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TUBERCULOUS PERICARDITIS DUE TO SILICON OXIDE EXPOSURE. A CASE REPORT WITH AN IMAGING APPROACH

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Palabras clave: Pericardio; Derrame Pericárdico; Tuberculosis; Silicosis; Pericarditis Tuberculosa.

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RESUMEN

Introducción. Se presenta el caso de un paciente con pericarditis tuberculosa, una forma infrecuente de tuberculosis con una alta morbimortalidad. Este informe es un aporte a la literatura médica ya que representa una revisión completa del abordaje por imágenes de esta patología.
Presentación del caso. Hombre de 52 años con exposición a óxido de silicio, que fue remitido a la Unidad de Cuidados Intensivos de un hospital de cuarto nivel de complejidad en la ciudad de Bogotá (Colombia) con derrame pericárdico hiperdenso, inicialmente considerado de etiología maligna. Se hizo un seguimiento imagenológico con resultados sugerentes de pericarditis tuberculosa, por lo que se realizó una pericardiocentesis cuyos estudios microbiológicos y de detección molecular en líquido pericárdico fueron negativos para *Mycobacterium tuberculosis* y hongos; sólo la prueba de adenosina desaminasa (ADA) fue positiva, lo cual elevó la sospecha de pericarditis tuberculosa. El diagnóstico definitivo se obtuvo por biopsia de pericardio y se instauró tratamiento antituberculoso diario por vía oral durante 56 días, con lo cual se obtuvo una mejoría significativa del paciente.
Conclusiones. Se debe sospechar pericarditis tuberculosa en pacientes que presenten derrame pericárdico hemorrágico, el cual puede ser identificado por medio de ecografía/ecocardiografía, tomografía o resonancia magnética de forma confiable. Se recomienda que el abordaje diagnóstico estándar en casos con sospecha clínica incluya estudios diagnósticos de apoyo, como ecocardiograma, tomografía simple y contrastada de tórax, pericardiocentesis con examen de ADA en líquido pericárdico y biopsia de pericardio para obtener un diagnóstico definitivo.

ABSTRACT

Introduction: This is a case report of a patient with tuberculous pericarditis, a rare form of tuberculosis associated with high morbidity and mortality. It contributes to the medical literature, given that it provides a comprehensive review of the imaging approach to this disease.
Case presentation: A 52-year-old man previously exposed to silicon oxide who was referred to the Intensive Care Unit of a quaternary care hospital in the city of Bogotá (Colombia) due to hyperdense pericardial effusion, which was initially considered to have a neoplastic etiology. Imaging studies showed results suggestive of tuberculous pericarditis, prompting a pericardiocentesis, with microbiological and molecular detection studies in pericardial fluid that were negative for *Mycobacterium tuberculosis* and fungi. The only positive test was adenosine deaminase (ADA), thus raising the suspicion of tuberculous pericarditis. The definitive diagnosis was obtained via pericardial biopsy. Daily oral antituberculosis treatment was administered for 56 days, resulting in a significant improvement in the patient's condition.
Conclusions: Tuberculous pericarditis should be suspected in patients presenting with hemorrhagic pericardial effusion, which can be reliably identified by

ultrasound/echocardiography, CT, or MRI. It is recommended to include supportive diagnostic studies such as echocardiography, plain and contrasted CT of the chest, pericardiocentesis with ADA testing of pericardial fluid, and pericardial biopsy as the standard diagnostic approach in cases with clinical suspicion to reach a definitive diagnosis.

INTRODUCTION

Tuberculous pericarditis is a rare complication of tuberculosis, which occurs more frequently among people diagnosed with silicosis (relative risk of 2.8%) as a severe complication (1-3). Activities mainly related to silicosis include mining, demolition, automotive repair, foundry, stone cutting, glass production, jeans manufacturing, among others (4). Several of these activities are widely performed in Colombia.

The main manifestations of tuberculous pericarditis are pericardial effusion, constrictive pericarditis, and the combination of pericardial effusion and constriction (5). With respect to diagnosis, the imaging approach plays a fundamental role because, in some cases, symptoms are non-specific and diagnosis can be mistaken for other diseases (5).

