Hypersensitive Joint Reaction After Etanercept Treatment in a Patient with Juvenile Rheumatoid Arthritis

To the Editor:

Etanercept is a soluble tumor necrosis factor (TNF) antagonist used worldwide for autoimmune diseases, including rheumatoid arthritis (RA), juvenile RA (JRA)[1], psoriatic arthritis, and ankylosing spondylitis[2]. The optimal dose of etanercept that is both effective and safe may depend on individual patient factors, and it remains a topic that would benefit from further studies. We report the first case of hypersensitive joint reaction in a patient with JRA under etanercept treatment.

A 19-year-old woman was diagnosed with polyarticular JRA at the age of 15 years. Presentation at the time of diagnosis included swelling and arthralgia in the knees, ankles, and elbows for more than 6 weeks. She also complained of a painful sensation in both hip joints and morning stiffness in her hands during that period. The laboratory data showed antinuclear antibody (ANA) of 1:40 (speckled), rheumatoid factor 28.8 IU/ml (normal < 15 IU/ml), and C3/C4 levels 150/35 mg/dl at diagnosis. Because of a poor response to disease-modifying antirheumatic drugs (DMARD), including methotrexate (10 mg/m^2/week) and prednisolone (0.25 mg/day/kg), which were administered for more than 3 months, she took etanercept at a dose of 25 mg (0.6 mg/kg/week) subcutaneously once a week. However, she complained of swelling in multiple joints, which was most notable over the right knees and ankles and lasted for 2–3 days after each etanercept injection. Because of the adverse joint reaction to etanercept therapy, poor disease control was suspected at the time, and her etanercept dose was increased to 25 mg (1.2 mg/kg/week) subcutaneously twice a week. However, the symptoms of joint swelling and arthralgia became more pronounced; etanercept therapy was discontinued after 6 months. She was then treated with other antiinflammatory drugs and DMARD, but arthralgia and joint swelling were poorly controlled. Disease flares, including frequent swelling of the elbows, knees, and ankles, became so severe that she discontinued schooling for 1 year.

She was then transferred to our hospital at age 17 years. Because of the poor response to DMARD (including methotrexate and prednisolone), etanercept was reinitiated. She was given a starting dose of 25 mg (0.6 mg/kg/week) etanercept subcutaneously once a week for 1 month. Once again, she complained of painful swelling, redness, and mild local pruritus over the right knee and ankle within 12–24 hours of etanercept injection (Figure 1). The pruritus was noted mainly over the right knee joint after each etanercept injection despite an injection site not near the reaction site, and totally subsided 2–3 days later without any treatment (Figure 2). Medications were not used prior to etanercept injections. We then decreased the dose of etanercept to 16.5 mg subcutaneously once a week (0.4 mg/kg/week) and the redness and swelling over the right knee and ankle were no longer observed. Laboratory tests after a month of etanercept therapy revealed C3 and C4 (serum complement) levels of 110 mg/dl and 23.3 mg/dl, respectively. Laboratory data showed C-reactive protein (CRP) 9.6 mg/l, eosinophil 0.9%, and ANA 1:40 before episode, and CRP 12.4 mg/l, eosinophil 0.8%, and ANA 1:40 after episode. The total immunoglobulin E (IgE) level before the episodes was not available. The elevated IgE level was 717 KU/l 5 months after the episodes. DNA and extractable nuclear antigen antibodies as well as antibodies to etanercept and immune complex levels were not available.

Since the episodes, etanercept therapy has been continued for 12 months without further recurrence of right knee swelling and with adequate control of rash and arthralgia.

Several studies have shown that etanercept therapy is effective in children with polyarticular JRA who are refractory to methotrexate and other immunomodulators[3,4]. Horneff, *et al*[5] also reported that disease activity improved during etanercept monotherapy and etanercept/methotrexate combination therapy after 12 months. Tolerability in both treatment groups was comparable[5]. However, the adverse effect profile of etanercept therapy still remains to be determined. Well documented complications of anti-TNF therapy include increased rate of granulomatous infections, especially tuberculosis, reactivation of chronic hepatitis C, and increased rates of lymphoma, malignancy and autoimmune diseases[1,6]. Injection site reactions also include local erythema, ecchymoses, urticaria, or pruritus that usually appear during the first month of injection and decrease with time[7,8]. There are several cases of urticaria reported to be related to etanercept in

