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RIFAMPICIN-RESISTANT PERICARDIAL TUBERCULOSIS ASSOCIATED WITH LUNG CANCER

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Abstract: Purpose: to report a case of *Rifampicin-resistant Pericardial Tuberculosis* with concomitant diagnosis of bronchogenic CA in a patient with no history of immunodeficiencies. **Method:** information was obtained through review of the medical record, interview with the patient, photographic record of the diagnostic methods to which the patient was submitted and review of the literature. **Conclusions:** The reported case and published publications bring to light the discussion of the therapy of a complex situation that is the disease *Pericardial Tuberculosis Rifampicin* resistant in patients with lung cancer and showed that, despite the low simultaneous occurrence of the two diseases in question, in the same patient, satisfactory results from the treatment of *Rifampicin-resistant Pericardial TB can* be obtained by the treatment recommended by Informative Note N9/2021 -CGDR/DCCI/ SVS/MS, in parallel with the treatment of lung cancer, in order to provide the patient with symptomatic relief, healing and improvement of their quality of life.
Keywords: *Mycobacterium tuberculosis rifampicin*. Pericardial tuberculosis, Lung cancer.

INTRODUCTION

Tuberculosis (TB) is one of the main causes of morbidity and mortality worldwide. Diagnosis, treatment, and prevention of TB has become more complex due to resistance to antituberculous drugs (NAHID et al., 2019). Among the different types of Tuberculosis (TB), pericardial TB is a rare manifestation of extrapulmonary TB. The predominant symptoms, although nonspecific, are cough, dyspnea, chest pain, night sweats, orthopnea, weight loss and lower limb edema. The most frequent signs are cardiomegaly, pericardial rub and tachycardia. It can also include paradoxical pulse, hepatomegaly, jugular stasis, pleural effusion. Tuberculous pericarditis is an important complication of tuberculosis (TB); the diagnosis could it be difficult to establish and is often delayed or missed, resulting in late complications such as constrictive pericarditis and increased mortality. Advanced management options of the disease are limited (SCHLUGER et al., 2021).

Initially, tuberculosis can be confused with lung cancer, as some symptoms are similar and lesions on imaging tests can also be similar in some cases. "In both diseases, the patient may experience weight loss, coughing up blood and shortness of breath. On the other hand, on tomography, sometimes a cavitated lesion, which is a classic characteristic of tuberculosis, can also be caused by some types of cancer" (SALIM (2019). According to the National Cancer Institute (INCA, 2022), there were between the years 2020 and 2022 a number of cases of 17,760 cases/year, being the third most incident type of cancer and the first cause of death from cancer among men. In the world, of every 100 cases of cancer related to work, 54 to 75 cases are lung cancer. Despite the similarities of symptoms, Tuberculosis (TB) and CA are different diseases, where tuberculosis is caused by a bacterium, while cancer involves other causes such as cigarette smoking, exposure to toxic substances and genetic inheritance", and TB does not can determine the incidence of CA in patients, according to SALIM (2019). However, the treatment of cancer through radiotherapy and chemotherapy, by conditioning the patient's immunity weakened by the oncological treatment, can favor the appearance of tuberculosis, infections such as recurrent pneumonia, among other complications that can worsen the health of the patient.

The diagnosis of pericardial Tuberculosis (TB) is based mainly on the demonstration of the tubercle bacillus in the pericardial

material, through biopsy, which is more sensitive than pericardiocentesis. Therapy is performed using a fixed-dose regimen combined with antituberculosis for 6 months, which has proven to be highly effective. However, management of drug-resistant TB can be difficult and may require the use of second-line drugs and/or surgical resection. The management of these patients must be carried out by individuals with experience in this area or in close consultation with these people, in the context of a supportive public health infrastructure (NAHID et al., 2019; C URRY INTERNATIONAL TUBERCULOSIS CENTER, 2016). Good patient outcomes depend on prompt and accurate diagnosis along with administering appropriate therapy with close monitoring to ensure adherence to the treatment regimen and patient safety. The treatment of rifampicin-resistant, multidrug-resistant and extensively drug-resistant TB is a rapidly evolving field of research. Precise treatment regimens must be informed by regional guidelines, as well as drug availability, local disease burden and local TB Resources program.

