Neurology Asia 2024; 29(2) : 507 – 509

IMAGING HIGHLIGHTS

Focal haemorrhage as atypical feature on MRI in progressive multifocal leukoencephalopathy

Lakshmi Priya *MD DM*, Mahendra Javali *MD DM*, Purushottam Acharya *MD DM*, Pradeep Rangaiah *MD DM*

Department of Neurology, MS Ramaiah Medical College, Bangalore, India

Progressive multifocal leukoencephalopathy (PML) is a severe progressive demyelinating disorder caused by the suppression of cell-mediated immunity and is diagnosed by typical imaging features on MRI and confirmed by the identification of the JC virus on CSF. We present a case of HIV positive adult male who presented with progressive hemiparesis and spastic dysarthria over 3 months duration, and MRI showed white matter T2 hyper, T1 isointense and peripherally diffusion restricting lesion in the right frontoparietal region with an additional focal haemorrhage within the lesion, which misled us away from considering PML. However, repeat imaging showed progression of the lesion and CSF analysis showed John Cunningham (JC) virus, confirming the diagnosis.

CASE REPORT

A 53-year-old male had insidiously developed weakness in his left upper limb, which progressed to impair his functional status over 2 weeks duration and was later followed by progressive left lower limb weakness, which required 1 person's support for ambulation over the next 1 month. He later became completely bedridden with bowel and bladder incontinence by 3 months from the onset of initial symptoms when he presented to us. In addition, he also had cognitive impairment in the form of inattention, reduced social interaction and apathy. He has had significant weight and appetite loss over the last 5-6 months. On examination, he was drowsy, easily arousable, and obeyed simple commands, and he had significant spastic dysarthria with left upper motor neuron facial palsy and left spastic hemiparesis with frontal release signs with no involuntary movements or meningeal signs. The clinical possibilities considered were intracranial space-occupying lesion like a tumour, metastasis, atypical intracranial tubercular, parasitic or fungal infection in view of associated significant constitutional symptoms. Progressive demyelination was also considered in view of the evolution of clinical features, though was considered least likely. Routine investigations showed normal blood counts, coagulation parameters, renal and liver functions. Viral markers showed HIV-positive status with a CD4 count of 85 cells/mm3, following which atypical intracranial infections and tumors in immunocompromised states like lymphoma were the considerations.

MRI Brain with contrast showed asymmetrical bilateral predominant subcortical white matter lesions, which were large on the right frontal region and very small on the left frontal area, that was T2 hyperintense, T1 iso to hypointense and diffusion hyperintense along the outer border of the lesion. T2 FLAIR showed small punctate hyperintensities scattered around the main lesion, and T2 showed multiple hyperintensities within the main lesion suggestive of probable vacuoles. In addition to the above findings, there was a small area of focal blooming within the main lesion, which was also hyper dense on CT scan, suggesting focal bleed. There was no contrast enhancement of the entire lesion on MRI. (Figure 1).

The differentials considered based on imaging were PML, except for the focal bleed within the lesion, which was odd for typical PML and resolving stages of a primary intracranial bleed, but the presence of vacuoles and multiple punctate lesions outside the primary lesions being odd. Routine cerebrospinal fluid analysis showed 5 lymphocytes with normal sugars and mildly elevated proteins of 51 mg/dL Given the clinical and radiological suspicion of PML, CSF for JC virus PCR was sent and was found to be

Address correspondence to: Dr. Lakshmi Priya, MD, DM, Assistant Professor of Neurology, MS Ramaiah Medical College, Mathikere, Bangalore – 560054, India. Tel: 8903211566, Email: lalithapriya.68@gmail.com

