UCLA Proceedings of UCLA Health

Title

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

Permalink https://escholarship.org/uc/item/8857z3g4

Journal Proceedings of UCLA Health, 23(1)

Authors Kurnick, Adam Schiller, Gary

Publication Date 2019-05-03

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

Adam Kurnick and Gary Schiller, MD

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 methotrex-ate, after which she received cytarabine 1g/m² 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/cm² 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.

REFERENCES

- Paul S, Kantarjian H, Jabbour EJ. Adult Acute Lymphoblastic Leukemia. *Mayo Clin Proc.* 2016 Nov; 91(11):1645-1666. doi: 10.1016/j.mayocp.2016.09.010. Review. PubMed PMID: 27814839.
- 2. **National Cancer Institute**. Cancer stat facts: leukemiaacute lymphocytic leukemia (ALL), http://seer.cancer.gov/ statfacts/html/alyl.html.
- Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, Reaman GH, Carroll WL. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *J Clin Oncol.* 2012 May 10;30(14):1663-9. doi: 10.1200/JCO.2011.37.8018. Epub 2012 Mar 12. PubMed PMID: 22412151; PubMed Central PMCID: PMC3383113.
- Pui CH, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC, Ribeiro RC, Rubnitz JE, Raimondi SC, Onciu M, Coustan-Smith E, Kun LE, Jeha S, Cheng C, Howard SC, Simmons V, Bayles A, Metzger ML, Boyett JM, Leung W, Handgretinger R, Downing JR, Evans WE, Relling MV. Treating childhood acute lymphoblastic leukemia without cranial irradiation. *N Engl J Med*. 2009 Jun 25;360(26):2730-41. doi: 10.1056/NEJMoa0900386. PubMed PMID: 19553647; PubMed Central PMCID: PMC2754320.
- Katz AJ, Chia VM, Schoonen WM, Kelsh MA. Acute lymphoblastic leukemia: an assessment of international incidence, survival, and disease burden. *Cancer Causes Control.* 2015 Nov;26(11):1627-42. doi: 10.1007/s10552-015-0657-6. Epub 2015 Sep 16. PubMed PMID: 26376890.
- Mathisen MS, Kantarjian H, Thomas D, O'Brien S, Jabbour E. Acute lymphoblastic leukemia in adults: encouraging developments on the way to higher cure rates. *Leuk Lymphoma*. 2013 Dec;54(12):2592-600. doi: 10. 3109/10428194.2013.789509. Epub 2013 Jun 21. Review. PubMed PMID: 23547835; PubMed Central PMCID: PMC5681222.
- Jabbour E, O'Brien S, Konopleva M, Kantarjian H. New insights into the pathophysiology and therapy of adult acute lymphoblastic leukemia. *Cancer*. 2015 Aug 1;121 (15):2517-28. doi: 10.1002/cncr.29383. Epub 2015 Apr 17. Review. PubMed PMID: 25891003.
- Moorman AV, Harrison CJ, Buck GA, Richards SM, Secker-Walker LM, Martineau M, Vance GH, Cherry AM, Higgins RR, Fielding AK, Foroni L, Paietta E, Tallman MS, Litzow MR, Wiernik PH, Rowe JM, Goldstone AH, Dewald GW; Adult Leukaemia Working Party, Medical Research Council/National Cancer Research Institute. Karyotype is an independent prognostic

factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. *Blood*. 2007 Apr 15;109(8):3189-97. Epub 2006 Dec 14. PubMed PMID: 17170120.

- 9. Tavernier E, Boiron JM, Huguet F, Bradstock K, Vey N, Kovacsovics T, Delannoy A, Fegueux N, Fenaux P, Stamatoullas A, Tournilhac O, Buzyn A, Reman O, Charrin C, Boucheix C, Gabert J, Lhéritier V, Vernant JP, Dombret H, Thomas X; GET-LALA Group; Swiss Group for Clinical Cancer Research SAKK; Australasian Leukaemia and Lymphoma Group. Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial. Leukemia. 2007 Sep;21(9):1907-14. Epub 2007 Jul 5. PubMed PMID: 17611565.
- Cazzaniga G, De Lorenzo P, Alten J, Röttgers S, Hancock J, Saha V, Castor A, Madsen HO, Gandemer V, Cavé H, Leoni V, Köhler R, Ferrari GM, Bleckmann K, Pieters R, van der Velden V, Stary J, Zuna J, Escherich G, Stadt UZ, Aricò M, Conter V, Schrappe M, Valsecchi MG, Biondi A. Predictive value of minimal residual disease in Philadelphia-chromosome-positive acute lymphoblastic leukemia treated with imatinib in the European intergroup study of post-induction treatment of Philadelphia-chromosome-positive acute lymphoblastic leukemia, based on immunoglobulin/T-cell receptor and BCR/ABL1 methodologies. *Haematologica*. 2018 Jan;103(1):107-115. doi: 10.3324/haematol.2017.176917. Epub 2017 Oct 27. PubMed PMID: 29079599; PubMed Central PMCID: PMC5777198.
- LeClerc JM, Billett AL, Gelber RD, Dalton V, Tarbell N, Lipton JM, Barr R, Clavell LA, Asselin B, Hurwitz C, Schorin M, Lipshultz SE, Declerck L, Silverman LB, Cohen HJ, Sallan SE. Treatment of childhood acute lymphoblastic leukemia: results of Dana-Farber ALL Consortium Protocol 87-01. J Clin Oncol. 2002 Jan 1;20(1):237-46. PubMed PMID: 11773175.
- Demopoulos A, DeAngelis LM. Neurologic complications of leukemia. *Curr Opin Neurol*. 2002 Dec;15(6):691-9. Review. PubMed PMID: 12447107.
- Lahiri RP, Burnand KM, Bandi A, Farooq N, Sathesh-Kumar T. Colorectal cancer presenting with dysarthria and ataxia: a case of isolated leptomeningeal metastasis. *Ann R Coll Surg Engl.* 2011 Oct;93(7):e133-5. doi: 10.1308/147870811X602104. PubMed PMID: 22004622; PubMed Central PMCID: PMC5826992.
- 14. Metcalf C, Villa D. Sugar Coating of the Cerebellum. *J Cancer Biol Res.* 2013;1(2):1010.
- Afzal S, Recio M, Shamim S. Paraneoplastic cerebellar ataxia and the paraneoplastic syndromes. *Proc (Bayl Univ Med Cent)*. 2015 Apr;28(2):217-20. PubMed PMID: 25829659; PubMed Central PMCID: PMC4365125.

Submitted March 27, 2019