12 Progressive Multifocal Leukoencephalopathy

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INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is an opportunistic subacute demyelinating infection of the central nervous system (CNS) first described in 1958.[1] The causative agent is the polyomavirus JC that has tropism for oligodendrocytes. Asymptomatic primary infection occurs in childhood, with the virus remaining latent in the kidneys and lymphoid tissue. With profound cellular immunosuppression, the virus reactivates and spreads to the CNS.[2]

Presenting symptoms from most to least common include limb weakness, cognitive deficits, speech and visual difficulties, ataxia, seizures, and headache. The preferred diagnostic method is cerebral spinal fluid polymerase chain reaction (CSF PCR) for detection of JC virus DNA. However, since the introduction of highly active antiretroviral therapy (HAART), more PML patients are now negative for JC virus DNA in their CSF. Stereotactic brain biopsy remains the reference standard for diagnosis.[3]

PML occurs almost exclusively in immunosuppressed patients, including those with AIDS (79%), hematologic malignancies (13%), organ transplants (5%), and autoimmune diseases on immunosuppressive therapy (3%).[3] PML has rarely been reported in patients with occult immunosuppression such as hepatic cirrhosis and renal failure.[4] Both the incidence and mortality of PML has decreased since the introduction of HAART.[5,6] Although there is no specific treatment for PML, restoration of the host adaptive immune response has been shown to prolong survival.[7]

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY IMAGING EVOLUTION

Optimal management of PML depends on timely and accurate diagnosis that requires an understanding of the disease's temporal evolution. Fortunately, the combination of characteristic imaging

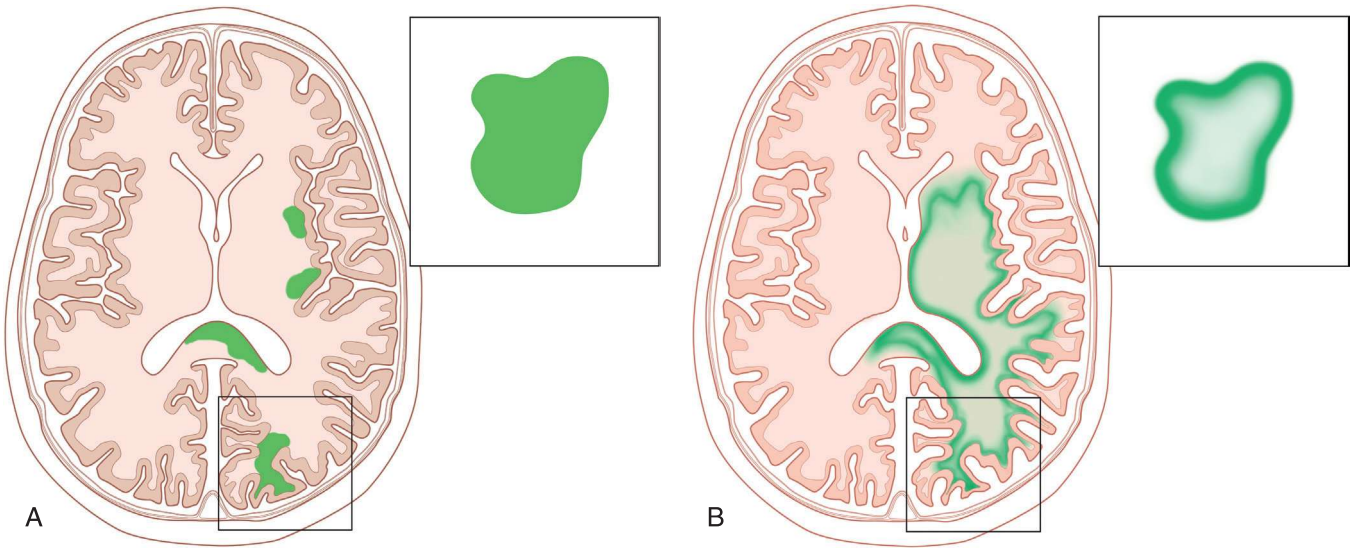

Figure 12.1. Progressive multifocal leukoencephalopathy (PML) temporal evolution. The white matter lesions (WMLs) in early PML (A) are small, round, or oval in shape, single to a few in number, and asymmetric. They form a sharp border with the cortex and can demonstrate restricted diffusion. The WMLs in late PML (B) are large, multifocal, and confluent. Mild atrophy of the brain parenchyma is often seen and the leading edge of the WMLs can demonstrate restricted diffusion corresponding to areas of active infection with elevated diffusion centrally.

