# Clinical Reasoning: A 66-Year-Old Woman With Progressive Encephalopathy and Bilateral Hearing Loss

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## Section 1

A 66-year-old woman with no medical history presented to an outside hospital for an acute alteration in cognition described as wandering aimlessly, combative behavior, and incomprehensible speech that progressed over 3 days. On arrival, she had altered cognition, psychomotor agitation, and inability to follow commands, but no weakness, dysarthria, sensation loss, vision loss, or meningismus. Vital signs and laboratory studies including complete blood count, comprehensive metabolic panel, urinalysis, and urine drug screen were normal.

### Questions for Consideration:

1. What is the localization for her presentation?
2. What is the initial differential diagnosis?
3. What studies should be conducted?

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## Section 2

Patients presenting with encephalopathy without focal features typically experience a disorder limited to the cerebral hemispheres. The differential diagnosis in such patients is broad, with the most common etiologies being metabolic, toxic, infectious, inflammatory, neoplastic, vascular, or epileptic. Initial studies for this differential should include CT of the head, MRI of the brain, CSF studies, and EEG. CT of the head showed a 5-mm hypodense lesion in the left temporoparietal region with surrounding edema and possible overlying hemorrhage. MRI of the brain with gadolinium revealed multifocal bilateral regions of subcortical edema and petechial cortical hemorrhage involving the insula, precentral gyrus, and parietal and lateral temporal lobes. CSF studies revealed 3 WBCs per mcL (normal 0–5/mcL), a glucose of 74 mg/dL (normal 50–80 mg/dL), a protein of 49 mg/dL (normal 15–60 mg/dL), a negative HIV and VDRL test, meningitis/encephalitis panel, autoimmune/paraneoplastic panel, and unrevealing cytology. A 24-hour EEG showed generalized slowing. The outside hospital treated her empirically with steroids and IVIg for suspected autoimmune encephalitis and discharged her after her cognition improved.

Four weeks later, she presented to our hospital with a similar encephalopathic episode combined with significant bilateral hearing loss. On examination, she exhibited bilateral cortical dysfunction characterized by a Glasgow Coma Scale of 11, Frank startle myoclonus involving distal bilateral upper and lower extremities, and inability to follow commands. Cranial nerves were intact other than severe bilateral hearing loss. She exhibited increased tone in the lower extremities and withdrawal to noxious stimulation in all extremities.

### Questions for Consideration:

1. What is the localization for acute/subacute hearing loss?
2. What additional studies should be considered?
3. What would be included in the differential diagnosis at this time?

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## Section 3

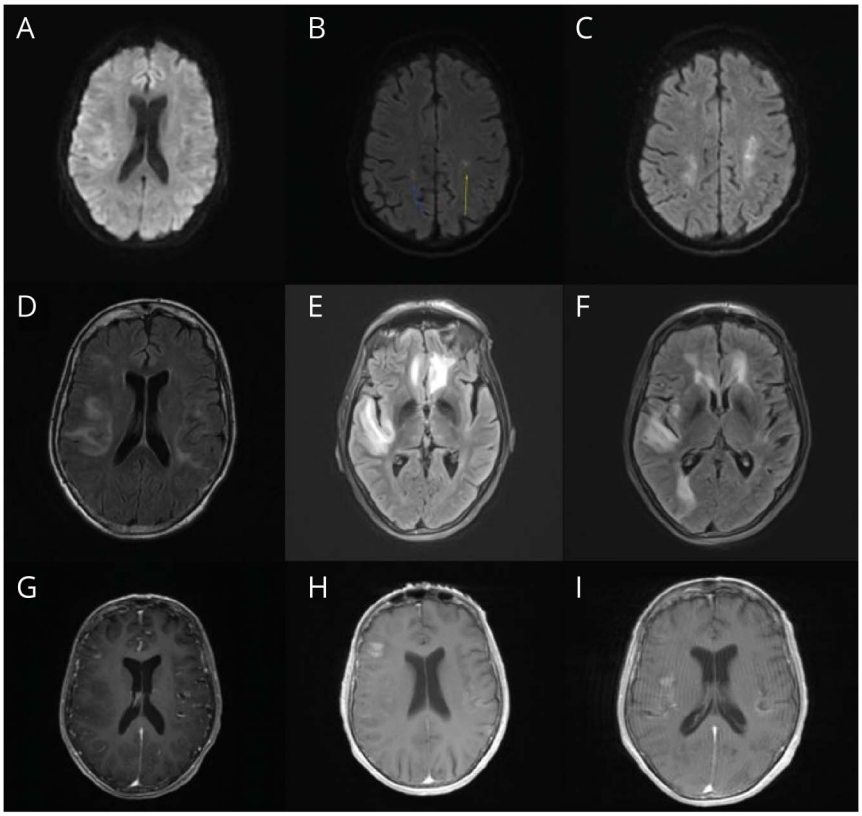
Hearing loss can either be conductive, suggesting a lesion in the outer or middle ear, or sensorineural, suggesting a lesion in the cochlea, cochlear nerve, or central auditory pathway. Although complex, the main tract of the afferent central auditory pathway begins in the cochlear nuclei, projects to the contralateral superior olivary nucleus and lateral lemniscus, and continues to the inferior colliculus, then medial geniculate body in the thalamus, and finally to the primary auditory cortex on the superior surface of the temporal lobe. Given the acute onset of bilateral hearing loss, there was a very low suspicion for conductive hearing loss. She had not taken any ototoxic agents, making ototoxic deafness unlikely.

