Clin Rheumatol (2011) 30:1095–1098
DOI 10.1007/s10067-011-1704-7

BRIEF REPORT

Development of sarcoidosis 6-month post discontinuation of etanercept: coincidence or real association?

Muhammad Haroon · John G. Ryan · Sinead Harney

Received: 30 August 2010 / Revised: 2 January 2011 / Accepted: 27 January 2011 / Published online: 8 March 2011

Abstract There have been numerous reports of granulomatous diseases developing in patients receiving anti-tumour necrosis factor (TNF) therapy. Herein, we report a patient who developed sarcoidosis 6 months after discontinuation of etanercept. To date, all reported cases have occurred in patients undergoing ongoing treatment with TNF blockers with resolution on its discontinuation. A 47-year-old man was diagnosed with seropositive rheumatoid arthritis (RA) in 2003. He was initially treated with methotrexate and corticosteroids. In 2005, adalimumab was added due to ongoing disease activity. However, he had persistent low-grade synovitis of bilateral wrist joints and remained oral glucocorticoids dependent. In October 2008, adalimumab was switched to etanercept with marginal benefit; however, etanercept was continued until March 2009. Rituximab was discontinued due to an immediate allergic reaction. In September 2009, he developed bilateral ankle synovitis with erythema nodosum. Further investigations (chest X-ray and CT scan of thorax) revealed new development of bilateral hilar lymphadenopathy and interstitial nodular changes typical of sarcoidosis. His baseline therapy of methotrexate was continued. His recent repeat chest X-ray and CT scan of thorax (March 2010) has shown significant spontaneous resolution of his mediastinal lymphadenopathy and pulmonary nodules. Apart from the initial brief course of NSAIDs, his sarcoidosis resolved spontaneously without requiring any further therapy. For his rheumatoid arthritis, he has been recently commenced on abatacept and his baseline therapy of methotrexate has been continued. It remains speculative as to whether the concurrence of RA and sarcoidosis is purely serendipitous, or is related to an immunodysregulatory state attributable to TNF blockade.

Keywords Etanercept · Sarcoidosis

M. Haroon (✉) · J. G. Ryan · S. Harney
Department of Rheumatology, Cork University Hospital, Cork, Ireland
e-mail: mharoon301@hotmail.com

Introduction

Sarcoidosis is a rare disease of unknown aetiology characterised by multisystem granulomatous inflammatory process. Lung involvement is the predominant clinical feature; however, it can affect almost any organ. The crucial role for tumour necrosis factor (TNF) during inflammatory granuloma formation is well described [1]. Case reports describe that TNF blockers, especially infliximab, have been successfully used in the treatment of sarcoidosis [2, 3]. Interestingly, there has been an increase in the reported cases of granulomatous diseases during treatment with TNF blockers. While etanercept has been implicated in most cases [3–7], there are reports of its association with anti-TNF monoclonal antibodies—adalimumab and infliximab [8, 9]. All reported patients developed granulomatous lesions during treatment with TNF blockers, which gradually resolved on its discontinuation. Herein, we report a patient who developed sarcoidosis 6 months after discontinuation of etanercept. To the best of our knowledge, there is no other report of the development of sarcoidosis following discontinuation of TNF blockers.

Case report

A 47-year-old Caucasian male was diagnosed with rheumatoid arthritis (RA) in 2003, when he presented with pain and

