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Case Report

Paediatrics Section

Isolated Protein S Deficiency Presenting in Neonatal Inferior Vena Cava as Right Atrial Thrombus: A Case Report

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ABSTRACT

Critically ill neonates are at the greatest risk of developing thromboembolic disease. Multiple risk factors have been identified, one of which is isolated Protein S deficiency-a rare cause. The free form of Protein S plays a role in anticoagulation, and its deficiency can manifest as deep venous thrombosis, pulmonary emboli, and superficial thrombophlebitis. Hereby, the authors present a case report of a two-day-old female neonate, born to a gestational diabetic mother, who was initially managed for hypoglycaemia and polycythaemia. On day 4 of life, the baby was shifted to the mother's side. Twenty-four hours later, she developed late-onset neonatal sepsis with disseminated intravascular coagulation and required management with a mechanical ventilator, Intravenous (IV) antibiotics, and inotropic support. Echocardiography (ECHO) revealed a thrombus (8.9×6.8 mm) attached to the septum of the right atrium, extending from the Inferior Vena Cava (IVC). Treatment with Low Molecular Weight Heparin (LMWH) was initiated, and a follow-up ECHO after three months showed complete resolution of the thrombus. Interval analysis revealed isolated Protein S deficiency with normal Protein C levels. The present report emphasises the importance of interval analysis in identifying causes of Neonatal Thrombotic Events (NTE). Early diagnosis and management can reduce associated morbidity and mortality.

Keywords: Central venous catheterisation, Coagulation disorder, Hereditary, Neonatal sepsis, Newborn

CASE REPORT

A term female neonate was born at 39+4 weeks of gestation to a 22-year-old primigravida mother via vaginal delivery. The mother was diagnosed with gestational diabetes at 34 weeks but was poorly compliant with oral hypoglycaemic agents. The baby had a smooth perinatal transition with {Appearance, Pulse, Grimace, Activity, and Respiration (APGAR)} scores of 8/10 and 9/10 at one and five minutes, respectively. The neonate was immediately placed with the mother and started breastfeeding within the first hour of life.

Anthropometric measurements (weight: 3160 g, length: 49 cm, head circumference: 33 cm) were plotted on Fenton charts and found to be normal [1]. Serial capillary blood glucose monitoring was performed according to the institution protocol. At the second hour of life, the capillary blood glucose monitor showed a "low" reading, with a corresponding random blood sugar level of 40 mg/dL. As a result, the baby was started on a glucose infusion rate of 6 mg/kg/min, which was titrated to reach 8 mg/kg/min to maintain euglycaemia. The glucose infusion was administered through an umbilical venous catheter. The baby remained euglycaemic with a glucose infusion rate of 8 mg/kg/min for 24 hours {Random Blood Sugar (RBS)=86 mg/dL}.

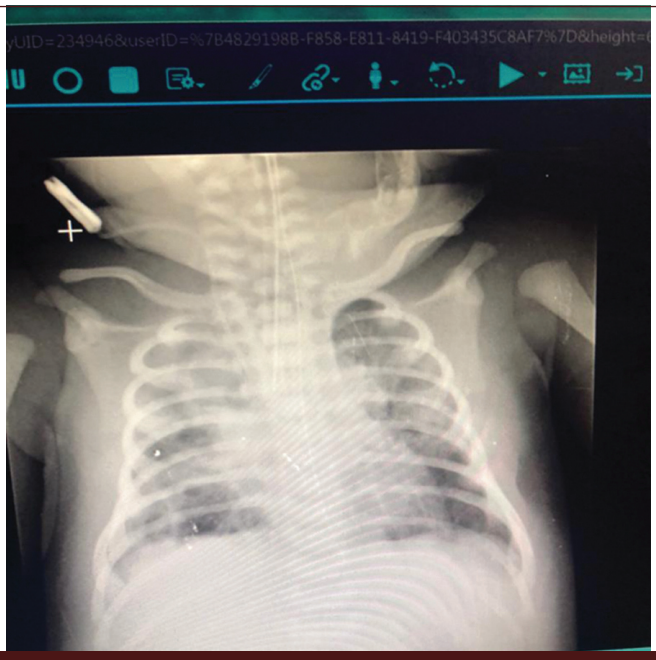
At 48 hours of life, the neonate exhibited polycythaemia (packed cell volume- 69.4%), thrombocytopenia (platelet count- 70,000/cumm), and deranged coagulation profile {Prothrombin Time (PT)=20.9/13.5, Activated Partial Thromboplastin Clotting Time (APTT)=67.7/32, International Normalised Ratio (INR)=1.61)}. However, there was no active bleeding. The differential diagnosis considered was Early Onset Neonatal Sepsis (EONS) and Disseminated Intravascular Coagulopathy (DIC).

