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CASE REPORT

EVOLUTION OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY IN HIV-INFECTED PATIENTS. TWO CASE REPORTS

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system (CNS) caused by reactivation of the John Cunningham (JC) polyoma virus. It occurs in patients with severe cellular immunodeficiency such as HIV infection, being one of the AIDS-defining illnesses. The prognosis of this disease was reserved before combined antiretroviral therapy (cART). Recently, it has been noticed a favorable evolution in patients receiving cART with good penetration in CNS. On the other hand, in PML, the location and the mass effect have prognostic implications. In this article the authors present two cases of PML in HIV positive patients, one who survived and other one who presented evolution to death.

Keywords: progressive multifocal leukoencephalopathy, HIV, AIDS, John Cunningham polyoma virus.

Résumé

Evolution de la leucoencéphalopathie multifocale progressive chez les patients infectés par le VIH. Rapports de deux cas.

La leucoencéphalopathie multifocale progressive (LEMP) est une maladie demyelinisante du système nerveux central (SNC) provoquée par la réactivation du virus du polyome de John Cunningham (JC). Il se produit chez les patients atteints d'immunodéficience cellulaire sévère, comme l'infection à VIH étant l'une des maladies définissant le SIDA. Le pronostic de cette maladie a été réservé avant la therapie antirétrovirale combinée (cART), ces dernières années, on a observé une évolution favorable chez les patients recevant cART avec une bonne pénétration dans le SNC. D'autre part dans la signification de LEMP pour le pronostic il a l'emplacement et l'effet de masse. Dans cet article, les auteurs présentent deux cas de LEMP chez des patients séropositifs, un survivant et un autre présentant une évolution jusqu'à la mort.

Mots-clés: leucoencéphalopathie multifocale progressive, VIH, SIDA, virus du polyome de John Cunningham.

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system (CNS) caused by reactivation of the John Cunningham (JC) polyoma virus. It occurs in patients with severe cellular immunodeficiency, such as HIV infection (being one of the AIDS-defining illnesses), hematological malignancies, organ and stem cell transplant or in patients receiving immune therapy with monoclonal antibodies (natalizumab, rituximab). Primary infection is asymptomatic and the prevalence of JC virus infection in the healthy population is estimated at 66% and 92%[1].

Regarding HIV infected patients, PML develops most frequently in the setting of a poor immunological status expressed by a low CD4 cell count (<200/μL) or during immune recovery following the initiation of highly active antiretroviral therapy. PML is one of the most common cause of encephalopathy after Toxoplasma encephalitis and HIV encephalopathy, in HIV infected patients.

The diagnosis of PML is sustained by clinical manifestations, magnetic resonance imaging (MRI) scan of the brain or cerebral computed tomography (CT), lumbar puncture for the detection of viral DNA in cerebrospinal fluid by PCR examination, and confirmed by brain biopsy in the cases in which JC virus is not detected by PCR.

The onset is insidious, with focal symptoms that include behavioral, speech, cognitive, motor and visual impairment, depending on the localization of the lesions. Common symptoms are motor weakness, especially hemiparesis, visual deficits such as hemianopsia, diplopia, mental changes[2], aphasia, limb apraxia, ataxia. On MRI of the brain, in the CNS white matter, single or multiple confluent lesions without mass effect are seen. The most frequently affected region is parieto-occipital white matter and occasionally may occur infratentorial lesions. CT scan may show hypodense lesions, while on MRI PML lesions are hypointense on T1-weighted images and hyperintense on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences[3]. Cerebrospinal fluid (CSF) is usually normal, but protein levels may be slightly elevated. CSF pleocytosis can sometimes occur, but the cell count is usually less than 20/μL. Polymerase chain reaction (PCR) of the CSF is used to detect viral DNA, and false negative results may be due to the low viral DNA in the CSF, storage or low volume of the specimen and loss of DNA during concentration[4].

Differential diagnosis of PML should consider other primary or opportunistic infections of CNS, demyelinating diseases (multiple sclerosis), vascular lesions, tumors and HIV encephalopathy with secondary changes in the white matter.

There is no standard therapy for PML and the principal approach is to improve the immunological status in patients with HIV infection, by immediately starting combined antiretroviral therapy (cART) in patients who are not on therapy, or optimizing the antiretroviral regimen for virologic suppression in those who are receiving it.

