LESSON OF THE MONTH

Chest pain in patients with rheumatoid arthritis

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Case reports

PATIENT 1

A woman aged 50 years who had rheumatoid arthritis (RA) presented with central chest pain with an audible pericardial rub. She had suffered classical seropositive RA for 10 years with an unremitting course; sulphasalazine, hydroxychloroquine, penicillamine, and mycristin either lacked efficacy or were not tolerated. During this time, she had had both knees, one hip, and her metacarpophalangeal joints replaced. At presentation she was taking a combination of azathioprine 50 mg daily and methotrexate 2.5 mg weekly. There was no evidence of concomitant infection (including prosthetic joints). She was afebrile with a normal total and differential leucocyte count. Pericarditis was confirmed by a small effusion observed on the echocardiogram; an electrocardiogram (ECG) was normal. The chest pain and rub persisted despite treatment with prednisolone 20 mg daily, so a single pulse of intravenous (IV) cyclophosphamide 500 mg was given and methotrexate was discontinued.

A few days later, the patient was admitted as an emergency with worsening chest pain, dyspnoea, and nausea. Upon examination, her temperature was 37.5°C, heart rate was 120 beat/min and regular, blood pressure was 130/60 mm Hg, jugular venous pressure was increased 8 cm, and heart sounds were normal, though bilateral basal chest crepitations were heard. Laboratory investigations revealed: haemoglobin 83 g/l, leucocyte count $9.6 \times 10^9/l$, platelets $651 \times 10^9/l$, C reactive protein 326 mg/l (normal value <10), plasma viscosity 2.31 mPa (normal range 1.55-1.75 mPa), rheumatoid factor titre 2560. QRS complexes were smaller than on a previous ECG, and a chest radiograph was normal. Echocardiography showed a pericardial effusion with normal wall motion and no right ventricular wall collapse.

A pericardial drain was inserted, from which pus was drained. *Staphylococcus aureus* sensitive to flucloxacillin and ampicillin was isolated from the fluid. Both antibiotics were given IV (500 mg four times a day) with IV hydrocortisone; azathioprine was discontinued. The pericardial drainage lessened, the culture becoming sterile over the ensuing four weeks. Repeat echocardiography showed a very small residual pericardial effusion with normal valve function and no evidence of pericardial constriction. Recovery was complicated by a pulmonary embolus requiring anticoagulation, but after seven weeks she was discharged home. To date she remains well but confined to a wheelchair. There is no evidence of

chronic pericardial disease, although hip and one knee prostheses have become infected, presumably secondary to the episode of pyopericardium.

PATIENT 2

A 64 year old man was admitted to hospital as an emergency with chest pain and vomiting. He had suffered with RA for 15 years and was being treated for mononeuritis multiplex and small vessel vasculitis with oral prednisolone 7.5 mg daily and cyclophosphamide for the preceding eight weeks (initially two pulses, then weekly 500 mg oral pulses: cumulative dose, 3250 mg). Three weeks before he was admitted to hospital, an infected olecranon nodule (*Staphylococcus aureus*) was treated with oral flucloxacillin. Weekly full blood count monitoring showed no evidence of marrow suppression.

Upon his admission to hospital his temperature was 35°C, and he was centrally cyanosed with a tachycardia (120 beat/min). Jugular venous pressure was increased by 3 cm, blood pressure was 110/60 mm Hg and heart sounds were normal. Bibasal crepitations were heard on chest auscultation and tender hepatomegaly was noted. Vasculitic lesions were present on his fingers and feet. Laboratory investigations revealed: erythrocyte sedimentation rate 10 mm/1st h, haemoglobin 122 g/l, leucocyte count $25.6 \times 10^9/l$ (lymphocytes 18%), platelets $286 \times 10^9/l$. Chest radiography showed minor pulmonary oedema and an ECG sinus tachycardia. Treatment for pulmonary oedema was instituted with high flow oxygen and IV diuretics. His condition deteriorated, cardiogenic shock supervened, and death occurred within a few hours of his admission to hospital.

At postmortem examination, the principal finding was of a pyogenic pericardial effusion, from which *Staphylococcus aureus* was cultured. There was also moderate left ventricular hypertrophy and mild pulmonary oedema.

Discussion

Pericardial disease is a well recognised extra-articular manifestation of RA occurring in up to 50% of patients in both postmortem¹ and antemortem echocardiography studies.² As pericarditis in RA is often asymptomatic, severe or prolonged pericardial pain, as experienced by our patients, should perhaps suggest an infective aetiology requiring appropriate investigation. Corticosteroid treatment is the cornerstone of treatment in non-infective pericarditis,

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with immunosuppressive medication such as azathioprine or cyclophosphamide suggested as adjuvant treatment.³ RA complicated by pyopericardium is rare, only a few cases having been reported,⁴⁻⁷ and *Staphylococcus aureus* being the infective organism in all but one. Opportunistic infection and metastatic spread are always of concern when immunosuppressive treatment is being used. In patient 1, it is likely that the patient had an 'aseptic' pericarditis that became infected from a source not clinically apparent. In patient 2, the infected olecranon bursitis was the obvious source of *Staphylococcus aureus* and, with hindsight, it would have been prudent to postpone further immunosuppressive treatment until this was fully treated.

Cyclophosphamide and, to a lesser extent, azathioprine both affect cellular and humoral immune responses, causing T and B lymphocytopenia and suppressing immunoglobulin production,⁸ thus predisposing to infection. It has been observed that, when such agents are used, the risk of opportunistic infection is small if the leucocyte count is maintained greater than $3.0\text{--}3.5 \times 10^9/\text{l}$,^{9, 10} albeit in treating Wegener's granulomatosis. It is interesting, however, that in one of our patients the leucocyte count was normal, and neither had leucopenia or fever.

Concomitant use of corticosteroid may further increase susceptibility to infection and mask fever. Therefore, even in the absence of the classical signs, a high index of suspicion should be maintained in RA patients being treated with corticosteroids and immunosuppressive drugs who develop a pericardial effusion, and infection should be excluded by pericardiocentesis. One might also advocate performing this procedure to exclude infection before the commencement of immunosuppressive therapy in those patients with persistent or severe pericardial pain with associated effusion.

In retrospect, it is worth speculating whether the direct cause of death in patient 2 was overwhelming septicaemia or pericardial

tamponade. A sinus tachycardia of low volume with pulsus paradoxus, increased jugular venous pressure with a prominent 'x' descent, hypotension, low voltage QRS complexes and electrical alternans on ECG, and a symmetrical globular enlargement of the heart on chest radiograph are features that would suggest the latter diagnosis, which can be confirmed by echocardiography and treated with emergency pericardiocentesis.

The lesson

- Infection should be considered if pericardial pain in a patient with RA is severe or prolonged and associated with an effusion.
- Signs of infective pericarditis can be subtle when immunosuppressive treatment is being used.
- Pericardiocentesis should be undertaken to exclude infection if a patient with RA who is receiving immunosuppressive treatment develops an effusion.

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