After reviewing the maternal records, no risk factors for EONS, such as maternal fever, foul-smelling liquor, or prolonged rupture of membranes. Perinatal hypoxia was also ruled out based on normal foetal heart rate tracings and good respiratory efforts at birth. Sepsis work-up yielded normal results. Under aseptic precautions, a partial exchange transfusion was performed. A repeat Packed Cell Volume (PCV) done after 24 hours of the partial exchange transfusion was reported to be normal (54.9%).

At 80 hours of life, since the baby maintained euglycaemia, the glucose infusion rate was gradually reduced by 2 mg/kg/min every six hours until reaching 4 mg/kg/min, after which it was stopped. The umbilical catheter was removed on day 4 of life using aseptic precautions. On day 5 of life, direct breastfeeding was resumed, and the baby was placed with the mother. The baby remained asymptomatic for the next 15 hours. However, on day 6 of life, she developed hypotensive shock, characterised by a respiratory rate of 45/min with grunting and subcostal retractions, Oxygen Saturation (SpO_2) of 95% in room air, a heart rate of 160/min with poor perfusion, and a low blood pressure of 56/40 (30) mmHg. Blood gas analysis showed a pH of 7.42, Partial pressure of Carbon Dioxide (PCO_2) of 49 mmHg, and Bicarbonate (HCO_3) of 22.5 mmol/L.

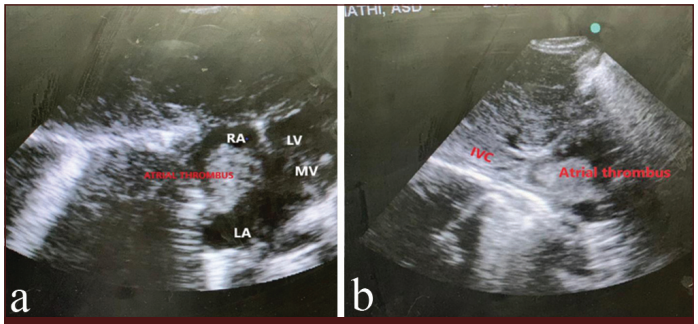
The baby was transferred to the intensive care unit and managed with mechanical ventilation {Assist-control:Pressure-control (AC:PC) mode with maximum Fraction of inspired Oxygen (FiO_2)=80%, Peak Inspiratory Pressure (PIP)=11, Positive End Expiratory Pressure (PEEP)=6, Ventilation Rate (VR)=45, Inspiratory to Expiratory ratio (I:E)=1:1.5} and a dobutamine infusion at 10 mcg/kg/min. Aspiration was ruled out as the mother denied any history of feed aspiration. Late-onset sepsis was considered, and a septic workup along with a chest X-ray was performed. The septic workup yielded positive results, with elevated micro Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) values of 20 mm/hr and 48 mg/L, respectively. The chest X-ray revealed opacities in the upper, middle, and lower zones of the right side [Table/Fig-1]. Intravenous antibiotics

(Meropenem: 20 mg/kg/dose every 8 hours and Vancomycin: 10 mg/kg/dose every 8 hours) were administered for seven days and then discontinued after blood culture showed no growth.



[Table/Fig-1]: Chest X-ray showing right-side upper, middle and lower zone infiltrates.

A 2D echocardiogram performed on day 6 of life, in light of the hypotensive shock, revealed a hyperechoic mass (8.9×6.8 mm) attached to the septum of the right atrium, extending from the IVC [Table/Fig-2a,b]. Risk factors for venous thrombosis, including DIC, impaired liver function, congenital heart disease, and exogenous factors such as indwelling venous catheter, were considered. Impaired liver function was ruled out based on normal liver function test results. The echocardiogram ruled out congenital heart disease, and thromboembolism due to the umbilical catheter was unlikely due to the short duration of catheterisation and proper care during insertion. To evaluate for DIC, Lactate Dehydrogenase (LDH) and D-dimer tests were performed and showed abnormal values (LDH: 650 U/L, D-dimer: 8963 ng/mL). The baby was diagnosed with neonatal thrombosis and started on once-daily subcutaneous LMWH (1.5 mg/kg/day).



[Table/Fig-2]: a) A 2D ECHO showing atrial thrombus attached to the inter atrial septum and protruding in to the right atrium. RA: Right atrium; LA: Left atrium; LV: Left ventricle; and MV: Mitral valve. b) A 2D ECHO showing IVC thrombus extending into the right atrium.
IVC: inferior vena cava

Coagulation profiles, D-dimer, LDH, and platelet counts showed an improving trend and were completely corrected on day 10 of life. On day 12 of life, a repeat ECHO was performed to assess the size of the thrombus, which showed a decrease to 3.8×7 mm. The baby continued to receive subcutaneous LMWH. Her condition gradually improved, and she was extubated to 02 prongs on day 19 of life, with direct breastfeeding re-established on day 22 of life.