Patients presenting with encephalopathy and acute/subacute hearing loss are limited to a few disorders such as Susac syndrome, intravascular lymphoma, primary angiitis of the CNS (PACNS), and neurosarcoidosis. MRI brain with gadolinium to evaluate for these conditions revealed contrast enhancement in the right primary auditory cortex, no contrast enhancement in the cochlear nerves and cochleae, and fluid-attenuated inversion recover (FLAIR) hyperintensities in the left superior olivary nucleus and left auditory thalamocortical pathway, implying that the patient's acute onset deafness was cortical deafness (Figure 1). Additional CSF evaluation including cytology for lymphoma, RT-QuIC for rapidly progressive encephalopathy, ACE for neurosarcoidosis, oligoclonal bands for demyelinating disease and neurosarcoidosis, and autoimmune/paraneoplastic panels were negative other than a glutamic acid decarboxylase-65 (GAD65) antibody level of 0.03 nmol/L (normal value < 0.02 nmol/L). A 48-hour EEG to evaluate for intermittent seizures was performed, revealing generalized slowing without delta-brush.

### Questions for Consideration:

1. Given the neuroimaging findings, what remains on the differential diagnosis?
2. What further evaluation is needed?

**Figure 1** MRI Brain Showing DWI, T2/FLAIR, and T1 Postcontrast Sequences From 3 Separate Admissions




(A–C) DWI images from the first (A), second (B), and third admission (C) showing a progression in foci of restricted diffusion, eventually involving the bilateral frontal lobes, bilateral parietal lobes, right occipital lobe, and right cerebellar hemisphere. (D–F) T2/FLAIR images from the first (D), second (E), and third admission (F) showing subcortical increased signal predominantly in the bilateral frontoparietal insular and lateral temporal lobes with progression to involvement of the bilateral gyrus recti, bilateral frontoparietal regions, lateral right frontal region, right insula, right temporal lobe, right occipital lobe, and right cerebellar hemisphere. (G–I) T1 Postcontrast images from the first (G), second (H), and third admissions (I) showing a progression of gadolinium enhancement, eventually involving the bilateral gyrus recti, bilateral frontoparietal regions, lateral right frontal region, right insula, right temporal lobe, right occipital lobe, and right cerebellar hemisphere.

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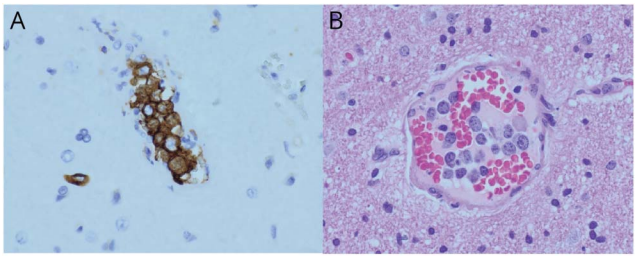
## Section 4

Given the bilateral hearing loss and MRI findings, we considered Susac syndrome. However, there were no classic "snowball" lesions in the corpus callosum on MRI or vision loss. A CT angiogram of head and neck was normal, making PACNS unlikely considering her lack of headache and focal deficits. Sarcoidosis was less likely given the absence of ACE in CSF and systemic manifestations of sarcoidosis. Ophthalmology did not find any ocular findings suggestive of small artery vasculitis. She had previously improved with steroids, so she was treated a second time with IV steroids for 5 days with improvement of her sensorium. Her ability to read, write, comprehend, and produce fluent speech was intact, but her hearing did not improve by the time of discharge.

