Elmer Press

Case Report

J Hematol. 2014;3(1):19-21

Systemic Capillary Leak Syndrome Presenting as Apparent Polycythemia Vera: A Critical Diagnostic Dilemma

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Abstract

Polycythemia vera presents with true erythrocytosis (elevated red cell mass) and an expanded plasma volume, while apparent erythrocytosis presents with plasma volume contraction and a normal red cell mass. Here we report a case with recurrent episodes of severe apparent erythrocytosis, closely mimicking polycythemia vera, due to a rare condition known as systemic capillary leak syndrome (SCLS). This syndrome typically presents with the triad of hypotension, hemocencentration and hypoalbuminemia, combined with a monoclonal serum M-protein. Empirical treatment with intravenous immune globulin (IVIG) has successfully led to resolution of symptoms and correction of hemoconcentration in several reported cases as well as in our patient's case. It is important for clinicians to differentiate true erythrocytosis from apparent erythrocytosis, and to be aware of this rare syndrome causing the latter, as aggressive phlebotomy and overtreatment with crystalloid fluids could result in serious adverse events and should be avoided.

Keywords: Hemoconcentration; Pseudoerythrocytosis; Monoclonal gammopathy; Intravenous immune globulin

Introduction

Polycythemia vera presents with true erythrocytosis (elevated red cell mass) and an expanded plasma volume [1, 2]. Apparent erythrocytosis in young men, which presents with plasma volume contraction and a normal red cell mass, may be associated with diuretic therapy, heavy smoking, hypertension (namely, Gaisbock's syndrome), obesity or alcohol consumption [3, 4]. At the time of initial presentation, the distinction between true and apparent erythrocytosis may be difficult. Whereas polycythemia vera is appropriately treated with phlebotomy to avoid complications of thrombosis and hyperviscosity, phlebotomy may result in volume depletion and anemia in patients with apparent erythrocytosis [5]. The distinction can be difficult when the presentation of apparent erythrocytosis mimics multiple clinical aspects of polycythemia vera. We report herein a case that illustrates the importance of carefully distinguishing true from apparent erythrocytosis in the acute setting.

Manuscript accepted for publication December 4, 2013

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doi: http://dx.doi.org/10.14740/jh116w

Case Report

First admission

A 23-year-old man without significant past medical history presented after 12 h of nausea, vomiting, abdominal pain and repeated syncope. On admission, he was hypotensive and tachycardic with systolic blood pressure 60 - 70 mmHg and a heart rate of over 140/min. He had bilateral lower extremity edema, numbness and pain. His hemoglobin and hematocrit were markedly elevated at 25.8 g/dL and 75.4% respectively, and his white blood cell (WBC) count was 54 × 10^9/L. His peripheral blood film revealed a shift to the left with metamyelocytes, myelocytes and promyelocytes. His creatinine was 3.9 mg/dL.

Because of hypotension and evidence of lower extremity vascular compromise, he received aggressive fluid resuscitation with 10 L of normal saline over 12 h. His hemoglobin and hematocrit fell to 14.3 g/dL and 42.8% respectively and his WBC count was 47.8 × 10^9/L. His serum albumin was 2.4 g/dL. He was provisionally diagnosed with polycythemia vera based on persistent erythrocytosis despite fluid resuscitation, marked left-shifted leukocytosis, and a clinical picture suggestive of bilateral lower extremity thrombosis. An attempt at therapeutic phlebotomy was unsuccessful because of whole blood hyperviscosity.

He had progressive pain and dusky cyanosis of the distal lower extremities with poor capillary refill. Popliteal and

dorsalis pedis pulses were difficult to appreciate via doppler ultrasound. His creatine phosphokinase was elevated and peaked at 21,000 units/L. An emergent vascular surgery consult found him to have painful lower extremities that were cool, insensate and paralyzed. Emergent bilateral femoral exploration, including direct palpation and bilateral angiography, demonstrated good femoral and popliteal pulses and patent femoral, popliteal and tibial arteries. He thus underwent bilateral four-compartment fasciotomies for symptom relief. The following morning his CBC revealed WBC 17.7 $\times 10^9$/L, hemoglobin 10.1 g/dL, HCT 29.3% and platelet count 155 $\times 10^9$/L.

The results of a workup for polycythemia vera and other myeloproliferative neoplasms revealed a normocellular bone marrow with maturing trilineage hematopoiesis, absence of JAK2 or BCR-ABL mutations, a serum erythropoietin level of 20.2 mIU/mL (reference range 3.7-31.5), and a normal size spleen on abdominal ultrasound. After 3 weeks in hospital, he was transferred to a rehabilitation facility.

