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CASE REPORT

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Anti-tumour necrosis factor-α-induced lupus in a patient receiving infliximab for sarcoidosis

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Abstract

Infliximab is a chimeric monoclonal antibody against tumour necrosis factor (TNF)-α, with a wide variety of uses. Monoclonal antibody therapies specifically targeting TNF-α, have emerged as a novel treatment option for patients with refractory sarcoidosis, with infliximab being the most widely used. This is not true of other TNF-α inhibitors, for example etanercept, which have a different mechanism of action, and are not effective in sarcoidosis. It is well documented that infliximab therapy can result in the production of autoantibodies, however clinical symptoms or disease is rare. In this report, we describe a 37-year-old male with a history of sarcoidosis requiring infliximab therapy, who presented during the course of his treatment with the onset of new migratory joint pain, increasing fatigue and positive serum autoantibodies, heralding the development of infliximab-induced lupus.

KEYWORDS
infliximab, lupus, sarcoidosis, TNF-α

INTRODUCTION

Lupus is a rare complication of treatment with infliximab, occurring in less than 1% of all patients treated.[1] In this report, we describe an adult patient who developed this clinical syndrome whilst receiving infliximab therapy for sarcoidosis.

CASE REPORT

A 37-year-old male with a history of sarcoidosis with multiorgan involvement, developed migratory joint aches after 10 months of treatment with infliximab, receiving eight doses in total. There was no previous history of any rheumatic disease, and serological testing for associated autoantibodies had been previously negative (Table 1). The patient had not reported these symptoms prior to initiation of infliximab therapy. Other medications taken at this time were prednisolone and esomeprazole.

The patient initially presented with a persistent cough and an area of parenchymal consolidation unresponsive to antibiotic therapy, as well as pancytopenia. Whilst malignancy was the initial concern, the diagnosis of sarcoidosis was made via bronchoscopic lung biopsy with histology demonstrating widespread non-necrotising granuloma formation, and no evidence of malignancy. Serum angiotensin converting enzyme (ACE) was not tested at the time of diagnosis, or during the emergence of later symptoms. The patient was found to have prominent bone marrow involvement from sarcoidosis at the time of diagnosis. Given this extensive bone marrow disease and resulting pancytopenia, the treating physician determined the potential risk of further myelosuppression with use of methotrexate or azathioprine was significant, and so opted to commence infliximab after prednisolone failed to adequately control the patient's disease. Figure 1A demonstrates widespread thoracic disease activity on ^{18}F-FDG PET scan prior to commencing infliximab therapy, with mediastinal, cardiac and vertebral involvement.

The patient described new onset joint pain, swelling and loss of function affecting the small joints of the right hand and wrist. There was some initial improvement in symptoms with non-steroidal anti-inflammatory drugs. However

TABLE 1 Key serological markers before and after discontinuing infliximab and commencing hydroxychloroquine

Key serological markers (normal reference interval)	Values prior to commencing infliximab	Values at time of diagnosis of infliximab-induced lupus	Values 1 month after discontinuation of infliximab	Values 3 months after discontinuation of infliximab
Antinuclear antibody	Negative	1:2560 Homogenous pattern	–	1:640 Homogenous pattern
Anti-dsDNA antibody (<5.0 IU/ml)	<5.0	39.3	22.0	8.7
C-reactive protein (<8.0 mg/L)	1.7	18.4	3.8	-

