Letters to the Editor

“Urinary Histoplasma range < methenamine silver stain revealed small round organisms mor-" granulomas with giant cells. AFB staining was negative. Gomori non-calcified nodule in the right lower lobe."

"/C2 2.2 test was negative. Radiography and CT scan of the chest aspirates were negative for acid-fast bacilli (AFB). Tuberculin skin bacteriology diagnosis was established, bone marrow studies were not pursued.

"She received oral itraconazole (200 mg/day) for 6 weeks. Fever resolved after 15 days, although her cough persisted. Histoplasma serologies one week after discharge were positive (mycelial complement fixation titer, 1:16; yeast complement fixation titer, 1:128; reactive H band on immunodiffusion).

"Histoplasmosis is the most common pulmonary and systemic mycosis in the United States and is endemic in the Ohio and Mississippi River valleys [1]. Fewer than 5% of infected people develop systemic illness; however, immunocompromised individuals are at greater risk for life-threatening, disseminated infections [1, 2]. Four prior reports have described six cases (all in adults) of disseminated histoplasmosis in patients receiving low-dose methotrexate (Table 1) [3–6].

"Symptoms of acute pulmonary histoplasmosis consist primarily of low-grade fever, chest pain and upper respiratory symptoms. Disseminated disease presents with evidence of extrapulmonary involvement including hepatosplenomegaly, lymphadenopathy, adrenal masses, CNS infection, haematological abnormalities, elevated hepatic enzymes, or isolation of Histoplasma capsulatum from extrapulmonary locations [1, 7]. In the absence of extrapulmonary cultures, symptom duration has been used to distinguish disseminated disease from self-limited infections, which generally resolve within 14 days [2]. Patients with disseminated histoplasmosis have a greater degree of antigenemia than patients with self-limited infections, though urinary antigen can be positive in ~20% of patients with acute, localized (non- diffuse) pulmonary histoplasmosis [8]. Antifungal therapy is indicated for histoplasmosis in immunocompromised hosts because of the risk for progressive disease.

"Two reviews have summarized 36 previous reports of OIs in adult patients receiving low-dose methotrexate (2.5–25 mg/week) for rheumatoid arthritis (58%), psoriatic arthritis (14%) and psoriasis (8%) among other conditions [3,7]. Slightly over 50% were also receiving prednisone. The most frequent OI (42%) was Pneumocystis jirovecii pneumonia. Four patients (11%) had disseminated histoplasmosis, with H. capsulatum isolated from bone marrow or liver biopsy. Other OIs included cryptococcal pneumonia (11%), Nocardia pneumonia (8%), CMV pneumonitis (6%) and disseminated herpes zoster (17%). In contrast, only two OIs are reported in pediatric patients treated with low-dose methotrexate. A 16-yr-old female with psoriatic arthritis receiving methotrexate (10 mg/week) and prednisone (3 mg/day) developed Pneumocystis pneumonia [9], and a 14-yr-old female with dermatomyositis receiving methotrexate (25 mg/week) and prednisone (150 mg/day) developed disseminated nocardiosis [10].

"Evidence for disseminated disease in our patient included prolonged fever, splenomegaly, anaemia, elevated ALT and significant antigenemia (in the setting of non-diffuse pulmonary"
Unstable diabetes in a patient receiving anti-TNF-α for rheumatoid arthritis

Sir, Tumour necrosis factor-α (TNF-α) is a cytokine well-recognized as having a significant role in the inflammatory process. Recent advances have led to the production of drugs that inhibit the action of TNF-α, producing significant improvement in the control of rheumatic diseases [1]. TNF-α may also play a role in other physiological processes.

Prolonged administration of anti-TNF-α drugs is increasingly common in the treatment of rheumatic disease and also inflammatory bowel disease. Here we report on a case of an individual whose diabetes became unstable following the administration of anti-TNF drugs.

Our case is a 55-year-old female who has had type 1 diabetes since the age of 30. Aged 33, she developed rheumatoid arthritis. Having failed a number of disease-modifying anti-rheumatic drugs (DMARDs), she was commenced on etanercept (25mg twice weekly) in April 2003 (DAS = 7.06). This led to significant improvement in her joints immediately. Having previously had stable diabetes, within 3 weeks of commencing the drug, she noticed that her blood sugars were erratic. She had a severe hypoglycaemic attack without warning, followed further by one more a few days later. After urgent clinical review, the etanercept was stopped and her glycaemic control stabilized.

Despite commencing subcutaneous methotrexate, her joints remained markedly active, which ultimately led to her admission in October 2004. Her Disease Activity Score (DAS) score was 6.8, and after much consideration the patient was commenced on adalimumab. Within 12 h of administration, she developed severe hypoglycaemia, which recurred again 24 h later. The adalimumab was subsequently stopped.

The patient has continued with severe active joint disease. She has had severe side effects with a number of DMARDs and lack of efficacy with others. She has currently just had her third infusion of infliximab, as yet without complication.

There is little doubt of the role of TNF-α in inflammation, and of the benefits of anti-TNF drugs. TNF-α also has specific effects associated with glucose homeostasis. Over-expression of TNF-α has been demonstrated in obese rats and subsequently humans [2]. Studies have also shown that weight loss in these individuals reduced levels of TNF-α and improved insulin sensitivity [3]. The correlation between TNF-α levels and insulin resistance has been confirmed in studies involving patients with and without type 2 diabetes [4].

It appears that TNF-α can block insulin-mediated uptake in adipose tissue, by down-regulation of glucose transporter mechanisms, hence leading to increased insulin resistance [2].

Type 1 diabetes is largely the result of β-cell destruction, of which TNF-α has been implicated [5]. However, insulin resistance does occur, frequently as the result of chronic hyperglycaemia. It is quite possible that the action of anti-TNF drugs in our patient led to increased sensitivity, as the result of blockade of the action of TNF-α in adipose tissue [6, 7].

Our patient has thus far been given both etanercept and adalimumab, with similar effects on glycaemic control. Studies have shown little or no effect on insulin sensitivity after administration of anti-TNF-α. Neither assessed the effects of chronic use of these drugs [8, 9]. Improved insulin sensitivity has been reported in subjects who prolonged treatment with infliximab [10], and it is thus possible that hypoglycaemia may again occur in our patient.

We suggest that patients who are treated with anti-TNF drugs, and suffer with diabetes, should be warned regarding possible disturbance of glycaemic control.

The authors have declared no conflicts of interest.

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