Clinical Reasoning: A 71-year-old Male with Horizontal Gaze Palsy, Anarthria, and Quadriplegia

Ikreet Cheema, MD1; Nicole Ng, MD1; Tychicus Chen, MD, FRCPC1

1. Division of Neurology, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada

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Corresponding Author:
Dr. Ikreet Cheema

(ikreet.cheema@alumni.ubc.ca)

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**SECTION 1:**
A 71-year-old right-handed male non-smoker with type 2 diabetes, hypertension, and chronic lymphocytic leukemia (CLL) never requiring active treatment, presented to hospital with one week of subacute-onset nausea, vomiting, and unsteady gait. On examination, he was afebrile with blood pressure 155/82mmHg and heart rate 62bpm. He had right hemiataxia with wide-
based gait. CT head and CT angiogram performed resulted in ischemic stroke diagnosis with no vascular abnormalities. Cardiac workup was unremarkable. He was managed with antiplatelet therapy and risk factor optimization.

Following discharge, his symptoms worsened with intractable nausea, hyperemesis, weight loss, slurred speech, and loss of independent ambulation resulting in hospital readmission two weeks later. Repeat imaging showed mild lesion expansion. Despite antiplatelets, he progressively deteriorated, becoming nonverbal, communicating with gestures, and eventually becoming seemingly non-responsive with no movement beyond eye opening. He required intubation, subsequent tracheostomy, and transfer to our centre for further evaluation three months into his presentation.

At this point, he remained afebrile and normotensive without meningismus. He was nonverbal with spontaneous eye opening and blinking. He could look up and down to written commands with preserved vertical saccades and tracking, but no horizontal eye movements. Pupillary and corneal reflexes were preserved with impaired cough. He had spasticity with no spontaneous limb movements or resistance to strength testing. Painful stimulation caused upper extremity extensor posturing and triple flexion in the lower extremities. Deep tendon reflexes were brisk with bilateral extensor plantar responses.

On further history, the patient was born in India, emigrating to Canada 40 years ago. He had no preceding infectious or constitutional symptoms, recent travel, previous tuberculosis, or sick contacts.

1. What is the expected localization of the patient’s deficits on initial presentation and subsequently following transfer?
SECTION 2:

Initial presentation with right-sided appendicular and gait ataxia is consistent with ipsilateral cerebellar hemispheric lesion seen on CT. Following worsening cerebellar symptoms, there was new hypodensity in the right middle cerebellar peduncle (Figure 1A).

Subsequent neurological deterioration with retained alertness, anarthria, horizontal gaze palsy, and spastic quadriplegia suggests lesion extension into the brainstem, particularly the ventral pons, and is clinically consistent with a locked-in syndrome. Decerebrate posturing suggests lower brainstem involvement. Lesions of the basis pontis involving bilateral corticospinal and corticobulbar tracts lead to quadriparesis, upper motor neuron signs, oropharyngeal, and facial paralysis. Horizontal gaze palsy with spared blinking and vertical eye movements is a result of selective pontine circuit involvement including the cranial nerve VI nuclei and paramedian pontine reticular formation but sparing of vertical eye control in the rostral midbrain. Preserved consciousness is secondary to reticular formation sparing. MRI brain revealed abnormal T2/FLAIR signal in the middle cerebellar peduncles extending into the cerebellum, pons, and pontomedullary junction (Figure 1B).

1. Given the patient’s clinical progression and neuroimaging, what is the differential diagnosis at this point?

SECTION 3

Gradual clinical and radiologic progression is not in keeping with initial diagnosis of acute stroke and this progressive brainstem involvement is more suggestive of an infectious, inflammatory, malignant, or toxic/metabolic process.
Rhombencephalitis refers to inflammation of the rhombencephalon, comprising the pons, medulla, and cerebellum. There are numerous causes including infectious, autoimmune, and paraneoplastic etiologies. Amongst infectious causes, the most prevalent are Listeria, Enterovirus 71, and the herpesviruses, including herpes simplex virus (HSV), Epstein-Barr virus (EBV), human herpesvirus type 6 (HHV-6), and less commonly, cytomegalovirus (CMV) and varicella zoster virus (VZV). Flaviviruses, particularly the mosquito-borne Japanese encephalitis virus endemic to Asia, are also associated, although this patient had no travel history. Progressive multifocal leukoencephalopathy (PML) is caused by John Cunningham virus (JCV) reactivation, typically in immunosuppressed individuals, and can cause infratentorial lesions. This patient was never treated with immunosuppressants for his stable CLL, but CLL itself may disrupt innate and adaptive immunity. Rare bacterial causes include Mycobacterium tuberculosis, brucella, borrelia, salmonella, legionella, and mycoplasma. Given gastrointestinal symptoms, Tropheryma whipplei was considered, as reported in one case of rhombencephalitis in a rheumatoid arthritis patient on methotrexate.

