AIDS-related progressive multifocal leukoencephalopathy

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Abstract

Introduction: Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by reactivation of JC virus (JCV). Methods: We described the profile of laboratory-confirmed PML cases among AIDS patients. Results: A total of 43 HIV patients with clinical conditions compatible with PML were obtained; 5 cases were confirmed by JCV testing. The main clinical finding was mental confusion. Median CD4 count was 54 cells/mm³. Conclusions: Three of the five confirmed PML cases died; the time between diagnosis and death was 2, 5, and 6 months. It is important to consider JCV infection as a differential diagnosis. Keywords: Progressive multifocal leukoencephalopathy. JC polyomavirus encephalopathy. JC virus.
aphasia, and/or coordination and gait difficulties. The period was determined from when the institution’s laboratory began providing molecular testing for JCV (March, 2013).

JCV testing in CSF was performed by a FRET real-time PCR assay. CD4+ T cell count was performed using a Multitest Facscalibur flow cytometer, and HIV viral load was measured by bDNA assay up until April 2013, and by Abbott real-time HIV-1 assay as of May 2013.

The reviewed medical records included age, sex, clinical symptoms, CD4+ T cell count, HIV viral load, ART, and results of the computed tomography (CT) and/or magnetic resonance imaging (MRI).

A total of 45 HIV-infected patients with clinical conditions compatible with PML were obtained. Two cases were excluded because they were duplicates, and the same patient was admitted more than once. Within the suspected cases, five were confirmed by positive JCV testing in CSF. Age varied from 46 to 62 years, with a mean of 51 years (standard deviation [SD]: 1.3 years), and 60% (3) were male (Table 1). The clinical manifestations were mental confusion and altered state of consciousness (2), gait disorders and motor deficits (2), and amaurosis and mental confusion (1).

Three patients were diagnosed with HIV upon hospital admission and two had been diagnosed 6 and 8 years previously, both having abandoned treatment. Median CD4+ T cell count was 54 cells/mm³, ranging from 6-130–cells/mm³. Median HIV viral load was 91,984 copies/mL (range: 1,469–2,647,418).

All of the confirmed cases underwent a head CT upon admission, which showed hypodensity areas of the white matter in three cases, the parieto-occipital region in one case, and the tempo-parietal region in two cases. Multifocal lesions occurred in four cases. Two patients had cerebellar lesions. Amongst all cases, three underwent a head contrasted MRI, which showed lesions compatible with the patients’ CT scans. The main alterations were confluent signal alteration compromising part of the left parieto-occipital transition area and the left occipital lobe, as well as the right precentral gyrus, with no mass effect or intravenous contrast impregnation. In both cases, bilateral signal alteration of the splenium of the corpus callosum and of the frontoparietal white matter were observed.

The above data concerning the five confirmed PML cases are summarized in Table 1. Table 2 describes the features of the suspected, non-confirmed cases. Specific tests were performed

### Table 1: PML cases in an infectious diseases reference hospital in Goias, Brazil, from March, 2013 to March, 2015.

| Case | Age (years) | Symptoms | CD4+ (cells/mm³) | ART | Imaging tests | Outcome |
|------|-------------|----------|-----------------|-----|--------------|---------|
| 1    | 62          | Mental confusion | 65 | AZT/3TC + LPV/r | CT - Multiple foci of asymmetric cortico-subcortical hypodensities in both cerebral and cerebellar hemispheres | Death |
| 2    | 48          | Mental confusion | 06 | AZT/3TC + TDF + LPV/r | MRI - Lesion in the centrum semiovale, periventricular and subcortical white matter of the occipital and right temporal lobes, in addition to involvement of the splenium of the corpus callosum. | Death |
| 3    | 46          | Psychomotor agitation | 54 | TDF + 3TC + EFV | CT - Cortico-subcortical hypopattenuation in the posterior aspect of the left cerebellar hemisphere | Discharged |
| 4    | 62          | Dizziness, Mental confusion | 54 | No ART | MRI - Foci of signal alterations of the splenium of the corpus callosum bilaterally, left frontoparietal white matter, right frontal high convexity, and left cerebellar hemisphere. | Death |
| 5    | 57          | Right hemiplegia | 130 | TDF + 3TC + EFV | MRI - Extensive area of confluent signal alteration compromising part of the left parieto-occipital transition area and the left occipital lobe, as well as the right precentral gyrus (less evidently), without mass effect or intravenous contrast impregnation | Discharged |

