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Editorial

Transient Abnormal Myelopoiesis of Down Syndrome Needs Further Study and Minimum WHO Diagnostic Criteria

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Editorial

Hematologic abnormalities are relatively common in individuals with Down syndrome (DS) and include both benign and malignant disorders. For example, in a frequently cited study of DS neonates who had a complete blood count (CBC) during the first week of life, 80% had neutrophilia, with thrombocytopenia in 66% and polycythemia in 33% [1]. The latter can persist until age two months irrespective of the presence of congenital cyanotic heart disease. In addition, one must be aware of red cell macrocytosis unrelated to folate or vitamin B12 deficiency since it can mask anemias typically presenting with a low mean corpuscular volume such as iron deficiency, thalassemia or lead toxicity. There is also an increased risk of leukemia which extends into the adult years. Between 1 in 100 and 1 in 200 children with DS will develop acute leukemia, and the likelihood of it being either lymphoblastic or acute myeloid leukemia is approximately equal; furthermore, it is argued that about 20% of the latter are preceded by a myelodysplastic phase [2].

One of the most fascinating hematologic disorders is unique to DS: transient abnormal myelopoiesis (TAM). TAM has variously been called transient myeloproliferative disorder or transient leukemia since it presents with circulating blasts whose morphologic and immunophenotypic features can be indistinguishable from acute megakaryoblastic leukemia (AMKL). The most interesting aspect relates to the natural history of TAM inferred from its name in that, although a subset of patients experience life-threatening or even fatal complications, the majority undergo spontaneous resolution without treatment by age three months [3]. TAM is due to acquired *GATA1* mutations in these blasts and it may be that this phenomenon is transient because of cessation of hematopoiesis by the liver after birth, since the blasts originate in the fetal liver [4] as the bone marrow during the fetal period is mostly committed to granulopoiesis. Evidence in support of this is the observation that the peripheral blood blast count may exceed the percentage of bone marrow blasts.

The diagnosis is important to make since 20 to 30% of children with a history of TAM will go on to develop a non-transient AMKL one to three years later [5], underscoring the need to ensure proper follow-up and monitoring. Nevertheless, although it is stated to occur in four to ten percent of infants with DS, the true frequency of TAM is unknown since it likely can precipitate intrauterine fetal demise, or on the other hand be clinically silent.

The aspects that initially attracted me most to hematopathology were: 1. the collaborative relationships between laboratory hematologists and clinical colleagues; and 2. that the current approach to diagnosis is multiparametric and relies on the convergence of morphology, immunophenotype, genetic abnormalities and clinical data (stated another way by one of my mentors, Daina Variakojis, "we are no longer in a 'look-and-tell' era"). The World Health Organization (WHO) Classification of Hematopoietic and Lymphoid Tissues [5] has largely been a great success due to those combined collaborative efforts. However, it has fallen short with respect to TAM by not having provided minimum diagnostic criteria.

The diagnosis of TAM is straightforward when the DS neonate has marked leukocytosis and most of the white blood cells in circulation are blasts. I have had cases like that recently and no one questions it. However, it is elusive when there are only rare blasts beyond the first two or three days of life when one might have reasonably been able to explain away (safely ignore) a couple of immature cells, or when mediastinal lymph nodes removed incidentally for access to correct a cardiac defect show extramedullary hematopoiesis which typically indicates a hematologic disorder. I have also recently seen and struggled with such cases. While we hope that our clinical colleagues trust our diagnosis, we cannot not forget the unseen impact we have on our patients and their families. Without a threshold for diagnosing TAM, we run the risk that some of these children will go on to develop AMKL which we would have otherwise predicted had there been minimum criteria.

Maybe all DS newborns at the very least must be screened with single or serial CBC, or perhaps we need more sensitive "minimal residual disease"-type flow cytometry assays or *GATA1* mutation analysis since certain mutations appear to associated with a higher risk of AMKL [6]. Further studies are required to determine best practice and more fundamentally how exactly to define TAM. In the meantime, it might be preferable to err on the side of over diagnosis to be sure our youngest patients get the follow-up they just might need.

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