Myeloid Neoplasms with Germline Predisposition

Julia T. Geyer

Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York, NY, USA

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Abstract

The updated 2016 WHO classification of hematopoietic tumors has a new category: “myeloid neoplasms with germline predisposition.” These entities are rare, but are also currently underdiagnosed and underreported. Recognition is critical for appropriate clinical evaluation and therapy, with potential implications for the patient’s entire family. The WHO includes 3 categories of myeloid neoplasms with germline predisposition: neoplasms without preexisting conditions, neoplasms with a history of thrombocytopenia, and neoplasms with other organ dysfunction. Specialized molecular testing is frequently necessary to make the diagnosis, as the presence of one of the implicated mutations is not sufficient for diagnosis and should be confirmed with germline DNA evaluation. Many families have unique mutations that are not detected by targeted sequencing panels. Periodic bone marrow (BM) examinations are recommended to assess patients’ baseline morphology and rule out evidence of disease progression. Thus, accurate diagnosis requires a careful recording of clinical history, a BM morphology evaluation, and advanced molecular testing.

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Introduction

The updated 2016 WHO Classification of hematopoietic tumors introduced a new category of “myeloid neoplasms with germline predisposition” [1]. These entities are rare, but are also currently underdiagnosed and underreported [1–3]. The recognition of these disorders is critical because a patient’s clinical manifestations, diagnostic bone marrow (BM) morphology, and disease course frequently differ from de novo myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Patients and their family members may be at risk for non-hematopoietic malignancies and dysfunction of other organs, and so they have to be closely monitored. Myeloid neoplasms with germline predisposition require specialized staging techniques and therapeutic modifications compared to standard treatment approaches [2]. Family members must be carefully screened if matched-related allogeneic stem cell transplant is to be considered. Family members may also benefit from genetic counseling, including preimplantation genetic diagnosis for potential future pregnancies [3].

The WHO includes 3 categories of myeloid neoplasms with germline predisposition: those without a preexisting disorder or organ dysfunction (due to *CEBPA* and *DDX41* mutations), those with preexisting thrombocytopenia

Table 1. Summary of selected recently described myeloid neoplasms with germline mutations

Mutated gene	Region	Inheritance	1st report	Median age at diagnosis (range), years	Low platelets	Other organ dysfunction	Type of neoplasm
<i>CEBPA</i>	19q13.1	AD	2004	25 (2–46)	no	no	AML
<i>DDX41</i>	5q35.3	AD	2015	62 (40–85)	no	no	AML, MDS, rarely CML, CMML, lymphoma, myeloma
<i>RUNX1</i>	21q22.12	AD	1999	39 (7–53)	yes	no	AML, MDS, rarely CMML, T-ALL, hairy-cell leukemia
<i>ANKRD26</i>	10p12.1	AD	2011	38 (1–84)	yes	no	AML, MDS, rarely CML, CMML, CLL
<i>ETV6</i>	12p13.2	AD	2015	uncertain	yes	no	B-ALL, AML, MDS, CMML, myeloma, PV, solid tumors
<i>GATA2</i>	3q21.3	AD	2010	20 (<1 to 78)	no	yes	AML, MDS, CMML, aCML
<i>SAMD9/SAMD9L</i>	7q21.2	AD	2016	uncertain	yes	yes	MDS, AML

AD, autosomal dominant transmission; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; ALL, lymphoblastic leukemia/lymphoma; CLL, chronic lymphocytic leukemia; PV, polycythemia vera; aCML, atypical chronic myeloid leukemia.

(due to *RUNX1*, *ANKRD26*, and *ETV6* mutations) and, lastly, those with other-organ dysfunction (*GATA2* mutations as well as myeloid neoplasms associated with BM failure syndrome or telomere biology disorders).