Case report 1

A 22-year-old woman with human immunodeficiency virus (HIV) had a 4-week history of headache, mild disturbance of fine movements, muscle weakness, dysarthric speech, memory and attention impairment.

She was in our evidence for 9 years with HIV infection, she was known with hepatitis B and she was previously treated for pulmonary tuberculosis. Over the years, she received more than one antiretroviral treatment regimen, but she was incompliant, so the evolution of CD4 cell count fluctuated frequently and viremia was detectable, such as after 7 years of antiretroviral therapy she decided to stop it. At that moment, the psychological evaluation revealed that she was unaware of the risks of stopping therapy, that she was involved in a relationship with an uninfected partner and that there was no motivation to restart treatment.

After no more than 2 and a half years of absence from the clinic, she returned to our hospital with the symptoms above.

Physical examination revealed lingual candidiasis, generalized lymphadenopathy, hepatomegaly, left hemihypoesthesia, with normal deep tendon reflexes.

Due to the neurocognitive deficiency, she was evaluated with PAOFI (Patient's Assessment of Own Functioning Inventory) questionnaire, which result was non conclusive and with International HIV Dementia Scale, with a score under 10.

Diagnostic tests

Laboratory tests revealed leucopenia, lymphocytopenia, anemia, elevated inflammatory tests and hepatocytolysis, the CD4 cell count was 8 cells/μL, HIV-RNA plasma was 18 400 copies/ml.

MRI scan showed lesions in the white matter, hyperintense on T2–weighted images, located bilaterally, asymmetric, periventricular and subcortical, multifocal, spreading in the entire cerebral hemisphere, with a greater extension in the right hemisphere and involving corpus callosum. The lesions had ill-defined margins, with peripheral contrast enhancement, without mass effect. (Fig. 1)

After 10 days the neurological disorders had progressed and the patient presented dysphagia, developed

flaccid left hemiparesis with left central facial paresis, dysarthria and positive Babinski reflex. According to the clinical symptoms and all the investigations, PML was suspected and a lumbar puncture was performed. The CSF was clear, normotensive, with pleocytosis and normal protein levels, HIV1-RNA <40 copies/ml. The serology for Cryptococus, Varicella-Zoster virus, Herpes Simplex virus, Epstein-Barr virus, Toxoplasma, Treponema Pallidum, Rubella and Rujeola was negative, but RT PCR for JCV DNA was positive. The CSF culture for Mycobacterium tuberculosis, bacteria and fungi was also negative.

The diagnosis of PML was confirmed. Given the gravity of the case, the immunological and virological

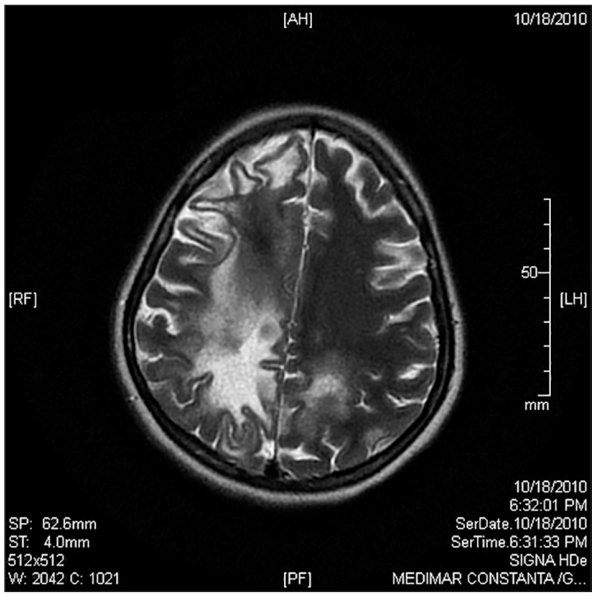

Fig. 1a. Cerebral MRI scan – hyperintense lesions on axial T2 weighted images; the lesions of the white matter are located fronto-parietal, bilateral and asymmetric

