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Symptomatic Pulmonary Hypertension in a Child with Sickle Cell Disease

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Only recently has it been appreciated that children with homozygous sickle cell anemia (SS) may have a clinically occult elevation of the tricuspid regurgitant jet velocity (TRJV).¹ The case presented in this report demonstrates not only occult elevation of TRJV but that symptomatic SS-associated pulmonary hypertension may occur during childhood, masquerading as acute chest syndrome, and can be difficult to treat.

CASE REPORT

A boy was diagnosed with SS on newborn screening. By 5 years of age, he had 6 hospital admissions for presumptive reactive airway disease and 3 for acute chest syndrome. At 6 years of age, his pulmonary function tests revealed mild restrictive disease (forced vital capacity, 76% predicted) with early obstructive impairment (forced expiratory flow, 25% to 75%, 43% predicted) and responsiveness to a bronchodilator. Room air pulse oximetry was 99%. Therapy for reactive airway disease was prescribed.

The child had a presumed fourth episode of acute chest syndrome at 7 years of age. At 7½ years, he presented with fatigue, tachypnea, chest pain, retractions, wheezing, hepatomegaly (4 cm), and pulse oximetry of 71% to 79%. Hemoglobin and reticulocyte counts were baseline: 6.9 g/dL and 39 %, respectively. Chest radiography revealed severe cardiomegaly and biventricular hypertrophy on the ECG. An echocardiogram showed mild biatrial, biventricular, and pulmonary artery dilation with a TRJV of 3.4 m/s and estimated right ventricular systolic pressure of 50 mm Hg on room air, reducing to 45 mm Hg with oxygen. Oxygen, red cell transfusion, furosemide, bronchodilators, and nasal steroids were administered and at discharge, he was receiving 0.75 L oxygen continuously to maintain pulse oximetry >90%. Subsequent TRJVs, hemoglobin, reticulocyte counts, and treatment are shown in the Figure.

Two weeks after presentation, the TRJV remained elevated and pulmonary function tests showed forced vital capacity and forced expiratory flow 25% to 75%, both 58% predicted, without response to albuterol. An evaluation to exclude thrombophilia revealed a normal protein C activity, free protein S, antithrombin III, vonWillebrand antigen and activity, and negative D-dimer. Prothrombin G20210A and Factor V Leiden mutations and antiphospholipid antibodies were absent. L-Arginine was prescribed at 4.5 g/d (0.18 g/kg per day) delivered as Arginaid (Novartis Oncology; East Hanover, NJ), and oxygen was continued.

Four and one-half months from presentation, the TRJV remained elevated and a transcranial Doppler ultrasound showed a mean flow of 178 m/s in the left middle cerebral artery. Therapy was commenced with monthly minor antigen-matched, red cell transfusions; hydroxyurea therapy was refused by the family.

One month after his first transfusion, the room air pulse oximetry was 91% and our patient was as active as his classmates, so only nocturnal oxygen was continued. The adenoids were removed for obstructive sleep apnea diagnosed by sleep study. The abdominal ultrasound showed a few gallstones, but, because he was asymptomatic, the family refused concurrent cholecystectomy.

Ten months from presentation, a TRJV could not be detected and arginine was discontinued. Due to difficulty suppressing hematopoiesis, transfusion therapy was intensified 1 month later, from 15 cc/kg of red cells every 4 weeks to every 3 weeks. He continued to present with low hemoglobin level, high reticulocyte count, and approximately 40% sickle hemoglobin. An evaluation for red cell antibodies was negative.

Sixteen and one-half months from presentation, the TRJV was again undetectable, our patient appeared well, and his mother ended transfusion therapy. About 2 months later, he presented with fatigue, chest pain, hepatomegaly, and a room air pulse oximetry of 80%.

There was a brisk hemolytic anemia with a markedly elevated TRJV (Figure). Mild biatrial and left ventricular dilation (5.43 cm) were present. He was again treated with oxygen, red cell transfusion, diuretics, and steroids.

Results of right heart catheterization performed 1 month later and simultaneously obtained laboratory data are shown (Table). After catheterization, sildenafil (20 mg 3 times daily) was added to the treatment regimen. Because of persistent elevation in TRJV and an ECG showing left ventricular hypertrophy with mild biatrial and left ventricular dilation, sildenafil was subsequently increased to 30 mg 3 times daily.

Twenty-nine months from presentation, 10 months from relapse, our patient appeared clinically well, but he had persistent mild biatrial dilation, left ventricular end-diastolic dilation (6.13 cm), and a TRJV unchanged from the time of right heart catheterization with a persistently elevated N-terminal pro-brain natriuretic peptide. He had development of a red cell autoantibody (e) but continued with transfusions every 3 weeks.

DISCUSSION

Pulmonary hypertension has traditionally been defined as a mean pulmonary arterial pressure at right heart catheterization ≥ 25 mm Hg at rest or ≥ 30 mm Hg with exercise. However, Gladwin et al² showed a TR jet of ≥ 2.5 m/s on echocardiography was predictive of pulmonary hypertension on right heart catheterization in adults with SS and is associated with sudden death. They also showed an elevated N-terminal pro-brain natriuretic peptide in adults is an indicator of risk for pulmonary hypertension-associated mortality.³ Further studies have confirmed that left ventricular diastolic dysfunction is also predictive of premature mortality in SS adults.⁴ Although our patient never had documented left ventricular dysfunction, he did have a persistently elevated N-terminal pro-brain natriuretic peptide, elevation of TRJV, and left ventricular dilation; however, their significance in childhood is unknown.

