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Neurotuberculosis in an immunocompetent patient: diagnostic challenge and treatment

Neurotuberculose em paciente imunocompetente: desafio diagnóstico e tratamento

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ABSTRACT: Neurotuberculosis is a serious disease, occurring in about 5 to 10% of cases of extrapulmonary tuberculosis. The clinical spectrum varies according to the affected site (meningeal, cerebral parenchyma or spinal cord). Herein we present the case of a 32-year-old male patient with cough and weight loss who presented with hemiparesis and disorientation, receiving a diagnosis of neurotuberculosis using the Xpert MTB / RIF® test. The present case aims to report the clinical and neuroimaging data of an immunocompetent patient with neurotuberculosis. The definitive diagnosis is made by the detection of tuberculosis bacilli in cerebrospinal fluid. The RIF® Xpert MTB test has similar sensitivity and specificity to other diagnostic methods for tuberculosis and the advantage of providing information on resistance to rifampicin. The prognosis depends on the stage and onset of treatment.

Keywords: Tuberculosis; Tuberculosis, meningeal; Tuberculosis, central nervous system; Immune system; *Mycobacterium tuberculosis*.

RESUMO: A neurotuberculose é uma doença grave, ocorrendo em cerca de 5 a 10% dos casos de tuberculose extrapulmonar. O espectro clínico varia de acordo com o local afetado (meninge, parênquima cerebral ou medula espinhal). Aqui, apresentamos o caso de um paciente do sexo masculino de 32 anos com quadro de tosse e perda de peso que apresentou à admissão hemiparesia e desorientação, recebendo diagnóstico de neurotuberculose através do teste Xpert MTB/RIF®. O presente caso objetiva relatar os dados clínicos e de neuroimagem de um paciente imunocompetente com neurotuberculose. O diagnóstico definitivo é feito pela detecção de bacilos da tuberculose no líquido cefalorraquidiano. O teste RIF® Xpert MTB apresenta sensibilidade e especificidade semelhantes a outros métodos de diagnóstico da tuberculose e a vantagem de fornecer informações sobre a resistência à rifampicina. O prognóstico depende do estágio e do início do tratamento.

Descritores: Tuberculose; Tuberculose meníngea; Tuberculose do sistema nervoso central; Sistema imunitário; *Mycobacterium tuberculosis*.

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INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* that mainly affects lungs, but can also affect other organs such as pleura, ganglia, meninges, bone, kidney and others.¹ The occurrence is increased in people with human immunodeficiency virus (HIV), especially the severely immunocompromised. It is estimated that one-third of the world population is infected with Koch bacillus². The occurrence of extrapulmonary tuberculosis (EPTB) in immunocompetent individuals is rare. In 2015, 10.4 million new cases of TB were reported worldwide and which approximately 1.6 million died³. In 2005 in The United States, central nervous system (CNS) involvement was observed in 5 to 10% of EPTB cases⁴.

The clinical spectrum of extrapulmonary forms varies according to the affected site. Pleural tuberculosis is the most common form of EPTB in individuals without HIV. Neurotuberculosis is responsible for 3% of TB cases in seronegative HIV patients and up to 10% of cases in seropositive HIV patients. In these cases, there is slower subacute evolution than other meningitis. Despite adequate treatment, neurotuberculosis has a high mortality rate (ranges from 17-30%) and a high frequency of disabling morbidity⁵.

This study aims to report a clinical case of a 32-year-old patient diagnosed with neurotuberculosis and discuss the clinical aspects, diagnosis, management and prognosis.

METHODS

The patient authorized publication of his case and image by written informed consent. The patient history and data were obtained from his medical report during the hospital stay in *Hospital São José de Doenças Infecciosas (HSJ)* in March 2017.

CASE REPORT

A 32-year-old man, unemployed (ex-convict), presented with a 3-month history of fever, dry cough, bloody vomiting, and unquantified weight loss. He reported 1-month low back pain radiated to costal arches and, for 2 weeks, presented disorientation and headache. He sought medical attention due to a focal convulsive crisis. He has reported using alcohol and marijuana since 17 years of age until 1 year ago. On admission, patient was disoriented, sleepy and febrile. He presented left facio-brachial-crural hemiparesis, right ptosis and altered ocular motricity in the third and fourth right cranial nerves. He denied any contact or familiar with tuberculosis. Fundoscopy revealed slight right blurring papilla. Heart and lung exams were