CASE PRESENTATION

A 52-year-old man with a history of occupational exposure to silicon oxide for 30 years was referred to the Intensive Care Unit (ICU) of a quaternary care hospital in the city of Bogotá (Colombia) due to hypoxemic respiratory failure. The patient reported having a fever, night sweats, cough, weight loss (7kg) and dyspnea for a month, all of which had worsened in the 3 days prior to his referral.

On admission to the ICU, the patient was tachycardic (111 bpm), dehydrated, and hypoxemic, requiring oxygen therapy (inspired oxygen fraction of 28%) to maintain a saturation of 97%. The results of laboratory tests on admission are summarized in Table 1.

Table 1. Laboratory test results.

Blood tests	Results
Sodium	140.9 mmol/L
Potassium	3.92 mmol/L
Chloride	101.0 mmol/L
Blood creatinine	1.17mg/dL
Blood urea nitrogen	15.13mg/dL
Leukocyte count (Complete blood count)	5.45 * 10^3/mm^3
Neutrophils	63.2%
Lymphocytes (complete blood count)	24.5%
Hemoglobin level	10.6g/dL
Hematocrit	33.2%

Source: Own elaboration.

In addition, a chest X-ray was requested on admission (Figure 1), which showed an enlargement of the cardiac silhouette in the shape of a water bottle (water bottle sign), suggesting pericardial effusion.

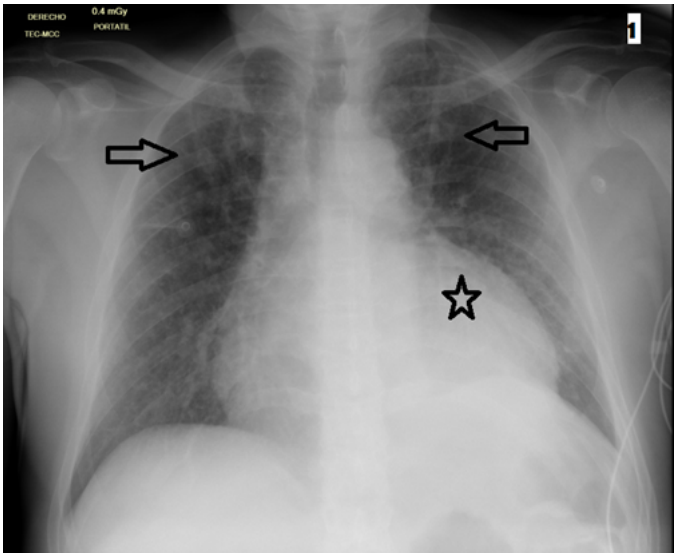

Figure 1. Chest X-ray. Nodular opacities were observed in both pulmonary apices (black arrows), as well as a water bottle shape of the cardiac silhouette (black star), suggestive of pericardial effusion. These guiding findings have low sensitivity and specificity, so complementary imaging was necessary.

Source: Image obtained while conducting the study.

Seven hours after being admitted to the ICU, a portable chest ultrasound was performed with emphasis on the pericardium (Figure 2), confirming an echogenic pericardial effusion compatible with bleeding.

