

Phenotypic switching to hypereosinophilia during cytoreductive therapy for transient abnormal myelopoiesis associated with Down syndrome

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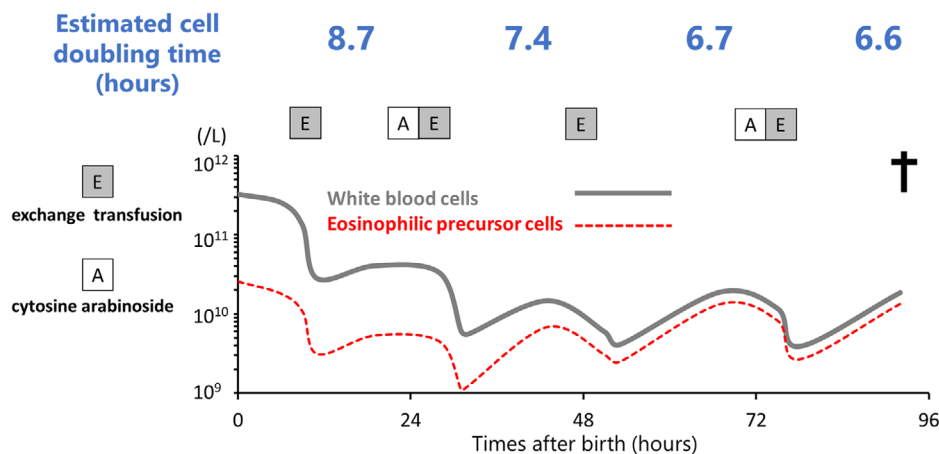
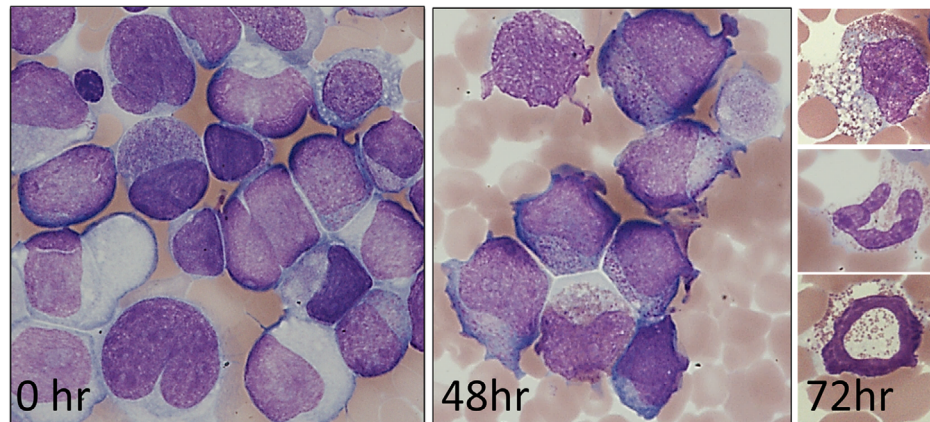
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Transient abnormal myelopoiesis (TAM) is a clonal hematological disorder originating from fetal liver hematopoiesis associated with Down syndrome. The pathognomonic *GATA1* mutation in conjunction with the gene dosage effect of 21 trisomy induces clonal proliferation of megakaryoblasts [1], but little is known for the cell differentiation plasticity, especially phenotypical switching during cytoreductive therapy. A male infant was born through emergency caesarean section due to fetal distress at 30 weeks of gestation with Apgar scores of 1 and 6 at 1 and 5 min, respectively. He weighed 1,338 g and presented with characteristic facial dysmorphism, hepatomegaly and bleeding diathesis. Cytogenic analysis showed trisomy 21. A complete blood count showed a haemoglobin of 7.8 g/dl, a platelet count of $742 \times 10^9/L$ and a leukocyte count of $326 \times 10^9/L$. Morphological findings were as follows: undifferentiated blast, 30%; megakaryoblast, 23%; promyelocyte, 7%; myelocyte, 1%; segmented neutrophil, 1%; monocyte, 2%; lymphocyte, 10% and erythroblast, 26% (top 0 h). Sanger sequencing detected *GATA1* exon 2 nonsense mutation (c.49 C > T) that preferentially induces overproduction of truncated protein isoform, *GATA1s*. The first round of low-dose cytosine arabinoside therapy was successful to ameliorate hyperleukocytosis, but we found the emergence of atypical immature myelocytes with large coarse basophilic granules (top 48 h). Despite the

continuation of cytoreductive therapies, we found a progression of hypereosinophilia with a following differential count: undifferentiated blast, 5%; megakaryoblast, 5%; neutrophil, 7%; lymphocyte, 12% and eosinophil lineage cells, 71% (top 72 h). He eventually died from multiple organ failure on the 4th day after birth (bottom). We confirmed that *GATA1* mutation ratio was largely unchanged during the clinical course, suggesting that all proliferating cells, including TAM and eosinophilic precursor cells, were clonal in nature. *GATA1s* can mediate not only eosinophilic cell differentiation but autonomous cell growth via derepressing *MYC* and *E2F* transcriptional network [2,3], we therefore would like to suggest that sustained activation of *GATA1s* and negative cell selection with chemotherapy had synergistically induced clonal hypereosinophilia. Minakata et al. also reported a female infant who developed late onset clonal hypereosinophilia (on the 18th day of age) during cytoreductive therapy for TAM, which coincided with the exacerbation of liver fibrosis and disseminated intravascular coagulopathy [4]. Given that clonal hypereosinophilia can potentially induce end-organ failure, we would like to stress that vigilant surveillance for immature myelocytes with coarse granules during the cytoreductive therapy is imperative to make an early diagnosis of such a life-threatening complication associated with TAM.

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ETHICS STATEMENT

Written informed consent was obtained from legal guardians for publication of this case report and any accompanying images. The authors affirms that no identifiable images/data of the patients have been utilized in the preparation of the paper.

CONFLICT OF INTEREST

On behalf of all the authors, the corresponding authors states that there are no conflicts of interest to declare.

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AUTHOR CONTRIBUTIONS

Kenichiro Kobayashi and Shumpei Mizuta conceptualised the research scheme, performed data curation and formal analysis, and drafted the paper. Asami Watanabe, Yoshinobu Nishida, and Toshio Heike analysed the data. All authors have approved the final revision of the manuscript for publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

- Wechsler J, Greene M, McDevitt MA, Anastasi J, Karp JE, Le Beau MM, et al. Acquired mutations in GATA1 in the megakaryoblastic leukemia of Down syndrome. *Nat Genet.* 2002;32:148–52.
- Klusmann JH, Godinho FJ, Heitmann K, Maroz A, Koch ML, Reinhardt D, et al. Developmental stage-specific interplay of GATA1 and IGF signaling in fetal megakaryopoiesis and leukemogenesis. *Genes Dev.* 2010;24:1659–72.
- Maroz A, Stachorski L, Emmrich S, Reinhardt K, Xu J, Shao Z, et al. GATA1s induces hyperproliferation of eosinophil precursors in Down syndrome transient leukemia. *Leukemia* 2014;28:1259–70.
- Minakata S, Sakata N, Wada N, Konishi Y, Marutani S, Enya T, et al. Liver fibrosis with hypereosinophilia causing transient abnormal myelopoiesis. *Pediatr Int.* 2016;58:1222–5.

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