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An Unusual Case of Severe Persistent Neonatal Thrombocytopenia in an Extremely Low Birth Weight, Extreme Preterm Neonate

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Abstract

Neonatal thrombocytopenia is a common hematological problem but refractory thrombocytopenia is very rare in neonates. A systematic and diligent workup will result in arriving at the proper diagnosis and providing accurate management in rare causes of neonatal thrombocytopenia. We report a case of severe refractory thrombocytopenia in an extremely low birth weight (ELBW)/extreme preterm baby who presented with early onset severe thrombocytopenia associated with anemia and required multiple platelet transfusions. After ruling out COVID-19 infection, sepsis and neonatal alloimmune thrombocytopenia (NAIT), the cause for severe refractory thrombocytopenia was diagnosed as Type II congenital amegakaryocytic thrombocytopenia (CAMT) by bone marrow examination and MPL gene mutation studies.

Keywords

CAMT, refractory thrombocytopenia, neonate, preterm

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Introduction

Neonatal thrombocytopenia defined as platelet count $<150\times10^3/\mu L$ is a common hematological problem in neonatal intensive care unit (NICU). Depending on the time of onset, thrombocytopenia is classified into early onset (<72 hours of age) and late onset (>72 hours of age), further based on the platelet count it is classified into mild ($<150\times10^3$-$100\times10^3/\mu L$), moderate (99×10^3-$50\times10^3/\mu L$), and severe ($<50\times10^3/\mu L$).[1] Early onset thrombocytopenia is usually secondary to placental insufficiency and caused by reduced platelet production. Thrombocytopenia presenting after 72 hours of age is usually secondary to sepsis or necrotizing enterocolitis and is usually more severe and prolonged. Severe persistent thrombocytopenia is a very rare event in neonates.[2]

Case Report

A 24 + 5 week extreme preterm, ELBW (500 g), baby girl was born by emergency lower segment cesarean section (LSCS) following premature preterm rupture of membranes (PPROM) with foot prolapse. The 28 year old mother had first trimester abortion in her previous 2 pregnancies and her work up for APLA and TORCH was negative. Blood group of the mother was AB positive. Current pregnancy was complicated by COVID infection at 20 weeks from which she had full recovery. She was gestational diabetic, controlled on Metformin and was on Thyroxine replacement therapy for hypothyroidism. At 24 + 3 weeks of gestation she developed PPROM and got admitted to hospital. Ultrasound

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showed severe oligohydramnios and transverse lie. Expecting a preterm delivery following PPROM, she had received complete course of antenatal steroids.

At birth baby was floppy, cried after intermittent positive pressure ventilation (IPPV) resuscitation for 45 seconds. The APGAR score was 5 and 7 at 1 and 5 minutes. She was intubated and placed on mechanical ventilatory support, received a single dose of surfactant for respiratory distress syndrome (RDS). The baby was pale and had bruising over the extremities. The hemoglobin level at birth was 6 g/dL and platelet count was $20 \times 10^3/\mu L$. Hemodynamic status was stable. The baby was transfused with packed cells and random donor platelet. Suspecting early onset sepsis, the baby was treated with antibiotics but the blood culture was sterile. The baby was extubated on day 10 to continuous positive pressure ventilation (CPAP) and received total parenteral nutrition (TPN) and phototherapy for neonatal jaundice. Neurosonogram on day 5 of life showed bilateral grade 1 germinal matrix hemorrhage (GMH).

In a week after first transfusion, the baby presented with petechiae and purpura and 1 episode of gastrointestinal bleed. Peripheral smear examination showed normocytic normochromic anemia and severe thrombocytopenia ($25 \times 10^3/\mu L$) with normal sized platelets with MPV 8.4 fL. There was no morphological or biochemical evidence of hemolysis. Direct Coomb test (DCT) was negative. Repeat sepsis screen was negative and fungal sepsis was ruled out. Renal scan and Doppler ruled out renal vein thrombosis. Echocardiogram was done to rule out structural abnormality of heart, intracardiac vegetations and central line associated thrombus. Ultrasound of liver was normal. The placental histopathology reported evidence of acute chorioamnionitis with no evidence of calcification or vasculopathy related changes.

