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Practical considerations for diagnosis and management of patients and carriers

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ABSTRACT

Newly diagnosed children and adults with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) need to be screened for presence of a genetic predisposition syndrome because the information on the genetic status is likely to influence clinical care and management of the patient and the family. Scenarios in which genetic counseling is advised include presence of a mutation on somatic screen that can be associated with a germline predisposition, hematologic or cytogenetic characteristics suggestive of an underlying susceptibility syndrome, non-hematological phenotype suspicious for a familial condition, history of previous malignancy, or a family history of cancer, cytopenia, autoimmunity, or organ-system manifestation fitting a predisposition syndrome. With increasing complexity on phenotypes, genetics, and leukemia risk of the recently recognized predisposition syndromes, specialized clinics for hereditary hematologic malignancies have been initiated to guide genetic testing and support hematologists integrating genetic data into therapeutic strategies and clinical care. Recommendations for surveillance of carriers are currently based on expert opinion and subject to future modification when a more complete picture for the distinct genetic entities will arise.

1. Introduction

Traditionally, inherited bone marrow failure syndromes (IBMFS) and Down syndrome have been associated with genetic predisposition to myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Within the last 15 years, other subtle constitutional mutations that render patients susceptible to the development of myeloid neoplasia have been defined [1]. Most of the affected genes are recurrently mutated in sporadic leukemia.

Some of these predisposition genes are involved in megakaryopoiesis and platelet production. They give rise to familial syndromes, which can present with mild to moderate thrombocytopenia and bleeding disorder. The three currently known disorders in this group are: Familial platelet disorder with associated myeloid malignancy (FPD/AML) caused by germline mutations in the *RUNX1* gene [2], thrombocytopenia 5 caused by *ETV6* mutations [3], and thrombocytopenia 2 with disease causing variants in *ANKRD26* [4,5].

Similar to the syndromic nature of the classical IBMFS, some of the recently recognized predisposition syndromes like GATA2 deficiency [6,7] or the telomere biology disorders [8] can exhibit a variable non-hematological phenotype. Other cancer susceptibility syndromes like AML with germline *CEBPA* mutations [9] and myeloid neoplasms with pathogenic *DDX41* variants [10] are limited to the hematopoietic system, and most of these patients have normal blood counts prior to diagnosis of MDS/AML. Other genetic predisposition syndromes for MDS/AML-like heterozygous germline mutations in *SRP72* [11] or duplication of the *ATG2B* and *GSKIP* gene [12] have been described in few families only.

Penetrance in these recently described autosomal-dominant inherited predisposition syndromes is variable. There is a wide interfamilial and intrafamilial variation in phenotype. With increasing availability of molecular testing, heightened awareness, and collaborative research, the number of afflicted patients and carriers will rise rapidly. In addition, it is likely that new susceptibility disorders caused by cooperating effects in less damaging mutations in multiple genes will be discovered. Thus, it will become increasingly challenging integrating all aspects of leukemia susceptibility into clinical care. This chapter summarizes

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practical considerations of diagnosis and management for patients and carriers focusing on the recently defined predisposition syndromes.

2. Screening for predisposition syndromes at diagnosis of MDS/AML: Physical examination and history taking

Early identification of an underlying predisposition syndrome in a patient with newly diagnosed MDS or AML is crucial because the genetic information is likely to influence the personalized care of the affected individual. All newly diagnosed patients with MDS and AML should therefore be screened for presence of a genetic predisposition syndrome by a meticulous physical examination and a carefully taken medical history. Although these screening tools are simple and easily performed, they are often omitted. Naturally, initial physician–patient contacts in malignant disorders focus on emergency care and issues related to therapy and overall prognosis. However, once these immediate challenges are handled, physicians are encouraged to complete their physical examination with respect to presence of non-hematological stigmata of underlying genetic disorders.

Like the classical IBMFS, some of the recently discovered predisposition syndromes can display overlapping dysmorphic changes of the head (facies, eyes, ears, oral cavity, and microcephaly), skeleton (forearm, fingers, and toes) and skin (pigmentation, warts, hair, and nails). Growth abnormalities (short stature), developmental delay or behavioral problems (autism, aggressive behavior) may be present. Importantly, changes in other organ systems such as pulmonary (telomere biology diseases) or lymphatic vessel system (GATA2 deficiency) can raise the suspicion for presence of a specific disorder and thus direct genetic testing.

