

LETTER TO THE EDITOR

Progressive multifocal leukoencephalopathy: Report of a case preceding the diagnosis of systemic lymphoma

Leucoencefalopatía multifocal progresiva: a propósito de un caso que precede al diagnóstico de un linfoma sistémico



Dear Editor:

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by reactivation of John Cunningham (JC) virus in immunosuppressed individuals.¹ Immunosuppressive treatment in patients with haematologic neoplasms predisposes to the development of the disease²; it is extremely rare for PML to be diagnosed before the neoplasm. We present the case of a patient with PML as the initial manifestation of systemic lymphoma.

In March 2020, a 74-year-old woman was admitted to our hospital due to a 2-month history of progressive muscle weakness of the left upper limb. Physical examination revealed left hemiparesis and ipsilateral central facial palsy. Blood analysis revealed mild anaemia (haemoglobin: 11.9 g/dL) and elevated erythrocyte sedimentation rate (62 mm/h) and beta-2-microglobulin level (6789 µg/L). Brain MRI showed altered signal intensity in the right frontal lobe, which displayed diffusion restriction, but no contrast enhancement on T1-weighted sequences (Fig. 1A–C). The patient was discharged with a diagnosis of ischaemic stroke and began rehabilitation treatment. Two months later, she was readmitted due to worsening of hemiparesis. A brain MRI study revealed progression of the lesion (Fig. 1D and E). PCR testing for JC virus in the CSF yielded positive results. Treatment was started with mirtazapine at 15 mg/24 hours and citalopram at 20 mg/24 hours, but symptoms did not improve.

Suspecting an underlying neoplastic disease, we performed a chest and abdomen CT scan, which revealed splenomegaly and adenopathic conglomerates in the abdomen and pelvis; these findings are suggestive of

a lymphoproliferative process. Finally, after an inguinal biopsy, the patient was diagnosed with high-grade B-cell non-Hodgkin lymphoma. In the light of the progressive worsening, chemotherapy was ruled out. However, we did start infusions of cidofovir dosed at 5 mg/kg, administered twice weekly. During treatment, the patient presented a partial motor improvement. A further brain MRI study showed a slight reduction in the size of the lesions. On account of the patient's significant clinical improvement after 8 months' treatment with cidofovir, we decided to start a cycle of chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone. A follow-up CSF analysis performed before onset of chemotherapy revealed a considerable reduction in the number of copies of JC virus (710 IU/mL, vs 15 960 IU/mL in the previous study). However, 14 months after symptom onset, the patient died due to massive intracranial haemorrhage.

Discussion

We present the case of a patient whose diagnosis of a haematologic neoplasm resulted from the detection of PML. We believe that the systemic lymphoma caused a state of immunosuppression that predisposed the patient to PML, as she was not receiving any immunosuppressive treatment. Differential diagnosis considered the possibility of lymphoma dissemination to the brain due to the diffusion restriction in the lesions; however, treatment with cidofovir led to a clear clinical and radiological improvement, and significantly decreased JC viral load in the CSF.

Primary asymptomatic infection with JC virus occurs during childhood in most patients, with the virus subsequently remaining latent.¹ In immunosuppressed individuals, the virus infects and destroys oligodendrocytes, causing progressive demyelination of white matter in the brain.³ After HIV-positive individuals, patients with haematologic neoplasms are the largest group at risk of developing PML. In addition to the immunosuppression caused by the haematologic-oncological disease itself, chemotherapy and immunosuppressive treatments cause a further deterioration of these patients' immune status. A retrospective study conducted at an oncology centre gathered clinical data from 16 patients with haematologic cancer and diagnosed with PML in the period 2000–2015. All but one of the patients had previously been treated with chemotherapy.² It is even rarer for diagnosis of PML to precede diagnosis of the neoplasm (Table 1). As shown in the table, our patient's survival time was somewhat longer than those of other patients with similar characteristics.

With respect to treatment, the available options are limited and the clinical outcomes are rarely satisfactory.^{3,4} Prognosis is generally fatal, with a mortality rate of approximately 90% at 2 months after diagnosis.^{5,6}

