Chapter

Tuberculous Pericarditis

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Abstract

The pericardium formed by two layers, pleural and visceral, fulfills the role of keeping the heart in position and in turn acts as a barrier against infections. Their commitment may be due to a wide variety of rare diseases where the causes are usually idiopathic, inflammatory, neoplastic, traumatic, congenital, or infectious. Within the latter they are of viral, fungal, and bacterial origin, being able to be caused by *Mycobacteria*. Tuberculous pericarditis is the entity in which inflammation of the pericardium is caused by Koch's bacillus. The access route to it includes three mechanisms: (1) lymphatic; (2) hematogenous spread, mainly in immunocompetent patients; and (3) by direct contact from adjacent structures such as the lung and pleura. In immunocompetent patients, the condition is usually paucibacillary, with manifestation at the level of a single organ, while in immunocompromised patients, the rate of bacterial replication is high. Tuberculosis (TB) is a disease that is far from being eradicated today. Despite the great majority of cases in which pulmonary involvement is confirmed, a large number of patients suffer compromises from other organs. If tuberculous pericarditis is suspected, it is important to be able to establish an early diagnosis in order to achieve an adequate treatment as soon as possible.

Keywords: pericarditis, pericardium, tuberculosis, infection

1. Introduction

Tuberculosis (TB) has decreased its incidence in the industrialized countries in the last 100 years; despite this it remains within the top 10 of infectious diseases that cause death (above HIV). Millions of people contract TB every year [1]. Tuberculous pericarditis, caused by *Mycobacterium tuberculosis* (Mtb), is a rare disease, observed in about 2% of people suffering from pulmonary tuberculosis and about 1% in autopsies of people who die from tuberculosis [2].

2. Epidemiology

According to the global report of TB 2018, it is estimated that about 10 million people developed the disease during 2017. Cases were reported in all countries and age groups, but the majority (90%) occurred in adults (>15 years old). Nearly 9% of infected people were HIV carriers (72% in Africa). Two thirds of the cases were reported in eight countries: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%), and South Africa (3%). Only 6% of the cases were reported in the European region and 3% in the region of the Americas [1].

3. Pathogenesis of tuberculous pericarditis

Tubercle bacilli access the pericardium via three mechanisms: (1) retrograde lymphatic spread from mediastinal, paratracheal, and peribronchial lymph nodes [3], (2) hematogenous spread (dominant in immunocompromised hosts) [4], and (3) direct contiguous spread from adjacent structures such as the lungs, pleura, and spine (infrequent) [3]. When the guest is immunocompetent, tuberculous pericardial disease is localized to the pericardial space. Usually in a paucibacillary condition, tubercle proteins trigger an important cell-mediated hypersensitivity response with T-helper cell (subtype 1) predominant cytokine release, leading to an inflammatory exudative effusion and its hemodynamic sequelae [5, 6]. The immune response to the viable acid-fast bacilli penetrating the pericardium is responsible for the morbidity associated with tuberculous pericarditis. In patients with dysfunctional immunity as occurred in HIV/AIDS, there is evidence that mycobacterial replication is active, bacillary loads are high, and the clinical manifestations of tuberculous pericarditis are related to the impact of the infectious and virulent nature of the Mtb itself in addition to the hemodynamic sequelae [4–7].

There are four pathological stages of tuberculous pericarditis: (1) fibrinous exudation, initial polymorphonuclear leukocytosis, abundant mycobacteria, and early granuloma formation with loose organization of macrophages and T cells; (2) serosanguineous effusion with a predominantly lymphocytic exudate with monocytes and foam cells; (3) absorption of effusion with organization of granulomatous caseation and pericardial thickening caused by fibrin, collagenosis, and, ultimately, fibrosis; and (4) constrictive scarring. The fibrosis generated between the visceral pericardium and the parietal pericardium can calcify and adhere to the myocardium, generating a cuirass around the heart, preventing the correct diastolic filling, and generating the clinical syndrome of constrictive pericarditis [8].

Tuberculous pericarditis presents clinically in three forms: pericardial effusion, constrictive pericarditis, and a combination of effusion and constriction.

4. Pericardial effusion

The triad of severe pericarditic chest pain: a pericardial friction rub, widespread ST segment, and T-wave abnormalities; and PR segment depression typical of acute pericarditis is an uncommon clinical presentation of tuberculous pericarditis, accounting for only 3–8% of patients who present with tuberculous pericarditis [9]. The pericardial effusion begins as soon as the tubercle bacillus enters the pericardium and develops slowly and insidiously. Is characterized pathologically by polymorphonuclear leukocytosis with abundant bacilli and granuloma formation, and is usually present with nonspecific systemic symptoms, such as fever, night sweats, fatigue, and weight loss. Chest pain, cough, and breathlessness are uncommon symptoms [10].

TB pericarditis should be considered in the evaluation of all cases of pericarditis without a rapidly self-limited course.

