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CLINICAL CASE

Familial erythrocytosis 2 and von Hippel-Lindau disease in the same pediatric patient

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Abstract

Background: *Patients with familial erythrocytosis type 2 have no increased risk of von Hippel-Lindau-associated tumors, although mutations in the VHL gene cause both pathologies.* **Case report:** *We present a case of a compound heterozygote patient with von Hippel-Lindau disease and familial erythrocytosis type 2. One of the mutations found in our patient, c.416C>G (p.Ser139Cys) of the VHL gene, has not been previously reported. This case is the second one reported where von Hippel-Lindau disease and familial erythrocytosis type 2 coexist in the same individual.* **Conclusions:** *Despite the low frequency of familial erythrocytosis type 2 in patients with von Hippel-Lindau disease, the possibility of this diagnosis should be considered to avoid unnecessary invasive studies to explain the polyglobulia in these patients and guarantee an adequate follow-up and vigilance of both diseases.*

Keywords: *von Hippel-Lindau Disease. Chuvash polycythemia. VHL gene. Hereditary cancer syndrome. Familial erythrocytosis type 2. Polyglobulia.*

Eritrocitosis familiar 2 y enfermedad de von Hippel-Lindau en el mismo paciente

Resumen

Introducción: *Los pacientes con eritrocitosis familiar tipo 2 no muestran un riesgo incrementado de desarrollar tumores asociados con la enfermedad de von Hippel-Lindau, a pesar de que ambas afecciones están causadas por variantes patogénicas en el gen VHL.* **Caso clínico:** *Se presenta el caso de un paciente heterocigoto compuesto con enfermedad de von Hippel-Lindau y eritrocitosis familiar tipo 2. Una de las variantes patogénicas en el paciente, VHL c.416C>G (p.Ser139Cys), no ha sido previamente reportada. Este es el segundo reporte de caso en que la enfermedad de von Hippel-Lindau y la eritrocitosis familiar tipo 2 coexisten en el mismo individuo.* **Conclusiones:** *A pesar de la baja frecuencia de la eritrocitosis familiar tipo 2 en pacientes con enfermedad de von Hippel-Lindau, la posibilidad del diagnóstico debe considerarse con el fin de evitar estudios invasivos innecesarios para explicar la presencia de poliglobulia en estos pacientes y para garantizar un adecuado seguimiento y una correcta vigilancia de ambas enfermedades.*

Palabras clave: *Enfermedad de von Hippel-Lindau. Policitemia de Chuvash. Gen VHL. Síndrome de cáncer hereditario. Eritrocitosis familiar tipo 2. Poliglobulia.*

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Introduction

Familial erythrocytosis type 2 or Chuvash polycythemia (MIM #263400), an autosomal recessive condition, presents high hemoglobin levels and normal or high erythropoietin levels characteristics of primary and secondary erythrocytosis. As mutations in *VHL* gene are the cause of this disease, homozygosity or compound heterozygosity variants could be found in affected individuals[1-4].

Von Hippel-Lindau disease (VHL), an autosomal dominant inherited cancer syndrome, is characterized by hemangioblastoma, pheochromocytoma, clear cell renal carcinoma, pancreatic neuroendocrine tumors, and other tumors such as epididymal cysts in heterozygous patients, who carry only one germline mutation in the *VHL* gene[5,6]. Polycythemia is a rare manifestation of VHL (5-20% of cases), in which elevated hemoglobin levels are secondary to tumor-produced erythropoietin[7]. In patients with familial erythrocytosis type 2, no increased risk for the formation of VHL-associated tumors has been reported[6,8-10].

We report a pediatric patient with both familial erythrocytosis type 2 and von Hippel-Lindau disease.

Clinical case

We describe a 9-year-and-5-month old male patient incidentally diagnosed with polyglobulia when performing routine laboratory studies after an accident at 8 years of age (hemoglobin, 21.4 mg/dl; hematocrit, 67%; mean corpuscular hemoglobin, 23.2; platelets, 229,000; leukocytes, 5,990; neutrophils, 3260; lymphocytes, 1,790; reticulocytes, 1.2%). The mother reported that the patient presented fatigue and peripheral cyanosis during exercise.

Several studies were conducted, including venous blood gas, lung VQ scan, echocardiogram, cardiac catheterization, bone marrow aspirate, bone biopsy, respiratory function analysis, and ocular fundus study, all of which were reported as normal.

The physical examination showed a tumor in the right testicle. A cyst in the right epididymis was identified by testicular ultrasound.

