Precursor B-Cell Acute Lymphoblastic Leukemia in a Pediatric Patient with Bainbridge Ropers Syndrome

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To the editor,

The Additional Sex Combs Like (ASXL) gene family is comprised of the*ASXL1* , *ASXL2* , and *ASXL3* genes which encode proteins involved in epigenetic regulation, embryogenesis, and carcinogenesis[1-3]. Despite the implication of somatic*ASXL* mutations in a variety of malignancies, germline *ASXL*mutations do not appear to have an association with increased malignancy risk. Bainbridge-Ropers Syndrome (BRPS) is a rare autosomal dominant genetic disorder that results from de novo mutations in the *ASXL3*gene[4], characterized by poor growth, hypotonia, intellectual disability, language delay, and dysmorphic facial features[5]. Many affected patients have autism disorder, and epilepsy is seen in approximately one-third of patients[6, 7].

The few published reports of cancer in patients with germline *ASXL* mutations are limited to patients with *ASXL1* mutations, implicating Bohring-Opitz Syndrome (BOS), a phenotypically similar neurodevelopmental syndrome to BRPS. These include two patients with bilateral Wilms tumor[8], and a father and son with identical germline *ASXL1* mutations with acute myeloid leukemia[9]. Unlike BOS, there have been no reported cases of malignancy in patients with BRPS. Here we report the clinical course of a 3-year-old male with known BRPS found to have precursor B-cell acute lymphoblastic leukemia (ALL).

At 10-months-old, the patient underwent neurologic evaluation due to developmental delay, feeding difficulties, and growth failure. He was hypotonic and had subtle dysmorphic features, including arched eyebrows and anteverted nares. An Autism/ID Xpanded Panel demonstrated a de novo pathogenic variant of the *ASXL3* gene (c.4678C>T; p.R1560X), consistent with BRPS.

At 3-years-old, he presented with acute feeding intolerance, fatigue, and abdominal pain. Laboratory analysis showed: white blood cell (WBC) 12.7/mm^3 with 27% peripheral blasts,

hemoglobin 8.3 g/dL, and platelet count 69,000/mm^3. Peripheral flow cytometry identified an immature lymphoid population consistent with precursor B-cell ALL (Table 1). Bone marrow analysis showed no detectable clonal abnormalities on standard cytogenetics and fluorescence in situ hybridization (FISH) analysis showed tetrasomy of chromosomes 4, 8q, 10, 12p, 21q, 22q sequences, trisomy of chromosome 9 and 11 sequences, and homozygous deletion of 9p21 (*CDKN2A*).

He underwent standard-risk three-drug induction therapy with dexamethasone, vincristine, and peg-asparaginase. Post-induction bone marrow evaluation was morphologically negative for malignancy and negative by FISH. Minimal residual disease (MRD) testing revealed a persistent immature clonal B-cell population representing 0.056% of nucleated cells prompting escalation to high-risk consolidation therapy[10], which was complicated by several toxicities. This included a prolonged episode of altered mental status with magnetic resonance imaging (MRI) findings suggestive of intrathecal methotrexate toxicity, and a subsequent episode requiring ICU admission for refractory status epilepticus. Notably, neither the timing of seizure onset nor the MRI findings were consistent with methotrexate toxicity during this episode, and there was no identifiable etiology for his new-onset seizure activity.

Repeat marrow evaluation following consolidation therapy was negative for malignancy by morphology, FISH, and MRD. He began interim maintenance therapy with intravenous (IV) high-dose methotrexate, vincristine, 6-mercaptopurine, and intrathecal methotrexate, and again suffered numerous toxicities and treatment delays. Following his second dose of IV methotrexate, he presented with increased irritability, fatigue, and new petechiae. Laboratory analysis showed: WBC 52.9/mm^3 with 37% blasts, 2% myelocytes, and 2% reactive lymphocytes, concerning for relapsed disease versus lineage switch (Fig. 1).

Bone marrow immunophenotyping revealed a persistent clonal immature B-cell population with increased myelomonocytic marker expression (CD13: 57%, CD33: 58%, MPO: 2%) compared to initial diagnosis. Homozygous loss of *CDKN2A* sequences in 74.3% was detected by FISH as observed in his original clone, as well as gain of 8q21.3 (*RUNX1T1*) sequences, consistent with relapsed pre-B ALL with aberrant myeloid marker expression. Shortly thereafter, he developed respiratory failure, severe electrolyte derangements, and his mental status declined. Due to his poor prognosis and concerns regarding poor tolerability of additional therapy, his family elected to forego further treatment. He was discharged on hospice care and ultimately succumbed to his disease.

Somatic *ASXL3* mutations have been reported in a subset of solid tumors but unlike *ASXL1* mutations, they are infrequently seen in hematologic malignancies[11, 12], potentially due to a more restricted pattern of *ASXL3* expression compared to*ASXL1* and *ASXL2* in hematopoietic cells[12-14]. To our knowledge, this case of pre-B ALL in a patient with a known germline *ASXL3* mutation represents the first report of malignancy in a patient with BRPS. His initial oncologic presentation followed a typical clinical course for a pediatric patient with new-onset ALL, however his disease proved to be highly aggressive and poorly responsive to standard therapy. He endured several complications during therapy, including neurotoxicity which he may have been predisposed to in the setting of by his underlying genetic disorder. While an isolated case cannot

determine cancer risk for an entire group of patients, the potential for malignancy should be considered in patients with this rare genetic diagnosis.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Legends:

TABLE 1: Immunophenotype of peripheral blast population at diagnosis

FIGURE 1: Peripheral smear demonstrating thrombocytopenia, leukocytosis with left shift, and scattered lymphoblasts with high N:C ratio and irregular nuclear contours.

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`BRPS_table1.docx` available at https://authorea.com/users/483402/articles/569540-precursor-b-cell-acute-lymphoblastic-leukemia-in-a-pediatric-patient-with-bainbridge-ropers-syndrome