Pulmonary artery thromboembolism in a critically ill neonate successfully treated using thrombolytic therapy

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ABSTRACT

Pulmonary artery thromboembolism is a common and treatable cause of adult pulmonary hypertension. Although rare in children, if undiagnosed, it can result in significant morbidity and mortality. We report a case of a cyanotic neonate found to have bilateral pulmonary arterial thrombi who successfully underwent thrombolysis using tissue plasminogen activator with prompt resolution of right ventricular hypertension.

Keywords: Cardiology, hematology, pediatrics, thrombosis

INTRODUCTION

Pulmonary artery thromboembolism (PTE) is rarely diagnosed in the pediatric population but can result in significant morbidity and mortality, especially if not promptly recognized and treated. Most cases involve children with risk factors, including central venous or arterial catheters, inflammation, disseminated intravascular coagulation, impaired liver function, fluctuations in cardiac output, or congenital heart disease. We present a rare case of a cyanotic neonate without risk factors or comorbidities who was found to have bilateral pulmonary arterial thrombi and who was successfully treated with tissue plasminogen activator (tPA) with prompt resolution of right ventricular hypertension.

CASE REPORT

A 13-day-old boy was brought to the emergency department with sudden cyanosis and difficulty breathing. His prenatal history was unremarkable. He was one of the twins, born at 34 weeks of gestation due to premature rupture of membranes with a birth weight of approximately 2200 g. His delivery was uncomplicated, and he was discharged home at 4 days of age. A routine pediatrician visit during the following week revealed no concerns.

On examination, the neonate appeared cool and mottled, with central cyanosis and agonal respirations. He was hypothermic, tachycardic, and hypoxemic with an oxygen saturation of 70% while breathing ambient air. His initial arterial blood gas demonstrated metabolic and respiratory acidosis with a pH of 6.9, carbon dioxide of 84 mmHg, and lactate of 9.3 mmol/L. Given his respiratory failure and evidence of low cardiac output, he was emergently intubated and given intravenous fluids, inotropic support, and an intravenous infusion of prostaglandin E_1 (PGE_1) at 0.05 μg/kg/min before an echocardiogram was done. Broad-spectrum antibiotics

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were administered for presumed septic shock. With these interventions, repeat arterial blood gas showed significant improvement in his acidosis, with a pH of 7.3, carbon dioxide of 50 mmHg, and lactate of 1.8 mmol/L. White cell count was normal for age (14,300/mm^3; normal range 9000–30,000/mm^3), while respiratory viral panel, as well as blood and urine cultures, were negative for infection. Liver transaminases including aspartate aminotransferase (31 IU/L; normal range 10–37 IU/L) and alanine aminotransferase (13 IU/L; normal range 9–50 IU/L) were normal. His hemoglobin was 12.6 g/dL (normal range 13–20 g/dL) and hematocrit was 35.7% (normal range 40%–60%).

Chest radiograph revealed a normal cardiac silhouette with decreased pulmonary vascularity and a left upper lobe opacity. An electrocardiogram showed sinus tachycardia with nonspecific ST and T-wave abnormalities. Transthoracic echocardiogram showed a patent ovale foramen with right-to-left blood flow and moderate right ventricular (RV) dilation with severe RV hypertension on the basis of posterior systolic bowing of the ventricular septum with an estimated RV pressure of 45 mmHg plus the right atrial pressure in the setting of a systolic blood pressure of 65 mmHg. The measured TR jet gradient likely underestimated the degree of RV hypertension in the setting of severe RV systolic dysfunction. All four pulmonary veins connected normally to the left atrium without obstruction. The right and left pulmonary arteries appeared to have normal vessel size; however, absent flow was noted in the right pulmonary artery on color Doppler, with a suspicion of thrombotic occlusion [Figure 1].

