CASE REPORT

Etanercept-induced myositis: do we have to stop it? A surprising outcome

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Accepted 18 December 2015

SUMMARY

We discuss a case of a 47-year-old man who presented with progressive proximal muscle weakness of the upper and lower extremities and unstable gait. He had been on etanercept for 6 months for severe psoriasis and psoriatic arthritis with good control of his disease. Serum creatine kinase (CK) level was found to be 5666 U/L and muscle biopsy showed a marked inflammatory myopathic process likely secondary to etanercept. He was started on high-dose steroids and advised to discontinue etanercept. Despite our recommendation, he never stopped using etanercept due to fear of a psoriasis flare. Three months later, he had significant improvement of clinical symptoms, normalised serum CK levels and discontinued prednisone.

BACKGROUND

Antitumour necrosis factor α (anti-TNF- α) agents are increasingly being used to treat a variety of rheumatic and autoimmune diseases, including psoriasis. In some rare cases, these agents can induce some of the very diseases they were designed to treat, including inflammatory myositis.^{1 2}

Psoriasis is a chronic, immune-mediated inflammatory disease affecting the skin and may occasionally cause a chronic inflammatory joint disease. Etanercept has been proven to be efficacious as either monotherapy or as combination therapy with other oral agents used for the treatment of psoriasis, and is considered first-line biological therapy for the treatment of moderate to severe psoriasis and psoriatic arthritis.³

The use of anti-TNF agents has been associated with adverse immunological events including the development of antinuclear antibodies (ANAs), anti-dsDNA antibodies and lupus-like illnesses, however, reports of inflammatory myositis associated with TNF-antagonist therapy have been extremely rare.⁴ In this report, we describe a patient treated with etanercept for severe psoriasis and psoriatic arthritis who developed inflammatory myositis that resolved on treating the patient with steroids without discontinuation of the TNF- α antagonist therapy.

CASE PRESENTATION

A 47-year-old man from Jamaica, diagnosed at 40 years of age with severe psoriasis and psoriatic arthritis, refractory to methotrexate, leflunomide and oral or topical steroids, had recurrent skin and arthritic flares requiring frequent hospitalisations and intravenous steroid therapy. Etanercept 50 mg

once weekly was started resulting in nearly complete resolution of psoriatic plaques and marked improvement of arthritis in a period of 2 months.

After 6 months on anti-TNF therapy, the patient presented to our clinic, with generalised myalgia associated with progressive weakness in upper and lower extremities and unstable gait of 2 weeks duration. He denied any dysphagia or difficulty breathing. On examination, vitals were normal and cardiorespiratory examination was unremarkable. Musculoskeletal examination revealed synovitis of the left wrist and boggiess of the right hand proximal interphalangeal joints. Upper and lower proximal muscle strength was decreased to 3/5 with unstable gait. Deep tendon reflexes were normal and proprioception and sensation to touch were preserved.

INVESTIGATIONS

Laboratory tests showed mild anaemia with haemoglobin of 11.3 g/dL (12–16 g/dL), and normal white cell count and platelet count. The patient had elevated transaminases with aspartate transaminase of 173 U/L (9–48 U/L), alanine transaminase 497 U/L (5–40 U/L) with normal alkaline phosphatase 71 U/L (53–148 U/L), serum bilirubin and renal function. The serum creatine kinase was found to be 5666 U/L (20–200 U/L), lactate dehydrogenase 1265 U/L (100–190 U/L), C reactive protein 51.69 mg/L (≤ 5 mg/L) and erythrocyte sedimentation rate was 112 mm/h (0–30 mm/h). Immunoassay for antibody to JO-1 was negative.

Our initial impression was that patient was presenting with a picture of inflammatory myopathy. A muscle biopsy was carried out, which showed

Figure 1 Muscle fibres in the perifascicular region (bottom of picture) are atrophic and greyish in colour, indicating perifascicular atrophy. Modified Gomori Trichrome, original magnification $\times 200$.

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To cite: Tariq H, Ayesha B, Weidenheim K, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-213577

perifascicular muscle fibre atrophy (figures 1 and 2). There was perimysial inflammatory activity and an inflammatory infiltrate around the blood vessels (perivascularitis) associated with the myositis, but no fibrinoid necrosis, hence ruling out vasculitis (figure 3).

DIFFERENTIAL DIAGNOSIS

At this point, various differential diagnoses were considered. First, our patient was using pravastatin for the treatment of his dyslipidaemia, and it was possible that he had developed myositis secondary to the use of statins. Muscle biopsy in patients with statin myopathy usually shows cytochrome oxidase negative fibres that occur secondary to mitochondrial dysfunction, increased lipid stores and cytoplasmic vacuolisation with intact sarcolemma.^{5 6} No such histological features were present in the muscle biopsy of our patient, hence statin-induced myopathy was unlikely. The other possibility was a viral myositis, but such patients usually have other symptoms and signs attributable to the causative viral pathogen.⁷ The patient did not report any symptoms suggestive of a viral aetiology. There was no evidence of viral infection, such as inclusion bodies, in the muscle biopsy. Our patient did not take any herbal, over the counter or prescription medications. The pathology, with perifascicular atrophy, was classical for autoimmune myositis. Hence, the temporal relationship of myositis and the exposure to etanercept in our patient raised the possibility of myositis being secondary to the TNF- α inhibitor.

TREATMENT

The patient was advised to stop etanercept and was started on prednisone 60 mg once a day. He recovered muscle strength within 3 months, and presented normal gait and normalised serum creatine kinase of 78 U/L.

