Case Report

Successful pulmonary thromboendarterectomy in a patient with sickle cell disease and associated resolution of a leg ulcer

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ABSTRACT

Pulmonary hypertension (PH) is a relatively frequent and severe complication of sickle cell disease (SCD). PH associated with SCD is classified as Group 5 PH. The exact pathogenesis of PH in SCD in not known. There are also very limited treatment options available at this time for such patients with Group 5 PH. Patients with SCD are predisposed to a hypercoagulable state and thus can also suffer from chronic thromboembolism. These patients can have associated chronic thromboembolic pulmonary hypertension (CTEPH), thus being classified as Group 4 PH. We present such a case of a patient with SCD diagnosed with severe PH who was found to have CTEPH and successfully underwent a thromboendarterectomy with resolution of his symptoms such as reduction of his oxygen requirements and healing of chronic leg ulcer. This case illustrates the importance of screening patients with SCD and elevated pulmonary artery pressures for CTEPH as this would offer possible treatment options such as pulmonary thromboendarterectomy and/or riociguat in this subset of patients.

KEY WORDS: Chronic thromboembolic pulmonary hypertension, leg ulcer, pulmonary hypertension, pulmonary thromboendarterectomy, sickle cell disease

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INTRODUCTION

Pulmonary hypertension (PH) is a relatively frequent and severe complication of sickle cell disease (SCD). The exact pathogenesis of PH in SCD in not known, but a number of factors have been implicated. These factors include endothelial injury due to recurrent sickling and associated vascular intimal hyperplasia, acute and chronic inflammation, and altered bioavailability of nitric oxide (NO). The vascular intimal hyperplasia can occur with or without a superimposed thrombus and can lead to chronic thromboembolism. Patients with PH secondary to SCD are classified as Group 5 PH as per the WHO guidelines.[1] Patients who suffer from chronic thromboembolism secondary to SCD can also have associated chronic thromboembolic pulmonary hypertension (CTEPH), thus being classified as Group 4 PH as per the WHO classification.[1] We present such a case of a patient with SCD diagnosed with severe PH who was found to have CTEPH and successfully underwent a thromboendarterectomy with resolution of symptoms.

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CASE REPORT

A 37-year-old male with SCD (hemoglobin (Hb) SS-disease) (treated with blood transfusion every 3 months) was diagnosed with pulmonary embolism (PE) and was being treated with enoxaparin. Apart from the SCD, the patient had a history of chronic venous stasis ulcer, which was being managed on an outpatient basis [Figure 1]. Eighteen months after the diagnosis of PE, the patient presented to the emergency department with worsening dyspnea on exertion. A ventilation/perfusion (VQ) scan was performed at the time that showed a right middle lobe perfusion defect consistent with PE. Ultrasound of both lower extremities revealed chronic deep vein thrombosis. The patient was also noted to have nocturnal hypoxemia and hypoxemia with exertion and was thus started on home oxygen therapy.

For further evaluation, the patient had a computed tomography pulmonary angiogram (CTPA), which demonstrated diffuse mosaic attenuation of lung parenchyma as seen in diseases such as chronic thromboembolic (CTE) disease [Figure 2a and b]. A mildly dilated pulmonary artery was also noted [Figure 2a]. A transthoracic echocardiogram showed right ventricular dilatation with estimated right ventricular systolic pressure (RVSP) of 103 mmHg. His most recent previous echocardiogram was performed 18 months ago and demonstrated a normal right ventricle with normal RVSP. A cardiac catheterization was performed which showed elevated pulmonary artery pressures with normal left-sided pressures [Table 1]. He was thus diagnosed with PH and started on sildenafil. Pulmonary function tests showed a restrictive pattern with decreased diffusion capacity (DLCO) [Table 2]. The 6-min walk distance (6MWD) was 416 M with supplemental oxygen at 5 L/min to keep the saturation above 90%. The patient required 2 L/m of supplemental oxygen at baseline. He was thus referred to the cardiothoracic surgery team for evaluation of CTEPH.

