

Congenital Amegakaryocytic Thrombocytopenia with Multiple Physical Anomalies in a Female Neonate

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ABSTRACT

Congenital Amegakaryocytic Thrombocytopenia (CAMT) is a rare disorder of infancy characterized by isolated thrombocytopenia along with hypoplasia or aplasia of megakaryocytes in the bone marrow. It is caused by *c-mpl* mutation which disrupts the function of thrombopoietin (TPO) receptor. CAMT in association with physical anomalies is a rare entity with only limited data from single case reports being available. Here we present a case of 35 days neonate who had CAMT together with facial malformations and cardiac defects.

Key Words: *Thrombocytopenia. Megakaryocytes. Physical anomalies. Congenital.*

INTRODUCTION

Congenital Amegakaryocytic Thrombocytopenia (CAMT) is an inherited autosomal recessive bone marrow failure syndrome which presents with isolated peripheral blood thrombocytopenia and absent or reduced megakaryocytes in the bone marrow.¹ Thrombopoietin (TPO) receptor gene, *c-mpl* mutation has a primary role in the pathogenesis of CAMT. It is involved in the regulation and promotion of megakaryopoiesis and thrombopoiesis.² On the basis of clinical severity the disorder is divided into three types with type-I being the most lethal one.

Association of CAMT with physical anomalies is an extremely uncommon condition. Literature review reveals only a few case reports in this regard. Three case reports from different authors including, Hoyeraal *et al.*,² Ihara *et al.*³ and Khabbaze *et al.*,⁴ have described cases of CAMT in association with CNS malformations. Martinon-Torres *et al.* reported a patient who had facial malformations and congenital thrombocytopenia with aplasia of megakaryocytes while MRI brain showed cerebellar agenesis and hypoplasia of the corpus callosum.⁵ King *et al.* studied 20 patients of CAMT retrospectively and found septal defects of heart, eye anomalies and cerebral malformations in only few of these patients.⁶

We report a case of a 35 days female neonate who presented with persistent thrombocytopenia since birth along with multiple physical anomalies including cardiac defects and peculiar facies and her bone marrow

revealed only a few megakaryocytes leading to the diagnosis of CAMT.

CASE REPORT

The patient was a 35 days old female neonate, who presented with complaints of bruises, two episodes of epistaxis and difficulty in sucking milk for which she was given formula milk through nasal tubing. She had been hospitalized twice and on her first admission, she was transfused with 20 ml of red cell concentrates on two consecutive days. She was again given 25 ml of red cell concentrate on her second visit to the hospital and total of nine units of platelet concentrates (7 random donor and 2 apheresis units). Patient was born to non-consanguineous Pakistani parents and was the first and only child with no other siblings. She weighed 2501 g, born at 39th week of pregnancy by Caesarean section due to fetal distress. Her mother had no history of miscarriages or abortions. Physical examination revealed petechiae over legs and arms, micrognathia with cleft palate, depressed nasal bridge and prominent forehead. On chest auscultation, ejection systolic murmur was audible in addition to first and second heart sounds. There was no visceromegaly.

Her serial laboratory data showed isolated and persistent thrombocytopenia with normal red and white cell counts. Her CBC at the 10th day of life showed WBC count of $4.0 \times 10^9/L$, with 60% lymphocytes, 35% neutrophils, 5% monocytes, Hb level of 8 g/dl and platelet count of $28 \times 10^9/L$. Her coagulation profile, blood biochemistry, C-reactive protein, ESR, thyroid profile and urine analysis were normal. MRI brain revealed no significant finding. Ultrasonography abdomen and the skeletal and chest radiographs were also normal. Echocardiography showed ventricular septal defect with right ventricular hypertrophy.

Parents' platelet counts were within normal range. Repeated bone marrow biopsies showed only few

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megakaryocytes with preserved erythropoiesis and leucopoiesis. Blood and bone marrow karyotype were normal. At the age of 30 days, patient's WBC count was $4.9 \times 10^9/L$, with 70% lymphocytes, 20% neutrophils, 10% monocytes, Hb level of 10.2 g/dl and platelet count of $31 \times 10^9/L$. The patient died at the age of 67 days as a result of intracranial hemorrhage confirmed on CT brain.

DISCUSSION

Thrombocytopenia is a common finding in neonates; with 0.7% having platelet count $< 100 \times 10^9/L$, but congenital amegakaryocytic thrombocytopenia is a rare underlying cause.^{1,7} CAMT is defined by isolated thrombocytopenia with reduced or absent megakaryocytes. King *et al.* classified CAMT into two types on the basis of clinical course and outcome of the disease with type-I, the more severe form, characterized by early onset of bone marrow failure reflected by pancytopenia and very low platelet counts.⁶ Patients with CAMT can present with mucocutaneous, gastrointestinal, pulmonary or intracranial bleeding.^{5,6}