TABLE 12.1 Progressive Multifocal Leukoencephalopathy (PML) Temporal Evolution

	Early PML	Late PML
Lesion Size	Small	Large
Lesion Number	Single to a few	Multiple
Atrophy	None	Mild
Mass Effect	None	None
Enhancement	None	None to minimal
Distribution	Asymmetric, separate lesions	Asymmetric, more confluent

features and appropriate laboratory tests can be used to confidently diagnose PML.

PML can be conceptually organized into early and late stages (Table 12.1). Early PML begins as single or multifocal round or oval white matter lesions (WMLs). The lesions are asymmetric in distribution and most commonly are located in the parietal and occipital lobes, as well as the corpus callosum (Fig. 12.1). Involvement of the arcuate or U-fibers forms a sharp or scalloped border between the lesions and the cortex. There is no significant mass effect or enhancement, and the lesions typically spare the periventricular white matter. Restricted diffusion may rarely be seen in very small acute lesions and more commonly along the advancing edge of larger lesions corresponding to areas of active infection and subsequent demyelination (Fig. 12.2). In late PML with disease progression, the lesions become larger and more confluent and atrophy can be seen.[3] The lesions tend to follow white matter tracts.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY IMAGING VARIANTS

There are several important imaging variants of PML that are essential for an expert understanding of the disease's imaging manifestations. The WMLs can be isolated to the cerebellum and/or brainstem.[8] Gray matter involvement is seen in up to 50% of patients.[9] A case of deep gray matter involvement with focal hemorrhage has been reported.[10] An inflammatory form of PML demonstrating mass effect and enhancement has also been described (Fig. 12.3).[11] In this case report the authors speculated the inflammatory response to be due to the patient's relatively preserved CD4 count compared with most PML patients and the patient's high HIV viral load. The HIV-1 encoded transregulatory protein TAT has been shown to upregulate the JC virus lytic cycle in vitro.[12]

DIFFERENTIAL DIAGNOSIS

The most important differential diagnoses for PML can be divided based on those patients who are HIV positive and those patients who are HIV negative.

For HIV-positive patients, HIV encephalopathy, primary CNS lymphoma, and toxoplasmosis are the most important differential considerations. The WMLs in HIV encephalopathy are diffuse and symmetric, typically spare the subcortical white matter, and have associated atrophy (Fig. 12.4).[13] The lesions in primary CNS lymphoma are most commonly periventricular in location, with subependymal involvement, and have associated enhancement.[14] The lesions in toxoplasmosis can involve the basal ganglia, thalami, and cerebellum and demonstrate enhancement (eccentric target sign).[15]

For HIV-negative patients, CNS vasculitis, multiple sclerosis (MS), and intravascular lymphoma should be considered. The basal ganglia and subcortical white matter (WM) are commonly involved in CNS vasculitis, multifocal arterial stenosis can be identified on angiography, and both acute and chronic ischemic lesions are often present (Fig. 12.5).[16] The WMLs in MS must be disseminated in space and time and typically involve the periventricular white matter (extending perpendicular to the long axis of the lateral ventricle), corpus callosum, posterior fossa white matter, and brainstem; active lesions may demonstrate enhancement.[17] There is a diversity of reported imaging findings in intravascular lymphoma, including infarct-like lesions, nonspecific WMLs, meningeal enhancement, mass-like lesions, and T2/FLAIR hyperintense lesions in the pons (Fig. 12.6).[18]

