v. 3, n. 42, 2023

International Journal of Health Science

CASE REPORT: "HEMOPHAGOCYTIC SYNDROME: A RARE INFECTIOUS COMPLICATION STRAIN"

Gabrielli Naiara Vieira Miranda
Doctor graduated by: Universidade José do Rosário Vellano (UNIFENAS) in 2021. Resident Doctor of the Internal Medicine Program at: ``Santa Casa de Misericórdia de Passos`` (2022-2024).
http://lattes.cnpq.br/9030203122060516

Otavio Dias Ferreira
Student studying the 10th period of Medicine at: ``Universidade do Estado de Minas Gerais`` (UEMG) in Passos.
http://lattes.cnpq.br/3978216451078403

Pedro Lucas Magalhães dos Reis
Student studying the 10th period of Medicine at: ``Universidade do Estado de Minas Gerais`` (UEMG) in Passos.
http://lattes.cnpq.br/2873343210707898

Priscila Freitas das Neves
Doctor graduated by: Universidade de Marília (2005). Medical Infectologist by: ``Faculdade de Medicina do Triângulo Mineiro`` (2010), specialist in Prevention and Control of Infection Related to Health Care (Nosocomial Infection). Currently, she is coordinator of the Commission for Control of Infections Related to Health Care (CCIH) at ``Santa Casa de Misericórdia de Passos``/MG. Principal Investigator in national, multicentric Clinical Trials of phases II, III and IV. Professor of the medical course at: ``Universidade do Estado de Minas Gerais`` (UEMG) Passos. MBA in Health Management.
http://lattes.cnpq.br/1570565311323664

Abstract: Objective: This report demonstrates an atypical and severe clinical condition that requires several differential diagnoses. **Introduction:** Hemophagocytic syndrome (hemophacocytic lymphohistiocytosis) is a rare and severe hyperinflammatory and hyperferritinemic immune response related to genetic disorders, lymphoproliferative diseases, collagenosis and infections, usually in immunosuppressed individuals. In rare cases of disseminated tuberculosis, this potentially fatal complication arises. **Case report:** Young, male patient, institutionalized, smoker, admitted due to sudden focal neurological deficit. History of chronic dry cough, weight loss, pleuritic pain and fever predominantly in the morning for 6 months, being treated for pneumonia, with partial response. Cranial tomography showed no changes, but brain MRI revealed nodular lesions with ring enhancement in the left nucleocapsular region. On chest tomography, multiple coalescing nodules distributed bilaterally, compatible with infectious granulomatous disease. Evolved with fever, respiratory distress, pancytopenia, lymphadenopathy, hepatosplenomegaly, liver dysfunction. Non-invasive ventilatory support and broad-spectrum antibiotics were started. Evaluated by hematology, which identified hemophagocytosis and granulomas with central necrosis in the anatomopathological study of the bone marrow. Subjected to bronchial lavage with positive BAAR research. Therefore, hemophagocytic syndrome was diagnosed as a critical complication of disseminated tuberculosis in an immunocompetent patient who survived after treatment. **Conclusion:** Severe forms of tuberculosis such as the reported neurotuberculosis demonstrate a poor prognosis, especially in the face of a rare complication induced in a context of diagnostic delay and disease dissemination. Despite the low survival in the hemophagocytic syndrome, the patient obtained a therapeutic response to dexamethasone and the RIPE regimen, recovering functionality.

Keywords: hemophagocytic syndrome, tuberculosis.

INTRODUCTION

Tuberculosis is highly prevalent in Brazil. Risk factors include HIV co-infection, diabetes, social vulnerability, smoking, alcoholism, malnutrition. [2, 5] Extrapulmonary forms occur by hematogenous or lymphatic dissemination and identification is difficult because AFB and PCR for mycobacteria are not very sensitive in pus, cerebrospinal fluid, lymph nodes and biopsies. Granulomas suggest miliary tuberculosis, which corresponds to the spread of the disease and has a mortality rate of around 80%. It can rarely course with sepsis and hemophagocytic syndrome. [2, 9]

Among the spectrum of miliary tuberculosis, neurotuberculosis is the most serious condition, including meningitis, tuberculoma and spinal arachnoiditis, being an independent factor of death (1, 3) It affects 2% to 5% of immunocompetent patients and 15% of patients with HIV. CSF shows increased protein, normal glucose and pleocytosis with a predominance of lymphomononuclear cells. [3, 5, 9]