The discovery of the thrombopoietin (TPO) receptor, *c-mpl* gene mutation has revolutionized the understanding of pathogenic basis of CAMT and has led to the development of better genetic testing. TPO or *c-mpl* ligand is a cytokine which manifests its effects after binding to the TPO receptor or *c-mpl* resulting in the proliferation and differentiation of both early and late forms of megakaryopoiesis. TPO receptors are present on hematopoietic stem cells along with other tissues including brain, fetal liver, spleen and other organs in addition to the platelets.¹ This fact somewhat explains the progression of these patients into bone marrow failure in the scenario of TPO receptor abnormalities. However, the association of *c-mpl* gene with the development of somatic anomalies of heart, brain, eyes, motor and mental development is still not clear.^{6,9}

Previously CAMT was considered without any physical abnormality, subsequently a number of case reports came up which described cases of CAMT with CNS malformations, the most common of which was intra or extra uterine intracranial hemorrhage reported in upto 25% of cases.⁶ In 1970, Hoyeraal *et al.* reported a case of two brothers with congenital hypoplastic thrombocytopenia with cerebellar atrophy.²

Muraoka *et al.* found that a 10 years old Japanese girl diagnosed with CAMT had a defective TPO response in megakaryocyte colonies along with reduced erythroid and myeloid progenitors in her bone marrow cultures.⁸ Ihara *et al.* followed the same patient and described *c-mpl* gene mutation in this girl and also gave a review of her associated brain abnormalities.³ Khabbaze *et al.* reported a case of amegakaryocytic thrombocytopenia with absent corpus callosum, cerebellar aplasia, facial malformations and developmental delay.⁴ These authors

suggested that *c-mpl* gene might be involved in brain development, supported by the study of Ehrenreich *et al.*⁹

Alter *et al.* divided CAMT patients in two groups, one with CAMT but no birth defects and others with physical anomalies and hypoplastic thrombocytopenia who did not fit into any other specific syndrome.¹⁰ In 2010, Martinon-Torres *et al.* reported a female patient diagnosed with CAMT and had peculiar facies along with cerebellar agenesis and hypoplastic corpus callosum and brainstem.⁵ Cardiac abnormalities in association with CAMT have been described in literature. In a large retrospective study, 2 out of 20 CAMT patients had cardiac defects, including interventricular and atrial septal defects.⁶

This patient had certain similarities with patient of Martinon-Torres *et al.* She had a combination of facial malformations and ventricular septal defects in addition to CAMT but no CNS anomalies were found. HLA typing of her family members was in process but she met a sad end only after a month of diagnosis due to intracranial hemorrhage.

The only curative treatment for CAMT is bone marrow transplant from a HLA matched donor. Supportive management includes judicious use of platelet transfusions and fibrinolytic agents for minor bleeding episodes. Steroids or intravenous immunoglobulins are not indicated in patients of CAMT. TPO-mimetics in cases of partially functioning TPO or *c-mpl* receptors are still in trial; they may prove to be an effective treatment in future.⁷

The prognosis of CAMT is poor especially after the development of pancytopenia. The major cause of death in these patients is bleeding complications.^{6,7} Physical anomalies, however, do not alter the course or outcome of the disease but may have an impact on quality of life.

REFERENCES

- Rose MJ, Nicol KK, Skeens MA, Gross TG, Kerlin BA. Congenital amegakaryocytic thrombocytopenia: the diagnostic importance of combining pathology with molecular genetics. *Pediatr Blood Cancer* 2008; **50**:1263-5.
- Hoyeraal HM, Lamvik J, Moe PJ. Congenital hypoplastic thrombocytopenia and cerebral malformations in two brothers. *Acta Paediatr Scand* 1970; **59**:185-91.
- Ihara K, Ishii E, Eguchi M. Identification of mutations in the *c-mpl* gene in congenital amegakaryocytic thrombocytopenia. *Proc Natl Acad Sci USA* 1999; **96**:3132-6.
- Khabbaze Y, Karayalcin G, Paley C, Shende A, Valderrama E, Lipton JM. Thrombocytopenia absent corpus callosum syndrome: third case of a distinct clinical entity. *J Pediatr Hematol Oncol* 2001; **23**:469-71.
- Martinon-Torres N, Vazquez-Dansion M, Loidi L. CAMT in a female with developmental delay, facial malformations and central nervous system anomalies. *Pediatr Blood Cancer* 2011; **56**:452-3.

6. King S, Germeshausen M, Strauss G, Welte K, Ballmaier M. Congenital amegakaryocytic thrombocytopenia: a retrospective clinical analysis of 20 patients. *Br J Haematol* 2005; **131**:636-44.
7. Fatma S. Al-Qahtani. Congenital amegakaryocytic thrombocytopenia: a brief review of literature. *Clin Med Insights: Pathol* 2010; **3**:25-30.
8. Muraoka K, Isii E, Tsuji K. Defective response to thrombopoietin and impaired expression of *c-mpl* mRNA of bone marrow cells in congenital amegakaryocytic thrombocytopenia. *Brit J Haemat* 1997; **96**:287-92.
9. Ehrenreich H, Hasselblatt M, Knerlich F. A hematopoietic growth factor, thrombopoietin, has a proapoptotic role in the brain. *Proc Natl Acad Sci USA* 2005; **102**:862-7.
10. Alter BP. Inherited bone marrow failure syndromes. In: Nathan DG, Orkin SH, Look AT, Ginsburg D, editors. Nathan and Oski's hematology of infancy and childhood. Philadelphia: *WB Saunders*; 2003; p. 281-365.

