When to consider inherited marrow failure syndromes in adults

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The inherited bone marrow failure syndromes (IBMFS) are a heterogenous group of disorders caused by germline mutations in related genes and characterized by bone marrow failure (BMF), disease specific organ involvement, and, in most cases, predisposition to malignancy. Their distinction from immune marrow failure can often be challenging, particularly when presentations occur in adulthood or are atypical. A combination of functional (disease specific assays) and genetic testing is optimal in assessing all new BMF patients for an inherited etiology. However, genetic testing is costly and may not be available worldwide due to resource constraints; in such cases, clinical history, standard laboratory testing, and the use of algorithms can guide diagnosis. Interpretation of genetic results can be challenging and must reflect assessment of pathogenicity, inheritance pattern, clinical phenotype, and specimen type used. Due to the progressive use of genomics, new IBMFS continue to be identified, widening the spectrum of these disorders.

LEARNING OBJECTIVES

- Understand the clinical features and laboratory testing used to distinguish immune from inherited bone marrow failure (IBMFS) in adults
- Review when germline genetic testing for IBMFS is indicated and the common diagnostic challenges
- Learn why timely diagnosis of IBMFS is crucial for proper patient management

Introduction

Bone marrow failure (BMF), characterized by decreased production of 1 or more hematopoietic lineages, is classified as either inherited, due to germline variants, or acquired, most commonly immune mediated. Inherited bone marrow failure syndromes (IBMFSs) have been traditionally considered pediatric onset disorders; however, it is increasingly recognized that many present first in adulthood. Classical IBMFSs, including Fanconi anemia (FA), dyskeratosis congenita (DC), Shwachman Diamond syndrome (SDS), and Diamond Blackfan anemia (DBA) are mostly diagnosed in children but can present later in life, sometimes due to genetic somatic rescue or mosaicism. In adults, typical clinical findings may be missing, and diagnosis may be challenging without the use of specialized testing. Increased use of genetic testing has further characterized the broad spectrum of known IBMFSs and identified a wide range of new ones, the latter of which often present in adulthood and with predominant nonhematologic features.[1,2]

CASE 1

A 23-year-old male presented to the emergency room with pallor and bleeding and was pancytopenic: hemoglobin (Hb) 7.5 g/dL, absolute neutrophil count (ANC) 0.6×10^9/L, platelets 17×10^9/L, absolute monocyte count 0.08×10^9/L, and absolute reticulocyte count 50×10^9/L. No prior blood counts were available. No vitamin deficiencies or paroxysmal nocturnal hemoglobinuria clone were detected. Bone marrow examination showed hypocellularity of 30% with no dysplasia and a normal karyotype. Flow cytometry of the bone marrow showed a reduction in B-cells, B-cell precursors, and natural killer (NK) cells. Personal history was significant for recurrent pulmonary infections and warts. Family history was negative for malignancy or hematologic disorders. A diagnosis of acquired severe aplastic anemia (AA) was made.

Inherited versus immune marrow failure

Cytopenias and evidence of marrow hyperproliferation are the defining features of BMF but are present in both immune

and inherited forms.[3] Therefore, in evaluating BMF patients, careful consideration should first be given to the patient's disease history, concurrent medical comorbidities, and family history to assess for potential immune BMF versus IBMFS.[4] When positive, family history can aid in diagnosing IBMFSs, but varied clinical phenotype and disease heterogeneity even among family members make it less helpful when negative. Other causes of cytopenia, such as vitamin deficiency, viral infection, direct toxicity, autoimmune diseases, and medications, should be excluded. Patients with IBMFSs may have distinct clinical patterns of disease to guide diagnosis; for instance, limb and/or renal abnormalities in FA, lung and/or liver abnormalities in TBD, or recurrent atypical infections in GATA2 deficiency (Table 1).[5] More recently, disease-specific molecular profiles, including mechanisms of somatic genetic rescuing, have also been identified as potential markers of underlying IBMFS.[6]

