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Sujit Sheth
Carrie Ruzal-Shapiro
Anne Hurlet-Jensen
Sergio Piomelli
Walter E. Berdon

Pulmonary embolism developing in patients with sickle cell disease on hypertransfusion and IV deferoxamine chelation therapy

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S. Sheth (✉) · C. Ruzal-Shapiro · A. Hurlet-Jensen · S. Piomelli · W. E. Berdon
Division of Pediatric Hematology, 180 Fort Washington Avenue, HP 5-554, New York, NY 10032, USA

Abstract Pulmonary disease, including thromboembolic problems, accounts for a large portion of the morbidity of sickle cell disease. Chronic transfusion therapy is now a part of long-term treatment of sickle cell patients with stroke and chest syndrome. The resultant iron overload must be treated with chelation therapy using deferoxamine. Poor compliance with subcutaneous chelation therapy has necessitated intravenous deferoxamine treatment. We describe two patients with sickle cell disease on such a regimen, who became hypoxic as a result of pulmonary thromboembolism, secondary to venous thrombophlebitis. The thrombophlebitis and subsequent pulmonary embolism probably reflect the hypercoagulable state seen in sickle cell and are not due to the deferoxamine therapy.

Introduction

Pulmonary complications account for a significant portion of the morbidity of sickle cell disease. As children, these individuals have episodes of pneumonia and "acute chest syndrome", and later, as adults, may have manifestations of chronic lung disease, which may progress to cor pulmonale. Chronic transfusion therapy (to reduce hemoglobin S concentration) may decrease sickling in the microvasculature, and thereby prevent such complications as acute chest syndrome and stroke from developing. However, iron overload soon develops and unless chelated, this extra iron may deposit in various organs, causing dysfunction. Chelation therapy consists of daily subcutaneous infusions of deferoxamine. Compliance with this therapy may be poor. Rising levels of ferritin often necessitate high-dose intravenous chelation therapy; central venous lines (CVL) are sometimes required for access. We report two patients with CVL, and the complication of pulmonary embolism, although the low concentration of Hb S negated the risk of developing acute chest syndrome. The thrombophlebitis and subsequent pulmonary embolism probably reflect the hypercoagulable state seen in sickle cell and are not due to the deferoxamine therapy.

Case reports

Case 1

An 18-year-old girl with sickle cell (SS) disease had a right-sided stroke in 1988 and was placed on a chronic transfusion regimen, keeping her hemoglobin S concentration below 20 %. Subcutaneous deferoxamine therapy began in August 1989. Serum ferritin levels rose gradually to 4000 ng/ml in 1994, but then rapidly increased to 8000 ng/ml in 1995, and 9000 ng/ml in 1996, probably due to poor compliance with deferoxamine therapy. A long, central venous catheter (Passport) was placed in her left arm in July 1996, and therapy with high-doses of intravenous deferoxamine was begun. She was admitted to a pediatric, long-term care facility for this therapy.

In September 1996, the patient had an acute onset of respiratory distress with concomitant swelling of her left arm. She was hypoxemic, with a saturation of 89 % in room air, which increased to 98 % on 4 l/min of oxygen. A plain chest film was negative. A duplex Doppler examination of the arms and neck showed thrombosis within the left axillary and subclavian veins; a ventilation perfusing (VQ) scan showed multiple, large perfusion defects in both lungs. Protein S, C and ATIII levels were normal. Heparin therapy was begun immediately, and the patient was transferred to the intensive care unit. The central venous line (CVL) was removed without further complication. There was no further deterioration in respiratory status, and thrombolytic therapy was not deemed necessary. MRA of the chest revealed poor flow in the

