Clinical Reasoning: Progressive Hemiparesis and White Matter Abnormalities in an HIV-Negative Patient

Edwin Jabbari, MD, PhD, Fernanda Ruiz, MD, Simon F.K. Lee, MD, PhD, Farrah Jabeen, MD, Sebastian Brandner, MD, Desmond P. Kidd, MD, PhD, Hadi Manji, MD, PhD, and Amit Batla, MD, PhD

Correspondence
Dr. Jabbari
edwin.jabbari@nhs.net

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Abstract

A 61-year-old man from India was admitted to hospital after being found unresponsive by the roadside. He was treated with dual-antiplatelet therapy for an acute coronary syndrome. Ten days into admission, he had mild left-sided face, arm, and leg weakness, which progressed significantly over the next 2 months in association with progressive white matter abnormalities on brain MRI. In this case study, we outline our clinical reasoning, which led to the detection of a rare underlying cause of a devastating neurologic disease. We also present our approach to treatment, which achieved a sustained clinical and radiologic response.

From the Department of Neurology (E.J., S.F.K.L., F.J., D.P.K., A.B.), Royal Free Hospital NHS Foundation Trust; The National Hospital for Neurology and Neurosurgery (E.J., F.J., H.M., A.B.), University College London Hospitals NHS Foundation Trust; and Division of Neuropathology (F.R., S.B.), UCL Queen Square Institute of Neurology and The National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, United Kingdom.

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Section 1

A 61-year-old man from India was brought to hospital after being found unresponsive and immobile by the roadside. He had been living in the United Kingdom for 17 years and worked as a laborer. He was a nonsmoker with no known medical, drug, or travel history. He was diagnosed with an acute coronary syndrome and started on dual-antiplatelet therapy. Ten days into his admission, he had mild left-sided weakness. On physical examination, he was alert and oriented with normal vital signs and temperature. There were no signs of meningism. Cranial nerve examination was normal aside from a left lower motor neuron (LMN) pattern of facial weakness. The tone of the upper and lower limbs was normal. Power examination revealed mild (Medical Research Council [MRC] scale 4/5) pyramidal-pattern weakness in the left upper and lower limbs. Deep tendon reflexes were rated 2+ throughout the upper and lower limbs with a mute Babinski reflex bilaterally. There was no ankle clonus. Co-ordination and sensory examination were normal. On systemic examination, there was no palpable lymphadenopathy or organomegaly, but a hyperpigmented macular rash of the shins was noted, resembling erythema nodosum.

Questions for Consideration:

