Case report

Treatment of metabolic abnormalities with rasburicase in a premature neonate

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Abstract

Transient leukemoid reactions are well-documented in the neonatal intensive care unit, however, hyperleukocytosis greater than 100 x 10^9/L remains a rare entity in premature neonates. We report the development of extreme hyperleukocytosis in an extremely low birth weight premature neonate born at 24-2/7 weeks of gestational age due to premature rupture of membranes in a mother who had received antenatal corticosteroids. The patient subsequently developed gross dyselectrolytemia similar to tumor lysis syndrome. Infectious workup remained unrevealing, flow cytometry of the peripheral blood showed no immunophenotypic evidence of acute leukemia, and a normal female XX karyotype was confirmed. A single dose of rasburicase was administered, with rapid and safe resolution of hyperuricemia, allowing for maintenance of kidney function. The patient was treated for presumed sepsis, although cultures remained negative. The white blood cell count gradually normalized over the first two weeks of life. The patient required treatment for a patent ductus arteriosus and was severely ventilator dependent for 33 days post-partum. To our knowledge, this is the first documented case wherein electrolyte abnormalities similar to those seen in tumor lysis syndrome had complicated the course of a leukemoid reaction in an extremely premature neonate necessitating the use of rasburicase

Keywords: *hyperleukocytosis; transient leukemoid reaction; premature infants; rasburicase; tumor lysis syndrome; extreme prematurity; extremely low birth weight*

Introduction

Transient leukemoid reactions (TLR) are well-documented in the neonatal intensive care unit and have been associated with antenatal corticosteroid usage, perinatal infections, chorioamnionitis, and Down syndrome [1-9] The incidence varies between 1.3% and 15% [1-2, 10-12] however, extreme hyperleukocytosis which is defined as a white blood cell (WBC) count of >100 x 10^9/L is a rare entity in premature neonates [2]. It has been suggested that a leukemoid reaction is the result of an exaggerated inflammatory response with amplified cytokine production, and has been implicated in the sequence of multi-organ inflammatory diseases of prematurity [10, 13, 14]. TLR, by definition, are self-limiting processes that usually do not require any acute intervention after malignant etiologies of extreme hyperleukocytosis have been excluded. Tumor lysis syndrome is a life-

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threatening constellation of metabolic disturbances primarily seen in rapidly proliferating malignancies after the initiation of cytoreductive chemotherapy and is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia and acute renal failure. Rasburicase, as an adjunct to aggressive hydration in order to preclude kidney injury, has been shown to effectively and safely reduce uric acid concentrations even in the neonatal period [15-17]. We report a leukemoid reaction in an extremely premature neonate complicated by metabolic derangements similar to those seen in tumor lysis syndrome necessitating the administration of rasburicase.

Case report

The mother of the patient is a 35-year-old Hispanic female with four prior pregnancies - three of which resulted in spontaneous abortions. She maintained good prenatal care throughout the course of the current pregnancy. She presented with abdominal cramping and leakage of fluids and was transferred to our institution due to preterm premature rupture of membranes. She had no significant past medical history, no complications during the current pregnancy and was on no medications other than prenatal vitamins and iron. She was rubella immune, and negative for syphilis, chlamydia, hepatitis B surface antigen, human immunodeficiency virus, and gonorrhea. Group B streptococcus status was unknown at the time of delivery, however, was subsequently found to be positive. She had no history of substance abuse, and urine toxicology prior to delivery was negative. One dose each of antenatal corticosteroids, penicillin and magnesium sulfate tocolysis were administered 10 hours prior to delivery. She also received one dose of preoperative cefazolin. The mother's vital signs remained normal with no clinical evidence of chorioamnionitis. An extremely preterm female neonate was born at 24-2/7 weeks of gestational age via urgent cesarean section due to preterm labor in breech presentation with Apgar scores of 4 and 6 at 1 and 5 minutes of life, respectively. Birth weight was 645 grams. The patient had no respiratory effort and had decreased muscular tone at birth, and was intubated in the delivery room. One dose of surfactant was administered at 5 minutes of life and the patient was subsequently placed on mechanical ventilation and transferred to the neonatal intensive care unit. Umbilical arterial and venous lines were placed, and blood cultures and initial laboratory investigations were drawn. The patient's complete blood count revealed a hemoglobin of 10.2 g/dL, hematocrit of 33% and platelets of 357 x 10^9/L, and a corrected WBC count due to the presence of nucleated red blood cells of 60.7 x 10^9/L including 50% neutrophils, 19% lymphocytes, 10% bands, 7% myelocytes, 7% metamyelocytes, 1% promyelocytes, 5% monocytes, and 1% blasts. Empiric antimicrobials were initiated, including ampicillin, gentamicin, cefotaxime and fluconazole which were eventually discontinued on the fifth day of life due to negative cultures. A chest radiograph exhibited a mild reticulogranular pattern with no focal consolidation consistent with respiratory distress syndrome. Except for features of prematurity and respiratory distress, physical exam was otherwise unremarkable with no gross dysmorphic features or hepatosplenomegaly. The patient remained hemodynamically stable with no temperature instability and maintained adequate urine output. The patient's corrected WBC count peaked at 38 hours of life to 101.6 x 10^9/L (52% neutrophils, 6% bands, 16% myelocytes, 2% metamyelocytes, 1% promyelocytes 3% lymphocytes, 20% monocytes and 0% blasts) with a drop-in hematocrit to 28.9% and platelet count of 417 x 10^9/L, at which point the patient received 15ml/kg of irradiated leukoreduced packed red blood cells. Concurrently, laboratory data disclosed gross dyselectrolytemia including hyperuricemia peaking at 600.8 µmol/L (10.1mg/dL), hyperkalemia of 6.4mmol/L (6.4mg/dL), hypocalcemia of 1.3mmol/L (5.2mg/dL), and elevated lactate dehydrogenase of 27.91 µkat/L (1671 U/L); phosphorus however, remained within age appropriate limits. The alterations of this infant's uric acid, calcium, potassium,

