints with the exception of his knees. His ESR had decreased to 32 mm/hour. Three months later, he reported that his finger nodules were more numerous and painful. His joint symptoms remained well controlled, apart from chronic synovial hypertrophy

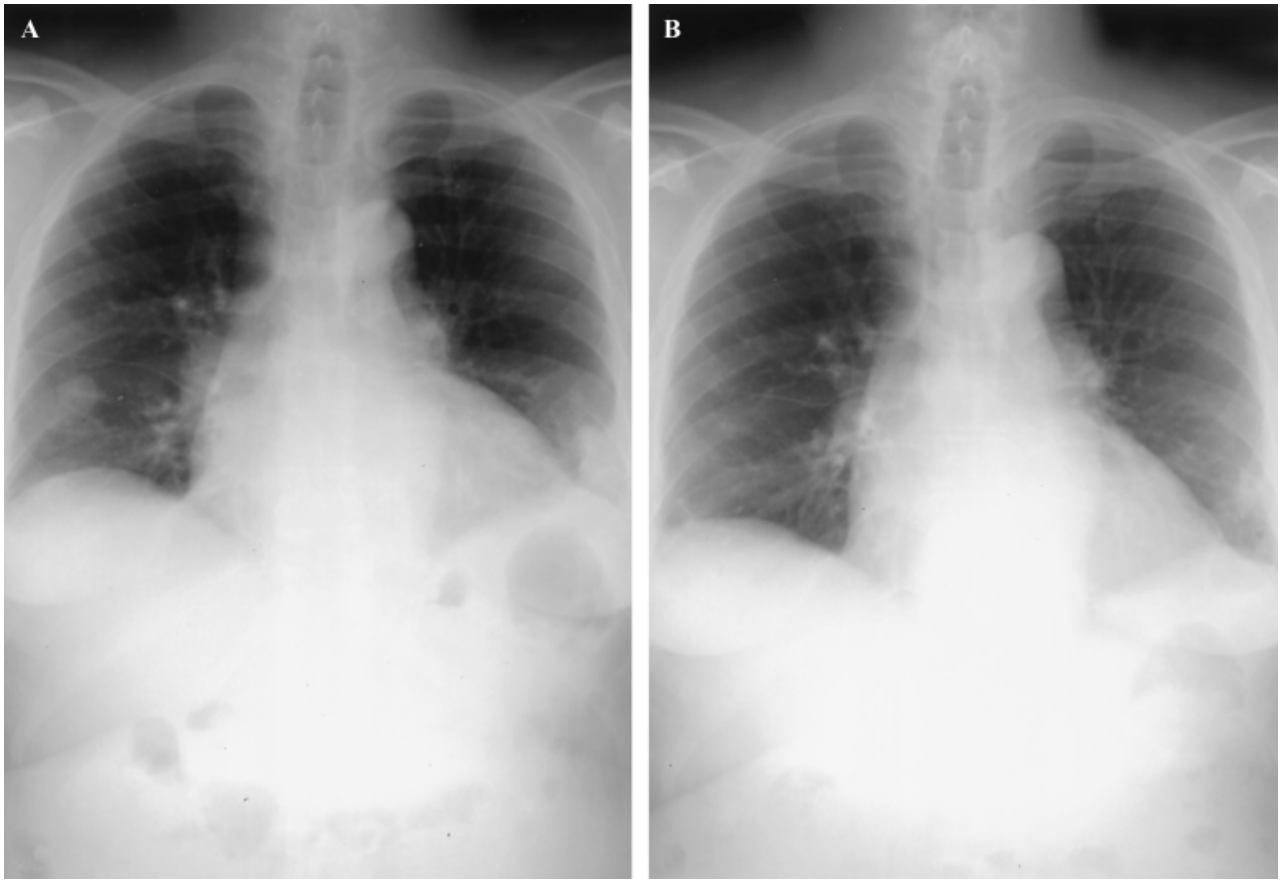

Figure 1. A, Chest radiograph of Patient 3, December 1999. Multiple large nodules are present in the left lung base and a single large nodule is apparent in the right lung base. A cavitating lesion is present in the right midzone. **B,** Chest radiograph of the same patient, November 2000, demonstrating resolution of pulmonary nodules and cavitatary lesions with residual scar formation.

of both knees. Prednisone (10 mg/day) was added to his drug regimen in July 2000 and he received multiple corticosteroid injections to his knee joints during the next year. In December 2000, his finger nodules were noted to be more numerous and he developed nailfold infarcts consistent with cutaneous vasculitis, although his joints were asymptomatic. At this time, the patient had a rheumatoid factor titer of 1:20,480 and an ESR of 59 mm/hour; he was antinuclear antibody (ANA) negative and hepatitis B and C negative. Because of the good clinical response to etanercept, this medication was continued and leflunomide (20 mg/day) was added. By March 2001, there was slight improvement in both the nodules and cutaneous vasculitis, and his ESR was 42 mm/hour. His joint symptoms remain well controlled with the combination of etanercept and leflunomide.

