Reminder of important clinical lesson

Late presentation of *Pneumocystis jiroveci* pneumonia after cardiac transplantation

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Summary

We report the case of a 64-year-old man who had received a heart transplant 9 years previously and was on long-term immunosuppression. He was referred to the intensive care unit of our district general hospital with acute respiratory distress and was diagnosed with community-acquired pneumonia. He was treated with antimicrobials, whose spectrum was extended empirically to cover *Pneumocystis jiroveci*, and respiratory support was provided with continuous positive airway pressure (CPAP). PCR analysis subsequently confirmed a diagnosis of pneumocystis pneumonia (PCP). Despite appropriate therapy the patient unfortunately died 8 days after admission to the unit. To the author's knowledge, this is the first report in the literature of such a late presentation of PCP after cardiac transplantation. We discuss current diagnostic and treatment strategies for PCP.

BACKGROUND

As the number of patients undergoing cardiac transplantation expands and long-term outcomes improve, non-specialist hospitals and general critical care units are likely to become increasingly exposed to patients with cardiac allografts. This case report indicates that physicians should maintain a high index of suspicion for the possibility of *Pneumocystis jiroveci* pneumonia, even if presenting many years after transplantation.

CASE PRESENTATION

A 64-year-old man was referred to the intensive care unit of our district general hospital with respiratory failure, after a 13-day history of increasing dyspnoea and cough productive of mucopurulent sputum.

His past medical history included orthotopic heart transplantation 9 years previously for ischaemic cardiomyopathy. Other medical history included chronic renal dysfunction, bilateral venous insufficiency, avascular necrosis of both hips with right total hip replacement and recent percutaneous coronary intervention with stenting of the donor heart diagonal artery. Of interest in his drug history was mycophenolate mofetil 500 mg thrice daily and prednisolone 10 mg once daily. He was independent regarding all activities of daily living and free from symptoms of angina.

On examination of his respiratory system he was notably dyspnoeic. His respiratory rate was 30 breaths per minute and his oxygen saturations were 89% on high flow oxygen. Reduced air entry to his left lower thorax was noted, with corresponding dullness to percussion.

On examination of his cardiovascular system, a sinus tachycardia was evident at a rate of 119 bpm. His blood pressure was 126/83 and bilateral pitting oedema was noted up to the mid-thighs. His core temperature was recorded as 38.1°C.

INVESTIGATIONS

Plain chest radiography revealed bilateral lung field opacification with loss of the normal cardiac outline bilaterally. This represented progression from a chest radiograph 6 days previously, which had demonstrated left lower lobar consolidation. Blood biochemistry was within normal limits, as were full blood count and coagulation screens. No leucocytosis was evident. C-reactive protein was elevated. Transthoracic echocardiography revealed good systolic function and normal function of the mitral, aortic, tricuspid and pulmonary valves. Six peripheral blood culture samples were reported as sterile. Sputum microscopy and culture revealed no organisms. Broncho-alveolar lavage (BAL) and bronchial biopsy, for exclusion of pneumocystis pneumonia (PCP), were not possible because of the patient's clinical state. Sputum and serum samples were sent to an external laboratory for PCR analysis for *P jiroveci*.

DIFFERENTIAL DIAGNOSIS

On admission the most likely diagnosis was considered to be community-acquired pneumonia. Alternative organisms considered in the initial treatment strategy included viruses, *P jiroveci* and other fungi. Interstitial lung disease and primary and secondary neoplastic disease were also considered.

TREATMENT

Respiratory support was supplied with continuous positive airway pressure (CPAP) via a tight-fitting hood, which gave both immediate symptomatic relief and improvement in clinical parameters. A radial arterial line was sited for continuous haemodynamic and intermittent arterial blood gas monitoring. Initial antimicrobial treatment consisted of meropenem, fluconazole and oseltamivir, the patient having previously been treated with piperacillin and tazobactam with no response. Co-trimoxazole, with concomitant high dose corticosteroid, was commenced 1 day after

admission to extend empirical antimicrobial cover to *P jiroveci*. Immunosuppression with mycophenolate mofetil was continued on the advice of the patient's parent cardiac transplant institution, which felt that PCP was unlikely.

