# Myeloid Neoplasms with Germline Predisposition

## A New Provisional Entity Within the World Health Organization Classification

David R. Czuchlewski, MD[a,*], LoAnn C. Peterson, MD[b]

**KEYWORDS**

• Germline predisposition mutation • Familial cancer • Acute myeloid leukemia
• Myelodysplastic syndrome

## ABSTRACT

The forthcoming update of the World Health Organization (WHO) classification of hematopoietic neoplasms will feature "Myeloid Neoplasms with Germline Predisposition" as a new provisional diagnostic entity. This designation will be applied to some cases of acute myeloid leukemia and myelodysplastic syndrome arising in the setting of constitutional mutations that render patients susceptible to the development of myeloid malignancies. For the diagnostic pathologist, recognizing these cases and confirming the diagnosis will demand a sophisticated grasp of clinical genetics and molecular techniques. This article presents a concise review of this new provisional WHO entity, including strategies for clinical practice.

### *Key Features*

- Some cases of myeloid neoplasms are associated with predisposing germline mutations, and the new revision of the World Health Organization (WHO) classification specifically recognizes such cases as a provisional diagnostic entity.
- Some cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) with germline predisposition mutations are associated with specific clinical phenotypes, whereas others may lack any identifying clues, thus demanding a high index of suspicion.
- Recognizing the true genetic basis of these cases is important for proper clinical management and follow-up.

## OVERVIEW

Among all areas of diagnostic pathology, the field of hematopathology has long been a leader in the application of molecular genetic information to the classification of malignancies. Beginning with the identification in 1960 of the Philadelphia chromosome and continuing through the recognition of the *PML-RARA* fusion as pathognomonic for acute promyelocytic leukemia, genetic findings have been closely linked with advances in the understanding and classification of myeloid neoplasms. The importance of genetics was recognized in the original WHO *Classification of Tumours of Haematopoietic and Lymphoid Tissue* released in 2001. These trends continued in the 2008 revision of the WHO classification, which saw the creation of categories of AML defined either by genetic features (for example, the provisional AML with mutated *NPM1*) or by clinical history (for example, therapy-related myeloid neoplasms).

The upcoming revision of the WHO classification continues to highlight the central role of genetic

Disclosure Statement: The authors have nothing to disclose.
[a] Department of Pathology, University of New Mexico, 1001 Woodward Place NE, Albuquerque, NM 87102, USA; [b] Department of Pathology, Northwestern University Feinberg School of Medicine, NMH/Feinberg Room 7-344, 251 East Huron, Chicago, IL 60611, USA
* Corresponding author.
*E-mail address:* DCzuchlewski@salud.unm.edu

Surgical Pathology 9 (2016) 165–176
http://dx.doi.org/10.1016/j.path.2015.09.010
1875-9181/16/$ – see front matter 

and clinical data in the diagnosis of myeloid neoplasms, as exemplified by the new provisional diagnostic category "Myeloid Neoplasms with Germline Predisposition." These cases are associated with inherited or de novo mutations within the germline that markedly increase the likelihood that a patient will develop a myeloid neoplasm, especially MDS or AML. As such, they are defined and characterized by specific genetic and clinical phenotypic findings. These mutations and syndromes are rare and, consequently, somewhat outside the current scope of daily pathology practice. This article provides a primer for this new diagnostic area. Because the WHO chapter remains in final revisions at the time of this writing, the authors strongly recommend correlation with the forthcoming published classification for final diagnostic considerations and terminology.

## SPECIAL CLINICAL FEATURES OF MYELOID NEOPLASMS ASSOCIATED WITH GERMLINE PREDISPOSITION MUTATIONS

An initial question that might be asked on learning of this new category is, "Why create a special provisional diagnostic category for these cases? Perhaps these should just be considered ordinary cases of MDS or 'AML, not otherwise specified' that happen to occur in genetically predisposed individuals." The committee charged with revising the WHO thought that the genetic and clinical features were sufficiently unique that MDS/AML arising in this setting should be specially recognized. In particular, these patients frequently require specialized approaches to therapy and other aspects of clinical management.

In cases of MDS, for example, patients with germline predisposition mutations often have a poor outcome that is not apparent if traditional diagnostic and risk assessment tools, such as the Revised International Prognostic Scoring System, are applied. (Such prognostic systems exclude cases of MDS with known underlying genetic predisposition.) Patients with MDS and certain types of germline predisposition may benefit from early hematopoietic cell transplantation.[1] Furthermore, patients with MDS in the setting of a classic hereditary bone marrow failure disorder (BMFD) often present at a young age with a hypocellular bone marrow. In patients with nonsyndromic MDS, these are features associated with better response to immunosuppressive therapy.[2] In the setting of BMFD, however, immunosuppressive therapy is ineffective and possibly detrimental, increasing the risk of infectious complications.[1]

Cases of MDS/AML with germline predisposition mutations also differ from typical sporadic MDS and AML in that they are frequently associated with unique nonhematopoietic manifestations. Patients with Fanconi anemia, for example, are at greatly increased risk for developing other solid tumors, with up to 75% developing a nonhematologic cancer by age 45.[3] Possible clinical events in the disease course of dyskeratosis congenita include a wide range of nonhematopoietic pathology, from esophageal stenosis to avascular necrosis of the femoral head, pulmonary fibrosis, and retinal detachment.[4] Patients with germline *GATA2* mutations may be susceptible to infection by nontuberculous *Mycobacteria*, such as *M avium* complex or by other opportunistic pathogens, in addition to developing pulmonary alveolar proteinosis.[5] Patients with *RUNX1*, *ANKRD26*, or *ETV6* mutations may bleed out of proportion to their platelet counts due to underlying platelet dysfunction. Because a diagnosis of AML or MDS may be the initial presenting sign of these underlying syndromes, classification as uncomplicated MDS or AML, not otherwise specified, would tend to understate the full clinical picture and potentially deprive these patients of necessary follow-up care and surveillance. One important aspect of follow-up care that is common to all cases of myeloid neoplasia with germline predisposition mutations is the necessity of formal genetic counseling with a certified genetic counselor and/or geneticist, including consideration for testing of at-risk relatives.

Finally, special treatment approaches may be called for in some cases of AML/MDS associated with germline predisposition mutations. Patients with BMFD characterized by increased susceptibility to genotoxic stress must follow reduced-intensity conditioning regimens prior to allogeneic bone marrow transplantations.[6] Extra scrutiny of related stem cell donors is also indicated due to the familial nature of the pathogenic mutation. Screening of the potential related donor for the mutation in question is necessary to avoid transplanting cells that harbor the very defect the transplant procedure is intended to correct.[5] Some parents consider and/or undergo preimplantation genetic diagnosis in an effort to provide transplantable stem cells free of the mutation.[7] If a germline susceptibility mutation is present, some clinicians may consider the eradication of cells with the mutation from the hematopoietic compartment as an added advantage of allogeneic transplant.[8] Special considerations in the post-transplant settings include high rates of graft-versus-host disease in Fanconi anemia and cardiac toxicity in Shwachman-Diamond