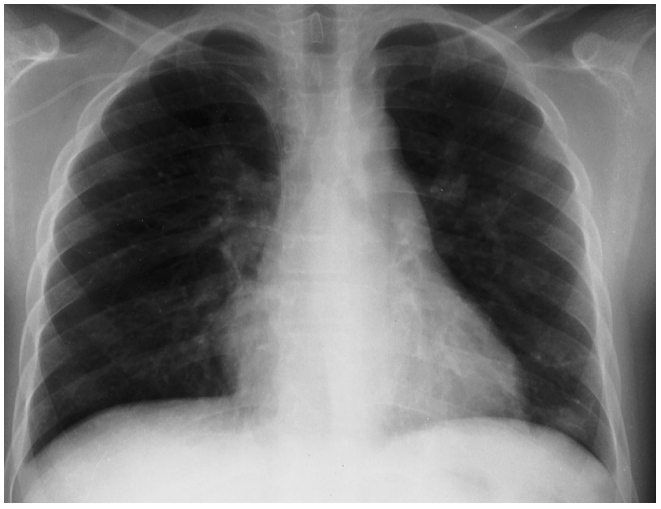

Fig. 1 CXR: Central venous access line is seen coming from the right arm with its distal tip in the superior vena cava. The film fails to show evidence of thromboembolic disease

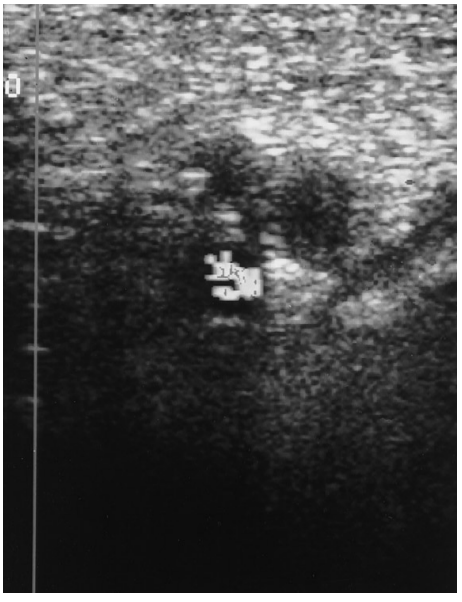

Fig. 2 Doppler US of the right subclavian vessels shows normal flow within the artery *(arrowhead),* and thrombus within the vein *(arrow)*

veins of the left upper extremity. With gradual improvement, the patient was switched to oral coumadin and discharged. Transfusion therapy and intravenous deferoxamine via peripheral veins have been continued.

Case 2

A 16-year-old boy with sickle cell (SS) disease and a thalassemia-2 trait was chronically transfused between 1982 and 1986 for splenic

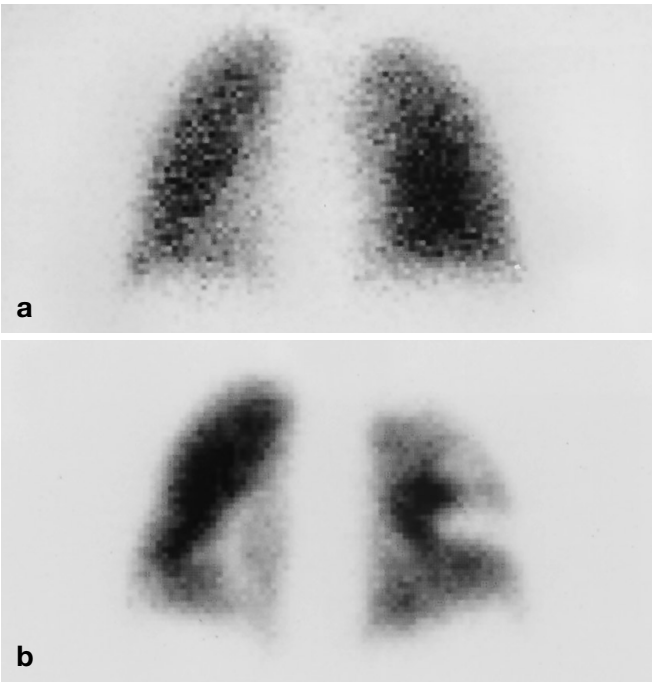

Fig. 3 **a** VQ scan, posterior view of normal ventilation. **b** VQ scan of abnormal perfusion, posterior view showing multiple predominantly right-sided wedge-shaped defects leading to the conclusion of high probability scan for pulmonary embolus

sequestration. Transfusions were stopped after splenectomy but they were resumed following several episodes of acute chest syndrome, the last one requiring ventilator support. His hemoglobin S concentration was maintained below 30 %. Chelation therapy with subcutaneous infusion deferoxamine began in 1989. Initially, the ferritin levels remained in the 2000–3000 ng/ml range, but they gradually began to rise, presumably due to poor compliance with chelation therapy, reaching 5970 ng/ml in January 1996. Though the level was reduced to 5400 ng/ml, compliance remained a problem. Intravenous high-dose deferoxamine was begun in September 1996 at a pediatric long-term care facility. A central venous catheter (Passport) was placed in his arm for this purpose.

