Extreme Thrombocytosis in Trisomy 21 Infant Negative for GATA1 Mutation

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Introduction

TAM is characterized by a transient proliferation of abnormal myeloid cells in the bone marrow, leading to an excess of immature cells circulating in the peripheral blood [2]. TAM diagnosis is associated with the presence of *GATA1* mutations, but other features such as blasts on peripheral blood smear, flow cytometry immunophenotype or cytogenetics can be indicative of TAM. This patient's case is unusual due to the *GATA1* mutation-negative status. The *GATA1* gene encodes a transcription factor crucial for normal hematopoiesis and mutations in this gene are associated with myeloid disorders including TAM [3]. TAM leads to a wide range of hematologic abnormalities and clinical complications including hyperviscosity syndrome with potential for thrombosis, hydrops fetalis, pericardial effusion, respiratory distress, hypereosinophilia, pseudohyperkalemia, hyperbilirubinemia with liver failure, multi-organ failure and potential for death [1,2,5,14]. Patients with TAM require timely diagnosis as well as close follow up, as 20-30% of these patients subsequently develop myeloid leukemia associated with Down Syndrome (ML-DS) before the age of four [4]. *GATA1* mutations have, to date, been discovered in nearly all patients with TAM and ML–DS [7]. The absence of a*GATA1* mutation in this case raises the question of an alternative molecular mechanism contributing to the development of TAM and extreme thrombocytosis in this patient.

Case Presentation

The patient is a 37-week gestation male delivered via cesarean section due to breech presentation. Birth weight was 2880g. Promptly upon delivery, the neonate exhibited respiratory compromise necessitating urgent endotracheal intubation and conventional mechanical ventilation.

He was noted to have distinct facial dysmorphology consistent with Trisomy 21. Initial complete blood count (CBC) showed a white blood cell (WBC) count of 25,100/mL with 21% blasts, hemoglobin of 16.7 g/dL, and a platelet count of 633,000/mL.

While the neonate's oxygen saturation exhibited some improvement following mechanical ventilation, his PaO2 remained low. A chest X-ray showed no acute cardiopulmonary process. A discrepancy between pre- and post-ductal saturations prompted an echocardiogram which demonstrated elevated right ventricular pressures, with pulmonary pressures measuring at two-thirds the systemic level, and a patent ductus arteriosus (PDA) characterized by bidirectional flow.

In light of deteriorating respiratory function and severe pulmonary hypertension, the infant was switched to high-frequency jet ventilation (HFJV). Subsequently, the neonate was transferred to our tertiary care facility. Despite high-frequency jet ventilation, adjunctive inhaled nitric oxide therapy, and administration of corticosteroids at stress dosages, his oxygenation index and clinical condition continued to decline. This downward trajectory necessitated the initiation of veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) on the third day of life, with successful decannulation on the sixth day. This infant required ECMO secondary to his pulmonary hypertension that was not thought to be a consequence of his TAM.

A CBC on the third day of life revealed a reduction in the white blood cell count to 16,000/mL with 45% blasts, hemoglobin of 11.4 g/dL, and a platelet count of 252,000/mL.

Peripheral blood specimen was sent to Hematologics and it was found to have 12% blasts and 1% micromegakaryocytes. Platelets were noted to be increased in number and in size. (Fig. 1). Flow cytometry confirmed blasts that expressed CD4 and CD36 but lacked CD64 and HLA-DR; an immunophenotype that is associated with myeloid proliferation in patients with Down syndrome. Sequencing of Exon 2 of *GATA1* did not find any mutations. Hematologics does not sequence the entire *GATA1* gene, so next generation sequencing (NGS) was performed by NEO genomics using their expanded myeloid panel called NeoTYPE ?? Analysis, Myeloid Disorders Profile. No pathogenic mutations were detected in any of the genes on the NGS panel (Figure 2).

Between day 3 and day 15 of life, there was a progressive rise in platelet count, as shown in Table 1. Prophylactic administration of aspirin was started on day 14 due to a platelet count of greater than two million and the infant's significant risk factor for thrombosis; his carotid end-to-end anastomosis after coming off of ECMO. On day 13, Cytarabine chemotherapy was initiated due to a platelet count of 2,595,000/mL. On the second day of Cytarabine therapy, the platelet count peaked at 2,764,000/mL. Patient completed the seven day course of low-dose Cytarabine therapy (1.5mg/kg/day) on day 19. The platelet count declined after completion of the Cytarabine course. Beyond the anticipated myelosuppression, the infant did not have any side effects from the chemotherapy. The infant has ongoing close follow up with Hematology/Oncology. He has been clinically well. The platelet count normalized and the WBC count remains normal.

