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The management of neonatal venous thrombosis – an interdisciplinary team effort

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ABSTRACT

Managing venous thrombosis in neonates poses numerous difficulties. Thrombotic events, whether arterial or venous, in newborns, can lead to significant morbidity and mortality within the hospitalized infant population. Neonates represent the age group with the highest susceptibility to developing thrombosis among pediatric patients. The evolving coagulation system, the necessity for intensive care, which often involves invasive procedures, and the presence of coexisting medical conditions collectively render neonates more prone to developing thrombosis compared to older children. Neonatal thrombosis is intertwined with the well-being of the mother and the newborn. We report a case of a very preterm newborn (30 weeks of gestation), extremely low birth weight (900g), with a multitude of prematurity-related complications, who developed venous thrombosis at 5 weeks of life. She underwent prolonged hospitalization in the NICU, required mechanical ventilation, received nutritional and metabolic support via a central venous catheter, and complex treatments for sepsis with Staphylococcus CoNS. Genetic and hematology consults raised questions about the genetic basis of the thrombosis pathology, specifically thrombophilia or a RASopathy (Phenotype Noonan-like Syndrome). The prompt identification of risk factors leads to early therapeutic intervention, and multidisciplinary assessments are necessary to manage it.

Conclusions. Neonatal thrombosis is impacted by many risk factors, encompassing genetic predispositions and perinatal complications. Notably, the NICU's environment is pivotal. Extended periods of immobility, invasive procedures, and the utilization of medical devices such as central venous catheters heighten the vulnerability to thrombosis in these fragile patients.

Keywords: prematurity, neonatal thrombosis, central catheterization, genetic predisposition

Abbreviations (in alphabetical order):

APTT – activated partial thromboplastin time
ASD – atrial septal defect
CPAP – continuous positive airway pressure
CVC – central venous catheter
IPPV – intermittent positive pressure ventilation
IUGR – intrauterine growth restriction
NICU – neonatal intensive care unit
PDA – patent ductus arteriosus
PICC line – peripherally inserted central catheter line
PT – prothrombin time
VTE – venous thromboembolism

INTRODUCTION

Managing thrombosis in critically ill infants presents a challenging clinical issue. Although the occurrence of bleeding and thrombosis is comparatively low in the general pediatric population when compared to adults, these critically ill children en-

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counter distinctive hemostatic challenges. Our comprehension of coagulation has progressed from a sequential cascade of enzymatic reactions to a fluid network involving interactions among plasma proteins, endothelium, foreign surfaces, and inflammatory cells. The reactions to tissue or endothelial injury and exposure to foreign surfaces are intricate and dynamic, posing challenges for timely, precise, and comprehensive hemostasis assessment in clinical settings. In the neonatal patient group, additional complexity arises from age-related alterations in hemostatic components. This is due to variations in levels, characteristics, and interactions of pro- and anticoagulant factors from infancy to adulthood [1].

The incidence of neonatal thrombosis ranges from 4.0 to 5.5 cases per 100,000, with increased occurrences observed among newborns hospitalized in intensive care units, where the incidence rises to 3–15 cases per 1000 patients [2]. Several factors contribute to this heightened vulnerability of critical infants in NICU: acute respiratory distress syndrome, immature hemostatic system, lung ventilation, systemic viral infections and complications, gestational age, preterm birth, low Apgar score, presentation anomalies, central venous catheter, immobility [2-4]. Neonatal thrombosis is intertwined with the well-being of the mother and the newborn [3]. Among the risk factors associated with maternal condition, we can highlight preeclampsia, placental insufficiency, systemic inflammatory disorders, gestational diabetes mellitus, maternal thrombophilia, and hypertension [2-4].

The clinical manifestation, diagnostic approaches, and therapeutic interventions for thrombotic complications in neonates exhibit variability contingent upon several factors, such as the cause of the thromboembolic incident, the specific anatomical site affected, and the concurrent medical conditions of the patient. In cases where thrombi are asymptomatic, the recommended approach entails allowing for spontaneous resolution without intervention, particularly upon catheter removal, as conservative management reduces the potential for bleeding complications linked to anticoagulant therapy. Commencing anticoagulant therapy becomes a feasible choice when the catheter removal is impractical, given the patient's clinical condition [5].