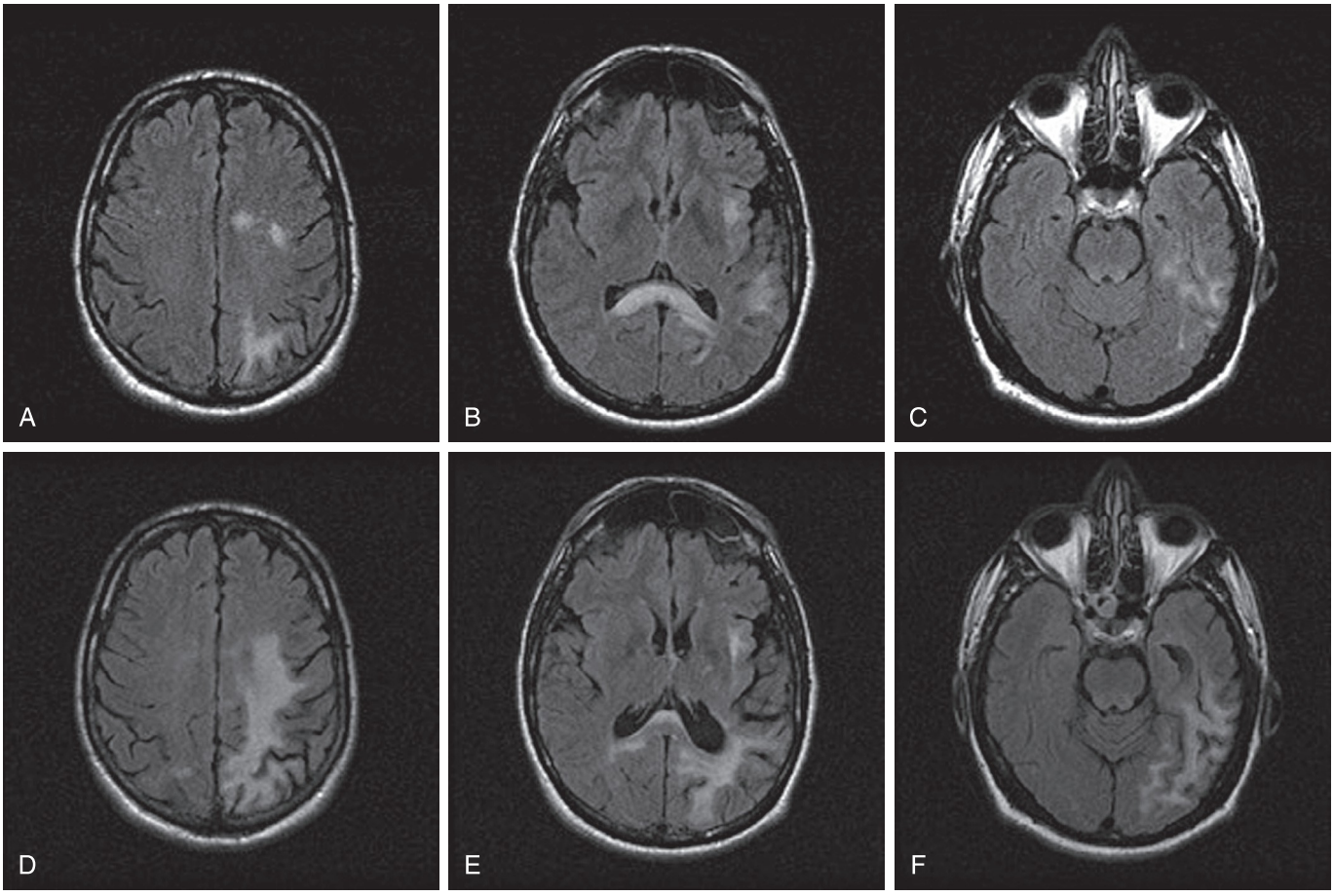

Figure 12.2. Progressive multifocal leukoencephalopathy (PML) case example. A 44-year-old male, HIV positive, presenting with 1 month of progressive neurologic changes. CD4: 148; cerebral spinal fluid: JC virus DNA positive. Axial FLAIR images (A–F). In early PML (A–C), the white matter lesions are multifocal and asymmetric, form a sharp border with the cortex, and have no significant local mass effect. In late PML (D–F), the lesions become larger and more confluent and there is associated atrophy.