4.1 Diagnosis of pericardial effusion

ECG is abnormal in most cases of tuberculous pericardial effusion, usually in the form of nonspecific ST-T-wave changes. The presence of microvoltage (complexes <5 mm in limb leads and <10 mm in precordial leads) suggests a large pericardial effusion [11]. Chest radiograph usually shows an enlarged cardiac shadow in more than 90% of cases and demonstrates features of active pulmonary TB in 30% of cases and pleural effusion in 40–60% of cases (**Figure 1**) [12]. The advent and

accessibility of echocardiography have made it possible to diagnose the pericardial effusion when suspected; however, it does not determine the etiology. The presence of fibrinous strands on the visceral pericardium is typical but not specific for a tuberculous pathogenesis (Video 1, https://bit.ly/2JNuQdB) [13]. Computed tomography of the chest shows typical changes in mediastinal lymph nodes (enlargement >10 mm with matting and hypodense centers and sparing of hilar lymph nodes) in almost 100% of cases [14].

4.2 Direct methods for the diagnosis of tuberculous pericarditis

The pericardial fluid is bloodstained in 80% of cases of tuberculous pericarditis, but malignant disease and the late effects of penetrating trauma may also cause bloody pericardial effusion, so confirmation of TB as the cause is important [15]. Tuberculous pericardial effusions are typically exudative and characterized by a high protein content and increased leukocyte count, with a predominance of lymphocytes and monocytes. Light's criteria (whereby an exudate is defined as having one or more of the following: pleural fluid protein divided by serum protein >0.5, pleural fluid lactate dehydrogenase [LDH] divided by serum LDH >0.6, and/or pleural fluid LDH level > 66% of the upper limit of normal for serum LDH) [16] is the most reliable diagnostic tool for identifying pericardial exudates.

The definitive diagnosis of tuberculous pericarditis should be established as soon as possible, by searching for the acid-alcohol bacilli resistant in sputum, lymph nodes, or pericardial fluid [17]. Culture of tubercle bacilli from pericardial fluid can be improved by inoculation of the fluid into double-strength liquid Kirchner

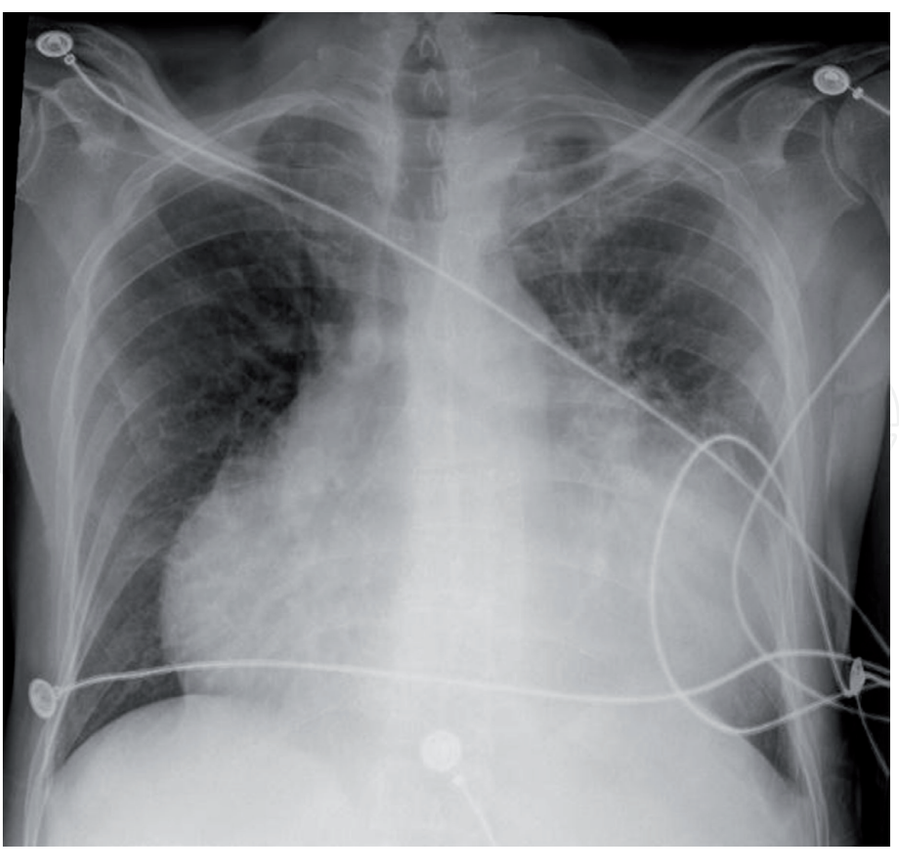

Figure 1.
Chest X-ray in front of a merchant marine patient who consulted due to progressive dyspnea for months of evolution. In the consultation, he presented signs of cardiac tamponade, so an echocardiogram (Video 1, https://bit.ly/2JNuQdB) was performed with an evacuating pericardiocentesis of 3 liters of hematopurulent fluid. Bacteriological isolation was not obtained, but there was increased ADA activity.

culture medium, resulting in a 75% yield, compared with a 53% yield with conventional culture [18]. Pericardial biopsy specimens may also be used to diagnose tuberculous pericarditis. The polymerase chain reaction (PCR) has also been suggested for detecting *M. tuberculosis* DNA in pericardial fluid [19]. The probability of obtaining a definitive bacteriological result is greatest when pericardial fluid and biopsy specimens are examined early in the effusive stage [18].