CASE REPORT

The 900-g, 30-week female infant with intrauterine growth restriction (IUGR), was delivered by cesarean section from breech presentation. The mother, a primigravida primipara, 40 years old, had pregnancy-induced hypertension controlled with Methyldopa and a uterine fibroid of 7 cm. To promote lung maturation, she was given one cure of Dexamethasone at 29 weeks of gestation. No noticeable results were observed during the infectious and genetic testing during pregnancy. The Apgar score was 6 at 1 minute and 7 at 5 minutes. The infant's early hospital course included respiratory distress syndrome, requesting non-invasive mechanical ventilation (nasal CPAP/ IPPV) for 4 days, subsequently oxygen therapy, with a concentration of 30% for another 4 days, metabolic and nutritional support, caffeine, prophylactic antibiotic therapy via central vein catheter made of polyurethane material, inserted at the left lower limb, located in an external vein (posterior tibial). In the third week of life, she presented mild increased work of breathing on clinical examination, and CO_2 retention and transition to invasive mechanical ventilation (endotracheal intubation) was performed and maintained for 19 days. She had episodes of feeding intolerance and remained on a slow feeding advance with formula (maternal contraindication for breast milk collection). At 5 weeks of life, she presented high inflammatory markers and a "left shift" on the white cell count. A blood culture subsequently grew Staphylococcus coagulase-negative (CoNS). On clinical evaluation, on the 38th day of life, the infant presented inguinal edema, color modifications (cyanosis and redness), and a visible, sinuous vein pathway on the median line of the right limb. Imaging evaluations, consisting of radiology and ultrasound examinations, concluded that the central vein catheter was still in place, inserted on the left leg, the tip located at the fourth lumbar vertebrae above the branch of the inferior vena cava.

DISCUSSION

Thrombotic events are rare among newborns, yet they are becoming more acknowledged as complications of modern neonatal care, adding to neonatal morbidity and mortality [6]. Critically ill and premature infants face numerous risk factors pre-

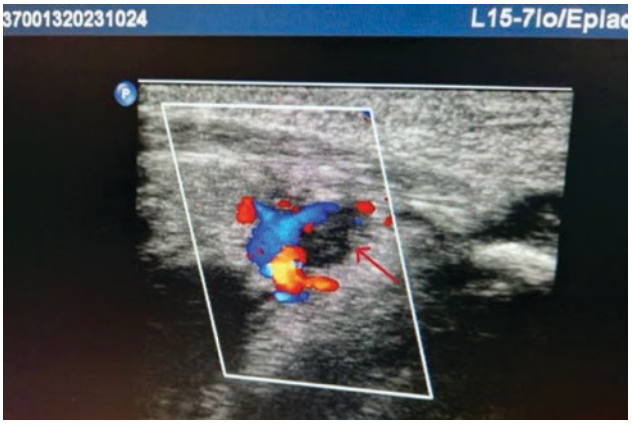

FIGURE 1. Vascular Doppler color ultrasound with a transverse axis at the level of the external iliac vessels, showing an occlusive thrombus at the distal level of the external iliac vein (arrow)

TABLE 1. Multidisciplinary consultations

Pediatric Cardiology	First examination • Cardiac ultrasound showed a moderate ASD and a small PDA. • Doppler examination on the lower right limb showed an occlusive thrombosis located in the distal segment of common iliac vein, right external iliac vein to right femoral vein, with significant collateral flow around the occlusion (Figures 1,2,3)			
	Second examination and third examination Conclusions: Right external iliac vein occlusive thrombosis			
Abdominal ultrasound	Normal kidney structure with a slight dilatation on the suprahepatic veins			
	Test	27/10/2023	21/11/2023	12/12/2023
	Antithrombin liquid	53%	53%	49%
	APTT	33.6s 1.08 ratio	33.7s 1.09 ratio	31.2s 1.01 ratio
	D-Dimer	467 ng/mL	248 ng/mL	183 ng/mL
	Fibrinogen Clauss	202 mg/dL	263 mg/dL	244 mg/dL
	Protein C	30%	25%	-
	PT	11.5s 97% 1.05 INR	11.7s 95% 1.06 INR	11.2s101% 1.02INR
	Protein S	88.5%	-	-
	Liquid Anti-Xa	0.00 IU/mL	0.10 IU/mL	0.06 IU/mL
Hematology consult	Presumptive diagnosis of thrombophilia vs. Noonan-like syndrome			
Genetic consult	Pregnancy history: genetic testing with normal results • Clinical exam: craniofacial dimorphism, broad forehead, larger anterior fontanelle, facial edema appearance, macrocrania, low and posterior implanted ears, large internipple distance, axial hypthonia • Sexual ambiguity, clitoral hypertrophy • Conclusions: RASopathy (Phenotype Noonan-like Syndrome) in observation			