phosphorus, blood urea nitrogen and creatinine with respect to WBC count are demonstrated in the table (Table 1).

Table 1. Depiction of alterations in electrolytes as well as renal parameters including creatinine (Cr) and blood urea nitrogen (BUN) in relation to hours of life and white blood cell count (WBC). Rasburicase was administered at 24 hours of life

Hours of Life	WBC (x10^9/L)	Uric Acid µmol/L	Calcium mmol/L	Phosphorus mmol/L	Potassium mmol/L	Cr µmol/L	BUN mmol/L
19	85.2	600.8	1.3	1.68	6.4	70.72	12.86
26		404.5	1.4	1.78	5.9	79.56	15.36
31		249.8	1.5	1.97	5.4	79.56	15.71
38	101.6	59.5	1.5	1.94	4.7	70.72	13.93
53	88.9	23.8	1.9	1.39	3.2	61.88	12.50
61	74.8	11.9	1.9	1.20	3.2	53.04	10.00
87	65.8	53.5	2.2	1.20	3.6	53.04	10.36
111	55.7	101.1	2.2	1.58	4.5	70.72	13.57
159	40.9	226.0	2.0	2.26	4.3	70.72	18.57
255	24.8		2.5	1.74	5.5	53.04	10.00
351	17.3	130.9	2.4	1.94	4.5	44.20	2.50

Flow cytometry of the peripheral blood reported marked leukocytosis composed of granulocytes in various stages of maturation including rare blasts with no immunophenotypic evidence of acute leukemia. A single dose of rasburicase (0.2mg/kg/dose) was administered on the 24th hour of life in addition to thrice daily allopurinol, careful hydration and strict control of body fluid balance. A dramatic decrease in uric acid levels, as well as normalization of electrolyte parameters and salvage of kidney function resulted with creatinine values decreasing after treatment from a peak 79.6 µmol/L (0.9mg/dL). The WBC count gradually decreased by the tenth day of life to 24.8 x 10^9/L (Figure 1).

