CASE REPORTS/CLINICAL VIGNETTES

Cyanotic Congenital Heart Disease (CCHD) with Symptomatic Erythrocytosis

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Secondary erythrocytosis of cyanotic congenital heart disease (CCHD) is pathologically different from primary erythrocytosis of polycythemia vera (PV). An association between elevated hematocrit and thrombosis has been established in PV patients, and treatment guidelines recommend maintaining hematocrit <45%. Although an association between elevated hematocrit and thrombosis has not been established in CCHD and secondary erythrocytosis, the current clinical practice is to phlebotomize these patients to hematocrit <65%. We report a 21-year-old woman with CCHD who presented with symptomatic erythrocytosis with numbness and tingling with hemoglobin 25.2 g/dl and hematocrit 75.8%. Her symptoms resolved with IV hydration. Other factors, including dehydration and iron deficiency, may precipitate hyperviscosity symptoms. The treatment is volume replacement and low-dose iron therapy, not phlebotomy. Repeated phlebotomy causes iron deficiency with microcytic erythrocytes, which increases the whole blood viscosity and, therefore, can potentially accentuate rather than decrease the risk for a cerebrovascular accident.

KEY WORDS: cyanosis; hyperviscosity; erythrocytosis; transient ischemic attack (TIA); hematocrit; venesection.

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INTRODUCTION

Adults with cyanotic congenital heart disease (CCHD) often develop secondary erythrocytosis. The pathophysiology of secondary erythrocytosis associated with CCHD is different from primary erythrocytosis associated with polycythemia vera (PV). In PV, the serum erythropoietin level is usually low or normal,¹ and the erythroid progenitors are capable of proliferation in vitro in the absence of erythropoietin.² Conversely, secondary erythrocytosis associated with CCHD is a physiological response to tissue hypoxia with resultant increase in serum

erythropoietin level, thereby stimulating the bone marrow erythropoiesis causing an elevated red cell mass, hematocrit, and whole blood viscosity.^{3,4} The increase in circulating red cells provides increased oxygen carrying capacity.⁵ However, this effect is offset by the increase in serum viscosity that reduces blood flow and tissue perfusion^{6,7} and impairs tissue oxygen delivery with resultant hyperviscosity symptoms such as headache, visual disturbance, loss of concentration, paresthesia, muscle weakness, and fatigue.⁸ In general, the major consequence of hyperviscosity is thrombosis, which may manifest as a cerebrovascular accident (CVA), myocardial infarction, or other overt thrombotic event. Studies have indicated a direct correlation between hematocrit level above 45% and vascular occlusive episodes including CVA in PV patients.^{9,10} Unlike PV, the relationship between hyperviscosity and thrombosis is not clearly demonstrated in adult patients with CCHD and secondary erythrocytosis. Therefore, the treatment implications are different for the two disorders. The current treatment guidelines recommend phlebotomy with or without cytoreductive therapy to maintain a hematocrit <45% to reduce the risk of thrombosis in PV patients.¹¹ To date, there are no studies defining the optimal hematocrit in patients with CCHD. The current clinical practice is to phlebotomize patients with CCHD and secondary erythrocytosis when they present with symptomatic hyperviscosity to reduce hematocrit to less than 65%. Phlebotomy causes a fall in red cell mass and serum viscosity. This leads to reduced peripheral vascular resistance that, in turn, increases the cardiac output, stroke volume, and systemic blood flow. Improved circulation results in increased tissue oxygen transport. Improvement in cardiac output and tissue oxygen uptake provides the patient relief of hyperviscosity symptoms.¹² Phlebotomy, in addition to providing relief of symptoms, was also perceived to reduce the risk of thrombotic strokes in these patients. This stems from prior studies showing high hematocrit as a risk factor for cerebral infarction¹³ and studies from PV patients showing an inverse relationship between cerebral blood flow and whole blood viscosity.¹⁴ However, studies have failed to demonstrate similar risk in patients with CCHD and secondary erythrocytosis.¹⁵ Repeated phlebotomies in patients with CCHD and secondary erythrocytosis may, in fact, increase the risk of a CVA by causing chronic iron deficiency, which leads to microcytosis and increased whole blood viscosity.^{16,17}

We report a 21-year-old woman with CCHD and secondary erythrocytosis who presented with hyperviscosity symptoms with numbness, tingling, and blurred vision. The purpose of this case report is to illustrate the clinical significance of

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elevated hematocrit in primary and secondary erythrocytosis and to highlight that adult patients with CCHD and secondary erythrocytosis may present with neurological symptoms because of hyperviscosity, which could be misinterpreted as a transient ischemic attack (TIA) or CVA leading to injudicious venesection. It is important to look for and correct dehydration and iron deficiency, which can precipitate hyperviscosity symptoms, prior to assessing the need for phlebotomies.

