



Case Report/Relato de Caso

Progressive multifocal leukoencephalopathy as an AIDS-defining condition in a patient with high CD4⁺ T-lymphocyte count

Leucoencefalopatia multifocal progressiva como condição definidora de AIDS em paciente com contagem alta de linfócitos T CD4⁺

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ABSTRACT

We present the case of a 31-year-old man with acute manifestation of progressive multifocal leukoencephalopathy (PML) as an AIDS-defining disease. The patient presented with a three-day history of neurological disease, brain lesions without mass effect or contrast uptake and a slightly increased protein concentration in cerebrospinal fluid. A serological test for HIV was positive and the CD4⁺ T-cell count was 427/mm³. Histological examination of the brain tissue revealed abnormalities compatible with PML. The disease progressed despite antiretroviral therapy, and the patient died three months later. PML remains an important cause of morbidity and mortality among HIV-infected patients.

Keywords: Progressive multifocal leukoencephalopathy, AIDS, HIV, CD4⁺ T-lymphocytes, JC virus.

RESUMO

Apresentamos o caso de um homem de 31 anos com leucoencefalopatia multifocal progressiva (LMP) de manifestação aguda como doença definidora de AIDS. O paciente apresentou-se com doença neurológica com três dias de evolução, lesões encefálicas sem efeito de massa ou captação de contraste e leve aumento de proteínas no líquido. Sorologia para o HIV foi positiva e a contagem de linfócitos T CD4⁺ era de 427/mm³. O exame histológico de tecido cerebral revelou alterações compatíveis com LMP. A doença progrediu a despeito da terapia antirretroviral, e o paciente morreu após três meses. LMP permanece como causa relevante de mortalidade e morbidade em pacientes infectados pelo HIV.

Palavras-chaves: Leucoencefalopatia multifocal progressiva, AIDS, HIV, Linfócitos T CD4⁺, Vírus JC.

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of immunocompromised patients caused by John Cunningham virus (JCV), which is a human polyomavirus. It has become more frequent due mainly to AIDS^{1,2}. The prevalence

of PML in HIV-infected patients ranges from 3 to 5% and it is an AIDS-defining illness in as many as 57% of patients presenting with PML^{1,3}.

John Cunningham virus predominantly infects oligodendrocytes and astrocytes, resulting in multifocal cell lysis and demyelination, which can develop in all central nervous system regions, but especially in cerebral white matter^{1,4}. The classic presentation begins with focal deficits that vary depending on the location of the lesion, and these worsen with time, reflecting the spread of individual lesions. Mono or hemiparesis are the most common symptoms (52%), followed by cognitive (45%) and speech deficits (31%)². Seizures are less common, and headache and fever are usually absent.

Diagnosis is based on clinical suspicion, image identification and etiological confirmation by means of cerebrospinal fluid (CSF) or brain tissue analysis. PML should be considered as a possible diagnosis in any HIV-infected patient with focal neurological signs^{4,5}. Imaging techniques on the brain provide additional and more specific diagnostic information. Magnetic resonance imaging (MRI) has been found to be more sensitive than computed tomography (CT) for detecting the extent of the disease. CT and MRI on the brain usually show multiple foci in subcortical white-matter regions, without mass effect or contrast enhancement. Lesions show low attenuation on CT and are hyperintense on T2-weighted and hypointense on T1-weighted MRI sequences, thus indicating white matter destruction⁴.

Routine analysis on CSF is usually unhelpful for diagnosing PML. Evaluation of CSF for the presence of JCV by means of the polymerase chain reaction (PCR) has been the least invasive procedure for etiological identification, and this is the method of choice for PML diagnosis⁶. When no JCV DNA identification from CSF is available, or the analysis is inconclusive and clinical suspicion remains, brain biopsy is desirable⁴. PML is identified from the characteristic tissue histopathology and virological identification.

The differential diagnosis with PML includes diseases that can cause neurological deficits in HIV-infected patients, such as infectious conditions (toxoplasmic encephalitis, cryptococcal meningitis, cytomegalovirus infection or brain abscess), neoplasms (primary or metastatic) and vascular brain complications (ischemic events or vascular malformations)^{5,7}.

Given the absence of specific therapy for PML, antiretroviral agents remain the only option. However, a significant number of cases appear unresponsive to antiretroviral therapy⁴.

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Received in 05/08/2010

Accepted in 26/10/2010

The aim of this article is to present the case of a man with a CD4⁺ T-lymphocyte count of 427/mm³, who presented acute illness due to severe PML as an AIDS-defining condition.