Genetic molecular testing is the cornerstone of the diagnostic approach. Routine cytogenetic analysis may be normal. Most of the involved genes (*CEBPA*, *RUNX1*, *GATA2*, and *ETV6*) are also well-known somatic driver mutations in de novo MDS/AML, so the presence of these mutations in a patient with new diagnosis of MDS/AML is insufficient to suggest a myeloid neoplasm with germline predisposition. It is critical to confirm the molecular findings with specialized germline testing on constitutional DNA [3, 4]. Several types of samples can be used for this purpose, but skin fibroblast culture is considered the gold standard to obtain germline DNA. Hair and nails also provide adequate material, but are rarely used. On the other hand, saliva, and buccal mucosa swabs are used frequently but are often contaminated by leukocytes, and so the results should be evaluated with caution [2]. Similarly, samples of peripheral blood and BM are not recommended, since they may be contaminated and provide false-positive results [2]. Some authorities have recommended performing T cell-sorting by flow cytometry prior to DNA evaluation, if using peripheral blood or BM samples.

Another layer of complexity with genetic testing is the vast number of genetic variants that have been associated with myeloid neoplasms with germline predisposition. Many families have unique mutations in the genes of interest. If these mutations have not been previously reported as

pathogenic in the literature, the terminology “variant of uncertain significance” is commonly used. If such a mutation has been found, it cannot be assumed to have clinical significance. Finally, more than half of the families tested have no mutations detected by targeted next-generation sequencing (NGS) panels [3]. These families may benefit from whole-exome sequencing to look for novel mutations.

This review will briefly cover the main diagnostic categories of myeloid neoplasms with germline predisposition, focusing on the recently described entities and excluding the better-known inherited BM failure syndromes and telomere biology disorders (see summary in Table 1). Special emphasis will be placed on available data regarding BM histology and its role in the differential diagnosis.

AML with Germline *CEBPA* Mutation

AML with germline *CEBPA* mutation was initially described in 2004 in a family from the UK [5]. *CEBPA* is a single exon gene in the chromosomal region of 19q13.1. It encodes for a granulocyte differentiation factor. Patients inherit 1 copy of mutated *CEBPA*; this germline mutation is typically found in the N-terminal of the gene. Development of AML is associated with a biallelic or double mutation of *CEBPA*, including an acquired somatic mutation in the C-terminal region. Penetrance is close to 100% [5–7]. All reported germline mutations have been frameshift, while the somatic *CEBPA* mutations corre-

spond to in-frame insertions/deletions, frameshift, or missense mutations [7].

Patients usually develop AML as children and young adults (a median age of 25 years and range 2–46 years). Prior to the development of AML, they do not have hematologic abnormalities. Morphologic and immunophenotypic features of AML with germline *CEBPA* are similar to cases of sporadic *CEBPA*-mutated AML. There are no distinctive morphologic features. The majority correspond to AML with or without maturation. Multilineage dysplasia is present in approximately 25% of cases and does not appear to portend an adverse prognosis. Myeloid blasts may have a higher frequency of HLA-DR, CD7, and CD15 expression, and a lower frequency of CD56 expression than AML cases with a single *CEBPA* mutation [7].

Standard testing for new cases of AML currently includes *CEBPA* gene assessment. *CEBPA* mutations can be detected by PCR amplification, fragment analysis, and targeted DNA sequencing of *CEBPA* coding and junctional regions. Approximately 10% of AML cases with biallelic mutations represent a germline and a somatic mutation [7]. Therefore, identification of biallelic *CEBPA* mutations in AML should prompt the evaluation of a possible germline inheritance. Presence of biallelic mutations may be inferred in cases of AML with 2 *CEBPA* mutations fitting the right pattern in terms of their type and location in the gene. The biallelic nature of the *CEBPA* mutations is also suggested if the allele frequencies are present at a similar level for both mutations.

One of the peculiar features of this entity is that somatic *CEBPA* mutations appear unstable throughout the disease course, with novel independent clones frequently identified at recurrence. In the study by Tawana et al. [7], >50% of patients had recurrent disease, often after prolonged (>5 years) remission. Despite this clonal instability, patients appear to have a favorable prognosis compared to cases of both single *CEBPA*-mutated AML and double nonfamilial *CEBPA*-mutated AML, with an overall survival of 67% at 10 years [7]. After the first relapse, familial patients demonstrated a median survival of 8 years, whereas sporadic AML patients, in particular with single-mutation *CEBPA*, displayed a rapid decline in survival within 2 years of relapse [7].

