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AN UNUSUAL CASE OF MILIARY PML-IRIS IN AN HIV+ PATIENT

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A 45-year-old female patient recently diagnosed with HIV infection ($CD4^+$ cell count 64 cells/mm^3 and plasma HIV viral load 1.4×10^6 copies/mL at diagnosis) started antiretroviral therapy (ART). At the time, she presented with gastric cryptosporidiosis and an oral candidiasis, which subsided rapidly on treatment. One month after ART initiation, the patient noticed progressive generalized slowness, speech difficulty, and a slight weakness of her right arm and leg. She also reported headache, generalized fatigue, night sweats, and weight loss. She was admitted to the hospital 4 weeks after symptoms onset. The neurologic examination revealed psychomotor slowing, mild memory and executive dysfunction, meningeal signs, dysarthria, mild lower-limb ataxia, and right faciobrachial weakness (Medical Research Council grade 4). Generalized adenopathy and wasting syndrome were also identified. Brain MRI showed a pattern of multiple miliary-enhancing parenchymal nodules (1–4 mm in diameter) more marked in the brain stem and basal ganglia (figure, A–D).

$CD4^+$ cell count was 89 cells/mm^3 (11.8%), and plasma HIV viral load had dramatically dropped at 47 copies/mL. Serological testing revealed past exposure to *Toxoplasma gondii*, Epstein-Barr virus (EBV), and cytomegalovirus (CMV). *Cryptococcus neoformans* antigen and serologies for rubella virus, herpes simplex viruses (HSV) 1 and 2, varicella zoster virus (VZV), Borrelia sp, *Bartonella henselae*, and hepatitis B and C were negative. Serum *Treponema pallidum* hemagglutination assay and venereal disease research laboratory test (VDRL) were nonreactive. Peripheral blood flow cytometry showed no malignant cells. Antinuclear antibody (anticytoplasm) titers were positive (1/640), but C3 and C4 complement titers were within normal limits. Erythrocyte sedimentation rate was 110, and C-reactive protein was inferior to 2 mmol/L.

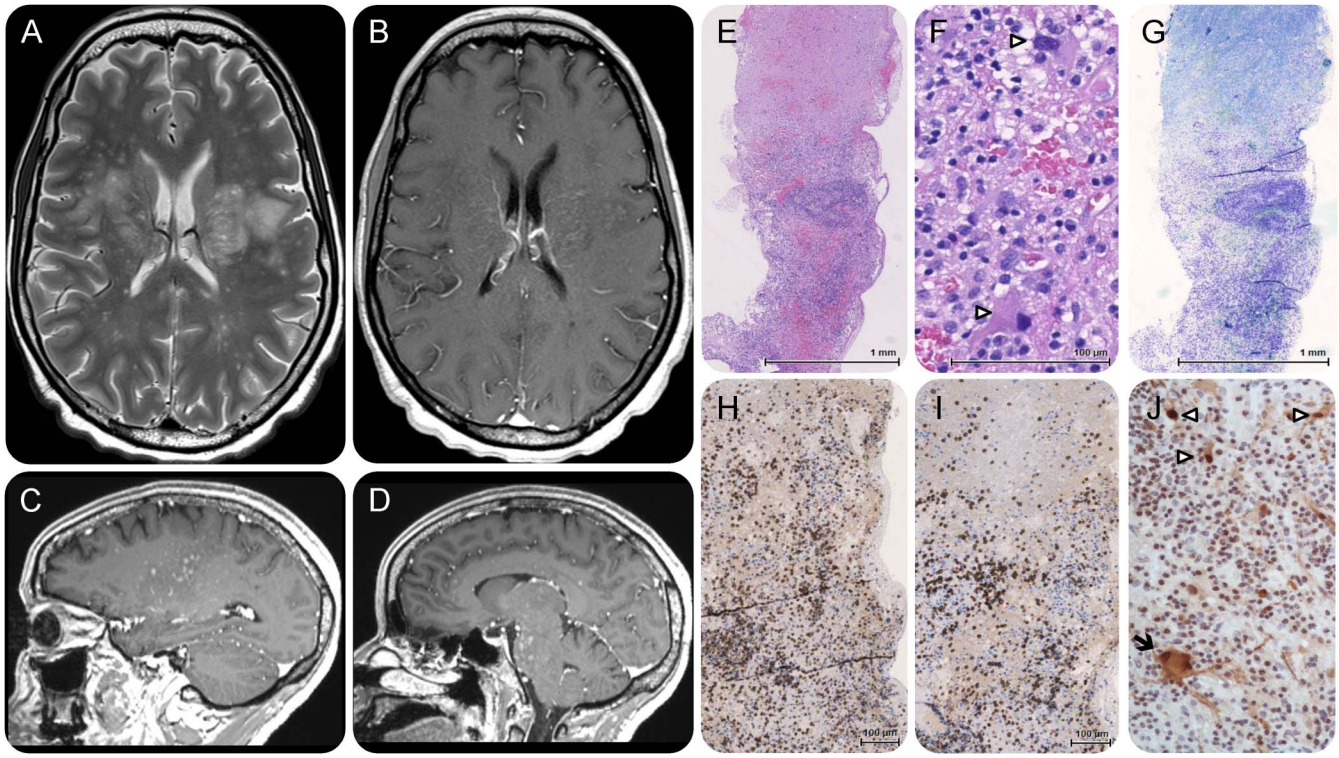
CSF examination did not reveal any leukocyte or erythrocyte; the protein content was within normal limits (431 mg/L); and the CSF-to-serum glucose ratio was 0.7. There was no intrathecal IgG synthesis. A quantitative PCR for JC virus (JCV) DNA was positive in CSF at 965 copies/mL. All the following analyses performed in the CSF were negative or normal: cryptococcal antigen, bacterial, fungal, and acid-fast cultures; PCR for *Toxoplasma gondii*; CMV, HSV, VZV, and *Tropheryma whipplei*; VDRL; and cytology. CSF HIV viral load was not measured. Stool specimen analysis revealed no *Entamoeba histolytica*, *Giardia lamblia*, microsporidies, or Cryptosporidium.

