CASE REPORT

RING ENHANCING INTRACRANIAL LESION RESPONDING TO ANTITUBERCULOUS TREATMENT IN AN HIV-INFECTED PATIENT

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SUMMARY

Cerebral tuberculomas constitute a major differential diagnosis of cerebral toxoplasmosis in human immunodeficiency virus (HIV)-infected patients in developing countries. We report the case of a 34-year old woman co-infected with HIV and possible disseminated tuberculosis (hepatitis, lymphadenopathy, and pleural effusion) who presented a large and solitary intracranial mass lesion. Despite extensive diagnostic efforts, including brain, ganglionar, and liver biopsies, no definitive diagnosis was reached. However, a trial with first-line antituberculous drugs led to a significant clinical and radiological improvement. Atypical presentations of cerebral tuberculomas should always be considered in the differential diagnosis of intracranial mass lesions in HIV-infected patients and a trial with antituberculous drugs is a valuable strategy to infer the diagnosis in a subset of patients.

KEYWORDS: Cerebral tuberculoma; Tuberculosis; Central nervous system; HIV.

INTRODUCTION

Central nervous system tuberculosis results in high mortality and morbidity in human immunodeficiency virus (HIV)-infected patients from South America. Cerebral tuberculomas constitute the main differential diagnosis of cerebral toxoplasmosis in resource-limited settings, including Brazil. Here, we report an HIV-infected patient with a solitary and large intracranial mass and discuss the caveats of its diagnosis and treatment.

CASE REPORT

A 34-year old woman was admitted to this hospital because of a two-week history of right side weakness and cognitive impairment. HIV infection had been diagnosed four months earlier, as well as a possible disseminated tuberculosis with pleural and ganglionar involvement. Her medication included stavudine, lamivudine, efavirenz, rifampicin, pyrazinamide, ethambutol, and streptomycin. This treatment was started in another facility, where poor adherence and hepatotoxicity secondary to isoniazid were reported. On physical examination, she presented peripheral lymphadenopathy, hepatoesplenomegaly, disorientation, decreased level of consciousness, right sided hemiparesis, right central facial paresis, and aphasia. Altered laboratory tests included hemoglobin 8.4 g/dL, platelets 41,000/mm³, aspartate aminotransferase (AST) 161 U/L, alanine aminotransferase (ALT) 201 U/L, and albumin 2.5 g/dL. IgG Toxoplasma gondii serology was positive. CD4+ T-cell count was 241 cells/mm³ and viral load was > 500,000 copies/mL. A tuberculin skin test was not performed. A chest X-ray showed mild bilateral pleural effusion. An abdominal ultrasonography revealed hepatosplenomegaly and retroperitoneal lymphadenopathy. A cerebral computed tomography (CT) scan showed an irregular, solitary large lesion in the left fronto-temporo-parietal region, with a thick ring-enhancing pattern and extensive perilesional edema. Empirical treatment for cerebral toxoplasmosis with clindamycin 600 mg QID, pyrimethamine 50 mg QD, folinic acid 15 mg QD along with dexamethasone 4 mg QID was initiated. Antituberculous agents and HAART were maintained. Two weeks later, a new CT scan (Fig. 1A) showed an increase on the size of the cerebral lesion and the patient developed right hemiplegia. Cerebral toxoplasmosis treatment was discontinued but dexamethasone was maintained. As the patient presented a worsening of liver enzymes levels (AST 459 IU/L, ALT 509 UI), rifampicin was switched to ofloxacin. Four weeks after admission, a magnetic resonance imaging (MRI) revealed a large expansive brain lesion with intermediate signal intensity and ring enhancement on T1-weighted image after gadolinium administration and with intermediate signal intensity on T2-weighted image (Fig. 2A and 2B). The lesion was hypointense on diffusion-weighted MRI (DWI),
A computed tomography (CT) scan of the brain showing an irregular, solitary large lesion in the left fronto-temporo-parietal region, with a thick ring-enhancing pattern and extensive perilesional edema. After two months of regular treatment with first-line antituberculous agents, a new CT scan showed important improvement of the lesion.

A magnetic resonance imaging (MRI) showed a large expansive brain lesion with intermediate signal intensity and ring enhancement on T1-weighted image after gadolinium administration. MRI showed intermediate signal intensity on T2-weighted image.

indicating absence of restricted diffusion. A stereotactic brain biopsy was performed. Histological examination yielded reactive gliosis and astrocytosis. Neither acid-fast bacilli (AFB) nor malignant cells were identified. Culture of brain biopsy specimens failed to show growth of *Mycobacterium tuberculosis*. Histopathological examination of an axillary lymphadenopathy evidenced only reactive lymphocytosis without identification of any microorganism. Histopathological examination of the liver disclosed epithelioid granulomas with caseous necrosis associated to chronic inflammatory infiltrate, suggestive of tuberculosis, however, AFB were not seen at direct microscopic examination and cultures were negative. Liver enzyme levels were persistently increased.

Considering the hypothesis of disseminated tuberculosis (cerebral tuberculoma, hepatitis, lymphadenopathy, and pleural disease), first-line antituberculous agents were reintroduced gradually in a sequential manner (rifampin, isoniazid, pyrazinamide, and ethambutol) each three days, without complications. After two months of regular treatment with isoniazid, rifampin, pyrazinamide, ethambutol, and dexamethasone, the systemic and neurologic alterations showed important improvement. Pyrazinamide and ethambutol were discontinued and the dose of dexamethasone was tapered in the next four weeks. The patient was oriented, without alteration of the level of consciousness, her speech was normal and she presented a mild right hemiparesis. A new CT scan showed important reduction of the cerebral lesion (Fig. 1B).

