Case Report

Granulomatous Hepatitis Associated with Etanercept Therapy

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ABSTRACT. Etanercept has recently been implicated in the induction of granulomatous reactions. We describe a patient with rheumatoid arthritis who developed granulomatous hepatitis after taking etanercept. Infectious and metabolic causes of liver disease had been excluded and the liver biopsy was not typical of sarcoidosis. Liver enzyme abnormalities improved after etanercept was discontinued. We suggest that etanercept was responsible for the development of granulomatous hepatitis. This has not been previously described and adds to the increasing reports of rare granulomatous reactions induced by etanercept therapy. (J Rheumatol 2008;35:349–51)

Key Indexing Terms:
ETANERCEPT GRANULOMATOUS HEPATITIS RHEUMATOID ARTHRITIS

Etanercept, a synthetic tumor necrosis factor (TNF) receptor fusion protein, has well-demonstrated benefits in treating a variety of rheumatologic disorders. As with other anti-TNF therapies, there is a risk of reactivation of granulomatous infections. There are rare but increasing reports of cutaneous and pulmonary granulomatous reactions associated with etanercept and infliximab, a chimeric anti-TNF antibody[1-5]. The presentation may mimic systemic sarcoidosis[6-8].

Cases of cholestasis in the setting of infliximab have been described[9,10]. However, there have not been any descriptions of granulomatous liver disease related to TNF blockers, including etanercept and infliximab. Hepatic abnormalities are uncommon in rheumatoid arthritis (RA) and development of liver enzyme abnormalities during etanercept treatment thus prompted full evaluation.

CASE REPORT

In 1993 a 17-year-old Caucasian woman developed pauciarticular erosive arthritis, which became polyarticular in 1997. Investigations showed negative rheumatoid factor, positive antinuclear antibodies, negative anti-DNA, and negative extractable nuclear antigen. She had no history of uveitis. She was treated with intraarticular and systemic corticosteroids, nonsteroidal antiinflammatory drugs, sulfasalazine, methotrexate (MTX), gold, and cyclosporine. Despite treatment she had continuing active synovitis and joint damage.

In May 2004, etanercept 25 mg subcutaneous injections were started twice weekly in addition to preexistent MTX and prednisone treatment. Chest radiography, TB skin test, liver enzymes, and hepatitis B/C screen were normal/negative. Her arthritis improved and by August 2004 she was able to discontinue MTX and reduce prednisone to 3 mg daily.

By June 2005 she remained well, but laboratory tests showed hemoglobin 135 g/l, white cell count 4.0 10^9/l with neutrophil count 0.8 10^9/l, and platelet count 139 10^9/l. Ultrasound showed no hepatic or splenic abnormalities, and peripheral blood smears showed reactive blood lymphocytosis with no T or B cell clonality. Etanercept was withdrawn and her neutrophil and platelet counts normalized. By late July 2005 her arthritis flared and etanercept was reintroduced at 25 mg weekly, with subsequently normal complete blood counts.

In November 2005 a liver panel showed: ALP 267 U/l (normal 50–160), gamma glutamyl transferase (GGT) 302 U/l (normal 10–55), ALT 162 U/l (normal 20–35), AST 72 U/l (normal 10–38), bilirubin and lactate dehydrogenase normal. She had no systemic symptoms or skin changes. Her stated alcohol consumption was trivial and she denied illicit drug use. These abnormalities persisted into January 2006 and etanercept was again discontinued. Subsequently the following tests were recorded as either normal or negative: hepatitis B/C serology, alpha-1 antitrypsin, ceruloplasmin, antimitochondrial antibody, anti-smooth-muscle antibody, HIV screen, rapid plasma reagin, angiotensin converting enzyme, and repeat TB skin test.

A liver biopsy performed in May 2006 showed granulomatous hepatitis (Figures 1 and 2). The portal tracts were expanded and showed an infiltrate of mixed chronic inflammatory cells and occasional bile ductular damage. Scattered noncaseating granulomata were present in both portal tracts and hepatic parenchyma. Special stains for organisms were negative for acid-fast bacilli, fungi, and bacteria. Cultures were not performed. There was no fibrosing steatosis as would be expected in MTX-associated hepatotoxicity.

In June 2006 she commenced ursodiol 500 mg bid. As of December 2006 her arthritis was well controlled with a stable dose of prednisone 3 mg daily. Blood tests in May 2007 showed ALP 193 U/l, GGT 62 U/l, ALT 57 U/l, AST 46 U/l, and normal complete blood count.

DISCUSSION

Our patient with erosive RA had inflammatory joint symptoms and signs that responded well to etanercept, allowing increased physical functioning, discontinuance of MTX, and decreased prednisone dosing. Transient neutropenia and thrombocytopenia were considered secondary to etanercept.