4.3 Indirect methods for the diagnosis of tuberculous pericarditis

The difficulty of carrying out the diagnosis of tuberculous pericarditis, associated with its high mortality without proper treatment, has led to the use of indirect methods. Indirect methods such as dosing activity of adenosine deaminase (ADA) in the pericardial fluid, with cut-off levels between 30 and 60 U/L of ADA activity, are suggestive of tuberculous pericarditis [20]. In areas of the high endemic level of tuberculosis, a cut-off level of ADA activity <35 presents a sensitivity of 90% and a specificity of 74% for diagnosis [21]. The utility of ADA activity in pericardial fluid was also demonstrated in HIV-positive patients, although in patients with severe CD4 lymphocyte depletion, the ADA levels observed are lower [22].

Very high levels of ADA in pericardial fluid have strong association with constrictive pericarditis [23].

The measurement of interferon gamma (IFN-γ) levels in the pericardial fluid also helps early diagnosis. Cut-off values >200 pg/L have a sensitivity of 92% and specificity of 100% for the diagnosis of TB [21].

In summary, the "definitive" diagnosis of tuberculous pericarditis is based on the presence of the tubercle bacillus in the pericardial fluid or proving it in the pericardium biopsy and "probably" when there is evidence of tuberculosis elsewhere in the body and the presence of unexplained pericarditis, with high levels of ADA or good response to pharmacological treatment.

5. Treatment

Pharmacological treatment increases survival in tuberculous pericarditis, even in HIV-positive patients [24]. A regimen that includes rifampicin, isoniazid, pyrazinamide, and ethambutol for at least 2 months, followed by rifampicin and isoniazid (up to 6 months), proved to be effective in extrapulmonary tuberculosis [25]. Treatments beyond 6 months do not show better results, increasing cost and decreasing tolerance [26].

The treatment associated with corticosteroids would not be justified at present, given that the evidence for its use is not the best [27]. Although the results are inconclusive, adding corticosteroids to treatment may have benefits on morbidity and re-experiences, but randomized controlled trials with sufficient numbers of HIV-positive and HIV-negative patients are needed [28].

It is obvious that if pericarditis is associated with severe pericardial effusion, with hemodynamic compromise, the first treatment option associated with antituberculous treatment is drainage by subxiphoid puncture or by minimal thoracotomy.

6. Constrictive pericarditis

It is the most feared complication of tuberculous pericarditis; it is described in about 30% of patients, even in spite of antituberculous treatment and the use of

corticosteroids [29]. The clinical presentation can be variable, from asymptomatic patients and stress design to heart failure with preserved function, liver failure (due to retrograde passive congestion) with ascites, and generalized edema. The presence of pericardial knock, associated with protodiastolic murmur, splitting of the second heart sound, and Kussmaul's sign (paradoxical increase in jugular venous pressure in inspiration), is frequent in constrictive pericarditis but difficult to detect by non-experienced observers [30].

6.1 Diagnosis of constrictive pericarditis

Sometimes we can see a calcium shell surrounding the heart in the chest X-ray, but it is not the most frequent [31]. Other nonspecific radiographic findings are dilation of the superior vena cava [12].

In the electrocardiogram there are no specific signs, either atrial fibrillation, nonspecific alterations of repolarization (changes in the T wave), or complexes with low voltage.

The Doppler echocardiogram may show thickening of the pericardium; the presence of fibrin; restrictive transmitral filling pattern, associated with normal size of the cavities, in the absence of ventricular hypertrophy; and valvular insufficiency.

6.2 Treatment

The treatment must include antituberculous medication for 6 months. Consider pericardiectomy in all patients once antibiotic treatment has been instituted [32]. Surgery should be performed early if the patient presents hemodynamic deterioration (despite antituberculous treatment) [33] or if they present pericardial calcifications, which are markers of chronicity of the disease [34].

7. Effusive-constrictive pericarditis

It is the presence of increased intrapericardial pressure due to effusion and constriction of the visceral pericardium, which does not improve with pericardiocentesis. The signs and symptoms are similar to those of constrictive pericarditis.

The treatment is pericardiectomy associated with antituberculous treatment for 6 months.

8. Conclusions

Tuberculous pericarditis is a rare pathology in developed countries but frequent in developing countries. There is difficulty in the diagnosis due to low bacteriological and histological results. The usefulness of indirect methods for diagnosis should be taken into account, especially in patients with torpid pericarditis. The presence of positive serology for HIV can modify the clinical presentation and the outcome of tuberculous pericarditis.

There is still a lack of sustainable evidence for the use of systemic corticosteroids in this pathology.

Pharmacological treatment should be performed for at least 6 months in all patients with tuberculous pericarditis, regardless of drainage or pericardiectomy.

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