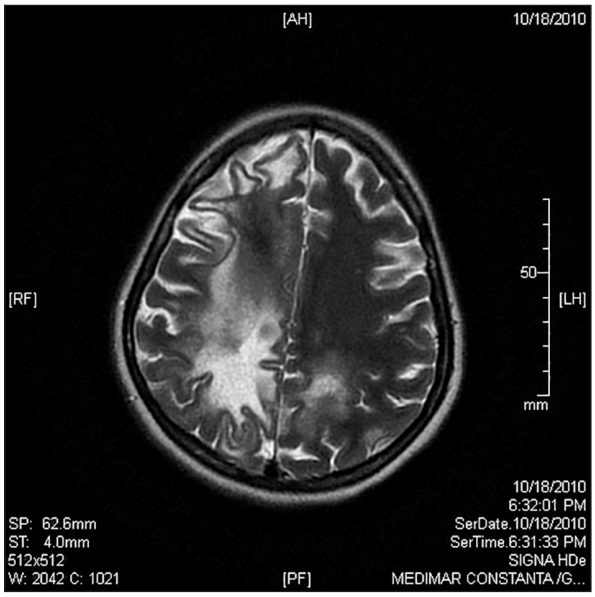

Fig. 1b. Cerebral MRI scan – hyperintense areas on axial T2 weighted images; the lesions are located predominantly right fronto-parietal, with no mass effect

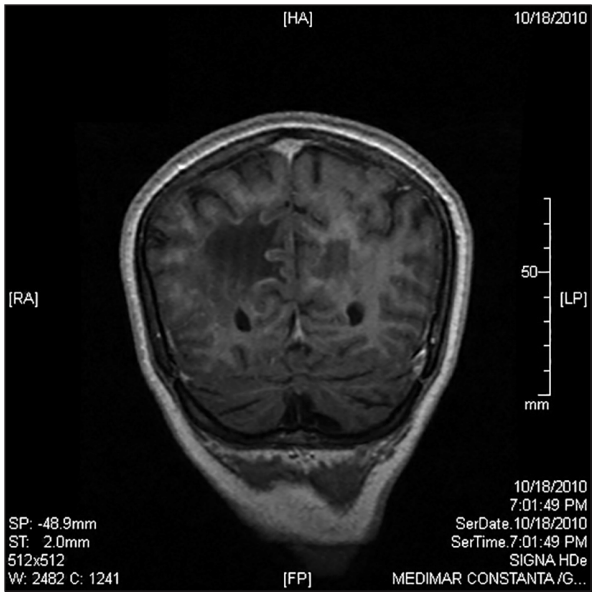

Fig. 1c. Cerebral MRI scan – the lesions appear hypointense on T1 weighted images, coronal view with peripheral contrast enhancement, without mass effect

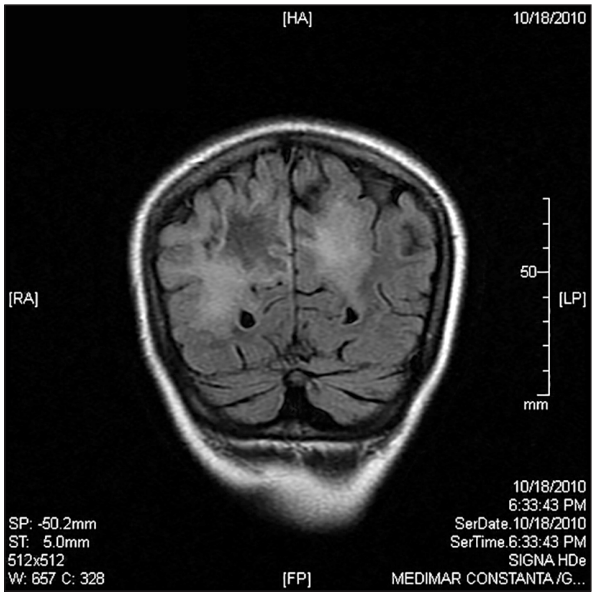

Fig 1d. Cerebral MRI scan – the lesions appear hyperintense on T2 weighted images, with surrounding edema but without mass effect

Figure 1. Cerebral MRI scan: a,b- hyperintense lesions on T2 weighted images, axial view; the lesions of the white matter are located fronto-parietal, bilateral, asymmetric; c,d – the lesions appear hypointense on T1 weighted images, hyperintense on T2-weighted images with peripheral contrast enhancement, without mass effect.

failure, the impossibility of an etiologic treatment for JVC, a cART regimen was started using Abacavir + Raltegravir + Darunavir/ritonavir, with good CNS penetrability, and Enfuvirtide (T20) to increase CD4 cell count and to decrease the viral load.

