



Successful treatment of HIV-associated tumefactive demyelinating lesions with corticosteroids and cyclophosphamide: a case report

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Dear Sirs,

A 43-year-old, previously healthy man presented to the emergency department due to subacute onset, in the previous month, of behavioral changes and speech impairment. Head CT scan revealed two large subcortical hypodense lesions in both frontal lobes, with large perilesional oedema. On admission, disorientation, and attention and memory deficits with failure at the immediate recall test were noted. Spontaneous speech was poor, with anomia and perseverative behaviors. The patient scored 0/18 at the Frontal Assessment Battery [1]. Neuropsychological tests revealed global cognitive impairment and anosognosia. The remaining neurological examination was unremarkable.

Brain MRI confirmed two large oedematous lesions in frontal lobes with moderate mass effect and mild midline shift. T1-weighted sequences showed open-ring enhancement of both lesions (Fig. 1). Proton magnetic spectroscopy showed an increased lactate peak, and reduction of N-acetylaspartate levels. Total-body CT scan was negative for systemic malignancies.

Complete blood count, standard laboratory tests and autoimmune panel were unremarkable. Serum screening for anti-AQP4, anti-MOG, anti-NMDAR, anti-LGI1, anti-CASPR2

and onconeural antibodies was negative. Search for VZV, CMV, EBV, syphilis (TPHA), HCV, HBV, *M. tuberculosis* was negative too. A 4th-generation HIV test was positive, subsequently confirmed by western blotting and polymerase chain reaction, showing plasma HIV-1-RNA levels of 87,900 copies/mL; serum CD4 count was 290/ μ L. Additional serological tests for toxoplasmosis and cryptococcosis were negative. Combined antiretroviral therapy (cART) with tenofovir alafenamide, emtricitabine and bictegravir was started.

Histology from stereotaxic biopsy of the right frontal lobe lesion demonstrated several areas of demyelination. PCR for JC virus and *Toxoplasma gondii* on biopsy was negative, as well as *Mycobacterium tuberculosis* complex and acid-alcohol-resistant bacilli tests (Fig. 1).

Neuroradiological and pathological findings were suggestive of tumefactive demyelinating lesions (TDLs). Intravenous 1-g methylprednisolone was administered for 7 days. Two days after the last dose, a follow-up brain MRI showed dimensional decrease of both frontal lesions, with disappearance of mass effect; gadolinium enhancement was substantially decreased (Fig. 1). However, a new small capsulo-lenticular lesion with analogous features was noted. Lumbar puncture showed mild lymphocytic pleocytosis (14/ μ L), proteinorachia (84 mg/dL) and no oligoclonal bands; CSF glucose was 58 mg/dL. CSF was negative for infectious agents, including PCR for JC virus; CSF HIV-RNA count was 90 copies/mL.

Due to the persistent inflammatory activity observed at brain MRI, a single dose of cyclophosphamide (800 mg/m² i.v.) was administered, with benefit. At hospital discharge, the patient was oriented, with mild persisting memory deficits and sporadic anomia. At 3-month follow-up MRI, a marked reduction of FLAIR hyperintensities and absence of post-contrast enhancement were observed (Fig. 1). Neurological examination was normal, as well as cognitive function. A clinical and neuroradiological 6-month follow-up has been scheduled to assess the stability of patient's condition;

