RELATO DE CASO

EPITHELIOID GRANULOMA IN PLEURA BY BIOPSY AS A DIAGNOSTIC TOOL FOR PLEURAL TUBERCULOSIS: A CASE REPORT

GRANULOMA EPITELIÓIDE EM PLEURA POR BIÓPSIA COMO INSTRUMENTO DIAGNÓSTICO DE TUBERCULOSE PLEURAL: UM RELATO DE CASO

Lucas Yago Souza Schmidt[1], Dowglas Pereira de Oliveira[1], Valdair Lopes de Oliveira Filho[1], Karitas Rocha Cardoso[2].

ABSTRACT

Tuberculosis, despite all the research and technological inputs developed in recent years, remains one of the most frequent causes of pleural effusion, especially in developing countries such as Brazil. In immunocompetent individuals, pleural tuberculosis is the most common form of extrapulmonary tuberculosis. The diagnosis of this form of the disease continues to be the detection of Mycobacterium tuberculosis in pleural fluid, or in pleural biopsy samples, either by microscopy and / or culture, and the histological existence of granulomas in the pleura, a valid instrument for the determination of the disease , although the agent is not isolated. We present in this paper the report of a male patient, 76 years old, referred to the Public General Hospital of Palmas (HGPP) in december 2018, with clinic suggestive of Tuberculosis and absence of isolation of M. tuberculosis in a classical research – acid fast bacilli (AFB) and cultures. The visualization of the granulomatous reaction in the pleura, in association with the clinic, proved to be safe for establishing the diagnosis and conduct.

Keywords: tuberculosis; pleural tuberculosis; Mycobacterium tuberculosis; tuberculosis diagnosis.

RESUMO

A tuberculose, apesar de todas as pesquisas e insumos tecnológicos desenvolvidos nos últimos anos, continua sendo uma das causas mais frequentes de derrame pleural, especialmente em países em desenvolvimento como o Brasil. Em indivíduos imunocompetentes, a tuberculose pleural é a forma mais comum de tuberculose extrapulmonar. O diagnóstico desta forma da doença continua sendo a detecção de Mycobacterium tuberculosis em líquido pleural, ou em amostras de biópsia pleural, seja por microscopia e / ou cultura, tendo-se demonstrado a existência histológica de granulomas na pleura, instrumento válido para determinação da doença, ainda que não isolado o agente. Apresentamos neste trabalho o relato de um paciente, masculino, 76 anos, encaminhado ao Hospital Geral Público de Palmas (HGPP) em dezembro de 2018, com clínica sugestiva de Tuberculose e ausência de isolamento de M. tuberculosis em algoritmo clássico de investigação – pesquisa de bacilo álcool- ácido resistente (BAAR) e culturas. A visualização de reação granulomatosa em pleura, em associação com a clínica, se revelou segura para estabelecimento do diagnóstico e conduta.

Palavras-chave: tuberculose; tuberculose pleural; Mycobacterium tuberculosis; diagnóstico de tuberculose.

ACESSO LIVRE

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Instituição: [1]Graduating the Bachelor of Medicine course at the Federal University of Tocantins, Palmas, Tocantins, Brazil. [2]Graduated in Medicine by the University of Gurupi and Medical Resident in Clinical Medicine by the Federal University of Tocantins, Palmas, Tocantins, Brazil.

Autor correspondente: Lucas Yago Souza Schmidt; lucasschmidt1901@hotmail.com

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INTRODUCTION

Tuberculosis (TB) remains a public health challenge, especially in underdeveloped countries such as Brazil, demanding high investments annually. The World Health Organization (WHO) estimates that there were 9.6 million TB cases worldwide in 2014. Brazil, along with 21 other developing countries, is responsible for about 80% of TB cases[1].

The pleural effusion found in TB is a result of infection of the pleura by *Mycobacterium tuberculosis* and characterized by an intense chronic accumulation of inflammatory and liquid cells in the pleural space, thus being an exudate with a classical predominance of mononuclear forms [2 14].

The organization of exsudate cells in the form of circumscribed aggregates gives rise to corpuscles called granulomas, resulting from the proliferation of macrophages that mature by assuming an epithelioid pattern, in an attempt to contain the bacillus and giving rise to patterns called G*iant cells* or *Langerhans cells* [3].

It is established in the world literature that even with the application of research and technological inputs developed in recent years and being the patient hard to investigate, about 11-20% of cases of pleural tuberculosis are not diagnosed, reflecting mechanization in the investigation process - especially in health services not specialized in the diagnosis of thoracic diseases[4].