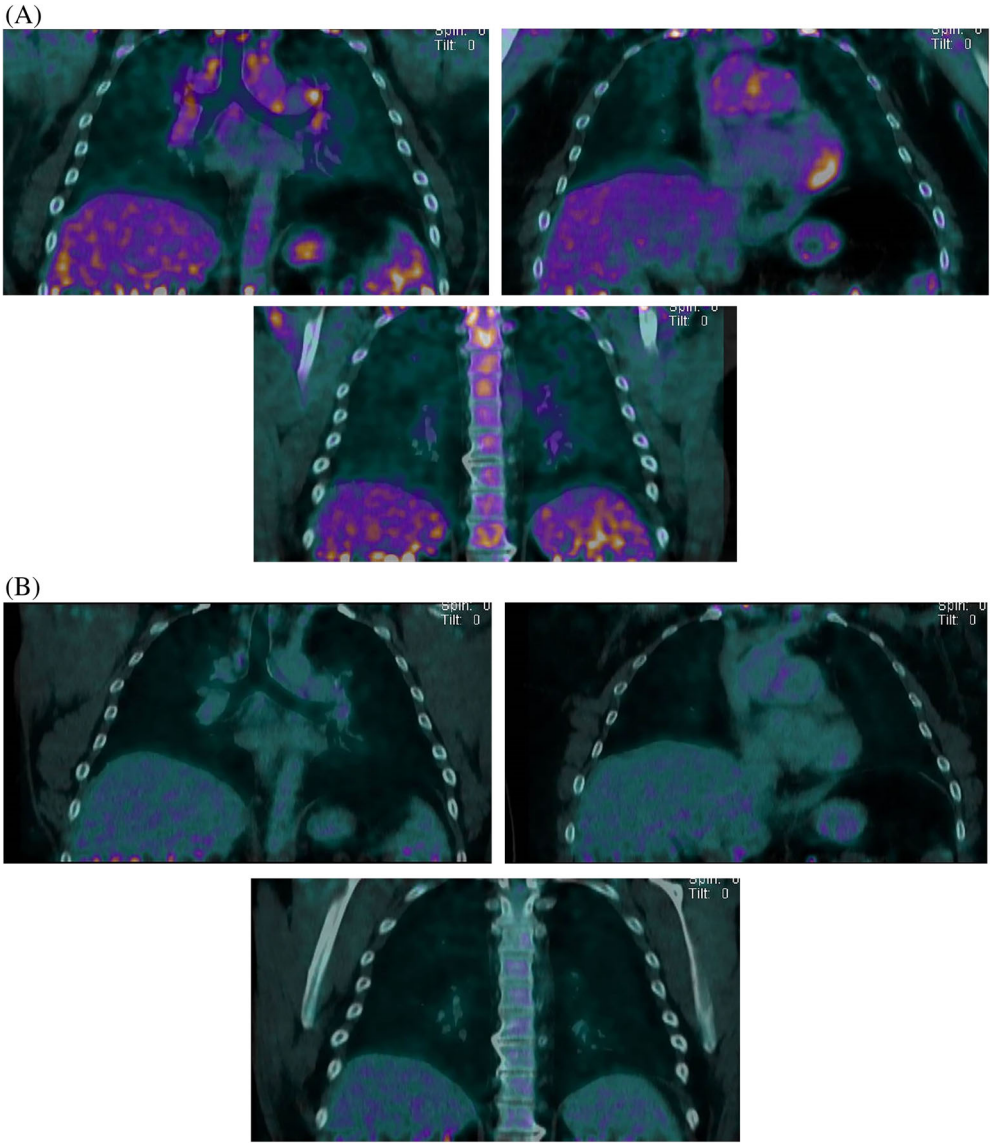

FIGURE 1 (A) ^{18}F-FDG PET scan prior to infliximab therapy demonstrating increased fluorodeoxyglucose (FDG) uptake in mediastinal lymph nodes, left ventricular wall, vertebral bone marrow and spleen, indicating extensive active sarcoidosis. (B) ^{18}F-FDG PET scan after eight doses of infliximab demonstrating complete resolution of previously observed sarcoidosis activity

similar symptoms subsequently arose in other joints in a migratory fashion, affecting his shoulders, knees, wrists and the small joints of both hands. These symptoms were again diminished somewhat with self-administration of 25 mg oral prednisolone. In addition, the patient described increasing fatigue and malaise in this same period. There was no

reports of a rash or photosensitivity. No other systemic symptoms were described. A repeat ^{18}F-FDG PET scan confirmed there had been complete resolution of previously observed sarcoid activity, and did not demonstrate any new disease sites (Figure 1B).

Clinical examination approximately 3 weeks after the onset of symptoms, whilst taking an increased dose of prednisolone, was largely unremarkable, with no evidence of active synovitis and no rash demonstrated. Chest examination was unremarkable. Initial bloods demonstrated persistent lymphopenia (lymphocytes 0.97 [normal range 1.50–3.50]), and a mildly elevated C-reactive protein (CRP). Other complete blood picture (CBP) parameters were within normal limits. There were no significant abnormalities on other initial laboratory tests, and renal function was normal.

