Transient Myeloproliferative Disorder- Diagnosis and Management using Cytarabine: Case Series

Mahvish Rahim[1], Jacquelyn Lajiness[1], Amanda Saraf[1], Riddhi Shukla[1], and Rebecca Rose[1]

[1]Riley Hospital for Children

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Abstract

Transient Myeloproliferative Disorder (TMD) is a rare diagnosis that clinicians should be aware of as early recognition and management is vital. There is little guidance regarding the details of management for TMD, with respect to dosing and duration of chemotherapy. We present our management in two cases of TMD.

INTRODUCTION

The presentation of lymphocytosis and peripheral blasts on newborn lab work is an alarming finding. A range of differential diagnosis are often considered with this presentation, however in the setting of a newborn with Trisomy 21, a strong consideration is Transient Myeloproliferative Disorder (TMD).

CASES

Case Number 1

A late preterm infant girl at 36 6/7 estimated gestational age was born via C-section due to concern for worsening placental insufficiency to a 38yo gravida 3 para 2 mother. APGARS were 3 and 8 at 1 and 5 minutes of life respectively. Pregnancy was complicated by suspected trisomy 21 (confirmed postnatally), fetal growth restriction, complete AV canal defect and enlarged liver noted on ultrasound (US) at 34 weeks GA.

Physical exam revealed small for gestational age, upward slanting eyes, low set ears, and palpable hepatomegaly 4cm below right costal margin. Infant was transferred to our institution for subspecialty care. Blood work demonstrated metabolic acidosis, grossly altered coagulation studies, significant hyperbilirubinemia, thrombocytosis, leukocytosis of $110\times10^3/\mu L$ ($110\times10^9/L$) with 15% peripheral blasts confirmed on hematopathology review as myeloblasts. Her coagulopathy was treated with fresh frozen plasma and cryoprecipitate. Pediatric hematology-oncology was consulted for treatment and management due to persistent severe leukocytosis and peripheral blasts.

Despite full enteral feeds and the addition of ursodiol, her direct bilirubin level continued to rise, peaking at 26.7 mg/dL (0.267 g/L) around 3 weeks of life. Bilirubin slowly improved but, her liver failure and portal hypertension led to intractable ascites requiring drain placement, systemic hypotension requiring inotropic support, and respiratory failure requiring mechanical ventilation. The decision was made with family for comfort care and the patient passed away at DOL 75.

Case Number 2

A late preterm infant boy was born at 36 4/7 weeks of gestation via urgent c-section due to non-reassuring fetal heart tones and a biophysical profile of 2/10, to a 27-year-old gravida 5 para 3 mother with negative prenatal serologies. APGARS were 6 and 8 at 1 and 5 minutes of life respectively, birth weight was 2620g.

On DOL 1 the patient was noted to have epistaxis which prompted the OSH to obtain a complete blood count, significant for a WBC of $184\times10^3/\mu L$ ($184\times10^9/L$) with 60% blasts. Initial work up included an abdominal US which confirmed a physical exam finding of hepatosplenomegaly. Due to leukocytosis and presence of peripheral blasts the patient was transferred to our NICU for further care with pediatric hematology-oncology consult.

Trisomy 21 was suspected based on facial features, single palmar crease, and sandal gap deformity and confirmed with a rapid karyotype. Repeat laboratory evaluation confirmed leukocytosis of $155\times10^3/\mu L$ ($155\times10^9/L$), peripheral flow cytometry revealed 77% myeloid blasts. Hemoglobin and platelets were within normal limits (WNL), electrolytes were WNL. Cytogenetics of the blasts showed a gain of 21q and RUNX1, both consistent with the diagnosis of Trisomy 21.

Laboratory evaluation showed hyperbilirubinemia and he received 4 days of phototherapy and was started on Ursodiol for management of direct hyperbilirubinemia. At 1 month of age the patient was discharged with no major complications.

