Sarcoid-related uveitis occuring during etanercept therapy

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ABSTRACT

We report the case of a 7-year-old boy who was initially diagnosed as having polyarticular juvenile idiopathic arthritis. Clinical and laboratory features of overt sarcoidosis became evident early during etanercept therapy when he developed acute panuveitis, papular skin rash and elevated levels of angiotensin-converting enzyme. Non-caseating granulomas were present in the liver. Uveitis resolved upon discontinuation of etanercept and systemic administration of corticosteroids. In rare cases expression of autoimmune disorders or expanded clinical features of these disorders may occur during etanercept treatment.

Introduction

Etanercept, a synthetic fusion protein that acts as a soluble receptor to tumor necrosis factor (TNF) α, is effective for the treatment of resistant-polyarticular juvenile idiopathic arthritis (JIA) (1). Etanercept is generally well tolerated (2). However, several patients developed autoimmune disorders or latent autoimmune diseases were "unmasked" during etanercept therapy, especially multiple sclerosis and diabetes mellitus (3-5).

Sarcoidosis is a multisystem autoimmune disorder, involving lungs, eyes, skin, joints, and lymph nodes. Approximately 15% of the cases develop during childhood, often in children < 5 years old (6, 7). Early-onset sarcoidosis is characterized by the triad of arthritis, uveitis and rash, without lymphadenopathy and pulmonary manifestations (8). The first manifestation of disease is often arthritis. Patients are thus diagnosed as having JIA and only later the diagnosis of sarcoidosis becomes apparent (7).

We report a case of a boy who was initially diagnosed as having JIA. Clinical and laboratory features of overt sarcoidosis became evident early during etanercept therapy when he developed acute panuveitis and skin rash. These features resolved upon discontinuation of etanercept.

Case report

A 4-year-old boy developed a limp, pain and complaints of joint swelling in 1998. He was referred to me (PJH) at the age of 5.5 years. Physical examination revealed arthritis of both wrists, with synovial cysts, elbows, knees and ankles, including tenosynovitis of the posterior tibial and peroneus longus tendons. Antinuclear antibodies and rheumatoid factors were negative. Since he had polyarticular disease and the anti-nuclear antibody was negative slit-lamp examinations were performed every six months without evidence of uveitis. He was treated with non-steroidal anti-inflammatory drugs (NSAIDs), intraarticular steroid injections and methotrexate (MTX) was started at 10 mg/m^2/week (orally). He responded partially to this dose of MTX. MTX was then increased to 30 mg/m^2/week (subcutaneous injection) as part of the PRINTO study protocol comparing medium-dose to high-dose MTX (9). The arthritis responded well to this dose with resolution of active inflammation in all joints. However, he developed mild elevations of liver enzymes that persisted despite reduction of the MTX dose to 10 mg/m^2/week. His arthritis flared following the dose reduction, including involvement of small joints of the fingers.

The parents were offered 2 approaches: either to undergo a liver biopsy or to change treatment to etanercept (0.4 mg/kg twice weekly). The latter approach was chosen. Mantoux test prior to starting etanercept was negative. There was no evidence of uveitis two months prior to starting etanercept. Etanercept was started in November 2001. The arthritis remained under good control and liver enzymes values normalized. One month later the patient developed a non-pruritic, macular and follicular rash on the neck, upper chest, shoulders, lower abdomen, lower back and proximal thighs. After another month he developed a painful pink eye, photophobia and decreased visual acuity of the left eye. His right eye was normal.

The left eye had a visual acuity of 5/24, with ciliary injection, and +3-4 flare and cells in the anterior chamber. He had posterior synechiae of the pupil. The retina could not be visualized due to flare and cells in the vitreous body.

Keratic precipitates were present on the cornea (without "cotton-fat" spots). Antinuclear antibodies remained negative. HLA-B27 was not present. Serologic tests for syphilis, toxoplasma,and toxocara were negative. No improvement was seen after administration of local therapy (steroid and mydriatic drops).

Systemic steroids were started (1 mg/kg/d) and etanercept was discontinued. Since the patient needed additional therapy for his arthritis (both wrists, with synovial cysts, tenosynovitis of the posterior tibial and peroneus longus tendons, and the third hand proximal interphalangeal joints) he underwent a liver biopsy prior to re-starting MTX. The biopsy revealed many non-caseating granulomas, without fibrosis. Angiotensin-converting enzyme (ACE) levels were 75 IU/L (normal for age < 52). Chest radiographs and pulmonary function tests were normal. The constellation of arthritis (mostly tenosynovitis), acute panuveitis, rash, noncaseating granulomas in the liver and elevated ACE levels was consistent with the diagnosis of sarcoidosis.

MTX was re-started at 15 mg/m^2/week. Systemic steroids were discontinued after 6 weeks. The rash and uveitis subsided and the patient has a visual acuity of 5/5 in the left eye. He still reports seeing floaters and has a mild degree of macular edema and flare without cells in the vitreous body. He has mild tenosynovitis and synovial cysts in the wrists and ankles. Hand radiographs did not reveal lytic bone lesions. Liver enzyme levels have remained within normal limits.

Discussion

We report a child with sarcoidosis who initially presented with arthritis only and was diagnosed and treated as having JIA. Other manifestations of sarcoidosis, including acute panuveitis and skin rash, occurred early during etanercept therapy and promptly resolved after discontinuation of etanercept and a short course of systemic steroids.

Uveitis in sarcoidosis is present in > 80% of young children and differs from the uveitis-associated with JIA. Sarcoid uveitis is granulomatosus and frequently involves both the anterior and posterior segment (7). The presentation is often acute. JIA-associated uveitis is a nongranulomatus chronic anterior uveitis.

Etanercept has been reported to "unmask" autoimmune disease, especially multiple sclerosis. Recently, a case of a child developing diabetes mellitus during etanercept therapy was described. Retrospective analysis of the child's serum prior to initiation of therapy revealed the presence of anti-GAD antibodies (4). Several cases of drug-induced lupus were reported during etanercept therapy (5). The pathogenesis is still unclear but about 10% of patients treated with etanercept develop anti-nuclear antibodies and 3% develop anti-DNA antibodies using the *Crithidia* assay (10).

The efficacy of etanercept in the treatment of uveitis in children has yet to be established. Etanercept was shown to be effective in an open series of 10 children with JIA-associated uveitis (11). However, in a randomized, blinded, controlled study, no beneficial effect of etanercept on uveitis was seen (12). Furthermore, on several occasions, children have developed uveitis while being treated with etanercept. Among 240 children in the German pediatric etanercept registry, 4 developed uveitis during therapy (oral presentation by Dr. Gerd Horneff, 2002 PRES meeting, Stockholm, Sweden). MTX remains an excellent alternative to steroids in the treatment of sarcoid arthritis and uveitis (13, 14).

In summary, we present a patient in whom features of sarcoidosis not previously present developed early during etanercept therapy and resolved upon discontinuation of etanercept. On rare cases expression of autoimmune disorders or expanded clinical features of these disorders may occur during etanercept treatment. The development of autoimmune phenomena as well as the effect of etanercept on uveitis needs further study.

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