

CEREBRAL TUBERCULOMAS IN AIDS PATIENTS

A forgotten diagnosis?

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ABSTRACT - The human immunodeficiency virus (HIV) infection epidemics increased the prevalence, multi-drug resistance and disseminated forms of tuberculosis. The central nervous system (CNS) tuberculosis has high mortality and morbidity, and it is usually divided into diffuse (meningitis) and localized (tuberculoma and abscess) forms. We report three cases of cerebral tuberculomas in AIDS patients: one with definitive diagnosis, confirmed with histopathology, and two with probable diagnosis, based on clinical information, radiological images, *Mycobacterium tuberculosis* isolation out of the CNS and adequate response to antituberculous treatment. Further, we discuss diagnostic, therapeutic and prognostic issues of tuberculomas, with emphasis in the distinction from cerebral tuberculous abscesses. Despite of their infrequent presentation, tuberculomas should be considered in the differential diagnosis of cerebral expansive lesions in patients with AIDS.

KEY WORDS: tuberculoma, tuberculosis, central nervous system, acquired immunodeficiency syndrome.

Tuberculomas cerebrais em pacientes com aids: um diagnóstico esquecido?

RESUMO - A epidemia da infecção pelo vírus da imunodeficiência humana (HIV) aumentou a prevalência, multiresistência e formas disseminadas da tuberculose. O acometimento neurológico da tuberculose apresenta elevada morbidade e mortalidade, classificando-se em formas difusas (meningite) e localizadas (tuberculoma e abscesso). Relatamos três casos de tuberculomas cerebrais em pacientes com AIDS: um deles com diagnóstico definitivo, confirmado com histopatologia e dois com diagnóstico provável, baseado em informação clínica, radiológica, isolamento de *Mycobacterium tuberculosis* fora do sistema nervoso central e adequada resposta ao tratamento tuberculostático. Discutimos também aspectos diagnósticos, terapêuticos e prognósticos dos tuberculomas, enfatizando suas diferenças com os abscessos tuberculosos cerebrais. Apesar de serem relatados de forma infreqüente, os tuberculomas devem sempre ser considerados no diagnóstico diferencial das lesões expansivas cerebrais em pacientes com AIDS.

PALAVRAS-CHAVE: tuberculoma, tuberculose, sistema nervoso central, síndrome da imunodeficiência adquirida.

Tuberculosis (TB) has become more frequent since the emergence of human immunodeficiency virus (HIV) infection epidemics. Nowadays, there are important challenges, which complicate the management of HIV-TB co-infected patients. Among them, it is emphasized the increase of disseminated and extra-pulmonary TB forms, the multi-drug resistance and the increase in mortality¹.

The central nervous system (CNS) TB is found in 5-10% of patients with pulmonary TB². These cases correspond to either latent infection reactivations or disseminated infections. Tuberculous meningi-

tis is the most common clinical form and it is five times more frequent in patients with HIV infection than in patients without it³. The focal forms of CNS tuberculosis are infrequently described and they are divided into tuberculoma and abscess⁴.

We describe three cases of cerebral tuberculoma in AIDS patients and discuss diagnostic, therapeutic and prognostic issues, with emphasis in the distinction from cerebral tuberculous abscesses. This study was ethically approved by the institutional review boards of the Institute of Infectious Disease Emilio Ribas, Sao Paulo, Brazil.

