Acute Megakaryoblastic Leukemia Without *GATA1* Mutation After Transient Myeloproliferative Disorder in an Infant Without Down Syndrome

Case Report

A 7-week-old full-term infant girl with unremarkable perinatal history was referred to our hospital for a 5-day history of hematochezia and mild epistaxis. Physical examination showed hepatosplenomegaly, scattered petechiae, and grossly bloody stool. No phenotypic features of Down syndrome (DS) were noted. CBC showed elevated WBC ($51.2 \times 10^9/L$) with 10% blasts, anemia (7.1 g/dL), and thrombocytopenia ($54 \times 10^9/L$). Bone marrow aspirate (BMA) showed hypercellularity, increased megakaryoblasts (15%), and dysplastic megakaryocytes (Fig 1A). Flow cytometric analysis

Fig 1.

Fig 2.

showed expression of megakaryocyte-specific membrane markers (CD41, CD42b, and CD61) but not myeloperoxidase in blasts. Cytogenetic analysis revealed karyotype $47,XX,+21[16]/46,XX[4]$ (Fig 2A, arrow indicates trisomy 21). Fluorescence in situ hybridization using *ETO-AML1* probes showed a normal pattern of signal distribution in buccal epithelial cells, without evidence of an extra *AML1* signal. There was a single base pair deletion of G at nucleotide 150 (relative to ATG) in *GATA1* exon 2 in megakaryoblasts (Fig 3, arrow). The patient was diagnosed with transient myeloproliferative disorder (TMD) and became transfusion independent 1 month later. Peripheral blood blasts disappeared within 3 months without administration of chemotherapy.

At 7 months of age (5 months postpresentation), the patient again developed hematochezia and thrombocytopenia ($10 \times 10^9/L$). WBC was $9.7 \times 10^9/L$ with 1% circulating blasts, and hemoglobin was 10.5 g/dL . BMA revealed marked megakaryocytic dysplasia and increased megakaryoblasts (34%; Fig 1B). The blast population expressed megakaryocyte-associated antigens similar to those seen in the TMD sample but lost expression of CD56 and CD8 and showed

Fig 3.

weaker CD117 expression. Cytogenetic analysis revealed karyotype 47,XX,+21[14]/47,idem,del(5)(p13) [3]/46,XX [8] (Fig 2B, vertical arrow indicates trisomy 21 and horizontal arrow shows a deletion of 5p). FISH using a 5p subtelomeric probe showed an interstitial deletion [del(5)(p13p15)] (arrow, Fig 4). Given these clinical and laboratory findings, the patient was diagnosed with acute megakaryoblastic leukemia (AMKL).

The patient was enrolled onto the multi-institutional protocol AML02 (A Collaborative Trial for the Treatment of Patients With

Newly Diagnosed Acute Myeloid Leukemia or Myelodysplasia).¹ Therapy consisted of standard doses of two courses of remission induction (cytarabine, daunomycin, and etoposide) and two courses of consolidation (cytarabine and mitoxantrone, and cytarabine and L-asparaginase). She had a complete response (negative minimal residual disease) to the first course of remission induction and tolerated chemotherapy well. The third dose of consolidation therapy was not administered because of refractoriness to platelet transfusions associated with development of platelet antibodies. She has been off therapy

Fig 4.

for 18 months and remains in complete remission. Cytogenetic analysis in remission marrow showed 46,XX. Retrospective analysis of *GATA1* gene using a BMA sample at onset of AMKL did not show any mutations with sequence of 30 clones.

Discussion

TMD, characterized by clonal proliferation of megakaryoblasts, develops almost exclusively in patients with DS during the neonatal period.^{2,3} The reported incidence of TMD in patients with DS is 10% but may actually be higher because some affected fetuses die in utero. TMD usually resolves spontaneously within 2 to 3 months, but 20% to 30% of patients develop overt AMKL 1 to 30 months post-TMD. TMD also occurs in children without DS who have either mosaicism for trisomy 21 or normal karyotype.⁴ The frequency and pathogenesis of TMD and subsequent AMKL in these children is not well known because TMD may go undetected.

Classic TMD in DS is characterized by elevated WBC (median, $47 \times 10^9/L$; range, 5 to $380 \times 10^9/L$) with varying percentages of circulating blasts.^{2,3} BMA usually reveals dysplastic megakaryocytes and megakaryoblasts that are typically negative for myeloperoxidase and express megakaryocytic markers (CD41, CD42b, and CD61). In both patients with DS and those who are phenotypically normal, blast cells show trisomy 21. Hematopoietic cells in TMD also have acquired mutations in transcription factor gene *GATA1* (Xp11.23), which controls erythropoiesis and megakaryopoiesis.⁵ The mutation, seen exclusively in exon 2, leads to truncated protein GATA1s, which lacks the N-terminal transactivation domain but is not leukemogenic in the absence of trisomy 21.⁶ The combination of GATA1s and trisomy 21 seems to confer a selective advantage to blasts. Mortality rate from TMD- and DS-associated complications (eg, liver failure, congestive heart failure, renal failure, disseminated intravascular coagulation, hyperleukocytosis, and/or sepsis) can be 10% to 20%.^{2,3} Our patient did not have a DS phenotype, and bleeding tendency was controlled by platelet transfusions only. The initial sole cytogenetic abnormality of trisomy 21 in leukemic blasts prompted us to analyze the *GATA1* mutation, which confirmed diagnosis of TMD. Cytogenetic analysis of somatic cells (eg, buccal mucosa and skin fibroblasts) is necessary to rule out DS as well as its mosaicism; in our patient, analysis of buccal mucosa and remission marrow ruled out mosaicism.

