In the initial evaluation of erythrocytosis, the differentiation must first be made between relative polycythemia and absolute polycythemia. Rehydration of the patient and a repeat of the complete blood count (CBC) can confirm relative polycythemia. Once it is evident that the patient has absolute erythrocytosis, the task turns to determining if this is primary or secondary polycythemia. A thorough history must be taken evaluating for history of neoplasms, tobacco use, or any carbon monoxide poisoning. A full physical examination should be followed by pulse oximetry reading, laboratory testing including EPO level, and imaging, to rule out secondary causes. One of the most important causes of primary erythrocytosis is Polycythemia rubra vera as this disorder increases the risk of thrombosis. In patients with primary erythrocytosis who are JAK2 V617F and exon 12 negative, congenital erythrocytosis syndromes should be explored.

In patients who present with erythrocytosis, one should first exclude secondary causes. Primary polycythemia is most often Polycythemia rubra vera, a myeloproliferative neoplasm associated with mutations in Jak pathway. However, when a patient is determined to have primary erythrocytosis but does not have a mutation in the Jak pathway, congenital erythrocytosis syndrome should be investigated. For some patients, long-standing erythrocytosis can be documented, like in our case. Once this diagnosis is considered, screening with P50 determination can help differentiate various congenital abnormalities. A normal P50 is seen in such disorders as VHL, PHD2, and HIF2a. We describe a patient who has a gain of function mutation in EPAS1 which encodes HIF2A. This mutation alters oxygen sensing and leads to increased EPO expression. While patients with congenital erythrocytosis may have few or no symptoms it remains important to differentiate these from Primary Polycythemia rubra vera as PRV must be treated by phlebotomy to reduce the risk of thrombosis while CE should not be phlebotomized.

A 46-year-old Caucasian male with a past medical history of osteoarthritis, presented to his primary care physician (PCP) complaining of fatigue. He did not use tobacco, alcohol, or illicit drugs. He had poor sleep hygiene and was previously referred for sleep testing which he did not attend. A CBC revealed an elevated hemoglobin (17.4 g/dL) and hematocrit (53.6%). A year later, the patient presented to his PCP for a 'fullness' sensation in his left flank without hematuria. Labs showed persistent erythrocytosis and he was referred to hematology where he endorsed fatigue and pruritis on his back and lower extremities which worsened with hot baths. A renal ultrasound was unremarkable for any masses or cystic disease. A hemoglobinopathy panel was normal and a JAK2 mutation analysis was negative for JAK2 V617F (Exon 14 in codon 17) as well as exon 12/13. Because of the negative JAK Pathway mutations, the polycythemia was felt to be secondary. The patient was sent for polysomnography which was negative for sleep apnea. The patient followed up annually for four years. Then in 2022, twelve years after his initial hematology appointment, he had additional work up performed. A hereditary erythrocytosis panel revealed a heterozygous EPAS1 (HIF2A) variant detected in exon 9 as the etiology of his prolonged erythrocytosis.

REFERENCES