Polycythemia vera in a 2-year-old child with a JAK2 exon 12 deletion

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Abstract

Polycythemia vera (PV) is a myeloproliferative neoplasm primarily characterized by erythrocytosis. PV incidence is exceedingly rare in the pediatric and adolescent population. In adult patients, approximately 96% are found to have a somatic mutation in exon 14 (JAK2 V617F) and 3% display a mutation in exon 12. We present a case of a 2-year-old female with symptomatic PV secondary to a deletion in exon 12 of JAK2, initially treated with phlebotomy and switched to PEG-IFNα-2a therapy. This therapy has been effective over 15 months with resolution of symptoms, reduced phlebotomy requirements, and minimal side effects.

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Abbreviations

PV	Polycythemia vera
MPN	Myeloproliferative neoplasm
WHO	World Health Organization
JAK2	Janus kinase 2
PEG-IFNα-2a	peginterferon alfa-2a
EPOR	erythropoietin receptor
SH2B3	SH2B adapter protein 3
BCS	Budd Chiari syndrome
AML	Acute myeloid leukemia
HSCT	Hematopoietic stem cell transplantation

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"Polycythemia vera diagnosis in a 2 year old child with a *JAK2*exon 12 deletional mutation"

Abstract:

Polycythemia vera (PV) is a myeloproliferative neoplasm primarily characterized by erythrocytosis. PV incidence is exceedingly rare in the pediatric and adolescent population. In adult patients, approximately 96% are found to have a somatic mutation in exon 14 ($JAK2^{V617F}$) and 3% display a mutation in exon 12. We present a case of a 2-year-old female with symptomatic PV secondary to a deletion in exon 12 of *JAK2* , initially treated with phlebotomy and switched to PEG-IFNα-2a therapy. This therapy has been effective over 15 months with resolution of symptoms, reduced phlebotomy requirements, and minimal side effects.

Introduction:

Polycythemia vera (PV) is a chronic myeloproliferative neoplasm (MPN) primarily characterized by an overproduction of erythrocytes. As defined by the 2016 World Health Organization (WHO) classification system, PV, essential thrombocythemia, and primary myelofibrosis comprise a subgroup of *BCR -ABL1* negative MPNs, notable for a high prevalence of a somatic mutation within a highly conserved residue of the pseudokinase domain of the Janus Kinase ($JAK2^{V617F}$).[1,2,3] Adult data demonstrates approximately 96% of PV patients have this hallmark somatic mutation in exon 14, while 3% are negative for *JAK2* ^{V617F}and display a deletional mutation in exon 12.[4,5]

PV incidence is approximately 10-20/1,000,000 people with less than 0.1% presenting before 20 years of age, making this disorder exceedingly rare in the pediatric and adolescent population.[6] With a median age of presentation of 60 years, published pediatric data on clinical characteristics and optimal treatment regimens are sparse and anecdotal. There is an increased risk for thromboembolic and hemorrhagic complications in both adult and childhood PV cases, however children may not have the same risk for development of post-polycythemic myelofibrosis or transformation into myelodysplastic syndrome/acute myeloid leukemia as has been shown in adults.[7] The possible complications associated with this disease demonstrate the need for further standardization of treatment.[8, 9,10] We present our diagnostic approach and management of a very young patient found to have the exceedingly rare *JAK2* exon 12 deletion.

Case Report:

A 2-year-old female, born at 35 weeks gestation, with a past medical history of asthma and a neonatal central line-associated portal vein thrombosis presented to hematology outpatient clinic with microcytosis (Figure 1A) and elevated red blood cell counts and hematocrit on repeat evaluations. She only endorsed intermittent bilateral leg pain. Lab results noted Hbg 13.7 gm/dL, Hct 49.9%, RBC 8.92 x 10^6/mcL, platelet 365 x 10^3/mcL, WBC 8.77 x10^3/mcL, MCV 55.9 fL, and ferritin 4ng/mL. Her newborn screen was normal, and her hemoglobin electrophoresis detected a low hemoglobin A2 level, attributed to iron deficiency. Molecular testing for *JAK2* ^{V617F} was performed on a peripheral blood sample and was negative. Subsequent molecular testing revealed a 6-nucleotide deletion in exon 12 of *JAK2*(p.E543_D544del), which removed 2 amino acids from the kinase domain of the protein (Figure 2). Variant allele frequency of this variant was estimated to be 45-50% via Sanger sequencing. Erythropoiten level was <1mU/mL, qualifying as subnormal. Based on the WHO revised 2016 diagnostic criteria for PV, the patient underwent a bone marrow biopsy, which confirmed hypercellularity with trilineage hyperplasia and pleomorphic megakaryocytes (Figure 1B and C); the patient, therefore, met 3 major criteria and one minor criteria for diagnosis of PV.

