Myeloid Malignancies

Recognizing the risk of germline predisposition and supporting patients and families

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In 2016, the World Health Organization (WHO) classification of myeloid neoplasms was updated to include a category of myeloid neoplasms with germline predisposition (Hasserjian, 2018). Since completion of the Human Genome Project in 2003, scientific and DNA sequencing advances have transformed the diagnosis and treatment of myeloid malignancies from being based solely on histopathology and morphology (how the transformed cells look under a microscope) to including molecular and genetic features. The 2016 WHO classification reflects these advances, classifying myeloid types based on the numerous identified oncogenic somatic variants (i.e., genetic changes that are acquired or sporadic). However, this article will focus on the germline pathogenic gene variants that predispose an individual toward developing a myeloid malignancy. It is critical to recognize and identify these variants not only because of their impact on patient prognosis and management, but also because many acute myeloid neoplasms will require allogeneic hematopoietic stem cell transplantation (HSCT). The presence of a germline pathogenic variant in a related but unaffected donor can lead to poor or failed engraftment and donor-derived leukemia (Sakata et al., 2021).

Prevalence and Epidemiology

Historically, there has been a perception that hereditary hematologic syndromes affect only pediatric patients. Indeed, the prevalence of hereditary hematologic malignancy is higher in the pediatric population and estimated at 4%-13% (Akpan et al., 2018), but it is now known that at least 5% of adult patients with a myeloid disorder, such as acute myeloid leukemia or myelodysplastic syndrome, carry inherited pathogenic gene variants that predispose them toward a myeloid malignancy (Akpan et al., 2018; Rafei & DiNardo, 2019). Pathogenic germline variations in the RUNX1 gene were first identified and linked to an inherited predisposition for hereditary myeloid malignancy in 1999 (Akpan et al., 2018). Since then, both the WHO and National Comprehensive Cancer Network (NCCN, 2021) clearly identify familial syndromes with genes associated with a predisposition syndrome (Arber, 2019). Heightened awareness and advances in genomic screening for the identification of germline pathogenic variants will result in increased identification of patients and unaffected family members who harbor germline pathogenic variants.

Screening and Identification of a True Germline Variant

It is well established that myeloid malignancies are stratified by risk and that risk is based on the presence of genetic abnormalities (e.g., complex karyotype or multiple cytogenetic alterations, somatic driver gene variants). In the diagnostic workup of a newly diagnosed myeloid malignancy, it is important to identify the biomarkers (genomic alterations) to...