OBJECTIVE

Report a case of *Pericardial Tuberculosis Rifampicin Resistant* with concomitant diagnosis of bronchogenic AC in a patient with no history of immunodeficiencies.

METHOD

The information was obtained through review of the medical records, semiological evaluation and evolutionary monitoring of laboratory data and images. of the patient, photographic record of the diagnostic methods to which the patient was submitted and review of the literature.

CASE REPORT

ANAMNESIS

Patient BMA, male, 63 years old, was transferred to ‘’Universidade Hospital Júlio Muller” (HUJM), of ‘’Universidade Federal do Mato Grosso” (UFMT) on 00/00/2022, after medical appointments at other health units. On admission, he reported dyspnea and pain in the right hemithorax for 2 months, without irradiation, denying triggering factors, with worsening after long periods of sitting, with relief after using dipyrone and Alenia (formoterol) before bedtime. He reported that for 3 days he had been presenting with a fever (without measurement), predominantly in the afternoon. He reported cough with sputum for 2 months, secretive at first, and later becoming dry. He showed hyporexia, with weight loss of 6 kg in the last 2 months, having started with progressive asthenia 1 month ago and limitation of daily activities due to dyspnea. He denied gastrointestinal or urinary disorders. He complained of persistent insomnia, with manifestation of chest pain when lying down. He referred LL edema for 5 days with progressive worsening. He denied smoking and alcoholism. He denied other comorbidities and drug allergies. He denied a history of Cancer in family members and claimed to have lived for more than 20 years in a rural area, in a wooden house, with frequent contact with smoke from petroleum products, in addition, he stated that he had worked as a mason for more than 30 years, with intense contact daily with sand and cement particles.

PHYSICAL EXAM

Upon admission: Regular general condition, lucid, oriented in time and space, colorless 2 +/4+, dehydrated, acyanotic, anicteric, afebrile, tachydyspneic on room air, with the need for oxygen supplementation by nasal catheter 3l/min, to maintain oxygen saturation in peripheral oximetry above 96%.

She had a large number of painless lymph nodes on palpation of fibroelastic consistency in the anterior cervical region, mainly on the right, without phlogistic signs. Jugular turgor present. On pulmonary auscultation, he had a universally audible diminished vesicular murmur with the presence of crackling rales in the lung bases bilaterally, with signs of respiratory distress, drawing of the furcula and intercostal bones. atypical chest. Cardiac auscultation showed regular heart rhythm, in two stages, hypophonetic sounds, absence of clicks, crackles and audible murmurs. She had a flaccid abdomen, present bowel sounds and no visible peristalsis, tympanic, free traube, painless on palpation and no signs of peritonitis, absence of viceromegaly or palpable masses. He had limbs with no pain when moving the main joints, no edema, calves without swelling. Palpable peripheral pulses – paradoal during inspiration; without changes in capillary refill. On neurological examination, patient Glasgow 15, awake, isochoric and photoreactive pupils, no signs of meningeal irritation.

DIAGNOSTIC HYPOTHESIS

A diagnosis of bronchogenic carcinoma, extrapulmonary tuberculosis resistant to rifampicin (nodal and pericardial) and wasting syndrome was made.