Immune AA remains a diagnosis of exclusion; age of onset is bimodal with disease more common in younger and older patients. Clinical testing is focused toward excluding IBMFS; however, some features, such as the presence of glycosyl-phosphatidylinositol–negative paroxysmal nocturnal hemoglobinuria (PNH) clones and loss of heterozygosity in the chromosome 6 p arms (6pLOH), are reassuring markers of an immune etiology,[7,8] as is a clonal profile dominated by *PIGA*, *BCOR*, and *BCORL1*.[9,10] *BCOR* and *BCORL1* are the most common somatic mutations seen in AA and are often seen in isolation or co-occurring with *PIGA*.[10] While also present in myelodysplastic syndrome (MDS), they are not predominant and also tend to co-occur with other mutations.[11] T-cell large granulocytic leukemia clones are also more common in acquired than in inherited BMF but are less specific than PNH or 6pLOH (Figure 1).

Most specialized centers have routinely incorporated chromosome breakage studies and telomere length (TL) measurement by flow fluorescence *in situ* hybridization (FISH) in the clinical assessment of newly diagnosed AA. Other specialized testing, such as pancreatic dysfunction for SDS and erythroid adenosine deaminase activity for DBA, may be reserved for clinically suspected cases (Figure 2). Testing for primary immunodeficiency syndromes, using lymphocyte subsets and serum immunoglobulins, is pursued when there is a clinical history suggestive of recurrent and/or atypical infections, autoimmunity, or presence of severe lymphopenia.

CASE 1 (continued)

As the patient had no matched sibling donors, immunosuppressive therapy (IST) was promptly administered. Given his young age and history of warts and pulmonary infection, diagnostic genetic testing was performed. After 6 weeks, blood counts had not improved; ANC remained >0.5×10^9/L. Meanwhile the patient developed fever, progressive cough, and dyspnea. Computed tomography of the thorax showed patchy and nodular pulmonary infiltrates within the right middle, left, and lower lobes. Bronchoscopy samples grew mycobacterium avium complex (MAC). Immunosuppressive therapy was discontinued, and matched unrelated donor transplant was pursued. His germline genetic report returned and showed a pathogenic variant in the *GATA2* gene.

When to consider genetic testing

One of the most difficult considerations in work up of BMF is when to perform genetic testing. Most BMF is classified as immune (>90%), and genetic testing is costly and not always available. However, missing an IBMFS has significant clinical implications, and genetic testing is currently our best method of detection.[3,12,13] Increasingly, it is recognized that omission of genetic testing results in missed IBMFS diagnoses. A retrospective study including immune severe AA (SAA) patients using pre–hematopoietic stem cell transplant samples from the Center of International Blood and Marrow Transplant Research (CIBMTR) showed an undiagnosed IBMFS in ~7% of patients, one-third of whom were adults.[14] Most were nonclassical IBMFS (such as *RUNX1*, *MECOM*, *ANKRD26*, and *GATA2*) or TBD. Similarly in MDS, 7% of patients were found to have underlying germline predisposition, highest in the younger age group (33% for aged 11-20 years) but still significant in older patients (6%-8%).[15] One-quarter of germline genes mutated in MDS were implicated in IBMFSs.

Screening for IBMFSs should be also considered in young patients with atypical oncologic presentations or unexpectedly high toxicity to cytotoxic chemotherapy or hematopoietic stem cell transplant (HSCT).[16]

Recently, we developed a machine learning model to predict for immune versus inherited in adults with AA. By using patients' baseline clinical and laboratory characteristics, our model accuracy correctly predicted 88% of cases; TL, cutaneous findings, long-standing cytopenias, macrocytosis, and age/sex were top predictors.[17] Omission of TL dropped the model's accuracy, highlighting its importance. Adult patients with SAA without a positive family history or a clinical phenotype suggestive of inherited disease were rarely diagnosed with an IBMFS. Where genetic testing is not feasible, selection of patients for germline genetic screening should take into account age, clinical presentation, family history, and available laboratory and specialized test results.

