Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Complication of etanercept treatment for rheumatoid arthritis – purulent pericarditis caused by a commensal organism

Gemma K Taylor,¹ Louise Elliott,² Michael D Sosin,² Shiu Shing Soo¹

¹Microbiology Department, Nottingham University Hospitals NHS Trust, Nottingham, UK;

²Cardiology Department, Nottingham University Hospitals NHS Trust, Nottingham, UK;

Correspondence to Dr Shiu Shing Soo, shing.soo@nuh.nhs.uk

Summary

The patient presented with increasing fatigue and dyspnoea. The patient had medical history of rheumatoid arthritis for which she had been taking methotrexate for the past 15 years and etanercept for the past 6 years. Initial diagnosis was cardiac failure but further investigation by echocardiogram revealed a large pericardial effusion. Empirical piperacillin-tazobactam was started due to moderately raised inflammatory markers. Four hundred millilitre of frank pus was aspirated from the pericardial sac and antimicrobial treatment was changed to meropenem. Gram positive cocci were seen in the initial Gram stain, but conventional cultures remained negative. However, 16S ribosomal RNA gene sequencing of the pus sample detected the presence of *Parvimonas micra* genome. Reaccumulation of the effusion required further drainage where again *P micra* was detected by 16S ribosomal RNA gene sequencing. Two weeks of meropenem was completed followed by treatment with benzylpenicillin and metronidazole.

BACKGROUND

It is well known that tumour necrosis factor (TNF) α ablation treatment predisposes to infections with invasive pathogens such as *Mycobacterium tuberculosis* and *Salmonella*. This case report highlights the emerging evidence that patients receiving anti-TNF α treatment are predisposed to deep seated infections with opportunistic commensal organisms without eliciting overt signs of sepsis.

CASE PRESENTATION

A 70-year-old lady presented with fatigue and dyspnoea with a working diagnosis of cardiac failure. Her medical history includes: hypothyroidism, ischaemic heart disease and rheumatoid arthritis (RhA) for 28 years, which is treated with methotrexate 25 mg once weekly for the past 15 years, and recombinant soluble TNF α receptor (etanercept) 50 mg once weekly for the past 6 years. She does not smoke or consume alcohol. Four weeks previously, she was briefly admitted with left basal pneumonia and bi-basal pleural effusions, which was treated with co-amoxiclav and clarithromycin for 6 days and discharged.

During this admission, she was tachycardic, hypotensive, with an irregular pulse. On auscultation, no murmurs were heard, but there were coarse respiratory crackles throughout her lung fields. There was pedal oedema to mid-calf. Chest x-ray showed a left-sided pleural effusion with consolidation and cardiomegaly. Liver function was abnormal with an alkaline-phosphatase of 219 and inflammatory markers were raised with a C reactive protein of 92 and a white cell count of 11.6. Empirical intravenous piperacillin-tazobactam was started. Crucially, she remained afebrile and otherwise showed no overt signs of sepsis throughout her admission.

INVESTIGATIONS

Echocardiogram showed a large pericardial effusion – 3.3 cm around the right heart and 1.7 cm around the left heart with some haemodynamic compromise (figure 1). A pericardial drain was inserted and 400 ml of frank pus was aspirated.

Gram stain of the pericardial fluid showed Gram-positive cocci. There was no growth on conventional culture after prolonged incubation. The sample was submitted for bacterial 16S rRNA gene PCR and sequencing (Molecular Identification Services, Health Protection Agency, Centre for Infections, Colindale, London). *Parvimonas micra* (previously *Peptostreptococcus micros*) genome was detected.

Repeat echocardiogram 2 weeks later showed re-accumulation of fluid (3.3 cm anteriorly and 1.4 cm posteriorly). Repeat pericardiocentesis drained 200 ml of orange fluid, which showed no organisms in the Gram film, and no growth on conventional media. Further 16S RNA gene sequencing again indicated the presence of *P micra* genome.

DIFFERENTIAL DIAGNOSIS

- Sterile pericarditis secondary to rheumatoid arthritis, or etanercept.
- Mycobacterial pericarditis.

TREATMENT

Empirical piperacillin-tazobactam 4.5 g three times a day was started on admission due to moderately raised inflammatory markers and her immunosuppressed status. This was changed to meropenem 1 g three times a day when frank pus was aspirated from her pericardium. Following identification of the organism, after 2 weeks

Figure 1 Transthoracic echocardiogram. (A) Parasternal long axis view (Pericardial effusion indicated by “*”). (B) Parasternal short axis view at the level of the papillary muscle.

treatment, meropenem was changed to benzylpenicillin 1.8 g four times a day and metronidazole 500 mg three times a day for further 2 weeks. Etanercept was stopped once the diagnosis of purulent pericarditis was apparent, but methotrexate was continued.

OUTCOME AND FOLLOW-UP

CT scan with intravenous contrast 4 weeks following initial pericardiocentesis demonstrated no obvious communication between the upper gastro-intestinal tract and pericardium. On discharge, her white cell count had normalised, and C reactive protein had fallen to 13. She is being followed up at cardiology out-patient clinic.

DISCUSSION

Peptostreptococcus pericarditis has previously been described in a single case report on a patient receiving anti-TNF α monoclonal antibody (infliximab) treatment.¹ Here we report a second case of infective pericarditis with *Parvimonas/Peptostreptococcus* in a patient receiving a different form of anti-TNF α medication.

Anti-TNF α medications are being increasingly used for the articular manifestations of RhA. Anti-TNF α therapy

leads to profound suppressive effects on the innate immune response. A study by Strangfeld *et al* showed that a number of risk factors are associated with developing serious infections in patients receiving anti-TNF α treatment. These include age (>65 years), co-morbidity, and especially long-term corticosteroid co-therapy. Other than her advanced age, our patient did not have any other significant risk factors, nor received long-term steroid therapy.²

While infections caused by invasive pathogens such as *Mycobacterium tuberculosis* and *Salmonella enterica*^{3 4} are well described, we present further evidence of deep-seated infection caused by mucosal commensal flora such as *Parvimonas* as an emerging problem in these patients. Furthermore, its association with TNF α ablation therapy is independent of the TNF α neutralising agent.

Although rare, RhA can cause an aseptic, effusive, constrictive pericarditis.⁵ Sterile pericarditis has also been described as a complication in patients receiving infliximab.⁶ However, this case highlights that clinicians and microbiologists should be vigilant of occult infections caused by fastidious commensal organisms in this patient group, in the absence of sepsis. We also advocate the use of bacterial 16S rRNA gene sequencing in culture negative samples when such infections are suspected.

Learning points

- ▶ Anti TNF treatment predisposes to deep seated infections with opportunistic commensal organisms.
- ▶ Patients receiving anti-TNF treatment may not show signs of sepsis despite deep seated purulent infections.
- ▶ There should be increased awareness of microbiologists for infections caused by fastidious commensal organisms in this patient group.
- ▶ The importance of 16S rRNA gene sequencing is highlighted in culture negative samples.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Taylor GK, Elliott L, Sosin MD, Soo SS. Complication of etanercept treatment for rheumatoid arthritis – purulent pericarditis caused by a commensal organism. *BMJ Case Reports* 2012;10.1136/bcr.01.2012.5644, Published XXX

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