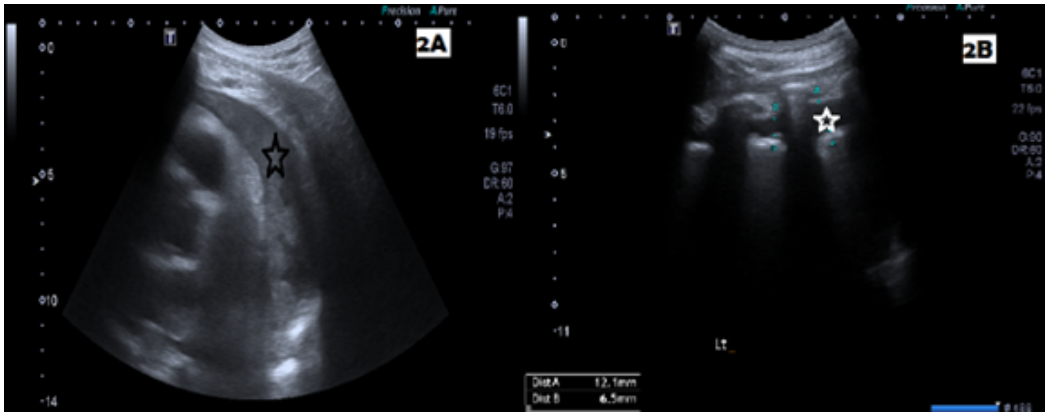

Figure 2. Chest ultrasound. Subxiphoid view (2A) and anterolateral intercostal view in mid-axillary line (2B). 2A: hyperechoic and particulate effusion, with suspected bleeding, exudate or fluid with high protein content (black star); 2B: hypoechoic pleural effusion with suspected exudate (white star).

Source: Image obtained while conducting the study.

Based on these results, a possible malignant or infectious etiology was considered. Therefore, 8 days after admission, a computed tomography (CT) scan with electrocardiogram synchronization (Figure 3), a high-resolution computed tomography (HRCT) of the thorax (Figure 4), and a cardiac magnetic resonance imaging (MRI) scan were performed, showing effusive-constrictive pericarditis and silicosis (Figure 5).

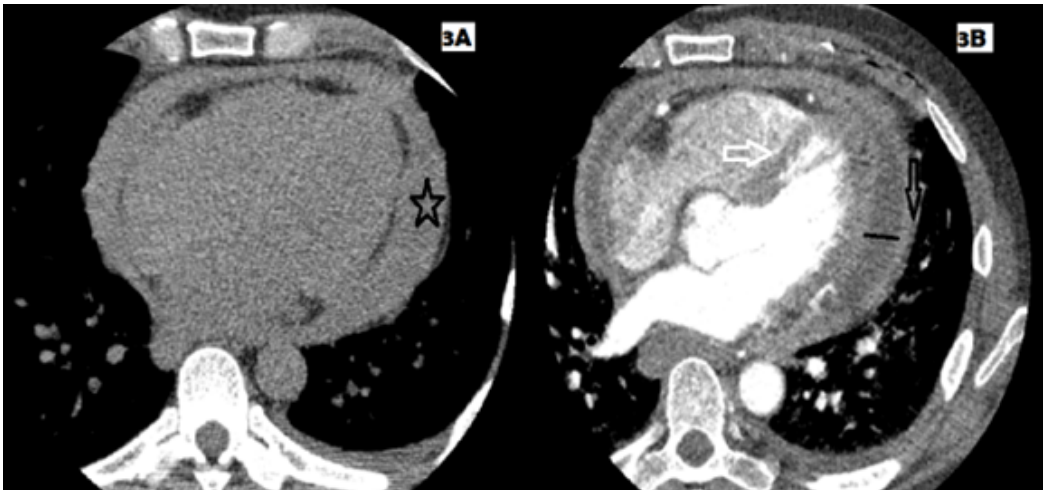

Figure 3. CT with single-phase (3A) and post-enhancement (3B) electrocardiogram (EKG) synchronization. Figure 3A: hyperdense pericardial effusion (40UH) (black star), in which no calcifications are identified; Figure 3B: homogeneous enhancement of the visceral and parietal layers of the pericardium (black arrow), both of which were found to be thickened (6 mm and 5.4 mm, respectively). Maximum distance between pericardial layers of 15 mm (black line), compatible with abundant pericardial effusion (greater than 500 mL). In addition, a displacement of the interventricular septum to the left was identified as a sign of overload of the right cardiac chambers (white arrow).
Source: Image obtained while conducting the study.