Due to von Hippel-Lindau disease's family history (Figure 1), a molecular genetic test was performed on his mother, in whom a deletion of exon 3 of the *VHL* gene (heterozygote) was identified. The mother of the patient died due to complications of a hemangioblastoma in the central nervous system.

The patient's DNA was obtained from a peripheral blood sample, identifying the deletion of exon 3 of the *VHL* gene by multiplex ligation-dependent probe amplification (Figure 2A).

Due to the antecedent of polyglobulia, where affected individuals could be homozygous or compound heterozygotes, complete sequencing of the *VHL* gene was performed in the patient's sample. A new missense mutation was found: the change of cytosine by guanine at nucleotide 416 results in the change from a serine to a cysteine (p.Ser139Cys) (Figures 2B, 2C and 2D).

The patient was a compound heterozygote. According to the clinical picture and molecular biology studies, the diagnosis of familial erythrocytosis type 2 and von Hippel-Lindau disease was established.

Discussion

Familial erythrocytosis type 2 or Chuvash polycythemia was first described by Polyakova (1974), who reported 103 cases in 81 families, where all patients showed elevated hemoglobin and hematocrit levels[1]. Additionally to the increase in hemoglobin and hematocrit, Sergeyeva et al. (1997) found elevation of erythropoietin, for which they suggested that the cause of this polycythemia could be related to genes different from those coding for erythropoietin and its receptor[2].

In 2002, Ang et al. reported that patients with familial erythrocytosis type 2 were homozygous for the c.598C>T mutation in the *VHL* gene. This mutation has been reported in Chuvashian, Italian, British, Bengalis, German, Turkish, African American, and Caucasian patients[3,4,11-14].

The pathophysiology of familial erythrocytosis type 2 is due to an alteration in oxygen homeostasis. The *VHL* tumor growth suppressor gene codes the VHL protein (pVHL), which plays a critical role in cell adaptation in response to hypoxia through downregulation of hypoxia-inducible factors (HIF)[7].

The principal transcriptional activator of gene expression in hypoxic cells is HIF-1. The c.598C>T mutation in *VHL* causes a decrease in the affinity of pVHL for HIF-1α, resulting in lower ubiquitination under normal oxygen levels, leading to an increased expression of genes such as *EPO* (erythropoietin) and *VEGF* (vascular endothelial growth factor), explaining the relatively high levels of erythropoietin in these patients[7,15,16].

It was thought that all patients with familial erythrocytosis type 2 should be homozygous for the c.598C>T mutation. However, Pastore et al. reported two Croatian homozygous patients for the c.571C>G mutation[8,17]. Both patients showed significantly higher levels of erythropoietin compared to patients bearing the c.598C>T mutation and no data of a primary polycythemia[8,17].

