Rhombencephalitis in an 86-year-old woman with chronic lymphocytic leukemia

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An 86-year-old woman presented to our emergency department with a 4-week history of new-onset balance difficulties resulting in falls, slurred speech, and worsening blurry vision, prior to which she was independent in activities of daily living and ambulation and had no problems with cognition. Her medical history was notable for chronic lymphocytic leukemia (CLL), which had been under surveillance for 15 years; hypertension; dyslipidemia; and chronic kidney disease with an estimated glomerular filtration rate at baseline of 30 (normal ≥ 90) mL/min. At presentation, she reported no sick contacts, recent travel, fever, illnesses, or constitutional symptoms. She also had no genitourinary, gastrointestinal, cardiovascular, infectious, or respiratory symptoms.

On examination, the patient was alert, intermittently inattentive, and had difficulty following instructions. She had no language difficulties. A formal cognitive assessment was not performed. Her neurologic examination showed full and painless eye movements with intermittent binocular diplopia in lateral gaze, but no evidence of cranial nerve III, IV, or VI palsy. She had gaze-evoked nystagmus, scanning dysarthria, bilateral dysmetria on finger-to-nose testing, left-sided dysdiadochokinesia, and gait ataxia. The neurologic examination was thus concerning for cerebellar dysfunction but the motor and sensory examination was otherwise normal. Cardiac, respiratory, abdominal, and dermatologic examination were normal as well, with no palpable lymphadenopathy or splenomegaly.

Initial bloodwork showed a leukocyte count of 14.8 × 10^9/L (lymphocyte predominant, normal reference range 4–11 × 10^9/L) and a creatinine of 149 (normal reference range 44–97) µmol/L, which was at her baseline. Her serum C-reactive protein level was 10 (normal reference range 0–3) mg/L. A noncontrast computed tomography (CT) scan of her brain was performed and showed no intracranial pathology.

We admitted the patient to our general internal medicine service. We ordered a magnetic resonance imaging (MRI) brain scan with gadolinium, which showed T_2 fluid-attenuated inversion recovery (FLAIR) hyperintensities bilaterally in the middle cerebellar peduncles and pons (Figure 1). Thereafter, we performed a lumbar puncture, which indicated an inflammatory cerebrospinal fluid (CSF) profile with an elevated leukocyte count of 8 (lymphocytes = 7, range 0–5) × 10^9/L, elevated protein of 500 (range 150–450) mg/L, and glucose of 2.7 (range 2.7–4.2) mmol/L. Given the inflammatory CSF profile and MRI findings, we concluded that her condition was consistent with rhombencephalitis (inflammatory disorder of the pons, medulla oblongata, and cerebellum). Therefore, we initiated treatment with intravenous methylprednisolone 1 g for 5 days. We also administered intravenous immunoglobulin, which was discontinued after the first dose owing to a febrile transfusion reaction. We detected no clinical or radiologic improvement on repeat MRI, which was done on the day that the 5-day course of intravenous (IV) methylprednisolone finished (day 12 of hospital stay). We additionally conducted several investigations to elucidate secondary causes of rhombencephalitis (Table 1). We performed CT of the patient's thorax, abdomen, and pelvis to assess for malignancy. The imaging showed widespread lymphadenopathy and splenomegaly, consistent with her known CLL, but no other evidence of malignancy. Her lymph nodes and spleen were not tracer avid on 18F-fluorodeoxyglucose positron emission tomography. Serum lactate dehydrogenase was not elevated. Cerebrospinal fluid cytology and flow cytometry revealed atypical lymphocytes immunophenotyped as nontransformed CLL cells. Together, these findings suggested the patient's CLL had not transformed into an aggressive large B-cell lymphoma.

Key points

- Rhombencephalitis is an inflammatory disorder of the cerebellum, pons, and medulla oblongata that can result in abnormal cerebellar function, pyramidal weakness, proprioceptive deficits, and altered level of consciousness.
- Causes of rhombencephalitis include infections, inflammatory or demyelinating conditions, and paraneoplastic disorders.
- In immunocompromised patients, atypical infections can cause rhombencephalitis, including John Cunningham virus; this virus causes primary multifocal leukoencephalopathy (PML), which can manifest as rhombencephalitis.
- Patients with chronic lymphocytic leukemia are at increased risk of developing PML owing to underlying immunocompromise from the leukemia.

