CLINICAL VIGNETTE

An Irritating Presentation of Primary CNS Lymphoma

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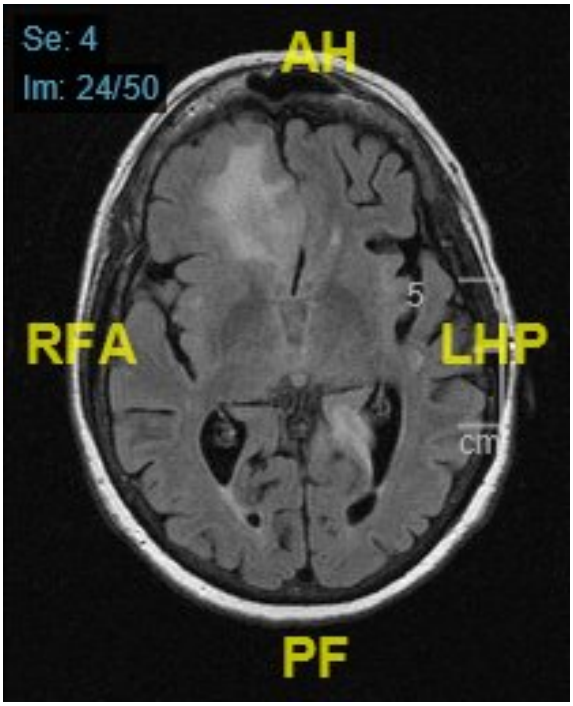
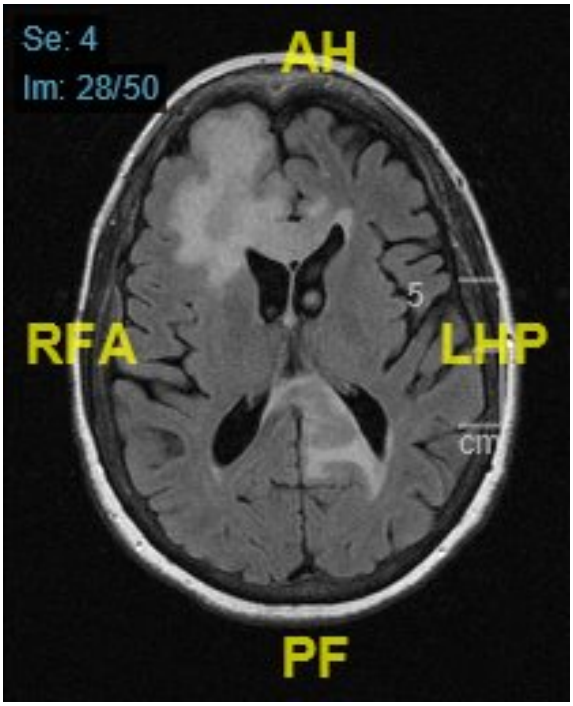
Clinical Case

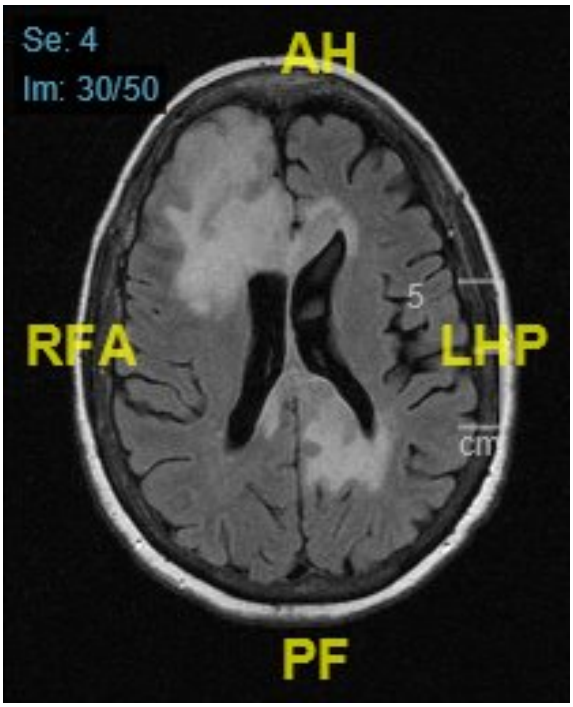
A 77-year-old female with COPD, hypertension, and depression presents to outpatient clinic with personality changes for the last three weeks. She was accompanied by her brother who reports new onset significant irritability and sudden mood swings. He has also noted that she is sleeping more than before, up to 12 hours per day with 2-hour afternoon naps. The patient reports more inattention, forgetfulness and increasing frustration with more difficulty understanding regular television shows. She also feels unbalanced and reports two episodes where she had to quickly sit back down after trying to get up out of bed. Patient denies any head trauma, speech difficulties, vision changes, hearing changes, or numbness/tingling. She has been eating and drinking normally with no recent weight changes. Her past medical history also includes breast cancer initially treated with chemotherapy and radiation, currently taking anastrazole. She had started methocarbamol medication for back pain 6 weeks ago, but had stopped 2 weeks ago as it had not been effective. Patient denies taking any other new medications, illicit drugs, supplements, or alcohol.

