Polyarticular late infection of total joint arthroplasties in a patient with rheumatoid arthritis treated with anti-interleukin-6 therapy

Sirs, The IL-6 receptor antagonist tocilizumab, a monoclonal antibody, has been highly effective in the treatment of certain inflammatory diseases such as RA [1, 2]. However, inhibition of IL-6 is associated with immunosuppression, which can lead to the development of serious infections and associated morbidity [3, 4]. A case of sudden-onset late infection of total joint arthroplasties (TJAs) caused by methicillin-sensitive Staphylococcus aureus (MSSA) following tocilizumab therapy in an RA patient is reported.

A 71-year-old man was diagnosed with RA. When he was 68 years old, with a diagnosis of bilateral hip destruction as a result of RA as viewed on a plain radiograph, bilateral total hip arthroplasties (THAs) were performed. At 70 years of age he underwent right total elbow arthroplasty (TEA) due to arthritis.

Eight months after the right TEA, his DAS using ESR was 3.77 (tender joints, 2; swollen joints, 3; ESR, 25 mm/h; CRP, 0.92 mg/dl) with severe left elbow pain, even though he had been taking MTX 8 mg/week (the highest dose approved in Japan at that time) and low-dose prednisolone 5 mg/day. Although his disease activity was moderate, he had severe left elbow pain. Because there was less bone destruction at the left elbow and flare of other joints, administration of tocilizumab was started, resulting in excellent control of joint symptoms, with his RA disease activity going into remission (DAS28-ESR, 0.29). Furthermore, his steroid intake was reduced to 2.5 mg/day of prednisolone after the fifth tocilizumab administration.

Eleven days after the ninth tocilizumab administration, the patient developed sudden onset of severe pain and swelling and a large joint effusion in his left hip. The next day he complained of right hip and right elbow pain. He was seen at our hospital 7 days after the left hip pain occurred. His vital signs were heart rate, 85/min; blood pressure, 142/87 mmHg; arterial O₂ saturation, 97%; temperature, 37.2°C. Laboratory tests revealed that both the white blood cell count (14550/µl) and CRP level (7.15 mg/dl) were increased. Procalcitonin (1.1 ng/ml), an early marker of bacterial infection, was also increased.

Gram-positive cocci were detected in the effusions of both hip joints and the right elbow joint on staining; the causative organism was later shown to be MSSA. Seven days later he underwent open debridement of all three joints. There were granulations into the joint gaps and surrounding tissue. The granulations were curetted with retention of their implants (Fig. 1a and b), while the bones around the hip joints were filled with antibiotic-impregnated calcium hydroxyapatite (CHA) (Fig. 1a). Several appropriate antibiotics were given intravenously for 6 weeks after the open debridement. Currently, 1.5 years after the operation, the patient is able to walk without pain, reports no symptoms in the previously infected hips and elbow and shows no elevations of inflammatory markers. Postoperative radiographs of the joints showed no abnormal osteolytic lesions and no loosening. Furthermore, interestingly, his RA disease activity remains in remission with only MTX (8 mg/week) and prednisolone (2.5 mg/day) since tocilizumab was stopped.

The goal of treating infection associated with a prosthetic joint is a pain-free, functional joint. This can best be achieved by eradication of the infection [5]. Early operative treatment and radical debridement would be the most important reasons why all prostheses in his infected TJAs were successfully retained. Another reason may be the use of antibiotic-impregnated CHA blocks, which was an excellent drug delivery system [6].

IL-6 and TNF-α have broad biological effects on immune cells. Thus their inhibition makes the hosts relatively immunodeficient, increasing the risk of infections. Momohara et al. [7] analysed perioperative complications after orthopaedic surgery in RA patients treated with tocilizumab. Post-operative infections in patients treated with tocilizumab were observed in 3 of 161 cases (1.9%), with 2 (2.2%) infections in 89 cases with joint replacement surgeries. The percentage did not seem to be extraordinarily high in view of the infection rates associated with RA surgeries reported to date and infection rates associated with TNF inhibitors. The anti-inflammatory effect of tocilizumab suppresses fever and increases CRP levels. Some patients may have normal CRP levels and may not have fever, even immediately after major surgery [7]. However, the increase in the CRP level is usually higher during infection than after surgery, and, indeed, significant

**Fig. 1** Post-operative anteroposterior radiographs of (a) both hips and (b) the right elbow.

Antibiotic-impregnated CHA was implanted in both major trochanters of the femurs after open debridement following revision TJAs.
increases in CRP levels were found in patients with severe infections during tocilizumab treatment [3]. In the present case, tocilizumab treatment may have delayed the onset of the clinical manifestations of the infection, and the delay in the appearance of clinical symptoms may have led to the multifocal nature of the infection. However, early diagnosis and operative treatment might be the key to controlling infected TJAs without removing the implants.

Rheumatology key message

- The delayed appearance of symptoms of clinical infection may have led to the multifocal nature of the infection following tocilizumab therapy of this RA patient.

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The interpretation of repeat renal biopsies in patients with lupus nephritis

Sir, The relevance of repeat kidney biopsy in patients with LN is controversial. Recent recommendations from the European League Against Rheumatism (EULAR)/European Renal Association-European Dialysis Transplant Association (ERA-EDTA) state that it provides useful prognostic information, suggesting a 6-month biopsy as an important adjunct to treatment [1, 2]. Given the toxicity of the immunosuppressive agents used in LN, the question remains as to whether persistent histological lesions should lead to a modification in immunosuppressive therapy. From a pathological standpoint, little is known about the time needed to clear immune deposits and proliferation within the kidney after successful treatment. Here we describe the histological evolution of a kidney transplant recipient whose donor was found to have proliferative mesangial LN at the pre-implantation biopsy. It provides a unique opportunity to assess the clearance of immune lesions in a kidney explanted from its lupus environment.

The donor was a 50-year old male, who died in a vehicle accident, with a past medical history limited to high blood pressure. Urine sediment showed mild proteinuria, but no haematuria. The pre-implant biopsy showed 4% glomerulosclerosis, moderate mesangial enlargement and mild hypercellularity, tubular atrophy and interstitial fibrosis (Table 1). IF revealed moderate to strong IgG, IgA, IgM, C1q and C3 mesangial staining. EM showed numerous immune complex deposits, mostly mesangial, with rare subepithelial, subendothelial and intramembranous deposits. There was a single lesion suspected of tubuloreticular inclusion in one endothelial cell. This biopsy was thus classified as a mesangial proliferative LN Class II according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification, with an activity index of 0/24 and a chronicity index of 3/12 [3].

The recipient was a 26-year-old man who developed end-stage renal disease secondary to vesico-ureteral reflux disease. The patient received induction therapy with daclizumab followed by maintenance immunotherapy with prednisone, MMF and tacrolimus. Within the first 36 months post-transplant, the patient underwent three graft biopsies (Table 1). A first biopsy at 1 month post-transplant, because of a rising serum creatinine, showed LM findings similar to pre-implant biopsy and a slight attenuation of all IF stainings. A protocol biopsy performed at 8 showed stable mesangial expansion, but persistent IgM, C3 and C1q staining. A third biopsy at 33 months displayed normal mesangium and completely negative IF. Nine years post transplant, the patient still maintains stable renal function.

There are only three other cases describing histological evolution of transplanted LN kidneys, all of which reported shorter histological follow-ups [4–6]. Our observations...