Date of Submission: 21 December 2023; Date of Acceptance: 6 March 2024

https://doi.org/10.54029/2024irw

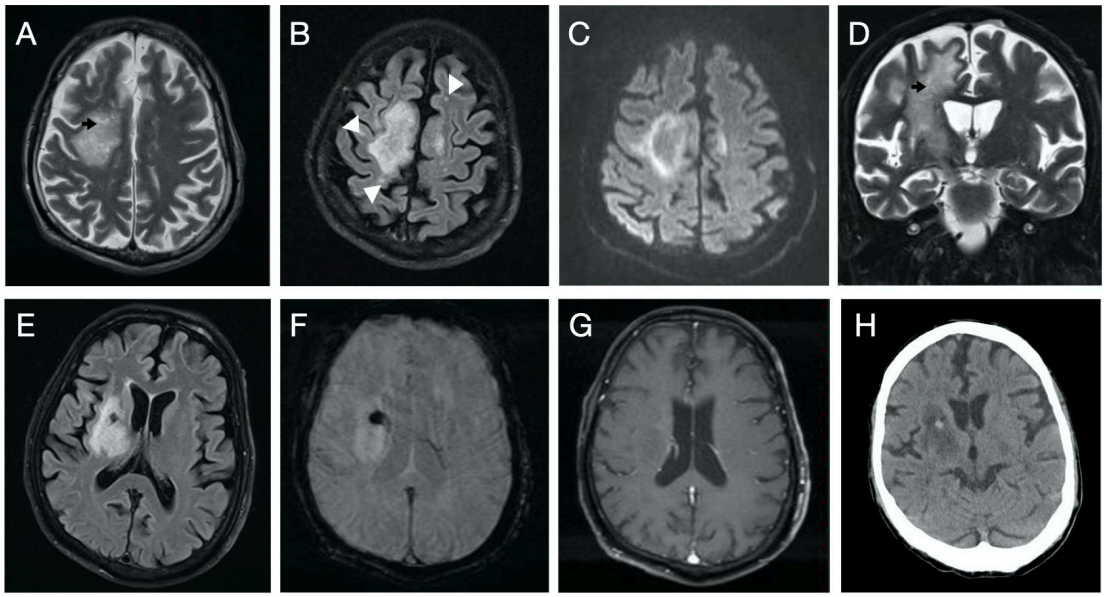

Figure 1. (A) Axial T2 showing white matter hyperintense lesion with vacuoles within (black arrows); (B) Axial T2 FLAIR showing small hyperintense lesions around the main lesion (milky way sign); (C) peripheral diffusion hyperintense along the spreading edge (rim and core pattern); (D) Coronal T2 section showing the extent of lesion; (E) Axial T2 section showing focal hypointensity within the main lesion; (F) SWI sequence showing blooming within in the lesion; (G) no contrast enhancement (H) CT Brain confirming bleed within the main lesion.

positive, confirming the diagnosis of PML. He was started on highly active antiretroviral therapy in addition to structured, regular physiotherapy and speech therapy. However, after a few weeks, he succumbed to respiratory failure due to aspiration pneumonitis.

DISCUSSION

PML is an opportunistic and potentially fatal infection caused by JC virus, which is an ubiquitous polyomavirus found to latently infect the healthy kidneys in about 50% of the general population and reactivates upon immunosuppression or with the use of monoclonal antibodies like natalizumab or rituximab.[1] The virus undergoes genetic rearrangement in noncoding region to become neurotrophic and predominantly affects oligodendrocytes and astrocytes in addition to neurons in cortical grey matter and granule cells in cerebellum causing irreversible demyelination and neuroaxonal damage leading to granule cell neuronopathy, JC virus encephalopathy and JC virus meningitis.[2,3]

The virus has a propensity to affect the nuclei of oligodendrocytes. It undergoes replication within, in addition to causing direct extension of the lesion and denovo lesions, which later coalesce to form a large necrotic mass of severely damaged axons. The affected oligodendrocytes are seen to concentrate within the spreading edge of the lesion, and the infected astrocytes show pleomorphic changes similar to those of neoplastic cells.[4] Classical PML is characterised by infiltration of numerous macrophages to phagocytose myelin debris and very few T cells, B cells and plasma cells, while PML-IRIS is characterised by numerous CD8+ T cells and plasma cells.[5] The definite diagnosis of PML had been the demonstration of histopathological triad of demyelination, bizarre astrocytes and oligodendroglial nuclear inclusion.[5] However, with the consensus statement from American Academy of Neurology, various grades of PML diagnostic certainty can be made based on clinical, radiological and laboratory data, based on which our patient had a definite certainty of PML diagnosis.[6]

Multi sequence MRI is a sensitive tool for initial diagnosis, identification of immune reconstitution and follow up of lesion progression after diagnosis. PML lesion is most commonly found in the frontal and parieto-occipital region and to a lesser extent in the temporal lobe, basal ganglia and posterior fossa, while the optic nerve and spinal cord are least likely to be affected.[7] The lesion is isointense to hypo intense on the T1 sequence and hyperintense on the T2 sequence

with a sharp spreading border towards the cortex with perilesional nodules, intralesional vacuoles and multiple small punctate lesions outside the main lesion, which may enhance with contrast sometimes. The lesion volume is found to correlate with viral load but ceases to correlate after immune reconstitution occurs.[8] A diffusion-weighted image (usually with b1000 s/mm2 values) shows increased signal in the periphery with isointense or occasionally low ADC values representing swollen oligodendrocytes. With PML-IRIS, when the blood-brain barrier breaks down, vasogenic edema occurs, causing increased ADC values, which expand, but the hyperintense rim on DWI remains the same.[9] SWI characteristically shows paramagnetic leukocortical rim or band, which is proposed to occur due to iron accumulation in subcortical U-fibres, possibly within phagocytes due to blood-brain barrier disruption and cortical laminar necrosis.[10,11]

