Rosai-Dorfman Disease: A Less Common Cause of Leptomeningeal and Nerve Root Enhancement

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Abstract

A 46-year-old male experienced progressive neurocognitive decline, weight loss, intermittent headaches, and weakness over 6 months. Magnetic resonance imaging of the brain revealed hydrocephalus and the spinal cord imaging showed diffuse leptomeningeal enhancement with prominent nerve root involvement. Intradural biopsy of lumbar arachnoid tissue found mixed inflammatory infiltrate consisting predominantly of histiocytes, S100 and CD68 positivity, and lymphocytaphagocytosis (emperipolesis) consistent with extranodal Rosai-Dorfman disease. Rosai-Dorfman disease, a non-Langerhans cell histiocytic disorder, can mimic the appearance of neurosarcoidosis and leptomeningeal carcinomatosis and should remain on the differential of a patient presenting with diffuse leptomeningeal enhancement, a common occurrence on a neurohospitalist service.

Keywords

histiocytosis, autoimmune diseases of the nervous system, neuroimmunology, polyradiculoneuropathy

Case Presentation

A 46-year-old-male with a history of bipolar disorder and type II diabetes presented with 6 months of headaches, vomiting, and worsening lethargy to a community hospital. Magnetic resonance imaging (MRI) revealed hydrocephalus with leptomeningeal enhancement in the basal cisterns. A lumbar puncture found 625 white blood cells/ μ L (47% neutrophils, 49% lymphocytes, 4% monocytes), 0 red blood cells, protein of 468 mg/dL and glucose of 65 mg/dL. Gram and fungal stains were negative as was rapid plasma reagin test. Although his quantiFERON tuberculosis (TB) gold test was positive, his cerebrospinal fluid (CSF) acid fast bacilli (AFB) stain was negative. Flow cytometry was normal and cytology found only predominance of neutrophils and lymphocytes. HIV was negative, but serum hepatitis C antibody returned positive with a viral load of 517 000 IU/mL. He was transferred to our facility for external ventricular drain placement and evaluation.

On arrival, the patient's mental status was intact without cranial neuropathies and only notable for bilateral hip flexor and dorsiflexor weakness, 4/5, with loss of proprioception below the ankles. Brain MRI redemonstrated leptomeningeal enhancement in the basal cisterns with cranial nerve involvement (Figure 1). Spinal imaging showed nerve root enhancement in the cervical, thoracic spine, and lumbar spine with leptomeningeal enhancement around the conus medullaris.

At this point, the differential was broad and included neoplastic, infectious and autoimmune inflammatory processes (Table 1). Cerebrospinal fluid cytology and cytometry was negative 3 times making neoplastic meningitis unlikely. From an infectious perspective, the CSF showed negative lyme polymerase chain reaction (PCR), West Nile virus immunoglobulin G (IgG) and IgM. In workup for TB, AFB stain, culture, and PCR were negative. The infectious disease team recommended isoniazid for latent TB. Given slow onset of disease in a nontoxic appearing patient, listeria was unlikely.

Regarding autoimmune disease, serum rheumatologic studies found only positive double stranded DNA (12 IU/mL), with otherwise negative extractable nuclear antigen testing, and normal complement studies. Computed tomography of the chest, abdomen pelvis revealed a 0.8 cm pulmonary nodule with no evidence of systemic lymphadenopathy. Given high suspicion for neurosarcoidosis due to the MRI findings,

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Figure 1. A, Magnetic resonance imaging (MRI) Brain T1 sagittal postcontrast: demonstrating diffuse abnormal enhancement surrounding the brain stem (arrows). B, MRI Brain T1 MP-RAGE axial postcontrast: demonstrating abnormal enhancement of CN 7 and 8 (arrows). C, MRI L Spine T1 sagittal postcontrast: demonstrating leptomeningeal enhancement surrounding the conus medullaris (arrows). D, MRI L Spine sagittal postcontrast: demonstrating abnormal enhancement of multiple nerve roots (arrows).

fluorodeoxyglucose positron emission tomography (FDG-PET) scan was performed to find a suitable biopsy site. Imaging revealed multiple mediastinal lymph nodes <10 mm but showed no uptake of the previously seen 0.8cm nodule. Biopsy of the pulmonary lymph nodes found abundant pigmented macrophages with “rare noncaseating granulomas,” suggesting pulmonary sarcoidosis and supportive of a diagnosis of probably neurosarcoidosis. Empiric steroids were not started given clinical improvement and risk due to latent TB, poorly controlled type 2 diabetes, and the new hepatitis C diagnosis with history of bipolar disease. Invasive central nervous system (CNS) biopsy was deferred at this initial hospitalization.

