CLINICAL VIGNETTE

Leptomeningeal Leukemia Presenting as Cerebellar Ataxia (CA) in a Patient with Ph+ ALL

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Introduction

Cancers such as acute lymphoblastic leukemia, that arise outside of the CNS, have the potential to involve the leptomeninges (LM), believed to be due to poor penetration of chemotherapy into the central nervous system. The leptomeningal space contains cerebrospinal fluid (CSF) which may allow for dissemination of leukemia throughout the brain. Cerebellar dysfunction has not been reported as a manifestation of hematologic LM disease. We report Cerebellar Ataxis in a patient with ALL who developed LM disease that resolved after administration of IT chemotherapy and resolution of the neoplastic meningitis.

Case Presentation

A 74-year-old female presented to the hospital due to increasing tremors, weakness, and generalized pain. These symptoms had been present for 3 months prior to admission and had increased in intensity in the previous few weeks. Upon admission, the patient was ataxic with hearing loss, blurry vision, constipation, and increased nocturia. The patient's husband reported that she was unable to walk for 2 weeks due to her increased tremors.

Three years earlier, she had been diagnosed with Ph+ ALL, believed to be secondary to prior chemotherapy for HER2+ breast cancer, diagnosed in 2009, for which she received Letrozole, Exemestane, Trastuzumab, radiation therapy, and had undergone two local resections. Treatment for her ALL also included GRAAPH-2005 induction along with IT methotrexate, after which she received cytarabine 1g/m^2 consolidation, followed by maintenance with vincristine and dasatinib. Family history included her brother with an unspecified cancer, heart disease in her father, hyperlipidemia in her mother, and depression in her paternal aunt. Prior surgical history included two lumpectomies, and a hip replacement. She was a former smoker who denied drug or alcohol intake.

At the time of presentation, respiratory and cardiovascular examinations were normal, aside from BP of 151/118. Back was notable for midline tenderness around T12. Other physical findings included tremors in the upper extremities at rest and with intention. The patient also had bilateral hearing loss, ataxia, and dysdiadochokinesis.

Laboratory examination revealed mild hyperglycemia (glucose = 110 mg/dL). Complete blood count with differential was essentially normal except for mild increase in MCV of 99.

CT of the brain revealed no evidence of acute hemorrhage, mass effect, or cortical infarction. Lumbar puncture showed CSF white blood cell count of 883/cm^2 with 12% lymphocytes and 88% blasts. The blast enriched gate (78% of total cells) consisted of a population of B-lymphoblasts (about 72% of total cells) positive for CD10, CD19, CD34, intracellular TdT, CD22, and CD79a (partial). Glucose was <10 mg/dL, protein measured 310 mg/dL, and infectious studies were negative. MRI of the brain revealed leptomeningeal disease, showing sulcal enhancement most evident within the cerebellum, parietal and posterior frontal lobes.

Bone marrow biopsy showed no morphologic disease or evidence of systemic relapse, and BCR-ABL1 fusion transcript testing resulted positive at a level of 0.02%, or 2 BCR-ABL1-positive cells per 10,000.

The patient was started on chemotherapy with 12mg IT methotrexate on Day 1. Following Day 1 of treatment, the regimen continued thereafter on Day 3 as alternating IT cytarabine 100mg with IT methotrexate 12mg every other treatment day (100mg cytarabine on Day 3, 12mg methotrexate on Day 5, and so on). The patient received clonazepam intermittently until tremors began to improve on Day 5 of chemotherapy. By Day 7 of the patient's chemotherapy treatment, the cerebellar ataxia had resolved, and therapy for the CNS relapse continued until the CSF was cleared of lymphoblasts by Days 9 and confirmed on day 12 of treatment.

Discussion

ALL is characterized by the impaired production and differentiation of lymphoid progenitor cells, which accumulate in the blood, bone marrow, and extramedullary sites.[1] The disease is more commonly seen in children with more than half of diagnosed patients being under 20 years of age, and the median age at diagnosis being 15 years old.[2] The management of pediatric ALL has been effective, with 5-year overall survival rates around 90%.[3-4] Adult ALL, is rarer with roughly 4 times lower incidence than childhood ALL.[5] Treatment for adult ALL

has not shown as great success as childhood treatment, with cure rates estimated between 20%-40%.[6]

After diagnosed, morphologic and flow cytometry studies to help identify surface markers such as CD19, CD20, and CD22, that may represent potential targets for treatment. Disease cytogenetics helps identify patients who have chromosomal alterations that also may determine prognosis and potential targets for treatment. For example, Philadelphia (Ph) chromosome abnormality, represented by BCR-ABL1 fusion protein, or t(9;22)(q34;q11) translocation, is present in approximately 25% of adults with ALL.[7-8]

Despite recent improvements in first-line ALL therapies, and 60-90% achieving a complete remission (CR), most adults with ALL eventually relapse. A second CR may be achieved; however, the median disease-free-survival is just 2-7.5 months.[5,9] In patients with the Ph+ t(9;22)(q34;q11) translocation, prognosis has been shown to be poor, with 40% of patients achieving a 5-year event-free survival (EFS).[10]

Within hematologic diseases, LM disease is primarily seen in ALL, as other leukemias rarely disseminate into the CNS. In fact, 10% of adults with ALL have CNS involvement at diagnosis. Adults have a lower lifetime risk of developing LM leukemia than do infants and children, and the presence of the Philadelphia chromosome increases the risk for CNS involvement.[11-12] CNS relapse is often asymptomatic and may be discovered upon lumbar puncture for CSF surveillance or when there are perceivable manifestations of CNS infiltration. Typical manifestations of CNS relapse include elevated intracranial pressure, that cause headaches, nausea, and vomiting, as well as focal neurologic deficits or seizures. Nerve root involvement can manifest as radicular pain with weakness and cranial neuropathies symptoms of leptomeningeal involvement. More common symptoms of LM disease include headache, abnormal mental state, gait difficulty, hearing loss, trigeminal neuropathy, pain, and lower motor neuron weakness.[11]

Although hematologic LM disease has not been reported manifesting as CA, CA has been documented in previous reports of LM carcinomatosis from solid primary tumors. Some examples are colorectal adenocarcinoma, breast carcinoma, and lung carcinoma.[13-14] The mechanism by which CA manifests in LM carcinomatosis is unclear. One possibility may be due to increased intracranial pressure due to obstruction of CSF flow due to inflammation on the cerebellum. Other possibilities may include inflammation of meninges surrounding the cerebellum, or a rare case of paraneoplastic cerebellar ataxia (PCA), by which neoplastic antibodies produced from the cancer result in cerebellar dysfunction. Nine antineuronal antibodies are associated with PCA and result in cerebellar dysfunction.[15]

Conclusion

We are unaware of previous reports in which CA was a symptom of hematologic LM disease. Despite proposed mechanisms which LM disease may manifest as CA, the exact mechanism of CA is unclear in our patient. In conclusion, CA may be a rare presentation of LM disease, and clinicians caring for patients with a previous oncologic history should include LM disease in their differential when presenting with CA.

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Submitted March 27, 2019