Neuro-Behçet disease is the most common autoimmune cause; however, this patient does not fit the typical age and demographic with no systemic symptoms including mucocutaneous ulcerations, uveitis, or rash. Cases have also been reported in systemic lupus erythematosus and relapsing chondritis. Primary CNS vasculitis may also be considered as it can affect any part of the CNS, although not specific to the rhombencephalon. This was deemed unlikely as the patient’s symptoms are gradually progressive with expansion of the primary lesion and absence of enhancement, hemorrhage, and vascular abnormalities such as arterial beading. Demyelinating disorders such as multiple sclerosis (MS), neuromyelitis optica, and acute disseminated encephalomyelitis were similarly considered unlikely given age and demographic.
Neurosarcoidosis is another inflammatory disease with diverse manifestations. Bickerstaff’s brainstem encephalitis is a consideration given symptoms of ataxia and ophthalmoparesis, although there was no antecedent infection. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPERS) is an inflammatory syndrome of the brainstem, particularly the pons, which classically presents radiologically with punctate enhancement not seen in this patient.

Paraneoplastic causes are typically associated with anti-Yo and anti-Tr antibodies secondary to gynecologic and breast cancer as well as anti-Hu, anti-Ri, anti-Ma, and anti-amphiphysin antibodies often from underlying small cell lung cancer. This patient was a lifelong non-smoker.

In addition to rhombencephalitis, neoplastic aetiologies such as lymphoma or a brainstem glioma are diagnostic possibilities given the patient’s older age and immunosuppression.

Toxic/metabolic causes with this appearance that may be considered include the brainstem variant of posterior reversible encephalopathy syndrome (PRES) given CLL history, but the patient was never on immunosuppressive medications and his blood pressure was not significantly elevated at presentation. Finally, although clinical history is not suggestive, osmotic demyelination syndrome resulting from rapid sodium correction typically presents with central pontine T2 hyperintensity and restricted diffusion.

1. What investigations will you order?
2. What treatments will you initiate?

SECTION 4

Peripheral lymphocyte count was stable. Serum protein electrophoresis, rheumatologic panel, and inflammatory markers were unremarkable. Broad spectrum antimicrobials including
acyclovir and ampicillin (for Listeria coverage) were initiated until lumbar puncture revealed unremarkable cell count (1 x 10^6/L leukocytes, 4 x 10^6/L erythrocytes), 339 mg/L protein, and negative culture. Subsequent MRI brain with contrast revealed no enhancement. Lumbar puncture was repeated following transfer, also unremarkable with normal cytology and JCV testing ordered. CSF PCR was negative for HSV, VZV, and enterovirus. Serologies for HIV, CMV, EBV, VZV, brucella, bartonella, histoplasma and cryptococcus were all negative. Interferon-gamma release assay was negative for tuberculosis. Paraneoplastic antibodies, angiotensin converting enzyme, and oligoclonal bands were negative with normal IgG synthesis rate.

He was then treated with pulse steroids, intravenous immunoglobulins, and plasma exchange (PLEX) therapy without improvement. CT chest, abdomen, pelvis, and testicular ultrasound were unremarkable. Duodenal biopsy was negative for Whipple’s disease. Brain biopsy was deemed unfeasible given location. EEG showed diffuse encephalopathy. Ultimately, CSF JCV DNA was detected at high titer and rhombencephalitis secondary to PML was diagnosed.

Mirtazapine was initiated. The patient continued to decline clinically and radiologically despite supportive care. Repeat MRI showed lesion extension into the midbrain as well as bilateral posterior internal capsules and subcortical white matter involvement (Figure 1C). He ultimately died of respiratory failure four months after initial presentation.

Autopsy revealed widespread PML corresponding to abnormal MRI posterior fossa regions and microscopic lesions in frontal and parieto-occipital subcortical white matter (Figure 2). Death was attributed to PML with CLL a contributory risk factor.
DISCUSSION

PML was first recognized in CLL and Hodgkin lymphoma patients in 1958\textsuperscript{6,7}. Following the 1980s AIDS pandemic, 80\% of cases were seen in HIV/AIDS patients with 13\% in hematologic malignancies\textsuperscript{7}. In the mid-2000s, a second wave of PML was observed with new therapeutic monoclonal antibodies, namely natalizumab in the treatment of MS and other immunosuppressants for autoimmune conditions and organ transplant patients. PML is rare in stable CLL patients under surveillance who have never received treatment with one report in the literature\textsuperscript{8}.