Regarding infectious complications, hemophagocytic syndrome is a rare immune and inflammatory disorder, characterized by prolonged and abnormal activation of T lymphocytes, macrophages and overproduction of cytokines, usually in immunosuppressed individuals. The etiology is unknown, but it is related to genetic mutations, viral, fungal, parasitic, bacterial infections, collagenosis, immunodeficiency and malignant tumors. Hyperferritinemia is one of the main markers. [2,9] There is infiltration of lymphocytes and histiocytes mainly in

the bone marrow (hemophagocytosis) and, when the triggering factor is tuberculosis, granulomas are evidenced. The reversal of the underlying cause is superior to immunosuppression, since the latter can worsen the course of tuberculosis, generating the fulminant disseminated form. [8, 9]

CASE REPORT

W.C.S, male, 31 years old, institutionalized, smoker for 12 years (1 pack a day), chronic alcoholic in abstinence and interruption of illicit drug use. Admitted to the Stroke Unit on 04/10/2023 with right hemiplegia and sudden dysarthria. History of persistent dry cough, pleuritic pain, morning fever associated with chills and weight loss, for 6 months and, in the last month, he received treatment for pneumonia, with partial response. He denied headache, sensory alteration, dyspnea and night sweats, as well as contact with individuals with a similar condition. He denied other pathologies, allergies and previous use of injectable drugs. On physical examination, malnourished, right hemiplegic, dysarthric, presence of clonus, irregular heart rhythm, pulmonary auscultation containing crackles and diffuse snoring. Cranial tomography initially showed no alterations. The cerebrospinal cerebrospinal fluid was collected on 04/11/2023 without alterations and fungus research, bacterioscopy and AFB were negative. The neurological investigation continued with brain MRI on 04/13/2023 showing nodular lesions with ring enhancement in the left nucleocapsular region, pons, left anterior lobe of the cerebellum, associated with perilesional edema. Doppler of carotid and vertebral arteries on 04/13/2023 and fundoscopy were normal.

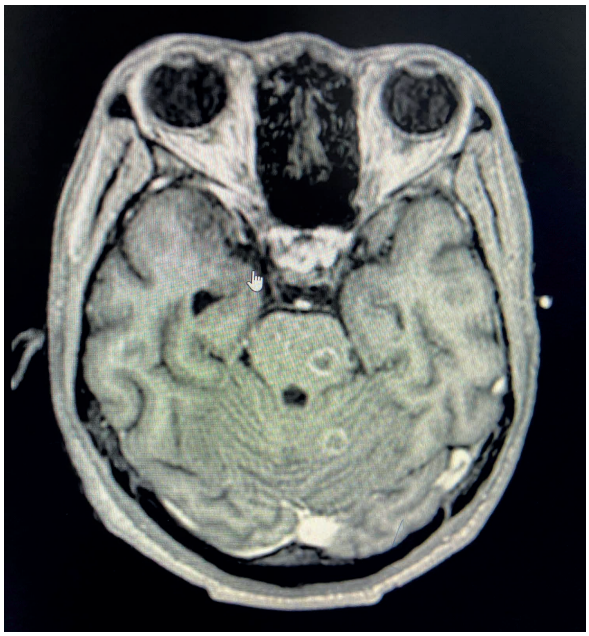
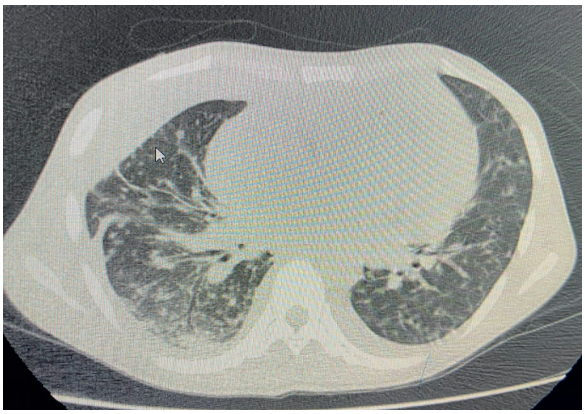


Image 1: Nodular lesion with ring enhancement in the left nucleocapsular region suggestive of tuberculoma demonstrated on brain MRI.

Serologies for HIV 1 and 2, VDRL, hepatitis B and C viruses, ANA and rheumatoid factor were negative. Transesophageal echocardiogram on 04/12/2023 demonstrating arrhythmia, thickened pericardium with mild effusion, absence of intracavitary thrombi or vegetation, preserved ventricular function.

Due to the epidemiological link and history of chronic cough, tuberculosis was investigated. AFB samples in sputum were negative. Contrast-enhanced chest tomography on 04/10/2023, showing multiple nodules distributed bilaterally with a coalescent appearance, forming small consolidations, discreet pleural effusion and mediastinal and paratracheal lymph node enlargement. Findings compatible with infectious granulomatous disease (miliary tuberculosis). Abdominal tomography with contrast on 04/18/2023 demonstrating hepatosplenomegaly, ascites, pleural effusion. Absence of lymphadenomegaly, lytic or blastic bone lesions.