Table 1: Right heart catheterization

Chamber	Pressures (mmHg)
Right atrium (a/v/m)	15/13/11 mmHg
Right ventricle (s/edp)	73/14 mmHg
Pulmonary artery (s/d/m)	70/27/44 mmHg
Pulmonary wedge (a/v/m)	13/13/8 mmHg

Table 2: Pulmonary function tests (restrictive pattern with reduced diffusing capacity of the lungs for carbon monoxide)

FVC - 2.84 L (69% of predicted)
FEV1-2.23 L (66% predicted)
FEV1/FVC - 82%
TLC - 4.00L (72% of predicted)
DLCO - 39% of predicted

DLCO: Diffusing capacity of the lungs for carbon monoxide, FEV1: Forced expiratory volume in the first 1 s, FVC: Forced vital capacity, TLC: Total lung capacity

The pulmonary angiogram demonstrated filling defects in the right lower and middle lobes and left lower lobe, consistent with CTE disease [Figure 3a and b]. Severely elevated pulmonary pressures were again noted [Table 3]. Two months later, the patient underwent a successful pulmonary endarterectomy (PEA) with removal of the thrombus [Figure 4]. He was also started on riociguat for residual PH and enrolled in the cardiopulmonary rehabilitation program. His repeat 6MWD increased to 432 M without any supplemental oxygen. Interestingly, on follow-up, it was also noted that the patient's chronic venous stasis ulcer showed remarkable improvement with

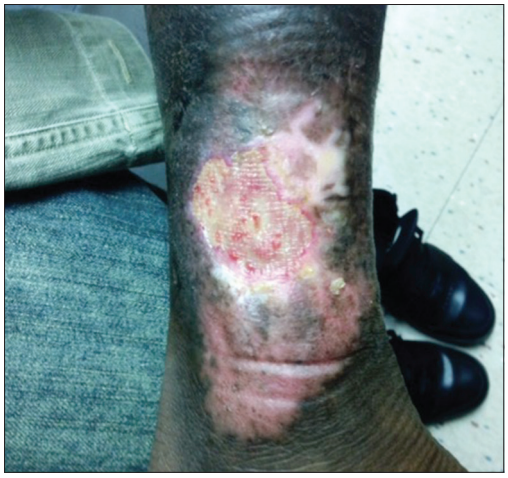

Figure 1: Patient with leg ulcer with sickle cell disease and pulmonary hypertension

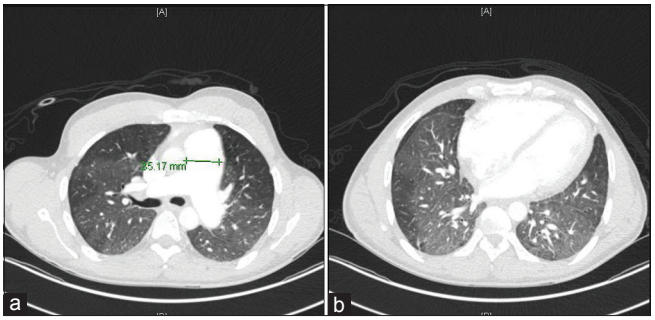

Figure 2: (a and b) Computed tomography of the chest showing a diffuse mosaic attenuation of the lung parenchyma

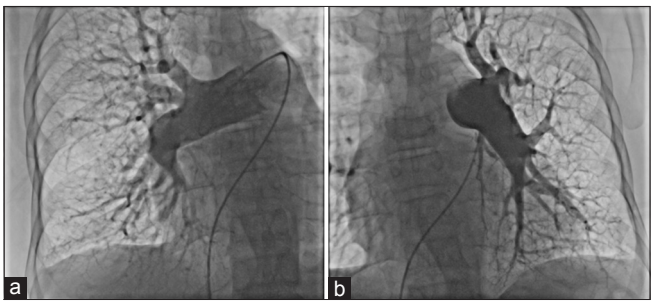

Figure 3: (a) Pulmonary angiogram showing filling defects in the right middle lobe and right lower lobe. (b) Pulmonary angiogram showing filling defects on the left side

