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Ductus Arteriosus Aneurysm and Pulmonary Artery Thromboses in a Protein S-Deficient Newborn

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Abstract

Ductus arteriosus aneurysm (DAA) asymptomatically occurs in newborn infants and resolves spontaneously. High-risk DAA with compression, rupture, and thrombosis requires early surgical intervention. Newborn infants have the highest risk of thrombosis among pediatric patients, but the genetic predisposition is difficult to determine in infancy. We herein report a neonatal case of massive thromboses in DAA and pulmonary artery. Desaturation occurred in an active full-term infant 2 days after birth. Echocardiography and contrast-enhanced computed tomography indicated thrombotic occlusion of the DAA and pulmonary artery thrombus. Urgent thrombectomy and ductus resection were successfully performed. After 6 months of anticoagulant therapy, the dissociated low plasma activity levels of protein S from protein C suggested protein S deficiency. A genetic study of *PROS1* identified a heterozygous variant of protein S K196E, a low-risk variant of thrombophilia in Japanese populations. There have been seven reported cases with neonatal-onset symptomatic thromboses of DAA involving the pulmonary artery. All survived without recurrence after surgical intervention in five and anticoagulant therapy alone in two. Two newborns had a heterozygous methylenetetrahydrofolate reductase (*MTHFR*) variant, but information on thrombophilia was not available for any other cases. A genetic predisposition may raise the risk of DAA thrombosis, leading to rapid progression.

Keywords
- ductus arteriosus aneurysm
- thrombophilia
- protein S deficiency
- K196E

Ductus arteriosus aneurysm (DAA) occurs in 8.8% of full-term newborn infants as a secondary event to altered intimal cushion formation or delayed aortic segment closure of the ductus.[1,2] It usually develops asymptomatically and resolves spontaneously but can present with murmur, cyanosis, respiratory distress, and feeble cry, along with a ductal bump on chest X-ray.[3] Urgent surgical repair is performed in cases at a high risk of compression or rupture.

Another lethal complication is occlusive thrombosis of DAA involving the pulmonary artery and systemic organs.

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Because intra-arterial thrombus formation affects approximately 30% of symptomatic cases of DAA,[4] the early detection of high-risk DAA is mandatory for curative intervention. However, little information is available concerning the genetic risk of progressive thrombosis in DAA.

Protein S deficiency is the leading cause of heritable thrombophilia in Japanese adults with thromboembolism.[5] The most prevalent allele is protein S-Tokushima (K196E), which is found in approximately 2% of the Japanese population as a type II phenotype of natural anticoagulant deficiency with almost normal total and free protein S antigen levels to decrease activated protein C cofactor activity.[6,7] The prothrombotic risk of the variant has been considered to increase with age and to also be augmented by the accompanied factors for the development of thrombosis. The risk of thrombosis in pediatric patients is highest in the early neonatal period. There have been only two reported cases of thrombosed DAA in association with a genetic predisposition toward thrombosis.

We herein report the first case of neonatal thromboses of DAA and the pulmonary artery associated with congenital protein S deficiency. Furthermore, based on a literature review on DAA thrombus and thrombophilia, we also discuss about the prothrombotic effect on the development of high-risk DAA thrombosis in newborns.

Case Presentation

A male infant who weighed 3,060 g at 40 weeks' gestation was born through vaginal delivery after an uneventful pregnancy. He was the first child of a family with no history of miscarriage, bleeding, or thromboembolism. There was no asphyxia at birth. Breastfeeding was started for the active newborn infant. Two days after birth, the infant's percutaneous oxygen saturation (SpO_2) levels at right upper extremity decreased to 93% without changes in the vital signs. Echocardiography showed a closed ductus arteriosus and a secundum atrial septal defect with a right-to-left shunt that did not require monitoring of central venous catheterization. Because follow-up echocardiography 7 days after birth revealed a massive lesion occupying the bifurcation of the left pulmonary artery (LPA), this infant was immediately transferred to the neonatal and pediatric intensive care unit of Fukuoka Children's Hospital.