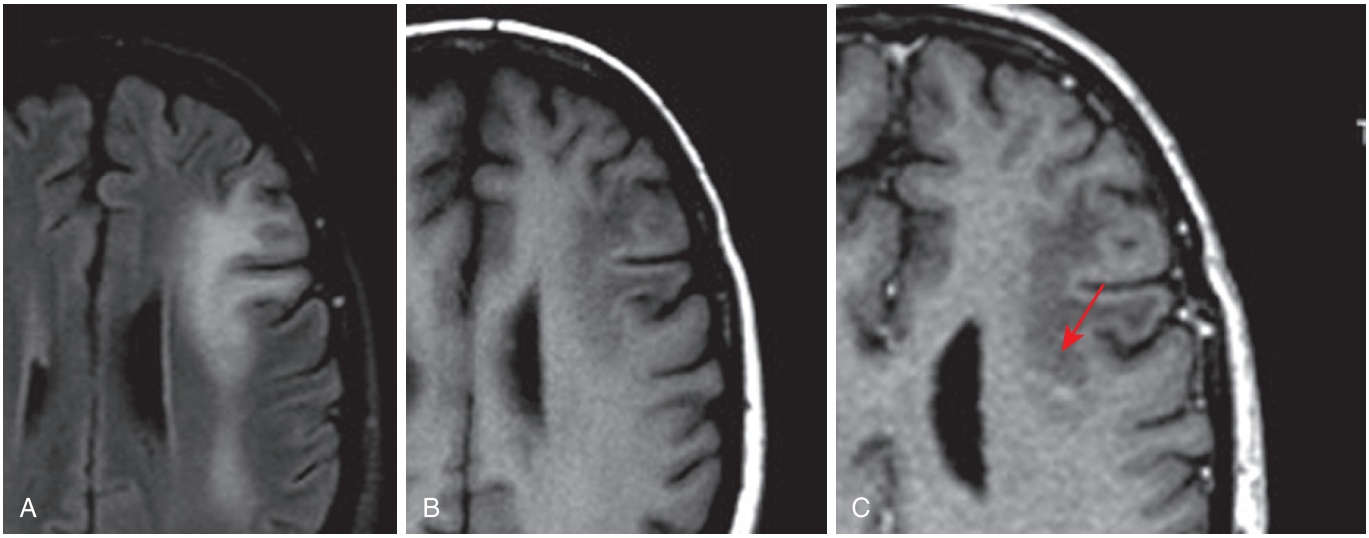

Figure 12.3. Inflammatory progressive multifocal leukoencephalopathy (PML) case example. A 48-year-old female, HIV positive, intermittently compliant with therapy. CD4: 137; cerebral spinal fluid: JC virus positive. Axial FLAIR (A), axial T1 precontrast (B), and axial T1 postcontrast (C) demonstrate a confluent white matter lesion with multifocal gadolinium enhancement *(arrow)*.

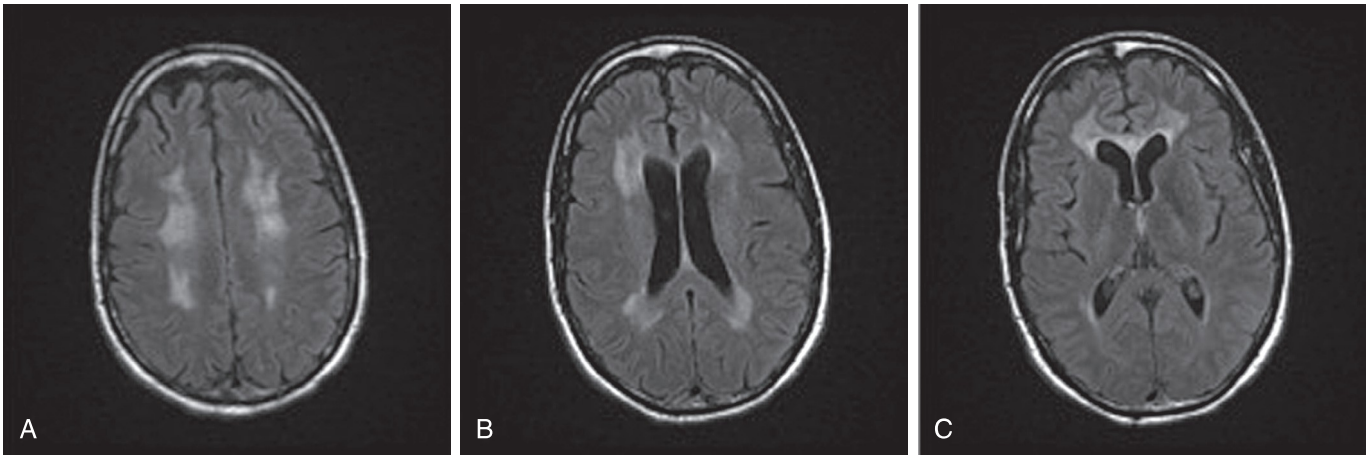

Figure 12.4. HIV encephalitis case example. A 42-year-old male, HIV positive for 15 years. Axial FLAIR images (A–C) demonstrate white matter lesions that are diffuse and symmetric with atrophy.

