Inherited predisposition to myeloid neoplasms

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Myeloid neoplasms include myelodysplastic/ myeloproliferative neoplasms (MDS/MPN) and acute myeloid leukemia (AML). While majority of these disorders are still sporadic, it is becoming clear that a subset of them have a germline predisposition and is familial in nature. With the advancement and integration of molecular studies, it has been recognized that approximately 5-10% of hematological malignancies have germline predisposition. Timely diagnosis of these cases is not only important for treatment purposes i.e. tailor-made conditioning regime for some of the bone marrow failure syndromes but also for genetic counseling, risk assessment and follow-up of the family members. Recent updates to “WHO classification of tumours of haematopoetic and Lymphoid tissues” (1) has also identified its importance and included this as a major change to its WHO revision. Now these myeloid neoplasms (MDS, MDS/MPN and Acute leukemia) have their own WHO sub-category “Myeloid Neoplasms with Germline Predisposition.” (Table 1) also known as familial predisposition to myeloid disorders (FPMD).

Table1: Classification of Myeloid Neoplasms with Germline Predisposition

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1. Myeloid neoplasms with germline predisposition without a pre-existing disorder or organ dysfunction
a. AML with germline CEBPA mutation
CEPBA encodes a critical transcription factor that regulates the maturation of granulocyte and monocyte. A lot has been known about somatic CEBPA mutation and its association with sporadic AML (2). In the setting of somatic mutation, biallelic mutations are associated with favorable prognosis and seen in approximately 10-20% of cytogenetically normal AML. In larger cohorts of AML it was recognized that approximately 7-11% of these cases, one of the mutations is in germline configuration. It was initially described in 2004 with many family members affected (3) Germline mutations predominantly localize to N-terminal with autosomal dominant inheritance with almost complete penetrance. However, rare C-terminal mutations have also been described. Acquisition of another mutation usually in the C-terminal domain of CEBPA gene by second hit leads to full blown conversion to AML. Both sporadic and germline mutations have similar pathological and clinical findings, a predominant subtype of M1 and M2, aberrant CD7 by flow cytometry, and normal cytogenetics. The average age of disease presentation is approximately 24.5 years. Since it is always not possible to distinguish between these two categories (lack of relevant family history), a consideration of germline predisposition mutation should be given in any case of AML with double mutation. Skin biopsy is the only definitive way to distinguish between these two. Overall prognosis remains good for both sporadic CEBPA as well as germline mutations with overall survival >50% and >65% respectively, however late recurrence is commonly seen in germline variant with distinct molecular profile.

**b. DDX41 mutation associated myeloid neoplasms**

DDX41 gene is likely part of the spliceosomal components, although its exact function is not known, it been shown to be mutated in MDS and AML. Similar to CEBPA, majority of the mutations are bi-allelic with one of them in germline configuration (4). These mutations are relatively rare and the exact incidence is not known. One of the interesting features of these mutations is the latency of presentation (median age of presentation at 65 years) compared to other germline predisposition mutations. These mutations might be underdiagnosed as a recent study of MDS and AML showed its incidence to be approximately 0.8% (5). Recognition of these mutations is important for assessment of prognosis, genetic counseling and may be more therapy as there are some data that these patients may respond to targeted therapies.

2. **Myeloid neoplasms with germline predisposition and pre-existing platelet disorders**

a. **Myeloid neoplasms with germline RUNX1 mutation**

RUNT-related transcription factor 1 (RUNX1) is a regular to hematopoiesis and has been seen frequently involved in chromosomal translocation i.e. t(12;21)/ETV6/RUNX1, t(8;21)/RUNX1/RUNXIT1. The clinical presentation is heterogeneous with mild to moderate thrombocytopenia with or without bleeding tendency with propensity to develop MDS/AML and rarely acute T-ALL. These mutations are inherited as autosomal dominant with variable penetrance ranging from 35-44% and dependent on the type of RUNX1 mutation and its location in the domain. The age range is broad from anywhere to 6-76 years with a mean of 33 years (6, 7) with many mutations showing anticipation. Although there is no clear cut explanation of
MDS/AML developing these cases yet, however involvement of second RUNX1 allele either by mutation or duplication of mutated allele leading to trisomy 21 have been implicated (8).