On admission, the afebrile and nondysmorphic infant showed no cyanosis, tachycardia, or respiratory distress. Resting SpO_2 was 99% at the right upper extremity, 98% at the left upper extremity, 98% at the right lower extremity, and 94% at the left lower extremity, with no significant differences among the extremities. SpO_2 at the right upper extremity dropped to the 70 to 80% range during crying, but measurements were not taken at the extremities at this time. Cardiorespiratory sounds were unremarkable. There was no hepatosplenomegaly. Chest radiography showed a cardiothoracic ratio of 51% and normal lung vascularity. Echocardiography showed a high-intensity mass of 6.5 mm × 4.3 mm diameter in the LPA bifurcation on short-axis imaging (►**Fig. 1A**), with a mild acceleration of 2.3 m/s at the same site. A sagittal view of the aortic arch showed a mass attached to the DAA (►**Fig. 1B**). There was no narrowing of the aortic arch due to thrombus protrusion to the aortic side. Contrast-enhanced computed tomography indicated a 4.6 mm × 13.2 mm thrombus within the DAA protruding into the LPA bifurcation (►**Fig. 1C**). No other thromboembolic lesions were identified in the brain or whole body. Peripheral blood counts showed a leukocyte count of 17.10^9/L, hemoglobin level of 15.2 g/dL, and platelet count of 408×10^9/L. Coagulation studies showed a normal prothrombin time (12.4 seconds, reference range [rr]: 10.0–15.0), activated partial thromboplastin time (33.6 seconds, rr: 24.0–39.0), fibrinogen concentration (291 mg/dL, rr: 200–400), and fibrinogen degradation product level (3.7 μg/mL, rr: 0.0–5.0). The D-dimer level was slightly elevated to 1.6 μg/mL (rr < 1.0). The plasma activity levels of total protein C and protein S were each 38%. These were subnormal levels according to the lower limits of age-dependent standards (age < 90 days: protein C 45%, protein S 42%),[8] no antigen or free level of protein S was measured.