Inheritance and penetrance as challenges for IBMFS diagnosis

IBMFSs can be linked to different inheritance patterns depending on the specific mutated gene being either autosomal recessive (AR) (2 mutated alleles required to cause disease), autosomal dominant (AD) (1 mutated allele required to cause disease), X-linked, or *de novo*. In general, AR disorders tend to have high penetrance and earlier disease onset while AD disorders have more variable penetrance and later onset, but there are exceptions to this.[18,19] *De novo* or AR variants represent a challenge for IBMFS diagnosis. *De novo* mutations first occur in the affected patient due to a mutation in the parental germ cell or during embryogenesis. In such cases, family history will be absent (as in case 1). Examples of IBMFSs that classically occur *de novo* are DBA (~50% of cases),[20] GATA2 deficiency, and the *TINF2* subset of TBD.[21] Family history may also be absent when consanguinity is present, family penetrance is incomplete, or due to AR inheritance. Therefore, one cannot omit specialized work up or genetic testing on the basis of family history alone.

Non-classical IBMFS

Newly described inherited monogenic diseases that may present as marrow failure have been defined, differing from the classical

Table 1. Inheritance and common clinical findings of inherited BMF syndromes

	Fanconi anemia[37]	Telomere biology disorders[1]	Shwachman Diamond syndrome[38]	Diamond Blackfan anemia[39]	GATA2	SAMD9/9L[28]	Platelet disorders[24]	MECOM-associated disorders[25]	ERCC6L2[2,40]	DADA2[41]
Affected genes	FANC genes, *BRCA2*	*DKC1, TERT, TERC, PARN, RTEL1, TINF2, CTC* + others	*SBDS, DNAJC21,* and others	RP genes, *TSR2, GATA1*	*GATA2*	*SAMD9/SAMD9L*	c-*MPL* (CAMT) *RBM8A* (TAR) *RUNX1, ETV6, ANKRD26,* and others	MECOM (MDS1 and EVI1 complex locus)	*ERCC6L2*	*ADA2*
Inheritance	AR except for FANCB (XLR) and FANCR (AD)	AD: *TERT, TERC, TINF2, RTEL1, PARN* AR: *CTC, RTEL1* XLR: *DKC1*	AR	AD, XLR or sporadic	AD	AD	AR: (CAMT, TAR) AD: *RUNX1, ETV6, ANKRD26*	AD	AR	AR
Common non hematologic clinic findings	- Limb abnormalities (absent radii/short thumbs) - Short stature - Renal anatomical defects - Café au lait spots - Microcephaly/ Microphthalmia	- DC triad: oral leukoplakia, dyskeratotic nails, reticulated skin - Pulmonary fibrosis - Liver disease (fibrosis, fatty liver) - AVM - Early grey hair - Immunodeficiency - Osteoporosis	- Failure to thrive/poor feeding - Steatorrhea - Recurrent infections - Skeletal abnormalities - Hepatomegaly - Intellectual disability - Congenital cardiac defects - Endocrinopathy	- Short stature/IUGR - Limb abnormalities (thumb) - Cardiac defects (VSD, ASD) - Cephalic malformation (microcephaly) - Developmental delay	- Immunodeficiency (atypical mycobacteria, recurrent warts from HPV) - Lymphedema - Thrombosis - Pulmonary alveolar proteinosis (dyspnea and cough)	- MIRAGE: myelodysplasia, infection, growth restriction, adrenal hypoplasia, genital problems, enteropathy - Ataxia Pancytopenia: cerebellar symptoms and pancytopenia - SAAD: nodular neutrophilic panniculitis, ILD, basal ganglia calcifications, cytopenia	- CAMT: some neurological associations, possibly related to ICH - TAR: skeletal defects (absent radii), cow's milk intolerance, renal tract abnormalities, cardiac defects) - RUNX1: platelet function defect	- Radioulnar stenosis - Clinodactyly - Hearing loss - Cardiac malformations - Renal malformations	- Microcephaly - Developmental delay	- Strokes - Vasculitis - Systemic inflammation - Hypogammaglobulinemia
Malignancy risk	- MDS/AML - SCC of skin, head/neck, anogenital	- MDS/AML - SCC skin, head/neck, anogenital - BCC skin	MDS/AML	- MDS/AML - Colon cancer - Osteogenic sarcoma	- MDS/AML - SCC skin, anogenital - BCC skin	MDS/AML	- RUNX1/ETV6/ ANKRD26: MDS/AML or ALL - ALL > ETV6, MDS/AML > RUNX1/ANKRD26	MDS/AML	MDS	None known

