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Reversal of pre-capillary pulmonary hypertension in a patient with sickle cell anemia who underwent haploidentical peripheral blood stem cell transplantation

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In patients with sickle cell disease (SCD), deoxygenated sickle hemoglobin (HbS) polymerizes, resulting in rigid, adherent RBC that obstruct microcirculation and cause hemolysis. Patients experience many acute and chronic complications, including pain crises, acute chest syndrome and pulmonary hypertension (PH), among others.

PH remains a serious complication in SCD, and has been reported as a major cause of morbidity and mortality.[1–3] It is defined as a resting mean pulmonary arterial pressure (mPAP) ⩾ 25 mm Hg measured by right heart catheterization (RHC),[4,5] and is estimated to impact 6–11% of adults with SCD.[5,6] Transthoracic echocardiography (ECHO) estimates pulmonary arterial systolic pressure via the surrogate tricuspid regurgitant velocity (TRV) to screen for PH.[6–8] Similarly, elevated N-terminal-pro brain natriuretic peptide (NT-proBNP) levels have been associated with increased TRV in adults with SCD;[9] furthermore, NT-proBNP level of 160ng/L or higher was independently associated with mortality.[9] While TRV and NT-proBNP are indirect estimates of pulmonary pressure, RHC is required for a definitive diagnosis of PH. For the purposes of this report, RHC, 6-min walk tests (6MWT), NT-proBNP and ECHO values were retrieved to monitor the change in estimated pulmonary arterial pressure in the patient presented.

We report a 32-year-old woman with severe homozygous SCD (HbSS) and a history of PH, recurrent episodes of acute chest syndrome and vaso-occlusive crises, and systemic hypertension. Her SCD-related complications did not improve with hydroxyurea or decitabine. At diagnosis of her PH 2 years earlier, she reported dyspnea on exertion (DOE), chest pain and occasional pre-syncope, consistent with New York Heart Association functional class (NYHA FC) III symptoms. Her RHC showed a mPAP of 30 mm Hg and pulmonary arterial wedge pressure (PAWP) of 12 mm Hg, indicative of pre-capillary pulmonary hypertension (Table 1). Baseline hemodynamic measurements also showed an elevated mean right atrial pressure (RAm) of 8 mm Hg and increased cardiac output of 8.5 L/min by thermodilution method. Concurrent ECHO revealed septal bowing and 6MWT progressive hypoxia, and a decline in distance (Table 1). Laboratory evaluation did not

CONFLICT OF INTEREST

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display evidence of connective tissue disease, ventilation-perfusion scan was low probability for pulmonary embolism, bilateral lower extremity Dopplers were negative and pulmonary function testing revealed a moderate diffusion defect without obstruction. She was initially treated with ambrisentan, an endothelial receptor antagonist with published experience in the treatment of SCD-induced PH,[10] and nocturnal oxygen.

Hematopoietic stem cell transplantation (HSCT) is the only established curative therapy for individuals with SCD, but has been infrequently pursued due to its associated risks. We have a nonmyeloablative haploidentical peripheral blood stem cell transplant (PBSCT) protocol for adults with severe SCD (Clinical-Trials.gov Identifier NCT00977691, approved by the National Heart, Lung, and Blood Institute Institutional Review Board and informed consent was obtained). Our patient was deemed eligible on the basis of her PH. Following the administration of ambrisentan for 9 months, her TRV improved from 3.9 to 2.8 m/s and her right ventricular systolic pressure (RVSP) improved from 67 to 36 mm Hg with resolution of the septal bowing (Table 1). Furthermore, she experienced significant amelioration in her DOE and she improved to NYHA FC II status. While many cardiopulmonary parameters improved pre-PBSCT, her echocardiogram parameters remained abnormal, she continued on oxygen, and reversal of her SCD with HSCT would be necessary to improve her other SCD-related complications and quality and perhaps quantity of life.

By 6 months after PBSCT, her supplemental oxygen was discontinued and she improved to NYHA FC I. By 1 year, her ambrisentan was discontinued, and her PH-associated symptoms subsided. Her donor chimerism was 88% in myeloid and 22% CD3+ cells. She had 43% sickle hemoglobin, which was identical to her donor who had sickle cell trait. Therefore, she no longer had SCD. Her exercise testing showed in excess of doubling of her 6MWT distance, and normalized resting and exertional oxygen saturation, with resolution of her PH on RHC (Table 1). As expected, her hemoglobin significantly improved from 76g/L to 108 g/L. The patient continued to report no chest pain, dyspnea, syncope or edema, and her overall quality of life dramatically improved. At 2 years post PBSCT, further pulmonary and cardiac testing showed further improvement of her TRV to 2.4 m/s and RVSP to 28 mm Hg (Table 1). She continued to do well clinically.

In recent years, cardiopulmonary complications such as PH have clearly emerged as a major threat to quality and quantity of life in individuals with SCD. Here, the patient's post-PBSCT evaluation showed vast improvement in both pulmonary and hematologic parameters. Because the transplant simultaneously led to resolution of her hemolysis, anemia and the sickling process, it is not possible to know whether one or all of those factors led to the reversal of her PH. Our patient's functional status became normal with the resolution of her PH and significant improvement in her hemoglobin. Our evaluation is, however, limited by the inclusion of only one patient. Additionally, she suffered a vaso-occlusive crisis immediately prior to the transplant date and was thus unable to undergo a RHC after the initiation of ambrisentan but before PBSCT. Despite the absence of this procedure, while her clinical presentation and studies improved with ambrisentan, her symptoms did not resolve and ECHO parameters did not normalize until after PBSCT. To our knowledge, this is the first report of the resolution of PH in a patient with SCD after

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successful HSCT. Comparable studies should be performed in a larger patient population to validate our findings.

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Table 1.

Cardiopulmonary parameters and hemoglobin before and after transplant

	Before ambrisentan[a]	Before transplant[b]	1 year post-transplant[c]	2 years post-transplant[d]
PAP s/d/m (mm Hg)	41/17/30	NA	28/11/17	NA
PAWP (mm Hg)	12	NA	6	NA
RAm (mm Hg)	8	NA	3	NA
CI (L/min/m2)	5.3	NA	2.8	NA
CO (L/min)	8.5	NA	4.56	NA
TRV (m/s)	3.9	2.8	2.8	2.4
RVSP (mm Hg)	67	36	37	28
LVEF (%)	60	70	54	66
6MWT distance (m)	252	359	456	452
6MWT O_2 (%) pre	92	96	100	100
6MWT O_2 (%) post	86	92	100	97
NT-proBNP (ng/L)	287	48	111	121
HGB (g/L)	74	76	104	108

Abbreviations: CI =cardiac index; CO=cardiac output; HGB= hemoglobin; NA =not available; LVEF= left ventricular ejection fraction; NT-proBNP =brain natriuretic peptide; O_2= oxygen saturation; PAP=pulmonary artery pressure; PAWP= pulmonary artery wedge pressure; RAm= mean right atrial pressure; RVSP =right ventricular systolic pressure; s/d/m = systolic/diastolic/mean; TRV =tricuspid regurgitant velocity; 6MWT= 6-minute walk test.

[a] April–May 2012, ambrisentan started 1 August 2012.

[b] April–August 2013. Date of haploidentical PBSCT: 9 August 2013. Ambrisentan discontinued 21 April 2014.

[c] August 2014.

[d] August 2015.

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