1. Where would you localize the lesion?
2. What is your initial investigation approach?

GO TO SECTION 2

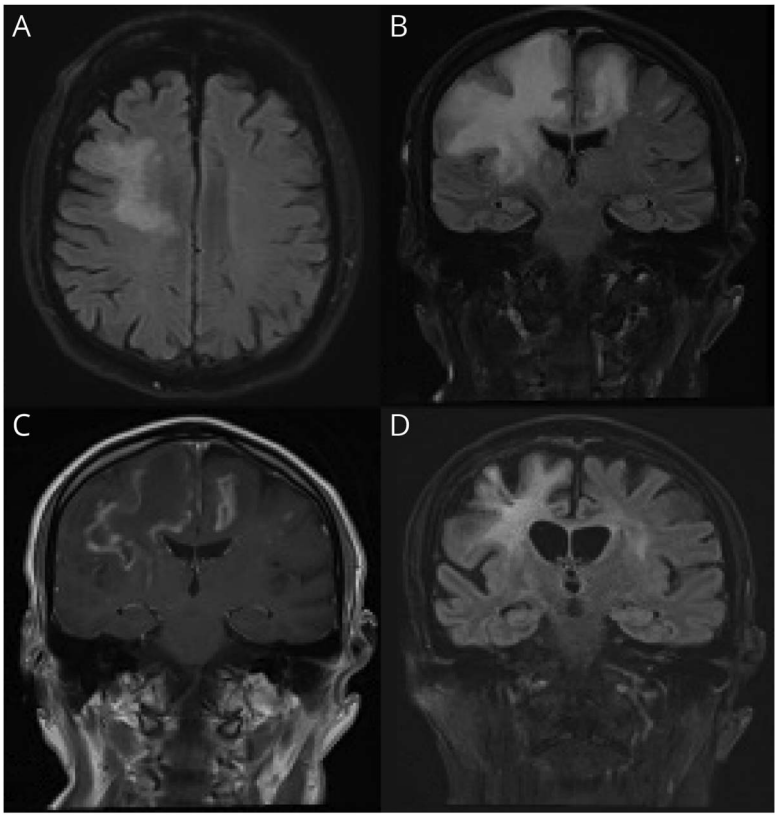
Section 2

Acute pyramidal-pattern left-sided arm and leg weakness localizes to the right side of the brain (cortex or brainstem), affecting the corticospinal tract. The LMN pattern of left-sided facial weakness localizes to the pons and/or facial nerve but could also be because of a leptomeningeal process.

The initial investigation approach should include a brain MRI scan, followed by routine blood and CSF testing to screen for neurovascular, inflammatory, infectious, and malignant etiologies. An unenhanced MRI scan of the brain showed confluent T2/fluid-attenuated inversion recovery white matter hyperintensity in the right frontal lobe with no mass effect, restricted diffusion, or cerebral microbleeds (Figure 1A). Initial blood tests were notable for a normocytic anemia (hemoglobin 100 g/L, normal range 135–170 g/L), hypercalcemia (2.75 mmol/L, normal range 2.20–2.60 mmol/L), hypoparathyroidism (<0.7 pmol/L, normal range 1.6–6.9 pmol/L), raised angiotensin-converting enzyme (ACE) (53 U/L, normal range 8–52 U/L), and positive treponema pallidum particle agglutination (TPPA) and rapid plasma reagin (RPR) testing. Important negative/normal blood results included white cell count, lymphocyte subsets, hematinics, thyroid function tests, liver function tests, protein electrophoresis, immunoglobulins, lupus anticoagulant, tumor markers, Lyme, HIV 1/2, human T-cell lymphotropic virus 1/2, and hepatitis B and C, as well as antinuclear, antineutrophil cytoplasmic, extractable nuclear antigen, double-stranded DNA, neuronal, aquaporin 4, and myelin oligodendrocyte glycoprotein antibodies. On lumbar puncture, CSF opening pressure was 18 cmH_2O. The CSF was acellular with mildly elevated protein (0.50 g/L, normal range 0.15–0.45 g/L) and no evidence of malignant cells on cytologic testing. CSF glucose was 2.9 mmol/L (4.0 mmol/L in serum), and oligoclonal bands (OCBs) were present in both CSF and serum. Important negative CSF results included viral PCR panel (herpes simplex virus, varicella zoster virus, parechovirus, enterovirus, Epstein-Barr virus, cytomegalovirus), Lyme, tuberculosis (TB), cryptococcus, toxoplasmosis, John Cunningham virus (JCV), TPPA, and RPR.

The patient was treated with a 3-day course of IV methylprednisolone for suspected inflammatory demyelination. Given no available history of past infection with syphilis and CSF results not suggestive of neurosyphilis, he was given a 15-day course of IV ceftriaxone to treat for latent syphilis. Despite these treatments, the patient continued to deteriorate over the next 2 months with dense (MRC scale 0/5) pyramidal-pattern weakness on the left, mild (MRC scale 4/5) right-sided weakness, fluctuating consciousness (Glasgow Coma Scale [GCS] 8–13), and dysphagia.

