CLINICAL VIGNETTE

Erythrocytosis

Evangelia Kirimis, MD

A 58-year-old woman presented to a primary care physician to establish care. She had had no medical evaluation in ten years. The patient was asymptomatic but mildly hypertensive on exam, and she was started on amlodipine. Labs collected included noted hemoglobin of 20.2 g/dL, hematocrit of 63.6%, and red blood cell count of 6.37 million/miL. Repeat testing confirmed the results and she was referred for hematology consultation.

At her hematology consult, the patient reported she felt well with negative review of systems and no notable past medical history. Her blood pressure had normalized on the new antihypertensive. She taking no other medications or supplements. Physical exam noted nontender lower abdominal mass extending nearly to the umbilicus. There was no hepatosplenomegaly, erythrocytosis included no Janus kinase-2 gene (JAK2) V617F or exons 12 or 14 mutations. Erythropoietin level was normal at 15.5 mIU/mL and complete metabolic panel was normal. Pelvic ultrasound showed a markedly enlarged uterus of 20.0 centimeters (cm) x 11.3 cm x 15.2 cm with two fibroids and question of adenomyosis. Abdominal ultrasound showed no hepatosplenomegaly, no kidney or liver lesions, but moderate dilatation of the renal pelvises. She was evaluated by gynecology for potential fibroid treatment. Magnetic resonance imaging of the pelvis noted a marked heterogeneous uterine enlargement measuring 21.5 cm concerning for extensive adenomyosis. The uterus compressed the bladder with moderate bilateral hydroureteronephrosis and described multiple pedunculated right fundal fibroids extending into the right lower quadrant measuring up to 6.4cm.

The differential diagnosis for erythrocytosis is broad and categorized into primary and secondary causes.[1] Primary erythrocytosis is due to changes in hematopoietic progenitor cells that lead to uncontrolled production of red blood cells.[1] Polycythemia rubra vera (PRV) is a myeloproliferative disorder due to in large part from point mutations leading to unregulated signaling pathways and cell replication.[1] The JAK2 V617F mutation is the most common and seen in more than 95% of PRV patients.[1] JAK2 exon 12 and 14 mutations are seen in an additional 2-3% of PRV patients.[1] The absence of JAK2 mutation essentially ruled out this diagnosis.

Secondary causes of erythrocytosis are related to increased release of erythropoietin, a hormone that acts on erythroid precursors in the bone marrow to stimulate more red blood cell production.[1] The most common secondary causes include conditions that lead to hypoxemia such as living at high altitude, cardiac or pulmonary disease.[2] It can also be related to tumors such as hepatocellular or renal carcinomas or even benign renal or hepatic tumors, cerebellar hemangioblastomas, and myomas.[2-4] Medications such as testosterone are also common culprits.[5]

Multiple case reports have noted erythrocytosis related to leiomyomas.[2,3] These uterine fibroids are very common especially in the post-menopausal group, but not all lead to erythrocytosis.[3,4] Based on early recognition of this issue, it was coined "Myomatous Erythrocytosis Syndrome (MES)."[2-4] The syndrome is defined by the triad of erythrocytosis, uterine myomas, and resolution of red blood cell abnormalities after hysterectomy.[3,4] While the presence of fibroids is not uncommon in women, the incidence of erythrocytosis related to the disease is reported between 0.02%-0.5%.[2,4] The mechanism of polycythemia related to uterine fibroids is not clear.[2-4] Theories include local hypoxemia in the uterus leading to increased erythropoietin production, erythropoietin-like protein secretion from the myomas, intrauterine shunting, and compression of the ureters leading to increased erythropoietin production by the kidneys.[2-4] Most of the supposition centers on increases in erythropoietin levels.[2-4] Interestingly, most case series report normal blood hormone levels, but some are high normal as in this case. Some believe elevated erythropoietin is not the underlying cause.[2-4] In several reports erythropoietin staining could be seen in myomas and was generally higher in patients with MES compared to patients with no erythrocytosis. However, findings have been mixed across studies.[2,4]

This patient had a normal erythropoietin level, but was relatively high given the extent of polycythemia and expected downregulation. Medications including erythropoietin-stimulating agents and testosterone are common exogenous culprits, but this patient reported no use. No liver or kidney masses were noted on her imaging. The most significant finding was extensive likely benign uterine disease, which was strongly felt to be the cause of her erythrocytosis given the size of her uterus. She was encouraged to proceed with hysterectomy. She deferred for some time due to a difficult work schedule and was treated with phlebotomy for several years with good control of her elevated blood counts. Upon retirement, she underwent hysterectomy and pathology confirmed a 2500 gram uterus with multiple leiomyomas measuring up to 21cm and otherwise benign findings. She had some post-operative anemia, and phlebotomy was held. Her blood counts slowly rose over the

next several months, and eventually plateaued within normal range. She was monitored closely until iron levels were corrected after cessation of her prior phlebotomy without further elevations of her hemoglobin with iron repletion, without identifying other potential etiologies for her erythrocytosis.

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