normal. His abdomen was painful in right hypochondrium. Liver was palpable at right costal border. Elisa Anti-HIV tested negative. Cranial Computed Tomography (CT) showed cerebral edema, mild hydrocephalus and meningeal enhancement (Figure 1). Cerebrospinal fluid (CSF) analysis showed an increase in white cells with a predominance of lymphocytes [white blood cell count of 45 cells/mm³ (lymphocytes 79%)], no red blood cells, CSF glucose of 36mg/dL, and CSF protein of 157mg/dL. CSF gram and fungal stains, as well as bacterial cultures, tested negative. Xpert MTB/RIF® test was positive and sensitive to rifampicin. Then, the case was notified. Brain magnetic resonance imaging (MRI) showed diffuse hyperintense signal intensity delineating the cortical gyrus in FLAIR sequence, associated with intense diffuse leptomeningeal enhancement. There was a focus of altered signal in the right internal capsule appearing hypointense on T1-weighted and hyperintense on T2-weighted images, without significant enhancement by the venous contrast (Figure 2). Also, it could be demonstrated that there was an intense restriction at diffusion-weighted imaging. Dilated supratentorial ventricular system with transependymal edema was seen as well. The treatment of tuberculous meningitis with rifampicin, isoniazid, pyrazinamide and ethambutol regimen plus dexamethasone was started. Pulmonary evaluation showed negative Xpert MTB/RIF® test of sputum and chest x-ray without significant changes. CT scan of the thoracic and lumbar spine showed osteolytic lesions in L3-L4, T8-T9 and T11-T12 suggestive of spinal tuberculosis. There was a significant improvement in symptoms, including the neurological deficit, and the patient became afebrile. He presented a 5-fold elevation of liver transaminases what obliged medical team to temporarily suspend the tuberculous meningoencephalitis regimen. He got discharged two months after admission.

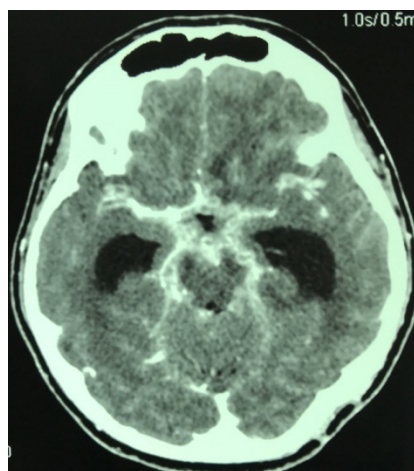
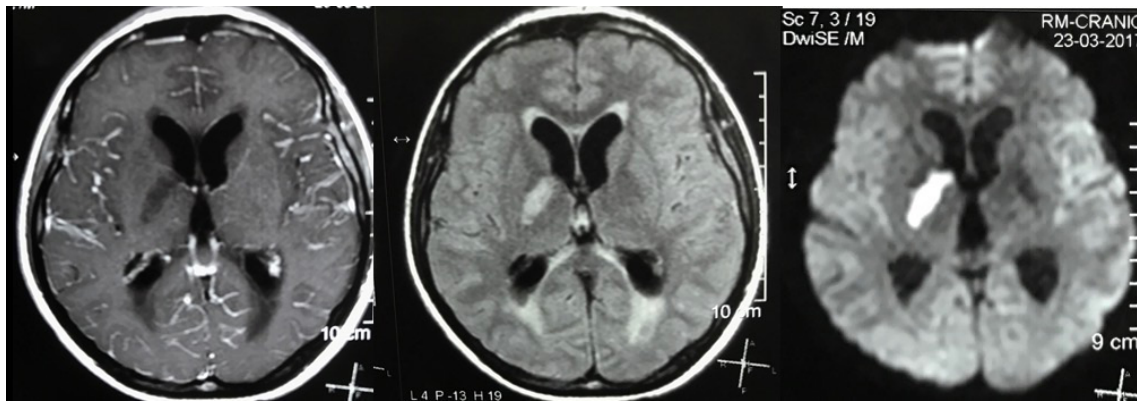


Figure 1. Brain CT scan shows extensive basal meningeal enhancement



MRI: magnetic resonance imaging, DWI: diffusion weighted imaging.