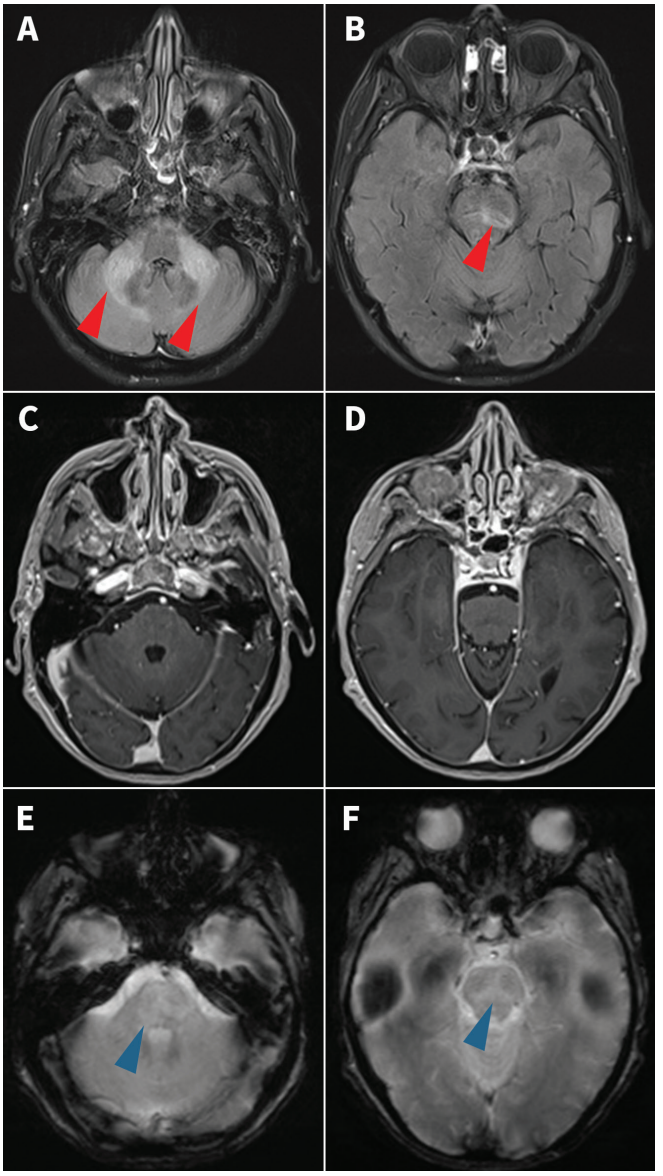

Figure 1: Axial T_2 fluid-attenuated inversion recovery sequence (FLAIR) magnetic resonance imaging scan of the brain of an 86-year-old woman, with sequences through the middle cerebellar peduncles (A) and rostral pons (B) illustrating hyperintensities in the bilateral middle cerebral peduncles and body of the pons (red triangles). There was no enhancement on T_1 postgadolinium sequences (C and D). Axial T_2 sequences (E and F) show faint hyperintensities in the body of the pons (blue triangles).

We ordered studies to exclude infectious causes, including serum HIV, *Borrelia burgdorferi*, syphilis, and leptospirosis serology, all of which were nonreactive. Blood cultures were negative. Cerebrospinal fluid herpes simplex virus, varicella zoster virus, and West Nile virus were negative, as were CSF culture, acid-fast bacilli and cryptococcal antigen tests. Blood and CSF autoimmune and paraneoplastic encephalitis antibodies were negative (including anti-NMDA, anti-GAD65, anti-Hu, anti-Ma2, anti-Tr, anti-amphiphysin, anti-glycine, anti-MOG, anti-AQP4, and anti-IgLON5). Serum antinuclear antibody test, cryoglobulins, and rheumatoid factor were negative, and so were serum immunoglobulins and serum protein electrophoresis. At this point, we were unable to identify a secondary cause of rhombencephalitis.

On day 14 of the patient's hospital stay, CSF qualitative polymerase chain reaction (PCR) returned positive for John Cunningham virus (JCV). We repeated a lumbar puncture on day 15 of her hospital stay, which again confirmed JCV. Therefore, we diagnosed progressive multifocal leukoencephalopathy (PML) caused by JCV, which manifested clinically and radiologically as rhombencephalitis. We concluded that she had contracted JCV owing to immunocompromise caused by CLL.