CONDUCT AND EVOLUTION

BMA patient, 63 years old, with a history of dyspnea and pain in the right hemithorax, associated with a weight loss of 6 kg in 2 months, admitted for etiological investigation. Upon admission, a patient with tachydyspnea was observed using auxiliary muscles, requiring the use of oxygen, initially through a nasal catheter (low flow), later evolving to oxygen therapy through a high-flow mask, 12l/min. With the absence of fever in the period, the use of Piperacillin + tazobactan DI: 06/07/2022 (ending on 06/18/2022), Ceftriaxone + Azithromycin (D1 06/06/22) + Levofloxacin 500 mg - 1 time a day was started day (used it for 11 days / ended on 06/05/22), Aerolin (salbutamol) 100 mcg SOS (used for 3 – 4x/day) + Acetylcysteine 600 mg – 1x/day in the morning + Dipyrone SOS. On 05/1/2022, the ECG was within normal limits. Chest CT (Performed on 05/11/22) showing small/moderate bilateral pleural effusion. Pericardial effusion. Bronchial parietal thickening inferring inflammatory bronchopathy. Diffuse thickening of the interlobular septa in the upper lobes inferring some degree of pulmonary vascular congestion. Multiple mediastinal lymph node enlargement with contrast enhancement and hypodense/necrotic center, scattered throughout the mediastinal chains and aortopulmonary window, some coalescing in the hilar regions. Fibroatelectatic streaks in the middle lobe, lingular segment of lung bases. Diffuse thickening with an infiltrative aspect in the peribronchovascular region on the left, in the transition between the lingular segment and the apical segment of the left upper lobe, with contrast enhancement. It followed with a request for some laboratory tests of sputum samples, which presented: on 05/13/22, AFB negative // fungi absent ; on 05/16/22, Tuberculosis molecular test (2 samples): not detectable ; on 06/06/22 - (admission): Pro calcitonin 0.2, HIV NR/ HBsag NR/ VDRL NR/ HCV NR/ albumin 3.0/ globulin 3.4/ A/G ratio 0.8; on 06/07/22 - Pericardial Fluid: BAAR: neg LDH: 179 total proteins: 4.2 glucose: 111 // direct fungal research: negative ; on 6/8/22 - Pro-calcitonin: 1.5 (previous: 0.2) ; on 06/17/22, HB 11.1// LEUCO 22790 STICKS 0 SEG 19599// PLAQ 216 MIL// TGP 18 // ALBUMINA 2.6 // TGP 28 // CAT 7.5 // CREATININE 1.1 // PHOSPHORUS 2 // GLUCOSE 96 // POTASSIUM 3.3// PCR 4.23// SODIUM 140// UREA 39// BT 0.90//;

