



Letter

Lymphopenia induced by etanercept

A 64-year-old woman (with a body mass index of 26) with seronegative nonerosive rheumatoid arthritis and biopsy-proven rheumatoid-associated lung disease presented to the clinic with lymphopenia. For the past 6 months, she has been taking prednisone, 20 mg/d, and leflunomide, 20 mg/d, each by mouth. She was treated previously for 2 years with methotrexate, adalimumab, and varying doses of prednisone, ranging from 5 to 20 mg/d. Six months ago, methotrexate treatment was discontinued for an open lung biopsy as was adalimumab treatment because of neuropathy. She subsequently received 5 doses of etanercept, 50 mg/wk, but this treatment was discontinued at her request secondary to injection site reactions.

One month later, she was asymptomatic, with a normal total leukocyte count of $9.0 \times 10^3/\mu\text{L}$ (reference range, $3.8\text{--}10.8 \times 10^3/\mu\text{L}$) and a low absolute lymphocyte count of $307/\mu\text{L}$ (reference range, $850\text{--}3,900/\mu\text{L}$) with a CD3 count of $134/\mu\text{L}$ (reference range, $840\text{--}3,060/\mu\text{L}$), a CD4 cell count of $45/\mu\text{L}$ (reference range, $490\text{--}1,740/\mu\text{L}$), a CD8 cell count of $76/\mu\text{L}$ (reference range, $180\text{--}1,170/\mu\text{L}$), and a CD19 cell count of $58/\mu\text{L}$ (reference range, $110\text{--}660/\mu\text{L}$). All values were confirmed on 2 occasions. One week before the initiation of etanercept treatment, her absolute lymphocyte count was normal ($2,015/\mu\text{L}$). Further laboratory testing revealed a slightly decreased IgG level of 666 mg/dL (reference range, 694–1,618 mg/dL), with normal IgA and IgM levels of 95 mg/dL (reference range, 81–463 mg/dL) and 49 mg/dL (reference range, 46–271 mg/dL), respectively. The lymphocyte proliferation assays to antigens and mitogens were decreased. Antibody titers to diphtheria, tetanus, and 8 of 14 *Streptococcus pneumoniae* serotypes were protective. Folate level, vitamin B₁₂ level, methylmalonic acid level, hemoglobin level, platelet count, and a complete metabolic panel were normal. Antinuclear antibody test results were negative. The lymphopenia resolved 3 months after discontinuation of etanercept treatment. The patient is currently taking abatacept, 750 mg intravenously once monthly, and prednisone, 3 mg/d by mouth daily, and was told to avoid tumor necrosis factor α (TNF- α) inhibitors in the future. To the authors' knowledge, this is the first case report of significant lymphopenia associated with the use of etanercept.

TNF- α inhibitors prevent inflammation by modulating the immune response in the treatment of rheumatoid arthritis and other autoimmune diseases. However, this immune modulation is not without adverse effects. Case reports describe leukopenia, neutropenia, thrombocytopenia, and pancytopenia with the use of etanercept and other TNF- α inhibitors.^{1–5} In a retrospective analysis, 49 of 218 patients taking etanercept developed neutropenia but isolated lymphopenia did not occur. Six percent of the neutropenic patients taking TNF- α inhibitors developed severe infections.⁶

The mechanism for leukocyte depletion with TNF- α inhibitors is unknown. TNF- α inhibitors, including etanercept, can induce

apoptosis of peripheral blood lymphocytes.⁷ Bone marrow suppression with etanercept is described in rare cases.⁶ However, normal bone marrow examination findings in patients with etanercept-induced neutropenia also are reported, supporting a mechanism for peripheral leukocyte depletion.² TNF- α also may modulate the expression of cytokines needed for normal immune cell development.^{3,6} As demonstrated in this case, biologic agents that do not directly affect TNF- α , such as abatacept, may be an option for patients who develop hematologic abnormalities associated with TNF- α inhibitors.

This patient did not experience any infectious complications while lymphopenic, but infections are reported in neutropenic patients taking TNF- α inhibitors.^{2,6} The British Society for Rheumatology updated their consensus guidelines in 2010 to recommend regular monitoring of complete blood cell counts in patients taking TNF- α inhibitors.⁸ However, the American College of Rheumatology has not yet followed suit.^{9,10} It seems reasonable to monitor complete blood cell counts in patients taking TNF- α inhibitors because of reported neutropenia, thrombocytopenia, pancytopenia, and, in this case, lymphopenia.

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