

Clinical reasoning: progressive hemiparesis and white matter abnormalities in a HIV-negative patient

Edwin Jabbari, M.D., Ph.D., Fernanda Ruiz, M.D., Simon F.K. Lee, M.D., Ph.D., Farrah Jabeen, M.D., Sebastian Brandner, M.D., Desmond P. Kidd, M.D., Ph.D., Hadi Manji, M.D., Ph.D., Amit Batla, M.D., Ph.D.

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 was noted to have mild left sided face, arm and leg weakness. A brain MRI scan revealed a focal abnormality in the right frontal lobe white matter. Initial blood testing was unremarkable aside from positive treponema pallidum particle agglutination and rapid plasma reagin testing. HIV testing was negative. CSF examination revealed no white cells, a mildly elevated protein, matched oligoclonal bands, and negative testing for syphilis, JC virus and TB. He was treated with a 15-day course of IV Ceftriaxone for latent syphilis. During this time, the patient was noted to have persistent hypercalcaemia and a mildly elevated serum ACE. A three-day course of IV Methylprednisolone was given for a suspected inflammatory demyelinating process. Despite these treatments, the patient's hemiparesis and white matter abnormality (with associated parenchymal enhancement) progressed significantly over the next two months. Metabolically active thoracic and inguinal lymph nodes were detected on whole body PET scanning and subsequent biopsy revealed granulomatous change with no evidence of TB or lymphoma. The patient underwent a brain biopsy which revealed the final diagnosis. Our case highlights a rare underlying cause of a devastating neurological disease. We also present a novel treatment approach which led to a sustained clinical and radiological response.

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 UK for the past 17 years and worked as a labourer. He was a non-smoker with no known past medical, drug or travel history. An ECG revealed T-wave inversion in the lateral leads and there was a mild Troponin-T rise from 53ng/L (normal range < 11ng/L) to 63ng/L 12 hours later. He was diagnosed with an acute coronary syndrome and started on dual-antiplatelet therapy. Ten days into his admission he was noted to have 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 were normal. Power examination revealed mild (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.

Questions for Consideration:

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

Section 2

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

The initial investigation approach should include an MRI scan of the brain followed by routine blood and CSF testing to screen for the aetiologies discussed above.

An unenhanced MRI scan of the brain showed confluent T2/FLAIR 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 anaemic (Hb 100g/L, normal range 135-170g/L), hypercalcaemia (2.75mmol/L, normal range 2.20-2.60mmol/L), hypoparathyroidism (<0.7pmol/L, normal range 1.6-6.9pmol/L), raised angiotensin-converting enzyme (ACE) (53units/L, normal range 8-52units/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, haematinics, TFTs, LFTs, protein electrophoresis, immunoglobulins, ANA, ANCA, ENA, dsDNA, AQP4, MOG, lupus anticoagulant, tumour markers (AFP, PSA, CEA, Ca19-9), antineuronal antibodies, Lyme, HIV1/2, HTLV1/2 and Hepatitis B and C. On lumbar puncture, CSF opening pressure was 18cmH₂O. The CSF was acellular, cytological testing revealed no evidence of malignant cells, and the protein level was mildly elevated (0.50g/L, normal range 0.15-0.45g/L). CSF glucose was 2.9mmol/L (4.0mmol/L in serum) and oligoclonal bands (OCBs) were present in both CSF and serum, although only a few weak bands were detected in serum. Important negative CSF results included: viral PCR panel (HSV, VZV, parechovirus, enterovirus, EBV, CMV), Lyme, TB, cryptococcus, toxoplasmosis, JC virus, TPPA and RPR.

The patient was treated with a 3-day course of IV Methylprednisolone for suspected inflammatory demyelination. As we had no available history of past infection with syphilis, and current CSF testing that was not suggestive of neurosyphilis, he was then given a 15-day course of IV Ceftriaxone to treat for latent syphilis. Despite these treatments the patient continued to deteriorate over the next two months with dense (MRC scale 0/5) pyramidal-pattern weakness on the left, mild (MRC scale 4/5) right-sided weakness, fluctuating consciousness (GCS 8-13) and dysphagia. During this time, he underwent an enhanced MRI scan of the brain which revealed 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**) with associated blood brain barrier breakdown and pathological peripheral edge parenchymal enhancement with no associated leptomeningeal enhancement (**Figure 1c**).