Myeloid Neoplasms with Germline *DDX41* Mutation

Myeloid neoplasm with germline *DDX41* mutation is an autosomal dominant MDS/AML syndrome, initially described in 2015 [8]. To date, approximately 20 families

have been described in the USA, UK, and Australia [8–11]. Myeloid neoplasms arise due to inherited mutations in the *DDX41* gene (DEAD/H-box helicase gene) on chromosome 5q35.3. The gene encodes an RNA helicase protein with a function in RNA splicing. Similar to AML patients with germline *CEBPA* mutations, many patients have biallelic mutations. *DDX41* mutations are found in approximately 1.5% of all patients with myeloid neoplasms and approximately 50% of these patients have germline mutations [10]. Multiple heterozygous germline variants have been reported, including frameshift, missense, and splicing mutations.

The clinical presentation of myeloid neoplasms is similar to de novo disease, with a mean reported age of 62 (range 40–85) years [8, 10]. Most patients have normal blood counts prior to the diagnosis. Myeloid neoplasms described so far include mostly cases of AML and MDS, but there have also been reports of chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), and rare lymphoid and plasma cell neoplasms. Three families with germline *DDX41* mutation also had a predisposition to immune disorders, such as lupus, eczema, or vasculitis [10]. Penetrance has not been well established.

Patients with MDS/AML usually present with cytopenias or macrocytosis. BM examination of several carriers showed hypocellularity, prominent dyserythropoiesis, and normal karyotype. AML was frequently of pure erythroid type (M6) [8, 11].

The *DDX41* gene is part of most targeted panels for myeloid neoplasms. The diagnosis is achieved by gene sequencing or PCR. The prognosis of these neoplasms is, as yet, uncertain.

Myeloid Neoplasms with Germline *RUNX1* Mutations

Myeloid neoplasms with germline *RUNX1* mutations are also known as “familial platelet disorder with predisposition to AML,” initially described in 1999 [12]. It has an autosomal dominant transmission. Approximately 70 families have been described to date [12–15]. *RUNX1* is a transcription factor that plays a key role in megakaryocyte maturation, differentiation, ploidy, and platelet formation.

The clinical presentation of myeloid neoplasms with germline *RUNX1* mutations is very variable, even within the same family. Patients typically present with mild-to-moderate thrombocytopenia. Platelet morphology is normal, but with an associated severe decrease in platelet aggregation [16]. Distinct families have varying risks of pro-

Fig. 1. Baseline bone marrow biopsy of a 36-year-old patient with a germline *RUNX1* mutation and mild asymptomatic thrombocytopenia. **a** The biopsy is hypocellular for age. **b** CD42b immunostain highlights small, hypolobated megakaryocytes.

gression to myeloid neoplasms (range 11–100%; median 40% of family members). The age at thrombocytopenia diagnosis has a wide range of 2–67 years. The median age of onset of MDS/AML is 39 (range 7–53) years.

RUNX1 gene mutations are distributed throughout the gene. Numerous mutations have been identified and, frequently, each mutation is unique to a given family. Genetic abnormalities described to date comprise complete deletions of *RUNX1* gene, splice-site, missense, nonsense, and frameshift mutations [15]. Some of the mutations appear to act by haploinsufficiency and have dominant negative effects. Acquisition of a mutation in the second *RUNX1* allele appears to be a common second hit, but it is not required for the development of myeloid neoplasm [12, 13].

At initial presentation, the thrombocytopenia is typically moderate ($>50 \times 10^9/L$). MDS and AML are the most common hematologic neoplasms in these families. Other neoplasms that have been described include CMML, T-cell lymphoblastic leukemia/lymphoma and, rarely, B-cell neoplasms including hairy-cell leukemia [15]. BM morphology in carriers was recently evaluated in a series of 11 patients from 7 families [17]. The BM is usually hypocellular for age and characterized by abnormal megakaryopoiesis (Fig. 1) [17, 18]. Frequent eosinophilia has also been noted. At the time of disease progression to MDS/AML, patients typically developed additional cytopenias, dysplasia in ≥ 2 lineages, and/or acquired clonal abnormalities [17].

Diagnostic molecular testing may be challenging due to the variety of molecular abnormalities described with-

in the *RUNX1* gene. Standard testing includes Sanger sequencing and NGS. Occasionally, comparative gene hybridization and single-nucleotide polymorphism arrays may be useful to demonstrate large deletions, duplications, and rearrangements which may go undetected by standard techniques [12, 13, 19]. The prognosis of patients with myeloid neoplasms with germline *RUNX1* mutations is currently uncertain.