In the diagnostic algorithm, instruments such as direct sputum smear culture and sputum culture, and procedures such as thoracentesis, closed needle pleural biopsy, thoracoscopy and thoracotomy are needed to establish this form of disease and the cause of pleural effusion – being the last two more invasives[4, 9]. The materials for examination resulting from these procedures are pleural fluid, fragments of the parietal and/or visceral pleura, as well as the pulmonary parenchyma[4, 9].

In Brazil, pleural effusion represents the most frequent manifestation of extrapulmonary tuberculosis in individuals considered to be immunocompetent, with the most common ganglionic form in seropositive HIV[5, 11]. Tuberculosis pleural effusion occurs in approximately 30% of TB cases [1, 4].

OBJECTIVE

To report the case of a patient with a clinic compatible with tuberculosis and pleural effusion, without confirmation of *M. tuberculosis* by bacteriological examination and anatomopathological study of biopsy specimens, the histopathological report of epithelioid granulomas in pleura being the diagnostic factor.

METHODS

The information contained in this study was obtained through a review of the medical record, interview with the patient, photographic record of the diagnostic methods to which the patient was submitted and literature review. The search for virtual articles occurred through the *Pubmed* platform, using the descriptors *Tuberculosis, pleural tuberculosis, Mycobacterium tuberculosis* and *Tuberculosis diagnosis*. The patient was duly informed about this article and signed an informed consent form.

CASE REPORT

Anamnesis

J.A.L., male, 76 years old, referred from the municipality of Redenção - Pará to the Pneumology Service of the Public General Hospital of Palmas (HGPP) due to the complaint of intense dyspnea 20 days ago, accompanied by chest pain in the right hemithorax, productive cough, generalized asthenia, and loss weight of 12 kg in the last 40 days. No history of fever.

Non-alcoholic, while historical consumption of two packs of firearm per day for about 12 years, having suspended use 40 years ago.

As comorbidities, reporting systemic arterial hypertension (SAH) for approximately 30 years, with continued use of acetylsalicylic acid (ASA) and Beslat of amlodipine (Pressat ®), permanent atrial fibrillation and asthma diagnosed 9 years ago, with an average of exacerbation every two years.

Resident of urban zone, home of 10 rooms with wife and eldest son, with no history of deprivation of liberty. Relatives with no experience of cough, chest pain, fever and recent weight loss.

Physical Exam

Regular general condition, pain fascias, with blood pressure of 130 x 80 mmHg. Respiratory auscultation with bilaterally present vesicular murmurs diminished in right base, with discreet snores in both bases, respiratory rate of 22 incursions per minute. No inspiratory effort by the use of accessory muscles.

Signs of good peripheral perfusion without edema and cyanosis. Absence of lymphadenopathy at the retroauricular, occipital, cervical, supraclavicular and axillary examination.

Conduct

Under the diagnostic hypothesis of Tuberculosis, requested a chest X-ray in postero-anterior position and profile, AFB survey in 02 samples and culture for mycobacteria, in addition to laboratory tests for the application of Light Criteria (TABLE 1), which takes into consideration laboratory parameters to determine the inflammatory character of the fluid [6].

LIGHT'S CRITERIA

PARAMETERS	TRANSUDATE	EXUDATE
Pleural fluid protein divided by serum protein	<0.5	≥0.5
Pleural fluid LDH divided by serum LDH	<0.6	≥0.6
Pleural fluid LDH ≥2/3 the upper	NO	YES

limit of normal serum LDH		

TABLE 1 - Light's Criteria: Exudative Effusions will have at least one or more of the following: Pleural fluid protein / Serum protein >0.5. Pleural fluid LDH / Serum LDH >0.6. Pleural fluid LDH > 2/3 * Serum LDH Upper Limit of Normal. **Interpretation: the presence of one or more criteria configure an exudative fluid.**

Complementary Exams

The chest radiograph requested (IMAGE 1) showed good penetration, clavicular symmetry, no signs of hyperinflation (rectification of intercostal spaces), normal cardiac area, vascular weft intensification, and right pleural effusion. The patient was submitted to thoracentesis of relief and subsequent request of a study of pleural fluid.