OUTCOME AND FOLLOW-UP

Despite our recommendation to stop etanercept, the patient had decided to continue using it on his own due to his concern of experiencing a possible flare of psoriasis. Oral steroids were subsequently tapered off in the next couple of months and the patient has remained stable on etanercept.

Figure 2 Confirmation of small muscle fibres at the periphery of a muscle fascicle is better seen on ATPase staining at pH 9.4. Original magnification $\times 200$.

Figure 3 Inflammatory activity was primarily perimysial, with only focal extension among the pink muscle fibres. There was an inflammatory infiltrate around the blood vessel (perivascularitis) associated with the myositis, but no evidence of fibrinoid necrosis. H&E, original magnification $\times 200$.

DISCUSSION

Psoriasis is a serious, chronic, debilitating, systemic inflammatory immune disease involving the skin, sometimes causing severe joint arthritis and other organ system involvement. Patients often require long-term treatment because of the chronic nature of the disease. Traditional systemic therapies such as methotrexate and cyclosporine are often limited by their cumulative and dose-related toxicities. Etanercept was first approved for use in psoriasis in 2004. It is a fully human, soluble tumour necrosis factor (TNF)-receptor fusion protein that is composed of the p75 receptor bound to the Fc region of human immunoglobulin G1 (IgG1). It has demonstrated improved disease symptoms and health-related quality of life in patients with moderate to severe plaque psoriasis. Safety analysis studies in patients with psoriasis indicate that etanercept is generally well tolerated, with a low risk of serious adverse events.^{8 9}

Anti-TNF therapy has been associated with various autoimmune phenomena, including lupus-like syndrome, cutaneous lupus, vasculitis, psoriasis, demyelinating neurological diseases, sarcoidosis, interstitial lung disease, autoimmune hepatitis, uveitis and antiphospholipid syndrome.^{1 10} On review of the literature, seven cases of anti-TNF-induced dermatomyositis (DM), three cases of anti-TNF-induced polymyositis (PM) and two cases of antisynthetase syndrome associated with a TNF inhibitor, have been reported. The most frequent anti-TNF therapy associated myopathy was etanercept (6 of 13), followed by adalimumab (5 of 13) and infliximab (2 of 13). In these reports, the time of onset between the initiation of anti-TNF therapy and DM, PM or antisynthetase syndrome, ranged from 2 to 54 months.¹

The notion that TNF inhibition exacerbates inflammatory myositis seems counterintuitive as TNF- α and its receptor is overexpressed in inflammatory myositis suggesting a contribution to the pathogenesis of the disease. However, TNF- α blockade has led to disease flares in patients with inflammatory myopathies. It is not a fully understood phenomenon and many hypotheses for its mechanisms have been proposed. The 'cytokine-shift' hypothesis suggests that the inhibition of TNF- α causes an increase in the expression of interferon- γ by altering the balance between TH1 and TH2 cytokine production.¹⁰ Interferon- γ inhibits muscle cell proliferation and

differentiation. IFN- γ is involved in the upregulation and in situ production of proinflammatory chemokines, which, in turn, participate in the recruitment of activated T cells, inhibit muscle regeneration and the repair of injured muscle fibres in myositis and contribute to the self-sustaining nature of endomysial inflammation.^{11 12}

Review on drug-induced inflammatory myositis indicates that more than 90% of patients noted improvement in their rash and myositis simply after discontinuing the medication. Sometimes, in mild to moderate myopathy, continuation of the therapy can be considered by closely following up with the patient, in order to keep the primary inflammatory process under control. In patients with severe manifestations, cessation of anti-TNF therapy is mandatory, together with initiation of oral corticosteroids and adding immunosuppressive agents according to the clinical evolution.^{2 10}

Our case was unique, as the patient despite developing myositis continued using etanercept along with corticosteroids and progressed to complete remission of the myositis, and his psoriasis is currently well controlled. Thus, in patients with severe psoriasis, in whom other therapies have failed and in whom inflammatory myositis has developed, a trial with steroids and continuation of anti-TNF therapy can be considered, as interrupting the biological agent may cause a relapse of psoriasis.

It has been three decades since etanercept's first human trials in 1993, and after almost two decades since its Food and Drug

Administration approval, etanercept remains an important and valuable option in the treatment of moderate to severe psoriasis and psoriatic arthritis. Although the use of this agent is increasing, practitioners should be aware of the possibility of anti-TNF-induced autoimmune disorders, including inflammatory myositis. The case described herein is unique in that the inflammatory myositis developed secondary to TNF blockade therapy, and it resolved with the use of steroids alone without discontinuation of anti-TNF, which raises a question as to whether discontinuation of these drugs is necessary, especially in patients with severe disease that failed other therapies in the past.

Contributors HT and BA wrote the manuscript. KW reviewed the pathology images. KW and GF undertook critical revision of the manuscript for important intellectual content. All the authors read and approved the final manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- Antitumour necrosis factor (TNF) therapy has been associated with various autoimmune phenomena, including lupus-like syndrome, cutaneous lupus, vasculitis, psoriasis, demyelinating neurological diseases, sarcoidosis, interstitial lung disease, autoimmune hepatitis, uveitis and antiphospholipid syndrome.
- Anti-TNF therapy can, rarely, cause inflammatory myositis.
- The most frequent anti-TNF therapy associated with myositis is etanercept.
- In patients with severe psoriasis in whom other therapies have failed and in whom inflammatory myositis has developed, a trial with steroids and continuation of anti-TNF therapy can be considered, as interrupting the biological agent may cause a relapse of psoriasis.

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