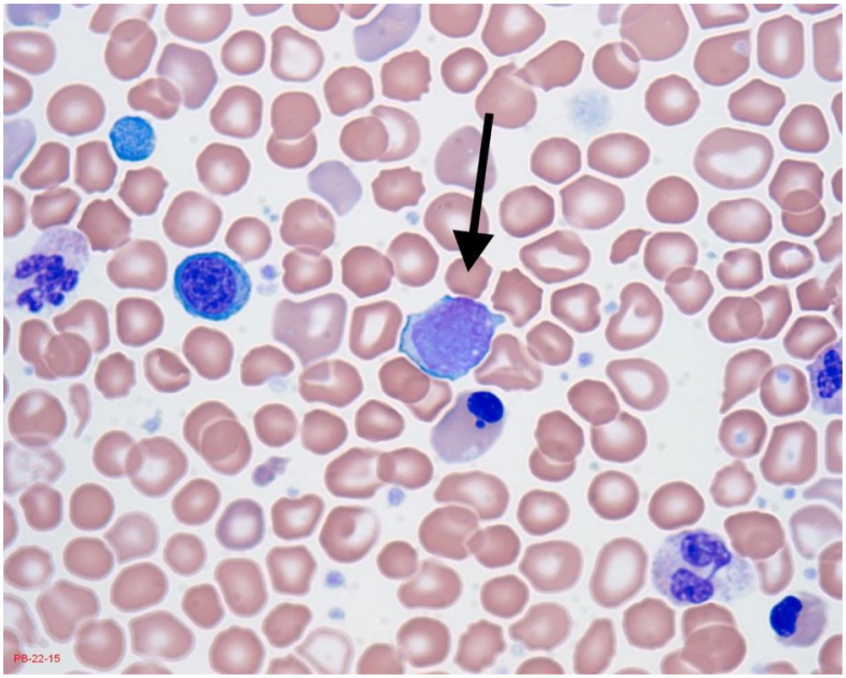

Figure 1 Peripheral blood smear of patient. Myeloblast (black arrow)

ABL1	CBLB	ETNK1	GNB1	KDM6A	NPM1	RAD21	STAG2
ASXL1	CBLC	ETV6	HRAS	KIT	NRAS	RUNX1	STAT3
ATRX	CDKN2A	EZH2	IDH1	KRAS	PDGFRA	SETBP1	STAT5B
BCOR	CEBPA	FBXW7	IDH2	MLL	PHF6	SF3B1	TET2
BCORL1	CSF3R	FLT3	IKZF1	MPL	PML	SH2B3	TP53
BRAF	CUX1	GATA1	JAK2 Exon 12-13	MYD88	PPM1D	SMC1A	U2AF1
CALR	DDX41	GATA2	JAK2 V617F	NF1	PTEN	SMC3	WT1
CBL	DNMT3A	GNAS	JAK3	NOTCH1	PTPN11	SRSF2	ZRZR2

Figure 2 Biomarkers evaluated and not detected by the NeoTYPE ™ Myeloid Disorders Profile

Table 1

Day of life as it correlates with white blood cell count, hemoglobin and platelet count

Day of Life (DOL)	White Blood Cell (WBC (10^3))	Hemoglobin (Hgb (gm/dL))	Platelet (PLT (10^3))
1	25.1	16.7	633
2	37.6	17	706
3	23.4	12	260
4	13.4	12	218
5	13.1	11	227
6	21.5	11.2	371
7	26.3	11.4	557
8	28.4	10.9	901
9	24.8	11.3	1096
10	20.4	10.6	1309
11	27.1	10.4	1690
12	34.4	10.1	2152
13	34.8	9.5	2595
14	30.7	9.2	2717
15	22.6	8.5	2764
16	20.7	8.2	2749
17	15.7	11.1	2499
18	10.4	10.7	2168
19	5.6	10.1	1284

Notes: Table includes only up until DOL 19. Patient's platelet count continued to downtrend with anticipated myelosuppression from DOL 22 to 29. By DOL 30, platelet count had returned to normal

Discussion

TAM is a rare hematologic disorder that affects approximately 10-30% of newborns with Trisomy 21 [8,9]. TAM is characterized by a transient proliferation of abnormal megakaryoblasts and myeloblasts in the bone marrow, leading to an excess of immature cells circulating in the peripheral blood. The underlying molecular mechanism of TAM involves mutations in the *GATA1* gene, which encodes a transcription factor crucial for normal hematopoiesis. *GATA1* mutations are detected in most patients with TAM and are considered a hallmark of the disease [10,11]. Notably, the neonate in this case was *GATA1* mutation negative. Despite the absence of a *GATA1* mutation, the patient's clinical course and laboratory findings strongly supported the diagnosis of TAM. The extreme thrombocytosis with a platelet count that reached 2,764,000/mL of blood is the highest platelet count ever reported in TAM upon our review of the literature. Low-dose Cytarabine resulted in a significant reduction in platelet count after a single cycle. This case presents extreme thrombocytosis in the setting of TAM in a patient without a *GATA1* mutation, suggesting an alternate molecular pathway contributing to TAM.

Consent

Not required.

Ethics Approval

Not required.

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Conflict of Interests

The authors declare that there is no conflict of interest.

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