Question for Consideration:

1. What is your differential diagnosis at this stage?

Section 3

In summary, our patient had an evolving left-sided hemiparesis and impairment of consciousness and cognition over the course of 2 months in association with an evolving right hemispheric white matter abnormality on serial MRI. This suggests a rapidly progressive process with several aetiologies potentially implicated. Similarly, there are several potential causes of the skin rash, including the maculopapular rash of secondary syphilis, or erythema nodosum which raises the possibility of infective, inflammatory, and malignant aetiologies.

An inflammatory disorder is a strong possibility at this stage. In particular, there are supportive features for a diagnosis of sarcoidosis including persistent hypercalcaemia and a mildly elevated serum ACE. A 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. Although focal leptomeningeal and parenchymal enhancement on MRI and positive CSF oligoclonal bands (OCBs) can be seen in neurosarcoidosis, one would expect a CSF pleocytosis and a very high (> 0.50g/L) protein level in active disease, neither of which were present in this patient, and so systemic sarcoidosis is more likely.

Inflammatory demyelinating disorders can also be associated with rapid clinical and radiological progression, such as tumefactive multiple sclerosis, ADEM and NMOSD. Of note, OCBs are more likely to be positive in MS compared with NMOSD **(1)** but these are usually restricted to CSF which was not the case in our patient.

There are many CNS infectious causes that could fit with the clinical and radiological progression of this patient, including progressive multifocal leukoencephalopathy (PML) due to JC virus reactivation, TB, neuroborreliosis and neurosyphilis, and in each of these causes it is common to find positive CSF oligoclonal bands +/- co-existing bands in serum **(2) (3)**. Blood brain barrier breakdown and pathological enhancement can be seen in many CNS infections such as TB and cryptococcus, but is atypical in others such as classic PML **(4)**.

Many types of malignant processes, such as a primary CNS tumour, metastases, CNS lymphoma or a paraneoplastic process can cause rapid focal neurological deterioration, with progressive white matter abnormality and pathological enhancement on imaging **(5)**. The negative blood tumour markers and antineuronal antibodies, and absence of malignant cells on CSF cytological examination do not rule out any of these processes.

Question for Consideration:

1. What would you do next?

Section 4

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

Although we initially suspected classic PML, the presence of pathological enhancement on MRI and negative JC virus testing in CSF was not supportive of this diagnosis so we decided to perform 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**). The immunohistochemical characterisation of the inflammatory cells confirmed a T-cell predominant inflammation whilst only rare B cells were seen (**Figures 2E-H**). Immunostaining for myelin basic protein showed only minute amounts of myelin debris whilst neurofilament staining showed relative preservation of axons (**Figures 2C-D**), i.e., the biopsy shows an almost complete demyelination. There was strong nuclear positivity for SV40, indicative of JC virus infection, thus confirming the diagnosis of PML (**Figure 2B**). Following the confirmation of the diagnosis, we re-tested the patient's previous CSF samples in a reference laboratory (Public Health England, Colindale) which confirmed the presence of a low-level JC virus titre (24IU/ml; threshold for reporting positive result = 100IU/ml).

With no evidence of HIV or haematological malignancy, sarcoidosis was felt to be the most likely cause of underlying immunosuppression that predisposed the patient to PML. He was therefore treated with IV Pembrolizumab (2mg/kg once per month) for 3 months and oral Prednisolone (30mg per day) which has continued to date. This 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). Additionally, there was regression of the white matter abnormalities on MRI (**Figure 1d**) and improvement in the pathological enhancement, with no evidence of immune-related adverse events including progressive multifocal leukoencephalopathy immune reconstitution inflammatory syndrome (PML-IRIS). 12 months after initial presentation, and 7 months after completing IV Pembrolizumab treatment, he has been discharged to a nursing home with PEG feeding.

Discussion

Our case highlights the importance of considering sarcoidosis as a rare cause of PML in patients who have no evidence of HIV, haematological malignancy or treatments for cancers, organ transplantation and chronic inflammatory disease, most notably natalizumab for multiple sclerosis (**6**) (**7**). In this case, systemic sarcoidosis was felt to be the most likely underlying cause of immunosuppression leading to PML due to many supportive features including persistent hypercalcaemia, mildly elevated serum ACE, a LMN facial palsy, possible erythema nodosum, metabolically active lymphadenopathy, and granulomatous pathology on lymph node biopsy.