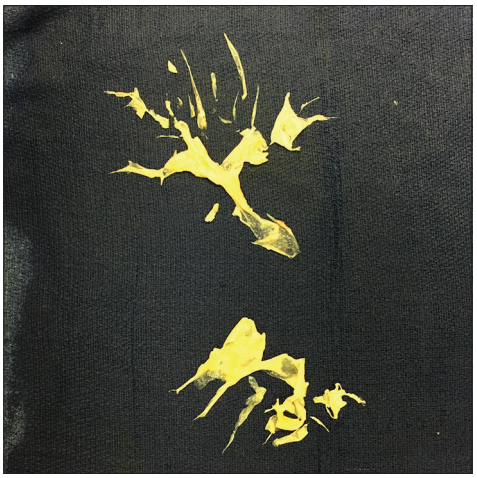

Figure 4: Clot removed after pulmonary thromboendarterectomy

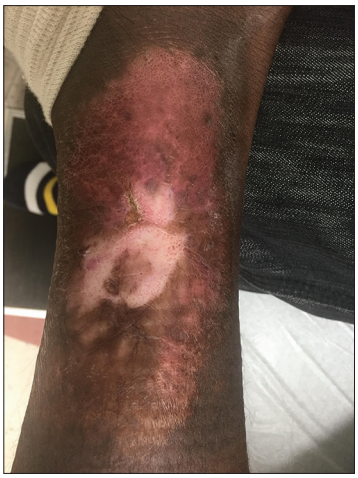

Figure 5: Healing lung ulcer status post pulmonary thromboendarterectomy

Table 3: Right heart catheterization/pulmonary angiography

Chamber	Pressures (mmHg)
Right atrium (a/v/m)	19/17/14 mmHg
Right ventricle (s/edp)	86/19 mmHg
Pulmonary artery (s/d/m)	81/35 (52) mmHg
Pulmonary wedge (a/v/m)	10/9/9 mmHg
Pulmonary vascular resistance	9.66 wood units

improvement in his oxygen saturation and improvement in his functional status [Figure 5]. The patient continues to have a stable follow-up course.

DISCUSSION

PH is a common complication of SCD. The prevalence of PH in this patient group is around 10%–20% and is a common cause of mortality.[2] Although there is evidence that patients with SCD have a hypercoagulable state, CTEPH in these patients is relatively uncommon. According to a study by Anthi *et al*., 23% of the SCD patients with PH had perfusion mismatch in the V/Q scan. About 11.5% of the patients had evidence of CTE disease on CTPAs.[3]

There have been multiple pathophysiologic mechanisms which have been postulated which lead to thromboembolism in SCD patients and subsequently can lead to CTEPH. In fact, every aspect of Virchow's triad, i.e., increased coagulability, endothelial dysfunction, and impaired blood flow, is present in patients with SCD and results in a highly thrombogenic environment.[4]

The repeated cycles of sickling and unsickling in SCD patients lead to an abnormal phospholipid asymmetry as well as adherence of the sickle erythrocytes to the vascular endothelium. The alteration of the membrane structure of sickle erythrocytes results in exposure of the anionic phospholipid, phosphatidylserine (PS). This phenomenon supports coagulation by PS acting as the cofactor for proteolytic reactions.[5] This phenomenon is also supported by the fact that a correlation has been found between PS-positive sickle cell erythrocytes and prothrombin fragments 1.2, D-dimers, and plasmin-antiplasmin complex.[6] Antiphospholipid antibodies are known to be both procoagulant and prothrombotic. Levels of these antibodies are markedly higher in patients with SCD.[7] These antibodies work by tissue factor induction leading to activation of the coagulation system.[8] Multiple studies have suggested that there is increased thrombin generation in SCD patients. Increased levels of prothrombin fragments1.2, D-dimers, and thrombin-antithrombin complexes support this hypothesis.[9] The level of factor V is also reduced in SCD patients suggesting ongoing thrombin generation.[10] Along with that, high plasma levels of procoagulants such as von Willebrand factor and factor VIII are found in SCD patients.[10-12] All these changes reflect the hypercoagulable state in SCD.

Circulating free Hb in the setting of hemolysis also causes NO depletion, which leads to chronic vasoconstriction and platelet activation.[13] Moderate thrombocytosis is a common feature of patients with SCD and sickle cell anemia. These changes can be attributed to the fact that splenic autoinfarction affects the majority of children with Hb SS-disease by age 1 year and a large proportion of patients with SC disease by middle childhood.[14] This could also lead to the development of secondary PH. Long-standing thrombocytosis after splenectomy has been shown in one case to be associated with elevated fibrinopeptide A, thromboxane B2, and β-thromboglobulin levels resulting in endothelial damage, local platelet activation, and thrombin generation leading to CTEPH. A similar mechanism could lead to CTEPH in SCD patients due to the functional asplenia.[15] Besides thrombocytosis, increased platelet adhesion may contribute to the development of pulmonary vasculopathy. There is evidence to support transmigration of intact megakaryocytes from the bone marrow to the circulation and the release of platelets from these megakaryocytes in the pulmonary capillary bed. These large-sized platelet precursors can

contribute to distal *in situ* thrombosis leading to CTEPH in asplenic SCD patients.[16]

Transthoracic Doppler echocardiography on patients with SCD is a cost-effective and established screening tool for PH. Elevated pulmonary artery systolic pressure on echocardiography should be confirmed by right heart catheterization (RHC). Due to the high incidence of thromboembolism in patients with SCD, patients with PH should be screened with a VQ scan and/or a CTPA. Patient with signs suggestive of CTEPH should undergo an angiography to diagnose CTE. Pulmonary function tests should be performed in all patients with SCD presenting with dyspnea. A restrictive pulmonary functional abnormality in this setting may represent areas of prior infarction.[17]