Aspirin therapy was initiated, and phlebotomy was performed as needed with a hematocrit goal of <45%, extrapolated from adult data given lack of pediatric guidelines. Intermittent headaches and leg pain continued several times a week despite treatment. Throughout her care, her ferritin levels remained low despite dietary efforts. Oral iron supplementation was avoided so as not to exacerbate her red blood cell production. Due to familial concern about neurodevelopment in the setting of iron deficiency, peginterferon alfa-2a (PEG-IFNα-2a) subcutaneous therapy was initiated, initially every 2 weeks, and then increased to weekly. To date,

after 15 months of PEG-IFNα-2a therapy, our patient has required only 2 phlebotomy treatments and is no longer symptomatic. With no significant side effects from this therapy approach, she will continue on a weekly regimen of PEG-IFNα-2a; however, she has remained iron deficient and long-term efficacy has yet to be determined.

Discussion:

This has been the youngest reported patient diagnosed with PV secondary to a *JAK2* exon 12 deletion. Cario et al. reported a cohort of 8 pediatric PV cases, noted to have two exon 12 mutation-positive patients, 12 and 16 years of age at diagnosis, both female.[11] Previous reports have conflicting data on the presence of the *JAK2* ^{V617F} mutation in pediatric PV, suggesting it may be less prevalent compared with adults.[10,12,13] Some theorize that children may become*JAK2* ^{V617F} positive at a later stage in the disease process. Primary polycythemia in children may also be familial, secondary to inherited mutations of the erythropoietin receptor gene (*EPOR*) or *SH2B3* (amongst others), in which there is a low probability of also carrying a *JAK2*mutation.[14,15,16]

Compared with *JAK2* ^{V617F}- positive patients, those harboring *JAK2* exon 12 mutations more commonly present with isolated erythrocytosis, lower platelet and leukocyte counts, subnormal erythropoietin level, and younger age at diagnosis. A trilineage pattern of hyperplasia is more common in *JAK2* ^{V617F}- positive patients. These variants share a similar incidence of thrombosis, transformation to myelofibrosis and leukemia, and survival.[17]

While PV can be an indolent disease, there is an increased risk for thrombotic and hemorrhagic complications. Cario et al. reviewed 36 pediatric and adolescent PV cases and noted that 25% developed severe thrombosis and 8.3% developed bleeding events.[10]While rare, Budd Chiari syndrome (BCS), an obstruction of the hepatic venous outflow tract, can be a typical presentation and complication of PV, and occurred in 19.4% of patients examined.[10,11]Several adult studies have also shown a higher prevalence of BCS in the young adult population, suggesting a predisposition of BCS in PV occurring in younger age groups.[10,18,19]

Treatment of PV is aimed at prevention of thrombohemorrhagic events, as well as symptom management. While it is well established that age >60 and history of thrombosis place patients at increased risk of thrombotic complications, it is unknown if this holds true for pediatric patients.[20] Leukocytosis >15 x10^9/L appears to be associated with thrombotic and hemorrhagic complications in pediatric PV cases.[10]Recent studies suggest that in addition to PV transforming into secondary myelofibrosis or acute myeloid leukemia(AML), there is also significantly increased risk for development of solid tumors.[9,21]

Historically, treatment approaches included phlebotomy, low-dose aspirin, and cytoreductive therapy, namely hydroxyurea.[11] Hematopoietic stem cell transplantation (HSCT) remains the only curative treatment for PV. However, as more prospective data is gathered, several novel therapeutic agents are emerging that may reduce the need for HSCT in the pediatric population.[22]

Interferon-alpha has been used in the treatment of PV for over 30 years.[23] While patients demonstrated both a hematological and molecular response, compliance was compromised by its cost and high prevalence of flu-like symptoms, fatigue, and neuropsychiatric side effects. The development of a pegylated form proved to be more tolerable, with less immunogenicity, longer half-life, and improved stability.[24] Adult data suggest a hematological response in 89% of patients within 3 months of therapy and reduction in *JAK2* allele burden with complete molecular response (undetectable *JAK2* ^{V617F} levels) in 24% of patients between 12-30 months.[25] Several cases have been reported of pediatric patients with PV who have shown response to interferon treatment without any significant dose-limiting toxicities.[22,26,27] Combination therapy of PEG-IFNα-2a and ruxolitinib, a *JAK2* inhibitor, are currently under investigation with some promising results.[28]

Our 15-month follow up has demonstrated resolution of symptoms, reduced phlebotomy requirements, and minimal side effects in PV treated with PEG-IFNα-2a therapy. Given the rarity of this disease in the pediatric population, this case adds to the growing knowledge behind alternatives to the currently more invasive and possibly leukemogenic treatment options.

Conflict of Interest Statement: All authors have no conflicts of interest related to the information in this manuscript

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Legends

Figure 1. A. Peripheral blood smear revealed microcytic hypochromic erythrocytes with mild to moderate anisopoikilocytosis. Wright's stain. B and C. Bone marrow biopsy section demonstrated hypercellular marrow with trilineage hyperplasia and polylobated megakaryocytes (arrow indicating an erythroblastic island). Hematoxylin and Eosin stain.

Figure 2. Sanger electropherogram showing the deletion in *JAK2*exon 12, NM_004972.3:c.1627_1632del, in the patient (above) compared to control (below).