Simultaneous Progressive Multifocal Leukoencephalopathy and Immune Reconstitution Inflammatory Syndrome in a SLE Patient successfully treated with Prednisone, Mirtazapine and Cidofovir

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BACKGROUND

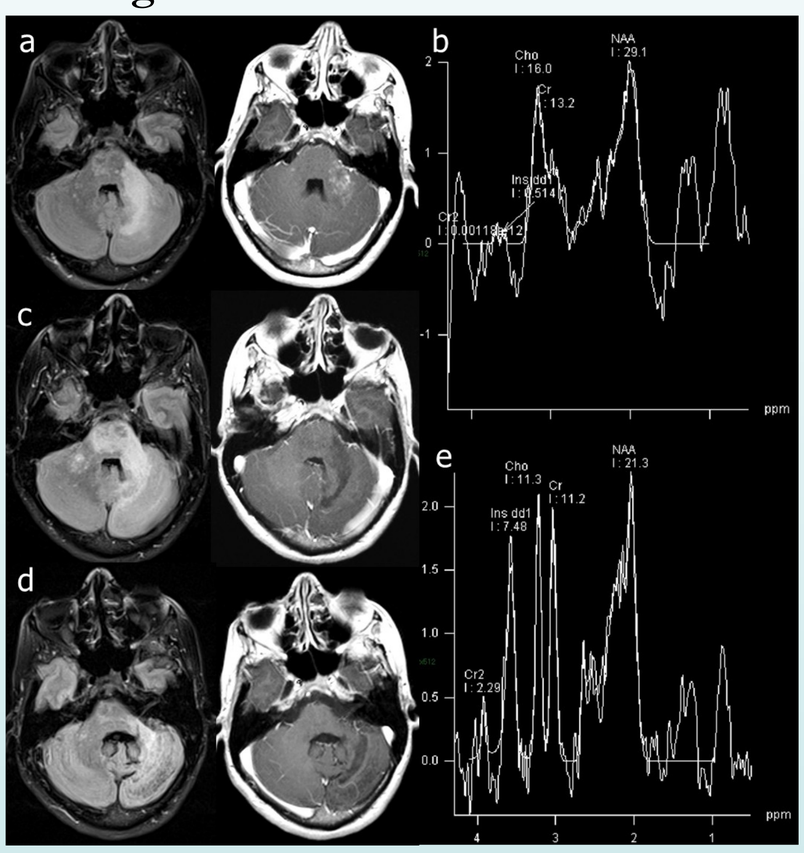
Progressive multifocal leukoencephalopathy (PML) is a devastating disease due to reactivation of the Polyomavirus JC virus (JCV) in immunocompromised patients. It has also been described in immune-mediated rheumatologic disorders such as systemic lupus erythematosus (SLE). PML can occur simultaneously with immune reconstitution inflammatory syndrome (IRIS) during immune recovery of HIV-infected patients treated by antiretroviral therapy, or in non HIV-infected patients after the withdrawal of therapeutic monoclonal antibodies or during corticosteroids tapering. To our knowledge, no case of simultaneous PML-IRIS has been reported in SLE patients.

CASE REPORT

A 39-year-old with a 10-year history of SLE treated with oral prednisone and azathioprine was referred to another institution for progressive dizziness and gait instability. Neurological examination showed ataxia, left arm dysmetria and gaze-evoked nystagmus. The positivity of Cerebrospinal fluid (CSF) polymerase chain reaction (PCR) for the JC virus (35,132 JCV DNA copies/mL) and the presence in Magnetic resonance (MR) images of a lesion in the left cerebellar hemisphere with an incomplete irregular marginal gadolinium-enhancement suggested a probable PML. Azathioprine therapy was stopped, corticosteroid treatment reduced and oral mirtazapine was started. Nevertheless, over the two following months, her neurological conditions deteriorated and she was referred to our institution. MR imaging showed increase of the lesion size, as well as of its irregular gadolinium-enhancement. These findings suggested PML-IRIS, initially unrecognized. The administration of intravenous prednisone lead to a remarkable clinical improvement. At this stage, a cyclic therapy with cidofovir was also associated. The patient regained her ability to perform daily living activities independently and CSF JCV DNA levels became undetectable. Follow-up evaluations at one and two years after admission showed stability of clinical and neuroradiological findings.