AD, autosomal dominant; AML, acute myeloid leukemia; AR, autosomal recessive; ASD, atrial septal defect; AVM, arteriovenous malformation; BCC, basal cell carcinoma; CAMT, congenital amegakaryocytic thrombocytopenia; DC, dyskeratosis congenita; HPV, human papilloma virus; ICH, intracranial hemorrhage; ILD, interstitial lung disease; MDS, myelodysplastic syndrome; RP, ribosomal protein; SAAD, SAMD9L-associated autoinflammatory disease; SCC, squamous cell carcinoma; TAR, thrombocytopenia absent radii; VSD, ventricular septal defect; XRL, X-linked recessive. References listed as superscript.

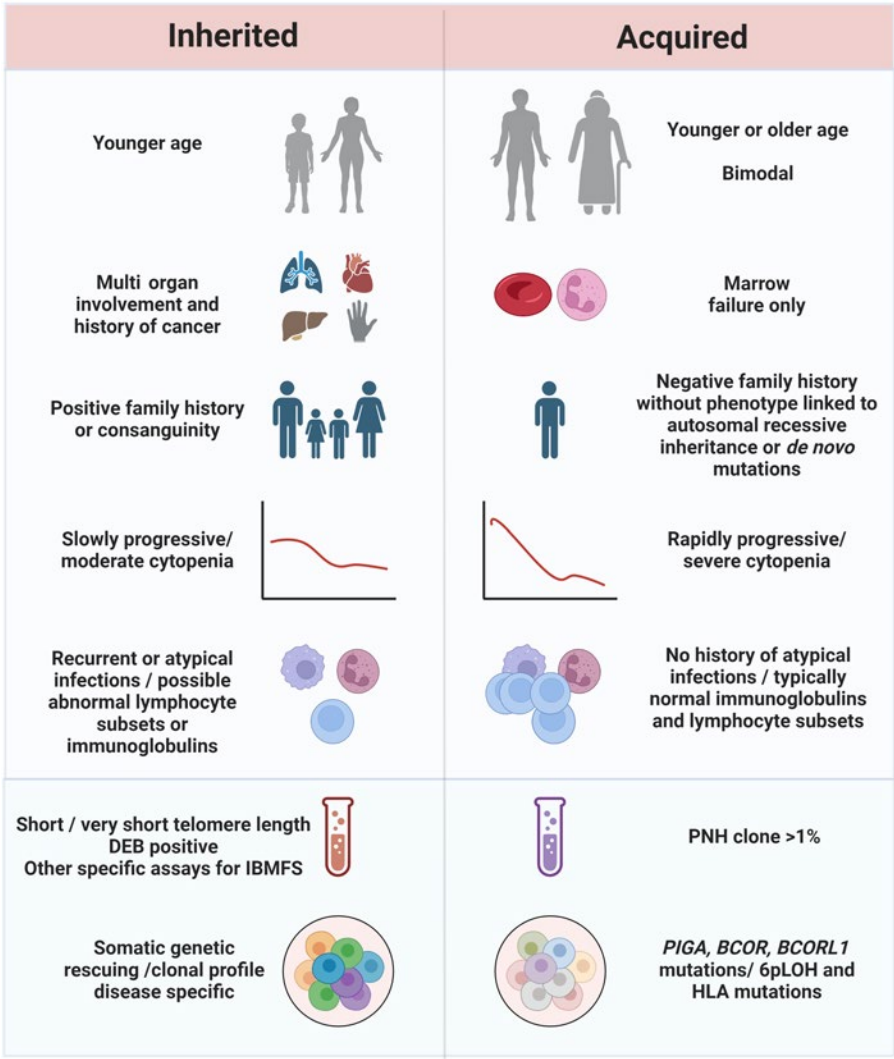

Figure 1. Considerations for inherited versus acquired bone marrow failure. Age, evidence of other organ involvement, and family history of cytopenia, hematologic malignancy, solid cancers, or other organ involvement (ie, familial pulmonary fibrosis in telomere biology disorders). Patients with IBMFSs may have had long-standing cytopenias for years; adult patients who present acutely with severe cytopenia more commonly have immune-mediated disease. Low immunoglobulins or lymphocyte subsets may point towards a primary immunodeficiency disorder; these are typically preserved in immune marrow failure. Paroxysmal nocturnal hemoglobinuria clones are commonly seen in immune bone marrow failure but very rare in IBMFS. Many IBMFS have disease specific clonal patterns and somatic genetic rescuing may occur. In immune BMF, ***PIGA*** (driver of PNH), ***BCOR/L1***, and human leukocyte antigen mutations predominate. DEB, diepoxybutane.

IBMFSs in terms of their typical age of onset, constellation of symptoms, and diagnostic testing. GATA2 deficiency was first described in 2010 as 4 different diseases based on the slightly different clinical observations. Patients can present in late adolescence or early adulthood, with a variable clinical phenotype, even among affected family members.[22] Patients with GATA2 deficiency may present with cytopenia and have a hypocellular marrow consistent with aplastic anemia. However, reduced numbers of B cells and precursors, NK cells, and monocytes are characteristic of GATA2.[23] Other manifestations include opportunistic infections, lymphedema, and predisposition to MDS and/or leukemia.[22]

Patients with isolated chronic thrombocytopenia, particularly with a pertinent family history, should be investigated for a familial platelet disorder. Congenital amegakaryocytic thrombocytopenia and thrombocytopenia with absent radii are usually apparent in early childhood. However, diseases related to RUNX1, ETV6, and ANKRD26 often present later in adolescence or adulthood; they are characterized by thrombocytopenia, variable bleeding phenotype, and predisposition to hematologic malignancy.[24] More recently identified, MECOM-associated syndromes (MDS1 and EVI1 complex locus) are typically pediatric and present with skeletal defects and amegakaryocytic thrombocytopenia.[25]

