LETTER TO THE EDITOR

Sarcoidosis complicating treatment with adalimumab for Crohn’s disease

Dear Sir,

Adalimumab is a humanised monoclonal antibody against tumour necrosis factor-alpha (TNF-α), with proven efficacy in several autoimmune diseases. We report the development of sarcoidosis with cutaneous and pulmonary involvement in a 37-year old white male with refractory Crohn’s disease of 13-years, commenced on maintenance therapy with adalimumab for 2 years following surgery and unsuccessful remission with methotrexate (Fig. 1). To the best of our knowledge, this is the fourth reported case in the literature of sarcoidosis complicating TNF-α therapy in Crohn’s disease; the second with adalimumab, others reporting paradoxical sarcoidosis with infliximab and natalizumab.1-3

Sarcoidosis and Crohn’s disease are both inflammatory barrier disorders consisting of non-caseating granulomas, dysregulated T-cell activation and similar organ involvement outside the primary affected organ system.1 Genome-wide analyses in sarcoidosis and Crohn’s disease have previously detected shared common susceptibility loci on 10p12.2 and 11q13.1, most likely representing a general predisposition toward an altered immune-mediated inflammatory response.

Crohn’s disease is characterised by granulomatous inflammation of the intestine, which can be difficult to differentiate from sarcoidosis. The loss of function mutation at the NOD2 gene results in failure of NOD2-mediated NFκB activation, and possibly failure in defensin-mediated protection. It is hypothesised that gastrointestinal immunity is directed to a granulomatous response against bacterial invasion as a consequence of this mutation. Juvenile onset granulomatous diseases are associated with gain of function mutations of the NOD2 gene and constitutive activation of NFκB. Interestingly, in Japanese patients, sarcoidosis has been associated with a loss of function mutation in the NOD1 gene, with reduced NOD1-mediated activity to the bacterium Propionobacterium acnes. Based on these findings, TNF-α inhibition would be expected to suppress NFκB-related granuloma formation and has been used with some success in refractory sarcoidosis.4

Granuloma formation characterises a spectrum of clinical entities ranging from infecting organisms and immunodeficiency to apparent excessive immune activity to specific antigens. TNF-α inhibitors decrease antigenic clearance and increase infections. Thus the mechanism of granulomatosis development in this setting could include increased susceptibility to infection and/or failure to control certain granuloma-inducing organisms resulting in modification of the cytokine environment and cellular recruitment within the tissues. Several lines of evidence support the idea that sarcoidosis results from exposures to environmental agents such as Mycobacterium tuberculosis and P. acnes, both of which have been reported with TNF-α inhibitors.5

The prognosis of sarcoidosis occurring during TNF-α blockade is generally favourable with granuloma resolution occurring within a year of withdrawing the inciting agent, although some patients require systemic steroids to dampen the inflammatory process. It is increasingly important for clinicians to be aware of this potential complication of TNF-α inhibitors when treating Crohn’s disease. In time, this counter-intuitive phenomenon may lead to critical insights into the pathogenesis of both these diseases.

Conflict of interest
None to declare (all authors).

References


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Figure 1  (a) Chest X-ray on presentation in 2011 showing new prominent hilar and mediastinal adenopathy with multiple ill-defined nodules of varying sizes scattered throughout both lung fields. Patient had no pulmonary symptoms on presentation with presenting features consisting primarily of bilateral ankle swelling and erythema nodosum. (b) CXR in 2012 following treatment with systemic steroids showing resolution of previous hilar and mediastinal adenopathy as compared to previous imaging. (c) Histological section taken from the right upper paratracheal lymph node on mediastinal biopsy showing extensive focally necrotising granulomatous inflammation (outlined in black) replacing the predominant part of the lymph node tissue, consistent with sarcoidosis. Stains for fungus (PAS, GMS) and acid-fast bacilli (ZN) were negative (H&E, ×10).

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