Monitoring and treatment of MDS in genetically susceptible persons

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Genetic susceptibility to myelodysplastic syndrome (MDS) occurs in children with inherited bone marrow failure syndromes, including Fanconi anemia, Shwachman Diamond syndrome, and dyskeratosis congenita. Available evidence (although not perfect) supports annual surveillance of the blood count and bone marrow in affected persons. Optimal treatment of MDS in these persons is most commonly transplantation. Careful consideration must be given to host susceptibility to DNA damage when selecting a transplant strategy, because significant dose reductions and avoidance of radiation are necessary. Transplantation before evolution to acute myeloid leukemia (AML) is optimal, because outcomes of AML are extremely poor. Children and adults can present with germline mutations in *GATA2* and *RUNX1*, both of which are associated with a 30% to 40% chance of evolution to MDS. GATA2 deficiency may be associated with a clinically important degree of immune suppression, which can cause severe infections that can complicate transplant strategies. GATA2 and RUNX1 deficiency is not associated with host susceptibility to DNA damage, and therefore, conventional treatment strategies for MDS and AML can be used. RUNX1 deficiency has a highly variable phenotype, and MDS can occur in childhood and later in adulthood within the same families, making annual surveillance with marrow examination burdensome; however, such strategies should be discussed with affected persons, allowing an informed choice.

Learning Objectives

- Understand the role of marrow surveillance in persons with susceptibility to myelodysplastic syndrome (MDS)
- Understand the importance of host phenotype in selection of treatment for persons with genetic susceptibility to MDS

Clinical case: part 1

A 16-year-old girl who played competitive lacrosse presents for evaluation of fevers and interstitial lung disease. Past medical history was notable for short stature treated for 2 years with growth hormone replacement. History was unremarkable for unusual, frequent, or severe infections, and family history was noncontributory. Initial evaluation showed white blood cells 2.2 with 64% neutrophils, 32% lymphocytes, 2% eosinophils, and 1% monocytes. Immunoglobulin G (IgG) and IgA were low, and B- and T-cell numbers were reduced. Lung biopsy showed pulmonary alveolar proteinosis. A diagnosis of common variable immune deficiency with interstitial lung disease was made, and IgG replacement was started.

Overview

Susceptibility to myelodysplastic syndrome (MDS) associated with inherited bone marrow failure syndromes (IBMFS) has been familiar to pediatric hematologists for decades, and diagnosis was facilitated by accurate and specific functional and genetic testing in previous years. Some children have a clear clinical phenotype, although a significant number with evident syndromic marrow failure would remain without a specific diagnosis.[1] Children with a less than typical phenotype often remained a diagnostic challenge. The recent emergence of sophisticated and widely available genetic testing has identified genetic susceptibility to MDS in an expanded phenotype of children and also, older persons without preceding marrow failure, focusing the attention of adult hematologists on this topic also.[2] Readily available genetic testing has also facilitated the identification of large kindreds of often asymptomatic people who will be at risk of MDS throughout their lifetime and will continue to need medical surveillance in childhood and adulthood. Moreover, improved identification of IBMFS in childhood and improved survival into adulthood with improved transplant outcomes and supportive care mean that young adults with complex disorders, such as Fanconi anemia (FA) or Shwachman-Diamond syndrome (SDS), are now presenting to adult hematologists or transplant physicians for care with MDS or acute myeloid leukemia (AML). In this review, I will first consider MDS in persons with genetic bone marrow failure syndromes and then consider genetic susceptibility to MDS in known genetically susceptible persons without overt marrow failure.

FA

FA is an IBMFS characterized by congenital anomalies, progressive marrow failure, and predisposition to MDS, AML, and solid tumors, specifically squamous cell carcinoma of head and neck and the genital region.[3] Mutations in at least 20 genes in pathways involved in DNA damage sensing and repair have been described in association with a Fanconi phenotype.[4] Impaired DNA repair leads to

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clinically significant sensitivity to chemotherapy and radiation, making delivery of the preparative regimen for allogeneic hematopoietic stem cell transplantation (HSCT), the only curative option for the hematologic complications of patients with FA, challenging.[5]

A majority of children with FA are diagnosed in the first decade of life and will develop marrow aplasia requiring transplantation. The outcomes of transplantation for FA in young children with aplasia are now excellent, with a large majority of children surviving, without the use of DNA-damaging, potentially mutagenic radiation therapy.[5] A well-organized and effective family advocacy group (the Fanconi Anemia Research Foundation) publication of treatment guidelines guided by expert opinion means that a majority of untransplanted children likely receive annual surveillance screening marrows, which are typically studied with fluorescence in situ hybridization (FISH) and karyotyping to identify specific chromosomal changes associated with development of clonal hematopoiesis in FA and for morphological changes of dysplasia. Marrow morphology in children with FA at baseline may have changes that will suggest dysplasia to a pathologist unfamiliar with FA, and caution must be exercised in interpretation of such changes in the absence of clonal abnormalities.[6] Moreover, some clonal abnormalities (eg, gain of 1q) do not seem to predict progression to MDS, whereas others do (eg, monosomy 7); therefore, careful consideration must be given to a decision that any clone alone justifies immediate transplantation.[7] The value of annual surveillance marrows is difficult to prove in a rigorous manner, because randomization to observation vs no observation is challenging for both parents and health care providers. In our clinical practice, there is no question that early FISH abnormalities can be detected in this way, allowing for, in some cases, immediate transplant and in some, more frequent surveillance, but in every case, surveillance allows more informed consideration of a decision regarding timing of transplantation.