Figure 2. Brain MRI showed right internal capsule appearing hypointense on T1-weighted (2A) and hyperintense on T2-weighted (Fig 2B) images. DWI shows (2C) restricted diffusion representing a parenchyma infarct area

DISCUSSION

Mycobacterium tuberculosis infection is acquired by inhalation of the bacilli through aerosols that reach and multiply in alveolar macrophages. The bacilli reach the CNS through the bloodstream after crossing the blood-brain barrier. Within CNS, the bacilli produce small granulomas in the meninges and cerebral parenchyma. These granulomas may remain inactive for several months or years. The decrease in host immunity may be a trigger for infection. After granuloma rupture in the cerebrospinal spaces, mycobacteria induce an intense immune response and, subsequently, the formation of exudate⁶.

Neurotuberculosis can be divided into subacute or chronic forms. The subacute form may have holocranial headache, irritability, behavioral changes, somnolence, anorexia, vomiting and abdominal pain, associated with fever, photophobia, vomiting and neck stiffness for more than two weeks. Eventually, it presents focal signs related to local ischemic syndromes or the involvement of cranial nerves (II, III, IV, VI and VII). There may be seen papilledema (intracranial hypertension). In chronic form, the patient may present headache and cranial nerve involvement for more than four weeks. Concomitant pulmonary disease occurs in up to 59% of cases. Another form of neurotuberculosis is the localized form (tuberculomas). In this presentation, slow growth of intracranial tuberculoma may occur, with signs and symptoms of intracranial hypertension. Fever may not be present⁵.

The delay in diagnosis and treatment usually leads to severe complications and even death⁷. Despite this, the clinical response to the treatment of neurotuberculosis is excellent when the diagnosis occurs before irreversible neurological damage. Early recognition is extremely important since clinical outcome largely depends on

the stage at which therapy is initiated. Antituberculous empiric therapy should be initiated immediately in any patient with neurological abnormalities and cerebrospinal fluid (CSF) with low glucose concentration, high protein, lymphocytic pleocytosis and if TB is suspected. Adenosine deaminase (ADA) measurement in CSF may be a useful adjunct test for the diagnosis of tuberculous meningitis. However, high levels of CSF ADA can also be observed in bacterial infections, and there is no clear threshold for distinguishing neurotuberculosis from meningitis caused by other infectious agents⁴. The Xpert MTB/RIF® test has high sensitivity and specificity for diagnosis. It is based on nucleic acid amplification and also detects the resistance of mycobacteria to rifampicin (RIF) in less than 2 hours. This test has improved the diagnosis and testing of drug susceptibility. It can be analyzed by sputum or CSF samples. However, its technical complexity and high cost still limits its adoption especially in low-resource institutions⁸.

CT or MRI of the skull may help in diagnosis. The three most common findings in tuberculous meningitis are hydrocephalus, basal meningeal thickening and cerebral parenchyma infarcts⁵. The reported patient had all of these three findings: (1) leptomeningitis, the most common, represented by meningeal enhancement, (2) hydrocephalus due to the exudative pattern of CSF and (3) arteritis at skull base that compromises the quality of life due to neurological sequelae.

The treatment begins with an “intensive phase” consisting of a four-drug regimen that includes isoniazid, rifampicin, pyrazinamide, and ethambutol daily. This is followed by a “continuation phase” consisting of isoniazid and rifampin. Treatment usually consists of an initial period of 2 months of intensive therapy (with four drugs) followed by a prolonged continuation phase (with isoniazid and rifampicin) lasting 9 to 12 months depending on clinical

response and sensitivity to drugs of the isolate. The regimen for tuberculoma treatment is usually performed for 18 months. Standard treatment regimens are equally effective in HIV-negative and HIV-positive patients with neurotuberculosis⁹. Studies suggest that corticosteroids have reduced CSF inflammation and recovery time in patients with neurotuberculosis. Corticosteroids seem to reduce mortality, at least in the short term. However, dexamethasone probably does not prevent severe disability in survivors¹⁰.

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Authors' contribution: AXCBM, ETSA, MHTSA, LABG, RSAL: designed the conceived the research. AXCBM, ETSA, JCA: collected the data. AXCBM, ETSA, MHTSA, LABG, RSAL: drafted the manuscript. AXCBM, ETSA, JCA, MHTSA, RSAL: revised the data. All authors edited and approved the final manuscript.

CONCLUSION

The reported case assumes importance because it is a common disease in clinical practice but with a rare presentation. The CNV involvement if not diagnosed soon could lead the patient to a increased morbidity and nearly to death. The clinical and radiologic findings associated with the availability of Xpert MTB / RIF® test for rapid diagnosis was crucial for the institution of early treatment and the favorable clinical outcome.

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