Unfortunately, she did not follow up with neurology. She returned 5 weeks later with a decline in cognition manifesting as disorientation, obtundation, and agitation. Repeat MRI brain with gadolinium was performed to evaluate interval changes which showed progression in the supratentorial and infratentorial scattered areas of T2/FLAIR hyperintensity with associated abnormal enhancement. There was a new T2/FLAIR hyperintense lesion in the right cerebellar hemisphere with hemosiderin deposition. Ophthalmology performed a fluorescein angiogram which did not reveal artery occlusions, vasculitis, glass plaques, or segmentation of arterioles suggestive of Susac syndrome.

There was a raised suspicion for lymphoma. We did not obtain a skin biopsy given the recent steroid course and lack of cutaneous manifestations. Neurosurgery performed a brain biopsy on an area of enhancement in the right frontal lobe (Figure 2). Biopsy findings were consistent with intravascular large B-cell lymphoma. She was treated with high-dose methotrexate. Despite treatment, her cognition continued to deteriorate. She died within 1 month of diagnosis.

**Figure 2** Brain Biopsy Revealing Intravascular Lymphoma Cells Consistent With Diagnosis of IVLBCL




Brain biopsy slides at ×400 magnification showing lymphoma cells are positive for CD20 by immunohistochemical stain (A) and H&E stain showing intravascular large lymphoma cells with prominent nucleoli and surrounding brain tissue with edema (B) which were both confirmatory for diffuse large B-cell intravascular lymphoma.

## Discussion

Intravascular large B-cell lymphoma (IVLBCL) is a rare subtype of large cell lymphoma. Much of the knowledge regarding IVLBCL comes from individual case reports and small case series. With increased awareness, IVLBCL is being diagnosed premortem with greater frequency. In the absence of timely treatment, IVLBCL is universally fatal.

Specific molecular features distinguish IVLBCL from typical large B-cell lymphoma. IVLBCL cells express molecules involved in cell migration and adhesion to the endothelium but lack those involved in extravasation.[1-3] Lymphocyte proliferation limited to the lumen of small vessels leads to the multivariant clinical presentation of IVLBCL making diagnosis challenging without a high level of suspicion and a representative tissue sample.

Presenting symptoms in IVLBCL may manifest with fevers, night sweats, and weight loss and involve organs such as the skin, CNS, peripheral nervous system, spleen, liver, and kidneys. The most common symptoms are typically associated with involvement of the CNS (39%–76%) and skin (17%–39%).[1,2,4] Symptoms are caused by tissue damage in the form of microinfarctions of arterioles. There is 1 case report of a pseudo-Susac presentation in IVLBLC. This patient's clinical course differed with the presence of myelopathy at onset and subsequent acute vestibular syndrome.[5]

Diagnosis of IVLBCL is made by identification of large lymphoma cells within small blood vessels of affected tissue. In cases with both cutaneous and CNS involvement, skin biopsy should be considered before brain biopsy given the less invasive nature of the procedure.[6,7] One study investigated the effectiveness of random skin biopsies in 16 patients with suspected IVLBCL and reported a 100% positive predictive value but also noted that a low soluble interleukin-2 receptor along with steroids administered before diagnosis can cause false-negative results.[7] Common image findings include abnormal patterns of susceptibility changes on SWI sequences and vanishing or migratory patterns of T2/FLAIR sequences, both of which our patient had.[8-10] Lumbar puncture has not been shown to be helpful in diagnosis. Common CSF findings are neither sensitive nor specific and include pleocytosis and a mild elevation in protein. Although lymphoma cells are found within the intracranial vasculature, patients with solely neurologic manifestations of IVLBCL have minimal to no lymphoma cells found on serum or CSF cytology studies. Serial lumbar punctures may increase the sensitivity of finding lymphoma cells on cytology.

The mainstay of treatment of IVLBCL with CNS involvement is a combination of methotrexate (MTX)-based intrathecal chemotherapy and R-CHOP. Intrathecal MTX can also be used as prophylaxis in patients without CNS involvement at the time of diagnosis.[11,12] Involvement of the CNS at diagnosis carries a poor prognosis. Cases with isolated skin

involvement have the best treatment response and survival. In one meta-analysis of case reports, case series, and retrospective studies including patients with and without CNS involvement, patients who received rituximab-containing chemotherapy, generally consisting of 6 cycles, had significantly longer survival (450 days vs 180 days).[13] There are few case reports of long-term remission after R-CHOP treatment in patients with CNS involvement.

We present a case of IVLBCL to bring attention to this rare form of lymphoma. Early diagnosis with appropriate skin or brain biopsies and treatment initiation will likely lead to better outcomes. This case is unlike any other documented case report, with an initial relapsing and ultimately a progressive course of encephalopathy accompanied by acute onset persistent bilateral sensorineural hearing loss without any additional systemic manifestations.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