JACC: CASE REPORTS VOL. 3, NO. 9, 2021

CASE REPORT

INTERMEDIATE

CLINICAL CASE

Occlusive Pulmonary Artery Thrombosis in a Healthy Neonate With No Identifiable Risk Factors

Cynthia Laviolette, PA-C, Jason Turner, MD, LaTasha Lewis, MD, Song-Gui Yang, MD, Tim Pettitt, MD, Kurt D. Piggott, MD

ABSTRACT

Pulmonary artery thrombosis is reported in neonates with risk factors for hypercoagulability. No consensus exists regarding standard therapy for this condition. We present a neonate, with no risk factors for thrombosis, who was admitted after birth to the Pediatric Cardiac Intensive Care Unit with an occlusive left pulmonary artery thrombus. **(Level of Difficulty: Intermediate.)** (J Am Coll Cardiol Case Rep 2021;3:1216–20) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

The patient was a 3.1 kg male born at 40-weeks gestation to a 22-year-old gravida 1, para 0 via caesarean section for fetal decelerations. There was prolonged rupture of membrane (PROM) for 7 days. The mother was Group B Streptococcus negative; there was no meconium, maternal fever, or chorioamnionitis. The Apgar scores were 9 and 9.

The infant was dusky after delivery with oxygen saturations at 70%, which did not improve with blow-by oxygen. Other vital signs included a heart rate of 152 beats/min, respiratory rate of 40 breaths/min, and blood pressure of 51/28 mm Hg. On examination, the patient was in not acute distress but was cyanotic in room air. Work of breathing was unlabored with clear lung fields bilaterally. Cardiac examination demonstrated a regular rate and rhythm without murmur, and distal pulses in all extremities were 2+. The abdomen was soft and not distended.

Respiratory support was escalated to 4 l/min via high-flow nasal cannula with 100% oxygen, increasing oxygen saturations to 80% to 90%.

LEARNING OBJECTIVES

- Be able to create a differential diagnosis for the hypoxic neonate.
- Understand the maternal and patient risk factors for neonatal thrombosis.
- Know management strategies for neonatal pulmonary artery thrombus treatment.

MEDICAL HISTORY

Maternal history was significant for anxiety, attention-deficit/hyperactivity disorder, and tetrahydrocannabinol use; it was negative for miscarriage, systemic lupus erythematous, or antiphospholipid syndrome.

From the Children's Hospital New Orleans-Heart Center, New Orleans, Louisiana, USA.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received December 3, 2020; revised manuscript received January 15, 2021, accepted February 5, 2021.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2021.02.009

DIFFERENTIAL DIAGNOSIS

Differential diagnoses included persistent pulmonary hypertension of the newborn, congenital heart disease, premature ductal closure, meconium aspiration syndrome, or sepsis.

INVESTIGATIONS

Chest x-ray showed no lung field abnormalities. A blood culture was obtained, and empirical ampicillin and gentamicin were started. An initial echocardiogram showed a structurally normal heart with possible left pulmonary artery (LPA) hypoplasia, right to left shunting across a patent foramen ovale (PFO), and no patent ductus arteriosus (PDA).

In the cardiac intensive care unit, a repeat echocardiogram revealed a large echogenic mass in the LPA with no anterograde flow (**Figure 1**). Additional findings included a significantly increased right ventricular (RV) systolic pressure estimate and moderately depressed RV function.

On day of life (DOL) 1, chest computed tomography angiography (CTA) confirmed the presence of an occlusive LPA thrombus (**Figure 2**). The left lung had no cystic changes, distal thrombi, or hypoplastic regions.

MANAGEMENT

Upon cardiac intensive care unit admission, a prostaglandin E_1 infusion was initiated at 0.03 μg/kg/min for possible LPA coarctation secondary to ductal closure. Once thrombus was confirmed by CTA, the infusion was discontinued (total infusion time: 9 h). The patient remained on 2-l high-flow nasal cannula with 100% oxygen, maintaining saturations in the mid-90%.

Hematology/oncology was consulted. The workup included: prothrombin time/international normalized ratio, partial thromboplastin time, fibrinogen, D-dimer, antithrombin III, factor V activity, and protein C and S antigens. All results were unremarkable. Enoxaparin therapy was initiated at 1 mg/kg subcutaneously every 12 h.

