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Overview of inherited bone marrow failure syndromes

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Abstract

Patients with inherited bone marrow failure syndrome (IBMFS) can develop peripheral blood cytopenia, which can ultimately progress to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). Although some cases of IBMFS are diagnosed based on their typical presentation, variable disease penetrance and expressivity may result in diagnostic dilemmas. With recent advances in genomic evaluation including next-generation sequencing, many suspected cases of IBMFS with atypical presentations can be identified. Identification of the genetic causes of IBMFS has led to important advances in understanding DNA repair, telomere biology, ribosome biogenesis, and hematopoietic stem cell regulation. An overview of this syndromes is summarized in this paper.

Key Words Inherited bone marrow failure syndrome, DNA repair, Telomere, Ribosome, Stem cell regulation

INTRODUCTION

Inherited bone marrow failure syndromes (IBMFSs) manifest as ineffective and stressed hematopoiesis owing to germline mutations that cause the failure of hematopoietic stem cell progenitor cells. Establishing an accurate etiology of bone marrow hypoplasia or BMF is challenging; however, it is absolutely critical for appropriate management, especially in differentiating between acquired and inherited forms of the disease. For example, the use of immuno- suppressive therapy in patients with IBMFS is not beneficial and could potentially be harmful.

With the evolution of diagnostic techniques, it is now known that different genes involved in diverse cellular functions underlie IBMFS. These disorders have a wide phenotypic spectrum and may present cryptically in adult patients with cytopenia of one or more lineages. The causes of BMF differ depending on the disease mechanisms, which include unresolved DNA cross-links in Fanconi anemia (FA), telomere shortening in dyskeratosis congenita (DC), and ribosomopathy in Shwachman-Diamond syndrome (SDS) and Diamond-Blackfan anemia (DBA). In some IBMFS, non-hematologic manifestations including congenital malformations, developmental delay, and other medical complications, may be present. Most IBMFSs are associated with a predisposition to aplastic anemia (AA), myelodysplastic syndrome (MDS), and malignancy.

SUSPICION OF INHERITED BONE MARROW FAILURE SYNDROME

Patients with IBMFS are usually diagnosed and followed up by pediatric hematologists, although some patients are diagnosed in adults. Clinical and family history can be useful for identifying the underlying cause, particularly prior documentation of long-standing cytopenia or macrocytosis can indicate a heritable cause. The suspicion of IBMFS is imperative in patients of all ages but is more important in pediatric and young adult assessments. A positive history and physical anomalies suggestive of IBMFS require a thorough workup for IBMFS. However, it is important to recognize that the usual symptoms and family history of IBMFS are absent in up to 40% of cases [1]. Recent advances in genomic evaluations using next-generation sequencing can be used to identify suspected IBMFS with an atypical presentation that remains undiagnosed after the initial workup [2]. Considering that the expected frequency of IBMFS among children and young adults aged ≤40 years with AA is 25% and 5–15%, respectively [3], a high index of suspicion is necessary for patients aged ≤40 years with BMF. However, the upper age cutoff for considering IBMFS remains challenging because IBMFS has been diagnosed in older patients. Careful

attention to findings that suggest the presence of IBMFS is necessary. The clinical manifestation and laboratory finding in IBMFS are listed in Table 1.

SUMMARY OF INHERITED BONE MARROW FAILURE SYNDROMES

The specific genetics and screening for each IBMFS are shown in Table 2.

Fanconi anemia

FA is a chromosomal instability disorder caused by germline mutations in the DNA repair genes of the FA/BRCA pathway. Currently, pathogenic variants of at least 22 genes are known to cause FA in humans [4]. Proteins encoded by FA genes play important roles in numerous cellular functions, including DNA repair, detoxification of reactive oxygen species and aldehydes, energy metabolism, and both proinflammatory and myelosuppressive cytokine homeostasis [5-7]. Patients with FA usually develop variable degrees of pancytopenia in childhood and often have short stature, hypopigmented or café au lait spots, thumb or radial ray abnormalities, micro- or hydrocephaly, structural renal anomalies, hypogonadism, and developmental delays. However, up to one-third of the patients with FA do not have congenital anomalies.

Approximately 40% of patients with FA develop severe BMF by the age of 20 years, and half of the patients with FA develop BMF by the age of 50 years. The risk of solid tumors and AML by the age of 50 years in FA is estimated to be 30% and 10%, respectively [8]. The major cancers in FA include head and neck squamous cell cancer, AML, and cancers of the vulva, esophagus, and brain [9]. The incidence of cancer among various IBMFS is highest in patients with FA. Given the impact of a diagnosis of FA has on treatment and surveillance strategies, a chromosomal breakage test is indicated in all patients with BMF [10]. The increased risk of cancer in patients with FA is related to defective DNA repair, which makes somatic cells more suscep-

Table 1. Clinical manifestations and laboratory findings in inherited bone marrow failure syndrome.