In the absence of a ductal-dependent structural abnormality, PGE_1 was discontinued, and the patient was started on inhaled nitric oxide at 20 ppm and a continuous infusion of milrinone. In the context of his echocardiographic abnormalities, a high-resolution computed tomography (CT) scan of the chest was performed, revealing a large thrombus burden including the right main pulmonary artery and bilateral lobar and segmental branches [Figure 2]. Further laboratory testing for coagulopathy included a low platelet count (105,000 cells/mm^3; normal range 150,000-450,000 cells/mm^3), low fibrinogen (135 mg/dL; normal range 162–378 mg/dL), elevated D-dimer (6920 ng/mL; normal level ≤230 ng/mL), elevated B-type natriuretic peptide (989 pg/mL; normal level ≤100 pg/mL), low protein C activity (14%; normal range 15%–50%), low protein S activity (25%; normal level ≥50%), and low antithrombin III activity (31%; normal level ≥35%). Both prothrombin time and activated partial thromboplastin time were normal.

The infant was diagnosed with extensive bilateral pulmonary artery thrombi with acute cor pulmonale, resulting in cardiogenic shock. A heparin infusion was started at 30 units/kg/h, and he was transferred to our hospital for further management of pulmonary artery thrombosis and RV hypertension with right heart failure. After a multidisciplinary meeting involving the critical care, cardiology, cardiothoracic surgery, and hematology teams, the decision was made to administer systemic thrombolysis with tissue plasminogen activator (tPA) rather than surgical thrombectomy. Low-dose tPA was initially started at 0.06 mg/kg/h for 6 h, at which time the concurrent heparin infusion was decreased to 10 units/kg/h. Approximately 6 h into treatment, a repeat echocardiogram revealed minimal improvement in forward flow through the pulmonary arteries with persistent bilateral pulmonary artery thrombi, prompting an increase in the dose of tPA to 0.1 mg/kg/h. Upper and lower extremity Doppler ultrasounds revealed no evidence of arterial or venous thrombi. The patient

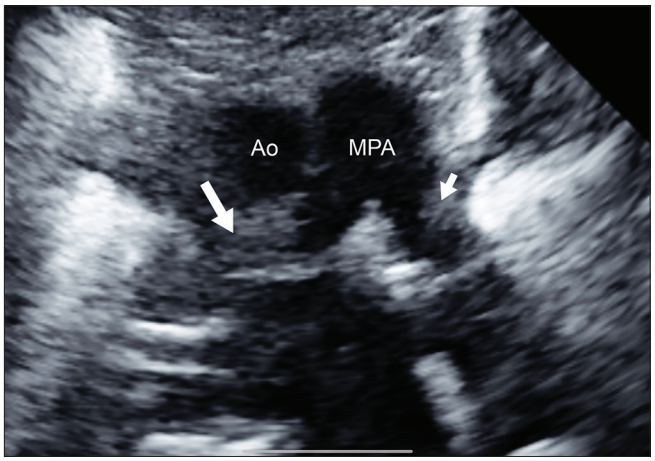

Figure 1: Transthoracic echocardiogram (parasternal view) showing the proximal pulmonary arteries. A large occluding thrombus (long arrow) is seen in the right pulmonary artery, whereas a smaller thrombus (short arrow) is seen in the left pulmonary artery. Ao: Aorta, MPA: Main pulmonary artery

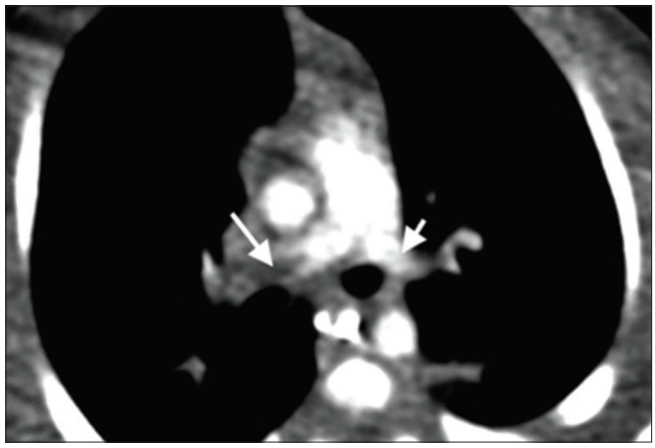

Figure 2: Computed tomography scan of the chest (axial view) showing a large thrombus (long arrow) in the right pulmonary artery and a small thrombus (short arrow) in the left pulmonary artery

had hourly neurovascular checks and continuous monitoring of vital signs including arterial pressures during thrombolysis, in addition to laboratory studies including complete blood count, coagulation factors, D-dimer, and fibrinogen, every 6 h. An echocardiogram and head ultrasound were repeated every 6–8 h during thrombolytic therapy.

