

Utility of Maternal 6-Thioguanine Nucleotide Levels in Predicting Neonatal Pancytopenia

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Am J Perinatol Rep 2013;3:25–28.

Abstract

Keywords

- ▶ azathioprine
- ▶ pancytopenia
- ▶ 6-thioguanine nucleotides

An infant with pancytopenia was born to a mother who used the common immunosuppressant azathioprine (AZA). Maternal and neonatal blood levels of 6-thioguanine nucleotides (6TGN; metabolite of AZA) were 1890 and 1480 pmol/ 8×10^8 red blood cells, respectively. Maternal 6TGN levels could be useful in predicting neonatal pancytopenia.

Azathioprine (AZA), a common immunosuppressant, has been reported to cause bone marrow suppression in infants when used during pregnancy and breast-feeding.^{1,2} AZA is rapidly metabolized to cytotoxic 6-thioguanine nucleotides (6TGN).³ Thiopurine methyltransferase (TPMT) is an important enzyme for AZA metabolism.⁴ Genetic polymorphisms in TPMT are associated with decreased enzymatic activity. Moreover, these polymorphisms are associated with increased myelosuppression risk,⁵ as decreased TPMT activity leads to elevated 6TGN levels.⁶ Severe renal dysfunction has been reported to raise 6TGN levels by 8- to >10-fold.⁷ Here we report a case in which an infant with pancytopenia was born to a mother who had used AZA during pregnancy and breast-feeding. Maternal and neonatal blood 6TGN levels were obtained with written informed consent from the mother.

Case Report

A boy was born to a 31-year-old primiparous woman with a history of renal transplantation at age 22 due to Goodpasture's syndrome. She had been well maintained on AZA,

cyclosporine (CsA), methylprednisolone (mPSL), and benz-bromarone. At pregnancy, dosages were: AZA 50 mg/d, CsA 150 mg/d, and mPSL 2 mg/d (maternal weight, 50 kg). Benzbromarone was changed to probenecid. Laboratory test results at 7 weeks 1 day were: blood urea nitrogen (BUN) 19 mg/dL, creatinine (Cre) 1.36 mg/dL, and uric acid (UA) 3.7 mg/dL (►Fig. 1). At 18 weeks, lower-extremity edema and elevated serum Cre levels were noted. She was admitted to the hospital at 20 weeks 2 days. At that time, fetal anatomy and growth were normal. At 23 weeks 6 days, AZA dose was increased from 50 to 75 mg/d, CsA dose was decreased from 150 to 80 mg/d, and mPSL dose was intermittently increased to 24 mg/d. Maternal blood test results at 33 weeks 2 days were: BUN 29 mg/dL, Cre 2.4 mg/dL, UA 7.2 mg/dL, white blood cells 7500/ μ L, hemoglobin 8.2 g/dL, and platelets 215×10^3 / μ L. Given the fetal growth arrest in a 2-week period, labor was induced at 34 weeks 0 days. The boy was born with a birth weight of 1810 g, height of 39 cm, head circumference of 31.2 cm, chest circumference of 25.8 cm, Apgar score of 8/9, and no major anomaly. The boy had dyspnea and was diagnosed with transient tachypnea,

received

May 24, 2012

accepted after revision

July 27, 2012

published online

December 3, 2012

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Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0032-1329683>.
ISSN 2157-6998.

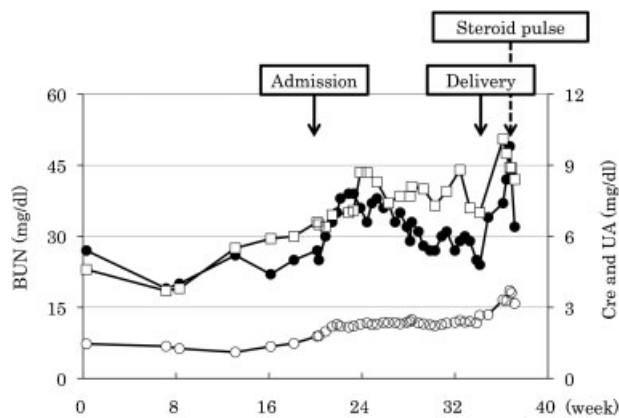


Fig. 1 Maternal blood urea nitrogen (BUN; filled circle), creatinine (Cre; open circle), and uric acid (UA; open square) during pregnancy are shown. These parameters gradually worsened despite changes in treatment. The mother was admitted to the hospital at 20 weeks 2 days. At 34 weeks 0 days, labor was induced. Steroid pulse therapy was performed from day 16 postdelivery.

