marker analysis of the infiltrate revealed a mixed lymphocytic 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 (9.2×10^9 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.

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

Alexis J. Joannides[1], Hamid El-Shaboury[1], Roshdy Guirguis[2], Julian J. Fasler[1] and Vivek Rajagopal[1,3]

[1]*Department of Medicine,* [2]*Department of Radiology and* [3]*Department of Rheumatology, West Suffolk Hospital, Bury-St-Edmunds, UK.*
Accepted 17 May 2011
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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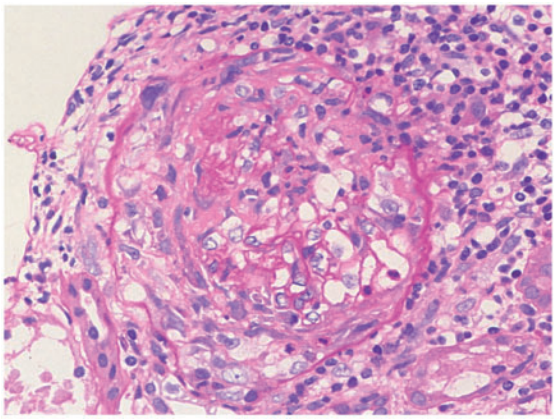
Rheumatology 2011;50:1928–1930
doi:10.1093/rheumatology/ker222
Advance Access publication 29 June 2011

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

FIG. 1 Light microscopy of renal biopsy shows cellular crescent with extensive necrosis and disruption of the Bowman's capsule, indicating necrotizing and CrGN (periodic acid-Schiff stain; original magnification ×400).



of oral prednisolone (PSL) and 4 mg of MTX per week. On admission, the physical examination was normal, except for swollen and tender joints of both hands. Urinalysis showed 0.70 g proteinuria/24 h and several dysmorphic red cells and red cell casts. Haematological results indicated a white blood count of 9.9×10^9/l, haemoglobin 14.1 g/dl, platelet count 402×10^9/l. Serum creatinine was 0.7 mg/dl, CRP 1.7 mg/dl, ESR 52 mm/h, RF 17 U/ml (normal 0–10 U/ml), ACPA 54.3 U/ml (normal <4.5 U/ml), ANA 1 : 80, MPO–ANCA 56 EU (normal <20 EU). Serum immunoglobulin (Ig) G, IgA, IgM, CH50 and components of complement were normal. Investigations for cryoglobulinaemia and antibodies to ENA, dsDNA, GBM and proteinase 3 were negative. Chest X-ray and CT were normal.

A renal biopsy was performed. On light microscopy, 11 glomeruli were observed, of which 2 were sclerotic. Of the nine non-sclerotic glomeruli, four showed fibrocellular crescentic formation and two showed cellular crescent with extensive necrosis and disruption of Bowman's capsule (Fig. 1). IF microscopy showed negative staining in the glomeruli. Electron microscopy showed partial thickening of the basement membrane and partial subendothelial oedema of the glomerulus with no immune deposits. These results indicated MPO–ANCA-associated pauci-immune GN with necrotizing and crescentic formation complicated with RA.

Intravenous CYC (IVCY; 500 mg), followed by oral PSL at 30 mg/day was initiated. Within 1 month after the administration of IVCY and PSL, her disease activity improved, except for the persistent haematuria. However, her disease activity worsened gradually with tapering of the PSL to 7.5 mg/day during the 6 years of follow-up. The administration of tacrolimus (3 mg/day) failed to suppress her disease activity with exacerbation of the arthritis, elevated CRP level and MPO–ANCA titre, and increased haematuria. At this time, the CRP and MPO–ANCA titre were 2.5 mg/dl and 120 EU, respectively, and haematuria was >30 erythrocytes per high-power field. Then, in September 2008, the tacrolimus was ceased, and intravenous administration of tocilizumab was started at 8 mg/kg/month. After 3 weeks, her symptom of arthritis and CRP level, as well as the severe persistent haematuria, improved dramatically. We were also able to taper off the PSL within 6 months. At present, after 2 years, the RA remains in remission without any haematuria or proteinuria, and the patient is still being treated with tocilizumab at 8 mg/kg/month without any adverse effects. Interestingly, although the activity of MPO–ANCA-associated GN as indicated by the CRP level and haematuria has improved completely; only the serum MPO–ANCA titre still remains high.

RA is a chronic, systemic autoimmune disease characterized by inflammatory changes in joints, and sometimes involves extra-articular features, including vasculitis. Although rheumatoid vasculitis with usually severe systemic manifestations may occur in the course of RA, kidney involvement including crescentic necrotizing GN has rarely been reported [6]. Messiaen *et al*. [2] reported two patients with RA who developed necrotizing CrGN with high titres of anti-MPO antibodies in the absence of overt extra-renal vasculitis, and suggested it to be a RA-related complication. Some reports have indicated that serum TNF-α and serum IL-6 were also increased in patients with MPO–ANCA-associated CrGN, in the active stage, and correlated well with anti-MPO antibody titre [7]. Anti-MPO antibodies have been demonstrated to activate endothelial cells and stimulate the production of IL-6 by endothelial cells *in vitro* [8]. In the pathogenesis of MPO–ANCA-associated CrGN with RA, we speculate that anti-MPO antibodies induced by RA activate neutrophils and endothelial cells, stimulate the production of IL-6 and precipitate endothelial injury and activation, resulting in necrotizing and CrGN in patients with RA.

The therapeutic options for MPO–ANCA-associated CrGN complicated with RA include the administration of CSs, MTX and CYC [1], and plasmapheresis [3]. There have been some reports of the efficacy of anti-TNF agents in treating MPO–ANCA-associated CrGN with RA [4, 5]. Recently, tocilizumab has proved effective for the treatment of not only RA but also systemic rheumatoid vasculitis [9]. In the present case, the administration of tocilizumab, which directly inhibits IL-6, could suppress both the articular inflammation and endothelial injury of the glomerular capillaries, and consequently, improve the symptoms of both RA and CrGN, i.e. haematuria. The persistently high MPO–ANCA titre despite improvement of the CrGN may support the possible association between MPO–ANCA and the induction of IL-6, which is the downstream cytokine that is induced by MPO–ANCA in B lymphocytes. Our observations strongly suggest that tocilizumab is a safe and effective treatment in MPO–ANCA-associated CrGN complicated with RA and may be a new therapeutic option not only for MPO–ANCA-associated CrGN complicated with RA, but also for MPO–ANCA-associated CrGN.

Rheumatology key message

- Tocilizumab may be a new and effective therapeutic option for MPO–ANCA-associated CrGN.

Acknowledgements

Funding: This study was partially funded by the Okinaka Memorial Institute for Medical Research.

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

Keiichi Sumida[1], Yoshifumi Ubara[1], Tatsuya Suwabe[1], Noriko Hayami[1], Rikako Hiramatsu[1], Eiko Hasegawa[1], Masayuki Yamanouchi[1], Junichi Hoshino[1], Naoki Sawa[1], Fumi Takemoto[1], Kenmei Takaichi[1] and Kenichi Ohashi[2]

[1]*Nephrology Center and* [2]*Department of Pathology, Toranomon Hospital, Tokyo, Japan.*
Accepted 23 May 2011
Correspondence to: Keiichi Sumida, Nephrology Center, Toranomon Hospital, 2-2-2, Toranomon, Minato-ku, Tokyo, 105-8470, Japan.
E-mail: k_sumida0504@yahoo.co.jp

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