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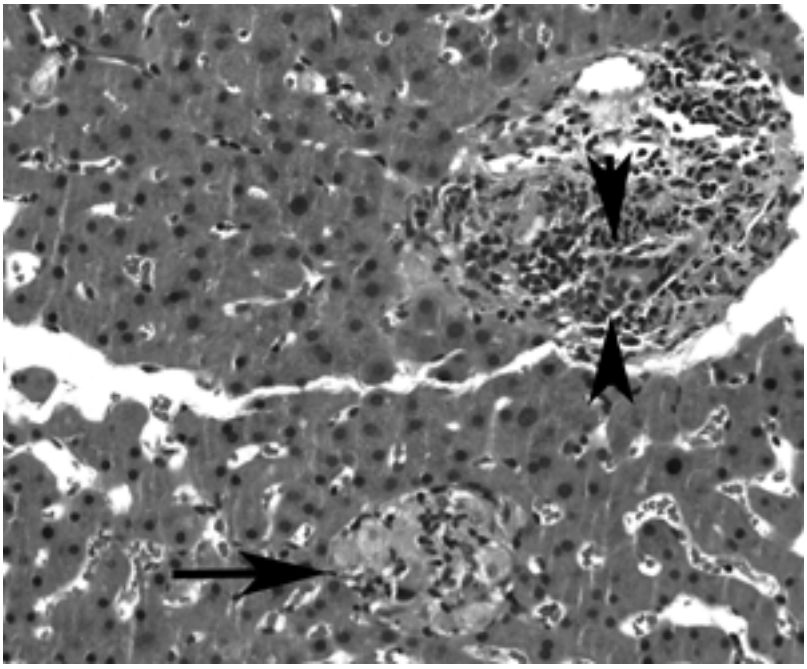

Figure 1. The liver biopsy shows a portal tract that contains a damaged bile ductule (arrowheads). Within the parenchyma there is a noncaseating granuloma (arrow).

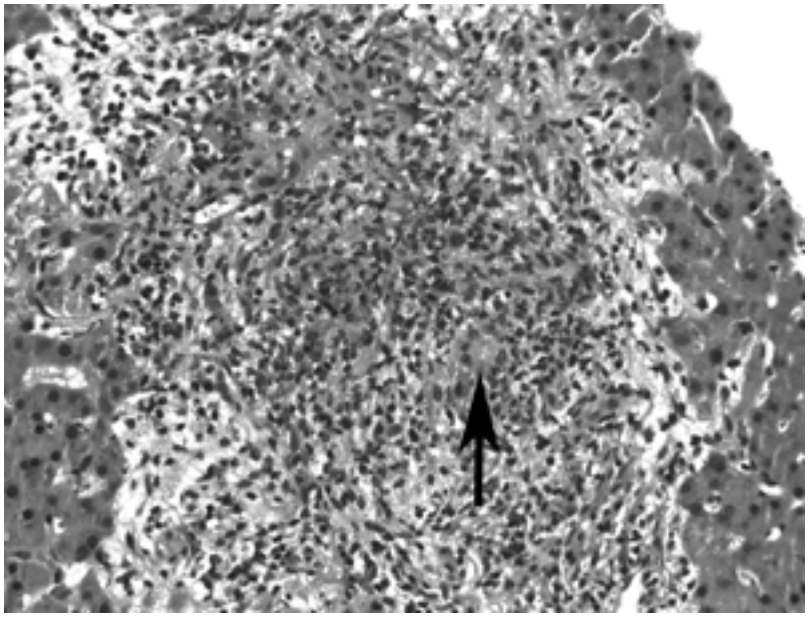

Figure 2. Expanded portal tract containing a damaged bile ductule (arrow).

The subsequent rise in liver enzymes prompted additional investigations with the unexpected pathologic finding of granulomatous hepatitis.

There was no clinical or pathologic evidence of tuberculosis, sarcoidosis, or bacterial, viral, or fungal infections. Liver enzyme abnormalities improved after stopping etanercept and the risks associated with repeat liver biopsy were not felt to be justifiable. The clinical course and the recent reports of granulomatous reactions associated with anti-TNF blockade suggest that etanercept was responsible for inducing the granulomatous hepatitis.

Interstitial granulomatous dermatitis is a rare disorder that may be associated with an inflammatory arthritis and other autoimmune disorders[1], but there are reports of patients with RA who developed granulomatous cutaneous changes in association with etanercept therapy[2].

Noncaseating pulmonary granulomata have been reported in RA patients treated with etanercept[3]. There are additional reports[4,5] of pulmonary granulomatous change attributed to etanercept treatment and recent cases of pulmonary, parotid, and cutaneous granulomata mimicking systemic sarcoidosis[6-8]. Our patient had no clinical evidence of granulomatous change other than in the liver.

Infliximab treatment has been associated with cholestasis and bile duct proliferation, but not ductular damage or hepatic granulomata[9,10]. In contrast, until now, etanercept has not been reported to induce significant adverse hepatic side effects.

We suggest that in patients who develop liver test abnormalities while being treated with etanercept, a possibility of granulomatous hepatitis induced by etanercept should be considered.

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