CLINICAL VIGNETTE

Primary Central Nervous System Lymphoma

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A 43-year old male presented to his Primary Care Physician for evaluation of persistent headaches. The patient had noted progressive headaches for the last three to four months. In the last couple of weeks, the patient had also noted onset of blurry vision and increasing problems with walking. His past medical history was otherwise unremarkable. The patient was transferred to Emergency Department (ED) to expedite diagnostic workup.

In the ED, the patient had a non-contrast CT brain, which showed extensive left temporo-parietal-occipital subcortical attenuation suggestive of a central lesion with contra-lateral 18 mm midline shift with mild associated trans-tentorial herniation. An MRI brain with intravenous contrast demonstrated a large mass in the left tempo-parietal occipital region measuring 5.7 cm with intense enhancement and vasogenic edema. In addition, smaller areas of enhancement up to 10 mm were noted in right basal ganglia. CT scan of the neck, chest, abdomen, and pelvis did not reveal evidence of extra-cranial masses. A testicular ultrasound was unremarkable. There was no evidence of peripheral adenopathy on physical exam. Complete blood count and comprehensive metabolic panel were within normal parameters. Serologies for HIV and viral hepatitis were negative

Neurosurgical consultation was obtained and patient underwent craniotomy with gross total removal of the left-sided intra-cranial mass. Pathologic was consistent with diffuse large B-cell lymphoma, non-germinal center type. Lymphoma cells were positive by immunohistochemistry (IHC) for CD20, BCL2, BCL6, MUM-1, and negative for CD10 with a Ki 67 proliferation index of 90%. Post-operative PET-CT scan and bone marrow biopsy did not show evidence of lymphoma. Hence, diagnostic evaluation was consistent with primary central nervous system lymphoma (PCNSL). The patient was started on systemic treatment with high-dose methotrexate in combination with rituximab on a biweekly basis. A repeat MRI brain after five treatments showed decreased enhancement surrounding resection cavity and resolution of contra-lateral areas of enhancement. The patient remains on current treatment regimen with a plan for consolidation treatment with cytarabine and thiotepa, followed by autologous stem cell transplant.

Primary CNS lymphoma (PCNSL) is a rare subtype of extra-nodal non-Hodgkin's lymphoma. It represents about 4% of all primary brain tumors.[1] It may involve different anatomical locations of the central nervous system (CNS) such as brain parenchyma, cranial nerves, eyes, meninges, and spinal cord. Although not common, intra-ocular involvement may be observed in 10-20% of patients.[2] In these cases, lymphoma cells can infiltrate the vitreous humor, the retina, the choroid, or optic nerve. There can also be concurrent meningeal involvement detected by positive cerebral spinal fluid cytology in 16% of otherwise asymptomatic patients. Spinal cord involvement is a rare manifestation of PCNSL. In general, patients can present with a range of neurologic symptoms such as headaches, ocular symptoms, confusion, and lethargy. Approximately 70% of patients can present with focal neurologic deficits, 43% neuropsychiatric symptoms, and seizures in 14% of cases. The median age at diagnosis is 60 years and the male-to-female ratio is 1.2 to 1.7. In the HIV positive patient population, its incidence increases to more than 1,000 times over the general population.[3] Primary CNS lymphoma is also considered an AIDS-defining hematologic malignancy.

A contrast enhanced brain magnetic resonance imaging (MRI) is the neuroimaging modality of choice in the initial evaluation of a patient with suspected PCNSL. In 60-70% of cases, patients are noted to have a solitary intra-cranial mass lesion. Most lesions are located in central hemispheric or periventricular cerebral white matter.[4] Linear enhancement along perivascular spaces is considered to be highly suggestive of PCNSL. All patients with suspected PCNSL should have histopathologic confirmation of diagnosis. A stereotactic needle biopsy is the diagnostic procedure of choice. In most cases, surgical resection is not performed given the deep location of malignant lesions and significant risk for surgical complications. In cases where there is evidence of cerebral spinal fluid involvement, a lumbar puncture with identification of malignant lymphocytes can establish pathologic diagnosis.[5] In immunocompetent patients, 95% of PCNSL are diffuse large B-cell lymphomas (DLBCL). Other less common variants include PCNSL of T cell origin, primary anaplastic large cell lymphoma, and Hodgkin lymphoma.[6] Microscopically, malignant lymphoid cells of PCNSL show a characteristic angiocentric pattern with cuffing of tumor cells within and around cerebral blood vessels. PCNSL may also show areas of necrosis and a prominent reactive astrocytic and microglial response along with reactive CD4-positive T cells.[6] Similar to nodal DLBCL, PCNSL can be further subcategorized into germinal center B-cell and activated B-cell subtypes based on staining patterns for CD10, BCL6, and MUM-1.

Previously whole brain radiation therapy (WBRT) represented the mainstay of treatment for PCNSL in immunocompetent patients. However, this particular strategy was often associated with significant neurotoxicity, especially in older patient populations. The modern approach to the treatment of PCNSL involves the upfront use of chemotherapy with radiation therapy reserved for residual disease. A number of combination chemotherapy regimens are used in clinical practice. Often these regimens include the use of high doses of methotrexate in combination with other agents capable of crossing the blood-brain barrier. A combination of high-dose methotrexate and high-dose cytarabine was shown to have a complete response rate of 46% with a 3-year overall survival rate of 46%.[7] High-dose chemotherapy with autologous stem cell transplantation is also being incorporated into the treatment of PCNSL as a consolidation strategy. A number of prospective trials have demonstrated the feasibility of this approach with one phase 2 trial showing a 3-year overall survival rate of up to 77%.[8] Despite improvements in efficacy, not all patients with a new diagnosis of PCNSL are able to tolerate the intensity and toxicity associated with newer treatment approaches. WBRT alone is not curative and median survival ranges from 10 to 18 months. Nonetheless, this is a reasonable treatment option for patients deemed unfit for upfront chemotherapy. In HIV-positive patients with PCNSL, the concurrent use of highly active anti-retroviral therapy (HAART) and high-dose methotrexate-based therapy has been shown to be effective and well tolerated. As it is the case with HIV-negative patients, rituximab can be judiciously incorporated into the treatment protocol in carefully selected immunosuppressed patients. In this patient population, radiation therapy has limited therapeutic value as it can only induce transient therapeutic responses associated with shorten survival.

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