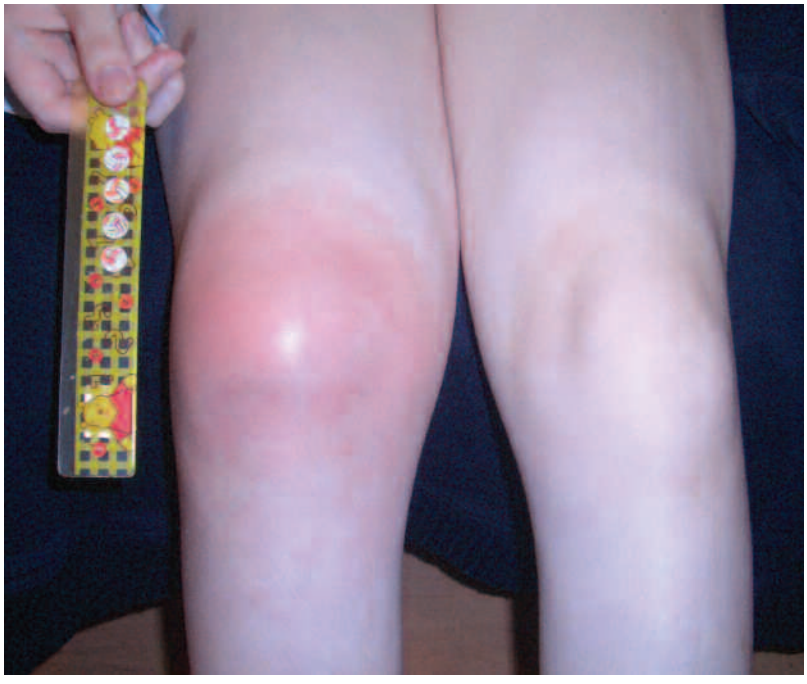

Figure 1. Painful swelling, redness, and mild local pruritus over the right knee, which developed within 12–24 hours of etanercept injection.

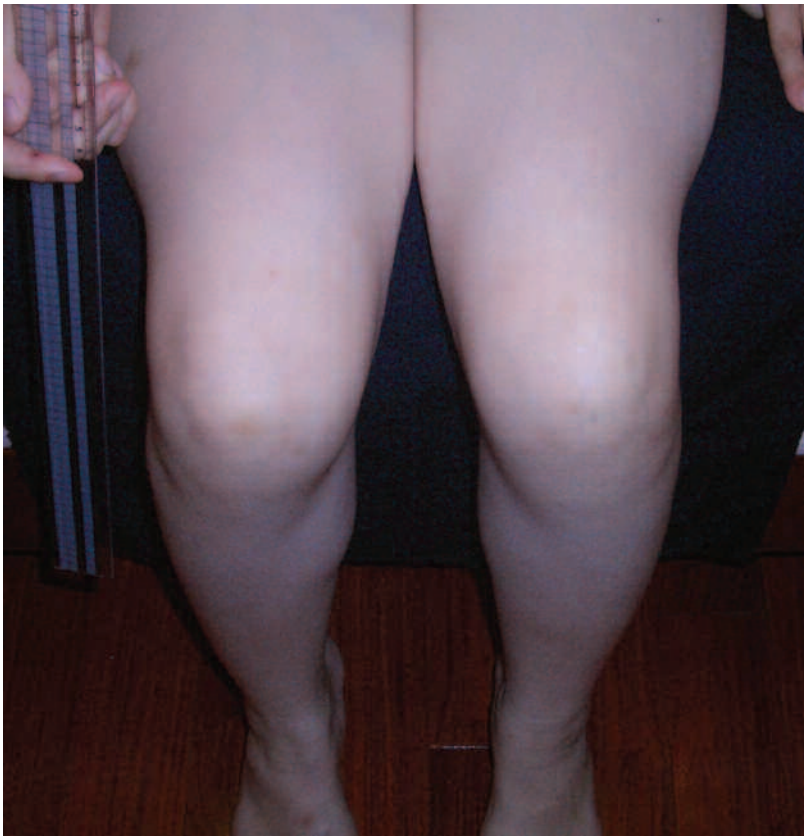

Figure 2. Swelling completely subsided 2–3 days after stopping all medications.

JRA[7]. According to the package insert, 7% of patients experience redness at previous injection sites on subsequent injections of etanercept. In this case, without wheal skin lesions, urticaria was less likely.

Thus the joint-related side effects of etanercept therapy in our patient may have one of several etiologies: activation of autoantibodies and formation of lupus-like syndrome, or immune complex reactions, or a local adverse injection reaction. The elevated IgE levels after the episode may support the hypersensitive joint reaction after etanercept, although there were various immune reactions to etanercept. According to the patient's clinical presentation, erythema of the knees and ankles occurred within 12–24 hours of therapy and subsided after 2 days. Initiation of etanercept in our patient did not lead to a decrease in C3 and C4 levels, elevation in erythrocyte sedimentation rate, or any related malar or discoid rash suggestive of lupus-like disorders. Our patient was first prescribed an initial dose of 25 mg/week subcutaneously. Joint swelling was limited to a period of about 12–24 hours after injection of etanercept and subsided spontaneously within 2 days after injection. This phenomenon subsided after the dose of etanercept was decreased to 16.5 mg once a week. An immediate type I immune reaction was less likely, despite the elevated level of IgE, as the reaction occurred 12–24 hours after the injection and was without systemic manifestations. If not a type I or type III reaction, the reaction is likely a type II reaction (although antibodies to etanercept were not checked). Type IV reaction would likely have occurred even if the dose were decreased.

According to several clinical trials, current recommendations for pediatric dosing suggest that etanercept be prescribed at 0.4 mg/kg twice a week subcutaneously or alternatively at 0.8 mg/kg once a week, with a maximum dose of 50 mg/week[9,10]. Dose escalation is not commonly done after etanercept failure. It is more common to switch to another anti-TNF or abatacept. In our case, there was previous joint reaction after etanercept, self-limiting swelling episodes without elevated inflammatory markers, and escalation of etanercept dose at another hospital. We decreased the weekly dosage of etanercept and the patient responded well.

We describe a novel case of hypersensitive joint reaction in a patient with JRA receiving etanercept therapy. This experience also suggests that titration of the etanercept dose on an individual basis may reduce the adverse reactions. An optimal dose of etanercept that is both effective and safe may depend on individual patient factors, and further studies on this topic will be beneficial.

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