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Review Article

Usefulness of imaging techniques in tuberculous pericarditis

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Abbreviations
CT: computed tomography
MRI: nuclear magnetic resonance imaging
PET: positron emission tomography
TB: tuberculosis

ABSTRACT
Tuberculosis bacillus has been around for 3 million years. This is an infectious disease caused by the Mycobacterium tuberculosis complex. It basically has three presentation forms: pulmonary, miliary and extrapulmonary tuberculosis, within the latter pericardial tuberculosis is included. Regarding the specific case of Imaging, radiological signs have been described with important findings in the cardiac area. Echocardiogram could be considered the best noninvasive diagnostic method for detecting the presence of pericardial thickening and pericardial effusion with or without fibrin. Chest computed tomography scan provides an excellent assessment of the anatomy of the heart and pericardium, the thickness of the latter, and the presence of fluid between its layers. Positron emission tomography (PET) study is very useful in discriminating tuberculous pericarditis from idiopathic one. Magnetic resonance imaging is very sensitive to assess myocardial structure, function, inflammation, and fibrosis. Pericardial tuberculosis infection remains a global health problem with challenging diagnosis for those specialists facing it, which requires several diagnostic imaging techniques and bacteriological tests, in order to achieve its confirmation.
Keywords: Tuberculosis, Pericardial tuberculosis, Diagnostic imaging, Echocardiography, Computed tomography, Magnetic resonance imaging

Utilidad de los medios imagenológicos en la pericarditis tuberculosa

RESUMEN
El bacilo de la tuberculosis existe hace 3 millones de años. Esta es una enfermedad infectocontagiosa causada por el complejo Mycobacterium tuberculosis. Básicamente se puede presentar de tres formas: tuberculosis pulmonar, miliar y extrapulmonar, dentro de esta última se encuentra la tuberculosis pericárdica. En el caso específico de la Imagenología se han descrito signos radiológicos con importantes hallazgos en el área cardíaca. El ecocardiograma podría considerarse como el mejor método diagnóstico no invasivo para detectar la presencia de engrosamiento pericárdico y derrame pericárdico con o sin fibrina. La tomografía axial computarizada de tórax proporciona una excelente evaluación de la anatomía del corazón y el pericardio, el grosor del mismo y la presencia de líquido entre sus capas. El estudio mediante tomografía por emisión de positrones (PET) puede ser muy útil para discriminar la pericarditis tuberculosa de la idiopática. La resonancia magnética es muy sensible para valorar la estructura miocárdica, la función, la inflamación y la fibrosis. La infección pericárdica por tuberculosis sigue constituyendo un problema de salud mundial y su diagnóstico un reto para los especialistas que la enfrentan, lo que requiere de varias técnicas de imágenes diagnósticas y

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de pruebas bacteriológicas, en aras de lograr su confirmación.
Palabras clave: Tuberculosis, Tuberculosis pericárdica, Diagnóstico por imagen, Ecocardiografía, Tomografía computarizada, Imagen por resonancia magnética

INTRODUCTION

The tuberculosis (TB) bacillus is more than three million years old; therefore, it is very likely that tuberculosis is the oldest known infectious disease[1]. This microorganism was discovered by the microbiologist Robert Koch, who named it *Mycobacterium tuberculosis*[2,3].

Three forms of presentation of TB are described: pulmonary, miliary and extrapulmonary tuberculosis[1]. This last one includes cardiac TB, which at the same time presents three clinical forms: pericarditis (most frequent form), myocarditis and aortitis[4,5].

This bacillus has reached developed countries due to the high rates of migration. The use of antituberculosis drugs has allowed a remarkable improvement in the prognosis, without it being absolute due to the persistence of strains that are resistant to multiple drugs[6], so that the microorganism persists and extrapulmonary dissemination takes place[7,8].

Some radiological signs of pulmonary tuberculosis have been described representinhg important findings for diagnostic suspicion. Echocardiography could be considered the best non-invasive diagnostic method for detecting the presence of pericardial effusion, but not for determining its pathogenesis. Chest computed tomography provides an excellent assessment of the anatomy of the heart and pericardium, the pericardium thickness and the presence of fluid between its layers. The pericardium, by computed tomography (CT), normally measures 2 mm. It is stated that a thickness greater than 4 mm is compatible with constrictive pericarditis. Nuclear magnetic resonance imaging (MRI) is very sensitive to assess myocardial structure, function, inflammation and fibrosis[9-13].