Myeloid Neoplasms with Germline *ANKRD26* Mutation

Myeloid neoplasms with *ANKRD26* mutations were initially described in 2011 as familial congenital thrombocytopenia with *ANKRD26* mutation [20]. It is one of the more common forms of congenital thrombocytopenia, with approximately 45 families identified. The transmission is autosomal-dominant. The germline mutations within *ANKRD26*, located on chromosome band 10p12.1, lead to increased gene transcription and signaling through the *MPL* pathway and impaired proplatelet formation by megakaryocytes. These patients have a normal platelet size, moderate thrombocytopenia, and an absent or mild bleeding tendency [20, 21]. The age at thrombocytopenia diagnosis is very variable (range 1–84 years; mean 38 years) [20]. The median age of patients with myeloid neoplasms is not well established.

Fig. 2. Bone marrow biopsies of a 53-year-old patient with germline *ANKRD21* mutation and life-long severe thrombocytopenia. **a** Baseline bone marrow is markedly hypercellular for age and has a high myeloid-to-erythroid ratio. **b** CD42b immunostain highlights increased micromegakaryocytes. **c** Subsequently, the patient

developed progressive anemia and splenomegaly. Bone marrow is persistently hypercellular for age. **d** CD34 immunostain highlights an increased number of blasts. There was also evidence of new erythroid and myeloid dysplasia and the appearance of new mutations, consistent with disease progression.

The myeloid neoplasms correspond predominantly to MDS/AML. Rare cases of CML, CMML, or chronic lymphocytic leukemia have also been described [18, 20–22], with BM morphology findings reported in 6 patients. All cases were characterized by prominent megakaryocytic atypia with an increased number of small hypolobated megakaryocytes (Fig. 2).

The diagnosis is based on targeted PCR of 5'-untranslated region of *ANKRD26*. Thus far, 12 variant mutations of the *ANKRD26* gene have been identified, most of which are missense mutations. The prognosis is uncertain.

Myeloid Neoplasms with Germline *ETV6* Mutation

In 2015, four publications identified 7 families with germline mutations in *ETV6* [23–26]. All patients had thrombocytopenia and hematologic malignancies. A subset also presented with macrocytosis [24]. There was evidence of autosomal-dominant transmission. Missense mutations identified to date have a dominant negative effect, that results in disrupted nuclear localization of the *ETV6* transcription factor and the subsequent reduced expression of platelet-associated genes. In vitro studies revealed that the maturation of the patients' megakaryo-

cytes was defective and that the patients have impaired proplatelet formation [27]. Affected patients have variable thrombocytopenia with normal-sized platelets and a mild-to-moderate bleeding tendency.

The reported hematologic malignancies in families with germline *ETV* mutations include predominantly B lymphoblastic leukemia/lymphoma (usually in children), but also cases of MDS/AML, mixed-phenotype acute leukemia, CMML, plasma cell myeloma, and polycythemia vera. There is also familial predisposition for solid tumors including colorectal, breast, kidney, and skin cancers, and meningioma.

There is a very limited number of BM biopsies from carriers without leukemia [24]. These cases show evidence of atypical, small, hypolobated megakaryocytes and mild dyserythropoiesis [24].

The *ETV6* gene is part of routine targeted NGS panels. The diagnostic testing can also be performed by Sanger sequencing. The prognosis is uncertain.

Myeloid Neoplasms with Germline *GATA2* Mutations

Germline *GATA2* gene mutations were originally identified in 2011 as 4 separate syndromes:

- MonoMAC syndrome, characterized by monocytopenia and nontuberculous mycobacterial infection [28, 29],
- Dendritic cell, monocyte, B, and NK lymphoid deficiency (DCML) with vulnerability to viral infections [30],
- Familial MDS/AML [31],
- Emberger syndrome, characterized by primary lymphedema, warts, and a predisposition to MDS/AML [32].

GATA2 mutations were also recognized in a minority of cases of chronic neutropenia and aplastic anemia [33]. All cases had autosomal dominant transmission. Due to the considerable overlapping features present in these disorders, it was subsequently recognized as a single genetic disorder with protean manifestations [34, 35].