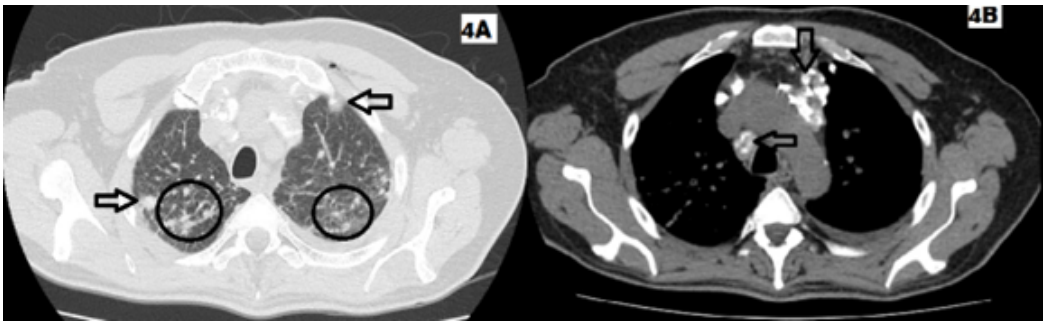

Figure 4. Chest CT in pulmonary window (4A) and mediastinal window (4B). Figure 4A: solid micronodules (<6 mm) of perilymphatic and centrilobular distribution (black arrows), predominantly in upper lobes; finding suggestive of simple silicosis or silicotuberculosis (indistinguishable on imaging) and irregular interstitial thickening (black circles), a nonspecific finding common to multiple diseases;
Figure 4B: prevascular and right paratracheal adenopathies with eggshell calcifications (black arrows), which are highly suggestive of simple silicosis.
Source: Image obtained while conducting the study.

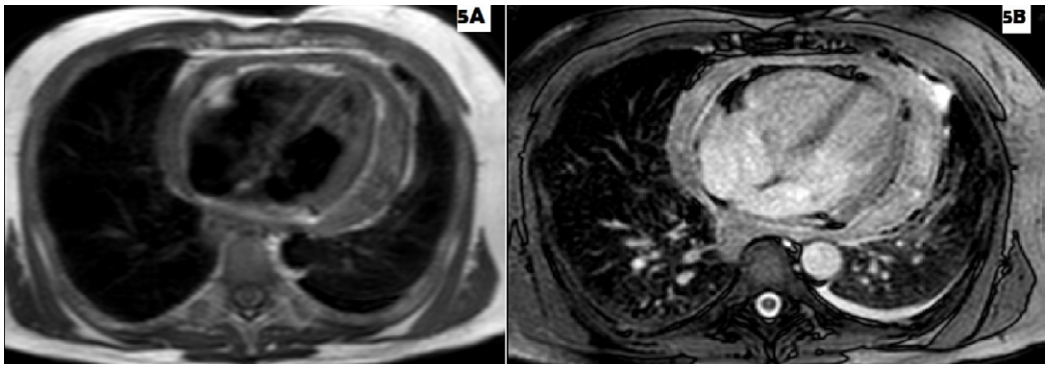

Figure 5. Cardiac MRI in black blood (5A) and white blood (5B) sequences. Figure 5A: Pericardial effusion with isointense to hyperintense signal, compatible with hemorrhagic pericardial effusion; Figure 5B: thickening of the visceral (5 mm) and parietal (6 mm) layers with hyperintense pericardial effusion compatible with hemorrhagic pericardial effusion.
Source: Image obtained while conducting the study.

Imaging data showing hemorrhagic pericardial effusion without calcifications and with thickening of the pericardium suggested a probable benign etiology. These findings, together with evidence of pulmonary silicotuberculosis raised the possibility of tuberculous pericarditis. In view of these findings, a pericardiocentesis was scheduled that same day, obtaining sterile pericardial fluid, on which the following tests were performed: Gram test, in which no bacteria were found, although a high erythrocyte (hemorrhagic) and mononuclear cell count (90%) was identified; and lactate dehydrogenase (LDH) test with a value of 2391 U/L (>66% from the upper limit of the normal serum LDH value), suggesting an exudate according to the modified Light's criteria. Additionally, Ziehl-Neelsen staining, a culture for *Mycobacterium* in Kircher medium, and polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* were performed, and all three tests were negative. An ADA test was also performed, yielding a positive result: 66 U/L (normal reference value: <40 U/L), which was suggestive of tuberculous pericarditis.