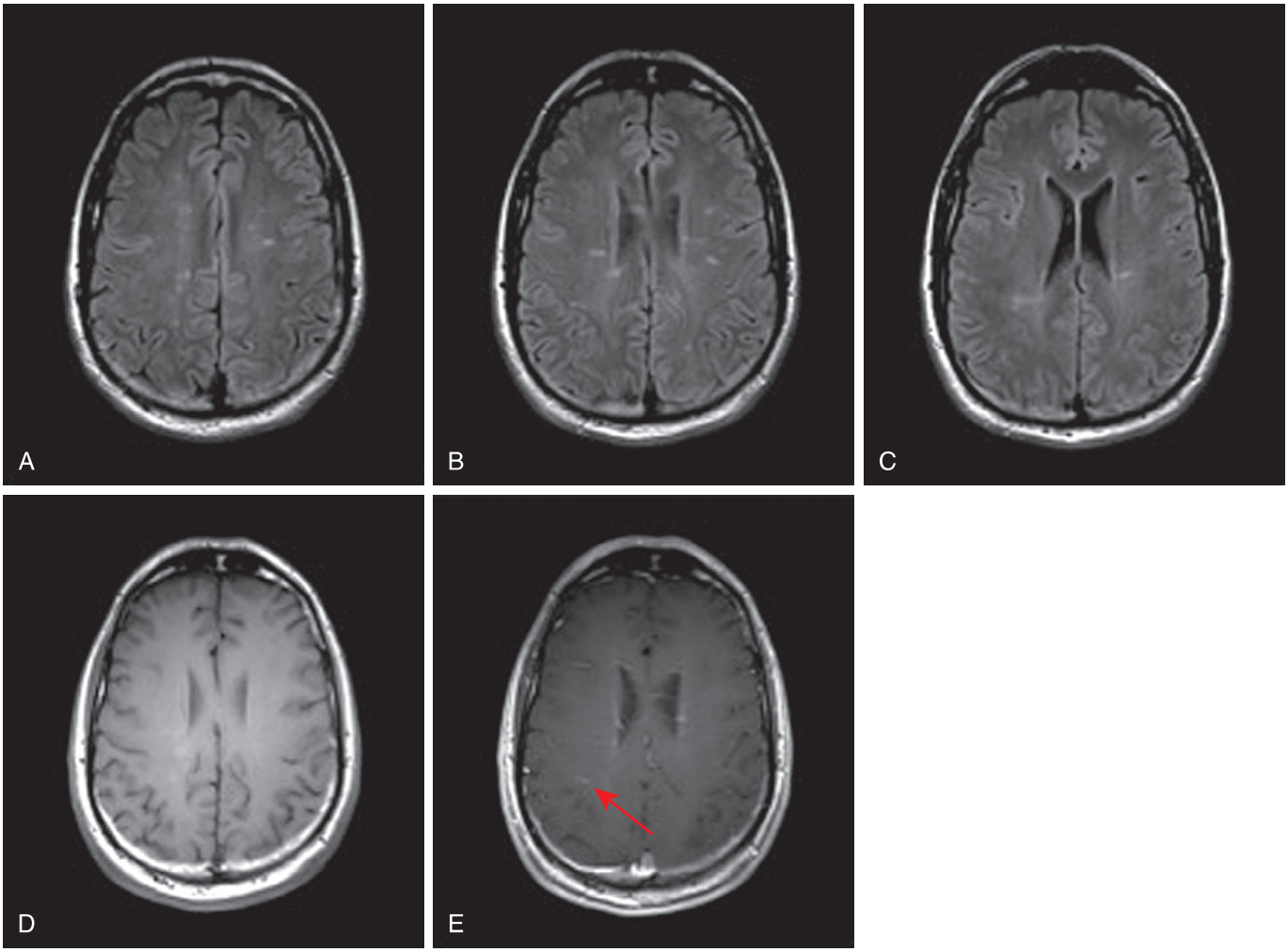

Figure 12.5. Multiple sclerosis (MS) case example. A 36-year-old male diagnosed with MS. Axial FLAIR (A–C), axial T1 precontrast (D), and axial T1 postcontrast (E) images demonstrate multifocal white matter lesions involving the periventricular white matter and corpus callosum with some lesions demonstrating enhancement *(arrow)*.

