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LETTER TO THE EDITOR

An unusual case of PML in HIV patient presenting with diplopia

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Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease secondary to JC virus reactivation presenting with multifocal neurologic signs [1]. Diplopia is a neurological symptom due to dysfunction at the level of the neuromuscular junction, cranial nerves, or brainstem. Infective, autoimmune, or neoplastic/paraneoplastic diseases may cause diplopia. Here, we present a case of diplopia at the onset of PML in a patient with positivity for human immunodeficiency virus (HIV). Informed consent was obtained from the patient included in the study.

A 43-year-old HIV-positive and favic female patient was admitted to Neurological Clinic of Sacco Hospital (Milan, Italy) on 1 July 2009 due to subacute onset of diplopia. Her HIV positivity was known since 1989. Notably, CD4 cell counts were 300 mm^3. Tick-borne and fever (37.5 °C) were reported 10 days prior to the onset of diplopia and 30 days prior to the admission. The neurological examination showed diplopia, horizontal nystagmus, ataxic gait, bilateral hypoesthesia on II and III trigeminal branch, and hyperreflexia on the left upper and lower limb. The ophthalmological examination was normal. Routine blood tests (including vitamin B12, folate, thrombophilic screening, and auto-antibodies) were normal. There was an increase of erythrocyte sedimentation rate, which was equal to 56 mm/h (normal value equal < 20 mm/h). Serology for *Borrelia burgdorferi* (ELISA) and *Treponema pallidum* was negative. The anti-Ach-R antibodies levels showed a positivity equal to 1.4 pmol/ml (normal value < 0.5). However, the electromyography with repetitive stimulation was normal and chest CT did not show any thymoma. The head CT scan as well as the spine MRI scan was normal. The brain MRI scan showed T2 hyperintensity at the mesencephalic tegmentum and quadrigeminal lamina (Fig. 1a, b) as well as at the bilateral superior cerebellar peduncles and right intermediate cerebellar peduncle, without enhancement (Fig. 1c, d). Cerebral spinal fluid (CSF) examination showed protein levels equal to 250 mg/l (normal value between 150 and 400 mg/l), glucose levels equal to 60 mg/dl (normal value > 40 mg/dl), and zero cells (normal value < 20×10^6/l). Of note, there was positivity for the intrathecal synthesis of IgG. Bacteriological and virological analyses, including JC virus DNA, were negative. The IgG and IgM levels for *Borrelia burgdorferi* were negative in the CSF. The HIV-RNA was > 11.000 copies/ml.

She reported a recent history of tick bite. However, she did not show the typical erythema migrans. In view of this reported event, the antibiotic therapy with oral doxycycline 100 mg twice a day and intravenous ceftriaxone 2 g daily was administered for 14 days. Additionally, the patient was started on vitamins B_1, B_6, and B_{12}. She was also started on highly active antiretroviral therapy (HAART) (lopinavir/ritonavir 100/25 mg, two tablets twice a day and emtricitabine/tenofovir disoproxil fumarate, one tablet a day).

Oral prednisone (1 mg/kg daily) was started due to the positivity of anti-acetyl choline receptors antibodies.

The clinical features of our patient showed a progressive clinical worsening in the followed month. Indeed, the patient presented dysphagia, dysarthria, bilateral facial paresis, ataxic tetra-paresis, and a general decline during the first week of September 2009. The brain MRI scan showed demyelinating lesions in left thalamus (Fig. 1e). A second lumbar puncture was performed showing positive for JC Virus this time and the diagnosis of PML was finally confirmed.

In view of this finding, intravenous methylprednisolone (1 g daily for 5 days) was administered. Additionally, Vistide (5 mg/kg: 230 mg IV every 15 days) was administered in three different doses. Of note, the patient was still on HAART during the worsening of her condition.

