



KMT2A-MLLT3 AML Masquerading as JMML may Disguise Fatal Leukemia

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ABSTRACT

We present a mortality case showcasing t(9;11)-positive acute myeloid leukemia/juvenile myelomonocytic leukemia (AML/JMML) overlap to shed light on this lethal molecular subtype of AML. In this case, the flawed assumption that JMML was to blame impeded the prompt undertaking of appropriate treatment for AML in our 14-month-old patient. This article aims to scrutinize the catastrophic sequel of such an overlap in leukemia and refutes the contemporary diagnostic methods.

Diagnostic cytogenetics are superior to any prognostic determinant in pediatric acute myeloid leukemia (AML). Chromosomal rearrangements involving the lysine methyltransferase 2A (KMT2A) gene are common genetic alterations in pediatric AML with an incidence of 15–25% (50–60% in children younger than two years). However, AML cases with KMT2A gene rearrangements do not comprise a single biological entity, but their prognosis is similar. In a large study of 1897 patients with AML, AML with KMT2A gene rearrangements had a dismal prognosis.¹ In particular, the prognostic impact of the KMT2A-mixed-lineage leukemia, translocated to, 3 (MLLT3) molecular subtype is contentious in the literature. KMT2A-MLLT3 and t(9;11) are terms often used interchangeably. t(9;11) has an incidence between 8–12% of pediatric AML. While the National Comprehensive Cancer Network guidelines labeled t(9;11)-positive AML as an intermediate-risk disease, many studies confirmed an aggressive clinical course for this biologic entity.^{2,3} In the following case, the biologic mimicry between t(9;11)-positive AML and juvenile myelomonocytic leukemia (JMML) lent t(9;11)-positive AML a peculiar adverse prognostic feature. Notably, the distortion of the clinical picture by the leukemic overlap led to a profoundly severe course due to hampering the

undertaking of the correct treatment that resulted in mortality.

CASE REPORT

A 14-month-old girl presented to our institution in September 2016 with a short history of fever, abdominal distension, and poor oral intake. On presentation, she was sick-looking, pale with generalized edema, and significant hepatosplenomegaly (liver 5 cm and spleen 6 cm below the costal margins). Initial investigations revealed anemia (5.8 g/dL), thrombocytopenia ($14 \times 10^9/L$), leukocytosis ($32.5 \times 10^9/L$), significant monocytosis ($8.8 \times 10^9/L$), and disseminated intravascular coagulation. Peripheral blood film showed a leukoerythroblastic picture with significant monocytosis (some are dysplastic), immature granulocytes, and occasional circulating blasts.

While an extensive septic workup was carried out, the child was treated with broad-spectrum antibiotics, packed red cell and platelet transfusions, and vitamin K. As treatment attempts were futile, bone marrow aspiration was carried out. This showed tri-lineage hematopoietic dysplasia with a significant increase in monocytes and its precursors and a blast percentage of 10%. Immunophenotyping revealed the presence of a small population of myeloblasts with possible monocytic differentiation (about

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2%). Molecular analysis by reverse transcription-polymerase chain reaction (RT-PCR) was negative for $t(15;17)$, $t(8;21)$, $inv(16)$, and the BCR/ABL $t(9;22)$ transcripts.

The subsequent course was stormy with rapid deterioration of her respiratory distress and worsening edema. As the treating team embraced the diagnosis of JMML, she was initiated on low dose cytarabine (100 mg/m²/day), but after two doses, she required intubation and ventilation due to increased oxygen requirements. As a final resort, intravenous (IV) cytarabine was switched to IV azacitidine (100 mg/m²/day), but her respiratory failure progressively worsened despite maximum intensive care support. In less than 24 hours post-intubation, she developed a refractory cardiac arrest and passed away. A day before death, we obtained the results of cytogenetics that revealed reciprocal translocation $t(9;11)$ in all cells analyzed. Fluorescence in situ hybridization (FISH) showed mixed-lineage leukemia (MLL)/MLLT3 fusion in 69% of nuclei analyzed.

