

Successful use of phlebotomy to treat severe secondary polycythemia due to chronic lung disease

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Abstract

Secondary polycythemia (SP) occurs as a result of increase erythropoietin levels most commonly as a result of tissue hypoxia. Symptoms such as erythromelalgia, pruritis, and bleeding, which are frequently seen in polycythemia vera (PV), do not commonly occur in SP. Phlebotomy is considered one of the mainstays of therapy for PV but is rarely used for treatment of SP due to concern about worsening tissue hypoxia. We present the case of a patient with severe SP due to chronic hypoxic lung disease who presented with erythromelalgia, pruritis, and bleeding and was treated successfully with therapeutic phlebotomy. This case illustrates the importance of considering the use of therapeutic phlebotomy in symptomatic patients with severe SP.

Introduction

Phlebotomy, also known as blood-letting or venesection, has been used for over five millennia to treat a multitude of illnesses. From febrile illnesses to heart failure, phlebotomy was used to treat inflammation that resulted from having excess blood in the body.¹ Although most bygone indications for phlebotomy have safer and effective treatments, the process is still a mainstay of therapy for polycythemia vera (PV), porphyria cutanea tarda, and hemochromatosis. PV is a myeloproliferative disorder which results in erythrocytosis and thrombocytosis. Erythromelalgia, pruritis, and bleeding usually only occur in PV. Complications can include ischemic cardiovascular disease, stroke, and arterial or venous thromboembolism.² Secondary polycythemia (SP) is a similar entity but occurs as a result of increased erythropoietin (EPO) levels. A common cause of SP is chronic hypoxia. In most cases, treating the underlying cause of hypoxia or long-term oxygen therapy is the preferred treatment for SP. However, phlebotomy can be considered in SP patients, particularly those with symptoms of hyperviscosity.³ We

report a patient who presented with erythromelalgia, pruritis, and bleeding but was diagnosed with severe SP. This case illustrates the utility of phlebotomy in SP. We believe that it will help physicians become aware of a rarely used but effective therapeutic modality in SP.

Case Report

A 60-year-old white male presented to the emergency department for intermittent erythromelalgia that had been occurring for the last year but had increased in frequency. He also had episodes of cyanosis of the lips, facial plethora, conjunctival injection, left upper quadrant pain (LUQ), pruritis unrelated to water, petechia, epistaxis, fatigue, and myalgias. His past medical history was significant for untreated chronic obstructive pulmonary disease (COPD) and recurrent episodes of epistaxis. He was on 81 mg of aspirin (ASA). He had last seen a health care provider 4 years ago.

On examination he was afebrile, heart rate was 64 beats per minute, respiratory rate was 15 respirations per minute, blood pressure was 152/106 mmHg and oxygen saturation was 83% on room air. Oxygen saturation improved to 93% on high flow nasal cannula (HFNC) with FiO₂ 90% and 45 LPM. The patient had mild discomfort on LUQ palpation. He was plethoric with conjunctival injection bilaterally, splenomegaly, bilateral pallor of the feet, and petechia to the left lower abdominal region. His physical exam was otherwise unremarkable. His initial hemoglobin was 25.0 g/dL, hematocrit of 74.6%, white blood cell count of 7,900/ μ L, and platelets of 160,000/ μ L. Peripheral blood smear showed normochromic, normocytic erythrocytosis and polychromasia. Other abnormal lab values included serum bicarbonate of 21 mEq/L and partial thromboplastin time (aPTT) of 66.2 seconds. His initial venous blood gas (VBG) showed a pH of 7.36, pCO₂ 46 mm/Hg, and pO₂ 27 mm/Hg while on 38% FiO₂. He had an otherwise normal basic metabolic panel, hepatic function panel, coagulation panel and urinalysis. Computed topography (CT) of the chest with intravenous contrast (IV) showed no evidence of a pulmonary embolism or aortic dissection but noted underlying bullous emphysema with prominent interstitial markings and ground-glass opacities. The patient was admitted with the diagnoses of hypoxic respiratory failure and polycythemia.

Upon admission, it was unclear if the patient had primary polycythemia or secondary polycythemia in the setting of

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COPD. The workup for PV revealed an increased EPO level of 32.4 mIU/mL, no mutations to JAK2 V617F, JAK2 Exon 12, or CALR. Serum ferritin was 38 ng/mL, serum iron of 91 μ g/dL, total iron binding capacity of 335 μ g/dL, and transferrin of 239 μ g/dL. He underwent a CT scan of the abdomen and pelvis with IV contrast which was negative for an EPO secreting tumor. The spleen was also found to be of normal size. Transthoracic echocardiography showed a normal left ventricular ejection fraction and no evidence of structural abnormalities or right heart failure. From this initial workup, the patient was diagnosed with polycythemia secondary to chronic hypoxic lung disease. He was continued on HFNC to maintain oxygen saturation above 90%. He was given ASA 81 mg daily, budesonide 80 mcg-formoterol 4.5 mcg inhaled twice daily, ipratropium 0.5 mg-albuterol 3mg by nebulization four times daily as needed for shortness of breath, prednisone 40 mg daily for five days, doxycycline 100 mg daily for 5 days, and enoxaparin 40 mg subcutaneous daily for venous thromboembolism prophylaxis.