After 18 h of continuous tPA at 0.1 mg/kg/h, the patient's echocardiogram showed significant decrease in the size of his thrombi with improved pulmonary arterial blood flow, as well as significant improvement in RV systolic function. To minimize the risk of thrombotic complications in the context of resolving thrombi, the tPA infusion was decreased to 0.03 mg/kg/h. Specifically, the infusion was continued at a lower dose to ensure that any embolic particles in the distal pulmonary vasculature were thrombolysed completely and to minimize the chance of recurrence distally. The tPA infusion was discontinued approximately 22 h later with an echocardiogram and chest CT scan, both showing complete resolution of his pulmonary artery thrombi [Figure 3].

The patient's heparin infusion was increased to achieve therapeutic partial thromboplastin time between 50 and 70 s and 48 h later, he was transitioned to subcutaneous enoxaparin (low-molecular-weight heparin) with goal anti-factor Xa level of 0.5–1.0 IU/mL. He was successfully extubated on hospital day 6, but continued to require supplemental oxygen for almost 2 weeks, shortly after which he was discharged. His parents declined genetic testing for heritable coagulopathies. At the time of discharge, the patient had normal RV function and no evidence of RV hypertension based on his TR jet and systolic septal position. He was discharged on subcutaneous enoxaparin and followed as an outpatient by a local hematologist. The patient had no recurrent thrombosis at his 6-month follow-up visit but was then lost to follow-up.

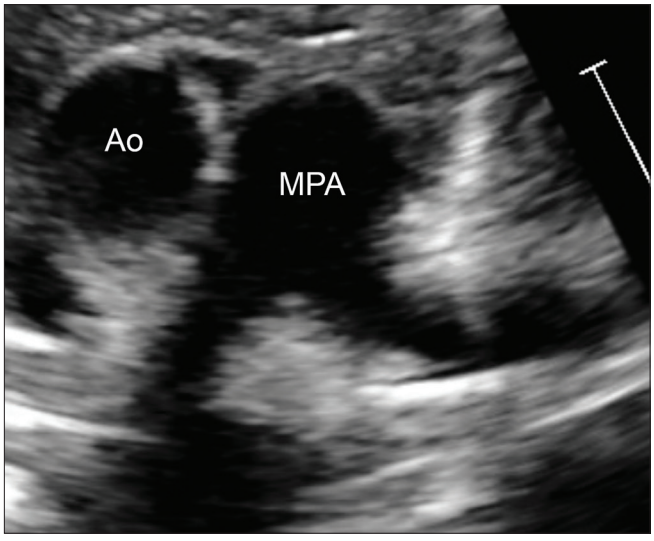

Figure 3: Transthoracic echocardiogram (parasternal view) showing complete resolution of pulmonary artery thrombi

DISCUSSION

Our case presents a critically ill neonate with pulmonary artery thromboembolism (PTE) without risk factors or comorbidities, who was successfully treated with tPA. PTE is rare in children, and it is particularly unusual in the absence of identifiable risk factors. Studies report an incidence of 5.1/100,000 live births, with symptomatic thromboembolism present in approximately 0.24% of infants admitted to neonatal intensive care units and 89% of cases being associated with indwelling intravascular catheters.[1,2] PTE may be underdiagnosed in children due to a low index of suspicion in this age group.[3] Mortality rates around 8% for children overall and 26% for infants (<1 year of age) have been reported.[4,5] In infants, risk factors include central venous or arterial catheters, inflammation, disseminated intravascular coagulation, impaired liver function, fluctuations in cardiac output, and congenital heart disease (e.g., hypoplastic left heart syndrome and tetralogy of Fallot), none of which were etiologic factors in the current patient.[4,6,7] Infants' increased risk for thrombi may be related to their immature coagulation systems that reach maturation at around 6 months of age.[8] Of note, polycythemia (i.e., hematocrit >55% in the 1st week of life) is also independently associated with neonatal thrombosis, possibly due to reduced blood flow within microcirculation and chronic activation of platelets.[9] While our patient had a normal hematocrit during his admission at our institution, his hematocrit within the 1st week of life remains unknown.