Pericardial infection due to tuberculosis continues to be a worldwide health problem and its diagnosis is a challenge for the specialists who face it, hence it requires several diagnostic imaging techniques and bacteriological tests in order to achieve its final confirmation. That is why to perform an updating in the diagnostic and pathophysiological aspects of tuberculous pericarditis is proposed.

TUBERCOLOUS PERICARDITIS

In the year 400 B.C.E. Hipócrates described a patient with a disease that was very similar to what it is known nowadays as tuberculosis[1]. The TB is an infectious disease caused by the *Mycobacterium tuberculosis* complex (*M. tuberculosis, M. bovis, M. africanum* and *M. microti*, among others), which was discovered by the German microbiologist Robert Koch and it was demonstrated in his "postulates" of the year, although detailed descriptions had already been available since the 17th century[2,3]. It is part of the history of humankind since it was initially an endemic disease in animals and it was transmitted to humans after the appearance of agriculture, its epidemiological study is a reflection of diverse cultures[2].

Despite being recognized since ancient times it still contributes significantly to a global diseases burden, with an estimated of 9.6 million new cases of global diseases in 2014. It has become a health problem, especially after the advent of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS), the deterioration of the socioeconomic conditions and the poor health care system infrastructure to interact with patients infected with the bacillus[4].

Only 22 countries account for 90% of the world's TB cases, which is a major cause of mortality due to infectious diseases[3,5]. It causes nearly two million deaths per year, 98% of which take place in developing countries, where socioeconomic conditions and the growing population with human immunodeficiency virus (HIV) have allowed a rapid spread of the disease[2].

Although an effective treatment has been used for decades, this has not prevented TB from continuing to represent one of the greatest health problems in the world, with eight million new cases of the disease and two million deaths each year, according to data from the World Health Organization (WHO). Its influence has reached developed countries, due to the growing internal and external migration, or to tourism or humanitarian purposes. In addition, the persistence of multi-drug resistant strains has increased the lack of control of this disease[6].

There are three forms of presentation of TB: pulmonary, miliary and extrapulmonary TB[1]. According to WHO classification criteria, extrapulmonary tuberculosis is defined as an infection caused by the *Mycobacterium tuberculosis* bacillus that affects tissues and organs outside the pulmonary parenchyma. It represents between 20-25% of cases of tuberculous disease and it is the result of hematogenous and lymphatic dissemination of this bacillus[7]. The sites where it is most frequently located are, in order: lymph nodes, pleura, genitourinary system, bones and joints, meninges, peritoneum and pericardium[1].

There are three clinical forms of cardiac TB, in order of incidence they are described as pericarditis; myocarditis, with or without formation of aneurysms of the myocardial wall and finally, aortitis, with or without formation of so-called mycotic aneurysms involving the aortic valve and sinuses of Valsalva. Each of them with their specific clinical manifestations and picture[4].

As mentioned, pericarditis is the most common form of cardiac TB, affecting between 1 and 4% of patients diagnosed with this condition, representing 10% of all cases of pericarditis and its mortality rate can reach 90% when correct diagnosis and treatment are not performed[5].

The first description of pericarditis dates back to the times of Galen (year 200 A.D.), who called it pericardial "hydrops". Later in the 19th century, a Viennese physician named Rokitansky identified TB as a cause of pericarditis after having performed nearly 30 000 autopsies. For a long time this type of pericarditis was recognized for its high mortality (80-90%), until the use of antituberculosis drugs was introduced, which significantly improved its prognosis[8].

For the bacillus to reach the pericardium, three mechanisms have been suggested, including the retrograde route from the mediastinal, paratracheal and peribronchial lymph nodes; the hematogenous route and rarely by contiguity of adjacent structures, such as the lung, pleura and vertebral bodies[4]. It may also suggest a bone focus and occasionally, during miliary TB[2].

This presence of lymph nodes concomitant with pericardial disturbances requires histological diagnosis because it can be caused by a variety of benign inflammatory conditions, such as sarcoidosis, unusual bacteria and fungal infections, associated or not with tuberculosis[9].