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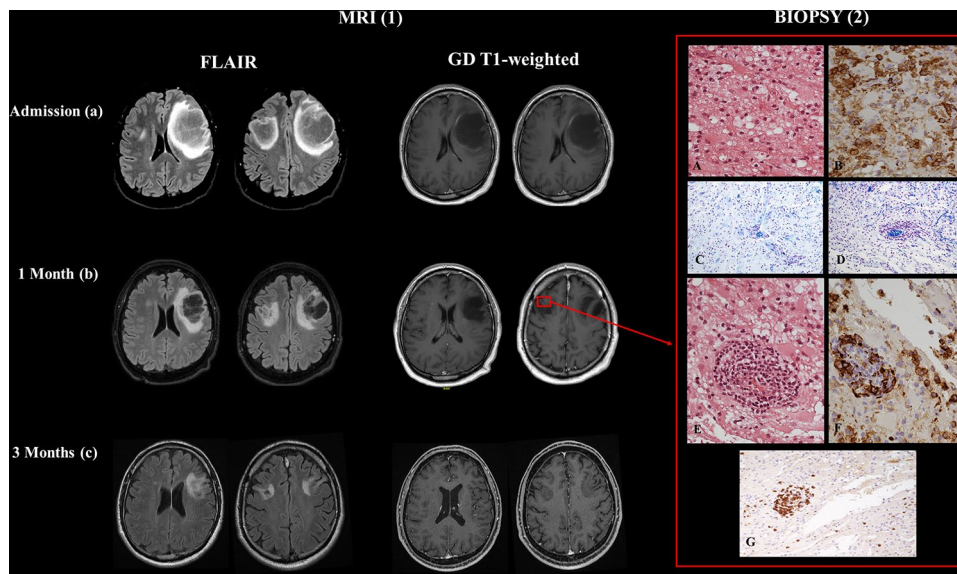


Fig. 1 (1) Serial 1.5-T MRI axial brain scans, performed after admission (a), at one (b) and 3 months (c) after the clinical onset of a frontal lobe syndrome due to large tumefactive demyelinating lesions. (2) A–D Images of brain parenchyma sample from stereotactic biopsies, haematoxylin and eosin-stained section showing increased cellularity due to the presence of numerous intraparenchymal foamy macrophages (A, $\times 40$); those cells are highlighted by anti-CD163

antibody (B, $\times 40$). Kluver–Barrera staining shows loss of myelin (C and D, $\times 20$). E–G Brain parenchyma sample with perivascular cuff is composed of mononuclear inflammatory cells stained with haematoxylin and eosin (E, $\times 40$); perivascular cuff is made of macrophages immunoreactive for anti-CD163 antibody (F, $\times 40$) and by T lymphocytes highlighted by anti-CD3 antibody (G, $\times 20$).

however, the absence of oligoclonal bands in the CSF and the neuroradiological characteristics of the lesions are highly suggestive of a monophasic event of TDLs. Only few cases of TDLs have been described among HIV patients [2, 3]. TDLs' pathogenesis is still not entirely clear and the relationship between HIV and TDLs is even less clear. A role of HIV in the dysregulation of immune response has been proposed [4], but we cannot even exclude a direct role for HIV in the demyelinating process.

The co-occurrence of HIV infection and TDLs implies obvious concerns about the treatment of this particular condition. Intravenous high-dose steroid treatment was reported to be successful in sparse cases [2, 3]. However, in literature, no data are available for steroid-unresponsive TDLs in HIV patients [5].

Given the concern to expose an HIV patient to prolonged lymphopenia, we chose cyclophosphamide to induce a quick-onset and short-duration immunosuppressive effect. We planned to administer a pulse regimen of 800 mg/m² every 4 weeks. However, due to the SARS-CoV-2 pandemic, the further doses were not administered. Nevertheless, after 5 months from the first dose, we observed a normalization of neurological examination and a significant improvement of neuroradiological findings.

In conclusion, in our case quick initiation of cART and cyclophosphamide led to a significant clinical and radiological amelioration, likely secondary to the restoration of

para-physiological immune function. Based on our experience, a treatment with cyclophosphamide may be a valid alternative in steroid-resistant HIV patients with TDLs.

Author contributions SML contributed to paper conception, data collection, analysis and interpretation, literature review and paper drafting. CM and TR contributed to data collection, analysis and interpretation, literature review and paper drafting. SF, CM, CB and ML contributed to data collection, analysis and critical review. FM contributed to paper conception, supervised data analysis and interpretation, critically reviewed the paper.

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Compliance with ethical standards

Conflicts of interest No relevant competing interest was declared by the Authors.

Ethics approval The Ethics Committee of San Raffaele Scientific Institute waived the need for ethics approval for publication of case reports.

Consent to participate Written informed consent was obtained from the patient's spouse for the usage of clinical data in anonymized fashion.

Consent for publication Informed consent for publication was obtained verbally from the spouse. The consent was audio-recorded in the presence of an independent witness.

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