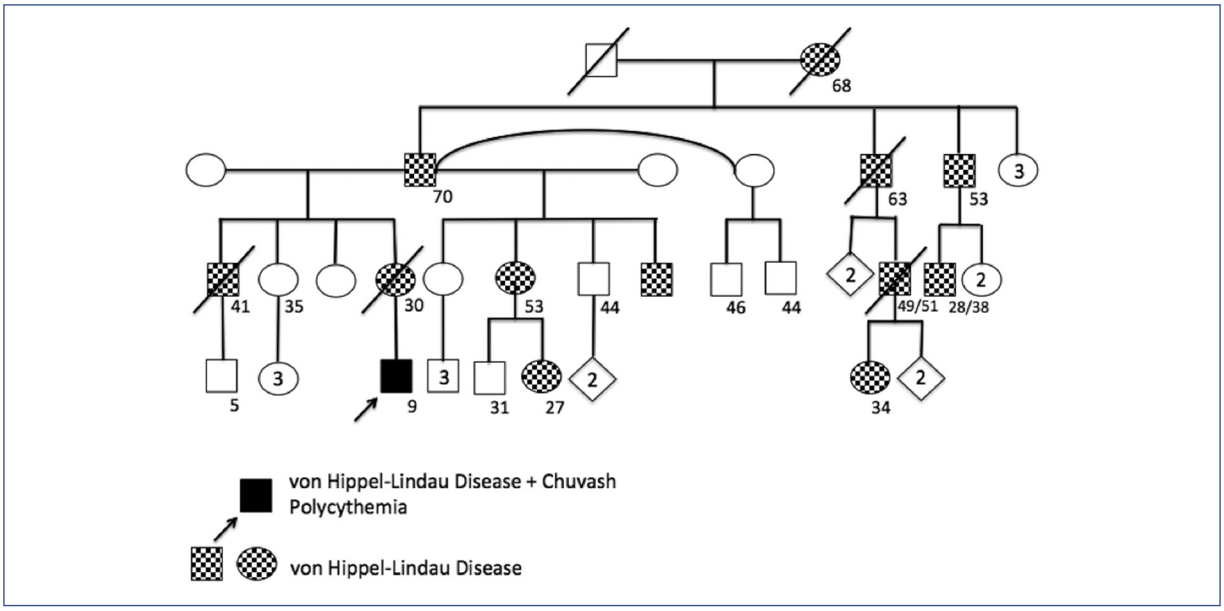

Figure 1. Family pedigree of four generations with von Hippel-Lindau disease.

To the present day, four mutations in the homozygous state that cause familial erythrocytosis type 2 have been described: c.598C>T, c.571C>G, c.413C>T, and c.586A>G[8,9,13,17]. Also, compound heterozygous variants have been reported[9,17,18].

Patients with familial erythrocytosis type 2 do not appear to be at increased risk for tumor formation, and less than 20% of patients with VHL have polycythemia due to erythropoietin tumor production[7]. In 2012, Capodimonti et al. reported a patient with familial erythrocytosis type 2 and von Hippel-Lindau disease. The patient was diagnosed with polyglobulia and pheochromocytoma and was a compound heterozygote with the c.598C>T and c.388G>C mutations. The c.388G>C mutation has been previously reported in patients with von Hippel-Lindau disease[10]. The pheochromocytoma study performed in the patient only reported the c.388G>C mutation, indicating that the allele with the c.598C>T mutation was lost, explaining the tumor development according to the Knudson hypothesis. Familial erythrocytosis type 2 was clinically expressed due to the absence of a wild-type *VHL* allele allowing the expression of the c.598C>T mutation allele responsible for most cases of familial erythrocytosis type 2[6,10].

The present case is a compound heterozygote. One of the mutations found in our patient, deletion of exon 3 in the *VHL* gene, has already been reported in patients with von Hippel-Lindau type 1 disease. In this case, we found a cyst in the patient's right epididymis, which has been associated with VHL disease. The second mutation found in the patient, c.416C>G in exon 2 of the *VHL* gene, has not been previously reported.

The nucleotide substitution changes the conserved amino acid serine to cysteine at the codon 139 (NP_000542.1) in the N-terminal domain (B-domain) of the VHL protein (Figure 2D). To test the potential impact of the amino acid substitution of this variant on the structure and function of the VHL protein, we used the web tools PolyPhen2, Mutationassesor, Provean, and SIFT. The prediction analysis for the novel variant S139C suggests it is deleterious (Condel score 0.59)[19]. This result explains the presence of polycythemia in the patient since individuals with familial erythrocytosis type 2 must be necessarily homozygous or compound heterozygotes. We know that the deletion of exon 3 was inherited from his mother. However, no information was available on the patient's father, nor were his current whereabouts to verify whether he is the carrier of the c.416C>G mutation found in the patient or whether it was a *de novo* mutation.

As part of our patient's follow-up, it is essential to monitor the possible complications associated with familial erythrocytosis type 2 since they are at high risk for peripheral thrombosis. Additionally, increased prevalence of vertebral hemangiomas, varicose veins, cardiovascular alterations, hypotension, and pulmonary hypertension have been reported[16,20-22].

