CLINICAL VIGNETTE

Langerhans Cell Histiocytosis in an Adult Patient

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Case

An 18-year-old male presented to his primary care doctor for a 2-week history of left-sided headache and a rapidly increasing lump on the left side of his head. Past medical history is significant for obesity, prediabetes and pericarditis. He denies any previous trauma, fever, cough or congestion. He notes that the headache increases in intensity when laying down and rates the headache an 8 out of 10 in intensity.

Physical exam is significant for normal vital signs and a large fluctuant tender mass in the left parietooccipital region with no overlying erythema, drainage or skin breakdown. There is no meningismus, bruising or petechiae. The remainder of the physical exam is normal. Given the rapidly growing lesion, a brain CT was scheduled and labs were drawn. Labs were significant for white cell count of 11.54 with absolute neutrophil count of 7.68 (1.80 - 6.90 x10E3/uL). Erythrocyte Sedimentation rate was 31 (< 12 mm/hr) and C-reactive protein was elevated at 3.0 (<0.8 mg/dL). CT of the brain showed "a lytic left parietal calvarial lesion with expansile soft tissue component; differential diagnosis includes inflammatory and infectious etiologies such as Langerhans' cell histiocytosis and osteomyelitis with neoplastic etiology not excluded." MRI revealed a "left parietal calvarial mass with slight intracranial and extracranial extension, edema and soft tissue thickening in the overlying soft tissues. Abnormal signal intensity and enhancement of the adjacent marrow. The main differential considerations again include Langerhans cell histiocytosis or osteomyelitis, though the elevated perfusion within the lesion would be unusual for infection. Neoplasm is considered less likely, though difficult to exclude. The mass has slight mass effect on the underlying left parietal cortex, but there are no reactive changes in the brain parenchyma and no midline shift." Patient was seen by Neurosurgery six days later for a biopsy which reconfirmed the diagnosis of Langerhans cell histiocytosis. Three weeks after initial presentation, the patient was seen by hematology/oncology. A skeletal survey showed a lytic lesion at the right supra-acetabular iliac bone which places him in Group 3 multifocal bone disease. As such, it was recommended that he start cytarabine IV therapy for 1 year. However, 4 months into his treatment, his course was complicated by fevers with the cytarabine treatment. The hip Langerhans cell histiocytosis lesion had not significantly improved despite 4 cycles of cytarabine and he was transitioned to dabrafenib, an oral drug used more in adults, with a better side effect profile.

Discussion

Langerhans cell histiocytosis (LCH) is a rare histiocytic disorder that can be seen in all ages but commonly presents in children from one to three years old. The disease is typically limited to one organ system (for example, bone) in approximately 55 percent of patients with the remainder of patients having multisystem disease.[1] A more indolent disease involving one organ system is common in older children and adults, whereas an acute disseminated multisystem disease is more common in children under the age of three.[2,3] Most bone lesions are asymptomatic but patients can complain of pain. On exam there is a tender raised soft mass. On radiographs, LCH is identified as lytic lesions with an accompanying soft tissue mass. Skin involvement is seen in about 40 percent of patients and typically looks like an eczematous rash or candida infection. Biopsy is diagnostic.[1] Lung involvement occurs in 10 percent of patients, usually in adults with smoking history.[4] Central nervous system (CNS) involvement is seen in approximately 6 percent of patients at the time of diagnosis. It can present with diabetes insipidus and symptoms of neurodegeneration including ataxia, cognitive dysfunction.[1] Lesions of facial bones or bones of the anterior or middle cranial fossae are "CNS-risk" lesions with an almost 25 percent incidence of CNS involvement. Diagnosis of LCH is based on the pathological evaluation of the involved tissue or bone. Osteolytic bone lesions are preferred for the diagnosis.

The treatment for LCH depends on system involvement. At the time of diagnosis, patients are risk stratified based on the extent of disease and whether or not "risk organs" are involved. "Risk organs" include the hematopoietic system, liver, and/or spleen and denote a worse prognosis. Patients with single system LCH are those with unifocal or multifocal involvement of one organ/system (eg, bone, skin, lymph node, soft tissue). Patients with multisystem LCH have two or more organs/systems involved with or without involvement of "risk organs." In contrast to the term "risk organs," the term "CNS-risk" areas include the mastoid, sphenoid, orbital, ethmoid, or temporal bones and denote an increased risk of involvement of the central nervous system.[1]

For single system involvement, treatment options include prednisone or the combination of vinblastine and prednisone, curettage of the bone lesions, and topical therapy for skin lesions. Patients with multisystem LCH are generally enrolled in clinical trials or start with induction chemotherapy with vinblastine plus prednisolone or cytarabine alone. Patients are

then reassessed at 6 weeks following induction chemotherapy to determine response. Long-term follow-up is required for patients with LCH with the probability of disease reactivation within 5 years is 46 percent. A second complete resolution is achieved in 85 percent of cases, with probability of a second reactivation within five years of achieving this second resolution of 44 percent.[2]

Adults with LCH require special consideration due to higher toxicity when patients treated with regimens usually offered to children. Following the completion of therapy, patients must be monitored for disease recurrence and late effects. The incidence of late effects is dependent on the extent of the disease at the time of diagnosis and the treatment received. For instance, children with low-risk disease most often complete treatment and have no long-term sequelae beyond mild obesity from prednisone treatment. However, patients with multisystem disease have a 71% incidence of long-term problems versus 24% of those with single-system involvement.[5-7] Growth and development problems are more frequent with younger patients due to prednisone. Cognitive defects and hearing loss may develop in long term survivors.[7] Neurological problems and orthopedic defects from lesions are also seen in 20% of patients. Diffuse pulmonary disease may result in poor lung function. Liver disease may be associated with ascending cholangitis which would necessitate liver transplant.[8] Dental problems from loss of teeth may necessitate aggressive dental surgery. Bone marrow damage from therapy is rare and associated with a higher risk of malignancy. Patients with diabetes insipidus are at risk of panhypopituitarism.

Patients with LCH have been reported to have malignancies before, coincident with or after the diagnosis of LCH. It is difficult to know if there is truly an increased risk of malignancy secondary to the therapy for LCH or if it's a coincidence.[9,10] Leukemia (usually acute myeloid leukemia) occurs after treatment as does lymphoblastic lymphoma. Concurrent LCH/malignancy has been reported in a few patients and some patients have had their malignancy before developing LCH. Solid tumors reported to be associated with LCH include retinoblastoma, brain tumors, hepatocellular carcinoma, Askin tumor, and Ewing sarcoma.

Our adult patient has multifocal LCH initially treated with IV cytarabine and then transitioned to oral dabrafenib. He will require ongoing surveillance for disease recurrence and to monitor for late effects including malignancy.

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