Pneumocystis carinii pneumonia following a second infusion of infliximab

Sir, Anti-tumour necrosis factor α (TNF-α) blockade is increasingly used for severe rheumatoid arthritis (RA). There is an increased risk of infection, including atypical infection associated with TNF-α blockade. We report the development of Pneumocystis carinii pneumonia (PCP) in a man with RA shortly after commencing therapy with the anti-TNF-α agent infliximab (Remicade). This occurred in the setting of concomitant therapy with low-dose weekly methotrexate and corticosteroids.

A 49-yr-old man who had had seropositive RA for 9 yr was admitted with a flu-like illness, which had started 10 days earlier. He described a persistent non-productive cough, and dyspnoea at rest, with sweats and rigors. He had been taking methotrexate 10 mg/wk for 8 months, but had ongoing active disease. He had not responded to intramuscular gold, azathioprine and cyclosporin.

There was a history of poorly controlled hypertension, resulting in a small occipital haemorrhage 3 months prior to presentation. Blood pressure was controlled on lisinopril 20 mg daily. Four weeks prior to admission, he had received a first infusion of infliximab 3 mg/kg and had a further infusion 2 weeks prior to admission. Chest X-ray before infliximab treatment was normal. He had received two intramuscular injections of methylprednisolone 120 mg 1 week prior to commencing infliximab. Before the second infusion of infliximab, he developed an extensive pruritic, erythematosus rash on the extensor surfaces of the elbows, knees and thighs, which settled with betamethasone cream and chlorpheniramine. There was a 25 pack year history of cigarette smoking.

Examination revealed pyrexia of 38.1°C, respiratory rate 20/min and tachycardia 105/min. There were fine crepitations in both lung bases. The erythrocyte sedimentation rate was 81 mm h (previously 30 mm h), white blood cell count $5.4 \times 10^9$/l (4–11), lymphocytes 0.8 (NR 1.5–2.5), platelet count $456 \times 10^9$/l (NR 150–400), alanine transaminase 51 U/l plasma (NR 12–40), plasma sodium 122 mmol/l (NR 135–145) and partial pressure of oxygen 8.66 kPa (NR 11–15). Chest X-ray revealed bilateral lower and middle zone infiltrates. Urinalysis, renal and bone profile were normal.

He was commenced on oral clarithromycin 500 mg twice daily, intravenous co-amoxiclav 1.2 g three times daily and oxygen. Over the ensuing 24 h, he remained pyrexial. Chest X-ray findings deteriorated (Fig. 1). Co-amoxiclav was discontinued and intravenous cefotaxime 2 g three times daily and piperacillin 4.5 g three times daily were commenced. Despite 3 days of these antibiotics, he remained pyrexial and unwell. Seven days after admission he underwent bronchoscopy with bronchoalveolar lavage (BAL). After the procedure, he was immediately commenced on intravenous co-trimoxazole (Septrin).

Grocott’s silver stain of the BAL revealed the presence of Pneumocystis carinii with no mycobacteria on Ziehl–Nielsen stain. Early morning urine for acid- and alcohol-fast bacilli X3 and Mantoux test were negative. Mycoplasma, Legionella, Q-fever, adenovirus, influenza, Chlamydia, cytomegalovirus, Epstein-Barr virus, hepatitis B and C and HIV titres were negative. He improved substantially over the next 24 h and his blood gas, lymphocyte count and plasma sodium returned to normal.

FIG. 1. Chest X-ray demonstrating bilateral mid and lower zone infiltrates secondary to PCP.

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normal after 3 days. Intravenous co-trimoxazole was given for 6 days followed by high dose oral therapy for a further 2 weeks. Methotrexate and infliximab were discontinued. Follow up chest X-ray showed substantial resolution of the consolidation.

Opportunistic infection in patients with RA is very uncommon. Only 12 cases of PCP have to date been reported in association with low dose methotrexate [2]. This indicates a very small incidence as methotrexate has been in widespread use for the treatment of RA for some years. Our patient had been taking methotrexate 10 mg/week for 8 months without side effects but developed PCP 4 weeks after commencing infliximab.

The rash that developed in this man 14 days after the first infliximab infusion was followed by the development of PCP a further 2 weeks later, after the second infusion. However, there has been no evidence to date that rash associated with infliximab is a marker for the development of opportunistic infection, although these two uncommon or rare side-effects followed one another within 2 weeks. Infection in those on infliximab needs to be treated aggressively. If there is no response to broad spectrum antibiotics within 48 h, bronchoscopy and biopsy and computed tomography of the thorax should be considered.

The strong temporal relationship between commencing infliximab and the onset of PCP suggests that infliximab was key to the development of the opportunistic infection. The manufacturers of infliximab (Schering-Plough/Centocor) have an additional five cases (at the time of writing) on file of PCP associated with the use of the agent [1]. A literature search using key words infliximab, PCP, TNF-α and opportunistic infection, revealed no published reports. Invasive pulmonary aspergillosis has recently been described in association with infliximab therapy [3].

As the use of anti-TNF-α therapy increases, the possibility of serious opportunistic infection occurring should inform decisions about the choice of therapy and patient selection, especially where concomitant, potentially immunosuppressant medication is given.

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