JCV is a double-stranded DNA virus of the polyomavirus family widespread among mostly asymptomatic individuals with seroprevalence between 33-90\%\textsuperscript{6}. After initial infection, it becomes dormant in tissues including the kidneys, bone marrow, and possibly CNS\textsuperscript{6}. Mechanisms of viral reactivation are not entirely understood but immune system dysfunction is the common underlying factor in predisposing conditions; thus, intact immune functioning is presumed to keep the virus dormant and prevent disease expression\textsuperscript{7}. When activated, infected oligodendrocytes become enlarged with prominent intranuclear inclusion bodies and lysis, resulting in myelin loss\textsuperscript{6}.

The clinical presentation of PML is diverse with subacute focal or multifocal neurologic deficits that can initially be mistaken for stroke\textsuperscript{6}. Symptoms and signs depend on area of CNS involvement. There is a single previous report of PML presenting as locked-in syndrome in a patient treated with rituximab for relapsed follicular lymphoma and this manifestation seems to be rare\textsuperscript{9}. Seizures have been reported in 20\% of patients\textsuperscript{7}. PML should be considered in immunosuppressed patients presenting with subacute progressive neurologic symptoms. CSF PCR for JCV DNA is preferred for minimally-invasive diagnosis, with reported sensitivity
ranging from 74–92% and specificity, 92–100%, although pathologic examination is definitive\textsuperscript{6}. MRI is sensitive in showing typically bilateral, diffuse, confluent T2-hyperintense white matter lesions, although single lesions can occur\textsuperscript{7}. Commonly there is subcortical involvement of the parieto-occipital and frontal lobes, the corpus callosum, pyramidal tracts, and the posterior fossa, particularly the middle cerebellar peduncles with cerebellar or pontine extension as in this case\textsuperscript{6-7}. Lesions tend to be non-enhancing with presence of diffusion restriction\textsuperscript{7}.

There is no direct anti-JCV therapy. Numerous agents have been studied with limited evidence and are not considered effective treatment including antiviral agents such as mirtazapine, cytarabine, cidofovir, mefloquine as well as immune response modulators such as interferon-alpha, interleukin-2, and most recently, immune checkpoint inhibitors\textsuperscript{10-11}. Outcomes depend on recovering immune system function, or immune reconstitution. If applicable, immunosuppressive therapy withdrawal and anti-retroviral therapy optimization in HIV patients are key treatment aspects. PLEX has been utilized in MS patients with PML secondary to natalizumab for peripheral drug clearance\textsuperscript{10}. PML remains incurable with high mortality within the first three months of diagnosis and worse prognosis portended by higher CSF viral load and involvement of crucial CNS areas such as the brainstem\textsuperscript{6}.

**Appendix 1: Authors**

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<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
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<tbody>
<tr>
<td>Ikreet Cheema, MD</td>
<td>University of British Columbia, Vancouver, BC, Canada</td>
<td>Study design, drafted the manuscript, revised manuscript for intellectual content</td>
</tr>
<tr>
<td>Nicole Ng, MD</td>
<td>University of British Columbia, Vancouver, BC, Canada</td>
<td>Revised manuscript for intellectual content; pathology acquisition and interpretation</td>
</tr>
<tr>
<td>Tychicus Chen, MD, FRCPC</td>
<td>University of British Columbia, Vancouver, BC, Canada</td>
<td>Supervision; study conception and design; revised manuscript for intellectual content</td>
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REFERENCES:


FIGURE LEGENDS

Figure 1. Serial neuroimaging with CT and MRI demonstrating lesion progression

A) Non-contrast axial CT head revealing right cerebellar hemisphere hypodensity with involvement of the right middle cerebellar peduncle (see arrows) and no supratentorial abnormalities; B) Axial MRI T2/FLAIR performed one month after the CT head demonstrating extensive abnormal hyperintensity in the right and left middle cerebellar peduncles extending into the cerebellum, pons, and pontomedullary junction. There was additional presence of restricted diffusion and no contrast enhancement in these areas (not shown); C) Repeat MRI two months later demonstrating extension of hyperintensity into the midbrain and posterior limbs of the internal capsules in addition to increased subcortical white matter foci.
Figure 2. Histopathology of PML

A) Hypercellularity with macrophagic infiltration of white matter (confirmed macrophagic by CD68 immunohistochemical staining, not shown); B) Astrocyte with bizarre-shaped, enlarged nucleus (arrow); C) Demyelination revealed by Luxol Fast Blue staining; D) Strongly positive SV40 immunohistochemical staining indicative of active polyomavirus replication in glial cells (arrow). Scale bars: 100 μm (A), 50 μm (B-D).
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