

β -Thalassemia Minor and Newly Diagnosed Polycythemia Rubra Vera in a 71-Year-Old Woman

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β -Thalassemia minor and polycythemia rubra vera (PRV) are hematologic disorders that give opposite results on some blood laboratory studies. Beyond this case report, only one other instance of the simultaneous occurrence of β -thalassemia minor and PRV within a patient has been reported.¹ When these conditions occur together within a patient, the effects of one of the disorders can blunt the effects of the other, rendering a physician less able to make a timely diagnosis of one or both of the disorders. This article describes a patient with a history of β -thalassemia minor and newly diagnosed coronary artery disease and PRV. The effects of the PRV had been somewhat masked by the patient's β -thalassemia minor; in effect, results from the patient's cardiac evaluation led to her PRV being discovered. In addition to this case presentation, the pathophysiology, diagnosis, and treatment of β -thalassemia minor and PRV are discussed.

CASE PRESENTATION

Initial Patient Presentation

A 71-year-old white woman was referred to our hematology clinic for evaluation, owing to abnormal results obtained on a complete blood count (CBC), which was performed as part of an evaluation for coronary artery disease. Her previous medical history included hypertension, β -thalassemia minor, hyperlipidemia, and 3 spontaneous abortions. Anemia during her pregnancies had required her to undergo blood transfusion therapy.

Previous Cardiac Evaluation

One month prior to her visit to our clinic, she had been referred to a cardiologist by her primary care physician, because of her complaint of exertional chest pressure and dyspnea. The discomfort radiated to her shoulder and back and was relieved by rest. At the cardiologist's office, an electrocardiogram showed an inferior infarct of undetermined age. An echocardiogram

showed an ejection fraction of 60% and possible diastolic dysfunction. The patient also underwent a cardiac catheterization, which showed severe triple vessel disease, an arterial oxygen saturation of 96%, inferior wall hypokinesis, and an ejection fraction of 53%. Also, abnormal results were obtained on a CBC. She was started on a medical regimen for ischemic heart disease and was referred to our hematology clinic owing to the CBC results. **Table 1** lists various laboratory results obtained during her visit to the primary care physician and the cardiologist and during her initial and follow-up visits to our clinic.

Hematologic Evaluation

It was 2 weeks after her catheterization that she was evaluated at our clinic. An initial interview did not reveal any additional pertinent history. She was 5'2" and 190 lb, and the results of her physical examination were grossly normal. The patient's peripheral blood smear was reviewed and showed microcytosis, some polychromatophilia, target cells, and a slightly elevated platelet count. An additional CBC performed at our clinic showed the following: leukocyte count, $14 \times 10^3/\text{mm}^3$ (normal, $5\text{--}10 \times 10^3/\text{mm}^3$); hemoglobin, 15.6 g/dL (normal, 12.0–16.0 g/dL); hematocrit, 48.1% (normal, 37%–47%); platelets, $486 \times 10^3/\text{mm}^3$ (normal, $150\text{--}400 \times 10^3/\text{mm}^3$); mean corpuscular volume, 65 fL (normal, 82–99 fL); red cell distribution width, 17.2% (normal, 11.5%–14.5%). Her total erythrocyte volume was 2365 mL, which is elevated for her age and weight. (For the patient's age and weight, the upper limit of normal was calculated at 2104 mL.) The following laboratory results from evaluations at her primary care physician, the cardiologist, and our clinic

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Table 1. Results of Case Patient's Blood Laboratory Studies