Figure 1 Serial MRI Scans of the Brain



Axial FLAIR noncontrast sequence at presentation showing right frontal lobe confluent white matter hyperintensity without mass effect (A). Coronal FLAIR sequence 2 months later showing marked progression of the white matter hyperintensity in the right hemisphere without mass effect and new involvement of the left hemisphere (B). Coronal T1 sequence post-gadolinium at the 2-month time point showing blood-brain barrier breakdown and pathologic peripheral edge parenchymal enhancement with no associated leptomeningeal enhancement (C). Coronal FLAIR sequence 2 months after completing a 3-month course of IV pembrolizumab showing regression in the white matter hyperintensity and ex-vacuo dilation of the ventricles (D). FLAIR = fluid-attenuated inversion recovery

During this time, he underwent an enhanced MRI scan of the brain, which revealed a progressive increase in the extent of the white matter hyperintensity in the right hemisphere without mass effect and new involvement of the left hemisphere (Figure 1B) as well as associated blood-brain barrier breakdown and pathologic peripheral edge parenchymal enhancement with no leptomeningeal enhancement (Figure 1C). Of note, there were no subcortical abnormalities or enhancement of the facial nerves.

Question for Consideration:

1. What is your differential diagnosis at this point?

GO TO SECTION 3

Section 3

An inflammatory disorder is strongly suggested. In particular, there are supportive features for a diagnosis of sarcoidosis including persistent hypercalcemia and a mildly elevated serum ACE. An LMN facial palsy may be part of a Heerfordt syndrome presentation of sarcoidosis, but no other features of this syndrome (uveitis and parotid swelling) were present. Similarly, erythema nodosum may be part of a Lofgren syndrome presentation of sarcoidosis, but no other features of this syndrome (bilateral hilar lymphadenopathy and arthritis) were present.[1]

Inflammatory demyelinating disorders can also be associated with rapid clinical and radiologic progression and positive CSF OCBs, including tumefactive multiple sclerosis (MS), acute disseminated encephalomyelitis, and neuromyelitis optica spectrum disorder.[2]

There are many CNS infections that could fit with the clinical and radiologic progression of this patient including progressive multifocal leukoencephalopathy (PML) due to JCV reactivation, TB, neuroborreliosis, and neurosyphilis. It is common to find positive CSF OCBs in each of these.[3,4] Blood-brain barrier breakdown and pathologic enhancement can be seen in many CNS infections, such as TB and cryptococcus, but is atypical in others, such as classic PML.[5] Many types of malignant processes, such as a primary CNS tumor, metastases, CNS lymphoma, or a paraneoplastic process, can cause rapid focal neurologic deterioration, with progressive white matter abnormality and pathologic enhancement on imaging.[6]

Question for Consideration:

1. What would you do next?

GO TO SECTION 4

Section 4

To further investigate the possibility of an infectious or malignant process, the patient underwent whole-body 18F-fluorodeoxyglucose (FDG) PET/CT scanning. FDG avid intrathoracic and inguinal lymph nodes were identified, and so, the patient proceeded to ultrasound-guided biopsies of left inguinal and intrathoracic nodes. Both biopsies revealed granulomatous inflammation consistent with sarcoidosis, with negative TB PCR testing and no evidence of bacilli, metastatic carcinoma, or lymphoma.