CASE REPORT

A previously healthy 31-year-old man was admitted to the Risoleta Tolentino Neves Hospital in Belo Horizonte, State of Minas Gerais, Brazil, presenting with a three-day history of confusion and alteration of motricity and coordination. Neurological examination showed right-sided hemiparesis and aphasia. Computed tomography showed irregular hypodense lesions without mass effect or contrast enhancement throughout the subcortical white matter of the left frontal lobe and basal ganglia (**Figure 1**). Initial blood cell counts revealed 4,600 leukocytes/mm³ (neutrophils 55%, lymphocytes 25%, eosinophils 9% and monocytes 10%). Cerebrospinal fluid analysis retrieved five cells with 64% lymphomonocytes; protein levels of 81mg/dl and glucose assay of 70mg/dl. Cerebrospinal fluid was negative for bacterial, fungal, and parasitic microorganisms. A positive test for HIV was obtained, and the CD4⁺ T-cell count was 427/mm³. Serological tests for cytomegalovirus and human T cell lymphotropic virus (HTLV I-II) were negative, while the patient was negative for IgM and positive for IgG for toxoplasmosis.

Even though the CD4⁺ T-cell count was higher than 200/mm³, empirical treatment for toxoplasmic encephalitis was started, using sulfadiazine, pyrimethamine and folinic acid. The neurological symptoms progressed, culminating in coma, and empirical treatments for bacterial abscess, herpes, tuberculosis and cryptococcosis were offered. A new CT showed expansion of the previous lesions, without mass effect or contrast enhancement. The lack of clinical response to the empirical treatment instituted, associated with compatible CT images, suggested PML. MRI was performed in order to better characterize the lesions. MRI showed diffuse irregular hypointense lesions without mass effect or contrast enhancement, throughout the sub-cortical white matter on T1-weighted images (**Figure 2**). The lesions were hyperintense in T2-weighted sequences. A cerebellar lesion was also noted. Since JCV DNA identification was not



FIGURE 1 - Axial computed tomography of the brain after contrast administration. An irregular hypodense lesion without mass effect or contrast enhancement in the sub-cortical white matter of left frontal lobe (arrows) is observed.

available, the definitive diagnosis of PML was achieved consequent to pathological examination of brain tissue that was obtained through biopsy. Histological examination revealed white matter with loss of myelin, vacuolization, presence of foamy macrophages and reactive astrocytes (**Figure 3**).

Combined antiretroviral therapy with zidovudine, lamivudine and efavirenz was instituted, but no improvement was observed. The patient did not recover from the coma; developed respiratory infections associated with hospital microorganisms; and died three months after hospitalization.

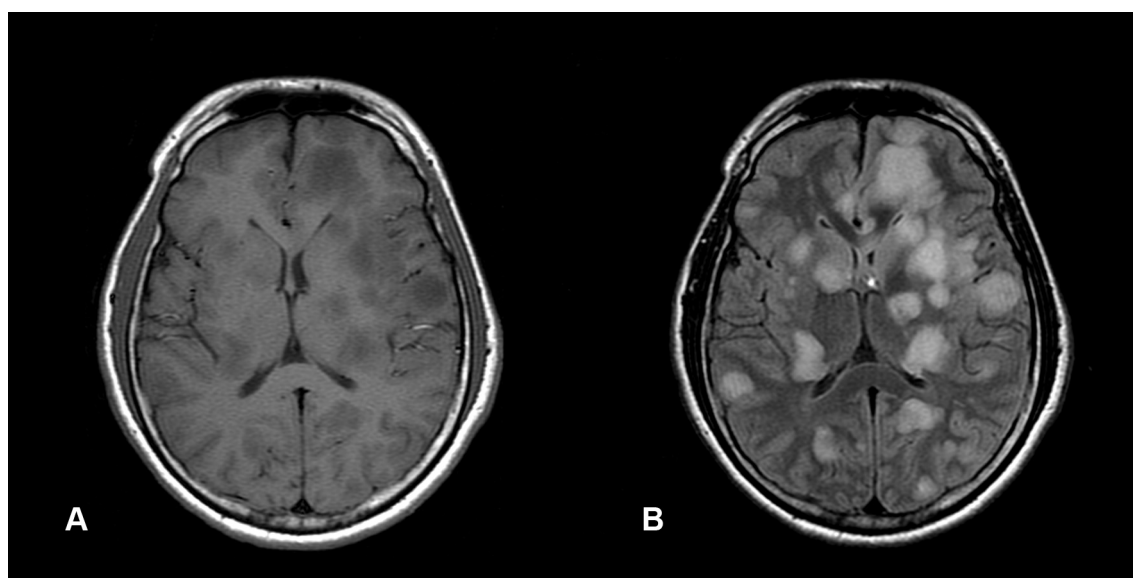


FIGURE 2 - Axial T1-weighted brain magnetic resonance imaging discloses multiple irregular hypointense lesions (A) without mass effect, which are better individualized in the FLAIR sequence (B).

