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Review

Pulmonary artery aneurysms in Behçet's disease treated with anti-TNFα: A case series and review of the literature

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ABSTRACT

Behçet's disease (BD) is a systemic inflammatory disorder of unknown aetiology. Pulmonary haemorrhage from ruptured pulmonary artery aneurysms (PAA) in this condition carries a high mortality but treatment has largely been empiric with use of glucocorticoids and cyclophosphamide. Tumour necrosis factor α (TNF-α) was recently recognised as a mediator in the pathogenesis of BD inflammatory lesions. TNFα inhibitors have been shown in various case reports/series to have beneficial effects in uveoretinitis, entero-Behçet's, neuro-Behçet's and BD arthritis. We describe the efficacy and tolerability of infliximab in 2 patients with Behçet's disease complicated by pulmonary vasculitis admitted to our unit during the years 2004–2015, and discuss the previously published data in this area.

Contents

1. Introduction

Behçet's disease (BD) is a systemic inflammatory disorder of unknown aetiology, characterized by recurrent oral and genital ulcers, cutaneous, ocular, articular, gastrointestinal, neurologic and vascular manifestations. The disease is most prevalent in the Middle East, Mediterranean region and Asia with a usual age of onset in the third decade of life [1,2]. The Chapel Hill Consensus Conference (CHCC) nomenclature system recognises BD as a variable vessel vasculitis that affects both the arterial and venous systems, including the pulmonary circulation [3]. Major vessel disease and central nervous system (CNS) involvement account for the majority of mortality and morbidity associated with this disorder and often appear late in the course of this disease [4]. Pulmonary haemorrhage from ruptured pulmonary artery aneurysms (PAA) is particularly feared as it carried with it a survival rate of only 62% at 5 years [5].

Although the aetiology of BD remains unclear, it has been postulated that interaction of a specific genetic background with infectious agents may occur to lead to immune dysregulation with altered microbiota of the gut having been identified in patients with BD [6,7]. HLA-B51 has long been identified as a predisposing factor with tumour necrosis factor α (TNF-α) more recently recognised as a mediator in the pathogenesis of BD inflammatory lesions [8,9]. Previous studies have identified increased expression of TNF-α by γδ T cells in the peripheral blood of patients with active BD and TNF-α mRNA expression has been shown to decrease in the ulcerative lesions of BD patients after treatment [9,10]. TNF-α thus appears to be a logical therapeutic target in BD.

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We describe the efficacy and tolerability of infliximab in 2 patients with Behçet's disease complicated by pulmonary vasculitis admitted to our unit during the years 2004–2015, and discuss the previously published data in this area.

2. Methods

Three patients with BD related pulmonary vasculitis were referred to the Louise Coote Lupus Unit at Guy's Hospital, London, during the years 2004–2015. Two of these patients did not respond to standard management of glucocorticoids and cyclophosphamide and underwent further investigations and treatment. Clinical and laboratory data were collected from their medical records. We reviewed the English language medical literature using the PubMed and Medline search terms 'Behçet', 'pulmonary artery aneurysms', 'infliximab', 'etanercept', 'adalimumab' and 'anti-TNF'.

2.1. Case 1

A 35-year old Romanian man presented to our unit with a 4-month history of productive cough, central chest discomfort, fevers and unintentional weight loss of 10 kg. He also described a five-year history of recurrent orogenital ulcers. Examination identified major and minor apthous ulcers and one penile ulcer and pustule. Laboratory tests showed raised C-reactive protein (CRP) and negative serology for anti-cycloplasmic antibody (ANCA) and anti-nuclear antibody (ANA). Computer tomography pulmonary angiogram (CTPA) demonstrated bilateral pulmonary embolism and right pulmonary artery aneurysms. After the diagnosis of Behçet's disease with pulmonary vasculitis, the patient received oral prednisolone 60 mg/day, warfarin, pulmonary artery embolisation and pulse intravenous (IV) cyclophosphamide (CYC) 500 mg every 2 weeks. However, he re-presented prior to his fifth dose of CYC with massive haemoptysis of 400 mL. CT confirmed widespread ground glass within the lungs, consistent with pulmonary haemorrhage. The right bronchial artery was selectively embolised. Warfarin was stopped and subcutaneous (SC) enoxaparin 80 mg daily was started. In view of ongoing pulmonary vasculitis despite treatment with CYC, he was commenced on IV infliximab 5 mg/kg (repeated at 2 weeks, 6 weeks, and then 8 weekly) and oral methotrexate 10 mg weekly. He responded extremely well to infliximab and had no further haemoptysis. His CRP fell to undetectable levels. He was able to wean off corticosteroid at his last clinic review 4 years after initial diagnosis. He remains on 2 monthly infliximab and weekly methotrexate therapy. The total duration of infliximab therapy was 4 years.