TABLE 2. Clinical evolution and treatment

Day of life	Clinical manifestations	Treatment
Birth	PICC line was inserted (right arm)	Heparin continuous infusion 0.5 IU/ml
38	Inguinal edema, changes of color (cyanosis and redness), sinuous vein pathway on the inner region of the right leg	Heparin continuous infusion 15 UI/kg/h – 3 days
48	Right lower limb edema	Heparin continuous infusion 15 IU/kg/h -10 days
59	Good evolution	Enoxiparin 150 IU/kg/dose/24h
114	Discharge	Enoxiparin 100 IU/kg/dose/24h

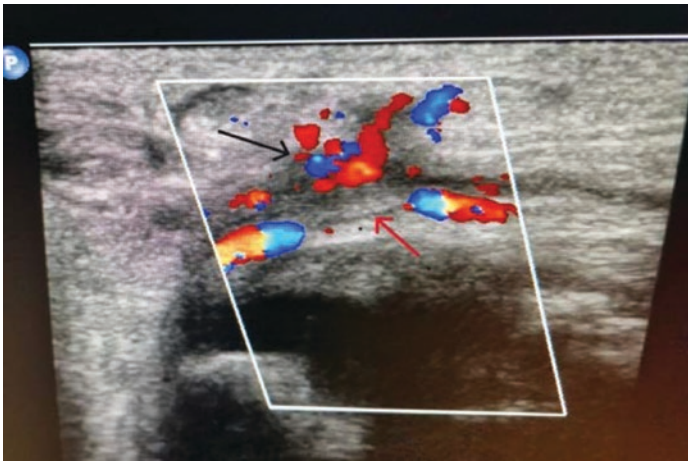

FIGURE 2. Vascular Doppler color ultrasound with a long axis at the level of the external iliac vessels, showing an occlusive thrombus at the distal level of the external iliac vein (red arrow); collateral venous circulation is also visible (black arrow)

disposing them to thrombotic events, such as developmental hemostasis, susceptibility to infections, and frequent requirement for central venous access. The clinical manifestation, diagnostic methods, and treatment approaches for thromboembolic complications in neonates differ depending on factors like the cause of the event, the affected anatomical site, and the infant's underlying health conditions [7].

Maternal risk factors associated with neonatal thrombosis include preeclampsia, placental insufficiency, gestational diabetes mellitus, hereditary or acquired thrombophilia, and hypertension [3,13]. In our case, the mother had pregnancy-induced hypertension and a uterine fibroid of 7 cm. Up to 56% of neonates diagnosed with venous thrombosis exhibit at least one ma-