DISCUSSION

Extreme leukocytosis and peripheral blasts at the time of birth is generally concerning for either congenital acute leukemia or TMD. Congenital leukemia is an aggressive disease in which the bone marrow of an infant is overwhelmed and will typically present with leukocytosis and other cytopenia, this diagnosis is often fatal. In both of our cases, the infants had appropriate platelet and hemoglobin, making congenital leukemia less likely.

The diagnosis of TMD is based on the finding of blasts in the peripheral blood and/or organs of newborns with down syndrome or trisomy 21 mosaicism. Confirmation with a second blood sample or >5% blasts in the bone marrow is required. TMD commonly presents with hepatomegaly, splenomegaly, lymphadenopathy, or pericardial/pleural effusion [1,2]. The incidence of TMD for neonates with trisomy 21 has mostly been reported as about 10%[1,3-5]. There are reports of intrauterine hepatomegaly noted on ultrasound, as with patient 1, indicating prenatal origin of the disease[6,7].

TMD is associated with an acquired truncating GATA1 mutation, which results in the formation of blasts from the megakaryocyte lineage which will over-populate organs that produce fetal blood, namely the liver resulting in hepatomegaly [3,8,9]. The majority of patients who develop TMD go on to achieve spontaneous resolution of blasts by 3 months of age. TMD can by complicated by liver failure, DIC, severe direct hyperbilirubinemia and, occasionally renal and cardiac failure[3]. One of the significant clinical concerns is potential for development of severe hepatic fibrosis, due to accumulation of peripheral myeloblasts in the liver. Patients with TMD need to be closely monitored as 20-30% of the cases can evolve into acute myeloid leukemia (AML) typically within the first five years of life[1,3,4,10].

The mortality rate for those diagnosed with TMD is 10-20% so close monitoring is warranted and treatment with chemotherapy is occasionally required [1,3]. Chemotherapy is indicated in the presence of a WBC count $> 100\times10^3/\mu L$ ($100\times10^9/L$), liver failure with hepatomegaly, bleeding complications, or pleural/pericardial effusions not better explained by another disease process[3].

Low dose cytarabine is an accepted treatment for TMD meeting the above criteria. Gamis et al. had attempted to treat TMD with a continuous cytarabine infusion of 3.33mg/kg/24hours for 5 days[11]. Since that time a cytarabine dosing schedules of 1.2-1.5 mg/kg per dose twice a day for 3-12 days has been reported[2,10,12]. The nuances of choosing the actual dose and duration of treatment are left to the treating physician's discretion[10,13,14].

Due to the significant leukocytosis and hepatomegaly in both of the presented cases, the decision was made to treat with low dose cytarabine. Patient 1 received 5 days of treatment and patient 2 received 4 days of cytarabine 1.5 mg/kg/dose BID. The decision to stop treatment was made based on down trending of peripheral blasts and WBC less than $100\times10^3/\mu L$ ($100\times10^9/L$). Even though peripheral blasts were still present in patient 2, cytarabine was discontinued due to myelosuppression, requiring transfusion support and

with the knowledge of the continued effect of immunosuppression. Both patients had resolution of peripheral blasts prior to DOL 30.

Clinically, patient 2 had resolution of hepatomegaly and splenomegaly as well as decreased bilirubin while on Ursodiol. The patient was discharged at 1 month of age with no notable complications from treatment or TMD and he will be monitored closely for potential development of AML.

The severity of prenatal manifestations of hepatomegaly for patient 1 might indicate increased severity of TMD and despite timely interventions after birth complications from TMD and hepatic fibrosis is likely what resulted in the patient's death.

Early recognition of TMD allows for early consultation with pediatric hematology-oncology for management. While observation is appropriate for most patients with TMD, both of these infants met criteria for treatment with cytarabine. TMD is treated with a range of cytarabine dosing, and dosing at the upper limit of the reported range of doses was decided on in attempts to aggressively treat the patients. Duration of chemotherapy was decided on to best balance toxicity and benefit. Physicians should screen for TMD in patients with trisomy 21 by obtaining a CBC with differential soon after birth.[15] Early recognition is important so that associated complications can be monitored allowing for treatment to be initiated when indicated.

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