In view of persistent thrombocytopenia in the absence of infection, the baby was evaluated for the possibility of neonatal alloimmune thrombocytopenia (NAIT). There was no response with 2 doses of IVIG (1 g/kg) and NAIT screening was reported negative. Platelet continued to drop to a base line of $25 \times 10^3/\mu L$ every week, which required platelet transfusion. At this stage of clinical course a bone marrow aspiration was done which showed reduced megakaryocytes which raised the possibility of amegakaryocytic thrombocytopenia of congenital or acquired etiology (Figure 1). The patient was started on weekly injections of Romiplostim starting with 1 µg/kg. The dose of romiplostim was increased 1 µg every week up to 5 µg/kg dose. As there was no improvement in platelet count it was stopped. The serial neurosonogram showed mild prominence of lateral ventricles. The ophthalmological screen showed stage 2, zone 2 (retinopathy of prematurity) ROP.

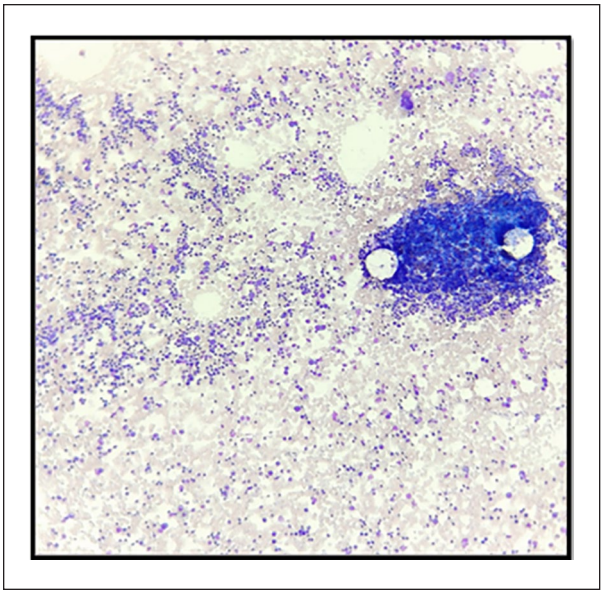

Figure 1. Leishman stained bone marrow aspiration smear showing cellular spicules and cell trails with reduced megakaryocytes.

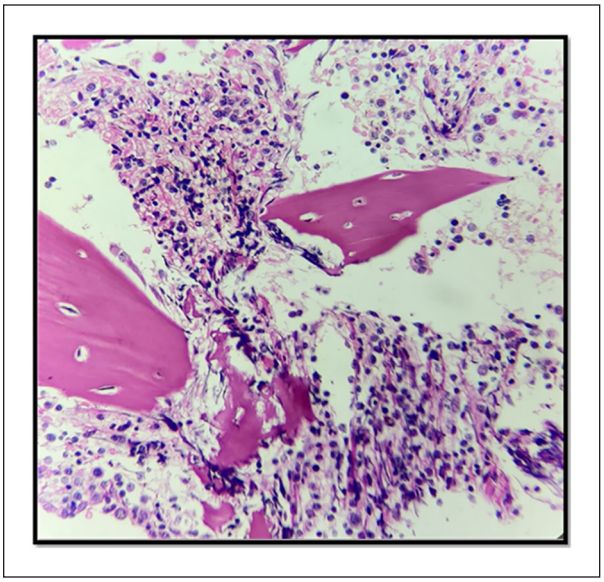

Figure 2. Hematoxylin and eosin stained bone marrow biopsy section showing erythroid and myeloid precursors.

The baby was discharged on day 101 of life and serially followed up for possible bone marrow failure syndrome/congenital amegakaryocytic thrombocytopenia (CAMT). The repeat bone marrow aspiration with biopsy confirmed amegakaryoctopoiesis (Figure 2). Genetic analysis of the baby showed a homozygous missense mutation in exon 5 of MPL gene.