Based on these results, 14 days after admission, a pericardial biopsy was requested, in which a large pericardial thickening with firm adherence to the diaphragmatic base of the pericardium was identified. Subsequent histopathological analysis showed granulomas with caseous necrosis (Figure 6), despite negative results for *Mycobacterium* and fungi in the microbiological and molecular tests.

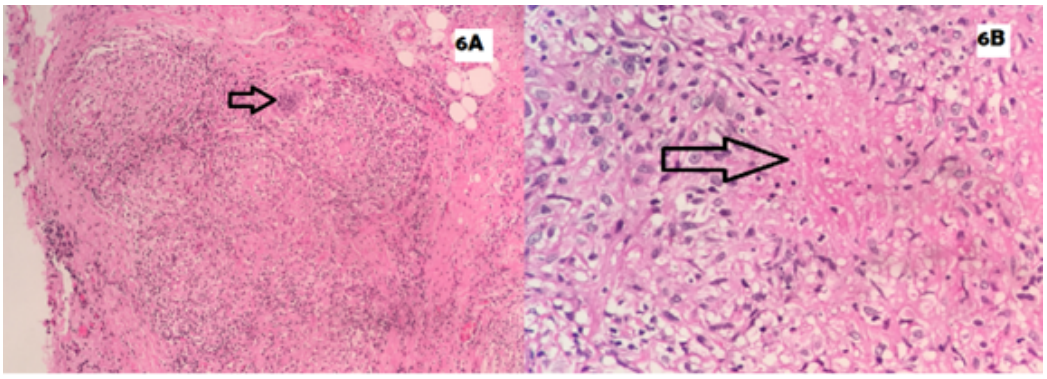

Figure 6. Tissue specimen examination under light microscopy 100x (6A) and 400x (6B). Figure 6A: multiple granulomas consisting of epithelioid histiocytes and multinucleated giant cells (black arrow); Figure 6B: granuloma with epithelioid histiocytes organized in palisades around its periphery, with a central area of caseous necrosis (black arrow). Ziehl-Neelsen and Grocott methenamine silver stains were negative in this pericardial tissue sample.
Source: Image obtained while conducting the study.

Given the positive ADA result in pericardial fluid and the diagnostic pericardial biopsy, 15 days after admission, treatment with HRZE was started (H: isoniazid 300mg, R: rifampicin 300mg, P: pyrazinamide 500mg, and E: ethambutol 400mg), administered orally every day (for 56 days), leading to clinical improvement. The patient was discharged 17 days after being admitted to the institution. Treatment follow-up was carried out by the institution's Epidemiology Department, ensuring the continuation of treatment until the end of the HR treatment phase. Follow-up appointments took place in a different institution, so we did not have access to follow-up information. In a later telephone call, the patient reported clinical improvement.

DISCUSSION

Tuberculous pericarditis, because of its complex diagnosis, requires the use of diagnostic imaging and microbiological and pathological tests. Diagnostic imaging plays a key role in characterizing the type of pericardial effusion (hemorrhagic or simple), identifying pericardial thickening and classifying its type (regular or irregular), detecting signs of tuberculosis in other organs (mainly the lung), and evaluating other conditions such as the presence of mediastinal adenopathy in metastatic disease (5).

From a clinical perspective, this case was a diagnostic challenge since the patient's signs and symptoms were nonspecific and suggestive of cardiac failure. A multimodal imaging approach allowed us to detect a hemorrhagic pericardial effusion, thickening of the pericardium, and signs of pulmonary silicotuberculosis,

which led to the suspicion of tuberculous pericarditis. A positive ADA test and lymphocytic infiltrate in pericardial fluid were necessary to initiate treatment, and pericardial biopsy demonstrated caseating granulomas. These results are sufficient for making a definitive diagnosis of tuberculous pericarditis, according to the criteria of Mayosi *et al.* (5)

