Methotrexate-associated lymphoproliferative disorder presenting as disseminated malignancy

SIR, An 83-year-old man referred from primary care presented with loss of appetite, lethargy and constipation over 3 months, 10 kg weight loss over 8 months and progressive anaemia. Pelvic pain and persistent leg weakness also developed 3 weeks before admission in the absence of trauma. Recent gastroscopy and abdominal US were unremarkable. Comorbidities included seronegative RA diagnosed in 2000 and successfully managed with MTX, prostatic hypertrophy and hypertension. Significant past history included squamous cell carcinoma of the neck excised 3 years previously. Current medication consisted of MTX 20 mg weekly, folic acid, aspirin, alfuzosin, omeprazole, olmesartan, lercanidipine and NSAIDs.

On admission, symmetrical global reduction in lower limb power [Medical Research Council (MRC) power grade 4/5] and sensory paraesthesiae were noted. Physical examination was otherwise unremarkable. Blood tests revealed hypercalcaemia (corr. Ca²⁺ 3.21 mmol/l) with suppressed PTH (<0.5 pmol/l), normocytic anaemia [haemoglobin (Hb 9.6 g/dl, mean corpuscular volume (MCV) 88 fl] and lymphopenia (0.2 × 10⁹ cells/l).

Paraprotein screen, including serum-free light chain, was negative. Viral serology demonstrated evidence of past EBV infection.

Body CT revealed a large left-sided presacral soft tissue mass and a mass arising from the right iliac bone, with associated bone destruction at both sites (Fig. 1A). Fractures of the right acetabulum, right inferior pubic ramus, multiple vertebral bodies and right eighth rib were also apparent. Bilateral pleural effusions and widespread lymphadenopathy involving iliac, para-aortic, subcarinal, aortopulmonary and paratracheal nodes were also evident. Abdominal organ appearances were unremarkable. The findings were thus interpreted as a diagnosis of metastatic disease arising from an unidentified primary. Spinal MRI further revealed a T9 collapse with canal stenosis, and vertebral wedge compression at T6. MTX, aspirin, simvastatin and anti-hypertensive treatment were discontinued, and iron supplementation initiated. Hypercalcaemia was treated with one dose of i.v. pamidronate and rehydration—this resolved over a period of 10 days without further intervention (Fig. 1B). Radiotherapy, CSs and spinal surgery were considered but deemed inappropriate following specialist advice.

Further investigations to establish a histological diagnosis were inconclusive. Pleural fluid aspiration, two radiologically guided biopsies of the right iliac wing and bone marrow trephine demonstrated a lymphoid infiltrate with no evidence of malignancy. In all samples, cell surface

Fig. 1 Temporal progression of radiological, biochemical and haematological parameters. (A) CT axial sections demonstrating temporal evolution of pleural effusions (upper panel), and right iliac and presacral masses with associated bone destruction (middle and lower panels) over 100 days following admission (see arrows). (B) Time course of blood investigations demonstrating reactive lymphocytosis following MTX withdrawal, rise in ALP consistent with bone repair, and resolution of hypercalcaemia and anaemia following treatment.
marker analysis of the infiltrate revealed a mixed lymphohytic composition predominantly consisting of CD8+ cytotoxic T cells co-expressing CD3 and CD5 and small numbers of B cells. During this time, the patient remained clinically stable despite no active treatment, and leg power was noted to improve. Presenting anaemia resolved and a self-limiting lymphocytosis (9.2 x 10^9 cells/l) and elevated CRP (126 mg/l) peaking at 15 days were noted, attributed to MTX discontinuation (Fig. 1B).

Open surgical biopsy of the right iliac lesion 29 days after presentation revealed pre-existing necrotic bone with reactive new bone and cartilage formation. Raised alkaline phosphatase (231 U/l) noted on blood biochemistry was also consistent with bone repair (Fig. 1B). Repeat CT at 35 days demonstrated complete resolution of pleural effusions and lymphadenopathy, and a significant reduction in the size of the iliac and presacral masses (Fig. 1A). Importantly, no new lesions were identified. By this time, the patient’s mobility had significantly improved and he was discharged from hospital. A further CT scan 100 days after initial admission showed further resolution of the pelvic masses (Fig. 1A), and no evidence of recurrence was apparent at 12-month follow-up.

Taken together, the clinical, radiological and histological findings in the context of spontaneous regression following MTX withdrawal are consistent with a diagnosis of MTX-associated lymphoproliferative disorder (MTX-LPD). The condition is defined as a lymphoid proliferation or lymphoma in a patient immunosuppressed with MTX, and 85% of cases have been reported in patients with RA [1]. To our knowledge, this is the first reported case of MTX-LPD presenting as widespread bone disease indistinguishable from disseminated malignancy.

The exact epidemiology of the MTX-LPD is unknown. Extranodal presentation has been reported in 32–40% of cases, and in 100% of cases with atypical lymphoplasmacytic infiltrates [1, 2]. Favourable factors associated with complete remission after discontinuing MTX include extranodal involvement and EBV infection [2]. The timeline of complete remission has been reported as 4 weeks in the majority of cases, with the remainder resolving over 6–12 weeks [2]. In the context of RA, the exact role of MTX and EBV in the pathogenesis of LPD is unclear. A case series comparing MTX- with non-MTX-associated LPD in RA demonstrated a shorter interval to LPD development with MTX treatment but no evidence of increased LPD risk with MTX treatment [3]. Interestingly, spontaneous regression without further chemotherapy was confined only to MTX-LPD cases, and EBV positivity in RA-LPD correlated with a higher 5-year survival [3].

Our reported case of LPD in the context of RA, MTX treatment and previous EBV infection showed spontaneous complete remission over a period of 6 weeks with no evidence of recurrence. Although the exact relationship between these factors is unclear, previous studies suggest that MTX treatment and EBV positivity may predict likelihood of spontaneous remission of LPD in RA, as illustrated in this case.

**Rheumatology key message**

- Consider spontaneously regressing LPD as a differential to malignancy in MTX patients before undertaking further treatment.

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**Alexis J. Joannides1, Hamid El-Shaboury1, Roshyd Guirguis2, Julian J. Fasler1 and Vivek Rajagopal1,3**

1Department of Medicine, 2Department of Radiology and 3Department of Rheumatology, West Suffolk Hospital, Bury-St-Edmunds, UK.

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Correspondence to: Alexis J. Joannides, Neurosurgery Unit, Box 167, Addenbrooke’s Hospital, Hills Road, Cambridge CB2 0QQ, UK. E-mail: aj238@cam.ac.uk

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**Complete remission of myeloperoxidase-anti-neutrophil cytoplasmic antibody-associated crescentic glomerulonephritis complicated with rheumatoid arthritis using a humanized anti-interleukin 6 receptor antibody**

Sir, ANCA-associated necrotizing and/or crescentic GN (CrGN) has been reported to be complicated with RA [1–3]. Recently, some reports have demonstrated the efficacy of anti-TNF agents in the treatment of ANCA-associated CrGN complicated with RA [4, 5]. However, no reports have demonstrated the efficacy of tocilizumab, a humanized anti-IL-6 receptor antibody for ANCA-associated CrGN complicated with RA.

In November 2001, a 74-year-old Japanese woman was admitted to our hospital with persistent proteinuria and haematuria, and elevated MPO–ANCA titre. She had been diagnosed with RA in 1995, and treated with 5 mg