swelling of small joints of his hands and wrists, and painful and stiff elbows and knees. Examination revealed bilateral and symmetrical polyarthritis involving proximal interphalangeal and metacarpophalangeal joints and wrists. He also experienced a synovitis of both knees with articular effusions. Laboratory testing revealed normal complete blood count, normal blood biochemistry, and elevated inflammatory markers—C-reactive protein of 69 mg/ml (normal range 1–10 mg/l) and erythrocyte sedimentation rate 53 mm/h (normal range <30 mm/h). He was positive for rheumatoid factor and cyclic citrullinated peptide antibody (anti-CCP). The patient had negative result on antinuclear antibody testing. He was initially treated with methotrexate and varying doses of corticosteroids. In 2005, he developed clinically and radiologically confirmed (plain films and MRI scan of cervical spine) anterior atlantoaxial subluxation. A decision was made to treat his destructive rheumatoid arthritis with adalimumab, which led to almost complete resolution of his neck symptoms; however, low-grade synovitis persisted in his bilateral wrist joints requiring intermittent low-dose glucocorticoids. In October 2008, adalimumab was switched to etanercept with marginal benefit; however, etanercept was continued until March 2009. At this stage, it was decided that his refractory disease to be treated with rituximab; however, this was discontinued due to an immediate allergic reaction. In September 2009, he developed bilateral ankle synovitis along with erythema nodosum on this shins, which resolved completely with NSAIDs in 6 weeks. His chest X-ray, which was normal in 2008, now showed bilateral hilar lymphadenopathy and interstitial nodular changes typical of sarcoidosis. A CT scan of thorax showed changes consistent with stage 2 sarcoidosis (Fig. 1). He was reviewed by a pulmonologist and underwent a bronchoscopy; infectious aetiology was excluded and lung biopsy was not deemed necessary. On laboratory tests, he had normal complete blood counts, blood biochemistry, muscle enzymes (creatine phosphokinase, lactate dehydrogenase, aspartate aminotransferase), and serum ACE levels. Repeat antinuclear antibody testing was also negative. The diagnosis of Lofgren syndrome, which is generally regarded as an acute variant of sarcoidosis, was made on the basis of characteristic triad of erythema nodosum, arthritis and bilateral hilar lymphadenopathy. He denied any respiratory or constitutional symptoms. His baseline therapy of methotrexate was continued and he did not require glucocorticoids. His recent repeat chest X-ray and CT scan of thorax (March 2010) has shown significant spontaneous resolution of his mediastinal lymphadenopathy and pulmonary nodules (Fig. 1). Apart from the initial brief course of NSAIDs, his sarcoidosis resolved spontaneously without requiring any further treatment. Now, 1 year since the development of symptoms and radiologic signs of sarcoidosis, he had no further clinical manifestations suggestive of sarcoidosis. For his rheumatoid arthritis, he has been recently commenced on abatacept, and his baseline therapy of methotrexate has been continued. It is important