OUTCOME AND FOLLOW-UP

The patient remained stable but dependent on CPAP for the first 5 days after admission to the critical care unit. On day 6 a diagnosis of *P jiroveci* was confirmed by serum and tracheal aspirate PCR analysis. Over the following 2 days, despite ongoing therapy, the patient became progressively dyspnoeic and his oxygenation deteriorated. At this time he made repeated requests that treatment be withdrawn, and clearly understood the implications of this decision. CPAP was therefore withdrawn and palliative care was commenced. He died later on the eighth postadmission day.

DISCUSSION

Outcome after cardiac transplantation has improved considerably in recent decades, with 50% of patients surviving over 9 years.¹ A consequence of this is an increase in the number of individuals in the community requiring long-term antirejection therapy, and an increased vulnerability to secondary infection.² Post-transplant maintenance immunosuppression commonly comprises triple therapy, with an antiproliferative agent, such as mycophenolate mofetil or azathioprine, a calcineurin inhibitor such as ciclosporin or tacrolimus and a steroid such as prednisolone. It is often possible to taper or discontinue steroid therapy in patients on long-term immunosuppression with no features of acute rejection.²

Infectious complications after heart transplantation are common, with 0.6 episodes per patient occurring over a mean time of 4.5 years in a recently analysed cohort.³ Gram-positive bacteria, Cytomegalovirus, fungi, *P jiroveci* and *Nocardia* have all been implicated.³ In one cohort study, the incidence of PCP up to 1 year after transplantation was 3.6%,⁴ although more recent studies have suggested that this incidence has fallen.³ Consequently, prophylaxis for PCP with trimethoprim-sulfamethoxazole in the immediate post-transplantation period has long been advocated.⁵

Late presentation of PCP after solid organ transplantation, however, appears to be substantially less common. After follow-up of 32 757 renal transplant recipients in the United States, the latest case of PCP observed was in the second year after transplantation.⁶ In heart transplant patients, the longest interval between transplantation and the development of PCP in one cohort study was 781 days.⁵

PCP is an opportunistic infection of the lung parenchyma caused by the fungus *Pneumocystis jiroveci*. In patients without HIV it commonly presents with acute-onset respiratory failure and bilateral perihilar infiltrates on the plain chest radiograph.⁷ Confirmation of the diagnosis requires identification of the organism in a relevant sample, typically by induced sputum or BAL. Identification may be achieved by conventional or immunofluorescence antibody staining, or by PCR assay. Sensitivity and specificity for real-time PCR has been reported as 94–100% and 86–100%, respectively.⁸ Mortality from PCP in HIV-negative patients is between 30% and 60%.⁸ Among HIV-negative patients admitted to an intensive therapy unit, outcome is even poorer, with one study quoting a 1-year mortality of 80%.⁹

Treatment regimens for PCP typically comprise a combination of antimicrobials and corticosteroids. The first choice antimicrobial regime is trimethoprim-sulfamethoxazole (co-trimoxazole) in doses of 15–20 mg/kg and 75–100 mg/kg, respectively.⁸ Alternative therapies include pentamidine, primiquine plus clindamycin or atovaquone.⁸ Corticosteroids have been shown to reduce mortality in HIV-infected patients with an alveolar-arterial oxygen gradient greater than 35 mm Hg.⁷ There is less evidence for HIV-negative patients, but one study suggested adjunctive corticosteroids reduce the duration of mechanical ventilation and ICU stay.¹⁰

This is, to our knowledge, the first report in the literature of a case of PCP occurring over 8 years after cardiac transplantation. Indeed, the patient in question was at relatively low risk for PCP given the absence of a calcineurin inhibitor in his immunosuppressive regimen. We recommend, therefore, that physicians maintain a high degree of vigilance for the presence of PCP in patients who have undergone heart transplants, even if many years previously.

Learning points

- ▶ Long-term survival after cardiac transplantation is improving.
- ▶ Patients with cardiac transplants are likely to make up an increasing proportion of patients treated in non-specialist centres.
- ▶ Physicians should maintain a high index of suspicion for *Pneumocystis jiroveci* pneumonia in patients presenting with respiratory symptoms after cardiac transplantation.

Competing interests None.

Patient consent Obtained.

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