

Title: Secondary Acute Lymphoblastic Leukemia in a Patient with Presumptive Weaver Syndrome

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Introduction: Weaver syndrome is a rare genetic disorder characterized by developmental delay, overgrowth, and characteristic dysmorphic faces and is associated with genetic mutations in the Enhancer of zeste homolog 2 (EZH2) gene. Less than fifty cases have been reported in existing literature. In patients with Weaver Syndrome, the mutations 2230_2232dupATC, D664V, and E745K are thought to be pathogenic as they occur at highly conserved residues and are identified in patients with confirmed clinical diagnoses. EZH2 is a histone methyltransferase which functions as a key epigenetic modulator by suppressing gene expression. Mutations in EZH2 causing dysregulation of gene transcription are associated with increased risk for developing malignancy. The mutations identified in Weaver syndrome show considerable overlap with mutations frequently identified in malignancies.

Case Presentation: We present the case of a 44-year-old female with past medical history of developmental delay, seizure disorder, and high-risk childhood Acute Lymphoblastic Leukemia (ALL) who presented with fatigue and easy bruising and was found to have leukocytosis on her CBC (WBC = 96,000). Immunophenotyping of the blood revealed a diagnosis of Philadelphia chromosome negative B-cell ALL. Molecular evaluation of the lymphoblasts revealed the following mutations: a TET2 p.R1516Ter variant, a EZH2 p.E745K variant, and a DNMT3A p. N501S mutation. The EZH2 mutation was present in 48% of cells, suggestive of a germline variant. After further discussion of the mutation profile with the patient's family, it was determined that she had significantly delayed developmental milestones which predated her diagnosis of childhood ALL. In addition, she had signs of prenatal and postnatal overgrowth, as well as characteristic facies. The current clinical evaluation is ongoing, and a skin biopsy is planned to evaluate for a germline EZH2 mutation to establish a diagnosis of Weaver Syndrome. Regarding the B-cell ALL, she is in complete remission following induction chemoimmunotherapy and an unrelated allogeneic hematopoietic stem cell transplantation is planned.

Discussion: Weaver Syndrome is a rare overgrowth disorder, but case reports have indicated an increased malignancy risk, especially of solid tumors. In general, overgrowth disorders are known to be commonly associated with an increased malignancy risk in childhood. In our review of the contemporary literature, only two cases were identified of patients with Weaver Syndrome developing ALL, both in childhood. If a germline mutation is confirmed in this patient, this case raises many further questions. These include questions regarding if this patient's current ALL clone is related to the childhood ALL clone, if patients with germline EZH2 mutations at risk for recurrent de novo ALL, and if germline EZH2 mutations predispose to clonal hematopoiesis. Somatic EZH2 mutations in leukemia are typically associated with poor overall survival outcomes and chemotherapy response. Further follow-up of this case is of great interest.