Case Report

A Case of Erythrocytosis in a Patient Treated with an Aromatase Inhibitor for Breast Cancer

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A previously healthy 79-year-old female was referred to hematology for further evaluation of erythrocytosis. Two years earlier she had been diagnosed with ER/PR-positive ductal carcinoma of the breast and was receiving hormonal therapy with exemestane. No secondary cause of erythrocytosis was identified. Serum erythropoietin (EPO) level was normal, and molecular testing for the JAK2 V617F and exon 12 mutations was negative. A bone marrow biopsy showed a mild increase in erythropoiesis, and no spontaneous erythroid colonies were demonstrated. Erythrocytosis is common reason for referral to a hematologist. The myeloproliferative disorder, polycythemia vera, and the rare congenital polycythemias represent primary erythrocytosis. Common secondary causes include smoking, obstructive sleep apnea, and other pulmonary diseases. Erythrocytosis is well described with certain classes of drugs, including androgens. We hypothesize that exemestane contributed to the development of erythrocytosis in our patient. To our knowledge, erythrocytosis has not been previously described in association with aromatase inhibitors. These drugs prevent the conversion of androstenedione and testosterone to estrogen; thus the physiologic mechanisms may be similar to those responsible for erythrocytosis seen with exogenous androgens. These mechanisms are not well understood, but may include altered iron metabolism by a reduction in hepcidin levels.

1. Case Presentation

A 79-year-old female was referred to a hematologist for evaluation of erythrocytosis. In late 2009, she was diagnosed with HER2-positive T1cN0M0 infiltrating ductal carcinoma of the left breast, which was treated with wide local excision, four cycles of chemotherapy with docetaxel and cyclophosphamide, radiation, and trastuzumab. Her tumour was ER/PR-positive, and so letrozole was started as adjuvant hormone blocking therapy. Letrozole was discontinued after a few months due to nausea. She subsequently started exemestane 25 mg daily in September 2010. Prior to commencing exemestane her hemoglobin and hematocrit were normal at 154 g/L and 44.1%, respectively. Her MCV was 88.7 fl, and her other blood counts were normal.

Her oncologist thereafter noted a gradual increase in her hematocrit, and she was referred for hematologic evaluation. She was seen in consultation in November 2011. At that time, she denied headache, visual changes, erythromelalgia, or other vasomotor symptoms. There were no neurological symptoms. She acknowledged mild pruritus associated with seasonal allergies. She denied fevers, night sweats, or weight loss. There was no history of peripheral edema, chest pain, dyspnea, or cough. She denied abdominal pain or changes in bowel habit. She had no urinary symptoms.

Her past medical history included asthma, hypertension, hypothyroidism, and osteopenia. She denied previous thrombotic or hemorrhagic events. At the time of consultation, her medications included fluticasone, salbutamol, amlodipine, levothyroxine, risedronate, and exemestane.

On examination, there was facial plethora, but she otherwise appeared well. There was no evidence of volume contraction. There was no hirsutism or other signs of virilization. Her blood pressure was 150/90, heart rate 88 beats per minute, and oxygen saturation 93%. She had no peripheral lymphadenopathy. Her cardiac examination revealed a normal JVP with normal heart sounds and no extra sounds, murmurs, or gallops. Peripheral pulses were normal in all four extremities. Her chest was clear on auscultation and
Secondary polycythemia
Appropriately increased EPO
Pulmonary disease
Cyanotic heart disease
Obstructive sleep apnea
Carbon monoxide, for example, smoking
High altitude
Inappropriately increased EPO
Tumour polycythemia, for example, renal cell carcinoma, hepatocellular carcinoma
Renal lesions, for example, polycystic kidney disease, kidney transplant
Endocrinopathies, for example, Cushing syndrome, primary aldosteronism
Drug-induced polycythemia, for example, exogenous EPO, androgens

Primary polycythemia
Polycythemia vera
Congenital polycythemias
Abnormalities of oxygen sensing, for example, Chuvash polycythemia
Alterations in oxygen affinity, for example, high affinity hemoglobins, methemoglobinemia
Low 2,3-DPG

Box 1: Differential diagnosis of erythrocytosis. EPO indicates erythropoietin; 2,3-DPG, 2,3-disphosphoglycerate.

therewerenosignsofclubbingorcyanosis.Herabdomenwas
softwithnopalpablemassesorhepatosplenomegaly.

Her hemoglobin and hematocrit at that time were 187 g/L
and 53.6%, respectively. Her white count was $5.9 \times 10^9$/L,
and her platelet count was $215 \times 10^9$/L. Hepatic enzymes
and LDH were normal. Creatinine was 71. She had never
received a red cell transfusion and did not have evidence of
iron overload. Iron studies showed a ferritin of $11\text{m}\mu g/L$ ($11$–$307\text{m}\mu g/L$), serum iron of $25\text{m}\mu mol/L$ ($9$–$30\text{m}\mu mol/L$), and total
iron binding capacity of $73\text{m}\mu mol/L$ ($45$–$81\text{m}\mu mol/L$). Her chest
X-ray showed mild hyperinflation, and pulmonary function
testing revealed mild obstruction. Abdominal ultrasound was
unremarkable. Serum erythropoietin (EPO) level was normal
at $3.51\text{IU}/L$ ($2.6$–$18.5\text{IU}/L$). This was confirmed on a second
occasion. Molecular testing for the JAK2 V617F and exon 12
mutations, as well as for the BCR-ABL1 translocation, was
negative. A bone marrow biopsy showed a mild increase in
erthrocytosis but was otherwise normal with no increase
in granulopoiesis, megakaryopoiesis, or increased blasts.