Clinicians should consider PTE in any patient presenting with unexplained acute respiratory distress or hypoxemia. These patients should undergo an infectious workup and receive empiric antibiotics, in addition to fluid resuscitation and respiratory support as indicated; these interventions resulted in significant improvement in our patient's clinical status. A transthoracic echocardiogram should be obtained to evaluate for structural abnormalities, with meticulous assessment of the pulmonary arteries and veins, but most importantly to assess RV size, function, and estimated systolic pressure. CT angiography is an excellent modality for assessing pulmonary vasculature and investigating lung parenchymal disease and ischemic injury in patients with suspected PTE.[10] Of note, angiography can detect a pulmonary thrombus in up to 75% of adult patients with a specificity of 99% but is significantly more challenging in small infants.[11]

Once the diagnosis of PTE is confirmed, a comprehensive workup for hypercoagulable disorders and maternal

autoimmune or rheumatologic disorders is warranted. Although our patient had low levels of protein C, protein S, and antithrombin III activity, these abnormalities are common in premature neonates and normalize throughout infancy, and they are not thought to be associated with thrombosis in this age group.[12,13] Moreover, D-dimer levels are often elevated in neonates and as a result, our patient's abnormal D-dimer result similarly did not serve as a reliable screening tool for pulmonary arterial thrombi.[14]

Management is especially challenging in preterm infants with hemodynamic instability requiring systemic thrombolytics. Premature infants have an increased risk for bleeding complications, including intracranial hemorrhage, and require close monitoring with frequent neurologic assessments and head imaging while undergoing treatment.[15] Surgical thrombectomy in neonates may be an option; however, removing small or distal pulmonary thrombi is technically challenging. Catheter-based approaches are also available, although 44% of patients require reintervention with angioplasty or repeat thrombectomy and in neonates, vascular size restrictions will limit the ability to use all percutaneous tools.[16] With regard to medical management, tPA is the thrombolytic agent of choice in children, but evidence-based guidelines regarding its optimal use, dosage, and efficacy are limited.[17-19]

When administering tPA, it is critical to minimize the risk of serious bleeding, which occurs in up to 15% of patients and can be life threatening.[20] Studies have shown that using a low-dose regimen of tPA (0.01–0.06 mg/kg/h) has equivalent resolution rates but is safer when compared to using standard adult-derived dosing regimens (0.1–0.5 mg/kg/h).[17,19,21] Patients receiving thrombolytic therapy should be monitored closely with coagulation testing for ongoing adjustments in therapy, along with frequent imaging by echocardiography and CT scans to guide the duration of treatment. Any concern for a serious bleed should prompt immediate discontinuation of the thrombolytic agent and administration of blood products as indicated. However, it is worth noting that minor bleeding occurs in over 25% of patients, most commonly from sites of intravenous lines or catheterization sites, and can often be treated with local control, including pressure bandages or topical hemostatic agents (e.g., topical thrombin).[17,19]

CONCLUSIONS

Although rare, the diagnosis of PTE should be considered in all patients presenting with unexplained respiratory symptoms and echocardiographic evidence of RV hypertension or right heart failure. RV hypertension and right-to-left shunting through an interatrial communication should not automatically result in a diagnosis of pulmonary arterial hypertension, and a thorough assessment should always include the possibility of acute thrombotic occlusion of the pulmonary arteries. PTE may result in the development of severe RV hypertension and right heart failure, as was the case for our patient. While prompt recognition and treatment of pulmonary thromboembolic diseases are of paramount importance for achieving a successful outcome, further studies are needed to establish concrete guidelines for the management of thromboembolic diseases in children.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's guardian has given consent for the child's images and other clinical information to be reported in the journal. The guardian understands that name 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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