Component Measured	Reference Value	7/17/97*	8/7/97†	8/23/97‡	11/6/97§	1/2/98	10/19/98¶	12/2/98#
Leukocytes (cells/mm ³)	5–10 × 10 ³	12.5 × 10 ³	14.5 × 10 ³	14.0 × 10 ³	13.6 × 10 ³	16.7 × 10 ³	15.6 × 10 ³	18.6 × 10 ³
Hemoglobin (g/dL)	12–16	15.7	16.0	15.6	13.3	14.3	16.0	15.0
Hematocrit (%)	37–47	50.00	49.80	48.10	42.60	46.20	48.50	51.00
MCV (fL)	82–99	66.3	65.6	65.0	61.5	57.8	56.9	57.6
Erythrocytes (cells/mm ³)	4.2–5.4 × 10 ⁶	7.54 × 10 ⁶	7.58 × 10 ⁶	7.39 × 10 ⁶	6.92 × 10 ⁶	7.97 × 10 ⁶	8.53 × 10 ⁶	8.86 × 10 ⁶
RDW (%)	11.5–14.5	17.0	16.7	17.2	17.7	20.9	23.7	21.4
Platelet count (cells/mm ³)	150–400 × 10 ³	385 × 10 ³	—	486 × 10 ³	536 × 10 ³	545 × 10 ³	540 × 10 ³	616 × 10 ³
Hg A ₂ (%)	2.1–3.2	—	—	5.50	—	—	—	—
Retic Ct (%)	0.3–2.0	—	—	4.10	—	—	—	—
Retic Ct (corr.) (%)	0.3–2.0	—	—	4.10	—	—	—	—
Erythropoietin (mU/mL)	4.2–27.8	< 1.4	—	—	—	—	—	—
PT (s)	11.5–15.0	—	—	10.6	—	—	—	—
PTT (s)	24–36	—	—	32	—	—	—	—
INR	0.8–1.2	—	—	1.0	—	—	—	—
B ₁₂ (pg/mL)	199–732	—	—	705	—	—	—	—
LAP (U/L)	89–135	—	—	161	—	—	—	—
Uric acid (mg/dL)	2.5–6.8	—	—	—	—	—	7.9	—

B₁₂ = cyanocobalamin (vitamin B₁₂); Hg A₂ = hemoglobin A₂; INR = international normalized ratio; LAP = leukocyte alkaline phosphatase; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RDW = red cell distribution width; Retic Ct = reticulocyte count; Retic Ct (corr.) = reticulocyte count corrected.

*Visit to primary care physician.

†Visit to cardiologist.

‡Visit to hematology clinic.

§Follow-up at hematology clinic 1 month after phlebotomy was discontinued.

||Further follow-up at hematology clinic.

¶Further follow-up at hematology clinic. Patient experienced bilateral parietal headaches and dyspnea. Phlebotomy was then restarted.

#Further follow-up at hematology clinic 6 weeks after the removal of 2 units of blood.

Reference data from the main laboratory of The Ohio State University Medical Center, Columbus, OH.

were enough to yield a diagnosis of PRV: a low erythropoietin level (primary care physician visit); normal room air arterial oxygen saturation and elevated leukocyte alkaline phosphatase level (cardiologist visit); and erythrocytosis, thrombocytosis, and an elevated total erythrocyte volume (hematology clinic visit). Hemo-

globin electrophoresis was performed and showed a normal phenotype AA, no evidence of abnormal hemoglobin molecules, a slight elevation of hemoglobin F (fetal hemoglobin) and hemoglobin A₂, and an elevated reticulocyte count—all of which are supportive of a diagnosis of β-thalassemia minor.

Management

Therapy for PRV was initiated the first week of September 1997. The goal was to reduce her hemoglobin level and hematocrit, thereby reducing blood viscosity to allow better perfusion of her severely diseased coronary vessels. The therapy consisted of weekly phlebotomy of 1 unit of blood to achieve a hemoglobin concentration of 13 g/dL. After a total of 4 units of blood were removed over a 1-month period, her hemoglobin fell to 12.8 g/dL (data not shown on Table 1). Phlebotomy was then discontinued. One month after stopping phlebotomy, the patient's hemoglobin level was 13.3 g/dL (Table 1), and she stated that she was feeling well with no complaints of chest pressure or dyspnea. Her hemoglobin level continued to rise slowly, increasing from 14.3 g/dL in January of 1998 to 16.0 g/dL in October of 1998. During this time her erythrocyte count increased as well. In October of 1998, she reported experiencing bilateral parietal headaches and a return of her chest pressure and dyspnea. Phlebotomy was restarted, and 6 weeks after the removal of 2 units of blood, 2 weeks apart, a blood count showed a hemoglobin level of 15.0 g/dL. The patient reported no complaints or symptoms at that point. There were no changes to her medical regimen for coronary artery disease since its initiation in early August 1997, supporting the theory that it was the phlebotomy that alleviated all of her symptoms.