Syndrome	Non-hematological clinical manifestations	Laboratory findings	Molecular mechanisms
Fanconi anemia	Short stature, low birth weight, microcephaly, microphthalmia, hearing loss, triangular face, micrognathia, cardiac anomalies, tracheoesophageal fistula, esophageal atresia, kidney anomalies, hypoplastic thenar eminence, clinodactyly, café-au-lait spots	Pancytopenia, macrocytosis, elevated HbF, increased chromosome breakage in clastogenic assay	DNA repair: FA/BRCA pathway
Dyskeratosis congenita	Mucocutaneous triad (skin pigmentation, nail dysplasia, oral leucoplakia), short stature, low birth weight, failure to thrive, pulmonary fibrosis, stenosis of the esophagus, liver fibrosis	Pancytopenia, macrocytosis, elevated HbF, very short telomeres	Telomere shortening
Diamond-Blackfan anemia	Low birth weight, short stature, developmental delay, anomalies in craniofacial skeleton, eyes, heart, visceral organs and limbs	Anemia, elevated red blood cell adenosine deaminase, macrocytosis, elevated HbF	Ribosome biogenesis and processing
Schwachman-Diamond syndrome	Exocrine pancreatic insufficiency, failure to thrive, malabsorption, short stature, neurodevelopment and skeletal abnormalities	Neutropenia, low serum isoamylase, low serum trypsinogen	Ribosome biogenesis and processing
Severe congenital neutropenia	Recurrent infection	Neutropenia	Myeloid lineage growth arrest
Congenital amegakaryocytic thrombocytopenia	Nonsyndromic (occasionally, growth retardation, cardiac anomalies, psychomotor developmental delay)	Thrombocytopenia, reduced megakaryocytes	Hematopoietic stem cell and megakaryocyte regulation
GATA2 deficiency	Lymphedema, immunodeficiency, atypical mycobacterial infections	Neutropenia, anemia, thrombocytopenia	Zinc finger transcription factor
SAMD9/SAMD9L disorders	MIRAGE (SAMD9): MDS, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy Ataxia–pancytopenia syndrome (SAMD9L): cerebellar atrophy and white matter hyperintensities, gait disturbance, nystagmus	Transient or permanent cytopenia	Defective antiproliferative function
MECOM-associated syndromes	Radioulnar synostosis, clinodactyly, hearing loss, cardiac/renal malformation	Thrombocytopenia	Zinc finger transcription factor

Abbreviations: HbF, hemoglobin F; MDS, myelodysplastic syndrome.

Table 2. Genetics and screening of inherited bone marrow failure syndrome.

Syndrome	Genetics	Screening
Fanconi anemia	FANCA, C, G account for 95% of cases	Increased chromosome breakage
Dyskeratosis congenita	DKC1, RTEL1, TERT, TERC, TINF2	Short telomere lengths
Diamond-Blackfan anemia	RPS19, RPL11, RPS26, RPS10, RPL35A, RPS24, RPS17	Elevated erythrocyte adenosine deaminase
Schwachman-Diamond syndrome	SBDS, SRP54, ELF1	Low pancreatic isoamylase (age >3 yr) and low fecal elastase
Severe congenital neutropenia	ELA2 (33–60%), HAX1, G6PC3, GFI1, WAS, CSF3R	
Congenital amegakaryocytic thrombocytopenia	MPL	
GATA2 deficiency	GATA2	
SAMD9/SAMD9L disorders	SAMD9/SAMD9L	Monosomy 7, del 7q and der(1;7)
MECOM-associated syndrome	MECOM	Suspected to have congenital amegakaryocytic thrombocytopenia, but without mutations in the MPL gene

tible to mutations that could initiate the carcinogenic process [11]. BMF in FA has been proposed to be a consequence of cumulative DNA damage in hematopoietic stem cells, leading to cell death due to genomic instability [12].