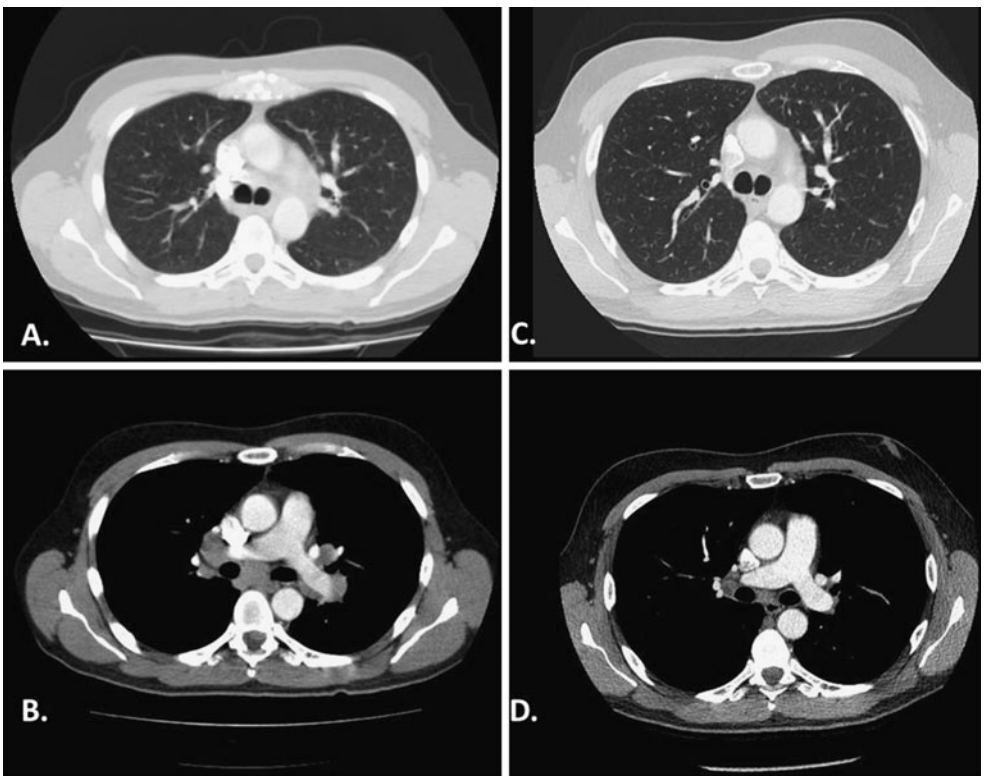

Fig. 1 Axial chest CT images from October 2009 (**a**, **b**) and March 2010 (**c**, **d**). **a** Initial CT images of the pulmonary parenchyma at the level of the carina during inspiration show minimal nodular thickening of the interlobular septae. The findings were consistent with early parenchymal sarcoidosis. **b** Initial CT images of the mediastinum show bihilar and subcarinal lymphadenopathy. **c** Follow-up CT images of the pulmonary parenchyma show complete resolution of the parenchymal changes. **d** Follow-up CT images of the mediastinum show interval reduction in the volume of bihilar and subcarinal lymph nodes

to note that his baseline strengths of immunosuppressive therapies were unchanged for 6 months prior to the development of sarcoidosis.

Discussion

Abnormal pulmonary radiologic features are not uncommon among patients with rheumatoid arthritis, and drug-related pulmonary disease is an important consideration in the differential diagnosis of such patients. Lung disease characterised by granulomatous inflammation has been reported during anti-TNF therapy. This association seems to be strong on the basis of some observations. For example, the occurrence of this granulomatous disease process appears to be more frequent with TNF soluble receptors compared to monoclonal anti-TNF antibodies, and etanercept has already been reported to cause worsening of pulmonary sarcoidosis [10, 11]. Similarly, etanercept has been shown of no clinical benefit in patients with other granulomatous diseases such as uveitis, Crohn's disease and Wegener's granulomatosis [12, 13]. Moreover, there are fewer cases of TB reactivation during etanercept therapy compared to monoclonal anti-TNF antibodies (adalimumab and infliximab) [14]. So, it seems that there is a differential efficacy and important distinction in the safety profile of etanercept and monoclonal antibodies in the development or treatment of different inflammatory processes, and etanercept appears to stabilise granuloma formation.

Few pathogenetic mechanisms can possibly explain the delayed etanercept-induced development of sarcoidosis: delayed immune reconstitution, long-term infection leading to an aberrant immunologic response, and increased susceptibility to pulmonary and skin infections related to immunosuppression induced by TNF blockers as exposure to an infectious agent has been considered a possible etiologic agent for sarcoidosis development. There are different lines of evidence suggesting that with etanercept therapy, sufficient levels of cytokines (TNF and gamma-interferon) persist and this could be enough to cause development of granulomatous diseases. Firstly, TNF exerts its effect with the help of two receptors: type I receptor (p55) and type II receptor (p75). Etanercept is a recombinant soluble p75 TNF receptor protein, and hence, leaves TNF receptor p55 mediated signalling partially intact [15]. On the other hand, monoclonal anti-TNF antibodies inhibit both TNF receptor p55- and p75-mediated events. Secondly, in contrast to infliximab which blocks TNF in an irreversible fashion, etanercept has been shown to make relatively unstable complexes with TNF [16]. Similarly, etanercept binding to soluble TNF is restricted to trimeric form; however, infliximab binds to both monomer and trimeric forms [16]. Thirdly, in contrast to infliximab, etanercept does not inhibit gamma-interferon, rather, it causes reciprocal increased production; gamma-interferon is another key cytokine for granuloma formation [17].