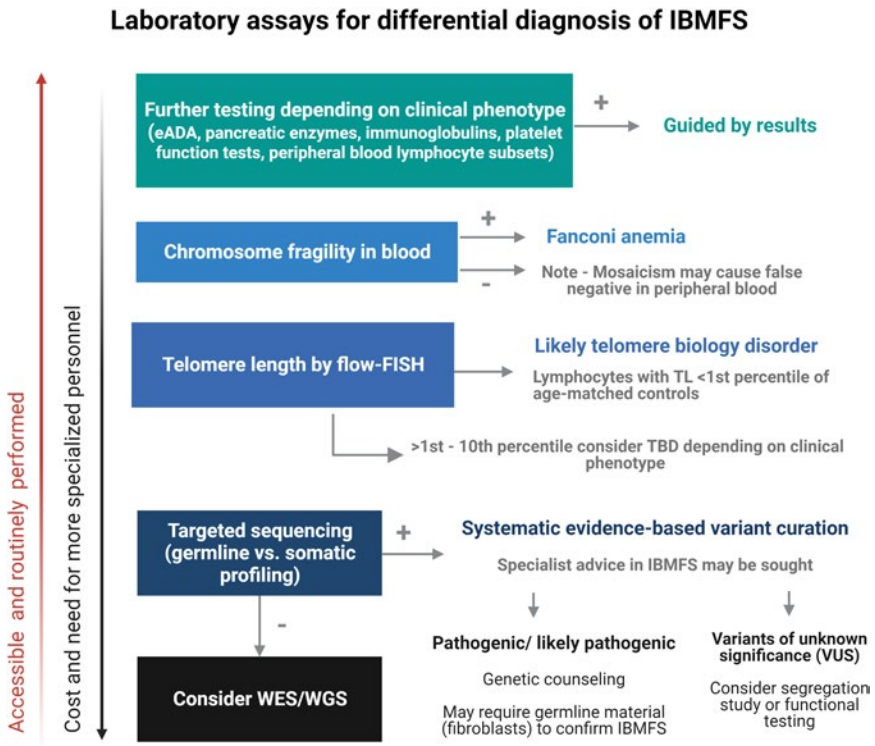

Figure 2. Approach to specialized work up of confirmed BMF. Specialized assays can be used for diagnosis of the IBMFS. Chromosome breakage studies for FA are performed by exposing cultured cells (usually peripheral blood lymphocytes) to diepoxybutane (DEB), a DNA cross-linking agents, and seeing how much chromosomal breakage is induced at a concentration of DEB that has little effect on normal cells.[42] Testing can be misleading or inconclusive for 2 reasons: 1) somatic reversion in the hematopoietic cells causes a false negative (this can be overcome by testing skin fibroblasts if you have a high clinical suspicion and negative peripheral blood DEB) or 2) recent chemotherapy administration (increase in baseline breakage). Telomere length is assessed in peripheral blood lymphocytes using flow-FISH and reported as a percentile for age. TL in lymphocytes <1st percentile is very sensitive and specific for TBD, ≥1st but <10th percentile is suggestive of possible TBD in the right clinical context, and ≥10th percentile is very unlikely to be TBD.[43] High erythroid adenosine deaminase (eADA) enzyme activity levels are found in cases of DBA. Targeted sequencing can identify both germline and somatic variants when peripheral blood is used; to confirm germline status, sequencing of a germline control tissue such as fibroblasts (skin biopsy) or testing of family members should be sought. Interpretation of genetic reports, particularly when VUS is reported, is challenging, and specialist input may be required. Testing for primary immunodeficiency syndromes is pursued when there is a clinical history suggestive of recurrent and/or atypical infections, autoimmunity, or presence of severe lymphopenia. Lymphocyte subsets and serum immunoglobulins are useful in this setting. FISH, fluorescence ***in situ*** hybridization; TBD, telomere biology disorder; WES, whole exome sequencing; WGS, whole genome sequencing.

Some inborn errors of immunity, characterized by immunodeficiency or other immune dysregulation, may also present as marrow failure, such as Toll-like receptor 8 gain of function mutations.[26] A careful history focused on infection and autoimmunity is required to identify such patients.

CASE 2

A 35-year-old female presented to the emergency department with dyspnea and pancytopenia: Hb 6.9 g/dL, ANC 1.2×10^9/L, platelets 6×10^9/L, and absolute reticulocyte count 55×10^9/L. Past medical history was significant for chronic immune thrombocytopenia and menorrhagia. Ferritin was 20 mcg/L with normal B12 and folate. Family history was significant for mother with chronic immune thrombocytopenia and iron deficiency and maternal aunt with leukemia. Bone marrow examination performed showed a mildly hypercellular marrow with megakaryocytic dysplasia (>10%), mild dysethryopoiesis, and dysgranulopoiesis. Blast count was 7% and karyotype was normal. Genetic testing identified variants in *RUNX1* (variant allele frequency [VAF] 55%) and *TET2* (VAF 35%). A diagnosis of MDS was made.

