Essential thrombocythemia during treatment of acute myeloid leukemia with JAK2 V617F mutation
A case report of a CARE-compliant article

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Abstract
Rationale: The JAK2 V617F mutation is frequently found in ET, while it is rare in de novo AML. ET has a low frequency of leukemic transformation. Both secondary AML (sAML) from ET and AML with JAK2 V617F mutation have poor prognoses. Because of the low incidence of JAK2 mutation in acute myeloid leukemia (AML), the clinical features of AML with JAK2 mutation are rarely reported so far, either transformed from essential thrombocythemia (ET) or de novo AML.

Patient concerns: In this article, we present a pediatric AML patient with the JAK2 V617F mutation.

Diagnoses: A diagnosis of acute megakaryoblastic leukemia was made and sAML was ruled out.

Interventions: The patient underwent chemotherapy.

Outcomes: In the first two complete remission periods, we found significantly increased numbers of platelets and bone marrow megakaryocytes, which are characteristic of ET. After the third chemotherapy phase, the disease relapsed; the platelet count was reduced and continued to decrease. When disease relapsed, her family abandoned treatment.

Lessons: These observations of our case raise two possibilities: either transient posttreatment thrombocytemia is a feature of AML with JAK2 V617F mutation, or this was a case of secondary AML. Additional information is required to reach better conclusions on the connection between AML and JAK2 mutations.

Abbreviations: AML = acute myeloid leukemia, ET = essential thrombocythemia, MPNs = myeloproliferative neoplasms, sAML = secondary AML.

Keywords: acute myeloid leukemia, JAK2 mutation, thrombocytemia

1. Introduction
Acute myeloid leukemia (AML) is a heterogeneous disease associated with many distinct genetic alterations. These alterations affect the function of proteins involved in a variety of pathways, including signaling, transcriptional regulation, chromatin modification, and nucleocytoplasmic shuttling. Several useful molecular markers have been identified for the diagnosis, risk classification, treatment, and follow-up of AML. Among these, the JAK-STAT signaling pathway plays important roles in cell proliferation, differentiation, and apoptosis; several activating mutations in JAK proteins have recently been described as the underlying causes of blood disorders. One of these mutations is JAK2 V617F, which is the most prevalent mutation observed in myeloproliferative neoplasms (MPNs), accounting for >95% of polycythemia vera cases and about 50% to 60% of cases of essential thrombocythemia (ET) and primary myelofibrosis. Meanwhile, the JAK2 V617F mutation is one of the notable landmarks in ET progression in both adults and children. In addition, it is well known that ET can progress to AML. In adults, ET develops into AML at a low rate of 1% to 4% during a median follow-up of 7 to 10 years. Conversely, the prevalence of JAK2 mutations in AML transformed from MPN is about 50%, Pediatric ET also has a low risk of disease transformation.

However, the JAK2 V617F mutation is rare in AML. The incidence of this mutation in de novo adult AML has been reported to be 1% to 2.7% or <5%, while the childhood rate has not been reported. Here, we present a 1-year-old patient with pediatric AML bearing the JAK2 V617F mutation, which manifested as ET during remission periods with thrombocytemia and megakaryocytic hyperplasia.

2. Case presentation
A 1-year-old female patient presented with irregular fever, weakness, and purpura emergence in our medical institution on
her platelet counts were increased to $580 \times 10^9$/L and $500 \times 10^9$/L, respectively, and remained elevated until the next chemotherapy injection. Her bone marrow showed increased megakaryocyte numbers; these megakaryocytes had enlarged cell bodies (Fig. 1) and produced large platelets (Fig. 2). Because these phenotypes were coupled with the JAK2 V617F mutation, we considered diagnosing ET. The platelet count and bone marrow smear after the 3 rounds of chemotherapy are summarized in Table 1. We then considered secondary AML, and given the high level of MRD (>0.1%), we recommended allogeneic hematopoietic stem cell transplantation. However, this was not adopted by the family. The patient underwent a third period of chemotherapy consisting of mitoxantrone and HiDAC. However, after the third round of chemotherapy, the platelet count did not rise to our desired value. Disease relapse was then confirmed by a bone marrow smear. She gave up treatment and died 1 month later.

The study was approved by the Ethics Committee of Women and Children’s Hospital of Qingdao. The patient’s parents have provided informed consent for publication of the case.