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CASES

Case 1 - A 36-year-old Brazilian man was admitted in December 2002 with a seven-days history of tiredness, headache, nausea and vomiting. He had diagnosed HIV and cerebral toxoplasmosis in October 2002. The patient irregularly used zidovudine, lamivudine, efavirenz, sulfadiazine, pyrimethamine, and folic acid. On physical examination, he showed a decrease in consciousness level and no focal neurological signs. Altered laboratory tests included hemoglobin 9.2 g/dl, leucocytes 1100/mm³, platelets 95000/mm³ and sodium 128 mmol/l. A chest X-ray showed a scary lesion in upper right lung. *Toxoplasma gondii* serology was positive and CD4⁺ lymphocytes count was 7 cells/mm³. A cerebral computed tomography (CT) scan showed a solitary lesion in the left cerebellum, with contrast enhancement and mass effect (Fig 1). The cerebrospinal fluid examination (CSF) was normal. Empirical treatment for toxoplasmic encephalitis with sulfadiazine 6 g, pyrimethamine 25 mg and folic acid 15 mg daily was initiated. Three weeks later, a new CT scan showed increase in size of the cerebellar lesion and surgery was indicated. The histological examination showed presence of few acid-fast bacilli (AFB), necrotic tissue and absence of microabscesses. Investigation for other causes, including bacteria and fungi, were negative. Thus, treatment with isoniazid 400 mg, rifampin 600 mg, pyrazinamide 2 g, and prednisone 50 mg daily was initiated. Four weeks later, the patient evidenced meaningful clinical and imaging improvement and he was discharged to complete nine months of antituberculous treatment.



Fig 1. Contrast-enhanced computed tomography scan of case 1, showing a large unique ring-enhancing lesion in the left cerebellum, surrounded by discrete edema.

Case 2 - A 31-year-old Brazilian woman was admitted in August 2002 because of weight loss, tiredness, fever, headache and productive cough for four weeks and a convulsive episode one week before. She had been diagnosed as being infected with HIV infection since 1985 and she had *Pneumocystis carinii* pneumonia in 1999 and pulmonary TB in 2001. The patient irregularly used zidovudine, lamivudine, efavirenz and trimethoprim-sulfamethoxazole. On physical examination, she had fever, diffuse non-painful adenomegalia and no neurological signs. Laboratory tests showed hemoglobin 8.6 g/dl, leucocytes 2.900/mm³, alkaline phosphatase 460 UI/l, aspartate aminotransferase 83 UI/l, alanine aminotransferase 62 UI/l and lactose dehydrogenase 657 UI/l. A chest X-ray showed bilateral pleural thickness and enlarged mediastinal area. Her tuberculin skin test, using purified protein derivative (PPD), and *T. gondii* serology were negative. The CD4⁺ lymphocytes count was 31 cells/mm³ and the HIV viral load was 234000 copies/ml. An abdominal ultrasonography evidenced hepatosplenomegalia, intra-abdominal adenomegalia and ascitic fluid. A cerebral CT scan showed multiple nodular and ring-enhancing lesions (Fig 2A), and one lesion with central calcification and ring-enhancement. The CSF was normal and a cervical node biopsy yielded abundant AFB with caseous necrosis. Isoniazid 400 mg, rifampin 600 mg, pyrazinamide 2 g, ethambutol 1.2 g, sulfadiazine 6 g, pyrimethamine 25 mg, and folic acid 15 mg daily were initiated. Three weeks later, the patient did not have any clinical improvement and the cerebral lesions remained unchanged. The culture of AFB yielded *M. tuberculosis* resistant to rifampin. Streptomycin 1 g was added to isoniazid, pyrazinamide and ethambutol, and the toxoplasmosis treatment was stopped. One month later, the patient was asymptomatic and she was discharged to com-

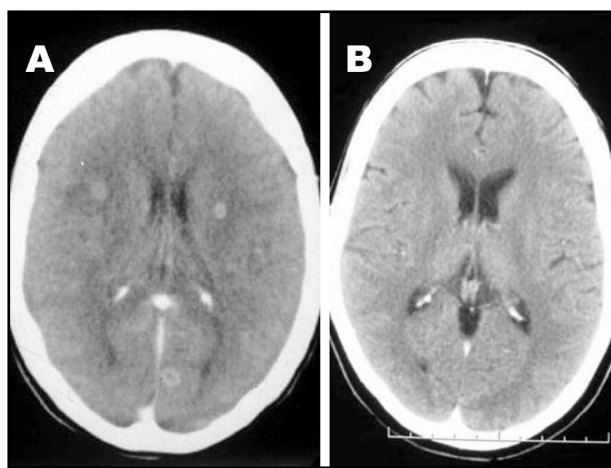


Fig 2. A. Contrast-enhanced computed tomography scan of case 2, showing multiple nodular and ring-enhancing lesions in subcortical areas, with discrete edema. B. After two months of treatment, CT scan showing absence of focal lesions.

plete nine months of treatment. Two months after, a CT scan showed moderate cortical and subcortical atrophy without focal lesions (Fig 2B).