GATA2 is a zinc-finger transcription factor regulating hematopoiesis, autoimmunity, and inflammatory and developmental processes. *GATA2* knockout mice die in utero due to the lack of hematopoiesis. Germline *GATA2* mutations result in the loss of function of the mutated allele, resulting in haploinsufficiency [35]. This, in turn, causes a loss of hematopoietic stem cells and leads to the depletion of dendritic cells, monocytes, B cells, and NK cells [36]. At least 44 distinct mutations have been identified in both coding and noncoding regions. These mutations are classified as missense, null, and regulatory [37].

The clinical presentation is very heterogeneous. In the largest study to date, on 57 patients, by Spinner et al. [35], the median age at presentation was 20 (range <1 to 78) years. The most common initial presentations were infection (64%), MDS/AML (21%), and lymphedema (9%) [35]. Among patients with hematologic malignancy, most patients were diagnosed with MDS, but a subset presented with AML or CMML [35]. MDS/AML developed in approximately 70% of affected individuals at a median age of 29 years. Many patients who developed MDS/AML had a concurrent *ASXL1* mutation, which is likely a collaborating event in the development of overt myeloid malignancy [38].

As opposed to the other entities in this review, the BM characteristics of patients with germline *GATA2* mutations have been relatively well-described [36, 39]. Typically, BM examination shows hypocellularity and multilineage dysplasia. Dysmegakaryopoiesis is the most prominent and consistent feature seen in 82% of studied cases. Many cases have increased reticulin fibrosis. In adults, the majority of cases are diagnosed as low-grade MDS (some cases of high-grade MDS, and rare cases of CMML and atypical [a]CML have also been described) [36, 39]. Children typically present with refractory cytopenia of childhood or high-grade MDS [40]. Flow cytometry analysis of the BM shows characteristic findings, with evidence of abnormal granulocytic maturation, monocytopenia, reduced numbers of NK cells and B cells, nearly-absent hematogones, frequent plasma cell abnormalities, and expansion of T-cell large granular lymphocytes [36, 39, 40].

Cytogenetic analysis is abnormal in approximately 60% of MDS/AML associated with germline *GATA2* mutations. Monosomy 7 is the most frequent abnormality, including 70% of MDS cases in adolescents [40]. Full-gene sequencing is recommended for molecular diagnosis of *GATA2* mutations. Prognosis in MDS/AML appears similar to matched sporadic cases [35, 40]. Improved outcomes have been reported with hematopoietic stem cell transplantation [35, 40].

Other Recently Described Myeloid Neoplasms with Germline Predisposition

Germline mutations associated with familial neoplasms is an area of very active investigation due to the now widespread availability of sensitive and sophisticated sequencing methods. Thus, numerous additional mutations are being identified and will likely become better-

known in the near future. A recent large-scale study from France analyzed a cohort of 179 young patients with BM failure of suspected inherited origin but unresolved diagnosis after a thorough medical evaluation [41]. A pathogenic germline mutation was identified in 48% of these patients using whole-exome sequencing of skin fibroblast genomic DNA [41]. The most frequently mutated genes were *SAMD9* and *SAMD9L* (18.6%), with frequent recurrent involvement of other currently underrecognized genes, such as *ERCC6L2*, *MECOM*, and *LIG4*. Germline variants in *SAMD9* and *SAMD9L* have been recently reported in clinical syndromes associated with familial MDS, usually accompanied by abnormalities of chromosome 7q. Schwartz et al. [42] identified these mutations in 17% of pediatric MDS patients. Germline variants in *SAMD9* and *SAMD9L* have been associated with multi-system disorders with a range of systemic abnormalities, including cytopenia, infection, intrauterine restriction of growth, adrenal hypoplasia, abnormal genital phenotypes, progressive cerebellar dysfunction, and enteropathy [43–46]. To date, there are no reports of expected BM morphology in mutation carriers.