Focal haemorrhage within the main PML lesion may be seen rarely, which may present clinically with acute worsening in sensorium, seizure, focal deficit or asymptomatic. However, previous literature on atypical imaging features like focal atrophy and subcortical grey matter involvement are scant but well described in case reports, yet the pathogenesis is not known.[12]

DISCLOSURES

Ethics: Informed consent has been obtained from patient's wife, as the patient himself was disabled to give consent.

Financial support: None

Conflict of interest: None

REFERENCES

1. Cettomai D, McArthur JC. Mirtazapine use in human immunodeficiency virus–infected patients with progressive multifocal leukoencephalopathy. *Arch neurology* 2009;66(2):255-8. doi:10.1001/archneurol.2008.557
2. Cortese I, Reich DS, Nath A. Progressive multifocal leukoencephalopathy and the spectrum of JC virus-related disease. *Nat Rev Neurol* 2021;17(1):37-51. doi.org/10.1038/s41582-020-00427-y
3. Major EO, Yousry TA, Clifford DB. Pathogenesis of progressive multifocal leukoencephalopathy and risks associated with treatments for multiple sclerosis: a decade of lessons learned. *Lancet Neurol* 2018;17(5):467-80. doi.org/10.1016/S1474-4422(18)30040-1
4. Richardson Jr EP. Our evolving understanding of progressive multifocal leukoencephalopathy. *Ann N Y Acad Sci* 1974;230(1):358-64. doi.org/10.1111/j.1749-6632.1974.tb14469.x
5. Astrom KE, Mancall EL, Richardson EP. Progressive multifocal leukoencephalopathy. A hitherto unrecognized complication of chronic lymphatic leukemia and Hodgkin's disease. *Brain* 1958; 81:93-111. doi.org/10.1093/brain/81.1.93
6. Berger JR, Aksamit AJ, Clifford DB, *et al*. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. *Neurology* 2013;80(15):1430-8. doi.org/10.1212/WNL.0b013e31828c2fa1
7. Brew BJ, Davies NW, Cinque P, Clifford DB, Nath A. Progressive multifocal leukoencephalopathy and other forms of JC virus disease. *Nat Rev Neurol* 2010;6(12):667-79. doi.org/10.1038/nrneurol.2010.164
8. Wijburg MT, Kleerekooper I, Lissenberg-Witte BI, *et al*. Association of progressive multifocal leukoencephalopathy lesion volume with JC virus polymerase chain reaction results in cerebrospinal fluid of natalizumab-treated patients with multiple sclerosis. *JAMA Neurol* 2018;75(7):827-33. doi:10.1001/jamaneurol.2018.0094
9. Bergui M, Bradac GB, Oguz KK, *et al*. Progressive multifocal leukoencephalopathy: Diffusion-weighted imaging and pathological correlations. *Neuroradiology* 2004;46(1):22-5. doi.org/10.1007/s00234-003-1115-9
10. Thurnher MM, Boban J, Rieger A, Gelpi E. Susceptibility weighted MR imaging hypointense rim in progressive multifocal leukoencephalopathy: The end point of neuroinflammation and a potential outcome predictor. AJNR *Am J Neuroradiol* 2019;40(6):994-1000. doi.org/10.3174/ajnr.A6072
11. Khoury MN, Alsop DC, Agnihotri SP, *et al*. Hyperintense cortical signal on magnetic resonance imaging reflects focal leukocortical encephalitis and seizure risk in progressive multifocal leukoencephalopathy. *Ann Neurol* 2014;75(5):659-69. doi.org/10.1002/ana.24144
12. Sarrazin JL, Soulié D, Derosier C, Lescop J, Schill H, Cordoliani YS. Aspects IRM de la leucoencéphalopathie multifocale progressive [MRI aspects of progressive multifocal leukoencephalopathy]. *J Neuroradiol* 1995;22(3):172-9. In French.