DISCUSSION

Thalassemia Syndromes

The thalassemia syndromes are a group of hereditary hemolytic anemias characterized by altered synthesis of the globin chains of the hemoglobin molecule. Normal adult hemoglobin (hemoglobin A) is a tetramer of 2 α and 2 β globin chain molecules ($\alpha_2\beta_2$). Mutations in the genes involved in the synthesis of a globin chain can lead to a reduction in the rate of synthesis of a chain or the termination of production of that chain.² Because there is normally a 1-to-1 binding relationship between an α and β chain, a reduction in the production of one (or the termination of the production of one) will result in a relative overabundance of the other. When unbound to its normal partner, the free globin chain forms aggregates with molecules of its same type. These aggregates precipitate out in the cytoplasm causing oxidative and structural damage to the cell membrane. These abnormal erythrocytes are then eliminated by the reticuloendothelial system in the spleen, and this leads to anemia of varying degrees, which is the main manifestation of the thalassemia syndromes. Thalassemia syndromes are probably the most

common genetic disorder throughout the world and are most prevalent in the Mediterranean basin and equatorial and near-equatorial regions of Asia and Africa.

β -Thalassemia

Abnormal genes leading to β -thalassemia are carried by close to 3% of the world's population and have the highest prevalence among inhabitants of Italy and Greece. There are at least 150 different mutations that result in β^0 (the absence of the β globin chain) or β^+ (reduction in output).^{2,3} Individuals with 1 abnormal allele (whether β^0 or β^+) have β -thalassemia minor. Those with 2 abnormal alleles have β -thalassemia major. The reduction in, or termination of, production of the β globin chain results in the aggregation and subsequent precipitation of unpaired α -globin chains. These precipitates are toxic to the erythrocyte membrane and lead to the elimination of the cell via the reticuloendothelial system in the blood and bone marrow.

β -Thalassemia minor (also known as β -thalassemia trait) is a codominantly inherited disorder in which the rate of synthesis of the β globin chain of hemoglobin molecules is reduced. β -Thalassemia minor is a more benign disease than β -thalassemia major and is characterized by microcytosis, a lesser degree of hemolysis, and a hemoglobin A level approximately 1 to 2 g below the normal range.

Signs and symptoms. Homozygotes for β -thalassemia often present with severe anemia that requires them to undergo transfusion therapy. Splenomegaly, bone changes caused by marrow expansion (which can lead to the so-called "chipmunk face"), and a predisposition to infection are also common findings. Extramedullary hematopoiesis can result in hepatosplenomegaly, sometimes leading to hypersplenism and cytopenias.

With regard to β -thalassemia minor, there is mild anemia. Even with this mild anemia, however, patients will often complain of weakness and fatigue of varying degrees.

Diagnosis. Hemoglobin electrophoresis on blood samples from homozygotes for β^0 shows a complete absence of hemoglobin A, low levels of hemoglobin A₂, and mostly hemoglobin F. When performed on blood samples from homozygotes for β^+ , it shows more variable levels of hemoglobin F, around 70%.

In general, a heterozygote for β -thalassemia is diagnosed owing to the patient presenting with a mild anemia (hemoglobin A level 1 or 2 g below normal range), low mean cell volume, low mean corpuscular hemoglobin, elevated hemoglobin A₂, and normal or elevated hemoglobin F. During pregnancy, women

with β -thalassemia minor will often show more significant anemia, which is often most prominent during the latter half of the second trimester and early third trimester.

Treatment. Treatment of β -thalassemia major consists of frequent erythrocyte transfusions for the anemia and iron chelation therapy, to avoid the complications of iron overload.^{2,4} With thalassemia syndromes, there is enhanced gastrointestinal absorption of iron. With this and frequent transfusions, patients are at risk for developing problems with iron overload. Thus, iron therapy is contraindicated in β -thalassemia major.⁵ Patients with β -thalassemia minor, however, usually do not require frequent transfusions and have very little need for iron chelation therapy.

Iron replacement can be used with success in pregnant patients with β -thalassemia minor to reduce the severity of the anemia. Normal development of the fetus during pregnancy and the formation of fetal hemoglobin requires iron, which is acquired from the mother's storage pool. With the normal female storage pool of iron being approximately 500 mg, about 1000 mg of additional iron is required, taking into account potential blood loss from birth. In addition, there is a high concentration of transferrin receptors, which bind and transport iron, in the trophoblastic membranes of the placenta.⁶ However, the erythrocytosis is often made worse by iron deficiency.^{7,8} Iron replacement therapy is rarely needed in nonpregnant patients with β -thalassemia minor.

The standard procedure for treatment of patients with β -thalassemia minor involves transfusions when required for symptoms and worsening anemia. However, young children requiring regular transfusions (which would be the case more for β -thalassemia major than minor) can often develop iron overload with associated growth failure and disrupted sexual maturation.

Polycythemia Rubra Vera

PRV is a clonal disorder of hematopoietic stem cells characterized by an absolute elevation in the total body erythrocyte volume. PRV, also known as Vasquez-Osler disease, was originally reported by Vasquez in 1892.⁹ The disease was more clearly defined by Osler in 1903.¹⁰ In 1951, Dameshek placed PRV in a group of diseases called the myeloproliferative syndromes along with essential thrombocytosis, agnogenic myeloid metaplasia (myelofibrosis), and chronic myelocytic leukemia.¹¹ Leukocytosis and/or thrombocytosis often accompany erythrocytosis in PRV. PRV is more common in the sixth and seventh decades of life, but there

are reports of the disease in younger patients.^{12,13} Median survival appears to be greater than 10 years in treated patients and about 18 months in untreated patients.¹⁴ There is no single causal factor in the development of this disease. The cause appears to be multifactorial, and the question of a definite genetic link remains unanswered. The incidence has been reported to be higher in residents of Japan who are survivors of the atomic bomb explosion in 1945¹⁵ and among United States military personnel who participated in the detonation of a nuclear device in 1957.¹⁶ Both groups had close to a 20-fold increase in the incidence of PRV as compared with the general public.

Signs and symptoms. Manifestations of the disease include an apparent increase in the incidence of both thrombotic and hemorrhagic events, including deep venous thrombosis of the lower extremity; pulmonary embolism; stroke; coronary and peripheral vascular occlusions; mesenteric, splenic, hepatic, and portal vein thromboses; and Budd-Chiari syndrome.¹⁷⁻¹⁹ Bleeding and thrombosis can occur together within a patient. Symptomatic complaints can include headache, weakness, pruritus, dizziness, excess sweating, and visual disturbances. The most common findings include conjunctival plethora, splenomegaly, hepatomegaly, ruddy cyanosis, and hypertension. Myocardial infarction and sudden death can occur in older and younger patients with underlying coronary artery disease.²⁰⁻²³

Diagnosis. Abnormal hemoglobin and hematocrit are the most common presentations of PRV. However, nonmalignant conditions causing an elevation of the hemoglobin/hematocrit, including cyanotic heart disease, chronic lung disease, and smoker's polycythemia, must be ruled out. This can be accomplished by an arterial blood gas analysis showing a normal oxygen saturation on room air. An increased total erythrocyte volume with increased plasma volume must also be demonstrated for the diagnosis of PRV. Erythropoietin level is typically low in patients with PRV. In PRV, hematopoietic stem cells show increased sensitivity to exogenous erythropoietin, hence the low level. The spleen can be evaluated by physical examination; for uncertain cases splenic ultrasound is the test of choice. In addition, an elevated leukocyte alkaline phosphatase, uric acid, vitamin B₁₂ and B₁₂-binding capacity can be present.

Treatment. Therapeutic options include phlebotomy, oral chemotherapy with chlorambucil or hydroxyurea, and intravenous radioactive phosphorus (³²P). Phlebotomy can be performed every other day, if needed, but in elderly patients with comorbid conditions, it

should be performed less frequently and/or with smaller volumes being removed. Phlebotomy addresses the issue of increased total erythrocyte volume, but it does not influence the underlying clonal disorder. Patients with a previous history of thrombosis or who require very frequent phlebotomy, with minimal response, should be treated with chemotherapy or ³²P. Studies by the Polycythemia Vera Study Group demonstrated a significant increase in the incidence of acute leukemia and lymphocytic lymphoma after certain chemotherapy treatments, particularly in patients treated with chlorambucil.²⁴ In patients with PRV, there is a chance that the disease will progress to myelofibrosis or transform into acute leukemia, with or without treatment. Most patients with PRV are iron deficient and iron can be used to reduce some of the symptoms of PRV, but it will often worsen the erythrocytosis.²⁵