CASE REPORT

A 21-year-old white woman with a history of complex CCHD presented to the emergency department complaining of bilateral upper extremity numbness, tingling, and blurred vision. The day before her symptoms began, it was a hot summer day and she was outside most of the day and not drinking adequately. The following day, upon awakening in the morning, she noted painful tingling in both hands extending up to the elbows and increased purple hue of her fingertips, which have been chronically cyanotic. Over the next 24 h, the tingling and pain in her upper extremities continued to worsen and she developed blurred vision. In addition, she noticed worsening of her chronic dyspnea. Her medical history included congenital situs inversus with levocardia and pulmonary atresia with multiple failed shunt revisions during childhood. She also had a history of gastric ulcers. Her current medications included ranitidine and home oxygen, which she was on for many years secondary to chronic hypoxia because of her underlying CCHD. Her prognosis is very poor because she has failed multiple shunt revisions and is not a transplant candidate.

On arrival at the emergency department, the patient was noted to be hypoxic with an arterial oxygen saturation of 74% on room air, temperature 97.1°F, heart rate 101/minute, blood pressure 118/78 mmHg, and respiratory rate 24/minute. Orthostatic vital signs were not obtained because she complained of dizziness. Pertinent physical examination findings included dry oral mucous membranes, a grade 2/6 systolic ejection murmur heard diffusely across the pericardium, palpable liver and spleen, cyanosis and clubbing of the digits in both upper and lower extremities, and a normal neurological examination.

Her baseline hemoglobin was 17.1 g/dl, and hematocrit was 50.8%. As shown in Table 1, when she presented to the emergency department, her hemoglobin was 25.2 g/dl and hematocrit was 75.8%. Her other laboratory data included a

Table 1. Laboratory Data

Result	Baseline	Range
Complete blood count (CBC)		
WBC	$7.9 \times 10^3/\mu\text{l}$	[4.0–10.0]
Hgb	25.2 g/dL	17.1 g/dL [12.3–15.5]
Hct	75.8%	50.8% [36.0–44.0]
MCV	72 fL	[78.0–99.0]
RDW	19.4	[0.0–15.0]
Platelet	$117 \times 10^3/\mu\text{l}$	
Iron studies		
Iron	52 mcg/ $^3\mu\text{l}$	[45–135]
Iron binding capacity	410 mcg/dL	[250–400]
Percent saturation	12.7%	[20.0–55]
Ferritin	10 ng/mL	[20–120]

MCV = mean corpuscular volume, RDW = red cell distribution width

Table 2. Symptoms of Hyperviscosity/Transient Ischemic Attack (TIA)

Symptoms
Hyperviscosity
Headache
Faintness, dizziness, lightheadedness
Altered mentation, impaired alertness
Visual disturbances (blurred vision)
Paresthesias of fingers, toes, or lips
Tinnitus
Fatigue, lassitude
Myalgias, muscle weakness
Symptoms of TIA
Carotid distribution
Hemiparesis and/or hemisensory deficit
Amaurosis fugax
Aphasia
Vertebrobasilar distribution (brainstem dysfunction)
Hemiparesis and/or hemisensory deficit
Diplopia
Dysarthria
Ataxia
Drop attacks
Cortical blindness

blood urea nitrogen (BUN) of 20 mg/dl and serum creatinine of 1.1 mg/dl with a BUN–serum creatinine ratio of 20:1, which placed her at the cusp of prerenal azotemia. Follow-up BUN was 12 mg/dl, and creatinine was 1.0 mg/dl. The above laboratory data are suggestive of dehydration as the cause of her worsening erythrocytosis. CT scan of the head performed without contrast showed no definite intracranial mass, enhancement, or midline shift. A 2-D echocardiogram performed in the emergency department showed a single atrium with a large nonrestrictive secundum atrial septal defect, probable tricuspid atresia, and single ventricle with a single A-V valve.