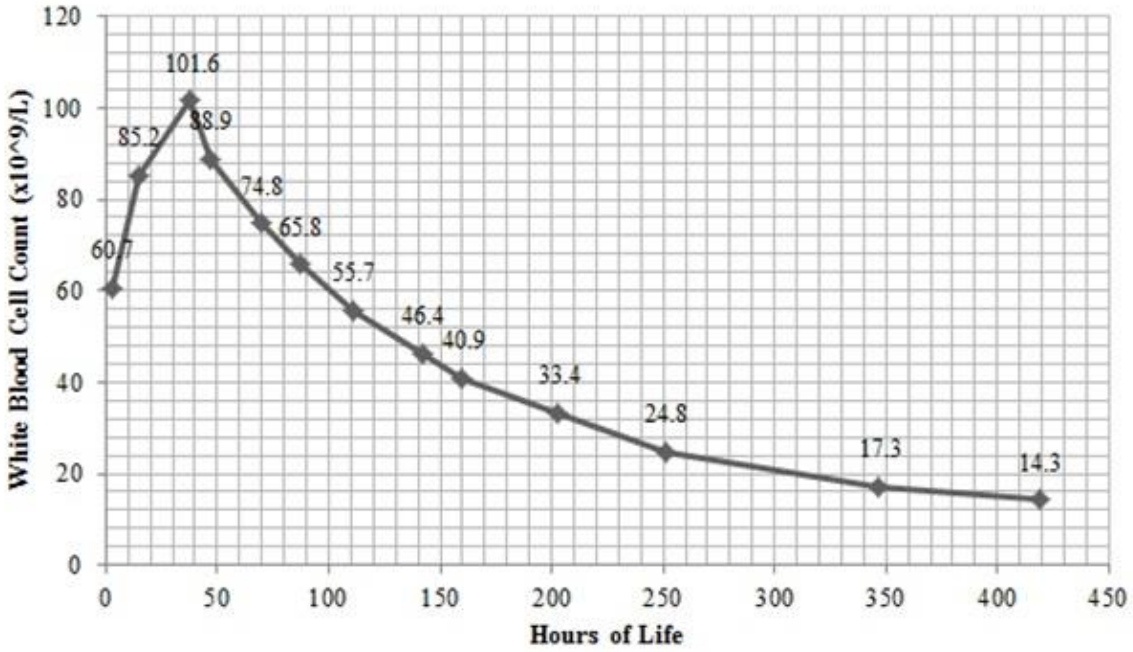

Fig. 1. The trend of leukocytes with respect of hour of life

Blood cultures and endotracheal tube cultures remained negative. Cytomegalovirus urine culture and toxoplasma titers revealed no evidence of infection. A normal female 46, XX karyotype was confirmed. A glucose-6-phosphate-dehydrogenase (G6PD) assay

could not be performed. State newborn screen was normal. Head ultrasound done on the third day of life revealed no acute germinal matrix hemorrhage, intraventricular hemorrhage, or periventricular calcifications. Similarly, follow up head ultrasounds performed on days 7 and 28 of life were unremarkable. Due to cardiorespiratory decline, at 80 hours of life the patient received a 3-dose course of indomethacin promoting successful closure of her patent ductus arteriosus. The patient was extubated after 33 days of mechanical ventilation, however, required 54 days of supplemental oxygen, during which time she was treated with diuretics, and inhaled and intravenous corticosteroids for the management of chronic lung disease. Enteral feeding was initiated on day of life 11 and the patient was able to tolerate full feeds by day of life 21. The infant was discharged home on the 98th day of life in stable condition with a normal WBC count and no evidence of renal disease.

Discussion

Extreme hyperleukocytosis is a phenomenon well documented in extremely premature neonates and has been attributed to antenatal corticosteroid use, perinatal infections, chorioamnionitis, and Down syndrome, though the exact causative mechanism is yet unknown [1-9]. Although in most cases, extreme hyperleukocytosis has been shown to be self-limiting without intervention, as in our patient, close monitoring is warranted for complications of leukostasis and acute kidney injury secondary to rapid cytolysis [5]. Infectious workup was negative in our patient, as was flow cytometry excluding an acute malignant hematological process. To our knowledge, this is the first documented case wherein electrolyte abnormalities similar to those seen in tumor lysis syndrome had complicated the course of a leukemoid reaction in an extremely premature neonate. Rasburicase, which catalyzes the oxidation of uric acid into the soluble metabolite allantoin, results in rapid and safe resolution of hyperuricemia allowing for maintenance of kidney function. Rasburicase was administered to our patient given the appearance of gross dyselectrolytemia suggesting a tumor lysis syndrome-like picture. The patient was at high risk for acute kidney injury, though her creatinine remained within reference range for age throughout the disease process. In addition to rasburicase, judicious hydration and thrice daily administration of allopurinol were employed to avoid renal compromise. It is important to consider the possibility of G6PD deficiency in a patient prior to administration of rasburicase, as it can lead to hemolysis in these patients [17]. In light of the urgency of administration of rasburicase and the expected long turnaround time of the enzyme assay, we administered the dose due to a negative family history and female gender of the patient making G6PD deficiency unlikely. The patient remained clinically stable after rasburicase administration with no significant drop in hemoglobin.

Fluid restriction is of utmost importance in the prevention of complications of prematurity such as chronic lung disease and patent ductus arteriosus, while the management of hyperleukocytosis and the associated dyselectrolytemia requires hyper-hydration. Neonatal leukemoid reactions are also associated with the development of bronchopulmonary dysplasia [1, 12, 13]. Additionally, the presence of extreme hyperleukocytosis has been implicated in long-term ventilator support, sepsis, intraventricular hemorrhage, and cerebral palsy, and a high mortality rate [1]. Our patient did eventually develop severe chronic lung disease, and was ventilator dependent for 33 days post-partum. There has been the suggestion of female predisposition to extreme hyperleukocytosis, however, the mechanism remains undetermined [14]. The extreme hyperleukocytosis in our patient was attributed to a combination of an exaggerated perinatal stress response, maternal antenatal corticosteroid administration, and presumed infection, although infectious workup remained unrevealing throughout this patient's hospital course. Further studies are warranted to elucidate the underlying pathophysiology and clinical significance of extreme hyperleukocytosis in the premature neonate.

We were able to demonstrate that the administration of rasburicase to reduce the uric acid level in this neonate was both safe and effective.

Competing interests

The authors have no conflicts of interest to declare

Informed consent

Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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