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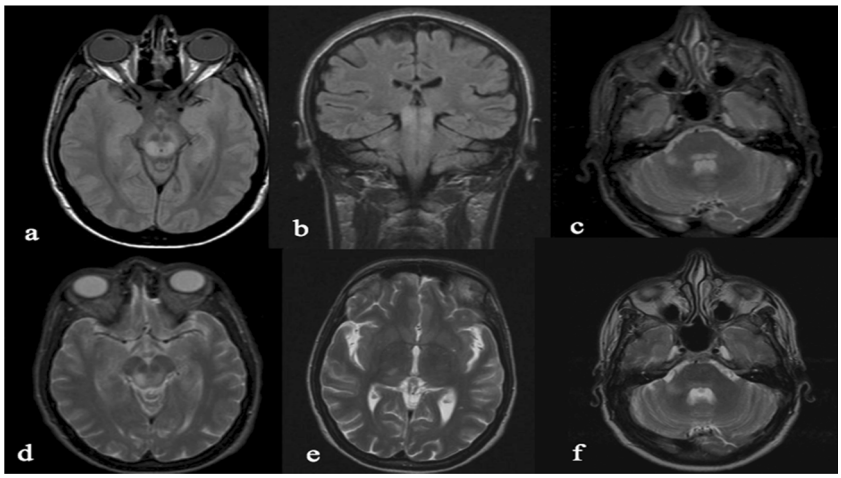

Fig. 1 Brain T2-weighted axial MRI shows hyperintensities at mesencephalic tegmentum and quadrigeminal lamina (**a**, **b** 15 July 2009), at middle cerebellar peduncles (**c**, **d** 30 July 2009); at left thalamus (**e** 07 July 2009). **f** Residual lesions of PML (19 February 2016)

The general and neurological features of our patient showed a progressive improvement until complete clinical remission in the following 7 months.

In December 2009, CD4 cell counts were 616 mm^3.

The follow-up brain MRI scan, performed 7 years after the PML onset (2016), showed the persistence of subtle signal alterations in the brainstem and right cerebellar peduncle (Fig. 1f). Interestingly, the immunological parameters were normal (CD4 > 1000/mm^3, HIV-RNA < 37 copies/ml) at the last follow-up, which has been 9 years after the onset of PML (2018).

PML is characterized by cortical-subcortical focal signs or encephalopathy features. The diplopia is a rare presentation. Brain MRI scan usually shows T2-hyperintensities and T1-hypointensities and the gadolinium enhancement is uncommon. The disease is rapidly progressive with severe prognosis and the efficacy of HAART as well as of cidofovir on PML is unclear.

Diagnosis of PML in HIV patients is a challenge because other leukoencephalopathies might affect this group of patients, especially the following types: viral (HZV-HHV-VZV-CMV-EBV) encephalopathies, the acute disseminate encephalo-myelitis (ADEM), the immune reconstitution inflammatory syndrome-PML (IRIS-PML), vasculitis with involvement of the central nervous system and not determined leukoencephalopathy (NDLE) [2, 3].

The unusual onset with diplopia and initial negative CSF for JCV-DNA delayed the diagnosis in our case. Of note, the specificity of the JCV-DNA in the CSF has 100% of specificity but 80% of sensitivity. Indeed, this test might be negative at the onset of the disease with the modest lesional load [4, 5].

Notably, in view of the tick bite history, the neuroborreliosis was a diagnostic hypothesis at the onset of the disease. However, the IgM and IgG levels for *Borrelia* were negative in the serum and in the CSF. Additionally, the patient did not show any response to the specific antibiotic therapy and the clinical course was not compatible with the borreliosis. Finally, the MRI lesions involving the thalamus were against the diagnosis of neuroborreliosis [6].

In conclusion, we have shown the long-term efficacy of HAART associated with cidofovir and high doses of IV methyl-prednisolone in a PML case involving a HIV-positive patient. The found positivity of anti-Ach-R antibodies in our patient might be a form of cross-reactivity. Indeed, although the patient showed clinical aspects of myasthenia, she did not show neurophysiological features of myasthenia and did not receive any benefit from anticholinergics. If the tick bite played a role in the pathogenesis of this case is still unknown.

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