in 06/17/22, Adenosine Deaminase (ADA) from pericardial fluid – 9.5 ; on 06/18/22, Procalcitonin - 0.1 ; on 06/21/22, hb 11.8/ ht 36.6%/ qt 265 000/ leuco 30 720/ b 3/ sec 90%/ LDH 180/ ur 34/ creat 1.2/ sodium 143/ pots 4, 1/ mg 2/ uric acid 3.9/ TGO 51/ TGP 37/ BD 0.4/ BI 0.4/ BT 0.8/ INR 1.22 / aPTT 30.1/ ionic ca 4.7; in 06/23/2022, Rapid molecular test - Tuberculosis (material: cervical lymph node) - DNA for Mycobacterium Tuberculosis: traces detected ; on 06/25/22: TGO 37 / TGP 26 / PCR 5.70 / Ur 43 / Cr 1.3 / Na 137 / K 4.5 / Mg 2.0 / Hb 10.4 / Ht 33.3 / Leuco 20,500 (N 88% / B 3% / L 3% / M 6%) / MDT 177,000 ; on 06/30/2022: Hb: 10.7 Ht 33 leuco 19760 (rods 198 segmented 16598 eosinophils 198 lymphocytes 1778// TGO 20// CREATININE 1.2// POTASSIUM 3.6// UREA 54// PCR 2.27// NA 138 ; Routine pleural effusion fluid: serous, NUCLEADED CELLS: 97 / mm^3 / POLYMORPHONUCLEAR: 27% / MONONUCLEAR: 73% RED CELLS: 0 / mm. Biochemistry: pH: 8.0 / GLUCOSE: 110.0 mg/dL / TOTAL PROTEIN: 3.0 g/dL / ALBUMINA: 1.5 g/dL /LDH: 88.0 U/L ; Culture for bacteria: negative; on 06/14/2022, a new chest CT scan was performed, showing adenomegaly in the visualized portions of the neck and mediastinum, with involvement of both pulmonary hila, some with central necrosis Atelectasis / consolidation of the lung parenchyma in the left lower lobe Bilaterally large pleural effusion and moderate pericardial effusion Thickening of the interlobular interstitium, more evident in the left lung, probably related to interstitial edema and/or lymphangitis), evidencing pericardial effusion and specks Diffuse swelling with an infiltrative aspect in the peribronchovascular region on the left, in the transition between the lingular segment and the apical segment of the left upper lobe, with contrast enhancement. Transbronchial biopsy was performed on 05/15/2022, Immunohistochemical Panel: Histological findings favor adenocarcinoma of the primary pulmonary site, infiltrating the airway wall with vascular embolization. Transbronchial biopsy on 05/15/22 – anatomopathological examination, fragments of the airways and lung parenchyma with infiltration by large cell carcinoma with lymphatic embolization of submucosal vessels, associated with mild inflammatory infiltrate and fibrosis. Absence of granulomas. The analysis of BAAR and fungi using the Ziehl´-Neels en and Grocott method was negative, with a diagnosis of large cell carcinoma infiltrating the airway wall with vascular embolization (lymphatic carcinomatosis). Suspended Tazocin on 06/18/22 with improvement in signs and symptoms (absence of fever, improvement in dyspnea) and laboratory tests (Procalcitonin 0.1). An echocardiogram was performed after detection of pericardial effusion on chest CT and citrine-yellow pericardial fluid drainage (20 ml), whose diagnostic investigation resulted in characters: positive ADA; Genexpert positive for Mycobacterium Tuberculosis/Rifampicin resistant, treatment of pericardial Tuberculosis being initiated with a recommended scheme, according to Informative Note N9/2021-CGDR/DCCI/ SVS/MS: Levofloxacin 1g /day, Terizidone 750mg/day, Linezolid 600mg/day, Bedaquiline 400mg/day, Lenia 12/200 2x a day, Enoxaparin 40mg SC - DVT/VTE prophylaxis, Prednisone 20mg - 3 tablets in the morning - Due to pericardial TB (BRASIL, 2021). Continuing the investigation for extrapulmonary forms of Tuberculosis, as well as for programming the staging of Bronchogenic CA, a relief/diagnostic thoracocentesis was performed with the withdrawal of 1 liter of light-yellow liquid material was sent for analysis on 06/23/2022. After oncological evaluation - Oncology Opinion, described below, two lymph nodes in the right cervical region are removed by the

general surgery/oncology team - Material sent for analysis on 06/23/22 with positive result for ganglionic TB (Request: 220103001022) and investigation of neoplastic cells (Request: 226090), indicating Metastatic Non-Small Cell Carcinoma in lymph node (Absence of extra-cellular invasion). BAAR research using Ziehl-Neelsen staining was negative.

Opinion of the Oncology: in view of the possibility that the disease is E: III C and that would change the form of treatment (instead of QT 1 palliative line for E: IV, consolidation radiochemotherapy was indicated), it is suggested to continue with the least invasive workup possible: a).excisional biopsy of the cervical lymph node for new AP and AFB research; b) diagnostic thoracocentesis with sending of material to oncotic cytologist plus AAR B investigation. It was also suggested to reassess the Infectology department if all tests did not show TB: suspend treatment and consider everything as a metastatic site. It was requested by the IHC for a definitive diagnosis, ruling out Spinocellular and also research for EGFR mutation/ALK ROS Fusion (such as adenocarcinoma in view of the possibility of targeted therapy in positive cases). It was emphasized on the request for a vacancy for CACON - SUS of reference: large cell carcinoma is one of the subtypes of non-small cells and must be treated as Adenocarcinoma if IHT does not come out in time.

On 05/13/22, a bronchial mucosal biopsy was performed: fragments of the bronchial wall partially covered by pseudostratified cylindrical ciliated epithelium with moderate fibroplasia of the subepithelial connective tissue. Presence of clusters of distorted and fragmented seromucous bronchial glands. Alveolar (pulmonary) tissue with mild vasocongestion and foci of anthracosis. Abundant amount of associated fibrinohemorrhagic material.