Discussion

The case we reported, was an extreme preterm, ELBW baby born at 24 (5) weeks by emergency lower segment cesarean section (LSCS). The baby required mechanical ventilation for RDS. At birth the baby was severely anemic (Hb 6 g/dL) and severely thrombocytopenic ($20 \times 10^3/\mu L$). The baby was given PRBC and platelet transfusion due to high risk of Intracranial bleed, presence of bruise and need for respiratory support. Since there was high risk of infection due to PPROM baby was treated with antibiotics. Apart from infective etiology, intraoperative bleeding from an anterior placed placenta during the cesarean section and feto-maternal hemorrhage were considered as the possible causes for anemia at birth, however the presence of severe thrombocytopenia at birth was a pointer against this cause, but favored causes like intrauterine infections, immune mediated, or congenital causes.

Neonatal thrombocytopenia is a common hematological problem in neonatal intensive care unit (NICU). The underlying pathogenic mechanism for thrombocytopenia are decreased production or increased consumption of platelets (including sequestration/pooling and activation/destruction of platelets). For planning diagnostic evaluation and management the neonatal thrombocytopenia is clinically classified in to early onset which occurs before 72 hours of age and late onset which occurs after 72 hours of age. The prevalence of thrombocytopenia in NICU has been reported as 22% to 35%. The prevalence is more in the preterm and ELBW infants than in term neonates.[1-3]

Most cases of mild thrombocytopenia seen in low birth weight neonates secondary to intrauterine growth restriction, maternal hypertension, placental insufficiency are transient in nature, which resolves in 7 to 10 days and does not require detailed evaluation. Severe thrombocytopenia ($<50 \times 10^3/\mu L$) in NICU is seen most commonly in preterm, ELBW, and sick neonates. Christensen et al observed thrombocytopenia among ELBW neonates at a rate more than twice that reported among the general NICU and can be associated with significant underlying causes and morbidity.[2,3]

Sepsis is the most common cause for late onset severe thrombocytopenia in preterm neonates, which results from a combination of increased consumption due to DIC and decreased production due to bone marrow suppression. Neonatal thrombosis secondary to sepsis and indwelling central line catheter has been associated with neonatal thrombocytopenia in NICU.[3-5]

In term neonates the platelet destruction that results from immune mediated mechanism is the most important etiology for persistent severe thrombocytopenia. NAIT causes perinatal intracranial bleed which results in mortality and severe long term neurological impairment in survivors. The well looking term baby with normal maternal platelet counts, affected siblings and fetal and neonatal intracranial bleed raise the suspicion of NAIT.[6]

Other predisposing factors for neonatal thrombocytopenia are Kasabach Merrit phenomenon, chromosomal anomalies (trisomy 21, 18, 13), Turner syndrome, and medications. Sometimes evaluation may not find an etiology in 48% to 60% cases of thrombocytopenia in NICU.[5-7]

Severe neonatal thrombocytopenia is uncommon in the general healthy new-born population, with a reported incidence between 0.14% and 0.24%.[1,7] However, infants admitted to the NICU have a higher risk of severe thrombocytopenia, with a reported risk between 2.4% and 5%.[7,8]

The risk of severe thrombocytopenia (platelet count $<50 \times 10^3/\mu L$) increases with decreasing gestational age (GA).[3,5] The risk is greatest in the most preterm infants (GA <28 weeks) as illustrated in a retrospective study of 284 extremely low birth weight (ELBW) infants (BW <1000 g) born between 2003 and 2004 that reported 28% of patients had severe thrombocytopenia, 56% had platelet counts of $<100 \times 10^3/\mu L$, and 73% of patients had platelet counts of $<150 \times 10^3/\mu L$ within the first 3 days of life.[5]