WBCs in patients with DS with AMKL and history of TMD (median, $10 \times 10^9/L$; range, 1.8 to $40.6 \times 10^9/L$) are lower than in those presenting with TMD, but BMA examinations are indistinguishable, and *GATA1* mutations are seen in both cases.^{2,3} Because not all patients with TMD progress to development of AMKL, additional genetic or epigenetic events are likely required for progression to overt leukemia. Altered telomerase activity, *TP53* mutations, and additional acquired karyotype abnormalities (eg, +8, -7, and -5/5q-) have been reported.⁷ A retrospective review reported that five of 16 patients with TMD without DS developed subsequent leukemia, three developed AMKL, and two developed non-AMKL acute myeloid leukemia, but patients were not checked for the presence of *GATA1* mutations.⁴

Our patient developed AMKL subsequent to TMD. She had high WBC with TMD, spontaneous remission, and reappearance of megakaryoblasts with lower WBC. Acquisition of an additional karyotypic abnormality—del(5p)—and development of several immunophenotypic shifts with progression to AMKL suggest that a subclone of TMD

cells evolved and acquired selective advantage. Most likely, *GATA1* mutation was lost with AMKL.

Event-free survival is more than 80% for patients with DS with AMKL but less than 50% in patients without DS with AMKL.^{2,3} In *in vitro* studies, AMKL blasts from patients with DS are more sensitive to chemotherapeutic agents, especially cytarabine, than those from patients without DS because of overexpression of the cystathionine β -synthase gene (localized to 21q22.3) and low expression of cytidine deaminase with *GATA1* mutation.^{8,9} Conventional AMKL therapy in patients with DS is associated with high treatment-related mortality.¹⁰ Thus, several collaborative study groups have adapted their standard AMKL protocol for patients with DS by reducing chemotherapy doses or prolonging intervals between courses. Our patient received standard doses of chemotherapy because we initially considered that the regimen would be well tolerated in a patient with no evidence of constitutional chromosomal abnormalities and efficacious against leukemia cells with acquired +21. This regimen seemed appropriate because *GATA1* mutation was absent in AMKL sample. Although such cases are rare, our case illustrates that the treatment regimen for AMKL preceded by TMD in non-DS children must be carefully selected. Efficacy of a DS-based reduced-intensity regimen for those who retain *GATA1* mutation remains to be determined.

Hiroto Inaba

St Jude Children's Research Hospital, Memphis, TN

Margherita Londero

St Jude Children's Research Hospital, Memphis, TN, and University of Trieste, Trieste, Italy

Scott H. Maurer and Mihaela Onciu

St Jude Children's Research Hospital, Memphis, TN

Yubin Ge and Jeffrey W. Taub

Wayne State University School of Medicine, Detroit, MI

Jeffrey E. Rubnitz and Susana C. Raimondi

St Jude Children's Research Hospital, Memphis, TN

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

REFERENCES

1. Rubnitz JE, Inaba H, Dahl G, et al: Minimal residual disease-directed therapy for childhood acute myeloid leukaemia: Results of the AML02 multicentre trial. *Lancet Oncol* 11:543-552, 2010
2. Xavier AC, Ge Y, Taub JW: Down syndrome and malignancies: A unique clinical relationship—A paper from the 2008 William Beaumont Hospital symposium on molecular pathology. *J Mol Diagn* 11:371-380, 2009
3. Gamis AS, Hilden JM: Transient myeloproliferative disorder, a disorder with too few data and many unanswered questions: Does it contain an important piece of the puzzle to understanding hematopoiesis and acute myelogenous leukemia? *J Pediatr Hematol Oncol* 24:2-5, 2002
4. Apollonsky N, Shende A, Ouansafi I, et al: Transient myeloproliferative disorder in neonates with and without Down syndrome: A tale of 2 syndromes. *J Pediatr Hematol Oncol* 30:860-864, 2008
5. Wechsler J, Greene M, McDevitt MA, et al: Acquired mutations in *GATA1* in the megakaryoblastic leukemia of Down syndrome. *Nat Genet* 32:148-152, 2002
6. Hollanda LM, Lima CS, Cunha AF, et al: An inherited mutation leading to production of only the short isoform of GATA-1 is associated with impaired erythropoiesis. *Nat Genet* 38:807-812, 2006
7. Roy A, Roberts I, Norton A, et al: Acute megakaryoblastic leukaemia (AMKL) and transient myeloproliferative disorder (TMD) in Down syndrome: A multi-step model of myeloid leukaemogenesis. *Br J Haematol* 147:3-12, 2009

8. Taub JW, Huang X, Matherly LH, et al: Expression of chromosome 21-localized genes in acute myeloid leukemia: Differences between Down syndrome and non-Down syndrome blast cells and relationship to in vitro sensitivity to cytosine arabinoside and daunorubicin. *Blood* 94:1393-1400, 1999

9. Ge Y, Stout ML, Tatman DA, et al: GATA1, cytidine deaminase, and the high cure rate of Down syndrome children with acute megakaryocytic leukemia. *J Natl Cancer Inst* 97:226-231, 2005

10. Lange BJ, Kohn N, Barnard DR, et al: Distinctive demography, biology, and outcome of acute myeloid leukemia and myelodysplastic syndrome in children with Down syndrome: Children's Cancer Group Studies 2861 and 2891. *Blood* 91:608-615, 1998

DOI: 10.1200/JCO.2010.32.3634; published online ahead of print at www.jco.org on January 4, 2011

Acknowledgment

We acknowledge the expertise of Vani J. Shanker, PhD, ELS, in the editorial review of the manuscript. This research was supported in part by Cancer Center Support Grant No. CA21765 from the National Institutes of Health and the American Lebanese Syrian Associated Charities.