Laboratory tests disclosed hemoglobin of 12.4 g/dL, platelets 238,000/mm³, AST 88 U/L, ALT 91 U/L, and albumin 3.4 g/dL. Three months after admission, the patient was discharged using rifampin, isoniazid, tenofovir, lamivudine, and efavirenz. The switch from stavudine to tenofovir was performed in order to improve adherence with a once daily dosing regimen and better tolerability profile. Her CD4+ cell count was 427 cells/mm³ and her viral load was < 400 copies/mL. Fortunately, her post-discharge course has been uneventful and the patient remains with a mild residual right hemiparesis.

**DISCUSSION**

Our report emphasizes the difficulties in obtaining an etiological diagnosis of expansive brain lesions in HIV-infected patients. The patient underwent three invasive procedures, including brain, ganglionic, and liver biopsies. Only the liver biopsy showed histopathological findings compatible with tuberculosis. Even though we were not able to confirm the etiology of the brain lesion, cerebral tuberculoma was the more likely diagnosis.

Atypical presentations of intracranial tuberculomas can be a challenging diagnosis, particularly in HIV-infected patients from developing countries, where tuberculosis is endemic. In our case, the presence of disseminated disease allowed us to maintain a high index of diagnosis suspicion.

Most patients with cerebral toxoplasmosis showed a CD4+ cell count below 100 cells/mm³, and in the case of primary CNS lymphoma, below 50 cells/mm³. However, intracranial tuberculomas or tuberculomas brain abscesses are not uncommon with CD4+ cell count above 100 cells/mm³. Cerebral toxoplasmosis lesions and tuberculomas are generally multiple, tuberculomas brain abscesses are usually single whereas in primary CNS lymphoma, solitary and multiple lesions may occur at approximately the same frequency. Lesions measuring more than 4 cm are more likely to be lymphoma, when compared with cerebral toxoplasmosis. Similarly, lesions measuring more than 3 cm are more likely to be tuberculomas brain abscesses when compared with tuberculomas. The focal forms of CNS tuberculosis show different anatomopathological characteristics, which were defined by Whitener. Tuberculomas have a central region with caseous necrosis, a capsule of collagen, and giant multinuclear, epitheliod, and mononuclear cells. On the other hand, abscesses have 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. tuberculosi*

Atypical presentation of solitary and large intracranial tuberculoma underscores that radiological findings are unspecific to identify etiological causes of focal brain lesions. However, MRI is particularly useful in identifying the pathological stage of tuberculomas. In our case, the MRI features were compatible with caseating granuloma with a solid center, but other neurologic diseases, including primary CNS lymphoma or cerebral toxoplasmosis can display similar findings.

In the present case, the contraindication to perform lumbar puncture precluded the use of molecular diagnosis. Hence, pathological diagnosis continues to be the gold standard for a subset of HIV-infected patients.
with focal brain lesions. However, definitive diagnosis is not reached in as many as 8-10% of patients who undergo brain biopsy. Since tuberculomas are usually firm masses, the blunt probe used in stereotactic biopsies may be pushed away, leading to sampling errors.

Guidelines from the US Centers for Disease Control and Prevention (CDC) and the British Infection Society recommend therapy for CNS tuberculosis with isoniazid, rifampin, ethambutol, and pyrazinamide. Isoniazid and rifampin are the key components of the regimen. In the present case, the antituberculous therapy was optimized (from rifampin, ethambutol, streptomycin, and ofloxacin to isoniazid, rifampin, ethambutol, and pyrazinamide), and important improvement of the CNS mass lesion was obtained, probably due to the fact that isoniazid penetrates the CSF freely and has potent early bactericidal activity. On the other hand, streptomycin does not penetrate the CSF well in the absence of inflammation. In addition, fluoroquinolones may represent an effective fourth agent, although data concerning their CSF pharmacokinetics and safety during prolonged therapy are limited.

Cerebral toxoplasmosis is the most frequent expansive brain lesion in HIV-infected patients and its differential diagnosis is broad. In this context, the present case illustrates that, considering our particular epidemiology, where primary CNS lymphoma is rare and tuberculosis is frequent, a common presentation of a rare disease is less likely than a rare presentation of a common disease.

In conclusion, probable cerebral tuberculoma should always be considered in the differential diagnosis of solitary and large focal brain lesions in HIV-infected patients, particularly in patients of tuberculosis endemic areas and with disseminated disease. Despite extensive diagnostic efforts, sometimes, a trial with antituberculous therapy is a valuable tool to confirm the diagnosis.

RESUMO

Lesão intracraniana que respondeu ao tratamento anti-tuberculoso em paciente infectado pelo HIV

Os tuberculomas cerebrais constituem diagnóstico diferencial importante da toxoplasmosa cerebral em pacientes infectados pelo vírus da imunodeficiência humana (HIV) de países em desenvolvimento. Os autores relatam o caso de uma mulher HIV positiva de 34 anos de idade, que apresentou provável tuberculose disseminada (hepatite, adenomegalia, e derrame pleural) associada à lesão expansiva cerebral única e gigante. Apesar dos esforços diagnósticos realizados, incluindo biópsia cerebral, ganglionar e hepática, o diagnóstico etiológico não foi confirmado. Porém, a resposta clínico-radiológica ao tratamento tuberculostático permitiu definir o diagnóstico de tuberculoma cerebral e a paciente teve alta hospitalar. Apresentações atípicas de tuberculomas cerebrais devem ser sempre consideradas no diagnóstico diferencial das lesões expansivas cerebrais em pacientes infectados pelo HIV e o uso do tratamento tuberculostático constitui ferramenta útil na definição diagnóstica em um sub-grupo de pacientes.

REFERENCES


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