Repeat CTA on DOL 2 showed no LPA thrombus change. The decision was made to use systemic tissue plasminogen activator (tPA) for thrombolysis. The patient's baseline fibrinogen was 228 mg/l, so fresh frozen plasma was transfused to maintain the level of ≥300 mg/dl. tPA was started at 0.05 mg/kg/h, then advanced to 0.1 mg/kg/h after 1 h. Supplemental oxygen was discontinued 18 h later; an echocardiogram subsequently confirmed a patent LPA. Total systemic tPA therapy was 41 h.

Admission head ultrasound (before anticoagulation) showed no hemorrhage. Daily head ultrasounds remained normal throughout tPA therapy and at discharge. Empirical antibiotics were discontinued after 48 h of negative blood cultures.

CTA on DOL 4 showed LPA thrombus resolution (**Figure 3**). Enoxaparin therapy was resumed at 1 mg/kg every 12 h for further thrombus prevention. A lung perfusion scan on DOL 7 was normal (**Figure 4**), and an echocardiogram demonstrated resolution of increased RV systolic pressure and function normalization. The patient was discharged on DOL 9.

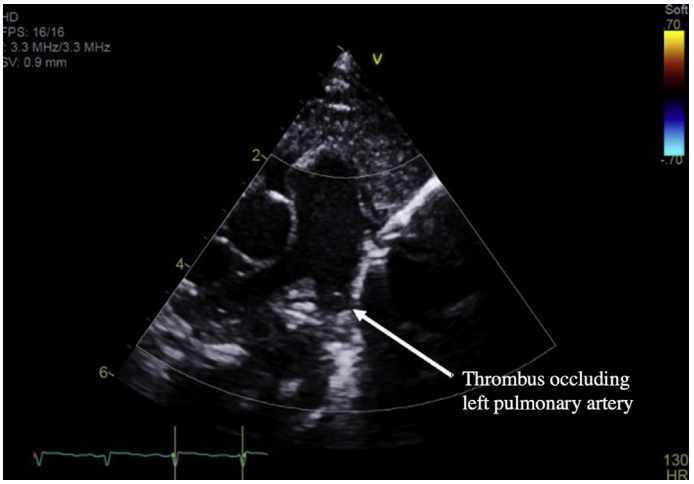
DISCUSSION

Among neonatal thrombi, 24% to 34% are arterial; among those, incidences isolated to the pulmonary artery are not described (1). Pulmonary artery thrombi are incidentally found as clinicians evaluate the hypoxic neonate for disorders, including persistent pulmonary hypertension of the newborn and

ABBREVIATIONS AND ACRONYMS

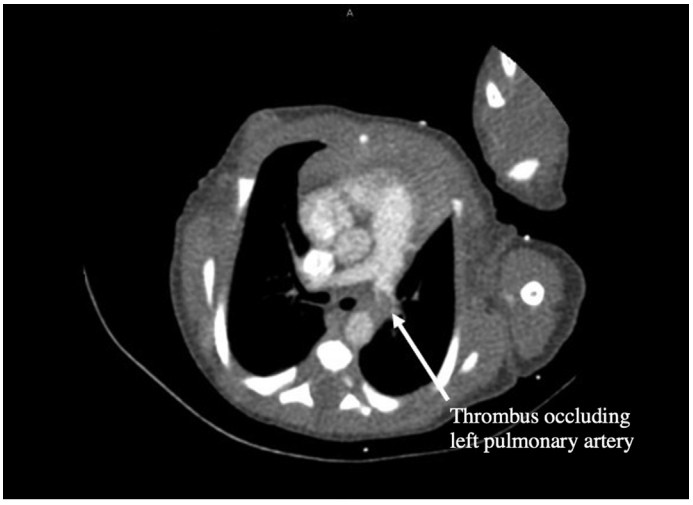
CTA = computed tomography angiography
DOL = day of life
LPA = left pulmonary artery
PDA = patent ductus arteriosus
PFO = patent foramen ovale
PROM = prolonged rupture of membrane
RV = right ventricle
tPA = tissue plasminogen activator

FIGURE 1 Left Pulmonary Artery Thrombus (Echocardiogram)



Echocardiogram demonstrating occlusive left pulmonary artery thrombus.