The diagnostic criteria for tuberculous pericarditis, according to Mayosi *et al.* (5), involve the identification of tubercle bacilli in pericardial effusion fluid in Ziehl-Neelsen staining (or positive culture for *Mycobacterium tuberculosis* in pericardial fluid) or the identification of tubercle bacilli or granulomas with caseous necrosis in pericardial tissue samples. In turn, diagnostic criteria for probable tuberculous pericarditis, according to Mayosi *et al.* (5), include evidence of pericarditis in a patient with tuberculosis elsewhere in the body, lymphocytic exudate with elevated ADA levels, positive unstimulated interferon gamma (uIFN-ϒ) or lysozyme levels above the normal cutoff level, and a good response to empirically administered antituberculosis therapy (5). It should be noted that there is a lower frequency of granulomas with caseous necrosis in HIV-infected patients, especially in cases of acquired immunodeficiency syndrome (AIDS) (6).

The most common sites of extrapulmonary tuberculosis are the nervous system and the cardiovascular system. Hematogenous dissemination is possible in cases of miliary tuberculosis, while dissemination in pulmonary or pleural tuberculosis may occur via the lymphatic route directly to the pericardium (7). Cardiovascular tuberculosis may develop in the pericardium, myocardium or the aorta, with the pericardium being the most frequent site, especially in patients with AIDS (7).

According to Mayosi *et al.* (5), 80% of pericardial effusions caused by tuberculosis are hemorrhagic, in which case neoplastic diseases, mainly metastatic, should be ruled out as the main differential diagnosis. The other ones are exudates and usually show a greater volume of fluid (5).

There are four stages of tuberculous pericarditis: fibrinous exudation, serosanguinous effusion, absorption of effusion with inflammatory organization, and constrictive scarring (5). These stages depict the evolution from acute inflammatory exudation, consisting of polymorphonuclear leukocytes, to chronic inflammatory exudation, comprised of mononuclear cells (lymphocytes, macrophages, dendritic cells, epithelioid cells, and multinucleated giants). This process leads to pericardial thickening caused by collagenosis and fibrin between the pericardial layers (5).

In the clinical context, there are three possible scenarios: the first is tuberculous (or simple) pericardial effusion, in which it is difficult to differentiate the effusion from other forms of acute pericarditis, except for the fact that it usually lasts for more than 1-4 weeks, exceeding the typical duration of other forms of acute pericarditis (5). The second scenario is constrictive pericarditis, characterized by pericardial fibrinous exudate that may have a constrictive effect in the absence of pericardial calcification. This phase represents 30-60% of cases

of tuberculous pericarditis because patients exhibit more evident symptoms (5), thus facilitating detection, as in this case.

The third scenario is effusive constrictive pericarditis, characterized by increased pericardial pressure due to effusion in the presence of visceral constriction associated with the formation of fibrinous pericardial bands and calcifications between the pericardial layers, which is considered difficult to treat and has a less favorable prognosis. Treatment at this stage is complex since pericardiocentesis cannot eliminate the restrictive effect, and surgical treatment for resection of the visceral pericardium is not possible. The administration of antituberculosis drugs is required until resection is possible using serial echocardiograms (5).

In order to diagnose tuberculous pericarditis, pericardiocentesis is the first recommended procedure: Ziehl-Neelsen stains for detecting acid-fast bacilli in the pericardial fluid can be requested (sensitivity of 64%) (6). Moreover, pericardial fluid culture can be performed on Kircher medium (sensitivity of 52%) with excellent specificity (100%) and a positive predictive value of 100% (6). However, the performance of both tests is considered to be low. Among the microbiological tests in pericardial fluid available, ADA quantification has the best performance (sensitivity greater than 90% and specificity of 55%) (6). The European Society of Cardiology (ESC) recommends a cutoff value of 40 U/L. Also, PCR detection for *Mycobacterium tuberculosis* (Xpert-MTB/RIF) shows a sensitivity of 95% and specificity of 100% (6,8). Regarding imaging findings, they can be explained by the evolutionary characteristics of blood and the phases of pericardial thickening (Table 2).

Table 2. Imaging features of hemorrhagic pericardial effusion in tuberculous pericarditis.