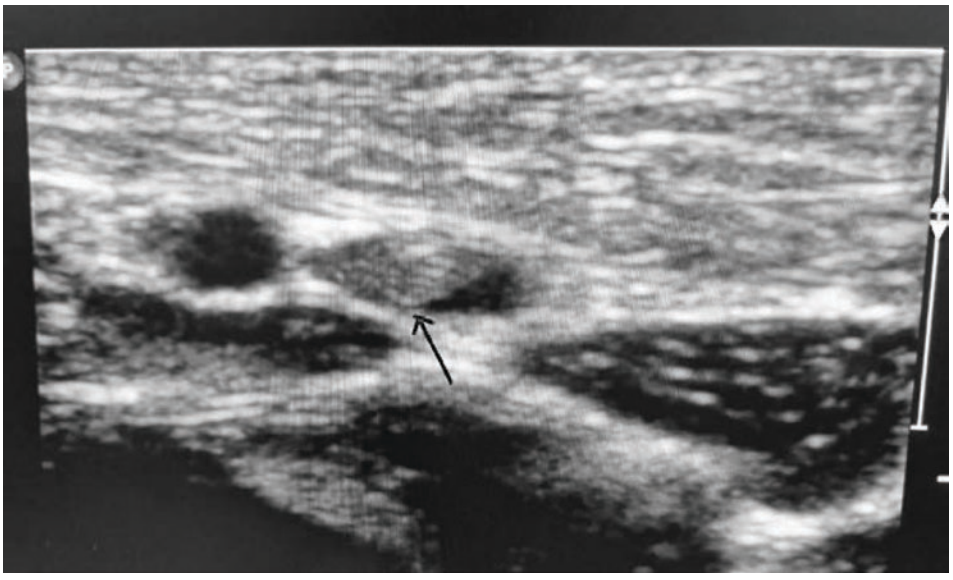

FIGURE 3. Vascular Doppler color ultrasound - transverse section at the level of the external iliac vessels showing a quasi-occlusive thrombus at the distal level of the external iliac vein (black arrow)

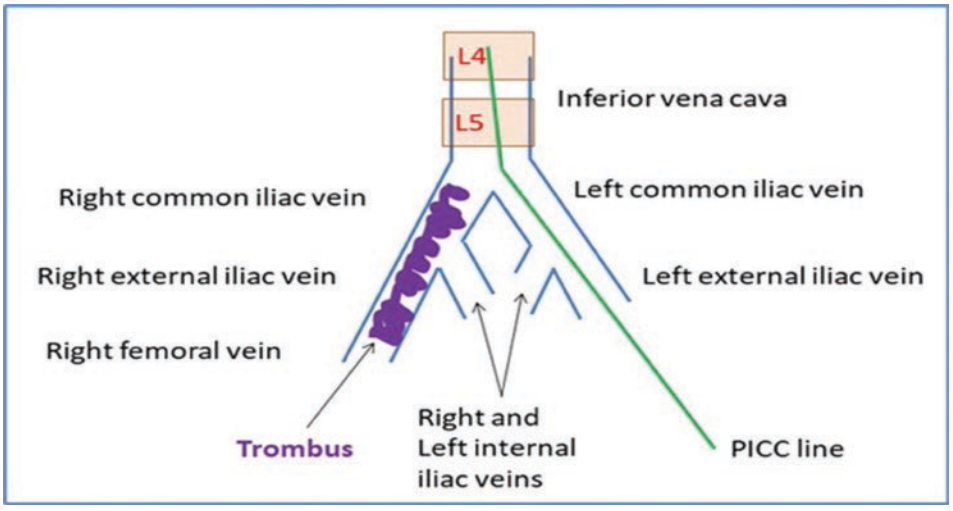

FIGURE 4. The anatomy of the iliac veins and the position of the percutaneous central venous catheter.
Legend: L4, L5 - lumbar vertebrae 4 and 5; PICC - percutaneous intravenous central catheter