Dyskeratosis congenita

Classic DC is characterized by a triad of abnormal skin pigmentation, oral leukoplakia, and nail dystrophy, but there is wide variability in clinical presentations. A growing number of older adults have been diagnosed with DC after the development of pulmonary fibrosis or hepatic disease, coupled with the expansion of genetic testing and appreciation of a broader clinical spectrum. DC is caused by germline mutations in telomere biology genes, which lead to dysfunctional telomere maintenance. Germline mutations in telomere components may result in short telomere length, which is associated with BMF, hepatic and pulmonary fibrosis, and cancer predisposition [13]. The term "DC" is now used interchangeably with telomere biology disorders (TBD) and short telomere syndromes (STSs). DC and the spectrum of DC-related TBDs are diagnosed by leukocyte telomere lengths less than the first percentile for the age when measured by flow cytometry with fluorescence *in situ* hybridization (flow FISH) [14]. Telomere length testing using flow-FISH is the gold standard because of its high reproducibility. Telomere shortening is highly sensitive but not specific to the diagnosis of these disorders and has been observed in other inherited disorders [15]. Currently, telomere length assessment is recommended in the initial diagnostic workup for BMF to rule out constitutional STS [10]. Overall, unlike in DC, telomere lengths in patients with non-DC IBMFS are usually within the normal range, albeit shorter than those in unaffected individuals [16]. Occasionally, telomere lengths below the age-adjusted first percentile have been reported in patients with IBMFSs other than DC, including FA and SDS; therefore, consideration of the clinical presentation and additional genetic testing results is necessary to establish the correct diagnosis [14, 17].

Diamond-Blackfan anemia and Schwachman-Diamond syndrome

Pathogenic variants of genes essential for ribosome assembly and function are associated with two IBMFS, DBA and SDS [18]. Although these two IBMFS share a common underlying biology, there are distinct biological and clinical differences between DBA and SDS.

DBA is usually diagnosed based on the early childhood onset of severe, persistent, and often macrocytic anemia with reticulocytopenia [19]. The BM of patients with DBA is usually normocellular or slightly hypocellular and shows characteristic erythroblastopenia with normal lymphoid, granulocytic, and megakaryocytic lineages. Inherited mutations in *RPS19* are the most commonly known cause of DBA, accounting for approximately 25% of DBA cases. Elevated erythrocyte adenosine deaminase (eADA) supports the diagnosis of DBA [20].

SDS is characterized by congenital anomalies, BMF with neutropenia being the most prominent feature, and exocrine pancreatic insufficiency. Failure to thrive during infancy may be the first presenting feature of SDS due to pancreatic insufficiency [21]. Biallelic mutations in the SBDS gene are the most common [22]. Approximately 20–30% of patients develop AML/MDS, which is frequently accompanied by a complex karyotype [23].

Severe congenital neutropenia

Severe congenital neutropenia (SCN) is characterized by absolute neutrophil counts consistently less than 200/μL with recurrent severe infections, which often develop within the first few months of life [24]. The most common cause is *ELANE* gene mutations (~50%), followed by *HAX1* and *G6PC3* mutations (10–20%) [25]. Maturation arrest of the myeloid lineage occurs at the promyelocyte and myelocyte stages. Patients with SCN usually do not have congenital anomalies suggestive of an inherited disorder. Patients with SCN have significantly elevated risks of MDS and AML, which appear to be related to their response to granulocyte

colony stimulating factor (G-CSF) [26]. Somatic mutations in *CSF3R* (encoding the G-CSF receptor) and *RUNX1* have been frequently observed in those who developed MDS/AML [25].

Congenital amegakaryocytic thrombocytopenia

Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare autosomal recessive disease characterized by an isolated and, severe hypomegakaryocytic thrombocytopenia that presents in infancy and progresses to pancytopenia and BMF in later childhood. CAMT occurs most commonly due to mutations in *MPL*, which encodes for the thrombopoietin receptor. CAMT mutations lead to diminished or absent thrombopoietin receptor signaling. In general, loss-of-function mutations are associated with more severe thrombocytopenia and early-onset pancytopenia [27].

Other bone marrow failure syndromes

Diseases such as *GATA2* deficiency, *SAMD9*, and *MECOM* syndrome are increasingly being diagnosed with advancements in precision genomics.

The *GATA2* protein is a transcription factor that is critical for embryonic development, maintenance, and functionality of blood-forming, lymphatic-forming, and other tissue-forming stem cells. *GATA2* mutation causes deficiency at the cellular levels of *GATA2* proteins and the affected individuals may develop hematological, immunological, lymphatic, or other presentations over time that may begin as benign abnormalities but commonly progress to organ (e.g. lung) failure, opportunistic infections, viral infection-induced cancers, AA, MDS, and/or leukemia. *GATA2* deficiency is a life-threatening precancerous condition.