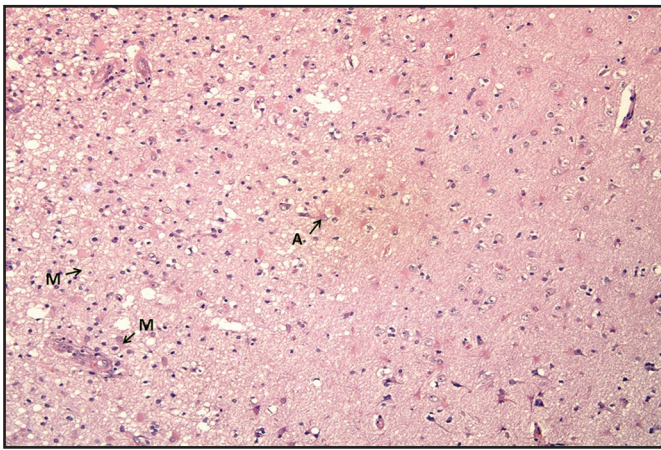


FIGURE 3 - Histological examination of brain specimen obtained by stereotactic biopsy of the frontal lobe, stained with hematoxylin and eosin, magnification 400x. White matter shows loss of myelin, vacuolization, presence of foamy macrophages (M) and reactive astrocytes (A), compatible with leukoencephalopathy.

DISCUSSION

The case reported here described a man who was acutely ill with severe PML, as an AIDS-defining condition, and with a CD4⁺ T-lymphocyte count higher than 200/mm³. The CD4⁺ T-lymphocyte count in HIV-infected patients with PML is typically < 100/mm³, and is inversely correlated with the likelihood of development of this opportunistic disease². The patient described in this case developed PML with 437 CD4⁺ T-cells/mm³, which favored the possibility of other diagnoses such as an ischemic event, brain abscess or cerebral tuberculosis^{5,7}. However, PML has been described in patients with CD4⁺ T-cell counts greater than 200/mm³, especially in those who are starting combined antiretroviral therapy, and, more rarely, in patients with full viral suppression resulting from long-term treatment⁴. The development of PML in patients with a high CD4⁺ T-lymphocyte count is partly explained by the differences between TH1 and TH2 responses in HIV-infected patients. In PML, JCV is associated with reduction of lymphocyte proliferation and reduced production of the TH1 cytokine interferon- γ . Production of TH2 cytokine IL-10 is usually elevated in PML. These findings point towards suppression of the T-helper function of the TH1 type^{2,8}. Patients who demonstrate major histocompatibility complex class I specific cytotoxic CD8⁺ T cell immune response, called JCV-specific cytotoxic T lymphocytes, show a prolonged survival time. In contrast, in the case described here, the patient presented only three months of survival.

The diagnosis of severe PML is based on clinical features and imaging signs followed by cerebrospinal fluid or brain tissue analysis. The patient described in this case presented with clinical and imaging signs compatible with the disease. The diagnosis was confirmed by means of brain histology, since the less invasive alternative procedure of PCR for JCV in CSF was not available. Among HIV-positive patients who were not being treated with highly active antiretroviral therapy (HAART) and who presented neurological diseases, the diagnostic sensitivity of PCR for JCV in CSF has been found to be 72-92% and the specificity, 92-100%⁹. Therefore, a positive result is seen as diagnostic in the appropriate clinical context. Because the ability to detect JCV DNA increases with progression of the disease, lumbar puncture is usually repeated if the first PCR analysis is negative but suspicion remains high⁴. However, recent evidence suggests that the sensitivity in patients undergoing HAART is lower, ranging from 58% to 81%¹⁰. The brain histological analysis in the present case was diagnostic. It revealed loss of myelin in the white matter, vacuolization and presence of reactive

astrocytes, which was compatible with leukoencephalopathy. Foamy macrophages that formed in response to myelin breakdown were also seen, although these are not specific to the disease^{1,4}.

The main approach to treatment of HIV-related PML involves combined antiretroviral therapy with the objective of reversing the immunological defect that interferes with the normal host response to JCV⁴. The currently available data suggest that prolonged survival is associated with immunological parameters (CD4⁺ T-cell count and JCV-specific cytotoxic T lymphocytes) and virological parameters (HIV-RNA plasma level and JCV load), rather than with treatment approaches that have the intention of being directly toxic to JCV². HAART is the only treatment that has proven effective in reducing mortality⁴. The survival of patients with PML has increased substantially over the past ten years, from 0-30% one year after diagnosis in the period before HAART to 38-62% since its introduction. However, the understanding of the factors associated with survival in PML cases remains incomplete. Patients with PML who harbor in their blood JCV-specific CD8⁺ cytotoxic T lymphocytes have a better clinical outcome.

In summary, PML results from brain infection with the JC virus and is usually rapidly fatal in cases of advanced HIV infection. This disease usually occurs in individuals with low CD4⁺ T-lymphocyte counts, but as in the case described here, it has been seen in HIV-positive individuals with counts of as high as 500 CD4⁺ T-cells. JCV-specific T cell response seems to be a critical determinant in PML cases, irrespective of the CD4⁺ T-lymphocyte levels. There is no specific therapy for PML, and HAART remains the only option. However, a significant number of cases appear unresponsive to antiretroviral therapy. Thus, PML remains an important cause of morbidity and mortality in HIV-infected patients.

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