The diagnosis of progressive multifocal encephalopathy (PML) was considered. However, because the radiologic findings were absolutely not typical for this disease, a stereotactic brain biopsy was performed. This examination showed diffuse and dense perivascular inflammatory infiltrate (figure, E), scattered atypical astrocytes with hyperchromatic nuclei (figure, F, arrowheads), and demyelinization (figure, G). Immunohistochemistry showed CD3 underlining dense T-lymphocyte infiltration, mostly $CD8^+$ and glial cells staining positive for JCV (figure, H–J). The diagnosis of PML in the setting of immune reconstitution inflammatory syndrome (IRIS) was established, and the patient was treated with CCR5 antagonist maraviroc with a favorable outcome. ART treatment was continued.

PML is typically associated with subcortical confluent nonenhancing lesions. However, rarely, PML may have a "miliary" presentation.[1] This form is characterized by enhancing punctuate lesions on brain MRI, which correspond, histopathologically, to a perivascular inflammation composed mostly of $CD8^+$ T cells in contact with JCV-infected glial cells.[2] Such a punctate pattern has been described in natalizumab-associated PML,[3] but may be also seen in PML classically associated with some sort of immunosuppression, such as neurosarcoidosis or hematologic diseases.[1] A similar radiologic pattern was also reported in a patient with myelofibrosis exhibiting a rare mutation of the JCV genome.[4] To the best of our knowledge, only one other case of miliary HIV-related PML has been reported so far in a patient who was initially diagnosed with EBV encephalitis.[5]

Our patient and the review of the literature suggest that miliary PML may occur at an early stage of JCV brain infection preceding the emergence of typical PML lesions.[1] In our case, the presence of a strong JCV-specific cellular immune response

Figure **Brain MRI**



T2 axial (A) showing diffuse hyperintensities in basal ganglia and centrum semiovale on both sides, T1 transverse (B) and sagittal (C and D) showing dilated enhancing perivascular spaces after gadolinium enhancement. Neuropathology: brain parenchyma showing diffuse and dense perivascular inflammatory infiltrate (E, hematoxylin and eosin [H&E]), scattered atypical astrocytes with hyperchromatic nuclei (F, H&E, arrowheads), and demyelinization (G, Luxol fast blue). CD3 (H, immunohistochemistry [IHC]) underlines dense T-lymphocyte infiltration, mostly $CD8^+$ (I, IHC). JC virus–infected oligodendrocytes (J, IHC, arrowheads) and bizarre astrocytes (J, IHC, arrow).

suggests that miliary PML represents a very early stage of unmasking PML-IRIS. In conclusion, this case illustrates that a miliary or punctate pattern on brain MRI should prompt clinicians to rule out PML.

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