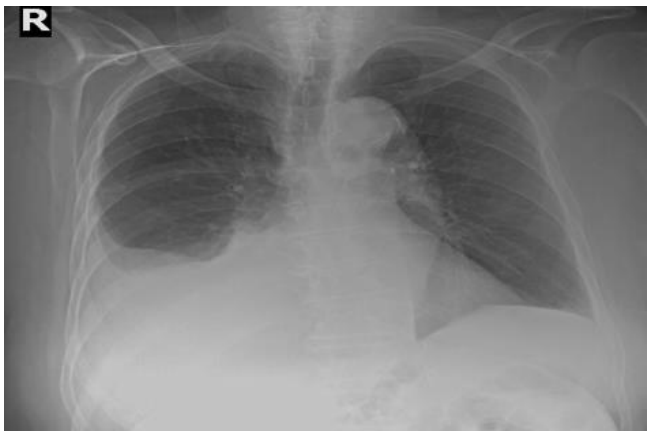

IMAGE 1 - Chest X-ray in postero-anterior incidence showing right pleural effusion.

The material collected was sent to the Laboratory of Bacteriology and also to the Laboratory of Pathological Anatomy for cytology examination. Considering the Criteria of Light, which include the pleural comparison of proteins and lactate dehydrogenase (DHL) with serum value, exudate was established with a predominance of mononuclear forms - characteristic of cavitary effusions due to tuberculosis. The values found are summarized in TABLE 2.

CYTOLOGICAL ANALYSIS OF PLEURAL FLUID	
PARAMETERS	**RESULTS**
Volume	40.0 mL
Apperance / color	Cloudy / yellowish
Redbloodcells	3960 / UL
Polymorphonuclearcells	22%
Mononuclear cells	78%
Glucose	78 mg / dL
Proteins	4.3 g /dL
Albumin	2.1 g / dL
Amylase	19 IU / L
DHL	673 IU / L

TABLE 2 - Parameters studied from the cytological analysis of the pleural fluid of J.A.L, containing their respective values.

The laboratory showed a serum protein value of 3.2 g / dL, being favorable the ratio between pleural proteins and serum proteins > 0.5 (0.74) and determining the liquid as an exudate, since it is necessary that 01 or more criteria are identified for the identification of the inflammatory fluid [6] – according to TABLE 1.

The hypothesis was not corroborated by the BAAR survey, both of which were negative. A third sample was also requested, also without isolation of the bacillus. The culture for mycobacteria did not show presence of the agent. The service did not have a rapid molecular test for TB (TR-TB), a highly specific test (98%) for *M. tuberculosis*, and to show resistance to rifampicin [7, 8].

For biopsy confirmation of pleural effusion, video-assisted thoracoscopic biopsy, invasive procedure with two incisions in the chest and simultaneous video camera and biopsy forceps were indicated[9]. Under direct camera vision, located area of interest and removed 04 pieces, addressed to histopathological study and general cytology. Biopsy revealed exudative tissue with multiple granulomas with and without caseing necrosis and no evidence for specific agents.

Evolution

In view of the existence of granulomas in exudative tissue with predominance of mononuclear cells and compatible clinic, was diagnosed pleural tuberculosis supported by literature and basic TB regimen was started with rifampicin, isoniazid, pyrazinamide and ethambutol - given the hepatotoxicity of the first three drugs, there is evidence of good hepatic function in the patienty [10].

After hospital discharge and oriented to the maintenance of the treatment for a period of six months (the last four with a double regimen of rifampicin and isoniazid), the patient returns after 30 days in outpatient clinic of Pneumologywith a good general appearance, with a significant regression of pleural effusion (IMAGE 2) and without complaints of dyspnea, chest pain, cough and weight loss.

Requested HIV rapid test, non-reagent, according to WHO recommendation that HIV testing be offered to all people with TB [11].

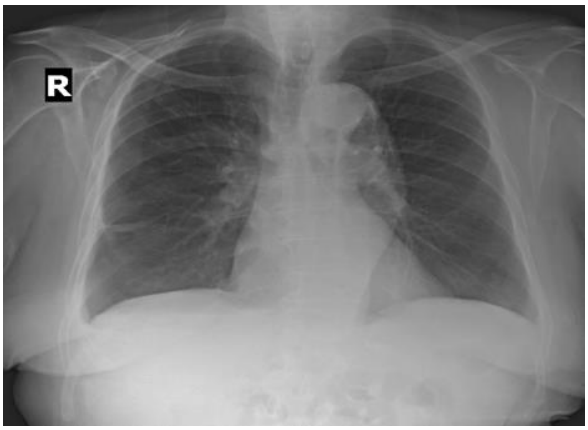

IMAGE 2 - Chest X-ray in postero-anterior incidence evidencing significant regression of right pleural effusion.