Clinical evolution

During the following year, her immunological status improved, the CD4 cell count increased to 674 cells/μL and the viremia became undetectable, even if she complained of visual disturbances, memory disorders, mild speech difficulties and presented left hemiparesis. On MRI scan, the sequelae of the lesions described above are visible, ventricular system was asymmetric, with the modified structure of the cerebral tissue affected by gliosis exerting a retractile effect on the right lateral ventricle. (Fig. 2)

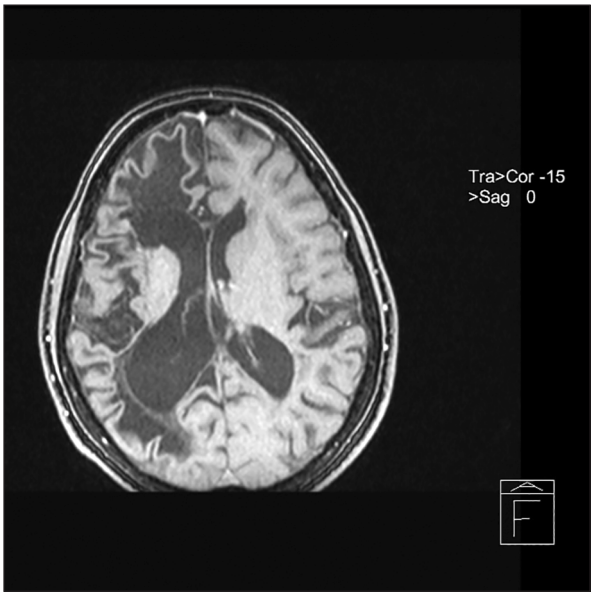

Fig. 2a. Cerebral MRI – large left lateral ventricle

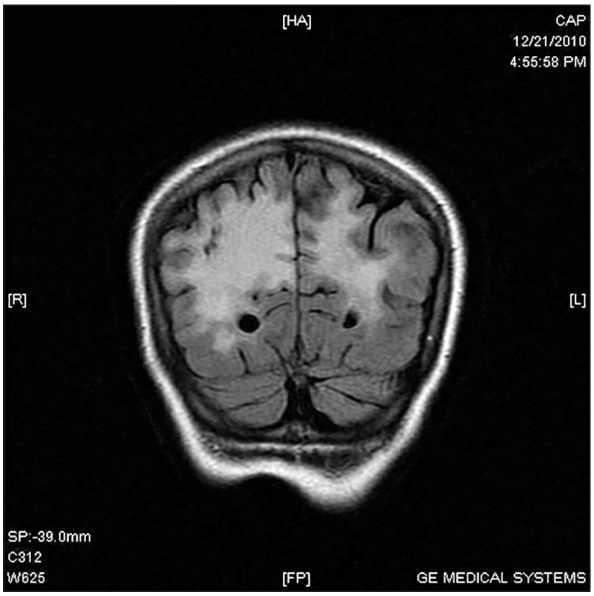

Fig. 2b. Cerebral MRI hyperintense areas on T2-weighted images, coronal view; the lesions are located parieto-occipital, bilateral

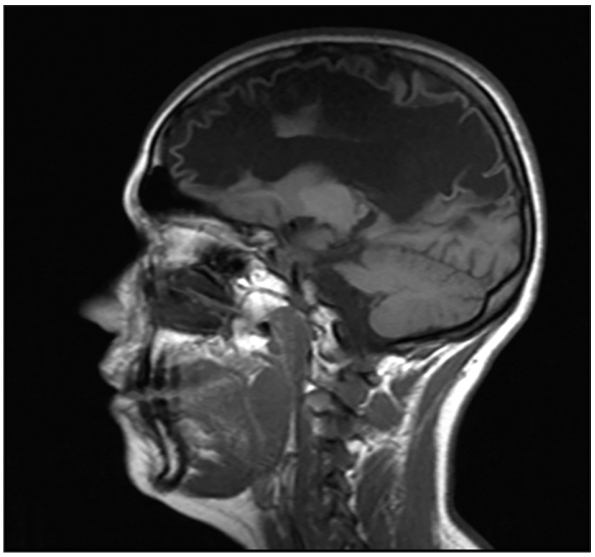

Fig. 2c. Cerebral MRI – large isointense T1-weighted area located fronto-parieto-occipital with ill-defined margins