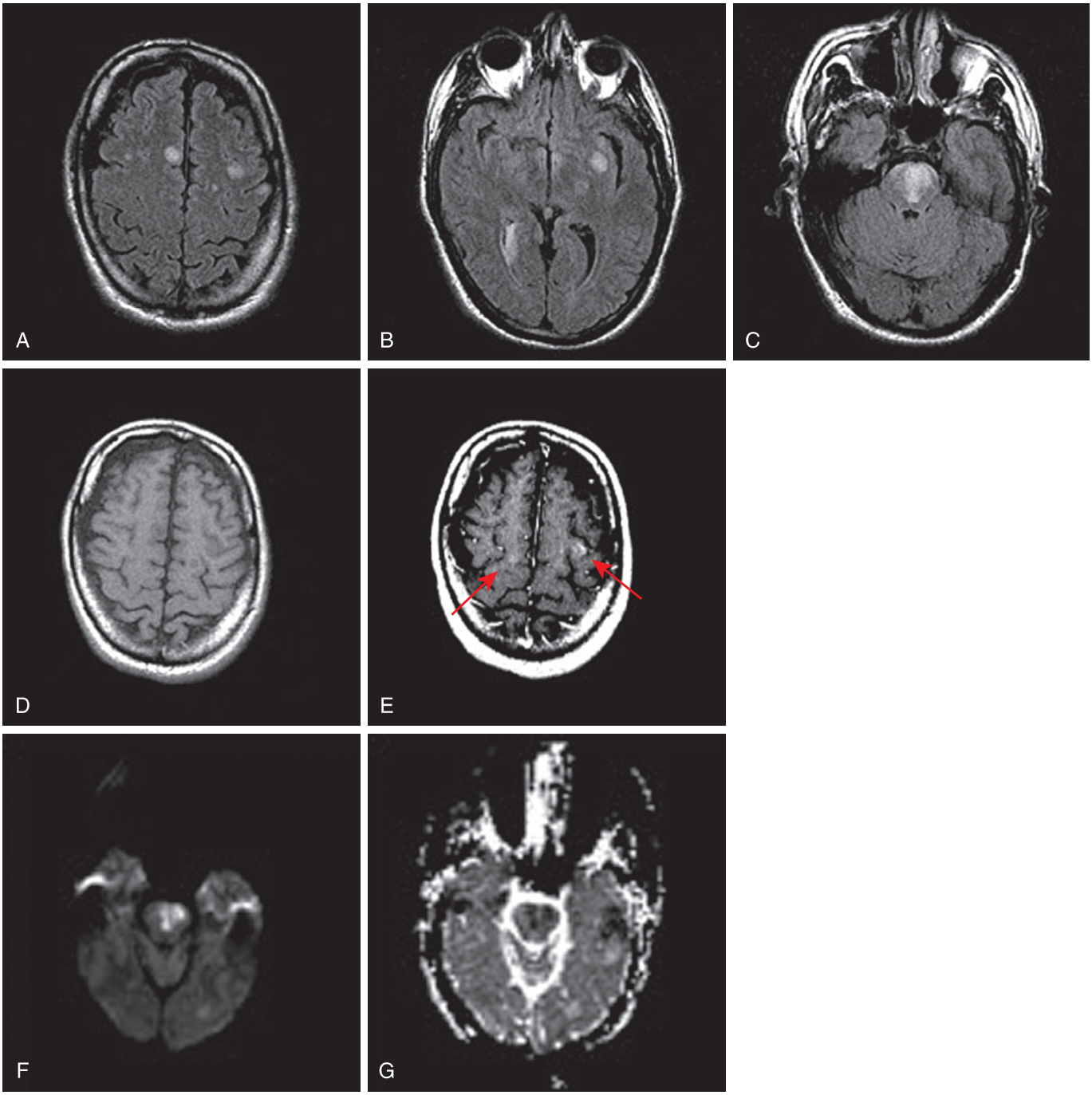

Figure 12.6. Intravascular lymphoma case example. A 50-year-old male with biopsy-proven intravascular lymphoma. Axial FLAIR images (A–C), axial T1 precontrast (D), axial T1 postcontrast (E), DWI (F), and ADC (G) images demonstrate multifocal white matter lesions involving both cerebral hemispheres and pons; some lesions have associated enhancement *(arrows)* and restricted diffusion (pontine lesions).

REFERENCES

1. Astrom KE, Mancall EL, Richardson EP. Progressive multifocal leukoencephalopathy: hitherto unrecognized complication of chronic lymphatic leukemia and Hodgkin's disease. *Brain*. 1958;81:93–111.
2. Weber T, Trebst C, Frye S, et al. Analysis of the systemic and intrathecal humoral immune response in progressive multifocal leukoencephalopathy. *J Infect Dis*. 1997;176:250.
3. Shah R, et al. Imaging manifestations of progressive multifocal leukoencephalopathy. *Clin Radiol*. 2010;65(6):431–439.
4. Gheuens S, Pierone G, Peeters P, et al. Progressive multifocal leukoencephalopathy in individuals with minimal or occult immunosuppression. *J Neurol Neurosurg Psychiatry*. 2010;81:247–254.
5. Engsig FN, Hansen AB, Omland LH, et al. Incidence, clinical presentation, and outcome of progressive multifocal leukoencephalopathy in HIV-infected patients during the highly active antiretroviral therapy era: a nationwide cohort study. *J Infect Dis*. 2009;199:77.
6. Koralnik IJ. New insights into progressive multifocal leukoencephalopathy. *Curr Opin Neurol*. 2004;17(3):365–370.
7. Calabrese L. A rational approach to PML for the clinician. *Cleve Clin J Med*. 2011;78(suppl 2):S38.