The diagnosis of CTE and related CTEPH can alter management strategies and the classification of PH. PH associated with SCD is classified as Group 5 PH. A recent guideline from the American Thoracic Society proposes the screening for PH in patients with SCD every 3 years.[18] A different guideline by the sickle cell expert panel did not endorse these recommendations, suggesting echocardiographic evaluation followed by RHC in symptomatic patients only.[19] PH related to CTEPH is classified as Group 4 as per the WHO classification system. Although PEA is recommended for patients with PH related to CTE disease, chronic hemolysis and the associated proliferative vasculopathy in the distal vessels put patients with SCD at increased risk of residual PH after PEA. CTEPH in SCD patients has been treated surgically with success [Table 1]. Jerath *et al*.[20] demonstrated normalization of pulmonary artery pressures, after a PEA in a patient with SCD and CTEPH. Deep hypothermic circulatory arrest (DHCA) during PEA exposes the SCD patient to a hypothermic, hypoxic, acidotic, and a low-flow state. These patients are thus at an increased risk of sickling during this procedure. While there is no consensus on the values of Hb S in patients with SCD, Firth and Head have proposed that the level of Hb S should be reduced to <30% for a major surgical procedure and to <10% for a cardiopulmonary surgical procedure.[21] Five cases in literature demonstrated a successful PEA under DHCA after exchange transfusion to reduced Hb S to <10% [Table 4].[20,23,24] Attention should be paid to maintaining good flow states, a normal acid-base balance status, and limit the duration of circulatory arrest periods. The use of specific PAH therapies for the management of SCD-associated PH is a controversial matter. Two randomized control trials have studied the role of bosentan but have been prematurely terminated.[25] Another trial addressing the role of sildenafil was discontinued due to increased hospitalization for pain crisis.[26] To date, there have been no studies to inform anticoagulation practices in patients with SCD.[27] Anticoagulation management of symptomatic VTE and CTEPH, therefore, currently relies on established general guidelines for VTE management.[28] Further studies are necessary to determine adequate treatment approach and to determine which subgroup of patients might benefit from PAH-targeted therapies and anticoagulation.

Leg ulcerations have been a long-recognized complication of SCD. Minniti *et al*. in their review concluded that the epidemiological relationship between leg ulcers and PH supported an overlap of pathobiological mechanisms.[29] The possible overlapping mechanisms include mechanical obstruction by dense sickled red cells, *in situ* thrombosis, anemia with decrease in oxygen carrying capacity, and decreased NO bioavailability leading to impaired endothelial function.[30] One interesting case report has noted leg ulcer healing during treatment of pulmonary arterial hypertension with an endothelin receptor antagonist.[31] Management of PH is currently recommended as one of the systemic interventions for managing this complication of SCD.[22] Our patient demonstrated healing of the ulcer after undergoing a successful thromboendarterectomy for management of his CTEPH. We hypothesize that the possible mechanisms of improvement of the leg ulcer include increased peripheral oxygen supply as evidenced by the decrease in supplemental oxygen requirement. Another possible contributing factor is the reduction of right-sided pressures after the endarterectomy leading to decreased venous stasis and decreased peripheral edema, thus helping the healing of the ulcer.

CONCLUSION

We present a case of a 37-year-old male with SCD and associated Group 4 PH due to chronic thromboembolism who underwent a successful PEA. This helped reduce his oxygen requirement, increased his 6MWD, and also helped with healing of his chronic venous stasis ulcer, all likely manifestations of his PH. Thus, the clinicians should screen and assess for CTEPH in patients with SCD with elevated pulmonary artery pressures as this would offer possible treatment options such as pulmonary thromboendarterectomy and/or riociguat in this subset of patients.

Table 4: All reported patients with sickle cell disease who underwent pulmonary endarterectomy

Reference/year	Age/gender	Condition	NYHA class	Circulatory arrest (min)	Outcomes
Yung *et al*., 1998[23]	44/male	Sickle cell - thalassemia (Hb S/beta+)	II	42	Discharged after 19 days
Yung *et al*., 1998[23]	41/male	SCD	III	33	Discharged after 9 days
Vocelka *et al*., 2001[24]	36/female	Hb SCD	NA	10, 22, and 24 (*n*=3)	NA
Jerath *et al*., 2011[20]	52/male	Hb SCD	III	32	Discharged after 6 days
Marques *et al*., 2014[32]	30/female	SCD	III	51	Discharged after 6 days

SCD: Sickle cell disease, NA: Not available, NYHA: New York Heart Association, Hb: Hemoglobin

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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