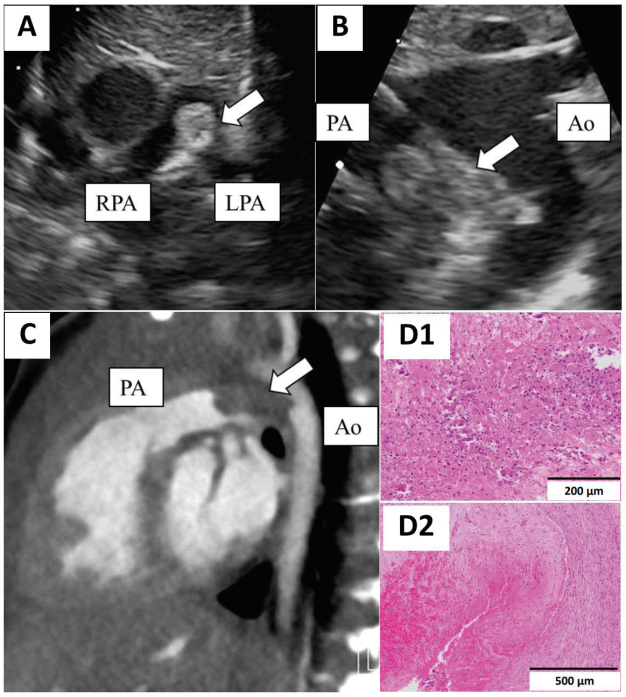

Fig. 1 Echocardiography and contrast-enhanced computed tomography (CT) findings on admission and results of a histological examination of the resected specimen. (**A**) An echocardiographic short-axis view shows a hyperintense mass ~ 6.5 mm × 4.3 mm in diameter in the left pulmonary artery (LPA) bifurcation upon short-axis imaging, with a mild acceleration of 2.3 m/s at the same site. (**B**) In the sagittal view of the aortic arch, the mass occupies the ductus arteriosus, indicating a thrombus. Ao, aorta; LPA, left pulmonary artery; RPA, right pulmonary artery; PA, pulmonary artery. (**C**) Sagittal reconstruction of contrast-enhanced computed tomography shows a 4.6 mm × 13.2 mm thrombus within the ductus arteriosus aneurysm (DAA) continuously protruding into the LPA bifurcation. Ao, aorta; PA, pulmonary artery. (**D1**) A histological examination shows that the vascular lumen is filled with blood clots with focal organization and calcification. (**D2**) A histological examination of the thrombus shows fibrinous materials with inflammatory cells and a few fibroblasts, accompanied by calcification.

Considering the complications of thrombolytic therapy and recurrent thromboembolism with residual DAA, the infant underwent thrombectomy and ductus resection 8 days after birth. A thrombus occupied the LPA bifurcation. The ductus showed a closed aortic side and dilated pulmonary artery side. A histological examination showed an organized thrombus and fibrous materials with few inflammatory cells, calcification, and blood clots within the vascular vessels in the ductus (►**Fig. 1D**). The patient received unfractionated heparin to keep around 40 seconds of activated partial thromboplastin time. Oral aspirin was administered at 5 mg/kg/day for 6 months postoperatively. He was discharged without complications.

The plasma activity levels of protein C, protein S, and antithrombin were then followed. At 1 year old, the protein C level had increased to 119%, but the protein S level had increased to 47% of the lower limit for age (the lower limits of each activity: age 90 days–2 years: protein C 64%, protein S 51%). The dissociation between the protein S and protein C levels prompted us to complete the genetic analysis of *PROS1*, which identified a heterozygous single-nucleotide substitution in exon 6 of *PROS1* (c.586A > G, p.K196E, protein S-Tokushima) in this infant. A family study after obtaining informed consent revealed a healthy mother, but the father had 45% of the borderline plasma protein S activity and the same heterozygous variant.

Discussion

This is the first case report of DAA and pulmonary artery thromboses in association with protein S deficiency. There have been eight cases of newborn-onset DAA complicated with pulmonary artery thromboses, including the present patient (►**Table 1**).[9–13] One prenatally diagnosed case resulted in stillbirth.[14] All eight diagnosed cases after birth survived without recurrence or complications. Three infants underwent surgical interventions and anticoagulant therapy for a median of 4.5 months, ranging from 3 to 6 months. Two received anticoagulant therapy alone for 5 weeks. Six infants presented with clinical signs or symptoms within the first 72 hours of life, reportedly defined as the high-risk period for neonatal thrombosis.[15] Two newborn infants had a heterozygous methylenetetrahydrofolate reductase (*MTHFR*) variant, C677T, one of whom had a trigger for thrombosis (central venous catheterization). No prothrombotic factors were described in the remaining cases. Considering the existence of two previous cases with a similar low-risk genetic predisposition toward thrombosis, the monoallelic variant of protein S might have augmented the progressive thrombus formation during the high-risk neonatal period. Because plasma activity levels of natural anticoagulants are unable to be used to diagnose newborn thrombophilia, follow-up studies and genetic testing are needed during and after anticoagulation therapy.

More than 60% of symptomatic DAA cases have aneurysms filled with thrombi that disappear with organization and fibrosis.[2] During the closure of aneurysm, initial changes begin on the pulmonary artery side because thrombogenesis is related to turbulent flow or endothelial injury within the narrowing pulmonary ductus segment.[16] Delayed closure of the pulmonary side can thus be a trigger for developing thrombosis. The histopathological findings in the present patient suggested the delayed closure of DAA followed by the progression to pulmonary artery thrombosis.

