

## CASE REPORT

## Failure of anti-TNF therapy to reactivate previously septic prosthetic joints

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## SUMMARY

A patient with long-standing rheumatoid arthritis was admitted with *Streptococcus pneumoniae* septicaemia and bilateral septic knee joints. He was treated conservatively with intravenous antibiotics and arthroscopic washouts and discharged home on oral antibiotics. Six months posthospital discharge, following re-exacerbation of arthritis, an informed consent was given by the patient to continue antitumour necrosis factor therapy. After 5 years of observation, there has been no recurrence of sepsis and the rheumatoid arthritis remains in remission.

## BACKGROUND

Subject to the inherent limitations of database searching, we believe that this is the first reported case of restarting an antitumour necrosis factor (TNF) agent in a patient with septic prosthetic joints, not surgically removed. The case highlights the specificity of the immune system in dealing with particular organisms, such that one encompassing consensus statement<sup>1 2</sup> about the use of anti-TNF agents in infections may not apply to all cases. Factors such as virulence of the organism, and the extent of cellular versus humoral immune system involvement, may bear important therapeutic considerations.

## CASE PRESENTATION

The patient a builder by trade was first diagnosed with sero-positive erosive rheumatoid arthritis (RA) in 1993, and maintained on a variety of non-steroidal anti-inflammatory drugs and intramuscular sodium aurothiomalate (myocrisin), having tried methotrexate, salazopyrine, hydroxychloroquine and leflunomide. He first presented to our unit in 2002 with a severe exacerbation of RA secondary to the cessation of myocrisin 2 years previously due to a world shortage at the time. The patient's past health included meningitis at the age of 6, a (L) pneumothorax, splenectomy following a work-related injury 5 years previously and varicose vein ligation. The patient had received pneumococcal vaccination following the splenectomy. At the time of presentation, the patient had an infusion of methylprednisolone and medications changed to include methotrexate, cyclosporine and oral prednisone. Reinstitution of myocrisin failed to give the same degree of relief as before. Despite several different drug combinations, he still had active on-going synovitis involving knees, ankles, wrists, shoulders and hands associated with at least 3 h morning stiffness. The erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) remained

persistently high (58 mm/h (N: <20), 78 mg/dL (N: <5), respectively) and the patient was started on an anti-TNF MAb (etanercept) in September 2003. The response was dramatic and the patient was maintained on oral methotrexate 20 mg/week, folic acid 0.5 mg twice daily, prednisone 5 mg/day and etanercept 25 mg subcutaneous injection twice a week. In 2004, he had bilateral total knee replacements for end-stage osteoarthritis without any post-operative complications.

In September 2007, the patient developed *Streptococcus pneumoniae* septicaemia with associated bilateral knee septic arthritis in the prosthetic knee joints proven by blood and direct synovial fluid culture. The patient was treated conservatively with intravenous antibiotics, and bilateral arthroscopic knee washouts and prostheses left in situ. All antirheumatic medications were ceased. Five months later, arthritis flared causing severe pain and immobility that did not respond to his usual disease-modifying oral medications. The patient suggested restarting etanercept. Having been advised of all possible complications including the recurrence of septicaemia, septic arthritis, reinfection of joint prostheses requiring removal, above knee amputations and possibly death, the patient chose to restart etanercept regardless of the consequences. The patient's medications included prednisone 5 mg/day, methotrexate 15 mg/week, folic acid 0.5 mg twice daily and etanercept 50 mg/week subcutaneous injection. CRP and ESR were closely monitored for a recurrence of infection. In December 2008, his RA again flared and the etanercept changed to a different anti-TNF agent, adalimumab. At this stage, the patient was not able to tolerate methotrexate because of nausea and this was ceased. Bone scans showed no increase in uptake in the knee joints. The patient's treatment response again was dramatic with no flares. At present, his ESR and CRP have remained within normal range and there is no active synovitis clinically. The patient's present medications include adalimumab 40 mg every fortnight subcutaneous injection, myocrisin injections 50 mg every month, caltrate plus vitamin D, intravenous injection bisphosphonate (zoledronic acid) and rabeprazole. In the intervening period of observation, he had a left hip replacement, ankle fusion, cataract surgery and removal of a basal cell carcinoma from his back without any incident or complication.