Some authors divide tuberculous pericarditis in four stages: dry stage, effusion stage, absortive phase and constrictive phase. In the first stage, diagnosis is difficult because it requires biopsy or necropsy, where isolated granulomas will be observed in the pericardium due to the inflammatory process. In the second stage (pericardial effusion), the pericardial fluid pressure produces disturbances which are typical of cardiac tamponade. It can also progress to granulomatous inflammation and caseous necrosis although it is described that 50% of the patients reabsorb the effusion and the symptoms resolve without treatment in a period of two to four weeks. Some patients, however, progress to the constrictive phase. In this stage, thickening of the visceral pericardium due to fibrosis and calcification, produces typical constrictive changes[4,10].

Constrictive pericarditis was described by Lower in 1669, it is a clinical condition produced by the presence of inflammation of the pericardial tissue culminating in cardiac constriction. Some 10-20% of cases with tuberculous pericardiatis (TBP) evolve towards a constrictive pericarditis[6]. The existence of this one is not pathognomonic of tuberculosis, since it has been described in other processes such as malignant lesions, hemopericardium and very rarely in viral infection; likewise, it can take place in patients who have received radiotherapy[10].

The risk of cardiac tamponade must always be considered, whose clinical signs include tachycardia, jugular vein engorgement and paradoxical pulse, with indication for drainage through open techniques of a performance higher than pericardiocentesis[2].

The diagnosis of tuberculous pericarditis must be confirmed through microbiological studies. However, the detection of acid-fast bacilli (AFB) in pericardial fluid is usually negative, culture is positive in 30-70% of cases and Mantoux is negative in up to 25%[6]. For this reason sometimes the diagnosis of TBP is confirmed through exclusion and response to therapy[5].

Electrocardiographic signs

Electrocardiographic signs are also nonspecific, among them are defined: sinus tachycardia, ST segment variations, low voltages and inverted T waves. Another sign that can be observed is electrical alternans, which is characterized by the variation in QRS amplitude from beat to beat, especially in anterior leads (V_2-V_4). It can also be associated to atrial fibrillation[4,10].

There are no pathognomonic electrocardiogra-

phy signs to suspect restrictive pericarditis, it depends on the clinical scenario and it can be differentiated between tamponade and pericarditis[11]. However, the differential diagnosis of pericardial constriction usually includes idiopathic, infectious, post-surgical or neoplastic causes[12].

Imagin studies

Nowadays imaging studies have come to play a preponderant role in the diagnosis of this condition. In pericardial effusion, the diagnostic approach begins with the confirmation of some signs described in conventional radiology, although the diagnosis is more certain through echocardiography. It should be taken into account that in developed countries the main cause of pericardial effusion is viral infections; but in developing countries such as ours, the suspicion of TB should always be kept in mind, especially in patients living with HIV[2]. Other methods can be used such as: CT, PET and MRI.

Radiological signs

Some radiological signs of pulmonary tuberculosis have been described which represent important findings for diagnostic suspicion. Widening of the cardiac area is evident in more than 90% of cases, with globular "water bottle" silhouette, demonstrating active pulmonary tuberculosis (30%) and pleural effusion in 40-60%[13] of cases. Cardiomegaly and pleural effusion are present in most patients[10], pulmonary infiltrates and mediastinal adenomegaly may also be demonstrated[4].

When pericardiocentesis is required, a good correlation has been found between the cardiomegaly observed on radiography and the amount of fluid aspirated during pericardiocentesis, which makes it a useful test for the identification of large pericardial effusions in developing countries[13].

Although pericardial calcifications are considered an important sign of constrictive pericarditis, about 75% of patients do not present calcifications, which only demonstrates the existence of a longer period of pericarditis development as well as a higher probability of death during pericardiectomy[5]. That is, pericardial calcifications can be observed in any form of chronic pericarditis[10,11].

Echocardiography

Echocardiography could be considered the best non-invasive diagnostic method for detecting the presence of pericardial effusion, but not for determining the pathogenesis, even considering that fibrin bands in the visceral pericardium are typical, but not specific for tuberculosis[13]. It is therefore essential to confirm the presence of pericardial effusions as well as to detect tamponade signs[10].

