Empirical treatment for suspected Tuberculous pericarditis – When is it justifiable?

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Introduction
Pericardial effusion (PE) is an abnormal accumulation of fluid within the pericardial space. A Pericardial effusion could be primary or secondary to cardiac or systemic disease and includes infectious, neoplastic, autoimmune, metabolic and drug related etiologies. The severity could range from mild asymptomatic effusion to cardiac tamponade which compromise the cardiac output.

TB is a leading cause of PE in African and Asian countries (1). Approximately 1 to 2 percent of patients with pulmonary TB develop tuberculous pericarditis. TB affects the pericardium by causing PE or chronic constrictive pericarditis, as a result of either direct spread of pulmonary TB from an adjacent pulmonary segment or from hematological spread.

Although pulmonary TB is the most common form of tuberculosis (TB) worldwide, extra pulmonary TB, where virtually any organ can be affected (2), causes significant morbidity and mortality (3). Immunodeficiency plays major role in extra pulmonary TB in developed countries (4) as well as developing countries (5) where TB is endemic. A recent review by S.K. Sharma & A. Mohan (2) showed extrapulmonary TB was more common among HIV infected individuals than non-HIV infected patients (70% vs 20%).

We report a case of pericardial effusion in an immunocompetent adult male who responded well to empirical anti-TB treatment.

Case Report
44-year-old apparently healthy male presented with 3-day history of fever with chills, arthralgia, myalgia and precordial pain. There was no history of headache, cough, abdominal pain, diarrhea or urinary symptoms. He also had loss of appetite for 2 weeks. There were no history of significant loss of weight or night sweats.
On examination he was febrile, anicteric. Pulse rate was 92 beats per minute and blood pressure was 110/80 mmHg. There was no clinically significant lymphadenopathy. Jugular venous pressure was not elevated. On precordial examination the cardiac apical impulse was in normal position the heart sounds were heard in normal intensity. A pericardial friction rub was heard over the apex. There were no audible murmurs. The respiratory, abdominal and neurological examinations were unremarkable.

Initial full blood count was normal, with white blood cells (WBC) of 6.6, hemoglobin (HBG) of 11.1 g/dL and platelets (PLT) 370. Urine full report, liver profile and serum electrolytes all were within normal range. Erythrocyte sedimentary rate (ESR) and C-reactive protein (CRP) were 92 mm/1st hour (normal <25 mm) and 108 mg/L (normal <6 mg/L) respectively. Chest radiograph (Figure 1) showed cardiomegaly with sharp cardiac margins, which was strongly suggestive of pericardial effusion. Trans-thoracic echocardiogram (TTE) confirmed the presence of a moderate pericardial effusion of 12mm size, which was mostly posterior without pericardial tags.

His temperature chart showed remitting pattern of fever with 1-2 spikes per day ranging 99-102 °F. Ultra-sonography of abdomen was normal. The blood and sputum cultures were negative. Repeat TTE after two weeks of admission showed 14mm of effusion behind the left ventricular wall and 6mm of fluid over right ventricular wall with bridging pericardial tags and exudative materials over visceral pericardium (Figure 2). ESR and CRP two weeks later were 117 mm/1st hour and 107 mg/L respectively and the HBG dropped to 10.7 g/dL. Blood picture showed normochromic normocytic red cells and mild thrombocytosis with PLT of 407 x 10^3/micL. Mantoux test was 12 mm and 3 samples of sputum for acid fast bacilli were negative.

Serum ferritin level was 581 ng/ml and thyroid stimulating hormone (TSH) level was 3.23 mIU/L (0.47-4.7 mIU/L). Anti-nuclear antibody (ANA) and rheumatoid factor (RF) were negative and lactate dehydrogenase (LDH) was 232 U/L. Serum creatinine and blood urea were 69 micmol/L and 15 mg/dL respectively. HIV antibodies were negative. The patient refused to undergo a contrast enhanced computed tomography of chest.

