

# Erythrocytosis in a Scleroderma Patient

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## Abstract

A 40-year-old black male with scleroderma lung disease presented with blurry vision and headache. His presenting hemoglobin was 22.3 g/dL and his serum erythropoietin level was surprisingly low. Although nocturnal hypoxemia was evident, his daytime resting arterial oxygen saturation was normal. The patient's symptoms of hyperviscosity improved after phlebotomy, as his hemoglobin gradually decreased to 18.3 g/dL. Repeat serum erythropoietin levels were in normal and high ranges. Patients with chronic interstitial lung disease and erythrocytosis could have normoxemia at rest and a normal or low serum erythropoietin level at the peak of erythrocytosis. A repeat sampling of serum erythropoietin and monitoring of oxygen saturation during sleep and exertion may help in diagnosis. Physicians should prescribe continuous oxygen therapy for patients with chronic interstitial lung disease and erythrocytosis, even if diurnal resting hypoxemia is absent.

**Key Words:** Scleroderma lung disease, erythrocytosis, erythropoietin, polycythemia vera.

## Introduction

ERYTHROCYTOSIS is a not uncommon complication of chronic hypoxic lung disease, yet it has rarely been reported in scleroderma patients. This heightened erythropoietic activity is thought to be an erythropoietin-dependent, compensatory response to hypoxia. We report an unusual case of erythrocytosis secondary to scleroderma lung disease with a low serum erythropoietin (sEPO) level.

## Case Report

A 40-year-old black male presented with blurry vision, headache, and left lower extremity pain for 3 days. He had a history of scleroderma complicated by pulmonary fibrosis and pulmonary hypertension. Admitting physical examination was notable for a cyanotic, erythematous, and mildly tender left foot. Laboratory data revealed that his hemoglobin was 22.3 g/dL, hematocrit 72.8%, white cell count 3,300/ $\mu$ L, and platelet count 199,000/ $\mu$ L. His daytime arterial oxygen pressure (PaO<sub>2</sub>) was 70 mm Hg with an oxyhemoglobin of 93% on room air by co-oximetry, while his nocturnal oxygen saturation by pulse oximetry ranged from 88–90%. His sEPO level on admission was surprisingly low at 3.3 mIU/mL (reference range: 4.2–27.8). Both leukocyte alkaline phosphatase scores and serum vitamin B<sub>12</sub> levels were within reference ranges. Pulmonary function tests indicated severe restric-

tive ventilatory defect. Chest and abdominal CT showed extensive interstitial thickening with peripheral honeycombing in bilateral pulmonary parenchyma consistent with diffuse pulmonary fibrosis, but no hepatosplenomegaly or mass lesions. A diagnosis of secondary erythrocytosis (SE) with erythromelalgia was made. In addition to supplemental oxygen, aspirin and intravenous hydration, phlebotomy was performed daily. The patient's symptoms of hyperviscosity soon improved, as his hemoglobin and hematocrit gradually lowered to 18.3 g/dL and 56.1%, respectively, after 8 sessions of phlebotomy. The patient's sEPO level was now 24.2 mIU/mL. He was discharged on continuous low-flow oxygen therapy. Follow-up hemoglobin and hematocrit 10 months later were stable at 18.6 g/dL and 56.4%, respectively, with an sEPO level of 71.4 mIU/mL.

## Discussion

Our patient had an unusually high hemoglobin level at presentation. Extensive evaluation substantiates our initial impression that he had an acquired erythrocytosis secondary to his underlying scleroderma lung disease. Despite the initial "inappropriately" low sEPO value, polycythemia vera (PV) was unlikely, since both leukocyte alkaline phosphatase and vitamin B<sub>12</sub> levels were normal, and the patient did not have splenomegaly or leukocytosis nor thrombocytosis.