DISCUSSION

It is well established that the etiological diagnosis of certainty of pleural tuberculosis requires demonstration by *M.*

tuberculosis bacillus in culture of sputum, pleural fluid or pleural biopsy samples[2, 12], which can be assumed with reasonable certainty by concentration adenosine deaminase (ADA) greater than 40 U/L or the presence of interferon gamma in pleural fluid, being essential a clinical and epidemiological history compatible with the natural history of the disease[13].

In clinical practice, the absence of isolation of the bacillus through traditional diagnostic methods signals other valid instruments for the identification of the disease, being the granuloma of epithelioid cells in pleura usually compatible with tuberculosis, since this is responsible for more than 95% of the pleural granuloma cases. In this way, the presence of pleural granulomas is accepted as a diagnosis of tuberculosis in the absence of immunosuppression or in the absence of pulmonary disease suggestive of sarcoidosis, rheumatoid arthritis, nocardiosis or fungal disease, since these conditions are also granulomatous [14].

The finding of the presence of epithelioid granulomas in the pleura is possible by histopathological examination after biopsy of the parietal pleura, which may occur with the use of needle with closed biopsy or via thoracoscopy - the last indicated in cases such as the patient, wherein less invasive techniques have not been sufficient for diagnosis[4, 9]. The copositiveness of the histopathological examination is established between 50% and 97% of cases with granulomas present in the inflammatory infiltrate, caseous necrosis or presence of acid-fast bacilli (AFB)[12, 15]. The copositiveness of the exam is between 39% and 80% of cases when the culture for mycobacteria is performed on pleural pieces from the biopsy [12, 15].

The predominant anatomopathological pattern in pleural tuberculosis is the formation of complete or incomplete granulomas, both of which are related to the diagnosis of TB[14]. The complete granuloma consists of lesion resulting from macrophage proliferation with epithelial cell-like differentiation involving nucleus of caseous necrosis, with minimal bacillary multiplication in this type of lesion. Incomplete granuloma consists of central suppuration accompanied by polymorphonuclear cells and involved by granulomatous inflammatory reaction with variable combinations of polymorphonuclear cells, lymphocytes and plasma cells, without caseification[3, 14].

The paucibacillary form, often found in this form of the disease, is associated with the absence of the demonstration of *M. tuberculosis* in the researched materials, corroborating the failure of the etiological investigation of pleural effusion initially[2]. The low sensitivity of conventional tests can't be ruled out, established in less than 10% for AFB and around 30% for mycobacteria culture[12, 15].

Pleural effusion is usually self-limited, with spontaneous absorption of the fluid between 4 and 16 weeks, however the absence of treatment tends to contribute to future forms of active disease[2]. The objectives of the treatment of pleural tuberculosis for the patient are therefore useful to prevent the subsequent occurrence of active tuberculosis, the relief of symptoms, as well as avoiding the formation of a fibrothorax – fibrous tissue formation and adhesions. Radiographic resolution may be safely associated with asymptomatic clinical outcome[2, 16, 17].

CONCLUSIONS

The case reported and literature review brought forth epithelioid granuloma in pleura as a considerable tool for the diagnosis of pleural TB. Detection of the disease is often impaired or even incomplete due to the non-isolation of *M. tuberculosis*, burdening the time to establish the conduct[4]. Diagnostic damage and lack of adequate treatment are directly linked to future forms of active disease[2, 16].

Considering the pathophysiological mechanism of pleural TB, granuloma is associated with tuberculosis in about 95% of the cases in which it is present in the pleura, safely configuring the diagnosis, when there is clinical symptoms of coughing, fever, dyspnea, chest pain and weight loss and absence of immunosuppression[14] – which is clearly observed in the case reported.

Since the disease is paucibacillary, epithelioid granuloma is further strengthened as a diagnostic tool, since it is expected that there will be failure of confirmation of the agent in the traditionally requested laboratory subsidies – AFB and cultures[2, 15].

Understanding the granulomatous formation in pleura as an anatomopathological pattern intrinsic to the containment of the tuberculous bacillus and associating its presence with the existence of pleural TB is therefore to contribute with an increase in the detection rates of the disease and consequently, symptomatic relief and improvement of the quality of life.

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