Based on positive Mantoux test, probable exudative PE on echocardiography indicated by the presence of pericardial tags on TTE and absence of possible alternative etiology, a tentative diagnosis of TB-pericarditis was made. Anti TB treatment (ATT) was initiated along with steroids on the 3rd week of illness. Within one week of initiation of anti TB drugs, his fever, arthralgia and precordial pain subsided. The patient was closely monitored for any sign of deterioration. Repeat TTE, confirmed at one month and 6 months after treatment, assured complete resolution of the pericardial effusion.

**Discussion**

Tuberculous pericardial effusions accounts for 60-80% of patients with PE in developing countries whereas TB accounts for only 4% of PE in developed nations(1). Though pericarditis is a rare form of TB, it carries high morbidity and mortality. Desai HN has shown that 28% of patients with TB-PE had developed constrictive pericarditis within four months (3). Without specific treatment, the mean survival is 3.7 months, with mortality approaching 85% at 6 months. Nevertheless, tuberculous PE has a favorable outcome with anti-TB treatment. Considering the high morbidity and mortality of the untreated tuberculous PE, empirical therapy may be justified.

The diagnosis of TB-pericarditis is challenging, especially as pericardiocentesis or pericardial biopsy, are invasive and carries a procedural risk about 5% (6). The definitive diagnosis of TB-pericarditis can only be made when there is granulomatous inflammation on pericardial biopsy or by isolating *Mycobacterium*
**tuberculosis** bacilli from pericardial fluid or from pericardial biopsy. The diagnostic yield of pericardiocentesis is of uncomplicated PE is significantly low, as much as 7%-19% (7,8), which makes it even more unjustifiable given the risk of the procedure.

Reuter et al (7) has studied 233 consecutive patients presenting with pericardial effusions who underwent a predetermined diagnostic work-up in Africa where TB is prevalent. Of them 162 (69.5%) were tuberculous effusions. Caseating granulomatous inflammation was demonstrated only in 50% of samples of confirmed tuberculous effusions. Pericardial fluid culture for AFB yielded positive results in 56% of patients with pericardial TB. Mercé et al (8) demonstrated a low diagnostic yield of pericardial effusion in Twenty-six patients who underwent diagnostic pericardiocentesis, with only two confirming a specific diagnosis. Finally, they have concluded that routine pericardial drainage procedures have a very low diagnostic yield in patients with large pericardial effusion without tamponade or suspected purulent pericarditis, and no clear therapeutic benefit could be obtained. Gamma interferon (IFN-gamma)> 50 pg/ml in pericardial fluid has shown high sensitivity (92%) and high specificity (100%) (9). But the high cost of IFN-gamma assay restricts its utilization in resource poor settings.

Empirical ATT carries its own side effects which include fulminant liver injury. ATT induced liver toxicity in western population is about 4% (10). The figures are higher in Asian population, probably due to presence of malnutrition, co-infection with hepatotropic viruses, HIV infection, and alcoholism. In India, the mortality rate of the patients who has developed acute liver failure following ATT was 67.1% (11). A recent prospective study in Sri Lanka, which included 31 patients who has received ATT for probable spinal TB, revealed no major ATT related side effects during standard treatment duration (12).

**Figure 2:** Trans thoracic echocardiogram showing bridging pericardial tags (circle) behind the posterior wall of the left ventricle
Conclusions

In countries with high prevalence of TB, we suggest that it is justifiable to start empirical anti-tuberculous chemotherapy for patients with suspected TB-pericarditis, who are hemodynamically stable, especially in situations where invasive procedures such as pericardiocentesis or pericardial biopsy are expected to be delayed or technically challenging, while monitoring for disease progression and ATT related side-effects.

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**Figure 1**: Chest radiograph showing cardiomegaly with sharp cardiac borders

**Figure 2**: Trans thoracic echocardiogram showing bridging pericardial tags (circle) behind the posterior wall of the left ventricle