On day 37 of life, oxygen support was discontinued, and blood investigations (including coagulation profiles, LDH, D-dimer, and platelets) were conducted, which reported normal values (PT 13.8, APTT 40.1, INR 1.13, LDH 320 u/l, and D-dimer 452 ng/mL). The baby was discharged on day 38 of life and continued to receive subcutaneous enoxaparin for a total duration of three months. After three months of stopping LMWH, serum Protein S and C levels were checked and revealed isolated Protein S deficiency (9%) and normal Protein C (114%). Although genetic work-up was recommended, it was not performed due to logistic issues. During the six-month follow-up, the baby thrived well with good neurodevelopmental outcomes. A six-month ECHO showed a complete resolution of the thrombus.

DISCUSSION

Critically ill neonates are at the greatest risk of developing thromboembolic disease. A recent study reported an incidence of neonatal thromboembolism ranging from 6.9 to 15 per 1,000 Neonatal Intensive Care Unit (NICU) admissions [2]. Various maternal and neonatal factors contribute to the development of thromboembolism [3]. Bhatt MD and Chan AK found that central venous catheters contribute to 75-95% of thrombotic events [2]. The most common locations for these thrombi are the IVC and the right atrium, as revealed by van Ommen CH et al., in a study conducted in the Netherlands [4]. Central venous catheters that extend into the right atrium are particularly associated with intracardiac thrombus formation [5]. Caregivers should exercise caution when handling neonates with central catheters. Although the reported neonate had an indwelling central catheter placed in the umbilical vein, the thrombotic event could not be attributed to the catheter due to the short duration of catheterisation and the care provided during its insertion. Therefore, the neonate was evaluated for other causes of thromboembolism and was found to be protein S deficient.

The prevalence of Protein S deficiency among the general population is 0.03 to 0.1%. It can present as deep vein thrombosis, pulmonary emboli, or superficial thrombophlebitis [6]. Hereditary Protein S deficiency is an autosomal dominant condition caused by a mutation in the PROS1 gene. Protein S activity assay and molecular genetic testing of the PROS1 gene can aid in diagnosing Protein S deficiency in suspected patients. Doppler ultrasonography is the most common investigation performed to diagnose intravascular thrombosis. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) can be used to evaluate intra-thoracic thrombi [3]. For intracardiac thrombosis, systemic anticoagulation therapy for a minimum duration of 3 months is recommended. Commonly used anticoagulants include unfractionated heparin, Low Molecular Weight Heparin (LMWH), and enoxaparin [5].

Andrew M et al., in their prospective study, found LMWH to be a safe and effective form of anticoagulation in term and preterm neonates [5]. The ease of subcutaneous administration, reduced risk of bleeding, and minimal monitoring requirements make LMWH the preferred anticoagulant in neonates with thrombosis. Thrombolytic therapy or surgical thrombectomy is recommended for haemodynamically unstable neonates or neonates with increased risk for embolisation. Tissue plasminogen activator, along with prior administration of plasminogen, is the recommended treatment for thrombolysis [7]. The reported case was successfully managed with subcutaneous LMWH, and complete resolution of the thrombus was documented after three months of therapy. The present report emphasises the importance of evaluating and managing neonatal thrombotic events early. Early diagnosis and appropriate

management will reduce the morbidity and mortality associated with neonatal thromboembolism.

CONCLUSION(S)

Sick neonates should be screened for NTE, and early initiation of specific therapy should be considered to prevent morbidity and mortality. Protein S deficiency should be considered as an aetiology for NTE, when the common co-morbidities are ruled out. LMWH is safe and effective for the management of NTE.

REFERENCES

[1] Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr [Internet]. 2013;13(1):59. Available from: http://dx.doi.org/10.1186/1471-2431-13-59.
[2] Bhatt MD, Chan AK. Venous thrombosis in neonates. Fac Rev [Internet]. 2021;10:20. Available from: http://dx.doi.org/10.12703/r/10-20.
[3] Mannucci PM, Franchini M. The real value of thrombophilia markers in identifying patients at high risk of venous thromboembolism. Expert Rev Hematol [Internet]. 2014;7(6):757-65. Available from: http://dx.doi.org/10.1586/17474086.2014.960385.
[4] van Ommen CH, Heijboer H, Büller HR, Hirasing RA, Heijmans HS, Peters M. Venous thromboembolism in childhood: A prospective two-year registry in The Netherlands. J Pediatr [Internet]. 2001;139(5):676-81. Available from: http://dx.doi.org/10.1067/mpd.2001.118192.
[5] Andrew M, Monagle PT, Brooker L. Thromboembolic complications during infancy and childhood. Shelton: PMPH USA; 2000.
[6] Haley KM. Neonatal venous thromboembolism. Front Pediatr [Internet]. 2017;5:136. Available from: http://dx.doi.org/10.3389/fped.2017.00136.
[7] Abdelghani E, Cua CL, Giver J, Rodriguez V. Thrombosis prevention and anticoagulation management in the pediatric patient with congenital heart disease. Cardiol Ther [Internet]. 2021;10(2):325-48. Available from: http://dx.doi.org/10.1007/s40119-021-00228-4.

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