### 3. Discussion

The JAK2 V617F mutation is located in the pseudokinase domain of the protein, which is involved in several cellular signaling pathways related to cell proliferation, differentiation, and stem cell self-renewal. These pathways include the STAT pathway, the mitogen-activated protein kinase pathway, and the phosphoinositide 3-kinase/Akt pathway. This mutation also confers on hematopoietic stem cells a hypersensitivity to cytokines such as thrombopoietin, erythropoietin, and granulocyte colony-stimulating factors, leading to expansion of blood cell lineages, which are found in ET, polycythemia vera, and primary myelofibrosis. It remains unclear how a single mutation can give rise to such a wide range of phenotypes. Recent reports suggest that the expansion of a heterozygous JAK2 V617F clone,[18] low levels of JAK2 V617F protein expression,[19,20] and STAT1/STAT3 activation, but not the activation of STAT5, probably lead to the ET development.[21–24]

Around 50% to 60% of adult ET patients present JAK2 mutations, while similar or lower frequencies have been observed in childhood, ranging from 0% to 50%.[25] The incidence of ET in children <14 years old is approximately 1/107 per year.[25] The age at diagnosis ranges from 0.8 to 19 years. So far, there are no evidence-based guidelines for the diagnosis of childhood ET. Tefferi and Vardiman[26] and Barbui[27] have suggested that the 2008 World Health Organization (WHO) diagnostic criteria for adults are also applicable to pediatric ET patients;[26] these criteria include a sustained platelet count, increased megakaryocyte numbers, the exclusion of other myeloid neoplasms, and the presence of the JAK2 V617F mutation or another clonal marker. ET has a low risk of progressing to AML, estimated at approximately 1% to 4% in several studies.[8,28–30] The pathogenesis of leukemic transformation is still unclear. Risk factors may include older age and unfavorable cytogenetics.
However, JAK2 V617F mutation is not one of these risk factors. While the AML leukemic blasts in essential thrombocythemia may develop from JAK2 V617F mutated clones, studies\(^1,^2\) have demonstrated that leukemic blasts in JAK2 V617F positive ET are always JAK2 V617F negative, and leukemic transformation frequently occurs in clones before JAK2 V617F mutation or from independent stem cell clones. Additional mutations can occur before, after, or independently from the JAK2 V617F mutation. Such mutated genes include TET2, DNMT3A, ASXL1, EZH2, and IDHI. These mutations may affect cell survival and genomic instability, in conjunction with the JAK2 V617F mutation or other mutations known to be associated with the pathogenesis of AML.\(^3\) In addition, AML transformation in ET frequently exhibits unfavorable cytogenetics, including complex karyotypes, monosomy, deletions of chromosomes 5 or 7, or trisomy 8.\(^4,^5\) After leukemic transformation, patients have poor prognoses with adverse outcomes within a few months.

The incidence of a JAK2 gene mutation in de novo AML was first reported by Lee et al\(^6\) in 2006. In this study, the authors discovered that 2.7% of de novo AML cases harbored JAK2 mutations,\(^1^,^6\) and these mutations were more commonly found in t(8;21) AML. Jelinek et al\(^7\) reported that de novo AML more commonly contains the JAK2 V617F in cases of erythroid or megakaryoblastic AML. The patient we have reported on had a case of acute megakaryoblastic leukemia. There have been few reports of JAK2 mutations in pediatric AML. One study showed that JAK2 mutations may occur in 8.4% (7/83) of pediatric non-Dow syndrome acute megakaryoblastic leukemia cases.\(^8\) Hidalgo-López et al\(^9\) described the clinical, morphological, and genetic findings of patients with AML associated with the JAK2 V617F mutation. They found that all patients showed multilineage dysplasia, monosomy or deletions of chromosomes 5 or 7 were present in 45% of patients, and approximately one-third of the patients had complex karyotypes. The median overall survival was 14 months from disease onset. Finally, another study showed that high levels of JAK2 autophosphorylation lead to low sensitivity to chemotherapy and poor outcomes.\(^10\)

Wang et al\(^11\) described an adult AML patient with transient post-treatment megakaryocytic hyperplasia who also had the JAK2 V617F mutation, similar to our 1-year-old patient. We considered the possibility that she had secondary AML (sAML) transformed from a preexisting undiagnosed MPN. We originally considered the possibility that she had secondary AML (sAML) from de novo AML, and to develop optimal treatment strategies.

The incidence of essential thrombocythemia in children is extremely low, and most children with ET are asymptomatic. These factors make it difficult to diagnose sAML in children. While the JAK2 V617F mutation occurs with very low frequency in AML, patients with AML and this mutation have poor outcomes. Therefore, we need more cases to analyze the clinical features of AML with the JAK2 V617F mutation, to distinguish sAML from de novo AML, and to develop optimal treatment strategies.

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**Author contributions**

Wenwen Ding: Conceptualization, Data curation, Investigation, Writing- original draft, Writing- review and editing; Danni Li: Investigation, Writing- review and editing; Chao Zhuang: Investigation, Writing- review and editing; Wenfeng Mou: Investigation; Hui Liang: Supervision; Yong Liu: Software, Supervision, Resources, Writing- review and editing, Visualization

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