She was ineligible for CLL disease-modifying therapies as they would worsen immunosuppression and thereby exacerbate her PML and associated symptoms. We discussed experimental therapies, including off-label pembrolizumab, but ultimately did not pursue these as the patient's condition worsened, and she chose palliative care. The patient passed away 7 weeks after her admission to hospital.

Discussion

Rhombencephalitis refers to inflammation of the rhombencephalon, which includes the cerebellum, pons, the pontine portion of the fourth ventricle, and cranial nerves V–VIII as well as the medulla oblongata, its fourth ventricle portion, and cranial nerves IX, X, and XII.[1] Rhombencephalitis does not involve the midbrain or cerebrum. Typical clinical features include altered level of consciousness, cerebellar signs (ataxia, dysmetria, and nystagmus), cranial neuropathies of affected nerves (which can manifest as eye movement abnormalities and bulbar dysfunction), and long-tract signs such as pyramidal weakness and proprioceptive deficits. Magnetic resonance imaging findings in rhombencephalitis typically include T_2 FLAIR hyperintensities in the pons, medulla, and cerebellum, which may enhance with gadolinium.[1] Cerebrospinal fluid analysis often suggests inflammation, with elevated leukocyte count and protein level. The differential diagnosis for rhombencephalitis (Table 1) includes infectious, inflammatory, demyelinating, paraneoplastic, and drug-induced etiologies.[1] Although the overall population-level prevalence of rhombencephalitis is unknown, a case series of 97 patients reported that its average age of onset was 37 years and 50% were female.[2] However, certain etiologies affect age groups and sexes differently. For example, *Listeria* infection is more common among older adults, whereas inflammatory etiologies such as Behçet syndrome and systemic lupus erythematosus more often affect females. *Listeria* is the most common cause of rhombencephalitis and typically presents with a febrile prodrome in 85% of patients, headache in 73%, nausea and vomiting in 64%, and meningismus in as many as 55% of patients.[3] Rhombencephalitis caused by *Listeria* leads to CSF neutrophilic pleocytosis in 78% of patients, elevated protein levels in 63%, and normal glucose in 79%.[3] Usually, either CSF or blood cultures are positive for *Listeria.* Our patient had no infectious prodrome, and both CSF and blood cultures were negative for *Listeria*.

Workup of a patient with rhombencephalitis aims to diagnose the potential underlying causes shown in Table 1. Infection is more common in immunocompromised patients.[4] A lumbar puncture

Table 1: Differential diagnosis of rhombencephalitis

Etiologic category	Examples
Infectious	Bacterial: listeriosis, Lyme disease, tuberculosis, mycoplasma Viral: herpes simplex virus, Epstein–Barr virus, cytomegalovirus, Japanese encephalitis, Coxsackievirus, SARS-CoV-2, progressive multifocal leukoencephalopathy secondary to John Cunningham virus Fungal: Aspergillosis, paracoccidioidomycosis, mucormycosis Parasitic: schistosomiasis, neurocysticercosis, toxoplasmosis
Autoimmune and inflammatory	Neuro-Behçet syndrome, systemic lupus erythematosus, Sjögren syndrome, neurosarcoidosis, anti–signal recognition peptide disease, Bickerstaff brainstem encephalitis, Vogt–Koyanagi–Harada syndrome, histiocytic necrotizing lymphadenitis
Demyelinating	Acute disseminated encephalomyelitis, neuromyelitis optica spectrum disorders
Paraneoplastic	Breast cancer: anti-Ri, antiglycine receptor, anti-Yo, anti-amphiphysin Lung cancer: anti-Hu, anti-Ri, anti-Yo, anti-amphiphysin Testicular or ovarian germ cell tumours: anti-Ma2, anti-NMDA Lymphoma: anti-Yo, anti-Tr, antiglycine
Drug-induced	Metronidazole toxicity, immune checkpoint inhibitors