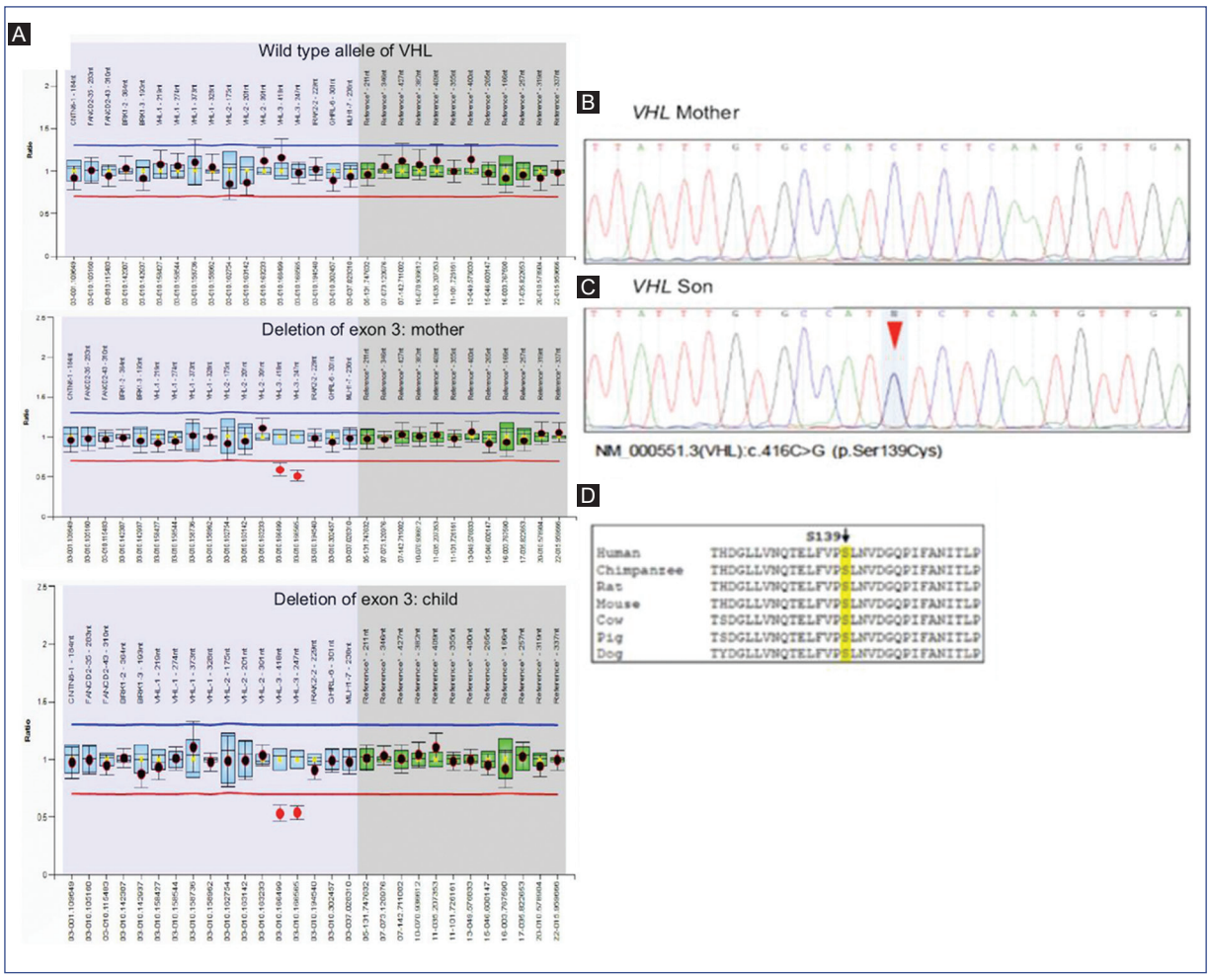

Figure 2. A: multiplex ligation-dependent probe amplification (MLPA) in which the deletion of exon 3 was identified in both mother and patient compared with a wild type allele. **B** and **C:** partial electropherograms of exon 2 of the *VHL* gene in the mother and the child, respectively. The heterozygous change 416 C>G (p.Ser139Cys) is observed (red arrow). **D:** conservation of S139 in VHL in different mammal species. The protein sequences of VHL orthologs at positions 124-154 are aligned. The arrow indicates the position of S139.

According to the patient's age, VHL disease surveillance consists of an annual pediatric assessment (complete physical examination and neurological examination), ophthalmologic assessment, determination of plasma or 24-hour urine sample metanephrines, and abdominal ultrasound. In the case of biochemical alterations, an abdominal magnetic resonance image (MRI) should be obtained every 2-3 years. Also, an audiology assessment is recommended, which should be annual in case of hearing loss, tinnitus, or vertigo. Head and spinal cord MRI should be performed annually[23-25].

This case is the second one reported worldwide where von Hippel-Lindau disease and familial erythrocytosis type 2 coexist in an individual. Despite the low frequency of familial type 2 erythrocytosis in VHL, the possibility of this diagnosis should be considered in a patient with a family or personal history of VHL in whom polyglobulia is present. On the one hand, it is important to avoid unnecessary invasive studies to try to explain the presence of polyglobulia, and on the other hand, it is necessary to ensure adequate follow-up and surveillance of both diseases.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on patient data publication.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflict of interest.

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