Stage/Modality	Ultrasound	CT	MRI
Acute (Deoxyhemoglobin)	Hyperechoic	Density >40-55 HU. Mild thickening of the pericardium and contrast enhancement.	Hyperintense in T1, T2, STIR and PSIR, and heterogeneous in SSFP - cine images. Mild thickening of the pericardium and contrast enhancement.
Subacute (Methemoglobin)	Mixed/heterogeneous echogenicity	Heterogeneous density with smooth pericardial thickening >4 mm (variable) and ≤10 mm, with late enhancement in the constrictive pericarditis stage.	High heterogeneous signal in T1 and STIR, low in T2 and SSFP-cine. Smooth pericardial thickening with late enhancement in the constrictive pericarditis stage.
Chronic (Hemosiderin)	Hypoechoic with particulate material or loculated. Pericardial calcifications with posterior acoustic shadowing.	Pericardial calcifications and effusion with fluid density (-20 to +20 HU) in the effusive constrictive pericarditis stage. Pericardial thickening >4 mm and ≤10 mm. Late enhancement less evident.	Hypointense signal in all sequences of pericardial layers (T1, T2, and cine), mainly due to calcification, with pericardial effusion that may have hypointense fluid signal in T1, hyperintense signal in T2, and cine sequences. Late enhancement less evident.

HU: Hounsfield units; STIR : short tau inversion recovery; PSIR: phase sensitive inversion recovery; SSFP: steady-state free precession

Source: Own elaboration based on López *et. al* (7), Ming *et al.* (9), Ming *et al.* (10), y Rajiah (11).

In the presence of tuberculous pericardial effusion, anti-tuberculosis therapy is recommended for 6 months. During the first two months, the HRZE scheme should be administered, followed by four months of HR (isoniazid and rifampicin) (7,12). In the reported case, HRZE therapy was prescribed for 56 days at the request of the Infectious Diseases Department, ensuring the continuation of treatment until the end of the HR treatment stage. In the case of constrictive pericarditis, pericardiotomy and the implementation of antituberculosis therapy in the scheme described for the simple pericardial effusion stage is recommended. In the case of effusive constrictive pericarditis, indefinite antituberculosis therapy is recommended until a pericardial layer can be subjected to pericardiectomy (5, 12-13).

In a systematic review conducted by Wiysonge *et al.* (14), it was found that steroid therapy is likely to reduce deaths from pericarditis in patients without HIV coinfection (RR 0.39). In individuals co-infected with HIV, steroids can prevent progression to constrictive pericarditis (RR=0.55). Likewise, pericardiectomy can reduce the need for pericardiocentesis in people without HIV coinfection (14). No trials measuring the effectiveness of pericardiectomy in patients with HIV coinfection were found.

Mortality associated with the disease, if adequately treated and regardless of its stage, is between 8-17%; in HIV-positive individuals, mortality increases to between 17-40% (5,14). If untreated, the average survival is 3.7 months; only 20% of patients are still alive after 6 months (15, 16).

CONCLUSION

Tuberculous pericarditis should be suspected in patients exposed to silica who present with hemorrhagic pericardial effusion. Therefore, the recommended diagnostic approach when it is clinically suspected includes imaging studies such as echocardiogram and contrast tomography of the thorax to confirm the presence of typical findings in the pericardium, such as hemorrhagic pericardial effusion, smooth pericardial thickening, thick pericardial calcifications, and tuberculosis in other organs (either by imaging or by microbiological analysis). The final diagnosis is made based on the initial detection of hemorrhagic pericardial effusion by means of diagnostic imaging, the detection of positive ADA, PCR or positive cultures in pericardial fluid, and biopsy of pericardial tissue demonstrating the presence of tubercle bacilli or granulomas with caseous necrosis in the absence of bacilli, as was the case in our patient.

ETHICAL CONSIDERATIONS

The patient's informed consent for the publication of their clinical data and images derived from the medical care process was obtained for the preparation of this case report. The confidentiality of the information was guaranteed at all times.

CONFLICTS OF INTEREST

None stated by the authors.

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