Case 3 - A 30-year-old Brazilian woman was admitted in August 2002 with a three-weeks history of fever, productive cough, headache, abdominal pain, vomiting and diarrhea. She had diagnosed HIV infection in June 2001 and she had a history of disseminated TB (pulmonary and nodal) in September 2001, with abandonment of antituberculous treatment at the third month. On physical examination, the patient had important weight loss, moderate dehydration, abdominal distention, hepatosplenomegalia, ataxia and psychomotor slowness. Altered laboratory tests were hemoglobin 11.2 g/dl, leucocytes 3100/mm³, alkaline phosphatase 514 U/l, aspartate aminotransferase 57 U/l and alanine aminotransferase 53 U/l, and lactose dehydrogenase 711 U/l. A chest X-ray showed multiple micronodular lesions in both lungs compatible with miliary tuberculosis. The PPD and *T. gondii* serology were negative, the CD4⁺ lymphocytes count was 35 cells/mm³ and the HIV viral load was 54800 copies/ml. The direct examination of sputum for AFB was positive. A CT scan showed two cerebellar lesions, one of them multiloculated (Fig 3A). The CSF examination revealed a protein of 150 mg/L with both normal glucose level and white cell count. No AFB were seen on Ziehl-Neelsen staining and culture was negative. Treatment with isoniazid 400 mg, rifampin 600 mg, pyrazinamide 2 g, and ethambutol 1.2 g daily was started. One month later, the patient evidenced important clinical and imaging improvement and she was discharged to complete nine months of treatment. The culture of sputum yielded *M. tuberculosis* sensible to isoniazid, rifampin and pyrazinamide. Three months later, the patient was asymptomatic and had a normal cerebral CT scan (Fig 3B).

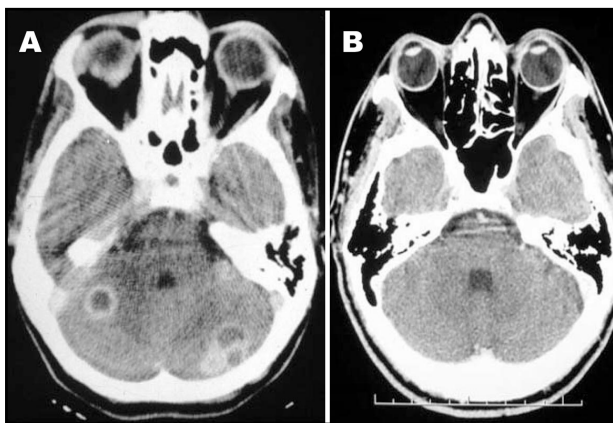


Fig 3. A. Contrast-enhanced computed tomography scan of case 3, showing two cerebellar lesions, including one multiloculated mass lesion in the left cerebellum. B. After three months of treatment, CT scan showing absence of focal lesions.

DISCUSSION

The introduction of highly active antiretroviral therapy (HAART) improved significantly the survival and quality of life of AIDS patients in developed countries and in Brazil⁵. TB prevalence has also decreased as a consequence of HAART. However, TB is still a public health problem in Brazil and represents the most frequent AIDS-defining disease⁵.

There is limited information about focal forms of cerebral TB in AIDS patients and recent reviews over CNS opportunistic infections did not include TB^{6,7}. This is possible due to the fact that the number of CNS TB cases in developed countries is very limited, as demonstrated in a detailed neuropathological study⁸. In the AIDS era, Lesprit et al.⁹ found only 21 cases of cerebral TB (including tuberculomas and abscesses), and Vidal et al.¹⁰ found nine cases of tuberculous abscess. The lack of reports of CNS TB in developing countries, where the TB prevalence is high, can be due to underdiagnosis and underregister of cases and, indeed, to the lack of publications.