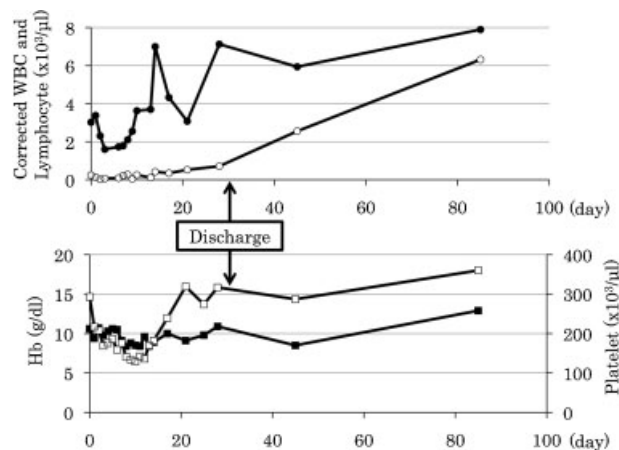


Fig. 2 Corrected white blood cells (WBC; filled circle), lymphocytes (open circle), hemoglobin (Hb; filled square), and platelets (open square) of the infant are shown. Corrected WBC, lymphocytes, and Hb were low at birth. Corrected WBC and lymphocytes increased after day 30. Anemia improved after day 80. The decreased platelet count recovered at around day 20. The infant was discharged on day 32.

requiring oxygen supplementation at day 1 and nasal directional positive airway pressure at day 3.

Leukocytopenia, lymphocytopenia, and macrocytic hyperchromatic anemia were noted at birth (→Table 1). There was no ABO incompatibility or fetomaternal transfusion. Maternal and neonatal blood levels of 6TGN were 1890 pmol/8 × 10⁸ red blood cells (RBC) at day 2 and 1480 pmol/8 × 10⁸ RBC at day 3, respectively. Neonatal CsA level was <30 ng/mL at day 3. Blood test results were negative for cytomegalovirus

infection. The boy later developed thrombocytopenia (→Fig. 2). Breast-feeding was started at day 0, and fortified milk was added at day 6; breast-feeding was stopped at day 16 due to maternal steroid pulse therapy. Neonatal 6TGN levels gradually decreased, which was well approximated to the exponential function: $y = 1659e^{-0.074x}$, $R^2 = 0.972$ (→Fig. 3).

The baby gained weight properly and was discharged at day 32. At 4 months of age (corrected: 3 months old), physical

Table 1 Laboratory findings at birth

WBC	8100/μL	RBC	2.23 × 10 ⁶ /μL	T-Bil	2.6 mg/dL
Stab	0%	Hb	10.6 g/dL	D-Bil	0.9 mg/dL
Seg	71%	Hct	30.2%	AST	24 IU/L
Eosi	0%	MCV	135.4 fL	ALT	2 IU/L
Baso	0%	MCH	47.5 pg	LDH	377 IU/L
Mono	13%	MCHC	35.1 g/dL	TP	4.2 g/dL
Lymph	8%	Plt	293 × 10 ³ /μL	ALB	2.8 g/dL
At-Ly	5%	pH	7.129	CK	220 IU/L
Myelo	0%	pCO ₂	49.3 mm Hg	BUN	23 mg/dL
Meta	1%	BE	-12.9 mEq/L	Cre	2.2 mg/dL
Promyelo	1%	Na	132.6 mEq/L	CRP	0.05 mg/dL
Blast	1%	K	4.24 mEq/L	IgG	760 mg/dL
Erb/100 WBC	168	Cl	107 mEq/l	IgA	<1 mg/dL
Corrected WBC	3022/μL	iCa	1.41 mmol/L	IgM	<1 mg/dL
		Glu	93 mg/dL		