Similar to adults with SS, the etiology of pulmonary hypertension in our patient probably is multifactorial; reactive airway disease, obstructive sleep apnea, and recurrent acute chest syndrome are recognized risk factors.⁵ Adults with SS-associated pulmonary hypertension

may have hypoxemia secondary to sickle cell–induced pulmonary vascular and parenchymal injury, which is also true for our patient.⁶ A more recently appreciated factor predisposing to SS-associated pulmonary hypertension in adults with SS is hemolysis. Intravascular hemolysis leads to elevated plasma-free hemoglobin and release of erythrocyte arginase with secondarily impaired nitric oxide availability. Again, similar to adults with SS described with pulmonary hypertension, our patient had significant hemolysis, as indicated by marked anemia and elevated reticulocyte count, AST, LDH, plasma hemoglobin, and nitric oxide consumption.^{1,7} He also had cholelithiasis, another hemolysis-associated complication described in adults.

Management guidelines for pulmonary hypertension recommend administration of hydroxyurea with or without erythropoietin, and, if not possible, long-term transfusion therapy.⁸ Due to initial maternal reluctance to any major intervention, and because arginine, a nitric oxide donor, has been shown to be efficacious in adults with SS and pulmonary hypertension, L-arginine was prescribed.⁹ We cannot assess our patient's response to arginine because red cell transfusions were started shortly thereafter. Hydroxyurea was not administered because of parental wishes.

Our case demonstrates that the pattern of hemolysis-associated complications, including pulmonary hypertension described in adults with SS, may occur during childhood. Right heart catheterization is an essential element of the evaluation for pulmonary hypertension, regardless of patient age, especially if the TRJV is ≥ 2.9 m/s. Our case also suggests that there may be a narrow window of opportunity for reversal of pulmonary hypertension as exemplified by our patient's need for daily supplemental oxygen for just 1 month initially but 6 months after relapse. TRJV normalization was observed within 6 months of transfusions initially but became refractory, even with the addition of sildenafil, after relapse.¹⁰ Ultimately, determination of preventive measures should lead to improved longevity for people with SS, but until then, safe, effective therapy for pulmonary hypertension must be defined.

Acknowledgments

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Glossary

SS	Homozygous sickle cell disease
TRJV	Tricuspid regurgitant jet velocity

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Figure.

Month and treatment are as follow: 0, red cell transfusion/continuous oxygen/bronchodilators/Lasix/nasal steroids; 0.5, begin arginine/continuous oxygen/stop bronchodilator and Lasix; 2.5, arginine/continuous oxygen; 4.5, arginine/begin red cell transfusion every 4 weeks; 5.5, adenoidectomy; 10, stop arginine/red cell transfusion every 4 weeks; 11, begin red cell transfusion every 3 weeks; 16.5, stop red cell transfusion; 19, restart red cell transfusion every 3 weeks/continuous oxygen/furosemide/steroids; 21, red cell transfusion every 3 weeks/continuous oxygen; 22, right heart catheterization/begin sildenafil 20 mg 3 times a day/every 3 weeks red cell transfusion/continuous oxygen; 24, sildenafil 30 mg 3 times a day/every 3 weeks red cell transfusion/stop day time oxygen; 26, sildenafil 30 mg 3 times a day/every 3 weeks red cell transfusion; 29, same as 26 months. TRJV, Tricuspid regurgitant jet velocity.

Table
Results of right heart catheterization and simultaneously obtained laboratory data

Laboratory	Child's Values	Normal Range
Lactate dehydrogenase	359 U/L	130–300 U/L
Total bilirubin	3.3 mg/dL	0.2–1.2 mg/dL
Direct bilirubin	0.4 mg/dL	0–0.3 mg/dL
AST	64 U/L	14–40 U/L
Plasma hemoglobin	9 mg/dL	<3 mg/dL
Mean nitric oxide consumption	5.21 μ M	1.17–2.76 μ M
Arginase	58.2 ng/mL	0.4–100 ng/mL
N-terminal brain natriuretic peptide	100 pg/mL	<35 pg/mL

Cardiac Catheterization	Room Air	1 L Oxygen	100% Oxygen	100% Oxygen + NO 40 ppm	1 L Oxygen + Sildenafil 20 mg
Mean pulmonary artery pressure (mm Hg)	29	23	18	16	21
Pulmonary capillary wedge pressure (mm Hg)	8	8.5	8	8	7
Mean aortic pressure (mm Hg)	61	69	74	65	68
Right atrial pressure (mm Hg)	6.1	6.9	6	7	7
Cardiac index (Fick)	10.34	8.18	7.32	6.65	8.81
Pulmonary vascular resistance (dyne/s/cm ⁻⁵)	162.4	141.6	109.6	96	127.2
Systemic vascular resistance index	5.22	7.82	9.29	8.72	6.92
PCO ₂ (mm Hg)	44.4	46.7	46.4	49	43.9
PO ₂ (mm Hg)	49	78	366	378	85

Anonymized samples were sent to the National Institutes of Health for measurement of plasma hemoglobin, nitric oxide consumption, and arginase.