Tuberculomas can develop through four pathophysiological mechanisms. First, invasion of bacilli from the CSF (TB meningitis). Second, as a consequence of a disseminated TB. Third, paradoxical reaction in patients with antituberculous treatment, with or without antiretrovirals. Finally, local reactivation of latent foci^{2,11}. Cerebral TB infection may produce local areas of cerebritis with formation of tuberculomas. It is unknown why an abscess is produced in some cases and in another it is a tuberculoma. Farrar¹² considers that if the quantity of bacilli is high enough or the immunity is depressed, a focal cerebritis may progress to an abscess. On the other hand, the most of authors consider that the abscesses result from the liquefaction of tuberculomas¹³.

The focal forms of CNS TB show different anatomopathological characteristics, which were defined by Whitener¹⁴. Tuberculomas have a central region with caseous necrosis, a capsule of collagen and giant multinuclear, epithelioid and mononuclear cells. On the other hand, abscess require to fulfill the following criteria: (1) macroscopic evidence of pus, (2) inflammatory reaction in the abscess wall, which consists of granulate vascular tissue and acute and chronic inflammatory cells, and (3) demonstration of AFB in the purulent material or in the abscess wall, or positive culture of *M. tuberculosis*. Definitive diagnosis of cerebral tuberculoma needs histopathologic evidence in the cerebral tis-

sue obtained by biopsy, trepanation or necropsy. Probable diagnosis of tuberculomas requires epidemiological, clinical and laboratorial information and also an adequate response to antituberculous treatment².

The clinical presentation of tuberculomas and tuberculous abscesses is similar to the main CNS expansive lesions in AIDS patients^{9,10}. However, the tuberculous abscesses usually have a more accelerated clinical course. Therefore, it is important to perform a detailed anamnesis and physical examination to find exposure information, previous TB disease and treatment as well as symptoms and signs out of the CNS.

Tomographic findings of the focal forms of CNS TB are unspecific and less clear than the findings of the magnetic resonance (MRI)⁴. However, it seems that there is an adequate correlation between histopathological and tomographic findings of tuberculomas. The radiological presentation depends on whether the granuloma is noncaseating, caseating with a solid center, or caseating with a liquid center⁴. The noncaseating granulomas are rounded or oval, multiple, isodense or lightly hypodense lesions, with nodular contrast enhancement. These are the classical lesions described for tuberculomas and they were present in the patient 2. The caseating granulomas with solid center and caseating granulomas with liquid center are isodense or hypodense lesions with annular contrast enhancement. The degree of surrounding edema is variable and is thought to be inversely proportional to the maturity of the lesion⁴. Usually, the caseating granulomas with solid center show thicker walls. On the other hand, the caseating granulomas with liquid center may be undistinguishable from the bacterial or TB abscesses. This fact was evident in patients 1 and 3. However, the TB abscesses might differ from tuberculomas because they show a more rapid course, usually have larger size (often > 3cm), thinner walls, and mostly unique and multiloculated lesions^{2,4,15}. Moreover, there are tuberculomas which are solitary and large (patient 1), multiloculated (patient 3) and with an important mass effect⁹. The "target sign", defined as a central nest of calcification or a central contrast enhancement surrounded by a ring of enhancement, is characteristic of tuberculomas^{16,17}. However, recent studies have suggested that only the "target sign" with central calcification is pathognomonic of tuberculoma⁴. Unfortunately, the "target sign" is an infrequent finding^{4,15}.

In contrast to the cerebral TB abscesses, which require surgical and pharmacological treatment^{10,12,14}, tuberculomas generally respond quite well with only pharmacological treatment^{16,17}. Nevertheless, like was verified in some of our patients, the differentiation between this two diagnoses is difficult and complicates the surgical decision.

We conclude that tuberculomas should be considered in the differential diagnosis of CNS expansive lesions in patients with AIDS. A careful individual evaluation, including clinical (anamnesis, physical examination), laboratorial (negative *T. gondii* serology, evidence of TB out of the CNS) and imaging information (previous or active images in chest X-ray, "target sign" in cerebral CT) could increase the diagnostic probability of tuberculoma. In contrast to TB abscesses, the conservative treatment of tuberculomas usually determines a good outcome.

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