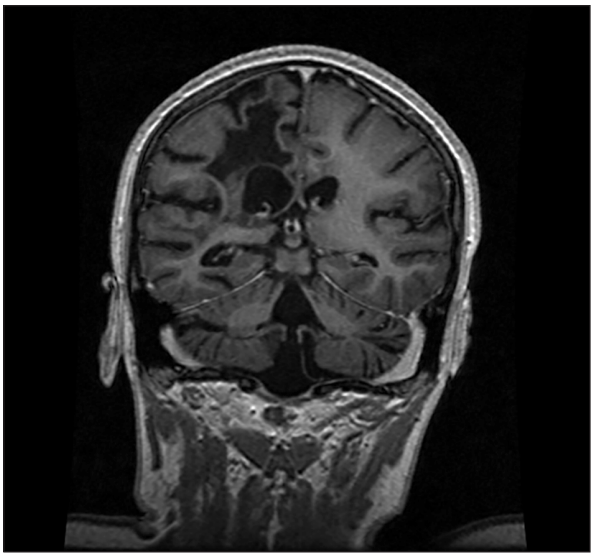

Fig. 3d. Cerebral MRI – isointense T1-weighted area of the left semioval center smaller than the isointense T1-weighted area in the right hemisphere

Figure no. 2 Cerebral MRI scan after 1 year: a. large left lateral ventricle; b. hyperintense lesions on T1 Flair, bilateral, supratentorial, fronto-parieto-occipital; c. large isointense area located fronto-parieto-occipital with ill-defined margins; d. isointense area of the left semioval center.

Case report 2

A 25-year-old woman known with human immunodeficiency virus (HIV) for 11 years, returned to hospital accusing headache, vertigo, asthenia with insidious onset, without fever for almost 2 months. From the moment of diagnosis she started antiretroviral therapy, but she had poor adherence and virological and immunological evolution were not favorable. We performed a resistance test 3 years before the moment of presentation, which revealed no resistance mutation. After discussion regarding poor adherence, she decided to stop therapy.

Clinical examination at the moment of presentation revealed generalized lymphadenopathy, hepatomegaly, horizontal nistagmus, mild speech disorders and muscle weakness.

Complete blood cell count revealed leucopenia, anemia, thrombocytopenia, elevated inflammatory tests, low CD4 cell count (35 cells/μl), HIV-RNA plasma- 463 copies/ml.

A cerebral CT-scan with contrast described a hypodense area, without enhancement, 37/33mm, located in the right cerebellar hemisphere, extending to middle cerebellar peduncle, with slight upward transtentorial herniation. (Fig. 3)

Clinical evolution

cART was restarted with Zidovudine+Lamivudine +Lopinavir/ritonavir. Unfortunately, in the next few

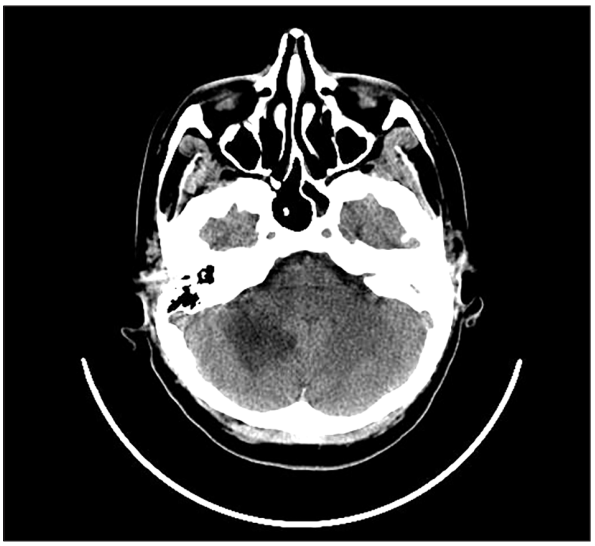

Fig. 3. CT scan: in the right cerebellar hemisphere – hypodense area, without enhancement, 37/33mm.

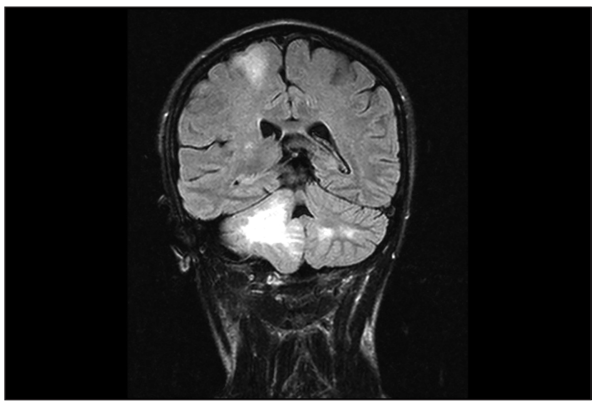

Fig. 4 a. Brain MRI – coronal section**:** hyperintense lesions on T2- weighted images, in the right cerebellar hemisphere, left cerebellar hemisphere and in the right frontoparietal region