DISCUSSION

The great overlap of the differential diagnosis of leukoerythroblastosis with hepatosplenomegaly has posed a daunting task for many pediatricians. The ensuing delay to reach the right diagnosis and start the proper treatment can be devastating. Malignant infantile osteopetrosis and hemophagocytic lymphohistiocytosis should be excluded in the first months of life, whereas infection and leukemia persevere to be plausible causes throughout childhood. In particular, the diagnosis of JMML is a hurdle to most hematologists as it is frequently confused with an infection or immunodeficiency syndrome. Consequently, the diagnosis of JMML almost always relies on the diagnostic criteria.⁴

In this case, a sepsis-like picture masked leukemia initially, but soon afterward the treating team was prompted to concede the diagnosis of JMML as bone marrow aspirate was suggestive of JMML. This was supported by the diagnostic criteria (complied with categories 1 and 3 for diagnosing JMML). Conversely, JMML had concealed $t(9;11)$ -positive AML that was only unveiled by cytogenetics. As $t(9;11)$ does not exist in the genomic landscape of JMML, the diagnosis of JMML was undoubtedly incorrect.⁵

The $t(9;11)$ is a surrogate marker of high-risk acute leukemia with equal prevalence in AML and acute lymphoblastic leukemia and a predilection for patients in the pediatric age group. Since 2008, the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues had adjoined $t(9;11)$ to a distinct category of AML (AML with recurrent genetic abnormalities) under the definition 'AML with $t(9;11)(p21.3;q23.3)$; KMT2A-MLLT3' (ICD-0 code 9897/3). KMT2A is the target gene at chromosome band 11q23 that becomes fused to various translocation partners when disrupted by the translocation. AF9-MLL, *Drosophila trithorax* homologue gene, and the most renowned MLL are synonyms for the KMT2A gene. The gene fusions are 'class 2 mutations' where fusion proteins override normal differentiation stimuli by triggering unrelenting expression of genes implicated in early hematopoiesis that instruct hematopoietic stem cells to convert into a preleukemic state. $t(9;11)$ is the most frequent translocation involving the KMT2A gene in AML and is usually associated with AML M5a (some are M5b or M4). The other translocations are called non-MLL3.

There is no kinship between JMML and AML. JMML is analogous to chronic myelomonocytic leukemia, but with a flavor of dysplastic proliferation of the granulocytic and monocytic series. Therefore, the current WHO classification envisages JMML as an overlap myeloproliferative/myelodysplastic neoplasm. Nevertheless, differentiating JMML from AML is nearly impossible on clinical grounds alone as significant hepatosplenomegaly and respiratory failure can occur in both. Interestingly, the overlap between JMML and $t(9;11)$ -positive AML was well-characterized in the medical literature.⁶ Therefore, we stipulate a possible functional homology between $t(9;11)$ and $t(9;22)$ that might confer features of chronic leukemia in the former.

Overwhelming evidence supports the devastating prognostic impact of MLL gene rearrangements in AML.⁷ Therefore, differentiating AML from JMML has profound implications on therapy decision-making strategies. Overall, chemotherapy regimens for JMML are mainly cytoreductive as a bridge to transplantation rather than curative as for AML. The $t(9;11)$ -positive AML/JMML overlap also casts doubts that undermine the reliability of the diagnostic criteria of JMML to establish the diagnosis of this greatly equivocal

disease. Hence, a combination of molecular testing and myeloid progenitors' hypersensitivity to granulocyte-macrophage colony-stimulating factor should be employed to diagnose JMML. Moreover, the biological behavior of JMML is variable as in the case of 'self-resolving' disease that occurs in the non-syndromic JMML where disease merits watchful waiting approach.⁸

CONCLUSION

The adverse prognostic impact of t(9;11)-positive AML/JMML overlap dictates that cytogenetics and FISH in combination with RT-PCR or long-distance inverse PCR should be immediately performed to detect MLL rearrangements in every suspicious case. Finally, we suggest that t(9;11) should judiciously be added to the so-called 'AML-defining cytogenetic mutations'. These are clonal cytogenetic abnormalities that, when present, establish the diagnosis of AML regardless of the blast percentage.

Disclosure

The authors declared no conflicts of interest.

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