Patient 3 is a 67-year-old African American man with erosive, seropositive RA of 26 years' duration. He had no evidence of cutaneous nodulosis, although he was diagnosed with bilateral nodular scleritis in 1990 and had multiple asymptomatic pulmonary nodules noted on chest radiographs since 1991. His arthritis was resistant to treatment with several agents, including azathioprine, sulfasalazine, plaquenil, methotrexate, and leflunomide. He had been taking prednisone (5–15 mg/day) for many years. In September 1999, etanercept (25 mg twice weekly) was added to his regimen in a further attempt to control his marked synovitis. He had a rapid symptomatic response and stated that this was the most effective medication to date. However, within 2 months of starting the etanercept, he complained of a troublesome dry cough and increasing exertional dyspnea. On physical examination, he was afebrile with a pulse of 78/minute, blood pressure of 140/80 mmHg, respiratory rate of 22/minute, and oxygen saturation on room air at 90%. Auscultation of the chest demonstrated only coarse crackles at the left base. Despite multiple chronic joint deformities, there was little synovitis and no evidence of subcutaneous rheumatoid nodules. A chest radiograph showed bilateral pleural effusions and cavitating pulmonary disease (Figure 1A) and chest computed tomography (CT) demonstrated several cavitating lung lesions (Figures 2A and B). An open lung biopsy was performed, revealing multiple necrotizing pulmonary nodules with a marked inflammatory cell infiltrate and evidence of vasculitis involving several muscular arteries and small veins in areas adjacent to the nodules (Figure 3). All cultures (including tuberculosis) from these lesions were negative. Laboratory studies revealed mild anemia (hematocrit 39.9%), elevated ESR (30 mm/hour), positive rheumatoid factor (1:160), negative ANA, negative antineutrophil cytoplasmic antigen, negative hepatitis screen, normal serum creatinine, and negative urinalysis. Because the pulmonary cavitations and vasculitis had occurred shortly after the commencement of etanercept, this medi-

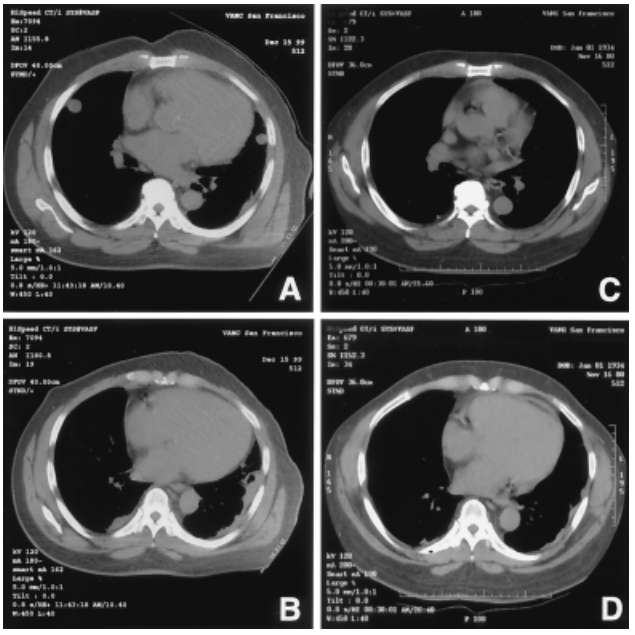

Figure 2. A, B, Chest computed tomographs of Patient 3 obtained in December 1999. Multiple nodules are present at the pleural surfaces bilaterally. A cavitating lesion can be observed in the left lung. **C, D,** Chest computed tomographs of Patient 3 obtained November 2000. Images from levels corresponding to the prior scan demonstrate remarkable resolution of these lesions.

cation was stopped. He was treated with azathioprine (150 mg/day) and his prednisone was increased to 60 mg/day. This regimen resulted in amelioration of his respiratory symptoms over the next month. Azathioprine was continued and his prednisone dosage was slowly tapered. A followup chest CT in March 2000 demonstrated interval improvement in the pulmonary nodules and healing of the cavitations. By July 2000, the chest radiograph and CT scan showed scarring in the lung periphery in areas where the nodules had previously been evident. Followup investigations in November 2000 again demonstrated resolution of these lesions (Figures 1B, 2C, 2D), and both his respiratory and arthritis symptoms remained quiescent.