Erythroid cultures were performed to look for spontaneous
erythroid colony formation in the absence of erythropoietin,
but none were demonstrated.

Her hematocrit peaked at 54.7% in March 2012, 18
months after starting exemestane, and she underwent five
phlebotomies between March and May 2012 with a resultant
drop to 42.9%. However, it was noted that the develop-
ment of her erythrocytosis correlated with the initiation
of the aromatase inhibitor, exemestane. Exemestane was
discontinued in May 2012. She has had no phlebotomies since
that time, and there has been no recurrence of erythrocytosis.

2. Discussion

2.1. Regulation of Erythropoiesis. Under physiologic con-
ditions, EPO production is upregulated in the setting of
decreased oxygen delivery to tissues. Hypoxia results in the
production of hypoxia-inducible factor (HIF)-1, the major
transcription factor responsible for activation of the EPO
gene [1]. EPO is produced primarily in the kidney and
interacts with the EPO receptor on erythroid progenitor cells.
When EPO binds, the EPO receptor interacts with JAK2,
resulting in phosphorylation of itself and STAT5 [2]. The
JAK2/STAT5 signaling pathway plays an important role in
erythroid development.

2.2. Differential Diagnosis of Erythrocytosis. Erythrocytosis is
a common referral to the hematologist. The first step in eval-
uation is to determine whether the erythrocytosis is relative or
absolute (Box 1). Relative erythrocytosis occurs when there is
plasma volume contraction. Absolute erythrocytosis results
from increased red cell mass. Absolute erythrocytosis may
be primary, most commonly polycythemia vera (PV), or sec-
ondary. Secondary erythrocytosis may result from hypoxic
conditions, including cyanotic heart disease, pulmonary
disease, carbon monoxide (e.g., smokers), obstructive sleep
apnea, and high altitude. These conditions are associated with
a serum EPO level that is appropriately increased.

Secondary erythrocytosis may also result from conditions
associated with an inappropriately elevated serum EPO.
These include EPO-secreting tumours, such as renal cell
carcinoma, hepatocellular carcinoma, and uterine leiomy-
oma, and following renal transplantation. Several medi-
cations, including recombinant erythropoietin and andro-
gen, may result in erythrocytosis. Rare congenital causes
include hemoglobin mutations resulting in increased oxygen
affinity, EPO receptor mutations, and mutations affecting
regulation of EPO production by HIF; for example, Chuvash
polycythemia.

Determining the cause of erythrocytosis requires consid-
eration of a patient’s risk factors for secondary erythrocytosis.
A careful history and physical and repeated documentation
of abnormal blood values are quite helpful. Measurement of
oxygen saturation can determine if hypoxia is present. In addition, a smoking history or history of sleep disordered breathing may help in determining if chronic obstructive lung disease or obstructive sleep apnea is present. Chest radiography, pulmonary function testing, or polsomnography may be warranted for confirmation. A history of congenital heart disease or renal disease is also important. Abdominal ultrasound may be helpful to rule out an EPO-producing tumour. Once these factors have been eliminated, investigations looking at primary causes should be considered.

2.3. Polycythemia Vera. PV is the most common of the classical myeloproliferative neoplasms. It is a clonal disorder characterized by splenomegaly, a predisposition to thrombohemorrhagic events, and an increased risk of progression to acute leukemia. The diagnosis of PV is aided by the testing for the JAK2 V617F mutation, which is typically positive in over 90% of PV cases [3]. The discovery of this mutation has been a major advance in the diagnosis of myeloproliferative disorders. The use of serum EPO levels can also be useful in elucidating the cause of erythrocytosis. Endogenous EPO levels should be suppressed or normal in PV. Elevated EPO levels in the setting of erythrocytosis signify either appropriate compensation, an exogenous source of EPO, or malignant production of EPO.

The diagnosis of PV can be difficult, especially in the absence of the JAK2 V617F mutation or any identifiable secondary causes. Testing for mutations in JAK2 exon 12 can also be performed in cases where the more common JAK2 V617F mutation is absent. Exon 12 mutations have been reported to be present in 80% of those with PRV who are JAK2 V617F negative [3]. Cultures of erythroid progenitors in PV patients demonstrate spontaneous erythroid colony formation in the absence of EPO. This autonomous proliferation is the hallmark of PV.

2.4. Possible Association between Erythrocytosis and Aromatase Inhibition. Our case involves absolute erythrocytosis in the absence of a definitive primary disorder. The absence of JAK2 V617F and exon 12 mutations in addition to the lack of spontaneous erythroid colony formation points to a secondary cause of the erythrocytosis. The timing from the initiation of exemestane to the first appearance of 12 months in the absence of phlebotomies has not shown any recurrence of erythrocytosis. Given the widespread use of this drug, this may represent an idiosyncratic reaction not previously seen.

Conflict of Interests
The authors have no relevant conflict of interests to declare.

References