Early onset severe thrombocytopenia persisting after excluding infection and immune mediated NAIT in a non-dysmorphic neonate, who needs multiple platelet transfusions and poor response to platelet transfusions should initiate work up for alternate diagnosis like inherited bone marrow failure syndrome (IBFS). In severe persistent thrombocytopenia the bone marrow examination is done for diagnosis. Clinical Course and bone marrow findings decide the need for genetic testing to look for rare IBFS.[9,10]

In our case we suspected CAMT from bone marrow aspiration and was confirmed by genetic study which identified missense *MPL* gene mutation. CAMT is a very rare disorder in extreme preterm neonates. The isolated persistent severe thrombocytopenia since birth is the common presentation of CAMT. It is characterized by the absent or reduced megakaryocytes in bone marrow without birth defects.[11,12] CAMT is inherited in an autosomal recessive pattern and is associated with the mutations in the *myeloproliferative leukemia virus oncogene, MPL* which encodes the thrombopoietin receptor, *c-MPL* and is an essential regulator of megakryocytopoiesis and platelet production. Serum thrombopoietin (TPO) levels are found increased. The usual presenting symptom of CAMT is

bleeding into the skin, mucous membranes, or gastrointestinal tract.[11-14] Pancytopenia develops in later childhood at a median age of 3.7 years.[15-18] A subset of patients experiences a transient rise in platelet counts and later onset pancytopenia. CAMT is not associated with skeletal abnormalities, which differentiates this disorder from the thrombocytopenia associated with absent radii.[14,18,19]

The diagnosis of Type II CAMT can be made in cases with missense mutation in exon 5 of the *MPL* gene. However, the finding of *MPL* gene mutations is not required for CAMT because there are reports of patients with the characteristic clinical and laboratory findings of CAMT who do not have a *MPL* gene mutation.[15,16] Patients with mutations that result in absence of *c-MPL* protein have earlier onset bone marrow failure compared with those patients with mutations that result in amino acid substitutions.[17] Infants and children with CAMT are at risk for life-threatening hemorrhages secondary to thrombocytopenia. Due to the risk of allosensitization leading to graft rejection associated with multiple platelet transfusions, a low platelet level threshold is set and platelet transfusion is reserved for symptomatic and high risk of bleeding neonates.[13]

Hematopoietic stem cell transplant (HSCT) is the only curative option for children with CAMT.[20-22] In a 2005 report of 20 patients with CAMT, 15 patients received HSCT at a median age of 38 months (range 7-89 months).[23] The outcome was poor for matched unrelated stem cell transplants. In a 2015 series of 5 children who had HSCT with unrelated donor umbilical cord blood had excellent outcome. Successful HSCT from unrelated donors using a reduced intensity conditioning regimen also has been reported.[23,24]

Though the general approach in evaluation of neonatal thrombocytopenia is based on searching for immune and nonimmune mediated causes, in persistent severe thrombocytopenia the poor response to platelet transfusion and the deviation from usual clinical pattern is a clue to suspect inherited bone marrow failures syndrome in an extreme preterm neonate.

Conclusion

Refractory thrombocytopenia is very rare in neonates. The early onset, severity, prolonged course, the need for frequent platelet transfusions, poor response to platelet transfusion, and absence of dysmorphism should raise suspicion and mandate evaluation for rare etiology for thrombocytopenia like IBFS. CAMT is a rare IBFS which presents as early onset refractory thrombocytopenia and progresses to pancytopenia later in life. The pathogenic mechanism is mutation of *MPL* gene which leads to TPO insensitivity by TPO receptor resulting in amegakaryocytopoiesis. HSCT is the mode of curative treatment.

Author Contributions

MP, AKS, LA, SMP and DV: Contributed to study design.
MP, AKS and LA: Contributed to data retrieval.
MP and LA: Contributed to laboratory analysis.
MP, AKS and LA: Contributed to the analysis of data and interpretation of the results.
MP, AKS and LA: Contributed to the drafting of the manuscript. All authors contributed to the writing and final approval of the manuscript.

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Ethical Approval and Informed Consent

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