The patient was readmitted 2 months later with intermittent headaches, progressive encephalopathy, and loss of ability to ambulate independently. On examination, he had become disoriented and inattentive, with limited upgaze and delayed left shoulder shrug. His lower extremities showed a mix of upper and lower motor neuron findings including loss of lower extremity bulk with increased tone. He was no longer antigravity at the hips and only able to 3/5 with knee flexion/extension and ankle dorsi/plantar flexion. Reflexes were symmetrically brisk throughout but with down going toes. Imaging again showed diffuse leptomeningeal brainstem enhancement, communicating hydrocephalus, cervical, thoracic, and lumbar nerve root

enhancement. Due to clinical deterioration and risks associated with empiric steroid treatment, he underwent cervical nerve root biopsy which was non diagnostic. However, given this negative result in the setting of clinical worsening, biopsy of the lumbar spinal roots was quickly undertaken, specifically targeting intradural thickened arachnoid tissue.

Neuropathology

Pathological differential diagnosis included neurosarcoidosis, IgG-related disease, lymphoma, amyloidosis, and TB. Lumbar arachnoid tissue ultimately revealed dense fibrosis with an associated mixed inflammatory infiltrate consisting predominantly of histiocytes, lymphocytes, and plasma cells. Immunohistochemical staining for IgG and IgG4 highlighted numerous IgG-positive plasma cells but very few were of the IgG4 subclass, making IgG4-related disease unlikely. Acid fast bacilli and congo-red staining were negative ruling out TB and amyloid, respectively. Polytypic kappa and lambda light chain expression in the plasma cells seen on kappa and lambda chromogenic in situ hybridization studies confirmed the absence of a clonal lymphoid process or myeloma.

Further immunohistochemistry for CD163 highlighted a population of histocytes within the inflammatory infiltrate

Table 1. Differential Diagnosis of Leptomeningeal Enhancement of the Basal Cisterns and Nerve Roots.

Causes of leptomeningeal enhancement with basal cisternal involvement		
Neoplastic	Infectious	Autoimmune
<ul style="list-style-type: none"> – Lymphoma – Leptomeningeal metastasis – Diffuse leptomeningeal glioma – Leukemia 	<p>Bacterial</p> <ul style="list-style-type: none"> – Lyme disease – Tuberculosis – Listeria – Syphilis <p>Viral</p> <ul style="list-style-type: none"> – West Nile virus – Enterovirus 71 – Epstein Barr virus – CMV <p>Fungal</p> <ul style="list-style-type: none"> – Coccidioidomycosis – Cryptococcus – Amoebiasis <p>Parasite</p> <ul style="list-style-type: none"> – Neurocysticercosis 	<ul style="list-style-type: none"> – Sarcoidosis – IgG4-related disease – Neuro-Bechet's – Paraneoplastic (anti-Hu)
Causes of nerve root enhancement		
Neoplastic	Infectious	Autoimmune
<ul style="list-style-type: none"> – Leptomeningeal metastasis – Lymphoma 	<p>Bacterial</p> <ul style="list-style-type: none"> – Lyme disease <p>Viral</p> <ul style="list-style-type: none"> – AIDS-related polyradiculopathy – West Nile – CMV polyradiculopathy – Enterovirus D68 – Epstein Barr – Varicella – Herpes simplex virus 	<ul style="list-style-type: none"> – Guillain Barre – Chronic inflammatory demyelinating polyneuropathy – Sarcoidosis – Paraneoplastic (CRMP-5/CV2 & anti-Hu) – Amyloidosis

Abbreviation: CMV, cytomegalovirus.

(Figure 2). A subset of the histiocytes demonstrated weak immunoreactivity with antibodies to S100 and some areas suggestive of emperipolesis (lymphohistiophagocytosis). The histiocytes were negative for CD1a and Langerin, excluding a diagnosis of Langerhans cell histiocytosis (LCH). An immunohistochemical stain for the *BRAF* V600E mutation was negative, providing no support for a diagnosis of LCH (approximately 50% of LCH cases harbor *BRAF* mutations) or other non-Langerhans histiocytosis such as Erdheim-Chester disease (which also frequently harbor *BRAF* mutations).^{1,2} As a recent study identified point mutations involving *MAP2k1* and *KRAS*, next generation sequencing (Trusight Tumor, Illumina) was performed using a 26 gene panel that included *BRAF*, *MAP2k1*, and *KRAS*.³ Sequencing showed no mutations in the 26 targeted genes. Given this conglomeration of pathologic and clinical findings, especially the population of S100-positive histiocytes demonstrating emperipolesis, Rosai-Dorfman disease was felt to be the most compatible diagnosis.

Patient Outcome

Treatment with intravenous methylprednisolone was initiated, which required transition to rifampin, isoniazid, pyrazinamide, and ethambutol for TB, and was further complicated by hyperglycemia from his known poorly controlled diabetes, and then by hallucinations likely due to exacerbation of underlying bipolar disorder. The patient had sustained improvement with return to normal mental status and recovery of ability to walk over several weeks. For the time being, he has declined any further therapy and continues to be monitored clinically and radiographically.