8. Kastrup O, Maschke M, Diener HC, et al. Progressive multifocal leukoencephalopathy limited to the brain stem. *Neuroradiology*. 2002;44(3):227–229.

9. Mark AS, Atlas SW. Progressive multifocal leukoencephalopathy in patients with AIDS: appearance on MR images. *Radiology*. 1998;173 (2):517–520.
10. Sarrazin JL, Soulie D, Derosier C, et al. MRI aspects of progressive multifocal leukoencephalopathy. *J Neuroradiol*. 1995;22:172–179.
11. Hoffmann C, Horst HA, Albrecht H, et al. Progressive multifocal leucoencephalopathy with unusual inflammatory response during antiretroviral treatment. *J Neurol Neurosurg Psychiatry*. 2003;74(8):1142–1144.
12. Chowdhury M, Taylor JP, Tada H, et al. Regulation of the human neurotropic virus promoter by JCV-T antigen and HIV-1 TAT protein. *Oncogene*. 1990;5:1737–1742.
13. Descamps M, Hyare H, Stebbing J, et al. Magnetic resonance imaging and spectroscopy of the brain in HIV disease. *J HIV Ther*. 2008;13(3):55–58.
14. Schlegel U, Schmidt-Wolf IG, Deckert M. Primary CNS lymphoma: clinical presentation, pathological classification, molecular pathogenesis and treatment. *J Neurol Sci*. 2000;181(1–2):1–12.
15. Batra A, Tripathi RP, Gorthi SP. Magnetic resonance evaluation of cerebral toxoplasmosis in patients with the acquired immunodeficiency syndrome. *Acta Radiol*. 2004;45(2):212–221.
16. Abdel Razek AA, Alvarez H, Bagg S, et al. Imaging spectrum of CNS vasculitis. *Radiographics*. 2014;34(4):873–894.
17. Filippi M, Rocca MA. MR imaging of multiple sclerosis. *Radiology*. 2011;259(3):659–681.
18. Yamamoto A, Kikuchi Y, Homma K, et al. Characteristics of intravascular large B-cell lymphoma on cerebral MR imaging. *AJNR Am J Neuroradiol*. 2012;33(2):292–296.