Transformation of an abnormal karyotype to acute erythroid leukemia in a pediatric patient with Fanconi anemia: a case report

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Fanconi anemia (FA) is a rare, inherited bone marrow failure and cancer predisposition syndrome. It is commonly associated with monosomy 7 in hematopoietic cells, which increases the risk for myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Acute erythroid leukemia (AEL), a high-risk leukemia, is recognized as a distinct subtype of AML by the 2022 World Health Organization (WHO) classification system. Though pediatric patients with FA are 15,000 times more likely to experience AML than the general population, the incidence of AEL in FA has not been reported. We report a case of transformation of partial loss of chromosome 7 to AEL in a pediatric patient with FA.

Our patient is a 13-year-old female with autism spectrum disorder who was diagnosed with FA with heterozygous mutations of the \textit{FANCA} and \textit{FANCD1} genes nine years prior in the setting of persistent thrombocytopenia. Given the increased risk of bone marrow failure in FA, she was offered an allogenic stem cell transplant at the time of diagnosis, but caregivers declined. The patient was prescribed eltromopag for refractory thrombocytopenia and danazol to help prevent progression of bone marrow failure. She had annual bone marrow biopsies until 2019, when the COVID-19 pandemic led to challenges with follow-up. In 2022, a repeat surveillance bone marrow biopsy demonstrated a new finding of deletion of the long arm of chromosome 7. Given the association of monosomy 7 and bone marrow failure, stem cell transplant was offered again, but caregivers declined. She continued with routine clinic visits and monthly complete blood counts (CBC).

In May 2023, she began experiencing weakness, dizziness, and abdominal pain. She was found to be anemic (hemoglobin 8.4 g/dL) and thrombocytopenic (platelets $26 \times 10^9$/L) with hyperbilirubinemia (total bilirubin 2.6 mg/dL, direct 1.3 mg/dL) and splenomegaly. A peripheral blood smear showed anemia, thrombocytopenia, and abundant red blood cell precursors. A bone marrow biopsy showed greater than 80% of nucleated bone marrow elements consisting of erythroid precursors, >30% of which were proerythroblasts, confirming the diagnosis of AEL [figure 1]. By immunohistochemical analysis, the immature erythroid precursors expressed CD71, CD33, CD34, and CD117, and were negative for other analyzed markers including CD3 and CD19. No \textit{TP53} abnormality was identified by molecular or cytogenetic testing. Variants of known/likely clinical significance in \textit{KRAS} and \textit{PTPN11} were identified on molecular testing. Cytogenetic analysis, again, demonstrated loss of 7q. Over the course of several days, she developed worsening pancytopenia and hyperbilirubinemia, as well as persistent fevers. Her caregivers proceeded with supportive care and enrolled her in hospice. She passed away three weeks later.

Fanconi cells have been noted to be hypersensitive to DNA replication stress, which induces monosomy 7 and bone marrow failure. There is significant documentation in the literature describing the association between complete or partial loss of chromosome 7 and the development of MDS and/or AML, some of which also have FA. Notably, patients who develop AML in the setting of FA have demonstrated a significantly higher incidence of monosomy 7 than those who developed AML spontaneously.
The definition of AEL has undergone many variations over the years, making it challenging for clinicians and hematopathologists to diagnose. Two new classification systems for hematopoietic tumors have recently been published. The 5th edition of the WHO Classification of Hematolymphoid Tumors, changes the term pure erythroid leukemia (PEL) to AEL, and is defined by proliferation of erythroid precursors, typically representing > 80% of bone marrow elements with at least 30% proerythroblasts\textsuperscript{6,11}. The 2022 International Consensus Classification (ICC) no longer considers AEL a separate entity; instead, it is classified it under a broader category of AML with mutated $TP53$\textsuperscript{11}.

While there are no molecular findings specific to AEL, commonly seen characteristics include overexpression of $TP53$ protein and biallelic $TP53$ mutations\textsuperscript{11,12}. Other less common mutations with potential associations with AEL include activating mutations in $PTPN11$. Mutations in $PTPN11$ have also been reported in childhood AML, bone marrow clonal evolution in Fanconi anemia, and juvenile myelomonocytic leukemia\textsuperscript{1,13,14}. Additionally, $KRAS$, which is common in childhood AML, has been reported in AEL, and in clonal evolution of FA\textsuperscript{13}.

In pediatrics, AEL is exceedingly rare. A 2020 report from the Children’s Oncology Group (COG) analyzed the clinical, morphologic, immunophenotypic, cytogenetic, and molecular findings from 24 pediatric cases of AEL, which made up 1.2% of all cases reviewed\textsuperscript{15}. None of these patients were reported to have FA\textsuperscript{15}. According to the 2022 WHO classification, only five patients within this report fit the current definition of AEL, with a median age of 2.3 years and a poor overall survival\textsuperscript{15}. Analysis of flow cytometry and immunohistochemistry of these patients most commonly revealed expression of CD36, CD71, CD61, and glycophorin A without expression of CD7, CD34, or myeloperoxidase (MPO)\textsuperscript{15}. Four of the five patients had abnormal karyotypes, but none had monosomy 7\textsuperscript{15}.

Our patient’s case demonstrates the potential of patients with FA, with clonal evolution of large scale chromosome 7 deletion, to transform to AEL, rather than non-erythroid AML. It also demonstrates the challenge associated with diagnosing AEL given various changes in definition over the past several years and lack of molecular findings specific to AEL.

Figures
FIGURE 1 The bone marrow aspirate demonstrates marked erythroid hyperplasia (93% erythroid precursors with numerous pronormoblasts, 33% by manual count).

References