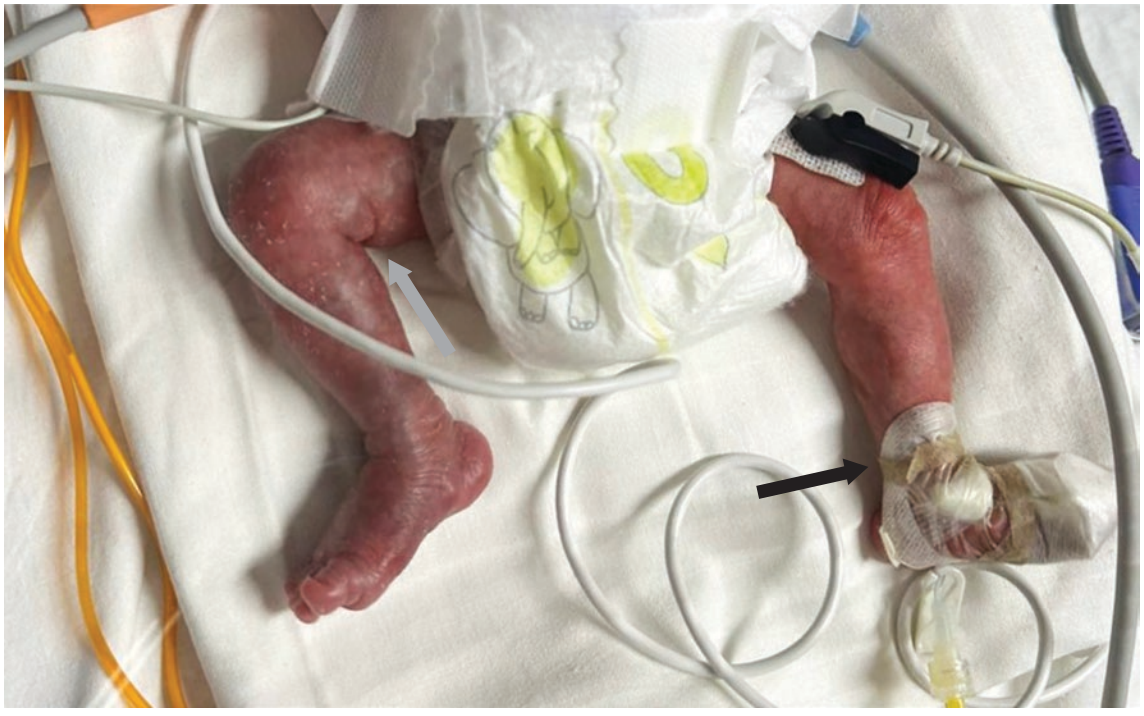

FIGURE 5. Clinical manifestation of venous thrombosis: edema, color modifications and sinuous vein pathway (gray arrow). PICC line located at the left limb (black arrow)

TABLE 3. Risk factors for neonatal thrombosis. Current literature vs our case [3,8-12]

	Current literature	Our case
Intrauterine risk factors	Preeclampsia Hypertension Placental insufficiency Gestational diabetes mellitus Maternal thrombophilia Maternal conditions leading to intrauterine growth restriction Emergency C-section Gestational age Preterm birth Presentation anomalies Antiphospholipid and anti-cardiolipin antibodies	Pregnancy-induced hypertension Uterine fibroid of 7 cm Gestational age (30 weeks) Preterm birth Breech presentation
Extrauterine risk factors	Low Apgar score Acute respiratory distress Mechanical ventilation Immature hemostatic system Hemodynamic instability ICU length of stay Sepsis Central venous catheter Intravenous medication and long parenteral nutrition Femoral venous catheter Immobility	Low Apgar score (6/7) Acute respiratory distress Mechanical ventilation (23 days) Immature hemostatic system Hemodynamic instability ICU length of stay (105 days) Sepsis with Staphylococcus CoNS Central venous catheter (28 days) Intravenous medication and long parenteral nutrition Immobility

ternal risk factor for neonatal venous thromboembolism (VTE) [12] (Table 3).

A 900 g newborn, with IUGR, born at 30 weeks of gestation by cesarean section, in breech presentation, with an Apgar score of 6, can accumulate numerous risk factors for developing thrombosis starting from intrauterine life, during birth and their prolonged hospitalization. The gestational age can contribute to thrombosis risk, with term newborns possessing a more mature coagulation system and thus being less prone to thrombosis than premature infants [3,14] (Table 3).

Central venous catheterizations stand out as a pivotal influencing factor for neonatal thrombosis. Several factors contribute to thrombosis related to neonatal catheters, encompassing the vessel's small diameter, endothelial injury, irregular blood flow, catheter material, design, insertion site, duration of catheter placement, and the composition of infused substances [13,15-17]. If limb swelling, pain, and either a cyanotic or hyperemic appearance are present, suspicion of venous thrombosis should arise. Late signs of venous thrombosis comprise the development of venous collaterals, diminished limb growth, and the onset of varicose veins [18]. In our case, the CVC was made of polyurethane material, inserted on the left leg in an external vein- posterior tibial vein, with the tip located at the 4th lumbar vertebrae above the branch, maintained for 28 days. The clinical manifestations were inguinal edema, color modifications (cyanosis and redness), and a sinuous vein pathway on the inner region of the right leg. At that moment, the functionality of the catheter was checked. After correlating the radiographic result with the clinical condition, it was decided that the catheter should be removed as a preventive measure, and the treatment with continuous heparin infusion should be started, with favorable results. Inserting a PICC line from the lower extremity and extending it into the veins within the abdominal cavity might result in vascular endothelial damage. This, coupled with changes in venous return due to the negative pressure within the thorax and inefficient calf muscle contractions and venous valves, could potentially trigger the formation of blood clots [14,19].

