Case Report

Development of Crohn's Disease in a Patient Taking Etanercept

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ABSTRACT. In addition to its well known proinflammatory effects, tumor necrosis factor-alpha (TNF-α) has complex effects on the growth, differentiation, and death of immune cells. TNF antagonists have had dramatic effects on the suppression of rheumatoid arthritis and other rheumatic inflammatory diseases. However, TNF inhibition of RA has led to an increased incidence of drug induced anti-dsDNA production, with cases of systemic lupus erythematosus as well as exacerbations of multiple sclerosis. While etanercept does not generally alter the course of Crohn's disease we describe a rare instance where this agent may have contributed to the development of clinically significant inflammatory bowel disease. (J Rheumatol 2005;32:752–3)

Key Indexing Terms:
CROHN'S DISEASE
ANTIINFLAMMATORY
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Tumor necrosis factor-alpha (TNF-α) has broad pleiotropic effects on the immune system, which include lymphoid organ development and the growth, survival, and function of immune cells[1]. In addition to these regulatory effects, TNF-α is well known for its proinflammatory activities. It has been implicated in the pathogenesis of many autoimmune diseases including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and Crohn's disease (CD)[2-4]. Patients with RA treated with TNF antagonists can develop anti-dsDNA antibodies and even systemic lupus erythematosus[5,6] and develop exacerbations of multiple sclerosis[7]. Thus TNF-α can be either pathogenic or protective. We describe a patient whose PsA was controlled with etanercept 50 mg weekly, but who nonetheless developed new onset Crohn's-like inflammatory bowel disease while receiving this agent.

CASE REPORT

A 21-year-old man with a 10-year history of PsA was in clinical remission after beginning etanercept 25 mg twice weekly 3 years prior. Previously, he had required longterm prednisone 20 mg daily to control his arthritis despite concurrent methotrexate therapy. He presented to our clinic with right upper quadrant and bilateral lower quadrant pain of 3 weeks' duration. Initially, the pain was intermittent, but had become constant with an associated rectal throbbing pain. The abdominal pain worsened upon eating. He had alternating bouts of diarrhea and constipation with occasional bright red blood in his stools. He denied fever, weight loss, or anorexia. His family history was significant for CD in an aunt.

Examination showed normal vital signs. The physical examination was pertinent for right upper quadrant tenderness to palpation without guarding or rebound. The musculoskeletal examination showed a kyphotic posture and chronic arthritic changes of multiple joints without synovitis. There were no psoriatic plaques. Laboratory examination was unremarkable: white blood count 10.6, hemoglobin 13, platelets 292, chemistry panel normal, erythrocyte sedimentation rate 39.

He underwent a colonoscopy that revealed deep ulcerations in the terminal ileum, deep ulcerations with cobblestoning in the cecum, and scattered aphthous ulcers extending from the rectum to the right colon. Six biopsies from the ileum to the rectum were taken. The histopathology showed areas of acute and chronic inflammation in all 6 samples. There was also some crypt destruction, but no transmural inflammation or granulomas were seen, as the biopsies were superficial. Although the histological features were nonspecific, the diagnosis suggested CD because of involvement of the terminal ileum, colon, and rectum. He continued taking etanercept for his arthritis and started mesalamine for his CD, with good control. He was offered infliximab to treat both his PsA and CD but he declined.

DISCUSSION

This case exemplifies the complexity of TNF-α inhibition and autoimmune diseases. Antagonism of TNF-α with etanercept reduced inflammation in the joints and skin, but inadvertently may have precipitated clinically significant inflammatory bowel disease. The presumed predominant mode of action of TNF-α in PsA and CD is its classic proinflammatory effect via mobilization of neutrophils, monocytes, macrophages, and T cells into target organs. Thus, blocking TNF-α should decrease inflammation and produce remission of disease. However, TNF-α also exhibits immunomodulatory effects via attenuating T cell receptor signaling, B cell growth, and dendritic cell maturation[8,9]. Therefore, although uncommon, blockade of TNF-α may

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have unexpected adverse side effects when used as a therapeutic agent.

Although in most instances the antiinflammatory effects of anti-TNF-α monoclonal antibodies and soluble TNF receptors are similar[10], there are some differences in the therapeutic profile and adverse side effects. Infliximab has been much more effective in CD than etanercept[11-15]. Marzo-Ortega, *et al* have recently published 2 case reports in which the arthropathy associated with CD improved with etanercept, but the colitis either worsened or remained the same[15]. The reasons for these differential effects are poorly understood.

Dysregulation of the normal immune system directed against dietary or microbial antigens found in the intestinal lumen appears to be important in the pathogenesis of inflammatory bowel disease. Increased T cell responsiveness to microbial antigens or a failure of regulatory T cells to control normal responses could trigger disease onset[16]. The normal mucosal immune system of the intestine contains cells that prevent T cells reactive to the bacterial flora from causing harmful immune responses. These cells include professional antigen-presenting cells and regulatory T cells. We have been able to induce human peripheral CD4+ and CD8+ cells to become potent regulatory cells with interleukin 2 and transforming growth factor-beta. In unpublished studies, we observed that blockade of TNF-α by neutralizing antibodies has inhibitory effects on these regulatory T cells. Others have documented that blockade of TNF by etanercept can enhance T cell production of both interferon-gamma (IFN-γ) and TNF-α. One group observed that following treatment of patients with RA with etanercept, T cells stimulated by microbial antigens produced increased levels of IFN-γ[17]. Another group reported increased T cell production of TNF-α and IFN-γ in patients with ankylosing spondylitis treated by etanercept[18]. In genetically susceptible individuals the increased levels of IFN-γ and TNF-α in the bowel mucosa could trigger inflammatory bowel disease. Individuals with the recently described NOD 2 gene variant[19] could be candidates for this paradoxical side effect. A similar effect of etanercept on T cell production of IFN-γ and TNF-α in the central nervous system could also explain the increased frequency of autoimmune neurological complications in these patients[7].

Patients with PsA and other spondyloarthropathies may have a low-grade colitis with features of CD[4]. It is not possible to exclude that the CD-like disease in this patient is a coincidental occurrence. The temporal relationship of disease onset with etanercept therapy, however, suggests that in this instance the inflammatory bowel disease reflects a rare adverse side effect of TNF-α inhibition on immune regulation.

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