Table 2: Neurologic syndromes associated with John Cunningham virus infection

Phenotype	Clinical features	MRI appearance
Classic PML	Supratentorial lesions: hemiparesis, hemisensory loss, seizures, encephalopathy Infratentorial lesions: cranial neuropathies, cerebellar signs including ataxia and dysarthria	T_1 hypointense lesions, T_2 and FLAIR hyperintense lesions in subcortical white matter. Nonenhancing. May have perilesional diffusion restriction.
Inflammatory PML	Acute aggravation of symptoms in a patient with classic PML	Rim-enhancing lesions, which may be associated with vasogenic edema and mass effect
JCV meningitis	Fever, meningism, photophobia	No specific imaging findings
JCV encephalopathy	Confusion, reduced level of consciousness, aphasia, progressive cognitive impairment	Cortical grey matter T_2 hyperintensities, spreading to white matter in the late stages of disease
JCV granular cell neuronopathy	Cerebellar signs including ataxia and dysarthria	Isointense cerebellar atrophy with T_2 hyperintensities in the late stages of disease

Note: FLAIR = fluid-attenuated inversion recovery sequence, JCV = John Cunningham virus, MRI = magnetic resonance imaging, PML = progressive multifocal leukoencephalopathy.

must be performed to assess for pleocytosis and elevated protein (suggestive of inflammation) and to exclude secondary causes. Additional investigations include testing for infection (blood cultures, serum HIV, hepatitis B, hepatitis C, syphilis, serum serology for *Borrelia burgdorferi*, sputum testing for *Mycobacterium tuberculosis* in those at risk, and CSF studies for bacterial, viral, and fungal etiologies), inflammatory disorders (erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody test, extranuclear antibodies, cryoglobulins), autoimmune diseases (serum and CSF antibody panels, anti–myelin oligodendrocyte glycoprotein and aquaporin 5 antibodies) and malignancy (CT chest, abdomen, pelvis; age-appropriate cancer screening; CSF cytology; serum and CSF paraneoplastic antibodies; CSF and peripheral flow cytometry). Clinicians can modify these investigations based on a patient's medical history, risk factors, and availability of testing.

John Cunningham virus, a human polyomavirus, causes PML, a rare neurologic condition with an incidence of 0.11 per 100 000 person-years that can manifest as rhombencephalitis.[5] The virus was first described in patients with CLL and Hodgkin lymphoma in 1958.[6] John Cunningham virus causes various neurologic disease phenotypes, including classic PML, inflammatory PML, JCV meningitis, JCV encephalopathy, and JCV granular cell neuronopathy (Table 2). The proposed diagnostic criteria for classic PML includes a typical clinical syndrome, JCV detection in CSF, or brain biopsy, and typical MRI findings of nonenhancing T_2 FLAIR hyperintensities.[7] Typical clinical syndromes associated with classic PML vary depending on the brain regions involved[8] and include encephalopathy, seizures, and hemiparesis with supratentorial disease. Rhombencephalitis ensues when classic PML affects infratentorial structures such as pons and middle cerebellar peduncles. This results in symptoms such as ataxia, eye movement abnormalities, and bulbar dysfunction. Given clinical, biochemical, and imaging features, the presence or absence of these 3 criteria allows clinicians to stratify cases into "presumptive" and "definite" classic PML. According to these criteria, our patient met the threshold of "definite" classic PML with clinical and diagnostic findings consistent with rhombencephalitis, as well as JCV PCR positivity in the CSF and typical MRI findings.

Risk factors for PML include immunosuppression, including HIV, hematologic malignancies, purine analogue therapies, and stem cell transplantation. Our patient's risk factor for PML was CLL. In a sample of patients with PML, hematologic malignancy was the second most common risk factor, accounting for 30% of cases.[9] Patients with CLL are at risk for PML owing to malignancy-associated immune dysfunction. However, they are also at significant risk for developing PML after initiating immunosuppressive chemotherapy to treat CLL.[10]

Treatment of PML focuses on reversing the underlying cause of immunosuppression. For example, in cases of HIV-associated PML, early diagnosis can facilitate prompt initiation of antiretroviral therapy, which can stabilize or improve PML manifestations.[11] In cases of HIV-negative PML, ameliorating the underlying immunosuppressive process may be beneficial if diagnosed promptly. Therefore, early consideration of this important diagnosis may help reduce its morbidity and mortality.[7] A 2019 case series of 8 patients, 2 of whom had CLL, showed that pembrolizumab, an immune checkpoint inhibitor, might be a promising option for achieving clinical improvement or stabilization.[12] Further studies are needed to validate the use of pembrolizumab and other treatments for PML.

In patients with underlying cancer or immunosuppression presenting with subacute central neurologic symptoms, expedited workup should focus on ruling out atypical and opportunistic infections, including JCV.

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