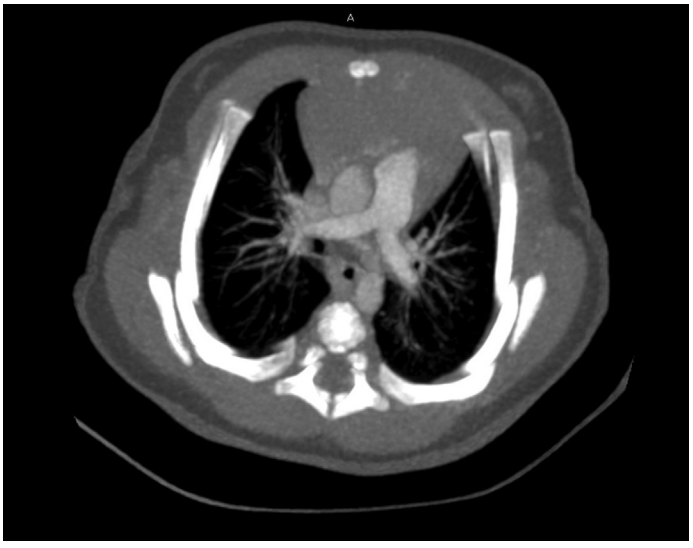
FIGURE 2 Left Pulmonary Artery Thrombus (Computed Tomography)



Chest computed tomography angiography demonstrating occlusive left pulmonary artery thrombus.

congenital heart disease (2,3). Reports of neonates with clinically significant, isolated pulmonary artery thrombi describe the presence of hypercoagulable risk factors. Management strategies vary, ranging from invasive (surgical or catheter-based) to pharmacological.

FIGURE 3 Left Pulmonary Artery Thrombus Resolution



Computed tomography angiography demonstrating patent left pulmonary artery after tissue plasminogen activator.

This case adds valuable information to the small body of evidence on neonatal pulmonary artery thrombosis. First, and most importantly, it is the only known report of a completely occlusive LPA thrombus in a neonate without an identifiable risk factor. Second, it adds credence to the hypothesis that this phenomenon may be associated with ductus arteriosus closure. Finally, it demonstrates safe and efficacious use of tPA in a neonate.

The neonatal anticoagulation system is immature; any insult affecting the coagulation cascade, vascular integrity, or intravascular blood flow increases hypercoagulability risk (4). Factors implicated in neonatal thrombosis are, maternally, diabetes mellitus, systemic lupus erythematous, coagulopathies, chorioamnionitis, and antiphospholipid syndrome. Thrombosis occurs in neonates with hypoxia, oligohydramnios, septicemia, congenital heart disease, congenital vascular anomalies, or inherited coagulopathies (1,5). Indwelling vascular access is also a cause (4); for our patient, LPA occlusion was noted before line placement.

The PROM duration was notable, but not thought to be contributory. PROM is associated with maternal and infantile infection, of which there was no evidence. In addition, PROM alone, without a concomitant infection, is not reported to be associated with hypercoagulable states in newborns.

Reports of neonates with comparable disease severity had hypercoagulable risk factors, whereas the maternal and birth histories and inpatient workup for our patient revealed no setup for the event. We questioned—could pulmonary artery thrombosis of this magnitude occur without risk factors? To answer, we turned to anatomical observations and comparisons, which suggested a new contributor—the ductus arteriosus.

Some case reports describe thrombus within, and extending out of, the PDA into the LPA and beyond (5,6). Although origins of these thrombi are indeterminable, their distributions suggest derivation from the ductus arteriosus, which possibly acts as a platform from which thrombus extension into the pulmonary arteries occurs. In 2005, Goble et al. (7) described 2 neonates incidentally found to have small, nonocclusive LPA thrombi. The investigators speculated these were related to premature ductal closure. One patient had a risk factor for thrombosis (maternal diabetes mellitus); the other did not.