The patient developed fever, respiratory distress, pancytopenia, cervical, inguinal and thoracic lymphadenopathy, hepatosplenomegaly, liver dysfunction. Non-invasive ventilatory support, Dexamethasone and broad-spectrum antibiotic therapy with Linezolid, Amikacin, Levofloxacin and Amphotericin were started. Among the main diagnostic hypotheses were disseminated miliary tuberculosis and lymphoma.



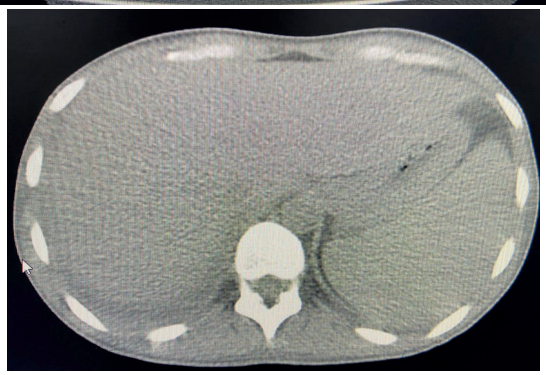


Image 2: Multiple coalescing nodules disseminated in lung fields and presence of an area of consolidation with air bronchogram on chest tomography. Image 3: Significant hepatosplenomegaly on abdomen tomography.

Laboratory tests with elevation of transaminases, canalicular enzymes, C-reactive protein, LDH, ESR and ferritin.

He maintained pancytopenia, especially severe thrombocytopenia, requiring 3 transfusions. Persistence of lymphadenomegaly and liver worsening, cervical lymph node samples were collected, in addition to bone marrow for myelogram, anatomopathological study and cultures. Anatomopathological examination of the cervical lymph node on 04/18/2023 with extensive necrosis; presence of lymphocytes in the periphery, grouping of epithelioid histiocytes, outlining a granuloma, negative fungal and mycobacterial research. Myelogram on 04/19/2023 compatible with hemophagocytosis and anatomopathological examination of bone marrow on 04/20/2023 containing granulomas with central necrosis and absence of atypical cells.

PCR for myobacteria in myelogram was requested and a new platelet transfusion and 300 ml of red blood cell concentrate was performed for bronchoscopy on 4/26/2023, however, severe thrombocytopenia made pleural and lung biopsies unfeasible. Bronchial lavage was positive for BAAR and the rapid molecular test identified *Mycobacterium tuberculosis*. The antibiotic scheme was replaced by RIPE (rifampicin, isoniazid, pyrazinamide and ethambutol) and Linezolid and Levofloxacin were maintained to combat neurotuberculosis. Initially, the patient had gastrointestinal intolerance to RIPE, suspecting acute pancreatitis that was ruled out through abdominal ultrasound.

Dexamethasone adjustment from 4 mg/day to 8 mg/day. Monitoring of transaminases and pancreatic enzymes in decline. Serologies requested on 04/28/2023, again negative.

On 05/04/2023, he went into respiratory distress, suspecting pulmonary thromboembolism. Presence of extensive pleural and pericardial effusions, absence of thrombi in chest angiotomography 05/05/2023. Meropenem was started.

Evaluated by thoracic and cardiac surgery that adopted a conservative approach because it was a pleural effusion secondary to infection and pericardial tuberculoma.

Showing tolerance to the RIPE scheme and

satisfactory clinical and laboratory evolution, completing Meropenem. There was platelet recovery, infection control and functional recovery of motor activity. The patient was discharged 50 days after admission, maintaining the prolonged RIPE regimen.

DISCUSSION

The delay in diagnosing tuberculosis led to the spread of the disease. Findings suggestive of miliary tuberculosis included cough, hypoxemia, snoring and pulmonary wheezing, presence of uniform reticulonodular infiltrate in the lungs and septal thickening, in addition to progression to respiratory failure and subacute deterioration of multiple organs. (1, 9)

The patient also had cholestatic jaundice and pancytopenia. In miliary tuberculosis, tuberculous meningitis or tuberculoma develops in 15% to 20% of cases. (1) Tuberculoma is the second most frequent neurological manifestation, constituting a differential diagnosis of neoplasms. Mycobacteria reach the blood and CSF, settling mainly in the supratentorial region, forming a conglomeration of cells (tubercles). Manifestations are headache, fever, sensory alteration and motor alterations. Diagnosis is made with evidence of tuberculosis at other sites, typical lesion on brain MRI, and empirical RIPE response. The diagnostic gold standard is positive AFB or PCR in the CSF; however detection is hampered by the low concentration of bacilli in the liquid. (5)

Empiric treatment must not be delayed, lasting from 9 to 12 months. The 4th drug of the RIPE regimen can be levofloxacin, ethambutol, ethionamide or streptomycin. In endemic areas, tuberculoma may persist after adequate treatment. It is not known whether it represents active disease or revascularization of the healing lesion, but does not indicate therapeutic failure. (4)