With a conclusive diagnosis of a genetic syndrome, we can also ask whether there is any anatomical peculiarity at the level of the patient's common iliac vein that led to the formation of the thrombus at this level.

Sepsis involves a clinical state resulting from an abnormal systemic inflammatory reaction to infection. It often involves blood clotting and tissue injury, leading to sepsis-induced coagulopathy [20]. In our case, late-onset sepsis with Staphylococcus CoNS had the following characteristics: clinically, fever was detected, along with an increased ventilation demand, and laboratory analyses revealed positive inflammatory markers and a left shift on the white cell count. In this context, clinical manifestations of venous thrombosis also began. In preterm neonates with Gram-positive sepsis, sepsis-induced coagulopathy presents as a hypercoagulable state [20], and it

can be considered an important risk factor for developing thrombosis in our case.

Thrombophilia refers to coagulation disorders, whether inherited or acquired, associated with an increased risk of thrombosis. Genetic mutations linked to thrombophilia in neonatal intensive care unit (NICU) patients, especially when central catheters are present, represent significant risk factors for neonatal thrombosis, as indicated by the study led by Ahmed Mokhtar et al. [21]. The RASopathies are a collection of human disorders resulting from germline mutations in genes encoding components or regulators of the RAS-MAPK pathway, and these disorders include, amongst others, Noonan syndrome (NS) [22]. The prevalence of hematologic abnormalities has been documented to range from 50% to 89%. Coagulation defects affect approximately one-third of patients with Noonan syndrome, with manifestations such as prolonged activated partial thromboplastin time (40%) and intrinsic pathway abnormalities (most commonly, factor XI deficiency, occurring in 50%). Additional hematological abnormalities comprise thrombocytopenia and platelet function defects [23,24]. Even though, in our case, the mother underwent genetic testing during pregnancy, it did not include this mutation. Family history did not reveal any pathology with a familial genetic basis. Considering the particular characteristics of the newborn, further genetic testing was indicated.

CONCLUSION

As our capacity to care for critically ill infants advances, there is an increasing imperative to enhance our comprehension, prediction, and management of neonatal thrombosis. With more of the tiniest and most critically ill infants surviving, they frequently undergo invasive procedures and surgeries, both of which elevate the risk of venous and arterial thrombosis [25].

The primary goal of preventing neonatal thrombosis in newborns is to mitigate the emergence of risk factors. This includes diagnosing various genetic disorders of the hemostatic system, such as antiphospholipid syndrome and genetic thrombophilia in both parents. It is advised to ensure proper management of pregnancy to avert placental insufficiency. Additionally, accurate diagnosis and treatment of maternal comorbidities play a crucial role in preventing neonatal thrombosis [3].

Central venous catheter-thrombosis may cause potential life-threatening acute and/or chronic complications. Central venous catheter-thrombosis in the right atrium may lead to tricuspid valve obstruction, pulmonary embolism with severe respiratory insufficiency, and heart failure. Cerebral embolism via a patent foramen ovale may cause stroke. The exact prevalence of these complications remains unknown. However, the potential life-threatening character of these complications warrants the use of antithrombotic measures, including anticoagulants, thrombolysis, and thrombectomy [26,27].

All newborns with a history of thrombosis require rigorous follow-up after an episode of thrombosis. The short-term prognosis in our case is satisfactory, as collateral vessels have formed around the occlusion in the affected limb, adequately vascularizing the area. The long-term prognosis depends on the need for continued anticoagulant treatment based on the recommendations of the hematologist. Anticoagulant therapy with Clexane (Enoxaparin) also comes with adverse effects in some cases, including osteoporosis, heparin-induced thrombocytopenia, or bleeding. This treatment requires monitoring through periodic measurement of anti-factor Xa [28,29].

In conclusion, neonatal thrombosis is influenced by various factors, including genetic predispositions and perinatal complications. Notably, the NICU environment plays a crucial role. However, a noteworthy correlation emerges when exploring the connection between neonatal thrombosis and the intensive care unit environment. Prolonged immobility, invasive procedures, and the use of medical devices, such as central venous catheters, amplify the susceptibility to thrombosis in these vulnerable patients.

Patient consent:
The patient's mother provided written and verbal consent for this case to be published.

Conflict of interest and author's contributions:
All authors contributed equally to this work. The authors have no conflicts of interest to disclose.

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