Patients with typical pericardial tuberculosis present pericardial thickening with reduced intermembrane slippage, and pericardial effusion with or without fibrin, hence it is possible to identify fibrin bands that scar the pericardium. Similarly, respiratory changes can be observed in each phase of the cycle, which causes the mitral E wave velocity to decrease by more than 25%. Pericardial stress may also take place with distension of the vena cava associated with decreased inspiratory collapse and atrial dilatation, which may cause paradoxical movement of the septum, right atrioventricular collapse in diastole, exaggerated transvalvular flow during Doppler and hepatical venous reflux during diastole with dilatation of the inferior vena cava[4,10-11,13]. After fluid extraction, changes in mitral E wave velocity are minimal. Restrictive mitral flow may be observed. All these changes should be carefully observed[11].

Despite its many advantages, echocardiography may have limitations in establishing the origin and characterizing cardiac masses, especially extracavitary ones. The CT and MRI allow to accurately define the origin of the mass, to perform tissue characterization and to better establish anatomical relationships by assessing myocardial, pericardial and extracardiac extension[14].

Chest CT

Chest CT provides an excellent assessment of the anatomy of the heart and pericardium, the pericardium thickness and the presence of fluid between its layers. The pericardium normally measures 2 mm by CT. It is stated that a thickness greater than 4 mm is compatible with constrictive pericarditis (**Figure 1**)[14,15].

In addition, it allows to define with accuracy the effusion location and degree. It usually appears as a smooth or irregular pericardial thickening and the presence of hyper-dense fluid between its layers

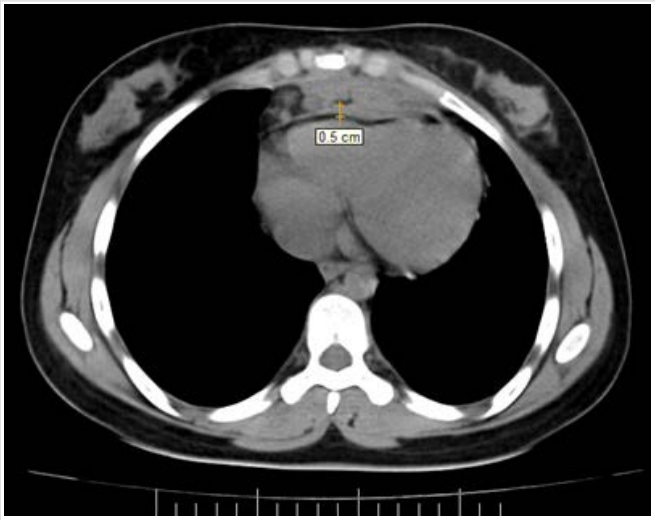

Figure 1. Pericardial thickening due to tuberculosis with extension to the mediastinum.

translates the effusion, which can give rise to loculi by the formation of septa that simulate a mass. It also details the precise site of calcification[14,15].

In addition, pulmonary parenchymal lesions can be found including consolidations, infiltrates, caverns and miliary nodules (**Figure 2**). Besides, pleural effusion and thickenings are easily defined through this method[9].

Similarly, tomographic sections allow the discovery of superficial lymph node involvement at the base of the neck, supraclavicular regions, axillae and mediastinum (**Figure 3**). This form represents the most frequent extrapulmonary manifestation of cardiac TB in childhood (60-70%), they are usually firm

Figure 2. Miliary tuberculosis (arrow).

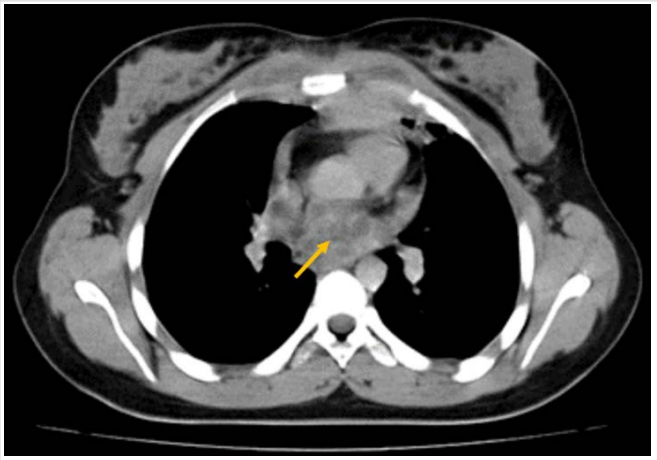

Figure 3. Mediastinal adenomegaly in TB patient (arrow).

adenitis, adherent to deep planes with a tendency to form fistulas. It may be accompanied by fever and general symptoms. It is suggested that scrofula appears more frequently in the supraclavicular, anterior cervical or submandibular areas. We have seen this abnormal duct opening to soft tissues from infiltration of the pericardium, the anterior mediastinal space and the anterior chest wall (**Figure 4**)[6].