PML: progressive multifocal leukoencephalopathy; ART: antiretroviral therapy; AZT: zidovudine; 3TC: lamivudine; LPV: lopinavir; r: ritonavir; TDF: tenofovir; EFV: efavirenz; CT: computed tomography; MRI: magnetic resonance imaging.
TABLE 2: Features of suspected, non confirmed cases of PML (n = 43).

| Sex Male (%) | Age-years Mean (sd) | Differential Diagnosis N (%) | Median CD4+(min.– max.) | Median Viral Load (min.– max.) | Death (%) |
|--------------|---------------------|------------------------------|-------------------------|-------------------------------|-----------|
| 28 (65.1)    | 40 (10.0)           | Neurotoxoplasmosis 21 (48.8) | 39 (1–905)              | 157,968 (undetectable–5,620,605) | 14 (32.5) |
|              |                     | Neurocryptococcosis 7 (16.3) |                         |                               |           |
|              |                     | Neurotuberculosis 5 (11.6)   |                         |                               |           |
|              |                     | Others 10 (23.2)             |                         |                               |           |

PML: progressive multifocal leukoencephalopathy; CD4+: CD4 lymphocyte count.

Radiographically, PML cerebral lesions appear as multiple white matter lesions, sparing the cortex, and frequently located in the subcortical region of the cerebral hemispheres and cerebellar peduncles. As the virus disseminates from cell to cell, each focus increases. The disease is bilateral, but asymmetrical, but it can be unilateral and have one single lesion. The parietal lobe is most commonly affected, followed by the frontal lobe. The lesions appear as hypodensities in the white matter on CT, and as T2 and FLAIR hyperintensities and T1 hypodensities on MRI. MRI is more sensitive than CT and is the first choice for the diagnosis of MPL.

Our study demonstrates the relevance of JCV infection in patients living with HIV/AIDS. A retrospective Brazilian study on HIV patients and CNS infection by JCV demonstrated a mean CD4+ T cell count of 65 cells/mm³, with a count of < 100 cells/mm³ being associated with a worse outcome. In our case series, the patients who died had a CD4+ T cell count of ≤ 65 cells/mm³. Incidence rates of 0.2 and 9.1/1,000 people per year at risk, for patients with a CD4+ T cell counts ≥ 200 versus < 200 cells/mm³ have been described. The estimated survival after one year is 48% in HIV patients with a CD4+ T cell count < 200 upon diagnosis, compared to 67% in those with a CD4+ T cell count > 200 cells/mm³. A worse prognosis is also observed in patients with a previous diagnosis of HIV infection, probably because this reflects a low adherence to ART or virus resistance. In our study, three patients had a recent diagnosis of HIV infection when PML was diagnosed; other authors have described PML as the first manifestation of immunodeficiency, but this is not usually the initial presentation of the disease. A definitive diagnosis is given upon detection of JCV in CSF using PCR, or in cerebral tissues through biopsy. A possible diagnosis is made when imaging exams and clinical manifestations are compatible in the absence of virus detection. We found 43 possible cases, but virus detection positivity was low at 11.1% (5/43).

Only two confirmed PML patients showed abnormal CSF analysis results, with a pleocytosis of 20 and 288 leukocytes, lymphomononuclear predominance, and one case showed hyperproteinorrhachia and hypoglycorrhachia.

Three of the five confirmed cases died. All deaths occurred in patients with a recent diagnosis of HIV, with a CD4+ T cell count of less than 65 and a viral load of more than 1,469 copies/mL. The time between diagnosis and death was 2 months, 5 months, and 6 months. The lethality rate observed in the whole sample of suspected cases was 32.5% (14/43).

We thank the director and staff at the Hospital of Tropical Diseases Dr. Anuar Auad/SES/GO.

ACKNOWLEDGMENTS

We thank the director and staff at the Hospital of Tropical Diseases Dr. Anuar Auad/SES/GO.

AUTHORS’ CONTRIBUTION

AOG: data analysis and writing of the manuscript. LRMS: Recruitment of the cases. COA: Recruitment of the cases and translation of the manuscript into English. LCSS: literature review. Discussion. NMB: execution of laboratory tests. MDT: planning of work execution and writing of the manuscript.

CONFLICTS OF INTEREST

The authors declare to have no conflicts of interest.

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