Tuberculous pericarditis leading to cardiac tamponade: importance of screening prior to immunosuppression

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Abstract
Mycobacterium tuberculosis (TB) presenting with pericardial disease complicated by cardiac tamponade is rare in the developed world, although it occurs more frequently in the context of immunosuppression. In this report, a 74-year-old man on methotrexate for rheumatoid arthritis presented with fever, productive cough and cough-induced syncope. During his admission, he developed clinical signs of cardiac tamponade confirmed on an echocardiogram, which showed a massive pericardial effusion. He was treated with an urgent pericardiocentesis and a pericardial window. Subsequently, TB polymerase chain reaction of pericardial fluid unexpectedly returned positive, and he was commenced on standard quadruple therapy for TB, as well as high-dose prednisolone. Notably, the patient did not have a history suggestive of previous TB exposure, and no screening investigations had been performed prior to initiation of methotrexate. This case highlights the importance of TB screening prior to immunosuppressive therapy, even in populations considered low risk for latent disease.

Introduction
Mycobacterium tuberculosis (TB) can present with unusual extrapulmonary manifestations, particularly in the context of immunosuppression. In developed countries, TB-related pericardial disease is uncommon (<1% of extrapulmonary TB), and cases complicated by life-threatening cardiac tamponade are extremely rare [1]. We report a case of tuberculous pericarditis leading to cardiac tamponade in an elderly patient on methotrexate for rheumatoid arthritis.

Case Report
A 74-year-old man presented to a local hospital with an episode of cough-induced syncope on the background of several weeks of progressive shortness of breath and productive cough. His past history was significant for inactive rheumatoid arthritis controlled on a stable dose of methotrexate, gout on allopurinol, and previous asbestos exposure. He was an ex-smoker with a 20-pack-year history. Significantly, he had never been treated with anti-tumor necrosis factor (TNF) agents.

Upon admission he was febrile (38.2°C) and suffered further syncopal episodes triggered by coughing. Blood examination revealed a normal white blood cell count, although inflammatory markers were elevated (Table 1). A chest X-ray and computed tomography of the chest incidentally revealed a large pericardial effusion and nodular opacities in the apex of the right lung. He remained hemodynamically stable and was transferred to our institution for further management.

Following transfer, he subsequently developed sinus tachycardia (120 beats per minute) and hypotension (80/60 mm of Hg) with signs of cardiac tamponade, including soft heart sounds and raised jugular venous pressure (6 cm). This clinical diagnosis was confirmed on echocardiogram, which showed a massive pericardial effusion (2.5 cm in thickness) and diastolic collapse of the right ventricle (Fig. 1).
An emergency pericardiocentesis and thoracoscopic pericardial window was performed, draining 1.1 L of blood-stained fluid. Postoperative recovery was complicated by a single episode of non-sustained ventricular tachycardia, but was otherwise unremarkable. His fever resolved and symptoms of breathlessness and cough greatly improved, with no further syncopal episodes.

Histopathology of the pericardial window revealed chronic active pericarditis with a few poorly formed granulomas and giant cells, and no malignancy or acid-fast bacilli. The underlying cause was thought to be most consistent with rheumatoid pericarditis. With TB cultures and polymerase chain reaction (PCR) pending but thought to be likely negative, the patient was discharged.

Several days later, the patient was urgently readmitted when PCR testing and later culture on pericardial tissue and fluid returned positive for TB. Further questioning revealed that his productive cough had not fully resolved, and that he had experienced night sweats and weight loss for several months prior to presentation. Interestingly, he had never traveled outside Australia and did not have any contact with any known TB cases. Subsequent microscopy and culture of early morning sputum samples revealed active pulmonary TB.

Standard quadruple TB therapy was commenced (rifampicin, isoniazid, pyrazinamide, ethambutol) in addition to high-dose prednisolone for 2 months (80 mg daily, subsequently weaned by 10 mg per week). This was later changed to isoniazid, rifampicin and ethambutol, which were to be continued for a further 4 months, as sensitivity testing revealed a low degree of isoniazid resistance (sensitive to 0.4 μg/mL, but not 0.1 μg/mL). The patient was kept in respiratory isolation until three early morning sputum samples were negative for smears of acid-fast bacilli.

At 2 months of follow-up, the patient reported full resolution of symptoms and no side effects of treatment. He was discharged to the care of a local infectious disease physician as well as his general practitioner.

**Discussion**

The clinical manifestations of tuberculous pericarditis are wide-ranging and varied. While chest pain, cough, and dyspnea are common, non-specific constitutional symptoms, including fevers, night sweats, weight loss, and fatigue, may also arise [2]. Patients may present subacutely with the development of constrictive pericarditis, or as described in this case acutely with pericardial fluid accumulation leading to cardiac tamponade [1]. In this case, the unusual symptom of cough-induced syncope was likely secondary to transient raised intra-thoracic pressure and impairment of cardiac output due to impending tamponade [3].

Pericardial TB has been reported with immunosuppressive therapy, such as that following renal transplant [4]. Reactivation of TB with immunosuppressive treatment, in particular anti-TNF agents, is well recognized, particularly in elderly patients with rheumatoid arthritis [5, 6]. In this case, pericardial TB was likely a reactivation of disease in the context of age and methotrexate treatment for rheumatoid arthritis. Immunosuppression secondary to HIV co-infection is also an important risk factor for pericardial TB [7], although our patient was HIV negative.

Prior to initiating disease-modifying anti-rheumatoid drugs, it is recommended that screening including a history of TB exposure or infection, chest X-ray, and Quantiferon testing be performed. This allows at-risk patients to be identified and treated with chemoprophylaxis. While our patient had no risk factors for prior exposure, the impor-
tance of screening is highlighted in this instance. Our patient had not undergone Mantoux or Quantiferon testing prior to initiation of methotrexate.

A diagnosis of tuberculous pericarditis requires analysis of pericardial fluid or tissue. Adenosine deaminase and interferon gamma activity are useful adjuncts to PCR testing, histopathology, and culture [8]. Nevertheless, as in this case, a definitive diagnosis with culture is the gold standard in guiding treatment as it allows for drug sensitivity testing. This is of particular importance given the growing incidence of multi-drug-resistant TB worldwide.

Assuming full sensitivity, recommended pericardial TB treatment is similar to that of pulmonary TB, with rifampicin, isoniazid, ethambutol, and pyrazinamide for 2 months, followed by rifampicin and isoniazid for a further 4 months [2]. Patients with reaccumulation of pericardial fluid or signs of tamponade should be treated with a definitive pericardial window [1]. The role of corticosteroids in TB pericarditis remains inconclusive, but is thought to benefit patients at highest risk of developing inflammatory complications leading to constrictive pericarditis. Interestingly, a recent large multicenter factorial design trial demonstrated that prednisolone reduced the incidence of pericardial constriction and hospitalization, but not mortality [9].

In conclusion, we report a case of tuberculous pericarditis complicated by cardiac tamponade in an elderly patient on methotrexate for rheumatoid arthritis. We recommend that TB screening be considered in all patients prior to immunosuppressive therapy, even in populations considered low risk for latent disease.

**Disclosure Statements**

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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