Similar to obtaining a complete physical status, medical and family history taking is often a multistep process. Patients and families may need some time to gather the necessary information and clinical records. While constructing a formal family pedigree spanning three or more generation is typically reserved for genetic counseling, a robust family history of first- and second-degree relatives needs to be obtained in all patients with myeloid neoplasia at diagnosis [13].

Checklists and other quality control measures may simplify screening procedures for predisposition syndromes in a busy hematology practice. In addition, they can increase awareness and educate medical staff. However, it is important to recognize that there is currently no scientific evidence that these screening measures capture a significant proportion of patients with underlying inherited disorders. Furthermore, the level of suspicion sufficient to initiate genetic testing is neither defined nor addressed in expert opinions.

3. Scenarios at diagnosis of MDS/AML requiring genetic testing for predisposition syndromes

Criteria for initiating screening for predisposition syndromes of MDS/AML are poorly defined. There are different scenarios, which require genetic counseling of the patient and subsequent testing (Table 1).

With implementation of MDS/AML panel diagnostics into clinical practice the question whether a specific gene mutation is somatic or possibly germline arises more frequently. Genes altered in inherited predisposition syndromes are key regulators of cellular function and hence often acquired drivers of clonal development in sporadic malignancy. While standard sequencing cannot distinguish between germline and somatic, there are clues from the somatic analysis, which indicate that a germline mutation is likely. They include a near-heterozygous or near-homozygous allelic frequency and/or the presence of multiple mutations within one of these genes [14]. In these cases expansion on the patient's history, counseling, and germline testing are appropriate next steps. For example, an 18-year-old male diagnosed with MDS and excess blasts (MDS-EB) and (1) a *RUNX1* mutation and a history of thrombocytopenia may have *RUNX1* germline disease, (2) a *GATA2* mutation, autism, and a hydrocele is likely to suffer from GATA2 deficiency, and (3) a *TERT* or *TERC* mutation and a hypocellular bone marrow will be diagnosed of a telomere biology disorder. In other instances, a high probability of underlying genetic disease calls for prompt germline analysis: approximately 10% of patients with AML and biallelic *CEBPA* mutations will have CEBPA-familial leukemia [15], and 60% of individuals with a pathogenic variant of the *DDX41* gene have inherited disease [16]. There is a clear need to develop and integrate algorithms for identification of probable inherited disease into the interpretation of targeted sequencing panels at diagnosis of MDS/AML.

Hematologic parameters can also trigger testing for a predisposition syndrome. Preceding monocytopenia [6] or lack of B cells [17] may point to GATA2 deficiency, while pale-appearing platelets can lead to *ANKRD26* germline mutations with alpha granule deficiency [4]. Bleeding diatheses and prior thrombocytopenia may indicate *RUNX1*, *ETV6,* or *ANKRD26* germline disorder. Thrombocytopenia is due to megakaryocytic dysplasia, which can be considered as a pre-leukemic abnormality reflecting disturbed maturation secondary to the transcription factor or transferase defect [18]. Dysmegakaryopoiesis with small megakaryocytes with hypolobulation, small amount of mature eosinophilic cytoplasma, and micromegakaryocytes is also noted in other susceptibility syndromes like GATA2 deficiency [19] and is consistent with but not specific for these disorders. Importantly, presence of atypical megakaryocytes is not a sign of overt MDS. Furthermore, low-grade MDS-like refractory cytopenia of childhood (RCC) cannot be reliably distinguished from IBMFS or leukemia predisposition syndromes by histopathological means only [20].

Conventional karyotypes can provide important clues. Simultaneous presence of del(7q) and monosomy 7 in an infant with cytopenia can be indicative of a germline mutation in *SAMD9*/*SAMD9L* [21,22], trisomy 8 and/or monosomy 7 in an adolescent may indicate GATA2 deficiency [7]. Isochromosome i(7)(q10) and del(20)(q) are particularly frequent in Shwachman-Diamond syndrome [23], while gain of chromosome 1q and 3q26q29 are the most common aberrations in MDS/AML in Fanconi anemia [24].

A patient's non-hematological phenotype can raise the suspicion of classical IBMFS, a telomere biology disorder or GATA2

Table 1
Scenarios when genetic testing for predisposition genes is advised in newly diagnosed patients with MDS/AML.

1.	Somatic testing identified a mutation associated with germline predisposition
2.	Hematologic or cytogenetic characteristics of MDS/AML suggestive of germline predisposition
3.	Non-hematological phenotype of patient suggestive of genetic syndrome known to predispose to cancer
4.	Previous malignancy
5.	Family history cancer, cytopenia, autoimmunity, or organ-system manifestation fitting a predisposition syndrome