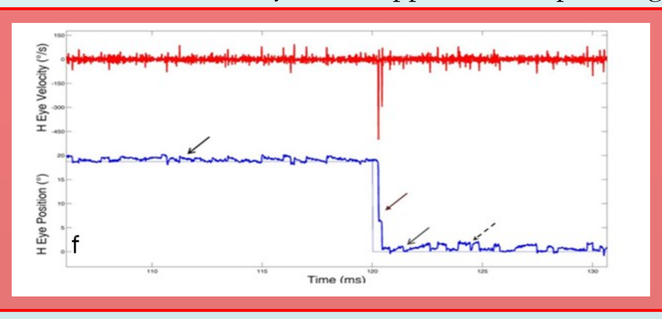
	December 2012 PML-IRIS onset	*February 2013* Patient's admission in our institution	*May 2013*	*September 2013*	*February 2014*
Clinical findings	dizziness, gait instability, uncoordinated walking, left arm dysmetria, g.e.nystagmus	slowing ideation, confusion, drowsiness, horizontal diplopia and g.e. nystagmus, gait ataxia and left cerebellar syndrome, diffuse weakness and hypereflexia	Regression of slow ideation, confusion, diplopia and diffuse weakness. Improvement of gait ataxia, left cerebellar s yndrome and g.e.-nystagmus	Regression of g.e. nystagmus, significant amelioration of gait ataxia. Persisted left arm dysmetria and diffuse hypereflexia.	Regression of gait ataxia, residual left hand clumsiness.
Laboratory investigations	Haematologic screening: lymphocytopenia with absolute CD4+ T cell count of 128 cell/mm³) Rheumathologic screening: inactive SLE status CSF test: normal cell count, glucose, protein. CSF PCR: 35.132 JCV DNA copies/mL)	Haematologic screening: lymphocytopenia with absolute CD4+ T cell count of 228 cell/mm³ CSF PCR: 2.500 JCV DNA copies/mL	CSF PCR: 543 JCV DNA copies/mL)	CSF PCR: (JCV DNA undetectable)	Haematologic screening: lymphocytopenia with absolute CD4+ T cell count of 203 cell/mm³)
MRI findings	findings consistent with PML-IRIS in the left cerebellar hemisphere.	worsening of the intracranial findings previously demonstrated, with involvement also of the brainstem	progression of demyelination, but no gadolinium-enhancement in the damaged regions		atrophy of the left ponto-cerebellar
Therapy	Azathioprine was stopped Prednisone was further tapered (5 mg daily) Mirtazapine was started (30 mg daily)	IV 1000 mg prednisolone per day for 5 days was administrated IV 5 mg/kg Cidofovir once every two weeks was started			

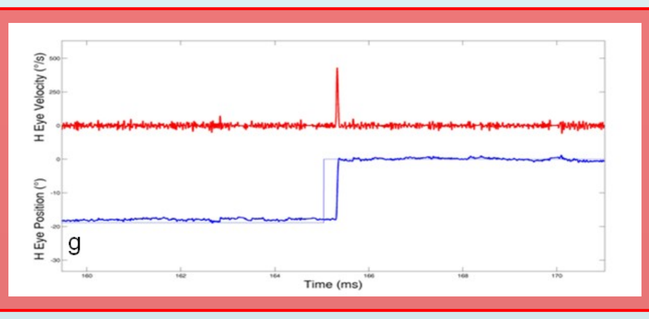
Table: focus on clinical and radiological features and therapeutic management of the described case.



(a,b,c,d,e): Magnetic resonance (MR) imaging and MR spectroscopy obtained in 2013, February (a, b) and April (c), and 2014, February (d, e), by fat-suppressed fluid-attenuated inversion recovery (left column), gadolinium-enhanced T1-weighted (middle column) axial MR images, and time of Echo: 35 ms (right column); (a,b) A predominantly left pontocerebellar lesion shows signal intensity alteration on long time of repetition images and inhomogeneous gadolinium-enhancement. MR spectroscopy shows decline in the NAA/Cr (0,36) and Cho/Cr (1,32) ratios, with marked increase of Lactate and Lipids, and subtle increase of Myo. Two months later, demyelination progresses involving the entire pons and also the right cerebellar peduncle, however there is no gadolinium-enhancement. (d, e) One year after admission, there is a clearcut shrinkage and decrease of the abnormal signal intensity of the left cerebellar hemisphere with lack of gadolinium-enhancement. Choline and lipids are still high.

(f,g): Neuro-opthalmological findings. (f) Saccadic eye movement recording before therapy; rightward eye displacement (18° amplitude, black arrow) and central eye position (0°, grey arrow) show hypometric and corrective saccades, gaze-evoked nystagmus at mean frequency of 1 Hz and quick-phase to the right and rebound nystagmus with quick-phase to the left (frequency of 0.3 Hz) (grey arrow). Square wave jerks saccadic intrusions, with mean frequency of 40/min and mean amplitude of 1.2° were also evident (dotted arrow). After therapy; leftward saccades (18° amplitude, black arrow) and central eye position (0°, grey arrow) shown. Notable improvement of saccadic accuracy and disappearance of pathologic oscillations.





CONCLUSIONS

PML-IRIS had been mainly restricted to patients with AIDS starting HIV treatment or in patients with multiple sclerosis interrupting natalizumab. Instead, the case reported herein testifies that PML can occur simultaneously with IRIS also in SLE patients, and that administration of IV corticosteroid therapy was associated with a dramatic improvement of its clinical condition. The addition of cidofovir and mirtazapine, previously tested with variable outcome in PML, may have played a role in stabilizing clinical and neuroradiological findings.

REFERENCES

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