2.2. Case 2

A 36-year-old Caucasian man presented with several months history of fevers, cough, pleuritic chest pain and unintentional weight loss of 20 kg in 2004. He also described recurrent oral and scrotal ulceration and pustular skin lesions within the previous year. Laboratory tests showed raised acute phase reactants and persistently positive lupus anticoagulant (LA). CT chest reported small areas of consolidation in various lobes and thromboembolic disease of the pulmonary arteries. He was treated with antibiotics for presumed pneumonia and anticoagulated for antiphospholipid syndrome (APS). Despite treatment, he remained unwell with ongoing pyrexia. An echocardiogram (ECHO) identified a mobile lesion in the right atrium attached via a stalk to the atrial appendage. Differentials included an atrial myxoma or infective endocarditis. He underwent open heart surgery to remove the atrial mass. Histology confirmed a cyst arising from the superior margin of the coronary sinus filled with an acute inflammatory exudate but with no growth of organisms. He remained on antibiotics for possible culture negative endocarditis. He continued to spike fevers despite antibiotics.

He developed haemoptysis 2 months later. A repeat CT showed new bilateral pulmonary artery aneurysms. A diagnosis of Behçet's disease with pulmonary and coronary vasculitis was made. He received coil embolisation to his right pulmonary artery and was commenced on pulsed IV methylprednisolone 500 mg daily for three days and IV CYC 500 mg every 2 weeks for 6 doses. His fevers resolved with immunosuppression. He continued low dose enoxaparin 40 mg daily due to ongoing risk of thrombosis with APS.

However, he represented 2 months later with recurrence of pleuritic chest pain and exertional dyspnoea. An extensive inferior vena cava (IVC) thrombus was identified. Enoxaparin dose was increased to 80 mg daily. He then developed massive haemoptysis from the left lower lobe. Emergency thoracotomy identified a large inflammatory aneurysm involving all branches of the left pulmonary artery requiring ligation of the left pulmonary artery and left bronchial trunk. He completed 6 doses of IV CYC and was switched to methotrexate (MTX) 15 mg weekly maintenance. He remained relatively well on moderate dose steroid (>20 mg daily of prednisolone) over the next 4 years.

In 2008, he developed recurrence of mouth and genital ulcers, pustular skin lesions, peripheral arthritis and massive haemoptysis over >1 L. Pulmonary angiogram showed enlarging pseudoaneuryms involving the apical branches of the right upper lobe artery. These were treated by coil embolisation. He had a further 6 doses of IV CYC 500 mg fortnightly and continued on MTX and prednisolone.

In 2010, he re-presented with increasingly frequent haemoptysis. Pulmonary angiogram this time showed no evidence of active vasculitis or aneurysms but severe pulmonary hypertension with pulmonary artery pressures of 54 mmHg confirmed at right heart catheterisation. He started bosentan and sildenafil and the haemoptysis resolved.

One year later, he again developed significant pulmonary haemorrhage of 300 mL. This was preceded by development of oral ulcers and nodular lesions on his legs with skin pustules. A CTPA confirmed considerable enlargement of the right pulmonary artery with an inflammatory mass surrounding it (Fig. 1A). He was restarted on IV methylprednisolone and IV CYC. However, fresh haemoptysis continued despite 3 doses of IV CYC. He commenced infliximab 5 mg/kg (repeated at 2 weeks, 6 weeks, and then 8 weekly) on top of ongoing IV CYC. He made excellent progress and a repeat CTPA confirmed considerable reduction in the size of the right pulmonary aneurysm with significant improvement in the surrounding inflammation (Fig. 1B).

He remained well on infliximab every 8 weeks until 2013, when he developed another episode of frank haemoptysis with reduced exercise tolerance. CTPA showed new bleeds from the right pulmonary artery aneurysm but the aneurysm had not increased in size significantly. His medical management was optimised and he was given a further 6 doses of IV CYC with infliximab withheld. He restarted infliximab 2 weeks after completion of CYC infusions. He had a further major haemoptysis of around two units of blood one year later and this was treated by insertion of Amplaz devices to completely occlude the right pulmonary artery aneurysm and further 6 doses of CYC infusions.

He has remained on infliximab infusions since with no further episodes of major bleeding. However, at the time of last review, he has developed bronchiectasis from recurrent chest infections due to long term steroid use. He remains on methotrexate and prednisolone 10 mg daily. The total duration of infliximab therapy was 4 years.

2.3. Literature review

There are five published case reports in the English language literature on the use of anti TNF agents for pulmonary artery aneursyms in BD. All five patients responded to TNFα-inhibitors. Two patients showed resolution of PAA after failing CYC [11–15]. Table 1 summarises these reported cases with Case 1 and Case 2.