

A Rare Cause of Erythrocytosis: *VHL* Gene Mutation

Eritrositozun Nadir Bir Nedeni: *VHL* Gen Mutasyonu

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To the Editor,

Congenital secondary erythrocytosis linked to von Hippel-Lindau (*VHL*) disease is most frequently strongly associated with c.598C>T (p.Arg200Trp) and this constitutes the molecular basis for Chuvash polycythemia. Chuvash polycythemia, the first hereditary hypoxia-sensing disorder to be recognized, develops as a result of hereditary mutations occurring on the *VHL* gene and is a rarely reported cause of hereditary erythrocytosis [1]. The mutation partially disrupts the regulatory function of the *VHL* protein in hypoxia-inducible factor (HIF)- α degradation, causing HIF stabilization and increased erythropoietin production, which results in erythrocytosis. This mutation differs from the classic tumoral *VHL* phenotype and progresses with erythrocytosis without clear neoplastic tendencies [2,3].

In this letter, we present two unrelated patients with *VHL* gene mutations causing erythrocytosis and draw attention to the clinical features of and diagnostic approach to this disease.

Case 1: A 40-year old male patient presented to the clinic with erythrocytosis and had clear plethora on physical examination, with erythema of the hands and widespread body itching after showering. There was no hepatomegaly or splenomegaly. Oxygen saturation was normal according to pulse oximetry. Smoking history was 10 packs/year. There was no chronic disease. There was no similar disease history in the family. Neither the patient nor his first-degree relatives had a history of early-onset thromboembolic events. The laboratory findings of the patient are summarized in Table 1. *JAK2* V617F, *JAK2* exon 12, calreticulin (*CALR*), and myeloproliferative leukemia (*MPL*) genetic mutations were negative. To exclude other causes of secondary erythrocytosis, next-generation sequencing (NGS) was performed, which identified the c.598C>T (p.Arg200Trp-R200W) mutation on the *VHL* gene. A diagnosis of Chuvash polycythemia was made. The patient was given low-dose acetylsalicylic acid. Phlebotomy was administered for symptoms.

Case 2: A 31-year old male patient with polycythemia since 10 years of age had complaints of headache and tinnitus. Physical

examination found no organomegaly. He did not smoke. He had a congenital single kidney. The patient had two sisters with high hemoglobin levels. One of the sisters had a hemoglobin level of 17.9 g/dL, whereas the other had a hemoglobin level of 18.1 g/dL. One sister had kidney failure. The laboratory findings of the patient are summarized in Table 1. *JAK2* V617F, *JAK2* exon 12, *CALR*, and *MPL* mutations were negative. NGS analysis for *VHL* identified *VHL* c.429C>T (p.Asp143=). The patient was monitored with phlebotomy for symptoms.

These two cases underline the importance of considering *VHL*-related erythrocytosis in patients with early-onset erythrocytosis, elevated erythropoietin levels, and negative myeloproliferative mutation analysis. The c.598C>T (R200W) *VHL* mutation identified in the first case is a genetic disorder strongly associated with Chuvash polycythemia in the literature. Early diagnosis of this mutation is critical for appropriate monitoring and management of patients [2]. Among the rarer *VHL* gene variants, such as that identified in our second case, c.429C>T (p.Asp143) heterozygote or homozygote forms have been associated with Chuvash polycythemia in erythrocytosis cases with unsuppressed erythropoietin levels [4,5]. In the literature, c.499C>T (p.Arg167Trp) and c.194C>G (p.Ser65Trp) *VHL* mutations are rarely reported [5]. The clinical and molecular phenotype caused by the R200W (c.598C>T) mutation is strongly associated with well-defined classic Chuvash polycythemia and strong HIF activation [4]. Patients with Chuvash polycythemia have been reported to exhibit an increased risk of thrombotic events, including both peripheral and central vascular complications such as stroke and myocardial infarction. The follow-up of these patients should be conducted in a multidisciplinary manner [6]. Treatment for erythrocytosis linked to *VHL* essentially takes a symptomatic approach, with periodic phlebotomy and antithrombotic precautions according to thrombosis risk administered for hematocrit elevation or hyperviscosity findings. Additionally, new agents like HIF-2 α inhibitors are being researched [4]. There are no clearly established data regarding the optimal frequency of phlebotomy or specific target hemoglobin/hematocrit levels for this disease [7].