Discussion

Rheumatoid nodules occur in approximately 25% of patients with RA (8). They are most commonly found subcutaneously at sites of external pressure, but may also involve internal tissues where major organ compromise can result. They have a distinctive pathologic appearance consisting of a central necrotic area surrounded by a palisade of macrophages and fibroblasts, and an outer vascular connective tissue layer infiltrated with T cells and macrophages. The early nodule is composed of newly proliferated capillaries with adjacent mononuclear cells and fibroblasts. Formation of the palisade and development of central necrosis characterize the mature nodule (8).

The pathogenetic mechanisms underlying the formation of rheumatoid nodules are unknown, although local trauma, proteolytic enzymes, immune complexes, and genetic factors have been implicated (8). Still being debated is the theory that vasculitis initiates nodular formation, and some compelling evidence indicates that endothelial cell injury is an associated and essential component of nodule formation. Complement activation and immunoglobulin deposition have been observed in the vessel walls of both early and long-standing nodules (9). The predilection of rheumatoid nodules for subcutaneous sites implies that local pressure may also be important. Furthermore, it has been suggested that the presence of subcutaneous nodules may denote the concomitant development of subclin-

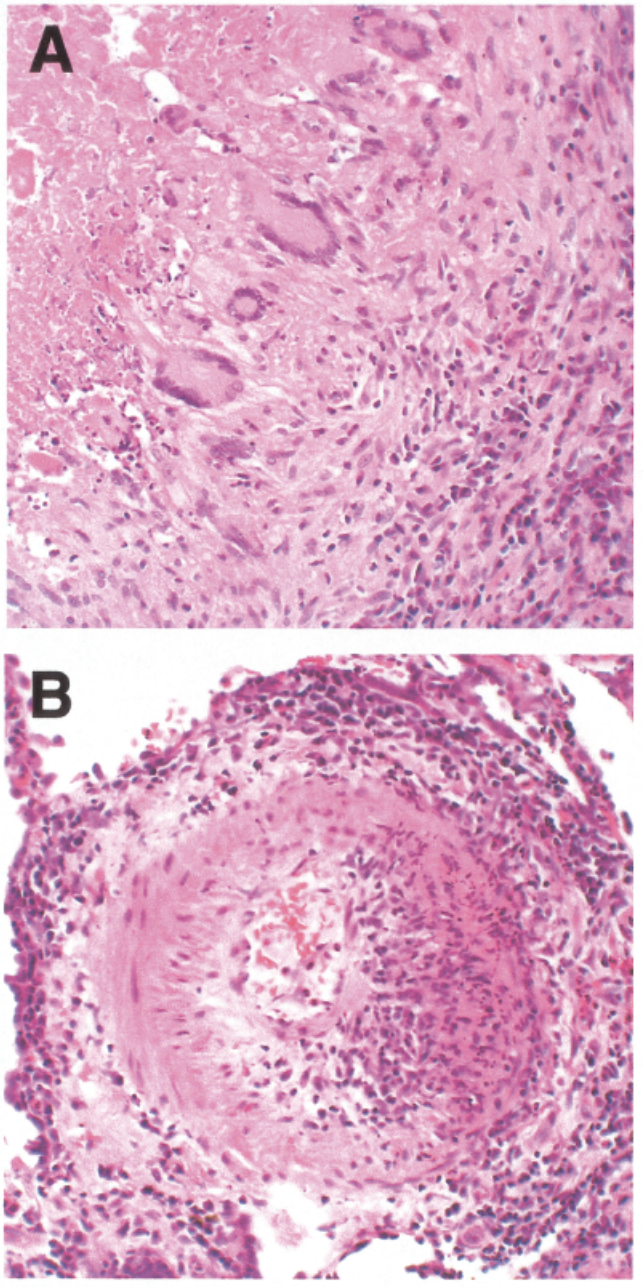

Figure 3. A, Hematoxylin and eosin stain demonstrating the wall of one of the pulmonary nodules. A zone of necrosis is rimmed by multinucleated giant cells, epithelioid cells, chronic inflammatory cells and fibroblasts (×250). **B,** Hematoxylin and eosin stain of an artery in the vicinity of a nodule. This muscular artery shows marked narrowing by segmental mural inflammation with neutrophils and chronic inflammatory cells (×250).

ical nodules in the internal organs, thus reflecting the presence of systemic disease.