Positron Emission Tomography

The use of 18F-fluorodeoxyglucose in positron emission tomography (PET) studies can be very useful to

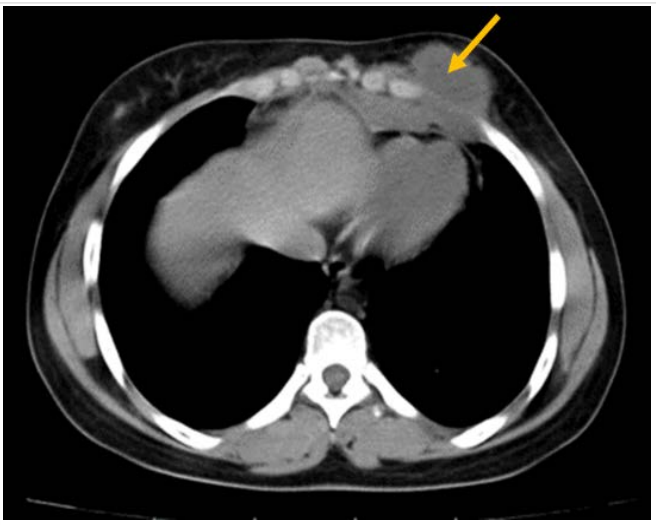

Figure 4. Fistula to soft parts from mediastinal tuberculosis (arrow).

discriminate TB pericarditis from idiopathic pericarditis. But the differentiation between physiological and pathological using 18F-fluorodeoxyglucose that can be performed through PET/CT remains a challenge[16]. The differential diagnosis should be made with mesothelioma and pericardial metastases[14]. Typical mediastinal lymph node changes can be found in almost 100% of cases (e.g. size greater than 10 mm and hypodense centers)[13,16].

In developing countries the use of PET is a very expensive method to be used as a diagnostic tool; chest X-ray is the first to be performed, followed by echocardiography and computed tomography. Cardiac MRI is reserved for developed countries or other diseases that truly require it[17,18].

Nuclear magnetic resonance imaging

The MRI is very sensitive in assessing myocardial structure, function, inflammation and fibrosis; however, despite its inaccessibility and cost, CT remains a crucial tool in the diagnosis of tuberculous pericarditis[13].

Cardiac MRI allows visualization of different pericardium states, it assesses pericardial inflammation as well as the development of constrictive pericardial effusion and pericardial abscess. It can also define pericardial calcifications in patients with chronic constrictive pericarditis[16].

The MRI is commonly used as a tool in the assessment of pericardial diseases. Like CT, it allows to define pericardial thickness and cardiac anatomy, as well as edema and effusion. Some constriction signs can be inferred due to the ventricular septum movement. It allows as well to define the dilation of the inferior vena cava during the increase of pressures on the right chambers. Its advantage is that it does not use radiation but it is still inaccessible compared to CT. The evaluation of pericardial inflammation is a great advance of NMRI MRI, which is performed using gadolinium and the result has therapeutic implications because it will differentiate active inflammation of the pericardium in long-standing constrictive pericarditis with predominantly fibrotic pericardium[15].

Post-pericarditis TB diagnosis requires the combination of a high index of suspicion, exhaustive clinical evaluation and integration of imaging methods such as: echocardiography, CT, MRI and occasionally, invasive hemodynamic evaluation[4].

Pericardial infection due to tuberculosis continues to be a worldwide health problem and its diagnosis is a challenge for the specialists who face it, since it requires several diagnostic imaging techniques and bacteriological tests in order to achieve the final confirmation of the cases. The use of echocardiography, CT or MRI in developing countries is crucial in the evaluation and final decision making, so there must be a multidisciplinary integration in the diagnosis and treatment of this disease.

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