Since the patient was symptomatic with a markedly elevated hematocrit and continued need for HFNC due to hypoxia, thera-

Table 1. Hematocrit level, supplemental oxygen, volume of phlebotomy, and oxygen extraction ratio by hospital day.

Hospital day	Hematocrit	Supplemental oxygen (FiO ₂), %	Volume of phlebotomy	Oxygen extraction ratio
1	74.6	80		
2	70.1	80		
3	69.7	65	250cc	
4	68.4	80	450cc	
5	64.7	80	450cc	
6	60.2	70	500cc	
7	57.7	60		7%
8	57.8	45	500cc	
9	54.4	36		15%
10	54.8	36		

peutic phlebotomy was initiated on day 3 of admission. Pruritis, erythromelalgia and LUQ pain improved immediately after phlebotomy was initiated but his oxygen requirement did not decline until hospital day 6. Supplemental oxygen requirement, hematocrit, and volume of phlebotomy are displayed in Table 1. Oxygen extraction ratios (O₂ER) were used to ensure that phlebotomy was improving oxygen consumption and not resulting in inadequate oxygen delivery to tissue. Arterial oxyhemoglobin level on day 7 was 93.6%, which correlated with the pulse oximeter, and venous oxyhemoglobin level was 86.9% with an O₂ER of 7%. Due to the low oxygen extraction, phlebotomy was continued. Venous oxyhemoglobin was obtained on hospital day 9 and was found to be 79.2% with a pulse oximeter reading of 94% showing an O₂ER 15%. The aPTT also normalized to 29.3 seconds after completion of phlebotomy. The patient was able to be discharged home on 4L/min of supplemental oxygen. ASA 81mg, umeclidinium 62.5mcg inhaled daily, and budesonide 80 mcg-formoterol 4.5 mcg inhaled twice daily were prescribed at discharge. Hematocrit 4 weeks and 8 weeks after discharge was 53.1% and 49.5% respectively. No further phlebotomy was performed after discharge.

Discussion and Conclusions

Polycythemia is defined by a hematocrit elevation greater than 49% in men and 48% in women. It can be further categorized as a primary myeloproliferative neoplasm (PV) or secondary to increased EPO levels (SP). SP is much more common than PV and is most frequently associated with chronic hypoxic states and less commonly EPO producing neoplasms. The symptoms this patient presented with, including erythromelalgia, pruritis, and epistaxis, are more commonly indicative of PV.⁴

However, elevated serum EPO levels, normal platelet count, and no evidence of genetic mutations along with an obvious history of chronic hypoxic lung disease made SP the most likely diagnosis. This was further supported by continued decrease in hematocrit after prolonged improvement of hypoxia without the need for further phlebotomy. Erythromelalgia is thought to be a microvascular thrombotic process associated with thrombocytosis commonly seen in PV and often responds to ASA and cytorreduction of platelets.⁵ The patient had been taking low dose ASA with no improvement. However, reducing the blood volume resolved the symptoms suggesting that the symptoms were a result of hyperviscosity from a massively increased red cell volume. Bleeding may be seen in patients with PV and is postulated to be a result of acquired von Willebrand Syndrome (avWS). One possibility is that the increased erythrocytosis results in shear stress that destroys the von Willebrand Factor multimer.⁶ Again, with the markedly increased red cell volume, this patient may have had avWS despite having SP and not PV. This is supported by normalization of the aPTT with subsequent phlebotomy.

The mainstay of treatment for SP resulting from chronic hypoxia is to restore adequate oxygenation to tissue. This is done with supplemental oxygen and reversing the primary cause of hypoxia if possible.³ Phlebotomy for SP due to hypoxia can be considered in patients with symptomatic hyperviscosity or hematocrit greater than 56%. The British Journal of Haematology endorses a Grade B recommendation to reduce hematocrit to 50-52% in selected patients with SP due to hypoxic pulmonary disease, but there is concern that reducing the red cell mass may theoretically worsen tissue hypoxia.⁷ However, previous studies have shown that phlebotomy may actually improve oxygen consumption without adversely affecting oxygen delivery in this

patient population.^{8,9} This patient continued to have symptoms of hyperviscosity and significant hypoxia requiring high amounts of supplemental oxygen. Once phlebotomy was initiated, his symptoms did improve and supplemental oxygen requirement began to decrease. Using the general rule that a normal O₂ER is around 25% at rest, calculation of O₂ER may be beneficial to ensure that phlebotomy is not overly reducing oxygen delivery to tissue which could result in further hypoxic complications. It may also be helpful to reduce the use of excessive supplemental oxygen.⁹

This case of SP in a patient with chronic hypoxic lung disease is unusual because of the markedly elevated hematocrit as well as clinical findings more commonly seen in PV such as erythromelalgia, pruritis, and bleeding. This case also illustrates the utility of phlebotomy in select patients with SP and chronic hypoxic lung disease which many physicians may not be aware of. The use of the oxygen extraction ratio may also be useful for avoiding excessive phlebotomy that may result in tissue hypoxia because of inadequate oxygen delivery and also to limit excessive supplemental oxygen.

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