Since the possible etiopathogenic factors to explain this association have not been well-established, our case may simply represent the concurrence of two relatively common conditions, rather than the direct involvement of the drug in question—etanercept. This is supported by the fact that etanercept has a very short half-life (the elimination half-life of 95.4 h) [18]), and in our patient, etanercept was discontinued 6 months prior to the development of erythema nodosum and subsequent diagnosis of sarcoidosis.

Conclusion

The development of sarcoidosis in a patient with long standing rheumatoid arthritis is probably not more than a coincidence, and hence, caution is prudent when interpreting the previous reports which attribute the development of sarcoidosis in RA patients to anti-TNF therapy. However, if one looks at the other side of the coin, the altered cytokine profile induced by anti-TNF agents may perhaps cause significant time lag between TNF blocker administration and the development of adverse events, such as sarcoidosis. We believe that reporting new aspects of such rare associations would help physicians to better understand these insufficiently explained clinical syndromes.

Disclosures None.

References

1. Lukacs NW, Chensue SW, Strieter RM, Warmington K, Kunkel SL (1994) Inflammatory granuloma formation is mediated by TNF-alpha-inducible intercellular adhesion molecule-1. J Immunol 152 (12):5883–5889
2. Baughman RP, Drent M, Kavuru M et al (2006) Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med 174(7):795–802
3. Phillips K, Weinblatt M (2005) Granulomatous lung disease occurring during etanercept treatment. Arthritis Rheum 53:618–620
4. Vavricka SR, Wettstein T, Speich R, Gaspert A, Bachli EB (2003) Pulmonary granulomas after tumour necrosis factor. Thorax 58:278–279
5. Peno-Green L, Lluberas G, Kingsley T, Brantley S (2002) Lung injury linked to etanercept therapy. Chest 122:1858–1860
6. Cunnane G, Warnock M, Fye KH, Daikh DI (2005) Accelerated nodulosis and vasculitis following etanercept therapy for rheumatoid arthritis. Arthritis Rheum 47:445–449
7. Oh J, Arkfeld DG, Horwitz DA (2005) Development of Crohn's disease in a patient taking etanercept. J Rheumatol 32:752–753
8. Metyas SK, Tadros RM, Arkfeld DG (2009) Adalimumab-induced noncaseating granuloma in the bone marrow of a patient

being treated for rheumatoid arthritis. Rheumatol Int 29(4):437–439
9. Daïen CI, Monnier A, Claudepierre P et al (2009) Sarcoid-like granulomatosis in patients treated with tumor necrosis factor blockers: 10 cases. Rheumatology (Oxford) 48(8):883–886
10. Louie GH, Chitkara P, Ward MM (2008) Relapse of sarcoidosis upon treatment with etanercept. Ann Rheum Dis 67(6):896–898
11. Utz JP, Limper AH, Kalra S et al (2003) Etanercept for the treatment of stage II and III. Progressive pulmonary sarcoidosis. Chest 124:177–185
12. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group (2005) Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med 352:351–361
13. Sandborn WJ, Hanauer SB, Katz S et al (2001) Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. Gastroenterology 121:1088–1094
14. Furst DE, Wallis R, Broder M, Beenhouwer DO (2006) Tumor necrosis factor antagonists: different kinetics and/or mechanisms of action may explain differences in the risk for developing granulomatous infection. Semin Arthritis Rheum 36:159–167
15. Tandon VR, Mahajan A, Khajuria V (2006) TNF inhibitors and tuberculosis: an Indian concern. J Ind Rheumatol Assoc 1(2):66–71
16. Scallon B, Cai A, Solowski N et al (2002) Binding and functional comparisons of two types of tumor necrosis factor antagonists. J Pharmacol Exp Ther 301(2):418–426
17. Shigehara K, Shijubo N, Ohmichi M et al (2001) IL-12 and IL-18 are increased and stimulate IFN-gamma production in sarcoid lungs. J Immunol 166:642
18. Lee H, Kimko HC, Rogge M, Wang D, Nestorov I, Peck CC (2003) Population pharmacokinetic and pharmacodynamic modeling of etanercept using logistic regression analysis. Clin Pharmacol Ther 73(4):348–365