Clonal hematopoiesis vs germline predisposition in IBMFS

Most IBMFSs have an increased risk of myeloid malignancy, in particular MDS and acute myeloid leukemia.[16] Clonal hematopoiesis in myeloid-cancer genes may predict for clonal evolution in many IBMFSs, and distinct patterns of clonality can guide clinical suspicion for a particular disorder. In FA, malignancy has been linked to chromosome 1 q gain and cryptic *RUNX1/AML1* lesions;

in TBD, with *U2AF1*$^{S34/Q157}$ mutations; in SDS, with biallelic *TP53* mutations; and in *SAMD9/9L* disorders, with monosomy 7.[27-30] The genes and variants commonly found somatically mutated in typical MDS and acute myeloid leukemia are the same found in germline disorders, most commonly *RUNX1, ETV6, DDX41, TP53, GATA2, BRCA1, BRCA2,* and others.[31] Therefore, determining whether a variant is germline or somatic is crucial to distinguish *de novo* MDS from that secondary to IBMFS or another germline predisposition syndrome.

DNA sequencing assays covering genes related to hematologic disease often cannot distinguish whether variants are germline or somatic. In peripheral blood bulk DNA sequencing, germline variants are expected to be at allele frequencies of ~50% or ~100%, if heterozygous or homozygous, respectively. In ranges outside these limits (VAF <30% and >70%-85%), variants are often considered somatic.[32] However, revertant genetic rescuing can change the VAF of germline variants into somatic ranges, resulting in a false negative result; this should be considered when a suspicious variant outside the typical germline range is detected. When variants in germline predisposition genes are found at VAFs >30%, sequencing of germline tissues or affected relatives is important to distinguish between somatic and germline variants.[15,31,32] Cultured fibroblasts obtained by skin biopsies are considered optimal controls, but because their collection is difficult in many centers and extra time is required to culture the fibroblasts, results are delayed. Alternative sources of DNA are buccal swabs and hair follicles; buccal swabs are not recommended due to contamination with blood cells, and large numbers of hair follicles may be required to yield results. Co-occurrence of adaptive clonal hematopoiesis with germline variants related to IBMFS (mechanisms of somatic genetic rescuing) can be a natural proof-of-concept that a potential germline variant is pathogenic and disease causing. Examples of somatic markers of IBMFS include *PPM1D*, *POT1*, and the *TERT* promotor in TBD; *EIF6* mutations in SDS; transient monosomy 7 in SAMD9/9L disorders; and concurrent somatic *DDX41* mutations with germline *DDX41*.[33,34]

CASE 2 (continued)

The patient underwent a skin biopsy (with cultured fibroblasts) that identifies the same *RUNX1* variant but not the *TET2* in cultured tissue. The same *RUNX1* variant is confirmed in her mother. The patient is ultimately diagnosed with MDS with germline predisposition due to germline *RUNX1* and begins a work up for HSCT. The family history of thrombocytopenia, bleeding phenotype, and family history of leukemia are suspicious for a hereditary platelet disorder.

Difficulties in interpretation of genetic testing

A systematic evidence-based curation of variants and the incorporation of practical guides, often gene specific, for interpretation of genetic reports has been increasingly used in practice. The type of sample, timepoint of evaluation, and sequencing platform and depth are considered. Different methods with various sensitivities can detect types of genetic alterations: structural variations, small insertions and deletions (indels), single nucleotide variants, large copy-number variations (duplications and deletions), translocations, inversions, and aneuploidy. Large copy-number variations and small alterations in genes or intronic regions may not be covered by a targeted next generation sequencing panel.[6] Whole exome/genome sequencing as well as deletion/duplication analysis may identify uncharacterized genes linked to IBMFS.