Abbreviations: WBC, white blood cell; Stab, stab neutrophil; Seg, segmented neutrophil; Eosi, eosinophil; Baso, basophil; Mono, monocyte; Lymph, lymphocyte; At-Ly, atypical lymphocyte; Myelo, myelocyte; Promyelo, promyelocyte; Erb, erythroblast; RBC, red blood cell; Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; Plt, platelet; BE, base excess; iCa, ionized calcium; Glu, glucose; T-Bil, total bilirubin; D-Bil, direct bilirubin; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase; TP, total protein; ALB, albumin; CK, creatine kinase; BUN, blood urea nitrogen; Cre, creatinine; CRP, creatinine protein; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M.

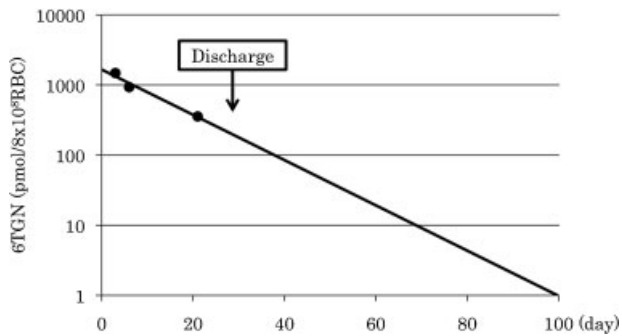


Fig. 3 The trend of neonatal 6-thioguanine nucleotides (6TGN) levels is shown. It was approximated to the exponential function: $y = 1659e^{-0.074x}$, $R^2 = 0.972$. RBC, red blood cells.

and mental development were normal. The TPMT genotype of the mother was not determined.

Discussion

Maternal AZA dose at the time of delivery was 75 mg/d (1.5 mg/kg/d), which is a normal dose used clinically.⁸ However, maternal 6TGN levels at day 2 (1890 pmol/8 × 10⁸ RBC) were extremely high, which could have been attributed to TPMT polymorphism and/or maternal renal dysfunction.^{5-7,9} Despite the high 6TGN levels, the mother did not present with leukocytopenia or thrombocytopenia. Hanai et al reported that leukocytopenia was observed when 6TGN levels exceeded 320 pmol/8 × 10⁸ RBC, with an incidence of approximately 20%.⁶ And Lennard et al showed that the patient had leukocytopenia when 6TGN level went over 300 pmol/8 × 10⁸ RBC.¹⁰ Thus, less than 300 pmol/8 × 10⁸ RBC would not be high. We did not check TPMT polymorphism or TPMT activity. There was an inverse relationship between 6TGN levels in RBC and TPMT enzyme activity in the patients who had 6 mercaptopurine,⁶ which was metabolized to 6TGN. The range of 6TGN level in the blood was from 100 to 700 pmol/8 × 10⁸ RBC. Thus, we could not easily estimate the 6TGN level. At day 3, when the infant did not have sufficient breast milk, neonatal 6TGN levels remained high, suggesting that these high levels were due to exposure through the placenta. As neonatal 6TGN levels declined, pancytopenia gradually improved.

In conclusion, there was no correlation between maternal AZA dose and maternal blood 6TGN levels. Furthermore, no distinct side effects were observed in the mother despite her high 6TGN levels. Taken together, our findings suggest that maternal blood 6TGN levels could be used to predict fetal pancytopenia.

Acknowledgments

We thank our colleagues Naoko Nakamura, Shigehiro Mori, Hirotsuke Morita, Akihito Takeuchi, Eiko Toda, Yoko Yamabe, Kazue Nakamura, and Makoto Nakamura at the Okayama Medical Center.

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