Our patient had an absent ductus arteriosus; we concluded it closed before birth. The occlusive LPA thrombus was located where the PDA insertion site is normally observed. Based on this, we agreed with the theory that premature PDA closure may create

FIGURE 4 Lung Perfusion Scan

	Left Lung		Right Lung	
	%	Kct	%	Kct
Upper Zone:	11.6	55.07	12.2	57.56
Middle Zone:	22.7	107.63	26.9	127.21
Lower Zone:	13.9	66.00	12.7	59.98
Total Lung:	48.3	228.70	51.7	244.75

No perfusion defects evident after thrombolytic therapy. Kct = number of counts; Ll = left lower zone; Lm = left middle zone; Lu = left upper zone; Rl = right lower zone; Rm = right middle zone; Ru = right upper zone.

substrate for thrombus formation (7); however, we must expound on that hypothesis. Our case suggested a neonate with no risk factors for thrombosis could experience complete thrombotic occlusion of the pulmonary artery secondary solely to PDA closure. In other words, ductal closure could precipitate a thrombotic incident of greater clinical significance than previously described.

The literature presents several management strategies. These include anticoagulation with heparin or low-molecular-weight heparin, surgical thrombectomy, catheter-based embolectomy, or thrombolysis with tPA (2,5,6,8). In our patient, because of complete LPA occlusion, elevated RV pressures, and persistent hypoxia without supplemental oxygen, thrombolysis was preferred for rapid clot dissolution. We sought to maximize medical therapies before pursuing an invasive procedure, which posed additional risks and recovery time. Had systemic tPA been unsuccessful, catheter-directed tPA administration was the preferred next management step.

FOLLOW-UP

A hematology/oncology appointment 6 months after discharge documented a healthy newborn with no acute concerns. Chest CTA was normal, and laboratory workup unremarkable. The patient was off of therapeutic enoxaparin for 3 months, after completing a 3-month course.

CONCLUSIONS

Although neonatal pulmonary artery thrombosis remains rare, the diagnosis should be considered in the cyanotic neonate. Based on our observations, further studies and information sharing are warranted to determine a relationship between ductal closure and thrombus formation. Premature PDA closure in the healthy neonate may be a risk factor for occlusive pulmonary artery thrombosis. Our experience can reassure clinicians that, with close observation, tPA can be efficacious and safe in neonates.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Cynthia Laviolette, Children's Hospital New Orleans, 200 Henry Clay Avenue, Cardiac Intensive Care Unit, New Orleans, Louisiana 70118, USA. E-mail: cynthia.laviolette@lcmchealth.org.

JACC: CASE REPORTS, VOL. 3, NO. 9, 2021
AUGUST 2021:1216–20

REFERENCES

1. Chalmers EA. Neonatal thrombosis. J Clin Pathol 2000;53:419–23.

2. Sawyer T, Antle A, Studer M, et al. Neonatal pulmonary artery thrombosis presenting as persistent pulmonary hypertension of the newborn. Pediatr Cardiol 2009;30:520–2.

3. Kenny D, Tsai-Goodman B. Neonatal arterial thrombus mimicking congenital heart disease. Aech Dis Child Fetal Neonatal Ed 2007;92:F59–61.

4. Rimensberger P, Humbert J, Beghetti M. Management of preterm infants with intracardiac thrombi: use of thrombotic agents. Paediatr Drugs 2001;3:883–98.

5. Clapp S, Bedard M, Farooki Z, et al. Pulmonary artery thrombus associated with the ductus arteriosus. Am Heart J 1986;111:796–7.

6. Pagotto L, Tani L, Raetz E, et al. Echocardiographic diagnosis of thrombus originating from the ductus arteriosus. J Am Soc Echocardiogr 1999;12:79–81.

7. Goble M, Gomez C. Neonatal pulmonary artery thrombosis: echocardiographic characteristics and possible contributing factors. J Am Soc Echocardiogr 2005;18:e1–4.

8. DeMeo SD, Sherwood A, Hornik CD, et al. Pulmonary artery thrombus in a premature neonate treated with recombinant tissue plasminogen activator. J Perinatol 2014;34:569–71.

KEY WORDS **cyanosis, neonate, pulmonary artery, thrombus, tissue plasminogen activator**