Germline *SAMD9* and *SAMD9L* mutations are associated with a clinical spectrum of disorders including MIRAGE (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital problems, and enteropathy) syndrome (*SAMD9*), ataxia–pancytopenia syndrome (*SAMD9L*), and myelodysplasia and leukemia syndrome with monosomy 7 [28]. Affected individuals display a highly variable clinical course that ranges from mild and transient dyspoietic changes in the BM to rapid progression to MDS/AML with monosomy 7.

MECOM (*MDS1* and *EVI1* complex locus) -associated syndromes can range from isolated radioulnar synostosis without hematopoietic defects to severe BMF with normal skeletal development. *MECOM*-associated syndrome was first described in the context of amegakaryocytic thrombocytopenia-2; however, congenital variants in the *MECOM/EVI1* complex on chromosome 3q26.2 have been associated with hematologic defects (e.g., B cell deficiency, BMF, and MDS) and various systemic manifestations (e.g., radioulnar synostosis, clinodactyly, presenile hearing loss, and cardiac/renal malformations) [29, 30]. A range of genetic variants has been identified, including gene deletions and point mutations [31].

CLONAL HEMATOPOIESIS IN INHERITED BONE MARROW FAILURE SYNDROME

The development of persistent severe cytopenia, morphologic dysplasia, or clonal cytogenetic alterations raises suspicion of progression toward MDS/AML. Recently, somatic point mutation in myeloid driver genes have been identified in patients with IBMFS who do not have leukemia [32, 33], raising the possibility that the presence of clonal hematopoiesis may be predictive of transformation. The distinct mechanisms by which somatic mutations drive clonal advantage in each disease and their associations with leukemia risk are not well understood.

More than 70% of patients with AA have clonal hematopoiesis with somatic mutations detected by whole-exome sequencing or single-nucleotide polymorphism arrays early in the course of their disease. Clonal hematopoiesis is commonly observed in patients with IBMFS at a much younger age than that in the general population. Clonal hematopoiesis does not equate to malignancy and reflects an acquired genetic change in hematopoietic stem cells, allowing for competitive outgrowth of mutated hematopoietic stem cell progeny. The mutational spectrum in IBMFS is different from that in the general elderly population, as epigenetic regulators, such as *DNMT3A, TET2,* and *ASXL1*, the most frequently mutated genes in the elderly population, are relatively rare. Instead, somatic genomic alterations that can restore the original function of a protein or allow pathological adaptation for survival are preferentially selected for clonal expansion [34]. Based on current knowledge, unless accompanied by high-risk cytogenetic abnormalities, progressive cytopenia and/or BM morphologic changes, clonal hematopoiesis itself does not require immediate definitive treatment even in the setting of IBMFS [34].

CONSIDERATION OF STEM CELL TRANSPLANTATION FOR INHERITED BONE MARROW FAILURE SYNDROME

The majority of patients with IBMFS present with or develop cytopenia or hematologic malignancies, and thus the option of hematopoietic cell transplantation (HCT) is attractive. Although HCT may cure the BM problem, it may introduce new and unanticipated problems in other organs. Patients with IBMFS commonly experience post-HCT late effects, including acute or chronic graft-versus-host disease (GVHD), delayed immune reconstitution, iron overload, pulmonary complications, infertility, renal insufficiency, endocrinologic complications, and psychosocial impairment [35]. The adverse effects of HCT in patients with IBMFS is often difficult to assess and distinguish from the complications of aging. The risk of solid tumors following HCT in FA and DC is significantly higher than that in non-transplanted patients [9]; however, causality to the preparative regimens or augmented inflammation associated with GVHD should be considered. Patients with DBA and SDS are less prone to

cancer. Because of the systemic nature of IBMFS, transplant strategies are modified to decrease immediate and late toxicities, for example, radiation-free reduced-intensity conditioning regimen. With improvement in HCT-related strategies, HCT from HLA-matched related or unrelated donors offers promising outcomes for young patients with aplasia [36]. The screening of family members is essential to exclude affected individuals as potential donors. For all IBMFSs, HCT does not correct the non-hematologic manifestations related to these diseases. The decision to proceed to HCT is complex, and all aspects of the transplant process should be considered.

CONCLUSION

Maintaining a high suspicion for rare IBMFSs is critical when evaluating patients of all ages with unusual cytopenia, especially in patients ≤40 years of age. Thorough physical examination and family history are important. An accurate diagnosis of IBMFS including laboratory workup, a surveillance schedule for malignancy, and potential therapeutic options according to disease severity, is critical for proper management. Additionally, cascade testing of at-risk relatives is required. Identifying markers of clonal evolution, thus enabling better monitoring and management of IBMFS is expected in future studies.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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