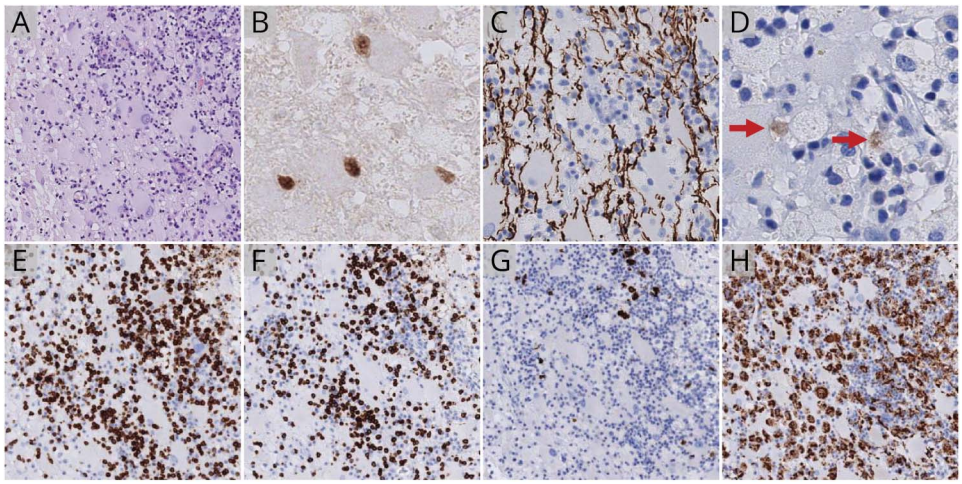
Although we initially suspected classic PML because of the rapid progression of clinical features and white matter abnormalities on imaging, the presence of pathologic enhancement on MRI and negative JCV testing in CSF were not supportive of this diagnosis. Thus, we performed a brain biopsy of the lesion in the right frontal lobe. Histology showed multiple fragments of CNS parenchyma with a dense inflammatory infiltrate composed of foamy macrophages, lymphocytes, and plasma cells (Figure 2A). There was strong nuclear positivity for SV40, indicative of JCV infection, thus confirming the diagnosis of PML (Figure 2B). Relative preservation of axons was seen in the neurofilament staining while the myelin basic protein staining identified only minute amounts of residual fragmented myelin debris (Figure 2, C and D), indicative of almost complete demyelination. The immunohistochemical characterization of the inflammatory cells present confirmed T-cell predominant inflammation while B cells were rarely seen (Figure 2, E–H). After confirmation of the diagnosis, we retested the patient's previous CSF samples in a reference laboratory (Public Health England, Colindale), which confirmed the presence of a low-level JCV titer (24 IU/mL; threshold for reporting positive result = 100 IU/mL).

With no evidence of HIV or hematologic malignancy, sarcoidosis was felt to be the most likely cause of underlying immunosuppression predisposing the patient to PML. He was, therefore, treated with IV pembrolizumab (2 mg/kg once per month for 3 months) and oral prednisolone (30 mg per day, ongoing). This treatment led to a significant improvement in the patient's conscious level (GCS 11–14), orientation, and dysphagia. Although his dense left-sided hemiparesis persisted, his mild right-sided weakness resolved (MRC scale 5/5). In addition, there was regression of the white matter abnormalities on MRI (Figure 1D) and improvement in the pathologic enhancement, with no evidence of immune-related adverse events including PML immune reconstitution inflammatory syndrome (PML-IRIS). Twelve months after initial presentation and 7 months after completing IV pembrolizumab treatment, he was discharged to a nursing home with percutaneous endoscopic gastrostomy feeding.

Discussion

Our case highlights the importance of considering sarcoidosis as a rare underlying cause of PML in patients who have no evidence of HIV or hematologic malignancy nor are receiving treatments of cancers, organ transplantation, or chronic inflammatory disease, most notably natalizumab for MS. It is of importance that PML can occur in both systemic sarcoidosis and neurosarcoidosis.[7-9] In this case, there were many supportive features of systemic sarcoidosis including persistent hypercalcemia, mildly elevated serum ACE, possible erythema nodosum, metabolically active lymphadenopathy, and granulomatous pathology on lymph node biopsy. Neurosarcoidosis can present with isolated facial nerve palsy. In such

Figure 2 Brain Biopsy Findings



Brain biopsy shows an inflammatory infiltrate composed of lymphocytes and frequent foamy macrophages with enlarged and clear nuclei, on hematoxylin and eosin staining (A). Immunostaining for SV40 antigen shows strong nuclear positivity, indicative of John Cunningham virus antigen expression (B). Relative preservation of axons is seen in the neurofilament staining (C) while the myelin basic protein staining (D) identifies only minute amounts of residual fragmented myelin debris, indicative of a widespread, severe demyelination (arrows point to 2 small fragments of myelin debris). There is widespread inflammation in the biopsy sample, with frequent CD3-positive (E) and CD8-positive (F) T cells and rarely CD20-positive B cells (G). Sheets of CD68-positive macrophages dominate the cell populations in all areas of the biopsy (H). Scale bar corresponds to 200 μm (A, E, F, G, H), 100 μm (C), and 50 μm (B, D).