Similarities in the histologic characteristics of the rheumatoid nodule and the inflamed rheumatoid synovial membrane have been highlighted previously (10,11). Features common to both processes are the formation of new blood vessels through which chronic inflammatory cells accumulate, the dominance of activated macrophages, and the association of mature macrophages with fibroblasts in a layered fashion. However, important differences between these structures also exist. In contrast to RA synovium, rheumatoid nodules lack B cells, plasma cells, and organized lymphoid structures (11). In addition, nodular fibroblasts and synoviocytes demonstrate several pathophysiologic differences (10), and E-selectin expression is higher in the blood vessels of rheumatoid nodules compared with those in the synovial membrane (11). Interleukin-1 levels were found to be significantly higher, and TNFα concentrations significantly lower in the supernatants of rheumatoid nodule cultures compared with those of the synovium from the same patients (11). Thus, variations in cytokine levels and adhesion molecule expression may result in different pathologic effects in the nodule and the joint, with prominent cell necrosis in one and the development of bony erosions in the other.

The consequences of anti-TNFα therapy on the rheumatoid synovium have been well described. Down regulation of synovial membrane cell adhesion molecule expression has been demonstrated in association with decreased inflammatory cell infiltration after TNFα inhibition in RA (12). The clinical effects of anti-TNFα treatment are also impressive. Rapid symptomatic improvement is often observed in association with objective decreases in synovitis and a marked reduction in the acute phase response (1,3,4). However, some pathologic effects linked to anti-TNFα treatment have been described recently, including leukocytoclastic vasculitis, cutaneous eosinophilic necrotizing vasculitis, discoid lupus, new-onset diabetes mellitus, and an increased incidence of autoantibody formation (5–7,13). In a recent study of infliximab in RA, the induction of anti-DNA antibodies was 7%, but the frequency of clinical lupus was just 0.6% (13). Thus, the link between the development of autoantibodies and the occurrence of disease is unclear, and many of the new autoantibodies observed in patients treated with anti-TNFα and other disease-modifying medications may not be pathogenic. On the other hand, the binding of anti-TNFα drugs to their target cells may induce apoptosis and secondary release of nuclear antigens into the circulation (13). In addition, C-reactive protein, a molecule that clears apoptotic debris, is rapidly down regulated by anti-TNFα therapy, possibly yielding a higher immunogenic load (14). Other putative mechanisms underlying the induction of autoimmune phenomena in patients treated with anti-TNFα agents include a change in the T cell cytokine profile and alterations in the functions of T or B lymphocytes. Furthermore, abnormally low TNFα levels might permit an exaggeration of the effects driven by other inflammatory mediators, as demonstrated in TNFα knockout mice (15). Thus, new autoimmune phenomena, such as vasculitis, may emerge concomitantly with an improvement in synovitis.

The development of new nodules in RA patients treated with etanercept may be linked to these immune abnormalities, particularly if vasculitis is the underlying pathologic event. On the other hand, nodulosis may be a separate process, precipitated by different mechanisms. The increased peripheral blood counts observed after anti-TNFα infusion are thought to be related to reduced cell traffic to the inflamed joint (16). It is conceivable that these migratory cells infiltrate other inflamed tissues, such as rheumatoid nodules. Such nodules have been found to contain lower TNFα concentrations compared with the synovium and thus may be less influenced by this cytokine (11). Furthermore, in contrast to the observed flares of synovitis that occur in patients with RA, the rheumatoid nodule may represent chronic inflammation that is less susceptible to the benefits of anti-TNFα therapy. However, it is possible that accelerated nodulosis, also seen in patients taking methotrexate, is a benign side effect of treatment, resulting from increased cell death and enhanced chemotaxis of inflammatory cells by the enlarging necrotic center of the rheumatoid nodule.

The development of vasculitis and accelerated nodulosis may be unrelated to treatment effects and may simply be part of the natural history of RA, particularly in patients who have already demonstrated evidence of disease resistance. The occurrence of new vasculitis or nodulosis was not reported in the recent clinical trials of anti-TNFα agents. Clearly, there are differences between typical patients and those who participate in clinical trials, especially with regard to the presence of comorbid illnesses and the use of concurrent medications. Examination of tissue from rheumatoid nodules and synovium before and after treatment with anti-TNFα or methotrexate might provide further insight into the differences between synovitis and the extraarticular manifestations of RA. It is likely that synovial inflammation and rheumatoid nodulosis/vasculitis follow different clinical courses, perhaps due to separate cytokine perturbations in these tissues. Therefore, anti-TNFα therapy benefits some but not all of the profound immunologic disturbances observed in patients with RA.

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