A case of certolizumab-induced interstitial lung disease in a patient with rheumatoid arthritis

Sr, A 66-year-old non-smoking woman with a 35-year history of widespread erosive RA presented with rapidly progressive breathlessness.

Her previous therapy had included CYC in the early 1990s, complicated by the development of haemorrhagic cystitis requiring bladder reconstruction in 1995. She had no other major medical history. Until 6 months prior to presentation, she had been taking MTX 20 mg weekly for 12 years and prednisolone 2.5 mg/day. In the setting of recurrent joint inflammation, LEF 20 mg/day was added to her therapy and her MTX was increased to 30 mg weekly. Two months later the patient had ongoing severe joint inflammation. Investigations revealed an anti-CCP antibody titre of >250 U/ml (normal <20), a CRP titre of 13 mg/l (normal <5), a normal chest X-ray (Fig. 1a) and negative Quantiferon-Gold assay. The following month, 400 mg of certolizumab subcutaneously was administered every 4 weeks was begun.

At presentation she described a 1-month coryzal illness. Breathlessness and dry cough had developed over the preceding 2 weeks, causing difficulty with minor exertion, such as dressing. On examination she demonstrated an oxygen saturation of 89% on room air, was afebrile and had an increased respiratory rate of 24. Basal crackles were audible within the chest. Peripheral examination demonstrated extensive erosive joint disease, maximal at the hands and feet.

A CT chest taken at presentation demonstrated bilateral ground glass and reticular change involving both lungs, maximally in the lower zones (Fig. 1b and c and supplementary figures, available at Rheumatology Online). Blood tests revealed a total white cell count within normal limits, a CRP of 28 (normal <5) and an ESR of 77 mm/h (normal 5–20 mm/h). She had a CCP antibody titre of 107 U/ml. Sputum culture could not be obtained and blood cultures were negative.

Treatment was initiated in a provincial hospital for presumed Pneumocystis pneumonia, using high-dose cotrimoxazole and prednisolone 50 mg orally daily, without clinical or objective improvement. On transfer to our hospital, surgical lung biopsy was performed and features consistent with organizing pneumonia were demonstrated. Histological features included thickening of the alveolar walls with areas of fibrosis with a mild myxomatous component. Only a light infiltrate of inflammatory cells was seen and there was no evidence of vasculitis or granuloma formation. PCR testing for Pneumocystis DNA was negative and fungal and bacterial cultures were negative.

The patient was treated with i.v. methylprednisolone 1 g/day for 3 days and thereafter prednisolone 30 mg twice daily. She remained hypoxic and oxygen dependent throughout her admission, but 1 month after presentation, had not significantly deteriorated. A repeat CT chest performed 1 month following her initial CT scan demonstrated changes restricted to those areas that had been involved at presentation (Fig. 1d and supplementary figures, available at Rheumatology Online). Significant architectural distortion and traction bronchiectasis had developed in those areas in keeping with rapidly evolving fibrosis. She was discharged back to her provincial hospital for restorative care prior to discharge home. She remained oxygen dependent at the time of discharge. At review 1 month post-discharge, having received prednisolone 1 mg/kg through that period, the patient had not made any clinical improvement, with ongoing exertional hypoxia and a total walk distance on the 6-min walk test of 88 m, consistent with severe functional impairment. Two months after review the patient entered palliative care and died shortly thereafter.

TNF-α inhibitors provide an important means for disease control in patients with RA not responding to DMARDs, reducing the risk of joint damage and improving physical function and quality of life [1]. Certolizumab is composed of the Fab antigen-binding domain of a humanized monoclonal anti-TNF antibody combined with polyethylene glycol to increase its half-life. It demonstrates equivalent efficacy to the other TNF-α inhibitors [2].

Pulmonary adverse effects of TNF-α inhibitor therapy include well-documented infectious complications, specifically mycobacterial infection [3]. Non-infectious complications include a range of interstitial lung diseases, including usual interstitial pneumonia, non-specific interstitial pneumonia, organizing pneumonia, lymphocytic interstitial pneumonia and diffuse alveolar damage [4].

This case represents the first description of certolizumab-induced pulmonary toxicity [5]. In conjunction with descriptions attached to each of the other TNF-α inhibitors, the risk of pneumonitis displays a class effect. Our patient demonstrated a number of features that have been recognized as risk factors for TNF-α inhibitor-associated pneumonitis, including age >60, female sex and concomitant disease-modifying agent use. Of note is the absence of pre-existing interstitial lung disease, a risk factor highlighted in one large case series [4]. In addition, this patient’s disease displayed a faster time of onset than occurred in that series, within which disease occurred generally only after 6 months. Despite aggressive immunosuppression, our patient displayed ongoing severe debility and persistent interstitial change in keeping with data from larger series, within which approximately one-third of cases have displayed no resolution.
Certolizumab, in similarity to other TNF-α inhibitors, may precipitate pneumonitis.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at Rheumatology Online.

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Accepted 21 March 2013

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Pyoderma gangrenosum (PG) is an ulcerative skin disease simulating pyoderma gangrenosum. Necrotizing vasculitis secondary to disseminated histoplasmosis was found in peripheral blood by the PCR technique, but no results were obtained from culture and biopsy of the ulcer. Immunosuppressive medication was discontinued and itraconazole was initiated, with excellent response (supplementary Fig. S1, available at Rheumatology Online).

Diagnosis of PG is based on clinical presentation and clinical course. Histopathology is non-specific and may show oedema, mixed inflammatory infiltrate with polymorphonuclear predominance, lymphocytic vasculitis or necrosis and haemorrhage. The relevance of histology is in PG differentiation with respect to one of its simulators in the differential diagnosis [6]. Classic PG (CPG) presents in middle age (30–50 years). Infective PG (IPG) has a bimodal pattern of presentation (under 25 and over 60 years) and is associated with conditions that predispose to infections such as immunosuppression. A significant finding to differentiate the two entities is the anatomical distribution of ulcers. IPG lesions are distributed throughout the body and CPG are generally in lower limbs. Furthermore, cultivation of the injury and peripheral blood may show evidence of a causative pathogen.

Skin lesions have been reported in 10–15% of patients with disseminated histoplasmosis (DH) and include papules, plaques, ulcers, boils, abscesses and widespread dermatitis. The most characteristic histological pattern is the presence of macrophages parasitized by the fungus. In rare cases, the pathological findings may mimic necrotizing vasculitis, causing misdiagnosis [7]. In 1976, Small et al. [8] described a patient with isolation of Histoplasma in the nasal septum who presented with palpable purpura and histological evidence of necrotizing vasculitis, but Histoplasma could be neither grown nor demonstrated histologically in the lesions.

The definitive diagnosis of DH should be performed by classical microbiological methodology comprising direct examination, culture and serology. However, Toranzo et al. [9] recently described a molecular method based on the PCR technique where diagnosis of histoplasmosis supports the diagnosis of PG.

**Fig. 1** Large ulcer with irregular borders and violet pigmentation with necrohaemorrhagic background supports the diagnosis of PG.