## OUTCOME AND FOLLOW-UP

This patient had a number of risk factors predisposing to the increased chance of infection. These

**To cite:** Manolios N, Burneikis A, Spencer D, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-009827

include RA, previous splenectomy and the presence of joint prostheses. The use of antiarthritic immunosuppressive medications and in particular anti-TNF therapy further predispose and significantly increase the rate of sepsis. Despite having been immunised with pneumococcal vaccine, it was not a surprise that he developed pneumococcal septicaemia. The boxed warning on the anti-TNFs product information sheet states that these products may predispose to serious infections leading to hospitalisation or death, including tuberculosis, bacterial sepsis, invasive fungal infections (such as histoplasmosis) and infections due to other opportunistic pathogens.<sup>3</sup> These agents should be discontinued if a patient develops a serious infection or sepsis during treatment and should not be restarted in the case of a septic prosthetic joint which is treated and left in situ: the rationale being that infected prostheses retain a biofilm or harness bacteria in immunologically protected sites able to reactivate and grow given the right conditions.<sup>4</sup> However, this case highlights the fact that this apprehension may need revisiting depending on the virulence factor of the organism, extent of drug resistance and the type of immune reaction required to eliminate the organism when considering whether to restart the drug.

## DISCUSSION

*S pneumoniae*, or *pneumococcus*, is a significant human pathogenic bacterium which is Gram-positive,  $\alpha$ -haemolytic, encapsulated with polysaccharide capsule, aero tolerant, anaerobic member of the genus *Streptococcus*.<sup>5</sup> It is recognised as a major cause of pneumonia, but may cause many other types of infection such as acute sinusitis, otitis media, meningitis, bacteraemia, sepsis, osteomyelitis, septic arthritis, endocarditis, peritonitis, pericarditis, cellulitis and brain abscess.<sup>6</sup> The major mode of elimination is through the humoral arm of the immune system which relies on antibody production with its subsequent pathogen and toxin neutralisation, classical complement activation and opsonin promotion of phagocytosis and pathogen elimination.<sup>7</sup> In the case of *S pneumoniae* and other similar organisms that possess a thick proteoglycan polysaccharide capsule, the role of anti-TNF may not be as important in normal elimination and eradication. As a corollary, anti-TNF therapy may have profound effects on organisms that require the cellular immune arm for elimination and includes organisms such as *Mycobacterium tuberculosis*, *Pneumocystis carinii*, *Listeria monocytogenes* and *Salmonella typhimurium*.

Currently, there are two classes of biological agents that target TNF: anti-TNF adalimumab and infliximab (MAbs) and soluble TNF receptor MAb (etanercept). The two groups have differences between them in binding and effector functions such as antibody-dependent cellular cytotoxicity and complement-mediated cytotoxicity killing of cells expressing membrane-bound TNF in vitro that may account for the clinical differences in efficacy and safety.<sup>8-9</sup> It is interesting to note that it did not

matter which class of anti-TNF was used in this patient (adalimumab or etanercept), there was no recurrence of infection. This case highlights the fact that TNF may not be so important in the immunological elimination of pneumococcal infections, or more broadly, the eradication of organisms involving the humoral system.

## Learning points

- This is the first case report to the best of our knowledge that reports the re-institution of anti-tumour necrosis factor (TNF) therapy in treated septic prosthetic joints with complete resolution of rheumatoid arthritis (RA) symptoms in the patient and with no recurrence of infection.
- The successful treatment of prosthetic joint infections is dependent on eliminating the biofilm-dwelling microorganisms while maintaining the patient's mobility and quality of life. The extent of the biofilm may vary from organism to organism.
- This case challenges our current thinking for the use of anti-TNF therapy in the management of rheumatoid arthritis patients with serious infections.

**Contributors** NM was the primary care physician. He wrote and submitted the article. GH and DS edited the article and provided intellectual input. AB was the surgeon who performed the arthroscopy and managed the patient in the acute stage of disease. He reviewed the article.

**Competing interests** None.

**Patient consent** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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