Although a polycythemia vera study group did not include a low sEPO level as one of the diagnostic criteria for PV, measurement of sEPO has since been embraced in the polycythemia work-up (1, 2). Generally, sEPO levels in PV are low, while those in SE are expected to be high since SE is a hypoxia-induced, EPO-driven process. However, using sEPO measurement alone provides a poor sensitivity in diagnosing either PV or SE, due to the considerable overlap of the sEPO values in dif-

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ferent erythrocytoses (1, 2). About half of the patients with either PV or SE could have an sEPO level well within reference ranges. Moreover, even though the specificity of a low sEPO level in diagnosis of PV is extremely high, false-positives can occur, as in this case and those reported by others (1, 2). Low sEPO values in the setting of SE are usually associated with high hemoglobin levels. This underscores the need for a repeat determination of sEPO values when treatment lowers the hemoglobin. In our case, the sEPO levels rebounded from a low pretreatment level to a high normal level after phlebotomy, and became elevated 10 months later, while the hemoglobin remained stable. These observations suggest that there is a built-in negative feedback control for regulating sEPO production, and this control mechanism appears to remain intact even at high hemoglobin levels. Thus, hypoxia at tissue and cellular levels would initiate a cascade of intracellular events leading to an increased production of sEPO, which in turn expands the red cell mass (RCM); the resultant elevation of oxygen delivery would then correct the hypoxia and turn off the triggering stimulus.

Although RCM is probably a more sensitive gauge of erythropoietin stimulation, clinically, hematocrit is often used as a surrogate for RCM because of their linear relationship (3). Increased hematocrit, especially if >60%, is usually associated with an increase in RCM. However, in patients with hypoxic lung disease, RCM can be misrepresented by hematocrit or hemoglobin because plasma volume tends to expand due to complicating pulmonary hypertension and/or right heart failure (4). Therefore, high normal hemoglobin levels in our case may be deceiving and the RCM may well be elevated, which would be consistent with the elevated level of sEPO.

Given the extent of pulmonary involvement and the erythrocytosis in this patient, normoxemia at rest was unexpected and initially puzzling. In general, hypoxemia and RCM are linearly related in normal people (3). However, in patients with chronic hypoxic lung disease, the degree of hypoxemia does not always correlate well with RCM. This poor association is not completely understood. Hypoxemia is often determined by isolated "snapshots" of arterial oxygen percent saturation (SaO<sub>2</sub>) or PaO<sub>2</sub>, which probably do not reflect overall oxygenation accurately in this group of patients. This point is supported by the observation that, despite adequate arterial oxygen saturation during wakefulness at rest, patients with chronic interstitial lung disease (ILD) can have brief, recurrent episodes of hypoxemia during sleep or after vigorous exercise (5). In addition, poly-

cythemic patients with hypoxic lung disease were reported to have more severe and more frequent hypoxemia than their nonpolycythemic counterparts did (6). These findings indicate that transient hypoxemic episodes during sleep and exertion are pathophysiologically relevant, and can be a robust stimulus for EPO-mediated erythropoiesis (7).

It is interesting to note that sEPO levels in our patient stayed elevated, even though his hemoglobin remained at normal high levels, and his hypoxia was presumably corrected with continuous supplemental oxygen. It is possible that even in patients receiving continuous low-flow oxygen therapy, situational hypoxemia during sleep and exertion (or due to occasional medical noncompliance) can still occur. Furthermore, while extremely high hemoglobin is a potent suppressor for sEPO production, leading to a low or normal sEPO level via negative feedback, high normal or marginally elevated hemoglobin is not. Therefore, if these intermittent periods of nocturnal or exercise-induced desaturation continue to exist, sEPO levels can remain high.

## Conclusion

Patients with chronic ILD complicated by erythrocytosis could have a low sEPO value and normal resting arterial oxygen saturation that may misleadingly suggest a diagnosis of PV. A repeat sampling of sEPO and monitoring of oxygen saturation during sleep and exertion may help to clarify the diagnosis. Practicing physicians should prescribe continuous oxygen therapy for patients with chronic ILD and erythrocytosis, even in the absence of diurnal resting hypoxemia.

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