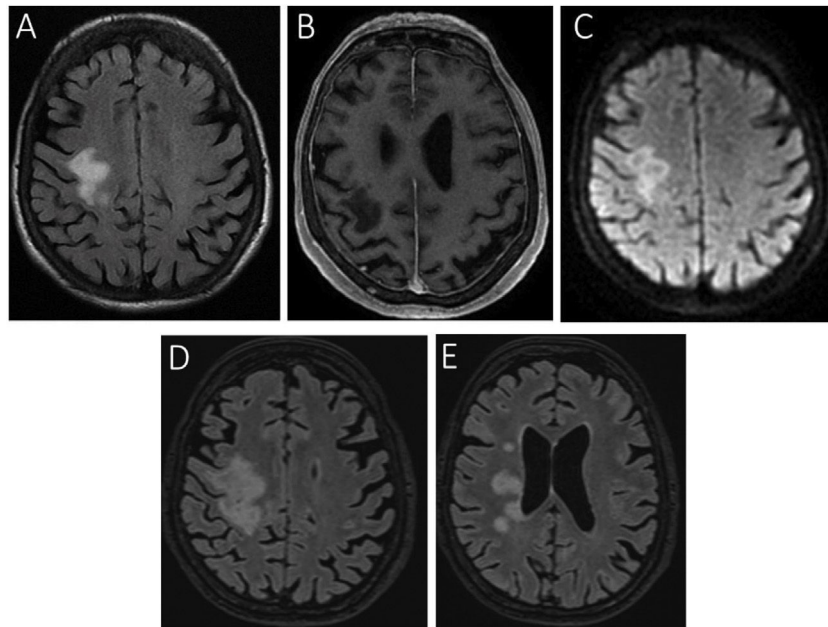


Figure 1 Brain MRI study.

Axial slices from FLAIR (A), gadolinium-enhanced T1-weighted (B), and diffusion-weighted sequences (C) at the time of the patient's first admission, showing altered signal in the right perirolandic area, extending to the centrum semiovale. The lesion presents no contrast enhancement, and appears hyperintense on the diffusion-weighted sequence. Two months later (D), the initial lesion had increased in size, extending to the corpus callosum and internal capsule; small satellite lesions were also visible in the adjacent white matter (E).

Table 1 Cases of progressive multifocal leukoencephalopathy preceding diagnosis of haematologic neoplasm.

	Sex/age	Type of neoplasm	Interval from diagnosis of PML to diagnosis of haematologic neoplasm	Treatment	Survival time after diagnosis of PML
Viallard et al., ⁴ 2005	M/61	Angioimmunoblastic T-cell lymphoma	6 months	Cidofovir, cyclophosphamide, vincristine, and prednisone	9 months
Bruce et al., ⁶ 2014	M/70	Chronic lymphocytic leukaemia	Simultaneous	None	2 months
Present study	W/74	High-grade B-cell non-Hodgkin lymphoma	3 months	Cidofovir, cyclophosphamide, doxorubicin, vincristine, and prednisolone	14 months

M: man; PML: progressive multifocal leukoencephalopathy; W: woman.

In conclusion, our case demonstrates that PML can be the initial manifestation of a haematologic neoplasm, and underscores the importance of tumour screening in patients presenting PML in the absence of any apparent cause of immunosuppression.

Informed consent

The patient gave written informed consent to the publication of this study.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Anti-NMDA-R encephalitis post-COVID-19: Case report and proposed physiopathologic mechanism



Encefalitis anti-NMDA-R post-COVID-19: descripción de un caso y propuesta de su mecanismo fisiopatológico

Dear Editor:

Coronavirus disease 2019 (COVID-19) has been linked to a wide range of neurological alterations. In many patients, SARS-CoV-2 induces an abnormal immune response, causing multisystem hyperinflammation. Some cases of autoimmune diseases triggered by COVID-19 have been described,^{1–4} including anti-N-methyl-D-aspartate (NMDA) receptor encephalitis.^{5–9} We present a case of anti-NMDA-receptor encephalitis of possible post-infectious aetiology in a patient with COVID-19.

Our patient was a 22-year-old woman erroneously diagnosed with non-lesional focal right frontal lobe epilepsy at the age of 20 years being seizure-free for the last year treated in monotherapy. In January 2022 she presented COVID-19,

with mild flu-like symptoms. Five days after symptom onset, she presented 4 focal to bilateral tonic-clonic seizures and a second antiseizure drug was started. Following this episode, the patient presented severe anxiety, dysphoric mood, and insomnia, and subsequently developed language block, which gradually progressed to motor aphasia, persisting despite adjustment of antiseizure treatment. Two weeks later, she presented 3 focal to bilateral tonic-clonic seizures within several hours, followed by a neurological worsening, developing bradyphrenia and delusions with visual hallucinations and psychomotor agitation; the patient was admitted to hospital. She did not present fever, systemic symptoms, consciousness alterations, or movement disorders. EEG revealed frontal intermittent rhythmic delta activity (FIRDA), with no other relevant findings (Fig. 1). Brain MRI and blood analysis results were normal. We initially suspected seizure control decompensation due to COVID-19, followed by postictal psychosis. The patient was started on benzodiazepines and antipsychotics. Psychiatric symptoms improved and the patient presented no further seizures, but dysphasia and bradyphrenia persisted. Four weeks a lumbar puncture was performed 4 weeks after symptom onset. CSF analysis revealed 7 cells per mm³, with normal protein and glucose levels; CSF cytology and microbiology studies (serology, cultures, PCR) yielded negative results. Anti-NMDA-receptor antibodies tested positive in the CSF and serum. Treatment with methylprednisolone dosed at 1 g/day for 5 days was started, achieving a partial improvement. Subsequently, intravenous immunoglobulins (0.4 g/kg/day for 5 days) were prescribed, gradually improv-

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