b. Myeloid neoplasms with germline ANKRD26 mutation
This is also known as thrombocytopenia 2 and has an autosomal dominant inheritance. These patients have mild to moderate thrombocytopenia all their life with normal platelet aggregation studies. Point mutations are usually seen in the promoter of the ANKRD26 gene and likely interfere with the transcription factor binding leading to increased expression of the gene. Based on the few affected family studies, it has been shown that these mutations are associated with almost 30 time’s higher risk of AML. CML and CMML have also been seen in association with these mutations. Megakaryocytes frequently show dysplastic features even in the absence of frank MDS (9).

c. Myeloid neoplasms with germline ETV6 mutation
ETV6 gene is a transcriptional repressor. The mutations are inherited as autosomal dominant and affect the DNA binding properties of the protein. They present with mild to moderate thrombocytopenia with or without bleeding tendency and a propensity to develop hematological malignancies including childhood B-ALL and many myeloid malignancies (10). Only few families have been described and our understanding of these disorders is not very clear.

3. Myeloid neoplasms with germline predisposition and other organ dysfunction
a. GATA2 associated myeloid neoplasms
GATA2 gene encodes for a transcription factor and is essentially for maintaining the stem cell proliferation. Germline mutations in this gene have a heterogeneous presentation ranging from mild cytopenia to inherited syndromes like Emberger and MonoMAC syndromes and MDS/AML phenotype. Emberger syndrome is characterized by lymphedema of the lower limbs and MonoMAC syndrome presents with monocytopenia as well as functional defects of B and NK cells and susceptibility to mycobacterial and fungal infections. Patients of MDS/AML with these clinical features in the past should be tested for GATA2 mutations (11). These mutations are inherited as autosomal dominant manner and have varied expressivity. About two thirds of GATA2 mutation are de-novo and might not have any family history. The life time risk of MDS is approximately 70%.

b. Myeloid neoplasms associated with classical bone marrow failure (BMF) associated disorders and telomere biology

These disorders are relatively well characterized and can be associated with cytopenia, bone marrow failure, aplastic anemia and MDS/AML. Classical syndromes include Fanconi anemia (FA), Dyskeratosis congenita (DC), Shwachman-Diamond syndrome, Diamond-Blackfan anemia and severe congenital neutropenia. While majority of the bone marrow failure syndrome (BMF) patients have syndromic association, it has been well recognized that a subset of these patients specially FA and DC might not have any underlying clinical findings or may present in adulthood or later. Moreover, these patients are at increased risk of treatment related toxicities particularly in the context of stem cell transplantation.
c. Myeloid disorders associated with Down syndrome, RASopathies and rare disorders

Trisomy 21 or Down syndrome patients are at increased risk for transient myeloproliferative disorder (TMD), seen in 5-10% of all Down syndrome neonates. Approximately 20% of these TMD neonates will develop acute leukemia of megakaryocytic lineage. Unlike TMD, acute leukemia needs treatment with a modified leukemia protocol. These myeloid disorders are caused by somatic mutations in GATA1 gene. This gene blocks the differentiation of fetal megakaryocytic erythroid progenitors. Since liver is a major hematopoietic organ in the fetus, liver failure is a major cause of death in these patients. RASopathies are characterized by abnormal constitutional RAS signaling pathway disorder and usually have a phenotype that resembles Noonan syndrome (abnormal growth, heart defects, and dysmorphism) and varies other phenotypes (12). Commonly mutated genes in RASopathies are PTPN11, SOS1, RIT1, KRAS, NNAS, CBL, NF1 etc.

References: