

Recurrent Thromboembolic Disease Following Splenectomy for Pyruvate Kinase Deficiency

Roger Chou^{1*} and Thomas G. DeLoughery²

¹Department of Medicine, Portland Veteran's Affairs Medical Center, Oregon Health Sciences University, Portland, Oregon

²Department of Medicine, Division of Hematology and Medical Oncology, Oregon Health Sciences University, Portland, Oregon

We report a case of recurrent thromboembolic disease and chronic pulmonary hypertension in an adult patient with pyruvate kinase deficiency who underwent splenectomy as a child. Thromboembolism has been reported as a complication following splenectomy for various hereditary chronic hemolytic anemias. To our knowledge, this association has not been described in patients specifically with pyruvate kinase deficiency. Our patient presented at age 37 with recurrent pulmonary emboli, 36 years after splenectomy for severe hemolytic anemia. Work-up for other hypercoagulable states was negative. The mechanism for hypercoagulability in this condition is unclear but may involve a quantitative or qualitative change in disrupted thrombogenic red blood cell membranes that would normally be removed by the spleen. Clinicians should have a high index of suspicion for thrombotic events in these patients, as early diagnosis and treatment can reduce morbidity and mortality, and chronic anticoagulation may help prevent the sequelae of repeated thromboembolic events. *Am. J. Hematol.* 67:197–199, 2001.

© 2001 Wiley-Liss, Inc.

Key words: pulmonary embolism; thrombosis; splenectomy; pyruvate kinase; hemolytic anemia

INTRODUCTION

Pyruvate kinase deficiency as a cause of hereditary nonspherocytic hemolytic anemia was first described by Valentine et al. in 1961 [1]. Although a rare disease, it is the most common erythroenzymopathy of the glycolytic pathway, with well over 300 cases described [2]. The clinical course varies widely, but transfusions are often needed for patients with severe disease as well as for those whose baseline well-compensated hemolysis is exacerbated by infection, pregnancy, or other stressors [3]. Splenectomy, although not curative, may be performed in order to ameliorate the anemia and reduce the need for repeated transfusions [4]. Thromboembolism has been reported as a complication following splenectomy performed for numerous disorders, including various hereditary chronic hemolytic anemias [5–8]. To our knowledge, this association has not been described in patients specifically with pyruvate kinase deficiency. We describe a case of recurrent thromboses in an adult patient with pyruvate kinase deficiency who underwent splenectomy as a child.

CASE REPORT

The patient is an adopted 37-year-old white female (family history unknown) who presented to this hospital with increasing dyspnea on exertion. Review of her past history showed that shortly after her birth in August 1960, she was noted to have a non-spherocytic hemolytic anemia (hematocrit as low as 15%), with a normal MCV and differential. At that time, Coombs direct and indirect tests, red cell osmotic fragility test, glucose-6-phosphate dehydrogenase assay, hemoglobin electrophoresis, starch block electrophoresis, acid hemolysis test, and fetal hemoglobin level were all normal. Bone marrow biopsy showed marked erythroid hyperplasia, and ⁵¹Cr-labeled red blood cell test revealed markedly decreased survival time with increased splenic sequestration.

Throughout infancy, the patient suffered frequent he-

*Correspondence to: Roger Chou, 9721 SW Morrison St., Portland, OR 97225. E-mail: chou@ohsu.edu

Received for publication 16 June 2000; Accepted 31 January 2001

molytic crises requiring transfusions. She underwent elective splenectomy in July 1961, and afterward had an initial mild increase in hematocrit with subsequent return to baseline levels (24%–28%), marked reticulocytosis (20%–60%), and normal platelet counts. In April 1962 the patient had a pyruvate kinase assay of 1.553 units (reference normal value 8–10, assay performed at Oregon Health Sciences University by Dr. Robert Koler), confirmed by 1-month repeat testing. The patient was diagnosed with homozygous erythrocyte pyruvate kinase deficiency.

The patient required less frequent transfusions as she grew older. Her hematocrit was stable, reticulocyte counts remained elevated, and at baseline she had 30–60 nucleated RBC/100 WBC. In March 1991 (age 30) she presented with extensive right greater saphenous vein superficial thrombophlebitis, which was treated with nonsteroidal anti-inflammatory agents and heat. Two weeks after her initial presentation, she was admitted to the hospital with increasing shortness of breath and mild hypoxia. Duplex ultrasound showed an extensive thrombus in the right common femoral and proximal external iliac veins. A high-probability ventilation–perfusion scan with multiple bilateral segmental and subsegmental mismatched perfusion defects was obtained. The patient was treated with intravenous heparin followed by 6 months of coumadin and had no clinical evidence of recurrence. Her only identifiable possible hypercoagulable risk factor was the use of oral contraceptives, which were discontinued. Antithrombin III, protein C, and protein S assays were within normal limits.

The patient presented again in January 1998 with a 3-month history of subacutely worsening dyspnea on exertion. She denied recent illness, chest pain, cough, or symptoms suggestive of deep vein thrombosis. She had no new identifiable risk factors for hypercoagulability. Her medications were folate, enalapril, and metered dose inhalers for asthma. Her initial room air saturation was 86%, and arterial blood gas on room air showed pH 7.42, $p\text{CO}_2$ 27, and $p\text{O}_2$ 58. She was jaundiced and dyspneic with minimal exertion but had no signs of overt heart failure or deep venous thrombosis, and her lung exam was normal. Total bilirubin was 6.4, lactate dehydrogenase 815, white blood cell count 22,000 with hematocrit 25% and platelets 142,000. Over the year prior to admission, platelet counts ranged from 435,000 to 492,000. Peripheral smear on admission showed 57% neutrophils, 6% monocytes, 33% lymphocytes, 4% monocytes, 47% reticulocytes, moderate anisocytosis, moderate macrocytosis, and marked polychromasia. Initially she had 398 nucleated RBC/100 WBC, increasing to 692 NRBC/100 WBC by day 2 of admission. Over the year prior to admission, she had 27–53 NRBC/100 WBC. Chest radiograph showed large central pulmonary vessels.

One day after admission, the patient reported acutely

worsening shortness of breath accompanied by desaturation to 80% on room air. A helical chest computed tomography scan revealed a large filling defect at the bifurcation of the right main pulmonary artery, consistent with acute pulmonary embolism, as well as several smaller defects in the segmental branches consistent with chronic pulmonary emboli. The patient was placed on intravenous heparin, and her hypoxemia gradually improved. She did not develop signs of acute right ventricular failure. Homocysteine level, partial thromboplastin time, fibrinogen level, and antithrombin III level were all normal. Tests for activated protein C resistance, lupus inhibitor, anticardiolipin antibody, and red blood cell sucrose lysis test were negative. A ventilation–perfusion scan prior to discharge revealed numerous large bilateral segmental and subsegmental mismatched perfusion defects. Although some were present on prior scan performed March 1991, new perfusion defects were also noted.

One month after discharge the patient was near baseline in terms of dyspnea. Follow-up ventilation–perfusion scanning in February 1998 and April 2000 showed persistent perfusion defects without changes. Echocardiogram in April 2000 estimated right ventricular systolic pressure at 95 mm. Prothrombin 20210A gene mutation test was negative, and factor XI assay was normal. She is being maintained on chronic lifelong anticoagulation and continuous supplemental oxygen because of desaturations below 90% with minimal activity. She is currently being considered for pulmonary thromboendarterectomy.

DISCUSSION

The hereditary hemolytic anemias are a heterogeneous group of disorders that can result from hemoglobinopathies, red cell membrane defects, or enzymopathies [9]. Alone, the hereditary hemolytic anemias are not associated with a hypercoagulable state. Over 30 years ago, however, Hirsh and Dacie observed an increased propensity toward thrombosis in post-splenectomy patients with chronic hemolysis, particularly when the anemia fails to respond to the surgery [10,11]. This observation has subsequently been corroborated by numerous reports of post-splenectomy thromboses in patients with hereditary hemolytic anemias. One report described eight patients with hereditary spherocytosis who had thrombotic events, including one with recurrent pulmonary emboli [6]. Another described nine patients with hereditary stomatocytosis who had thrombotic complications following splenectomy, with three developing pulmonary hypertension from chronic pulmonary thromboembolism [8]. Other vascular and thrombotic phenomena that have been described in patients following splenectomy for hereditary hemolytic anemia include priapism, arterial

thrombosis, portal vein thrombosis, and superior mesenteric vein thrombosis [5,8,12].

Our patient has a well-documented diagnosis of pyruvate kinase deficiency made as an infant. Although splenectomy is commonly performed for this condition, an association with subsequent thrombotic events has not been previously described. Our patient initially presented with superficial thrombophlebitis, deep venous thrombosis, and pulmonary embolism in 1991, and had recurrent acute pulmonary embolus with evidence of chronic thromboembolic pulmonary disease seven years later. As in many of the previous case reports for patients with other hereditary hemolytic anemias, the thrombotic phenomena occurred many years after splenectomy [5,6,8]. In our patient, the work-up for acquired or inherited hypercoagulable states has been negative, and she did not develop significant thrombocytosis following splenectomy. She was taking oral contraceptives at the time of her first documented thrombotic event but has not been on them subsequently.

The mechanism for thrombophilia following splenectomy in patients with hereditary hemolytic anemias remains unclear. Though there appears to be some correlation with the degree of thrombocytosis, there is also evidence of increased platelet adhesiveness following splenectomy even with normal platelet counts [11]. In our patient, platelet counts prior to this presentation were only marginally elevated. Our patient did have extremely high levels of nucleated red blood cells during this hospitalization, a factor that has been postulated to contribute to a hyperviscous state [13]. Over the year prior to this presentation, however, nucleated red blood cell counts were only moderately elevated, suggesting that the very high levels were a response to hypoxia or some other stress rather than a cause of recurrent thromboembolism. Low levels of protein C, protein S, and anti-thrombin III have been described in some cases, but none of these deficiencies were present in our patient [5,8]. It is possible that one of the newly characterized hypercoagulable states, for which investigations were not performed in previous case reports, could be a factor. In our patient, however, the prothrombin gene mutation test and the factor XI assay were both normal. Finally, disrupted red blood cell membranes may cause either a qualitative or quantitative change in surface thrombogenic phospholipids [6–8]. Although other chronic hereditary hemolytic anemias associated with post-splenectomy thrombosis involve red blood cells with potentially thrombogenic structural defects, pyruvate kinase deficiency does not

appear to be associated with similar defects (no Heinz bodies). Post-splenectomy thromboembolism in patients with pyruvate kinase deficiency suggests that chronic hemolysis alone might trigger thrombosis by exposing thrombogenic inner red cell membranes, which would normally be removed by the spleen.

In summary, we present a case of a patient with pyruvate kinase deficiency who underwent splenectomy as a child and has developed recurrent thrombotic events as an adult. A similar association has been noted in patients with other hereditary hemolytic anemias following splenectomy. Clinicians should have a high index of suspicion for thrombotic events in these patients, as early diagnosis and treatment can reduce morbidity and mortality, and chronic anticoagulation may help prevent the sequelae of repeated thromboembolic events.

REFERENCES

1. Valentine WN, Tanaka KR, Miwa S. A specific erythrocyte glycolytic enzyme defect (pyruvate kinase) in three subjects with congenital nonspherocytic hemolytic anemia. *Trans Assoc Am Phys* 1961;74:100–110.
2. Tanaka KR, Zerez CR. Red cell enzymopathies of the glycolytic pathway. *Semin Hematol* 1990;27:165–185.
3. Valentine WN, Tanaka KR, Paglia DE. Hemolytic anemias and erythrocyte enzymopathies. *Ann Intern Med* 1985;103:245–257.
4. Nathan DG, Oski FA, Miller DR, Gardner FH. Life-span and organ sequestration of the red cells in pyruvate kinase deficiency. *N Engl J Med* 1968;278:73–81.
5. Bertolotti M, Loria P, Martella P, Carulli L, DeSantis M, Carulli N. Bleeding jejunal varices and portal thrombosis in a splenectomized patient with hereditary spherocytosis. *Dig Dis Sci* 2000;45:373–377.
6. Hayag-Barin JE, Smith RE, Tucker FC. Hereditary spherocytosis, thrombocytosis, and chronic pulmonary emboli. *Am J Hematol* 1998; 57:82–84.
7. Kemahli S, Canatan D, Cin S, Uysal Z, Akar N, Arcasoy A. Post-splenectomy thrombosis and haemolytic anaemias. *Br J Haematol* 1997; 97:504–510.
8. Steward GW, Amess JA, Eber SW, Kingswood C, Lane PA, Smith BD, Mentzer WC. Thrombo-embolic disease after splenectomy for hereditary stomatocytosis. *Br J Haematol* 1996;93:303–310.
9. Matsunaga AT, Lubin BH. Hemolytic anemia in the newborn. *Clin Perinatol* 1995;22:803–828.
10. Hirsh J, Dacie JV. Persistent post-splenectomy thrombocytosis and thrombo-embolism. *Br J Haematol* 1966;12:44–53.
11. Hirsh J, McBride JA, Dacie JV. Thrombo-embolism and increased platelet adhesiveness in post-splenectomy thrombocytosis. *Aust Ann Med* 1966;15:122–128.
12. Thuret I, Bardakdjian J, Badens C, Wajcman H, Galacteros F, Vanuxem D, Perimond H, Giraud F, Lena-Russo D. Priapism following splenectomy in an unstable hemoglobin. *Am J Hematol* 1996;51: 133–136.
13. Jackson N, Franklin IM, Hughes MA. Recurrent priapism following splenectomy for thalassemia intermedia. *Br J Surg* 1986;73:678.