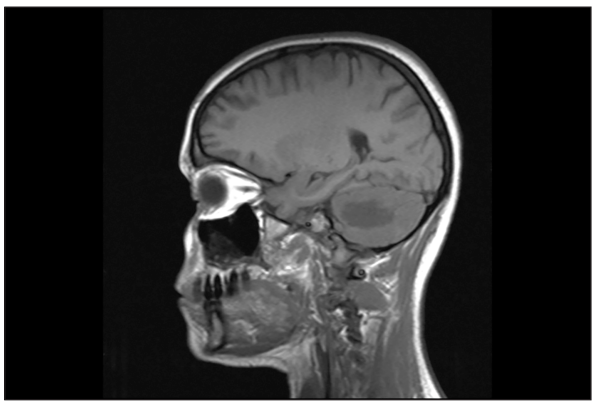

Fig. 4 b. Brain MRI – sagittal section – hypointense T1-weighted lesion located in the cerebellar hemisphere

Figure 4. Brain MRI: hyperintense lesions on T2- weighted images (a), hypointense on T1-weighted images (b), without enhancement, located in the right cerebellar hemisphere, left cerebellar hemisphere and cortical-subcortical right frontoparietal region.

days of hospitalization, the clinical evolution was unfavorable with significant progression of neurological disorders: the patient developed an unsteady gait, balance disorders, walked with a wide base of support, mild speech disorders, right hemiparesis, left ear discharge subsequently positive for Proteus.

Brain MRI described lesions situated in the right cerebellar hemisphere and extending to the vermis, right middle cerebellar peduncle and pons, cortical-subcortical right frontoparietal lesions and smaller areas affected in the left cerebellar hemisphere. (Fig. 4). The lesions were bilateral, but asymmetrical, hyperintense on T2 –weighted images, hypointense on T1- weighted images, without enhancement. A lumbar puncture was performed: the CSF was clear, normotensive, with pleocytosis and normal albumin levels but PCR for JC virus DNA was positive in this case too.

Unfortunately, her condition worsened and the patient developed left peripheral facial paralysis, right motor deficit with moderate axial muscle hypotonia, dysarthria, diplopia.

The cART regimen was potentiated by adding Enfuvirtide in order to improve her immunological status quickly. Unfortunately, her condition worsened in the next 5 days of hospitalization, with dysphasia, loss of sphincter control, coma, and the patient died.

Discussion

Different data from the literature highlights that diagnosis of PML should be taken into consideration when ataxia develops in any patient with underlying malignancy, chronic infection, or other disease that involve immunological deficiency. In immunocompromised patients, PML is caused rather by reactivation of a latent infection than a primary exposure to the JC polioma virus.[6,7]

As many as 90% of healthy people have serum antibodies to the JC virus, but less than 10% show any evidence of ongoing viral replication[4]. PML occurs in 4-7% of patients with AIDS[5] and the number of CD4 cells and the JCV specific immune response seem to be relevant as prognostic markers.

PML does not always indicate the final stages of HIV infection, but CD4 cells count less than 100/uL at baseline is associated with a higher mortality rate[8]. Complete remission is not the rule, even with a sufficient cART regimen. It seems that disease evolution is highly related with affected areas of the brain.

Regarding the first case, the PML lesions seen on MRI typically do not enhance, but enhancement could suggest a relatively good immune response and hence an improved prognosis as in this case also.

The mass effect described on the first neuroimaging investigation performed to the second patient is correlated with shorter survival. The great dimensions of the lesions in the first case, compared with the second case, do not correlate with a bad prognosis. Location and mass effect have a significant impact on prognosis.

Conclusions

Regarding our patients, at the moment of diagnosis, both had immunological failure, with CD4 cell count <100 cells/mmc. The diagnosis was suggested by the signs, symptoms, MRI changes and was confirmed by PCR of the CSF for the detection of JCV DNA. The location of lesions had more prognostic significance than the size of the lesions. cART, with good CNS penetration, and daily physiotherapy allowed partial recovery of motor deficit, language and communication for the surviving patient.

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