Table 1. Laboratory findings of the two patients.

Parameter	Case 1	Case 2	Reference range
Hemoglobin (g/dL)	17.9	18.2	11.9-14.6
Hematocrit (%)	58	62.4	36.6-44
White blood cells (x10 ⁹ /L)	6.2	6.99	4-10
Platelets (x10 ⁹ /L)	171	215	150-400
Ferritin (ng/mL)	5.76	5.9	30-400
Erythropoietin (mU/mL)	390	339	3.5-31.5

In conclusion, for erythrocytosis cases beginning at a young age and involving progression, family history, and unsuppressed erythropoietin levels, Chuvash polycythemia should not be forgotten in the differential diagnosis, especially by hematology experts. Erroneous diagnosis of polycythemia vera in such situations may lead to unnecessary treatments.

Keywords: Erythrocytosis, *VHL* gene mutation, Chuvash polycythemia

Anahtar Sözcükler: Eritrositoz, *VHL* gen mutasyonu, Çuvaş polisitemisi

Ethics

Informed Consent: Written informed consent was obtained from the patients for publication of this letter.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.Ş.; Concept: O.Ş., M.H.A.; Design: M.H.A.; Data Collection or Processing: Ö.F.Y.; Analysis or Interpretation: Ö.F.Y.; Literature Search: Ö.F.Y.; Writing: Ö.F.Y.

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References

1. Gordeuk VR, Stockton DW, Prchal JT. Congenital polycythemia/erythrocytoses. *Haematologica*. 2005;90:109-116.
2. Ang SO, Chen H, Hirota K, Gordeuk VR, Jelinek J, Guan Y, Liu E, Sergueeva AI, Miasnikova GY, Mole D, Maxwell PH, Stockton DW, Semenza GL, Prchal JT. Disruption of oxygen homeostasis underlies congenital Chuvash polycythemia. *Nat Genet*. 2002;32:614-621.
3. Polyakova LA. Familial erythrocytosis among inhabitants of the Chuvash ASSR. *Probl Gematol Pereliv Krovi*. 1974;10:30-36.
4. Lenglet M, Robriquet F, Schwarz K, Camps C, Couturier A, Hoogewijs D, Buffet A, Knight SJL, Gad S, Couv S, Chesnel F, Pacault M, Lindenbaum P, Job S, Dumont S, Besnard T, Cornec M, Dreau H, Pentony M, Kvikstad E, Deveaux S, Burnichon N, Ferlicot S, Vilaine M, Mazzella JM, Airaud F, Garrec C, Heidet L, Irtan S, Mantadakis E, Bouchireb K, Debatin KM, Redon R, Bezieau S, Bressac-de Paillerets B, Teh BT, Girodon F, Randi ML, Putti MC, Bours V, Van Wijk R, Göthert JR, Kattamis A, Janin N, Bento C, Taylor JC, Arlot-Bonnemains Y, Richard S, Gimenez-Roqueplo AP, Cario H, Gardie B. Identification of a new *VHL* exon and complex splicing alterations in familial erythrocytosis or von Hippel-Lindau disease. *Blood*. 2018;132:469-483.
5. ClinVar. *VHL* NM_000551.4:c.429C>T Variant Associated with Chuvash Polycythemia. Bethesda, National Center for Biotechnology Information, 2023.
6. Amaral PS, Mohan SR, Beckermann KE. von Hippel-Lindau syndrome-related congenital polycythemia and response to belzutifan. *Haematologica*. 2024;109:4145-4147.
7. Sergueeva A, Miasnikova G, Shah BN, Song J, Lisina E, Okhotin DJ, Nourai M, Nekhai S, Ammosova T, Niu XM, Prchal JT, Zhang X, Gordeuk VR. Prospective study of thrombosis and thrombospondin1 expression in Chuvash polycythemia. *Haematologica*. 2017;102:e166e169.



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