Discussion

Rosai-Dorfman disease (RDD) is a rare, heterogeneous group of non-Langerhans histiocytoses which uncommonly manifests in the CNS.⁴ Furthermore, typically RDD CNS involvement mimics meningioma or brainstem parenchymal disease.^{5,6} Rosai-Dorfman disease was first described in

Figure 2. A, Low power H&E stain reveals connective tissue with a mixed chronic, nongranulomatous inflammatory infiltrate, $\times 40$. B, Higher power reveals both small lymphocytes and larger histiocyte-like cells, some with forms suggestive for emperipolesis (arrow), $\times 400$. C, CD68 immunohistochemistry reveals numerous histiocytes with granular cytoplasmic staining, $\times 200$. D, S100 immunohistochemistry reveals a substantial proportion of S100-positive histiocytes, $\times 200$.

1969.⁷ It can be seen in conjunction with or without associated malignancies or autoimmune disease.⁴ The prevalence is estimated at 1:200 000, affecting children and young adults most commonly, with an unclear pathogenesis although recent evidence has suggested a viral stimulus, including Epstein Barr virus, HIV, or cytomegalovirus (CMV).⁸ Classically, RDD presents nodally, with 43% presenting extranodally, and may present over months to years like other forms of non-LCH.⁴ Patients typically have bilateral, massive, painless cervical lymphadenopathy, multisystem involvement, including the skin, bone, and gastrointestinal (GI), although CNS involvement is less common. Rosai-Dorfman disease requires pathologic confirmation to exclude alternative diagnoses.⁴

Central nervous system involvement is found in less than 5% of cases.⁴ Further breakdown of CNS involvement suggests 75% is found to be intracranial with only 25% of CNS cases presenting with spinal involvement.⁴ In contrast to the nodal presentation of RDD, neurologic RDD occurs in older patients without lymphadenopathy. Central nervous system RDD has a subacute progression over weeks to months, with patients presenting with headaches, seizures, gait ataxia, and heterogeneous peripheral nerve involvement including

cranial, motor, and sensory neuropathies.⁴ Imaging findings of CNS RDD classically mimic characteristics of meningiomas, an extraaxial homogeneously enhancing dural mass.⁹ Cases demonstrating infratentorial involvement are generally parenchymal. However, pachymeningeal lesions have been reported.⁴ Spinal and epidural lesions may present with spinal cord compression, originating from the cervical and thoracic regions.¹⁰ Although in some cases of CNS RDD the CSF is unremarkable, it may show a lymphocytic pleocytosis and elevated protein, as it does in this presentation.^{4,11}

After diagnosis of RDD it is essential to consider conditions known to be associated with the disease, including lymphomas, which itself can mimic RDD, as well as autoimmune diseases like IgG4-related RDD. Several investigators use full body FDG-PET for initial staging, as RDD is known to be FDG-avid and may have bone involvement.⁴

Algorithms have been proposed for the treatment of RDD for which treatment is determined based on 2 dichotomies, focal versus systemic presentations, and nodal versus extranodal involvement. Surveillance monitoring is often appropriate, particularly in nodal disease given approximately 20% to 50% of cases self-resolve.⁴ In CNS RDD, positive responses

to corticosteroids, with prednisone (40-70/d) or dexamethasone (8-20 mg/d) have had mixed success, with some cases having full resolution and others with partial responses; CNS RDD with focal lesions have often resolved with resection.^{6,9} Empiric evidence has demonstrated a less sustained response in cases of extranodal disease when steroids are used alone.^{4,12} Numerous chemotherapeutics and immunomodulatory therapies have been efficacious in some cases, largely depending on the extent and presentation of the disease.⁴ In nonresectable systemic cases of CNS disease, intracranial involvement has been treatment with single agent 6-MP, as well as with variations of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimens.⁶ Data currently does not provide consensus on treatment duration, with some advocating 6 to 12 months of systemic therapy followed by surveillance.⁴

Our case highlights the heterogeneous phenotypic manifestations of CNS RDD which can mimic multiple CNS pathologies including infectious, inflammatory, and neoplastic disease. The case is of particular curiosity to the neurohospitalist as RDD and other histiocytoses may not be among routinely considered etiologies of CNS disease. Finally, given the broad differential of leptomenigeal and nerve root enhancement, the case punctuates the indication for obtaining CNS tissue in the setting of radiographic ambiguity.

Authors' Note

The authors have abided by all ethical standards and have obtained informed consent.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Dr Mandell serves as Associate Editor for *Journal of Neuropathology and Experimental Neurology*; is author on a patent re: SIMPLE: Sequential Immunoperoxidase Labeling and Erasing Technology for multiplex immunohistochemistry; receives research support from NIH; and receives license fee payments for FIRM—fluorescent stain for resin sections from Electron Microscopy Sciences, Inc.

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