cases, CSF is more likely to be acellular with only a mildly elevated protein level and typical neuroimaging findings such as leptomeningeal or cranial nerve enhancement are more likely to be absent.[1] Similarly, because our brain biopsy sample did not include the leptomeninges, the absence of granulomatous pathology does not rule out neurosarcoidosis in this case. Indeed, both systemic sarcoidosis and neurosarcoidosis can respond well to oral corticosteroids, although the latter is more likely to require additional biological agents such as infliximab and methotrexate.[1]

PML is a rare, aggressive, and often fatal CNS disease caused by reactivation of latent JCV in the setting of compromised cellular immunity. Viral reactivation leads to a lytic infection of CNS oligodendrocytes with subsequent demyelination causing a range of clinical manifestations including cognitive and behavioral abnormalities, sensory and motor deficits, ataxia, and seizures.

Two atypical features in this case confounded the clinical reasoning process. First, although high CSF titers of JCV DNA are commonly detected in treatment-naive HIV and hematologic malignancy-associated PML, in patients with underlying autoimmune disease, the levels of JCV in CSF are commonly below the limits of conventional assay detection (as in this case). Thus, the reported number of PML cases is likely to be underestimated.[9] The false-negative JCV test result highlights the importance of pursuing brain biopsy in cases where the clinical and radiologic profile is consistent with PML and an alternative diagnosis has not been found. Second, the presence of parenchymal enhancement on MRI was felt to be atypical for classic PML. However, it is recognized that contrast enhancement on MRI can occur in PML in the context of immune reconstitution causing a PML-IRIS reaction. This is usually in the context of withdrawing a drug cause, for example, natalizumab for MS, or starting HIV antiretroviral therapy,[10] neither of which were relevant in this case. In our patient, parenchymal enhancement was detected on MRI after the initial 3-day course of IV methylprednisolone, which may have partially treated sarcoidosis-related immunosuppression leading to a transient immune reconstitution.

There has been limited success in using direct antiviral treatment strategies for PML.[9] Therefore, immune reconstitution remains the most effective treatment approach. Outside of stopping offending drugs or starting HIV antiretroviral therapy, a recent approach has been the use of the immune checkpoint inhibitor, pembrolizumab. Success rates with pembrolizumab are mixed, although outcome data are limited to patients with HIV and hematologic malignancy-related PML.[11] At long-term follow-up, our sarcoidosis-PML patient had a good clinical and radiologic response to treatment with pembrolizumab in combination with steroids, highlighting the safety and efficacy of this approach.

Data Availability

Anonymized data not published within this case study will be made available by request from any qualified investigator.

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Appendix Authors

Name	Location	Contribution
Edwin Jabbari, MD, PhD	Department of Neurology, Royal Free Hospital NHS Foundation Trust, London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation
Fernanda Ruiz, MD	Division of Neuropathology, The National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Simon F.K. Lee, MD, PhD	Department of Infectious Diseases, Royal Free Hospital NHS Foundation Trust, London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content
Farrah Jabeen, MD	Department of Neuroradiology, Royal Free Hospital NHS Foundation Trust, London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Sebastian Brandner, MD	Division of Neuropathology, UCL Queen Square Institute of Neurology and The National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Desmond P. Kidd, MD, PhD	Department of Neurology, Royal Free Hospital NHS Foundation Trust, London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content

Appendix *(continued)*

Name	Location	Contribution
Hadi Manji, MD, PhD	Department of Neurology, The National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content
Amit Batla, MD, PhD	Department of Neurology, Royal Free Hospital NHS Foundation Trust	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation

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