On 06/07/2022, an electrocardiogram was performed showing regular sinus rhythm, low QRS complex amplitude in precordial leads. It was presented by the Echocardiogram at the bedside - (without report) - presence of moderate pericardial effusion; EF 66.4%; IVSTd 6.8 mm, LViDd 52.5, LVPWTd 7.3 mm, EDV 132.4 mL, LV MASSd 100 g, LVIDs 33.1 mm; ESV 44.5 mL, SV 87.9 mL, FS 37% - Transesophageal echo due to anterior thickening of the mitral valve observed in Echo at the bedside on 06/08/2022.

CT of the total abdomen was requested: bilateral renal microlithiasis. Slight nonspecific water distention in colonic loops.

Thoracentesis and cervical lymph node biopsy performed on 06/23/22 showed, respectively, Doubtful focal cell atypia whether degenerative or neoplastic and Metastatic non-small cell carcinoma in lymph node, with absence of extra-capsular invasion. BAAR research by Ziehl-Neelsen staining was negative.

Corticosteroid therapy reduction was programmed after 30 days (60mg/day to 30mg/day - day 07/07/22).

A transfer request was made to the reference hospital - Mato Grosso Cancer Hospital. Maintaining therapeutic procedures, the patient remains in good general condition, eupneic on room air, hemodynamically stable until transfer.

PROGNOSIS AND FOLLOW-UP

This is a case of difficult diagnosis that involved the collection and qualified analysis of samples, such as pericardial fluid and bronchoalveolar lavage. The BMA patient was immediately diagnosed and treated for Rifampicin-resistant Pericardial Tuberculosis, according to Informative Note N9/2021-CGDR/DCCI/SVS/MS (BRASIL, 2021), while awaiting transfer to the Cancer Hospital of the State of Mato Grosso, with satisfactory response in the first week, demonstrating

clinical and laboratory improvement after introduction of the recommended medication, with improvement in the breathing pattern, oxygen weaning, demonstrating that the correct management of the case together with the correct use of the drugs recommended for the treatment, improves the strategy of cure for tuberculosis in a timely manner.

DISCUSSION

The patient in question presented with tachydyspnea while using accessory muscles, requiring the use of oxygen, initially through a nasal catheter (low flow), later evolving to oxygen therapy through a high-flow mask, 12l/min. With the absence of fever during the period, the use of Piperacillin + tazobactan was started. The chest CT scan showed pericardial effusion and bronchial parietal thickening, inferring inflammatory bronchopathy. Diffuse thickening of the interlobular septa in the upper lobes inferring some degree of pulmonary vascular congestion. Diffuse thickening with an infiltrative aspect in the peribronchovascular region on the left, in the transition between the lingular segment and the apical segment of the left upper lobe, with contrast enhancement. The histological findings of the transbronchial biopsy, Immunohistochemical Panel, signaled adenocarcinoma of the primary lung site, infiltrating the airway wall with vascular embolization. It presented fragments of the airways and lung parenchyma with infiltration by large cell carcinoma with lymphatic embolization of submucosal vessels, associated with mild inflammatory infiltrate and fibrosis. Absence of granulomas. With improvement in signs and symptoms (absence of fever, improvement in dyspnea), treatment with Piperacillin + tazobactan was discontinued. In the investigation of pericardial effusion, AFB and fungi were checked using the Ziehl Neelsen and Grocott method, with negative results. However, he was ADA positive; Genexpert positive for Mycobacterium Tuberculosis/Rifampicin resistant and Pleural fluid culture for small/moderate bilateral pleural effusion. After the patient was diagnosed with Rifampicin-resistant Pericardial Tuberculosis, alternative treatment was initiated in accordance with Information Note N9/2021-CGDR/DCCI/SVS/MS, which provides for updating of Recommendations for the treatment of drug-resistant tuberculosis with availability of bedaquiline and delamanida. The investigation for extrapulmonary forms of Tuberculosis showed a positive result for ganglionic TB. For the programming of bronchogenic CA staging, the investigation of neoplastic cells indicated metastatic non-small cell carcinoma in the lymph node (absence of extracellular invasion) and a BAAR investigation by Iehl-Neelsen staining was negative. Marchiori et al (2021) after observing negative AFB, elevated ADA, tomographic appearance of the lung lesion and clinical condition of the patient, started the treatment for TB and showed a satisfactory response to it. The authors point out that in cases of suspected tuberculous pericarditis, the dosage of ADA must be mandatory, as waiting for the culture of the pericardial fluid, which is not always positive, can significantly delay diagnosis. The diagnosis precocious and the institution of appropriate therapy are key to preventing mortality. JORGE et al. (2018) concluded that in patients with pericarditis in which the clinical and epidemiological features increase the suspicion of pericarditis due to tuberculosis, the treatment by the RIPE scheme associated with corticoids must be carried out even if the tests do not prove the agent presence etiological. RIBAS et al. (2015), when evaluating patients who have been presenting the reported and unexplained symptomatology of pericardial effusion, they must be investigated for pericarditis due to