The patient was admitted to the hospital in November 1996 with chest pain and low-grade fever. A plain chest film was negative (Fig. 1), and oxygen saturations in room air were 99 %. He quickly developed respiratory distress, and his neck veins were noted to be distended. A duplex Doppler study confirmed extensive thrombosis in the right axillary and subclavian veins (Fig. 2). A VQ scan showed multiple large segmental mismatch defects bilaterally, highly suggestive of pulmonary emboli (Fig. 3 a, b). Protein S, C and ATIII levels were normal. The patient was transferred to the intensive care unit and heparin therapy begun. The CVL was removed. With worsening chest pain and respiratory distress, systemic fibrinolytic therapy with TPA was initiated as the thrombosis was thought to be too extensive for local therapy. Repeat VQ scans showed both areas of improved and worsening perfusion, consistent with clot lysis and fragmentation. Heparin was continued for an additional 4 days and oral coumadin was then begun. Repeat duplex Doppler examination 4 days later showed no residual thrombus in the veins of the right upper extremity. Transfusion therapy was discontinued at the patient's request because of reluctance to continue with chelation therapy by any route.

Discussion

Pulmonary thromboembolic disease may occur asymptomatically in patients with sickle cell disease as they get older, contributing to the chronic restrictive lung disease that develops [1]. Changes in their VQ scans are usually irreversible. Those that develop acute chest syndromes may have symptomatic thromboembolism as a result, and it becomes difficult to interpret their VQ scans [2]. In this report, we have described yet another cause of pulmonary embolism in sickle cell patients.

A chronic transfusion regimen aimed at keeping hemoglobin S concentrations below 20 % (for patients who have had strokes) or 30 % (for those who are transfused for recurrent crises), renders most patients with sickle cell anemia asymptomatic from their underlying disease. The major complications of chronic transfusion is iron overload, which usually develops within 1–1.5 years of starting transfusion, and is treated with daily subcutaneous infusions of deferoxamine [3]. Compliance with this chelation therapy is often a problem, particularly when these patients become teenagers. High doses of IV deferoxamine then becomes necessary to bring down persistently elevated serum ferritin levels; central venous access is often required. Thrombosis and subsequent pulmonary embolization from IV deferoxamine therapy are unusual complications.

Individuals with sickle cell disease are known to be hypercoagulable. A variety of mechanisms are postulated, from low levels of proteins S and C, to enhanced platelet reactivity, to generation of hydroxyl radicals and liberation of fibronectin and thrombospondin [4]. In addition, there is an abnormal interaction between the red blood cells and the vascular endothelium, with enhanced expression of adherence sites. Whether these are affected by chronic transfusion is not clear at this time. The presence of an in-dwelling catheter may complicate the situation, further stimulating an already activated coagulation cascade. Central venous catheter-related thrombus formation and subsequent pulmonary embolus have been reported in a setting of critical care management in ventilated patients [5].

The role of deferoxamine in the pathogenesis of thrombosis is also unclear [6]. There is no reported evidence of a direct relationship of thrombophlebitis with the medication itself. Several chronically transfused patients, including those with other underlying disorders, such as thalassemia, receive high doses of deferoxamine through peripheral veins, yet thrombosis and embolization have been described only once to our knowledge [7]. A pulmonary syndrome of restrictive disease and interstitial fibrosis has been described, but this is of unclear etiology and without evidence of thromboembolism on imaging studies [8].

This report emphasizes the risk of pulmonary embolization from thrombophlebitis in patients with sickle cell disease after intravenous doses of deferoxamine. A high degree of caution and prompt intervention are necessary to manage this unusual complication.

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