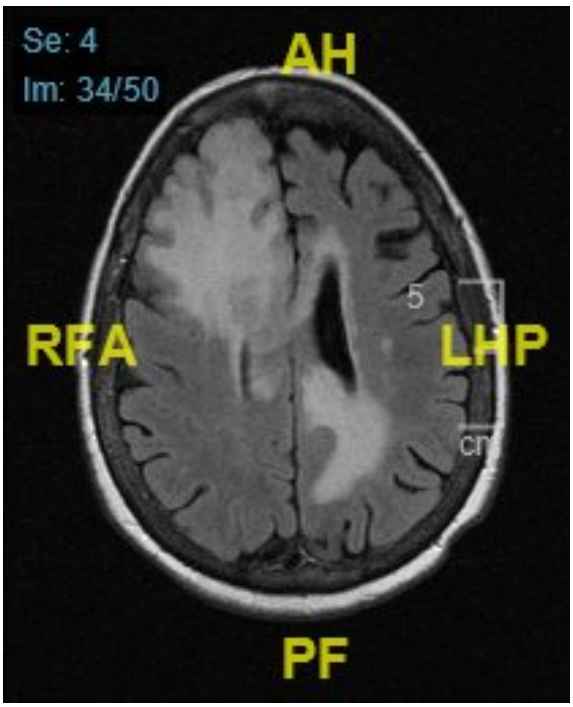
On examination, patient was afebrile, blood pressure was 140/91, heart rate was 84 and her BMI was 34. She was cooperative throughout the examination and was alert and oriented x 4. Her timed get up and go test was normal. She had a steady, but cautious gait. She had normal strength and sensation in all four extremities and there was no pronator drift. Labs including comprehensive metabolic panel, complete blood count, folate, thiamine, and HIV were unremarkable. Her thyroid stimulating hormone was slightly elevated at 5.3 mcIU/mL (Normal range 0.3-4.7 mcIU/mL).

MRI brain with and without contrast was completed and demonstrated multiple new homogenously enhancing lesions along the length of the corpus callosum, extending to the right frontal lobe with extensive adjacent vasogenic edema resulting in mild leftward midline shift at the level of the anterior interhemispheric fissure, concerning for primary CNS lymphoma. She was admitted for expedited evaluation.









She was hemodynamically stable on admission. CT chest, abdomen and pelvis showed no lymphadenopathy or metastatic disease. Ophthalmology noted no optic nerve head edema and no deficits with extraocular movements. Neurosurgery consultation, reported open basal cisterns and she was deemed safe for a diagnostic lumbar puncture. Cerebrospinal fluid analysis showed elevated protein, glucose, and lymphocytic predominant cells (see chart). However, CNS cytology was negative for malignant cells. Stereotactic brain biopsy revealed diffuse large B cell lymphoma (DLBCL).