Table 1 Reported cases of neonatal-onset thrombosis of ductus arteriosus aneurysm involving pulmonary artery

Case	Age at diagnosis	Signs and/or symptoms	Management/ Outcome	Thromboprophylaxis on anticoagulants	Associated conditions	Genetic predisposition	Reference
1	0 day	Heart murmur, cyanosis	Surgery/alive	3 months after surgery	Maternal GDM	Heterozygote of *MTHFR* C677T	Nyp et al, 2011[9]
2	0 day	Respiratory distress	Aspirin/alive	Aspirin for 5 weeks	Not described	Not described	Masood et al, 2015[10]
3	1 day	vomit, collapse, hepatomegaly	Surgery/alive	None	Prolonged PT and APTT	Not described	Fripp et al, 1985[11]
4	1 day	Respiratory distress, PH	Enoxaparin/ alive	Not described about period	Umbilical line	Heterozygote of *MTHFR*	Ciliberti et al, 2016[12]
5	1 day	Differential cyanosis	Heparin, surgery/alive	Not described about postoperative anticoagulants	Not described	Not described	Aly et al, 2020[13]
6	2 days	Cyanosis	Surgery/alive	6 months after surgery	Protein S deficiency	Heterozygote of *PROS1* A586G	Present case
7	5 days	Heart murmur, cyanosis	Surgery/alive	Not described	Not described	Not described	McArdle et al, 2017[1]
8	11 days	Heart murmur, cyanosis	Surgery/alive	Not described	Not described	Not described	Dyamenahalli et al, 2000[3]

Abbreviations: APTT, activated partial thromboplastin time; GDM, gestational diabetes mellitus; *MTHFR*, methylenetetrahydrofolate reductase; PH, pulmonary hypertension; PT, prothrombin time.

The major concern is the impact of protein S-Tokushima on thrombus formation in this patient with DAA. Among seven reported neonatal cases of symptomatic DAA and pulmonary artery thromboses (►**Table 1**), thrombotic predisposition factors were found in two: maternal diabetes, catheter insertion, and *MTHFR* variants. Maternal diabetes has been reported as a nongenetic risk factor of DAA as well as umbilical artery thrombosis.[17] Although the effect size of *MTHFR* variants (C677T, A1298C) is weak, a recent integrative study demonstrated the significant risk of heterozygous *MTHFR* C677T (odds ratio: 1.33).[18] We did not conduct a genetic study for *MTHFR* variants in the present patient because (1) approximately half of healthy Japanese individuals have an allele of *MTHFR* C677T (AV genotype), and (2) the VV but not the AV genotype is a significant risk factor for adult Japanese patients with deep vein thrombosis.[19] Both previous patients with a *MTHFR* variant had other nongenetic prothrombotic factors including maternal diabetes and umbilical line. However, the present patient with protein S-Tokushima did not have other nongenetic prothrombotic factors. Three heterozygotes of *PROS1* or *MTHFR* variants presented within the first 3 days of life, the period during which the majority of cases of neonatal thrombosis reportedly occur, regardless of heritable thrombophilia. Protein S-Tokushima is the most frequent allele, being present in approximately 2% of the Japanese population. The risk of deep vein thromboembolism in Japanese adults with *PROS1* A586G has been estimated to have an odds ratio of 2.15 (95% confidence interval, 1.16–3.99).[20] In this context, the rapid progression to massive thrombosis in the pulmonary artery of this patient may be attributable to the significant effect of the protein S variant during the critical prothrombotic period of the first 3 days of life. Hypercoagulability is associated with the circulating amount of free protein S, not total protein S. At present, plasma activity levels of free protein S are not measured as the clinical laboratory testing. Because of low complement C4-binding protein (C4BP) in the fetal and neonatal blood, protein S circulates as the free form during the perinatal period.[21] The relatively high levels of free protein S were reported in fetal blood but not always neonatal blood.[22] The balanced effect between the increasing C4BP and relatively decreasing free protein S on the hypercoagulability after birth may contribute to the progression of neonatal thrombosis. In this setting, we emphasize that the borderline levels of total plasma protein S activity need to be followed until a sufficient rise to age-dependent standard ranges. There is no consensus concerning appropriate thromboprophylaxis in patients with DAA. Future screening on thrombophilia may be required to reduce the developing risk of neonatal thrombosis in the era of genomic medicine.

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Conflict of Interest
None declared.

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