The patient was diagnosed with hyperviscosity symptoms perhaps secondary to dehydration and was given 2 l of intravenous normal saline over 3 h with complete resolution of her symptoms and was discharged home. Whereas iron deficiency parameters were not tested in the emergency department, at a later date in the outpatient hematology clinic, she was found to be iron-deficient, as shown in Table 1, because of repeated phlebotomies. The patient was on a regular phlebotomy regimen prescribed by her Internist to maintain hematocrit <65%.

DISCUSSION

The association between primary erythrocytosis of PV and CVAs is well established.¹⁸ Patients with PV are at increased risk of cerebrovascular events because of multiple risk factors including erythrocytosis, thrombocytosis, impaired fibrinolytic activity, platelet activation, leukocyte activation, endothelial damage, and increased whole blood viscosity.¹⁹ Current treatment guidelines in this disease recommend phlebotomy, the use of cytoreductive therapy, or both to maintain a hematocrit of <45% to reduce the risk of thrombosis.¹¹ In contrast to PV patients who present with panmyelosis with elevated red cells, white cells, and platelets, patients with CCHD present with erythrocytosis and normal or low normal platelet count.^{20,21} There is no clear association of adults with secondary erythrocytosis because of CCHD with CVAs. Perloff

et al. did not observe an increased incidence of stroke in 112 adult patients with CCHD and secondary erythrocytosis who were followed for 1–12 years (748 patient-years).¹⁵ Although Ammash et al. showed an increased incidence of CVAs in patients with CCHD, it was not associated with increased hemoglobin or hematocrit but rather with the presence of four other risk factors, namely, hypertension, atrial fibrillation, repeated phlebotomies, and iron deficiency.¹⁶

Patients with CCHD and secondary erythrocytosis can be divided into two groups; those with stable “compensated” erythrocytosis, adequate iron stores, and absent or mild hyperviscosity symptoms, and patients with “decompensated” erythrocytosis, iron deficiency states, and recurrent hyperviscosity symptoms.²² Table 2 illustrates hyperviscosity symptoms owing to erythrocytosis and symptoms of TIA.¹⁵ The neurological symptoms of hyperviscosity sometimes can be misinterpreted as a TIA or CVA leading to injudicious phlebotomies. Adult patients with CCHD and secondary erythrocytosis who undergo repeated phlebotomies are at risk for developing iron deficiency and microcytic circulating erythrocytes. Such microcytic erythrocytes have been shown to be rigid and resist deformation in high shear rates in the microcirculation,²³ which, in turn, increases the risk of hyperviscosity symptoms and CVAs in adults and children with CCHD and secondary erythrocytosis.^{16,17} Therefore, the short-term potential benefit of phlebotomy in lowering hematocrit in patients with CCHD and secondary erythrocytosis may be offset by development of chronic iron deficiency with increased risk of hyperviscosity symptoms and cerebrovascular events.

In conclusion, it is important to note that other factors, such as dehydration and iron deficiency, can precipitate or aggravate symptomatic hyperviscosity and must be corrected before resorting to phlebotomies in patients with CCHD and secondary erythrocytosis with a hematocrit of >65%. Dehydration can result in a rapid increase in the hematocrit level provoking hyperviscosity symptoms. Treatment is volume replacement, not phlebotomy.^{4,21} If there is evidence of iron deficiency, the treatment is low-dose iron therapy with close monitoring of blood counts to avoid excessive increase in erythrocytosis response, which could further accentuate the hyperviscosity.^{4,21} Once dehydration and iron deficiency are ruled out as precipitating causes of hyperviscosity symptoms, phlebotomy may be safely performed with concomitant volume replacement.^{4,21} Attempts at acute phlebotomy without adequate volume replacement may be followed by a sudden reduction in systemic blood flow, which could potentially increase the risk of a sudden thrombotic stroke.²⁴ Rarely, hyperviscosity symptoms mimic a TIA or a thrombotic CVA, which can be excluded by appropriate testing, and may be further aggravated by injudicious phlebotomies.

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