PML is a rare, aggressive, and often fatal CNS disease caused by reactivation of latent JC virus in the setting of compromised cellular immunity. This leads to a lytic infection of CNS

oligodendrocytes, subsequent demyelination and a range of clinical manifestations including cognitive and behavioural abnormalities, sensory and motor deficits, ataxia, and seizures. In this case, the patient had a clinical course and progressive white matter abnormalities seen in classic PML. However, there were atypical features in this case which influenced the process of clinical reasoning.

Firstly, although high CSF titres of JC virus DNA are commonly detected in treatment-naive HIV and haematological malignancy associated PML, in patients with underlying autoimmune disease the levels of JC virus in CSF are commonly below the limits of conventional assay detection (as in this case), such that the reported number of PML cases are likely to be underestimated **(7)**. This highlights the importance of pursuing brain biopsy in cases where the clinical and radiological profile is consistent with PML and an alternative diagnosis has not been found.

Secondly, the presence of parenchymal enhancement on MRI was initially felt to be atypical for classic PML. However, it is recognised 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, e.g., natalizumab for multiple sclerosis, or starting a specific treatment for PML, e.g., HIV antiretroviral therapy **(8)**, 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 systemic sarcoidosis-related immunosuppression leading to a transient immune reconstitution. The widespread inflammatory response seen on brain biopsy with frequent T cells would also be in keeping with this interpretation.

There has been limited success in using direct antiviral treatment strategies for PML **(7)**. 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 (PD-1) inhibitor, Pembrolizumab. Success rates with Pembrolizumab are mixed, although outcome data is limited to patients with HIV and haematological malignancy related PML **(9)**. In diffuse large B cell lymphoma-related PML, use of IL-2 therapy to boost T-cell CD4/CD8 populations before treatment with Pembrolizumab has been shown to improve clinical outcomes **(10)**. Immune reconstitution strategies in sarcoidosis related PML are limited to a handful of case reports and small case series. Approaches largely involve using corticosteroids and/or Infliximab **(11)** or Cyclophosphamide **(12)** with mixed responses. To our knowledge, ours is the first sarcoidosis-PML case to be treated with Pembrolizumab in combination with steroids, resulting in clinical and radiological stabilisation at long term follow-up, highlighting the safety and efficacy of this approach.

Data Availability

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

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Figure 1

Serial MRI scans of the brain. Axial FLAIR sequence of unenhanced scan at presentation showing right frontal lobe confluent white matter hyperintensity without mass effect (A). Coronal FLAIR sequence two 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 showing blood brain barrier breakdown and pathological peripheral edge parenchymal enhancement with no associated leptomeningeal enhancement (C). Coronal FLAIR sequence two months after completing a three-month course of IV Pembrolizumab showing regression in the white matter hyperintensity and ex-vacuo dilatation of the ventricles (D).

Figure 2

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 JC virus antigen expression (B). Relative preservation of axons is seen in the neurofilament staining (C), whilst the myelin basic protein staining (D) identifies only minute amounts of residual fragmented myelin debris, indicative of a widespread, severe demyelination (arrows point to two small fragments of myelin debris). There is widespread inflammation in the biopsy sample, with frequent CD3 positive (E) and CD8 positive (F) T-cells but only rare 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), 50 μm (B, D).

Appendix Authors

Name	Location	Contribution
Edwin Jabbari, M.D., Ph.D.	Department of Neurology, Royal Free Hospital NHS Trust, London, UK	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, M.D.	Division of Neuropathology, The National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, London, UK	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

Simon F.K. Lee, M.D., Ph.D.	Department of Infectious Diseases, Royal Free Hospital NHS Trust, London, UK	Drafting/revision of the manuscript for content, including medical writing for content
Farrah Jabeen, M.D.	Department of Neuroradiology, Royal Free Hospital NHS Trust, London, UK	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Sebastian Brandner, M.D.	Division of Neuropathology, UCL Queen Square Institute of Neurology and The National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation trust, London, UK	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Desmond P. Kidd, M.D., Ph.D.	Department of Neurology, Royal Free Hospital NHS Trust, London, UK	Drafting/revision of the manuscript for content, including medical writing for content
Hadi Manji, M.D., Ph.D.	Department of Neurology, The National Hospital for Neurology and Neurosurgery, London, UK	Drafting/revision of the manuscript for content, including medical writing for content
Amit Batla, M.D., Ph.D.	Department of Neurology, Royal Free Hospital NHS 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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