TB, because although it is a rare condition, TB is an endemic disease and its extrapulmonary forms must be included as a diagnosis differential. Appropriate treatment decreases the risk of progression to a pathology with a high risk of death.

This is a patient who throughout his life was exposed to pollutants from the burning of petroleum derivatives, because he used a kerosene lamp as a light in his residence. In addition to this exposure, patient BMA worked for several years as a mason, for which he was very exposed to dust from cement, lime, sand, among others present on construction sites. It is known that exposure to these inert materials, when inhaled for long periods, can cause respiratory diseases such as Pneumoconiosis and Bronchogenic CA.

The BMA patient, in addition to being diagnosed with Bronchogenic CA, was also diagnosed with Pericardial TB. According to SALIM (2019), initially, tuberculosis can be confused with lung cancer, since some symptoms are similar and lesions on imaging tests can also be similar in some cases. "In both diseases, the patient may experience weight loss, coughing up blood and shortness of breath. As for tomography, sometimes a cavitated lesion, which is a classic feature of tuberculosis, can also be caused by some types of cancer. To investigate whether it is tuberculosis, the microbacteria (causing the disease) is investigated by analyzing the sputum. If it is not conclusive, a bronchoscopy can be performed and, in rare cases, a biopsy of the lesion can be performed. The author emphasizes that Tuberculosis does not lead to Cancer because they are diseases with different causes. Tuberculosis is caused by bacteria, while cancer involves other causes such as smoking, exposure to toxic substances and genetic inheritance. However, those who already have lung cancer must be aware: immunity weakened by oncological treatment can be a fertile ground for the onset of tuberculosis and other complications.

The treatment of cancer through radiotherapy and chemotherapy can harm the lungs, favoring the appearance of tuberculosis and infections such as recurrent pneumonia, which can worsen the patient's health. It can also leave sequelae such as pulmonary fibrosis. It has been suggested that pulmonary inflammation and fibrosis resulting from tuberculosis may induce genetic damage, which may increase the risk of CP. (B ALLAZ & MULSHINE, 2003; ANGELS, 2008). The increased occurrence of CP in patients with tuberculosis may also be linked to the immunosuppression caused by the infection. On the other hand, immunosuppression caused by cancer or chemotherapy may also increase tuberculosis reactivation in patients with solid neoplasms (KIM et al. 2008). SILVA et al. (2013) concluded that most patients with tuberculosis and PC are smokers and that tuberculosis occurred both before and simultaneously with the diagnosis of PC. Non-small cell bronchial carcinoma, especially adenocarcinoma, was the most common histological type.

CONCLUSIONS

The reported case and published publications bring to light the discussion of the therapy of a complex situation that is the disease *Pericardial Tuberculosis Rifampicin* resistant in patients with lung cancer and showed that, despite the low simultaneous occurrence of the two diseases in question, in the same patient, satisfactory results from the treatment of *Rifampicin-resistant Pericardial TB can* be obtained by the treatment recommended by Informative Note N9/2021 -CGDR/DCCI/SVS/MS (BRAZIL 2021), in parallel with the treatment of lung cancer, in order to provide the patient with symptomatic relief, cure and improvement of their quality of life.

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