Hemophagocytic syndrome or hemophagocytic lymphohistiocytosis is a hyperinflammatory and hyperferritinemic immune response driven by dysfunctional T cells and macrophages, associated with a potentially fatal cytokine storm. (2) There is a defect of NK and cytotoxic cells in eliminating hyperactivated macrophages culminating in excess interferon and phagocytosis of marrow cells. (6)

The etiology is unknown, but there is a multifactorial relationship such as genetic mutations, cytokine overproduction, sustained *toll-like* receptor activation, and infections. The main trigger is Epstein-Barr, which has tropism for lymphocytes. (8, 9) Other agents are cytomegalovirus, herpes, parvovirus, measles virus, varicella-zoster, HIV, H1N1, COVID, Leishmania, fungi, mycobacteria. (6, 8, 9)

The most prevalent features are fever, elevated ferritin and hemophagocytosis, the latter caused by hyperplasia of histiocytes and phagocytosis in bone marrow, spleen, liver, lymph nodes, skin and meninges. (8) It manifests as an acute or subacute febrile illness associated with organ dysfunction. Diagnosis is made with at least 5 of the criteria: fever, splenomegaly, marrow biopsy demonstrating hemophagocytosis, cytopenias, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, detection of soluble IL-2 receptor, low NK cell activity. (6, 8, 9)

Cytopenias arise from high levels of interferon produced by cells of the Th1 profile, acting on precursor cells in the marrow, suppressing hematopoiesis and inducing cell apoptosis. (8)

There is an elevation of ferritin in a positive response of heme oxidase to cytokines. Hypertriglyceridemia occurs because high levels of TNF inhibit lipoprotein lipase. Hypoalbuminemia is a sign of poor prognosis in adults. (8)

Treatment consists of reversing the underlying cause associated with broad

antibiotic therapy and immunosuppression with dexamethasone, capable of penetrating the central nervous system, and/or etoposide. Also, assess the need for blood transfusions. In stable patients, avoid specific chemotherapy with etoposide. (2, 7, 8)

Median survival for hemophagocytic syndrome is 2 months. Neurological involvement worsens the prognosis, as well as persistent hyperferritinemia, thrombocytopenia and therapeutic failure after 8 weeks of treatment. (7, 8)

CONCLUSION

Hemophagocytic syndrome is a rare complication of infections, usually in immunosuppressed individuals, and may coexist with sepsis. Neurotuberculosis is a serious disease and early diagnosis and empirical treatment are essential to improve outcomes. The reported case demonstrates the rarity of lymphohistiocytosis in an immunocompetent patient who responded to RIPE therapy associated with dexamethasone and survived despite several unfavorable prognostic factors.

REFERENCES

1. BERNARDO, John. **Clinical manifestations, diagnosis and treatment of miliary tuberculosis. UpToDate**, USA, febraury 2023.

2. CAMPOS, Patricia; MANO, Diana; ANTUNES, Rui. **Tuberculosis presenting as acute sepsis and secondary hemophagocytic lymphohistiocytosis.** European Journal of Case Reports in Internal Medicine, EFIM Portugal, 2022. Disponível em: doi:10.12890/2022_003121

3. GARG, Ravindra Kumar. **Central nervous system tuberculosis: An overview.** UpToDate, USA, may 2022.

4. GARG, Ravindra Kumar. **Central nervous system tuberculosis: Treatment and prognosis.** UpToDate, USA, may 2022.

5. MA, Huanjie; LIU, Yuan; ZHUANG, Caiyu; SHEN, Yuanyu; WU, Renhua. **Clinical features and MRI findings of intracranial tuberculomas.** Radiology of Infectious Diseases, vol. 5, p. 154-159, 2018. Disponível em: https://doi.org/10.1016/j.jrid.2018.10.001

6. MCCLAIN, Kenneth L. **Clinical features and diagnosis of hemophagocytic lymphohistiocytosis.** UpToDate, USA, may 2022.

7. MCCLAIN, Kenneth L. **Treatment and prognosis of hemophagocytic lymphohistiocytosis.** UpToDate, USA, may 2022.

8. PONNATT, Tanya Sajan *et al*. **Hemophagocytic lymphohistiocytosis.** Archives of Pathology & Laboratory Medicine, USA, vol. 146, p. 507-519, april 2022. Disponível em: doi: 10.5858/arpa.2020-0802-RA

9. TROVIK, Lin Hereide; SANDNES, Mirian *et al.* **Hemophagocytic lymphohistiocytosis and miliary tuberculosis in a previously healthy individual: a case report.** Journal of Medical Cases Report, United Kingdom, 14:217, 2020. Disponível em: https://doi.org/10.1186/s13256-020-02555-x