	Ref. Range	**Results**
CSF Appearance	Unknown	Clear and Colorless
RBC Count CSF	0 - 10 /cmm	<1
WBC Count CSF	0 - 5 /cmm	16 (H)
Lymphocyte CSF	40 - 80 %	76
Monocyte CSF	15 - 45 %	24
Glucose CSF	43-73	62
Protein CSF	15-45	120
Bacterial Cult-Gm Stain, CSF	Neg	Neg
Cytology	Neg	Neg for malignant cells

Discussion

Epidemiology

Primary central nervous system (CNS) lymphoma is a type of non-Hodgkin lymphoma that is isolated to the brain, leptomeninges, eyes or spinal cord. This type of lymphoma is very uncommon and only accounts for 4% of newly diagnosed CNS tumors. Incidence is higher in males compared with females and in Caucasian patients older than 50 years.[1] Roughly 90% of primary CNS lymphoma cases are diffuse large B-cell lymphomas with the remainder T-cell lymphomas, poorly characterized low-grade lymphomas or Burkitt's lymphoma.[2] The cause of CNS lymphoma is unknown, but factors causing decreased immune systems have been linked, including Epstein-Barr virus infection, HIV, or patients who have undergone organ transplant.

Clinical Presentation

Symptoms that are common with other lymphomas, such as fevers, unintentional weight loss, and night sweats, do not typically appear with CNS lymphoma. Instead, more common symptoms include gait disorders, headaches, confusion, behavioral or cognitive changes. About 40% of patients with primary CNS lymphoma present with neuropsychiatric symptoms like depression, apathy, psychosis, confusion, or visual

hallucinations. These can be attributed to lesions found in the frontal lobes, periventricular white matter or corpus callosum.[3]

CNS lymphoma in the spine or cerebrospinal fluid is less common than CNS lymphoma in the brain. If the patient has involvement in the spine or CSF, the patient may have other symptoms such as numbness/tingling, weakness in extremities and bowel/bladder incontinence. Up to 20% of primary CNS lymphoma can have intraocular involvement. Presenting symptoms are often very subtle and easy to miss but can include eye pain, blurred vision, floaters or resemble chronic uveitis.[4]

Diagnosis

In addition to a thorough history and neurologic examination, a gadolinium-enhanced brain MRI is the most sensitive radiographic study for the detection of primary CNS lymphoma. On MRI, the most common locations of involvement are the corpus callosum and the deep periventricular white matter. Only approximately 25% of immunocompetent patients develop multifocal disease.[5] MRI findings alone are insufficient to diagnose primary CNS lymphoma as other diseases, such as neurosarcoidosis, multiple sclerosis, glioblastoma, and vasculitis can mimic radiographic features.[6]

If no mass effect is noted on imaging, lumbar puncture should be performed. CSF analysis often shows elevated protein, normal glucose levels and lymphocyte predominance. A finding of neoplastic lymphocytes on CSF cytology can diagnose primary CNS lymphoma with meningeal dissemination and a brain biopsy can be avoided. However, if cytology is negative, then the diagnostic procedure of choice is stereotactic brain biopsy. It is important to avoid corticosteroids treatment prior to biopsy as a single injection can alter the histopathology and a short course of steroids could cause the tumor to temporarily disappear.[7]

Because metastatic disease to the brain must also be excluded to establish a diagnosis of primary CNS lymphoma, CT/PET scans of the chest, abdomen, and pelvis are also typically performed. To evaluate for ophthalmic involvement, a comprehensive eye evaluation including slit-lamp examination with an ophthalmologist is also recommended.

Treatment and Prognosis

Whole brain radiation therapy was previously the mainstay of treatment, but because of significant neurotoxicity, especially in older patients, radiation therapy is now more often reserved for residual disease. There is no current standard treatment for CNS lymphoma; however, high dose methotrexate administration in combination with chemotherapy is commonly used. Surgery is helpful in diagnosing CNS lymphoma but has a limited role for treatment as primary CNS lymphoma is generally diffuse. Primary CNS lymphoma tends to be sensitive to radiation treatment, which differs from other malignant primary brain cancers. Treatment decisions in older adults should also take into consideration functional status and comorbidities. This patient was started on rituximab and high dose methotrexate while hospitalized and has been tolerating the initial treatment.

Unfortunately, most patients do not achieve long-term disease control. The median overall survival for immunocompetent adults with primary CNS lymphoma is roughly 24 months with five-year survival ranging from 30-40%.[8]

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