Identification of variants of unknown significance (VUS) is a common challenge for interpretation of results, and negative reports may lead clinicians to often mistakenly rule out an IBMFS. Interpretation of a VUS should incorporate the patient's clinical phenotype, family history, frequency in the normal population, and prior reports in the literature of the variant's pathogenicity.[32] Segregation studies (assessment of affected and unaffected family members for the variant) may be useful. In cases with a suspicious family history and either negative germline testing or a VUS in a suspicious IBMFS gene, referral to specialist is recommended to guide further assessment.

Importance of detecting IBMFS for therapeutics

With high index of suspicion, early diagnosis of an IBMFS may improve outcomes. HSCT offers a cure for all marrow failure syndromes, inherited and acquired; however, IST is also standard for immune mediated marrow failure in adults and in older patients who lack a matched sibling donor.[3] Patients with IBMFSs do not respond to IST, leading to increased cytopenia-related complications, delay in appropriate care, and, potentially, suboptimal therapy if misdiagnosed. A recent study reported worse survival after HSCT in patients with unrecognized IBMFS compared to those with immune AA, most commonly due to organ failure.[14] When broken down by IBMFS subtype, patients with DNA damage response disorders (including FA) and TBD had significantly poorer overall survival while those with ribosome biology disorders (DBA and SDS) and hematopoiesis disorders (familial platelet disorders [RUNX1, MPL, ETV6, ANKRD26], MECOM, GATA2 deficiency and DADA2) had similar overall survival to those with immune AA.

HSCT is undertaken as a potentially curative option for the hematologic manifestations of a wide range of IBMFSs,[3,33] all with disease-specific HSCT considerations and outcomes. Differing genetic defects and associated clinical phenotypes make a uniform HSCT approach problematic. IBMFSs predispose patients to particular post-HSCT complications depending on underlying disease pathophysiology, including specific organ damage, increased graft-versus-host or graft-failure risk, or development of secondary malignancy. Choice of conditioning regimen is known to play an important role in improving outcomes in DNA damage response disorders and in TBD. In FA patients undergoing HSCT, secondary malignancies and endocrine complications predominate, which have been mitigated but not eliminated using radiation-free reduced-intensity conditioning.[35] TBD patients often have disease involving major organs, particularly the lung and liver, and vasculature, which may worsen with HSCT, resulting in increased morbidity and mortality; studies are ongoing to assess alkylator and radiation-free conditioning regimens (NCT01659606).[35,36] Therefore, at minimum, specialized testing for FA and TBD should be performed before HSCT in all BMF patients, even if a full genetic panel is not possible.

In cases in which HSCT is urgently indicated, the risks and benefits of waiting for genetic testing should be weighed against the likelihood of an IBMFS in an individual patient. Genetic

screening of familial donors in known IBMFS is also important and should occur prior to transplant, even in absence of clinical manifestations, to prevent unknowing use of an affected graft, although screening should also be balanced against the urgency of proceeding to HSCT.

Conclusions

Ideally, all new patients presenting with new onset BMF should undergo germline genetic screening regardless of age or clinical phenotype. Diagnostic work up of IBMFS can be challenging; in nonspecialist centers or poor-resource settings, specialized testing such as chromosome breakage studies, TL, or genetic testing may not be easily available. Interpretation of genetic results can be tricky and may require specialist input. Missing an IBMFS has important clinical consequences: such patients are at increased risk of other organ involvement and malignancy, and these patients require disease-specific monitoring. Identification of an IBMFS significantly impacts therapy; IST is typically ineffective, and HSCT may require modification from standard regimens or other special considerations.

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Conflict-of-interest disclosure

Fernanda Gutierrez-Rodrigues: no competing financial interests to declare.
Bhavisha A. Patel: no competing financial interests to declare.
Emma M. Groarke: no competing financial interests to declare.

Off-label drug use

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