Second admission

The patient was readmitted after 3 months with complaints of nausea, vomiting, hematemesis and bilateral lower extremity edema. His CBC revealed WBC 28.6 $\times 10^9$/L, hemoglobin 22 g/dL and hematocrit 68.3%. Serum albumin was 3.1 g/dL. The patient again received aggressive IV fluid resuscitation. By hospital day 4, his CBC WBC was 5.2 $\times 10^9$/L, hemoglobin 11.9 g/dL and hematocrit 36.5%.

With polycythemia vera ruled out by bone marrow biopsy and genetic studies, and with repeated episodes of apparent erythrocytosis characterized by hypotension, hemoconcentration and hypoalbuminemia, a diagnosis of systemic capillary leak syndrome (SCLS) was considered [6-9]. Serum protein electrophoresis revealed an abnormal band of 0.4 g/dL in the gamma region. Serum immunofixation electrophoresis confirmed it to be an IgG lambda monoclonal band.

The patient was treated with terbutaline and theophylline [10] which were discontinued because of symptomatic tachycardia. He was then treated with intravenous immune globulin (IVIG) 1 g/kg/day for 2 days [11-13] with significant improvement in lower extremity edema and tenderness. His blood counts normalized and remained in the normal range with a stable hematocrit of 36-42%. As of this report, the patient has been hospitalized on five more occasions with marked recurrent hemoconcentration, hypotension and lower extremity edema, all treated with IVIG with resolution of symptoms and correction of hemoconcentration.

Discussion

SCLS is a rare disorder characterized by unexplained recurrent episodes of severe hypotension, hemoconcentration and hypoalbuminemia, likely due to a derangement of the vascular endothelium that results in capillary hyperpermeability and leakage of plasma and proteins into the interstitial space [6-9]. Several studies describe a monoclonal gammopathy of uncertain significance (MGUS) in the majority of patients [14]. The specific role of paraproteins in the pathogenesis of SCLS has not been defined. Elevated levels of vascular endothelial growth factor and angiopoietin 2, contraction of endothelial cells due to apoptosis during SCLS attacks, and involvement of IL-2 and other inflammatory mediators, including leukotrienes and tumor necrosis factor alpha, have been implicated in the pathophysiology of SCLS [15-19].

The initial presentation of our patient with severe erythrocytosis, a leukemoid reaction and lower extremity vascular compromise was suggestive of polycythemia vera. However, the presentation with hypotension and hypoalbuminemia, and the rapid correction of his erythrocytosis and leukocytosis with fluid resuscitation was not consistent with this diagnosis. The absence of a JAK2 kinase or BCR-ABL mutation and the normal bone marrow morphology and erythropoietin level were also at odds with a diagnosis of a myeloproliferative neoplasm.

The recurrent episodes of nausea and vomiting, and the triad of hypotension, hypoalbuminemia and hemoconcentration, were suggestive of SCLS. The identification of MGUS and the responsiveness to IVIG further supported this diagnosis. A prodromal phase with flu-like symptoms including respiratory or GI involvement is typical. This is followed by an extravasation phase where capillary leakage leads to the triad of hypotension, hemoconcentration and hypoalbuminemia [6-9]. Aggressive fluid resuscitation may lead to a compartment syndrome during the extravasation phase, and rhabdomyolysis may occur, as in this case [20, 21]. Acute tubular necrosis, ischemic brain injury or ischemic hepatitis have been reported. After several days, the extravasation phase is followed by a recovery phase during which extravasated fluids are recruited back into the intravascular space. SCLS patients may be at high risk for intravascular volume overload and pulmonary edema during this period, depending on the extent of fluid resuscitation during the extravasation phase [22].

In summary, here we report a case who presented with recurrent episodes of severe apparent erythrocytosis that turned out to be SCLS masquerading as polycythemia vera. The presenting triad of hypotension, hemocencentration and hypoalbuminemia, with a negative workup for myeloproliferative disorder, in combination with a monoclonal gammopathy, can be considered diagnostic for SCLS. This case illustrates the sometimes critical importance of differentiating true from apparent erythrocytosis: aggressive phlebotomy combined with volume expansion with crystalloid fluids in the latter can result in serious adverse events including anemia, pulmonary edema and further intravascular volume

depletion. When common external factors causing apparent erythrocytosis, such as diuretic therapy or dehydration, are ruled out, an intrinsic process such as SCLS should be considered. Clinicians should be aware of this syndrome and the role of IVIG in its treatment.

Funding

None.

Conflicts of Interest

All authors have no financial or other conflicts of interest.

Author Contributions

All authors had access to the data and a role in writing the manuscript.

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