On subsequent outpatient review, the patient's joint symptoms and fatigue persisted. Serological testing for autoimmune markers was consequently performed which demonstrated a positive antinuclear antibody (ANA) at high titre, and positive anti-dsDNA antibody using the Farr assay (Table 1). These serological markers had previously been negative shortly prior to commencing infliximab therapy. Tests for rheumatoid factor, anti-cyclic citrullinated peptide (anti-CCP), extractable nuclear antigen (ENA) antibodies, anti-histone antibody and complement C3/C4 were within normal limits. Erythrocyte sedimentation rate (ESR) similarly remained within normal limits (8 mm [normal 1-10 mm]), and of note, CRP was only mildly elevated throughout this period, peaking at 18.4 mg/L.

As a result, the patient was referred for outpatient Rheumatologist review. He was given a diagnosis of anti-TNF-α-induced lupus secondary to therapy with infliximab. No further doses of infliximab were administered, and the patient was commenced on hydroxychloroquine.

With cessation of infliximab, the patient's joint symptoms resolved, autoantibody and inflammatory marker levels are decreasing, and his prednisolone dose has been successfully reduced. Table 1 shows key serological markers before and after the discontinuation of infliximab. The patient's sarcoidosis has remained in remission since ceasing infliximab, with no new symptoms and an ongoing normal CBP.

DISCUSSION

Lupus is an uncommon complication that can occur as a result of treatment with a broad spectrum of different medications, all of which trigger an autoimmune response via varying mechanisms. Risk of developing this clinical syndrome varies widely depending on the therapeutic agent, however is reported to be as low as 2 cases per 1000 patients treated with anti-TNF agents, including infliximab.[1]

Anti-TNF agents, in particular infliximab, have long been known to incite production of autoantibodies, particularly ANA and anti-dsDNA antibody. The exact mechanism for this remains unclear, but it has been hypothesised that this may be a result of a 'cytokine shift' due to the suppression of Th1 cytokines by TNF-α inhibition, resulting in an augmented Th2 cytokine response and a resulting increase in autoantibody production. In addition, it is thought that blockade of TNF-α may interfere with cellular apoptosis, and promote formation of autoantibodies due to impaired clearance of nuclear debris.[2,3] Whilst the formation of autoantibodies is well documented, clinical disease in the presence of these antibodies is rare.

Anti-dsDNA antibodies are highly specific for lupus, and can be identified via several different mechanisms. These antibodies exist in multiple different immunoglobulin subclasses, and whilst IgM antibodies may appear commonly in anti-TNF-α-induced lupus, it is the IgG antibodies that are largely responsible for producing symptoms and disease.[4] In this case, the Farr assay was used to confirm the presence of anti-dsDNA antibodies. This is a highly specific test that is able to detect antibodies of all subclasses, thus fulfilling European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) classification for lupus in this patient.[5]

Case series of patients with anti-TNF-α-induced lupus have demonstrated the majority of patients present with mucocutaneous symptoms (67%), arthralgias/arthritis (31%) and pleuropericardial abnormalities, with symptoms closely mimicking those of classic systemic lupus erythematosus.[6] Of note, the patient in this report did not exhibit any mucocutaneous or pleuropericardial symptoms. Renal and neurological involvement is rare.[1,6] ANA is the most commonly detected autoantibody (79%–100%), followed by anti-dsDNA antibody (72%–91%). Whilst anti-histone antibodies are the hallmark in other forms of drug-induced lupus, the frequency of these antibodies in anti-TNF-α-induced lupus ranges from only 17% to 57%, and were not detected in this patient.[6,7]

The optimal treatment of anti-TNF-α-induced lupus remains unclear, however the clinical syndrome responds to the withdrawal of the causative agent in the majority of cases. One study demonstrated resolution of symptoms in 94% of patients after cessation of the anti-TNF-α therapy, however, a number of these patients also received corticosteroids or additional immunosuppressive agents.[6] The use of additional immunosuppression is recommended for patients with more severe disease.

As the use of anti-TNF-α agents, and more specifically infliximab, increases amongst patients with sarcoidosis and other systemic conditions, prescribing physicians should be aware of the risk of this rare but clinically important syndrome, and monitor for its development accordingly.

AUTHOR CONTRIBUTION

Lachlan Stranks: primary author. **Sally Chapman**: supervising clinician, editing of manuscript.

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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