Discussion of Case Patient

β -Thalassemia minor and PRV occurring simultaneously in a patient has only been reported once before in the literature.¹ The patient presented in this report gave a history of microcytic anemia thought to be related to β -thalassemia minor. We confirmed this with a review of the peripheral blood film, which demonstrated microcytosis and target cells, and by hemoglobin electrophoresis, which showed a normal phenotype, increased hemoglobin A₂, and increased hemoglobin F. Laboratory values from our initial evaluation revealed leukocytosis, microcytosis, erythrocytosis, thrombocytosis, an elevated red cell distribution width, and an elevated leukocyte alkaline phosphatase, suggesting the diagnosis of PRV. A measurement of her total erythrocyte volume, revealing an elevated erythrocyte volume based on her age and body weight; a previously obtained erythropoietin level; and normal room air arterial oxygen saturation helped confirm the diagnosis of PRV.

After 4 units of blood were removed over a 1-month period, her hemoglobin level fell to 12.8 g/dL, but she maintained an increased erythrocyte count. This shows that despite a reduction in total hemoglobin and removal of erythrocytes through phlebotomy, there remained a large number of circulating erythrocytes, in relation to the PRV. However, with the low-grade hemolysis resulting from precipitation of unpaired α -globin chains in association with the β -thalassemia minor, the often substantial elevations in hemoglobin and hematocrit seen in PRV were probably blunted. In the same regard, the low-grade anemia of β -thalassemia was not seen because of the overproduction of erythrocytes and hypersensitivity to erythropoietin found in PRV. Perhaps

the clonal proliferation from the PRV was enough to slowly override the low-grade erythrocyte destruction from the β -thalassemia minor. Had β -thalassemia major been present, there may have been a slow decline in the hemoglobin and hematocrit because of more rapid erythrocyte destruction.

After the initial phlebotomy series and reduction in hemoglobin, her symptoms improved. As time passed and her hemoglobin/hematocrit increased, some of her symptoms returned. Once phlebotomy was restarted, her symptoms resolved. There were no changes to her medical regimen for coronary artery disease since her evaluation in our clinic. We conclude that the phlebotomy program was enough to reduce her blood viscosity and allow better coronary artery perfusion, and was responsible for the elimination of her symptoms.

The patient's heart disease is a separate issue. Neither β -thalassemia minor nor PRV caused her to develop triple vessel disease. However, the elevated hematocrit and erythrocyte number probably did make her symptoms more pronounced because of the increased blood viscosity. As we demonstrated by repeat phlebotomy (October 1998), we were able to alleviate symptoms without a change in her medication regimen.

CONCLUSION

PRV is a clonal proliferation at the level of the hematopoietic stem cell, resulting in erythrocytosis, often with leukocytosis and thrombocytosis. Hypertension, cardiac symptomatology, thrombosis, bleeding, or simply an abnormal CBC can be presenting signs and symptoms. An increased plasma and erythrocyte volume and erythrocytosis with normal room air arterial oxygen saturation are necessary to make the diagnosis. In PRV, there is overproduction of erythrocytes and other blood cell components, as well. β -Thalassemia minor is characterized by a reduced production of β -globin chains, normal hemoglobin phenotype, elevated hemoglobin A₂, elevated hemoglobin F, mild anemia caused by low-grade hemolysis, and enhanced iron absorption from the gastrointestinal tract.

β -Thalassemia minor and PRV can be thought of as 2 indirectly opposing processes. PRV causes overproduction of erythrocytes, and β -thalassemia minor causes low-grade reduction in hemoglobin and hematocrit by erythrocyte destruction. In the patient presented, these 2 entities were present at the same time. Apparently, the PRV was significant enough to cause a slow increase in hemoglobin and hematocrit to a point where symptoms developed. When the erythrocyte number and hemoglobin concentration were reduced

by phlebotomy, symptoms disappeared only to recur in the future as erythrocyte number and hemoglobin concentration increased. It is quite possible that the PRV was significant enough to not be offset by the low-grade hemolysis of the β -thalassemia minor. For the long term, therapy with chemotherapy (oral hydroxyurea) or intravenous ^{32}P could be considered if the patient develops a blood clot or requires phlebotomies too frequently. As with all myeloproliferative syndromes, the patient presented in this report does have a small risk of developing acute leukemia.

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