Diagnostic Challenges in Disease Progression

Patients with congenital thrombocytopenias, rare conditions with a variety of clinical findings and the unifying feature of inherited thrombocytopenia (30 different entities described to date, including the WHO entities of germline *RUNX1*, *ANKRD26*, and *ETV6* mutations [47–49]), as well as germline *GATA2* mutations, BM failure syndromes, and telomere biology disorders, have to be closely monitored due to the increased risk of developing a myeloid neoplasm. However, the morphologic distinction between baseline marrow morphology and disease progression can be very challenging. Clinical history may be lacking or incomplete. Data on expected BM findings in disease carriers is currently very limited. For example, most studies report that patients with germline *RUNX1*, *ANKRD26*, *ETV6*, or *GATA2* mutations have immature or dysplastic megakaryocytes. However, it is not clear if this finding alone is sufficient for the diagnosis of MDS in these patients.

A recent study undertaken at the Weill Cornell Medical College included detailed BM biopsy evaluations in a cohort of 8 patients with various entities within the group of congenital thrombocytopenia followed for up to 50 years [18]. The majority of patients had atypical, small, hypolobated megakaryocytes on the first BM biopsy

(Fig. 1b, 2b). Three morphologic patterns were identified: a hyperplastic MDS/myeloproliferative neoplasm (MPN)-like pattern (50%, Fig. 2a), a hypoplastic BM failure-like pattern (25%, Fig. 1a), and normal BM-like morphology. Patients with an MDS/MPN-like pattern had marked marrow hypercellularity, an increased myeloid-to-erythroid ratio, marrow fibrosis, and numerous micromegakaryocytes. Three of four patients with MDS/MPN-like pattern had evidence of disease progression noted on subsequent marrow biopsies. Disease progression was characterized by the presence of new erythroid and myeloid dysplasia, increasing blast numbers, and new cytogenetic and/or molecular abnormalities (Fig. 2c, d). This pattern of disease progression was also noted in a subsequent study on patients with germline *RUNX1* mutations [17]. Features of disease progression developed slowly in these patients with life-long thrombocytopenia, and finally resulted in a firm diagnosis of MDS/AML at the age of 40, 47, and 52 years, respectively. Therefore, patients with congenital thrombocytopenia with an MDS/MPN-like BM morphology pattern appear to have a long and indolent clinical course [17, 18].

Conclusion

Myeloid neoplasms with germline predisposition are relatively obscure and remain underdiagnosed by pathologists and clinicians. The BM biopsy examination is an important and currently underutilized diagnostic tool to provide baseline characteristics of these patients and evaluate for disease progression. An adequate and complete clinical history is also of paramount significance. Thus, a BM biopsy of a patient with presumed immune thrombocytopenia that has small hypolobated megakaryocytes should raise the question of myeloid neoplasm with germline predisposition and a preexisting platelet disorder. These cases should also not be automatically diagnosed as MDS, as patients may receive unnecessary treatment [50]. Similarly, the presence of MDS in children and adolescents should prompt an evaluation for germline mutations.

Most patients with a new diagnosis of AML and many new patients with MDS currently undergo an upfront molecular evaluation by NGS. Even in the appropriate clinical setting, detection of a characteristic mutation with the targeted panel is not sufficient for the diagnosis of germline inheritance. Results should be confirmed by germline testing, preferably a skin biopsy for fibroblast culture analysis. At the same time, the majority of patients

with hereditary myeloid neoplasms have unique mutations, that are, as yet, not part of targeted sequencing panels. In such cases, whole-exome sequencing may uncover new variants and mutations.

In patients with known germline mutations which predispose to myeloid neoplasms, the diagnosis of disease progression may be challenging and requires close collaboration between pathologists and clinical colleagues. In 1 study of BM findings in carriers of germline *RUNX1* mutations, the suggested criteria for progression to MDS/AML included [17]: the development of anemia and/or neutropenia, dysplasia in erythroid and/or myeloid precursors, and an acquired cytogenetic or molecular abnormality together with the exclusion of nonneoplastic

causes. In our experience, the presence of increased BM cellularity, dysmegakaryopoiesis, BM fibrosis, and even borderline increase in blasts is of uncertain significance in patients with congenital thrombocytopenia. These changes have been found to persist for up to 25 years prior to the development of overt manifestations of disease progression [18]. Thus, the pathologist plays a critical role by suggesting diagnostic possibilities, describing the baseline BM morphology, and ruling out disease progression. BM biopsy is an important part in the diagnostic workup and subsequent patient monitoring. Current results are not conclusive, so further studies on the evaluation of both BM morphology and the molecular genetic characteristics of these entities are warranted.

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