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Progressive Ataxia in an AIDS Patient on Antiretroviral Therapy

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a debilitating neurological condition caused by the opportunistic John Cunningham Virus (JCV). Clinical manifestations traditionally develop with severely immunosuppressed states. The AIDS pandemic led to a preponderance of PML diagnoses in patients with CD4 counts less than 200/microliter. The advent of HAART dramatically improved the morbidity and mortality among patients within the last decades. However, antiretroviral therapy may paradoxically lead to the development of PML in the setting of an immune reconstitution inflammatory syndrome (PML-IRIS).¹

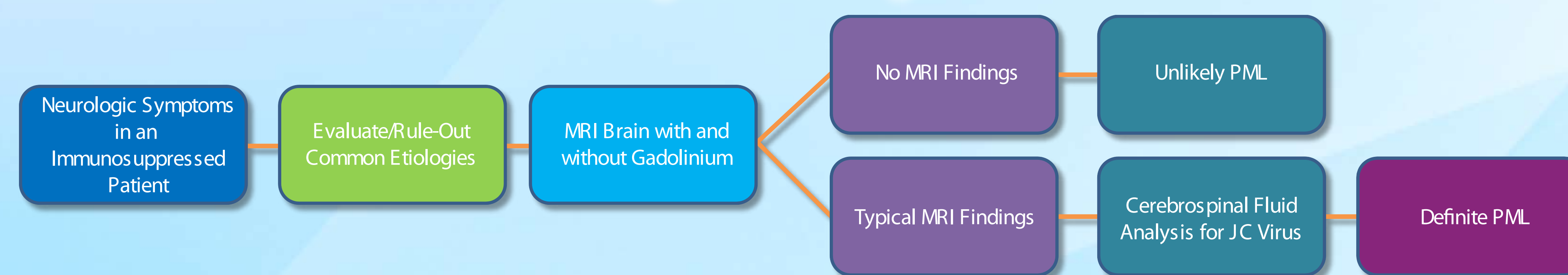
Traditional diagnosis involved brain biopsy, revealing the pathognomonic triad of oligodendroglial nuclear inclusions, demyelination, and bizarre astrocytes.² More recently, the diagnosis can be made based on a constellation of clinical, radiologic, and laboratory findings. Clinicians should suspect PML in any immunosuppressed patient presenting with neurologic signs and symptoms. The most efficacious imaging modality is an MRI of the brain with and without gadolinium; traditional findings include hyperintense lesions on T2-weighted and FLAIR images, hypointense lesions on T1-weighted images, and may include gadolinium enhancement.⁵ Although findings typically involve multifocal subcortical white matter areas, lesions can also be monofocal and involve atypical sites such as the cerebellum.³ Cerebrospinal fluid analysis (CSF) using a high-sensitivity polymerase chain reaction (PCR) assay reveals elevated JCV levels.

Risk factors associated with PML-IRIS include prior exposure to the JCV, a low CD4 count, a low HIV load, a higher baseline CD8 cell count, a history of multiple opportunistic infections, and the initiation of antiretroviral therapy in close proximity to the onset of the opportunistic infection.¹ Unfortunately, treatment options are limited. However, there are few studies demonstrating the clinical efficacy of steroids, particularly in patients with PML-IRIS.¹

Case

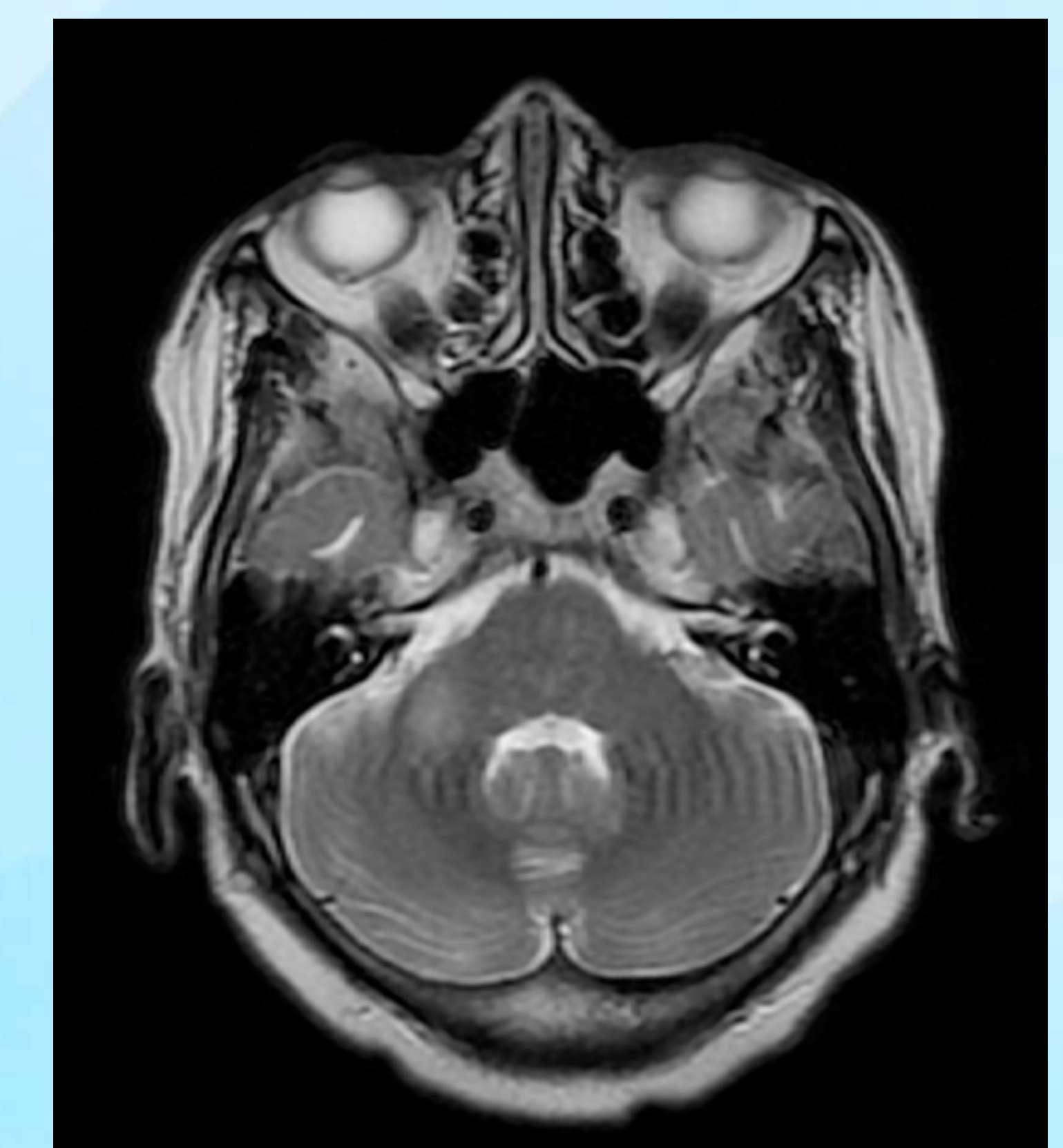
A 66-year-old female immigrant from Kenya with AIDS presented with progressively worsening ataxia. The patient was initially diagnosed with AIDS upon discovery of pulmonary tuberculosis in August 2013, for which she completed a nine-month course of treatment. She has since been on a fixed-dose combination therapy of Efavirenz, Tenofovir, and Emtricitabine. Her most recent CD4 count was 61/microliter, with a viral load of 25 copies/mL. She had developed a wide-based ataxic gait and left-sided deficits approximately 10 months after beginning antiretroviral therapy. An MRI of the brain with and without gadolinium revealed a 18mm focal area of T2-hyperintensity in the right middle cerebellar peduncle, along with prominent cerebellar leptomeningeal enhancement. Cerebrospinal fluid analysis revealed 1400 DNA copies/mL of the JC Virus. The patient's progressive ataxia, low CD4 count, significant JC Virus positivity in the CSF, and MRI findings led to the diagnosis of PML. Because her neurologic symptoms began approximately 10 months after beginning therapy, a more definite diagnosis of PML-IRIS was made, which can present up to 26 months after beginning antiretroviral therapy.¹ The patient was promptly begun on high-dose intravenous steroid therapy for symptomatic relief.

Diagnostic Algorithm



Serum Studies	
Absolute Lymphocytes	2.12
% CD3	69
Absolute CD3	1443
% CD4	3
Absolute CD4	61
% CD8	65
Absolute CD8	1353
CD4/CD8	0.04
Viral Load	25

Cerebrospinal Fluid	
RBC	16 (Ref: 0/cm)
WBC	88 (Ref: 0-5/cm)
Neutrophils	0 (Ref: 0-6%)
Lymphocytes	96% (Ref: 40-80%)
Monocytes	4% (Ref: 14-45%)
Glucose	57 (Ref: 40-70mg/dL)
Protein	120 (Ref: 15-45mg/dL)
TB Culture	Negative
Epstein Barr Virus PCR	Negative
Bacterial Culture	No growth
Listeria	Negative
Cryptococcal Antigen	Negative by Latex Agglutination
Cytology	No Clonal Proliferation
JC Virus PCR	1400 DNA Copies/mL



18mm focal area of T2 hyperintensity in the right middle cerebellar peduncle with prominent leptomeningeal enhancement involving the cerebellum.

Key Points

- Clinicians must maintain a high index of suspicion for PML in any immunosuppressed patient presenting with new or worsening neurologic signs or symptoms.⁴
- Implementation of antiretroviral therapy in AIDS patients does not exclude the possibility of PML.
- The diagnosis of PML incorporates a constellation of clinical, radiographic, and laboratory data. A pathologic diagnosis is not mandatory.
- MRI with and without gadolinium is the image of choice, and any focal or nonfocal finding may suggest PML.
- CSF analysis for the JC Virus is essential in diagnosing PML.
- Prompt diagnosis is crucial, as implementing steroid therapy may slow progression of the disease, and may lead to clinical improvement.

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