A proportion of children (estimated at around 15%-20% in our own practice) with FA will not develop aplasia requiring transplantation in the first decade of life. Svahn et al[3] similarly report a frequency of 33% of cases with relatively stable marrow function in an Italian observational cohort. These observations indicate that, although marrow failure is frequent in FA, it is not inevitable, although those who retain host hematopoiesis seem to be at accumulating risk of myeloid malignancy in early adulthood and should be watched closely. In our clinical experience, these children are at significant risk of presenting with acute leukemia in the second or third decades of life without preceding critical pancytopenia or aplasia. Additional challenges in the management of young adults with FA are the natural transitions that occur as children enter adulthood. Most FA adults assume responsibility for their own care as they enter higher education or work, and compliance with recommended screenings, both of marrow and for head and neck as well as genital cancer, may decline. Moreover, transition to adult hematological care can be challenging because of the rarity of the disorder in adult populations and the lack of availability of dedicated and informed FA care managers to facilitate care. Lack of adherence to recommended screenings, including marrow examinations in untransplanted persons, is common at this time.

Transplantation from a related or unrelated donor and in a few cases, a haploidentical donor can be very successful in treating MDS in the setting of FA, increasing the value of screening marrows to detect early change.[5,8] In contrast, AML is extremely difficult to manage in FA.[8] AML cells in an FA person often need significant chemotherapy for clearance, chemotherapy that is tolerated poorly by the DNA repair–deficient host.[9] Data are too few to determine whether administration of chemotherapy to try to achieve remission is wise before attempted transplantation. Antimetabolites, such as cytosine arabinoside, are well tolerated in FA and may at least induce aplasia.[10] Urgent transplant donor identification is necessary as soon as AML is diagnosed in FA, because count recovery may not occur after chemotherapy. A small number of persons with FA have achieved sustained remission after transplant with active AML or aplasia, but overall results remain very poor.[11] AML in FA presents more commonly in the third decade of life, and the transplant process is more poorly tolerated at this age than it is in younger children, likely owing to the premature aging effect of FA.[11]

A special subset of children, those with biallelic mutations in the *BRCA2* gene, will commonly present in the first decade of life with AML, sometimes with and sometimes without preceding MDS.[12,13] These children also have a very high frequencies of solid tumors, such as brain tumors, neuroblastoma, and Wilm's tumor as well, often in the first 5 years of life. MDS can be treated with prompt transplantation, but AML is also difficult to treat in this setting.[5] AML blasts in this clinical setting seem particularly resistant to chemotherapy, and treatment commonly fails. Prophylactic transplant has been proposed in these high-risk children but is controversial, because risk of transplant is accepted without immediate need in children at high risk of fatal neoplasms occurring at other sites, perhaps being accelerated by exposure to mutagens in the transplant process.[14]

SDS

The clinical phenotype of SDS is quite variable, although neutropenia, which may be intermittent, occurs in 98% of cases.[15] Anemia and thrombocytopenia are much less frequent and may also vary significantly over time. A minority of children with SDS require transplantation for aplasia or MDS. A modest proportion of persons with SDS will present with AML, usually in adulthood, and few of those cases survive. In our clinical practice, we do recommend annual surveillance marrows in children with SDS. Similar to FA, care should be taken with interpretation of marrow morphology in children with FA, because pathologists unfamiliar with morphology in SDS will tend to overcall dysplasia.[15] Clonal hematopoiesis can occur in SDS and can be stable for many years, or clones may be transient.[16-18] In particular, isochromosome 7 and del20q are well tolerated and do not by themselves indicate need for immediate transplant. Some literature suggests that isochromosome 7 and del20q are to a degree protective from clonal progression, but these data should be viewed with caution.[19] Acquisition of additional mutations can clearly be followed by clonal progression in persons with isochromsome 7 and del20q in our own clinical practice, and surveillance bone marrow examinations should continue in those with isochromosome 7 or del20q.

The true frequency of MDS in persons with SDS and the prevalence of SDS in the population are likely significantly underestimated. A report from the Center for International Blood and Marrow Transplant Research studying 1541 patients receiving unrelated donor transplant for MDS identified compound heterozygous mutations in the *SBDS* gene in 4% of young people (aged younger than 40 years old) studied, people previously unaware that they had SDS.[20] Accurate diagnosis of *SBDS* mutation is important, because persons with SDS tolerate full myeloablative transplant poorly, and pretransplant diagnosis of SDS can inform selection of preparative regimen. A multicenter group led by Kasiani Myers and Akiko Shimamura of the North American Shwachman Diamond Registry recently pooled data regarding myeloid malignancy in persons known to have SDS and reported in abstract form at the American Society of Hematology

2018 meeting. In this registry study, medical records were reviewed for 36 SDS patients with MDS or AML from 18 institutions. Blinded central review of bone marrow pathology was performed in 27 available cases. Median follow-up was 4.9 years. Median age was 18 years old, with 44% male subjects. Central pathology review concurred with the local diagnosis of MDS or AML in only 56% of available cases, illustrating the challenge of interpreting morphology in SDS. Treatment was heterogeneous, with 10 different chemotherapy regimens and 16 HSCT regimens. Only 1 of 10 patients initially treated with chemotherapy for AML achieved a complete remission. Median survival from diagnosis was 0.99 years in the AML group and 7.7 years in the MDS cohort. Survival rates at 3 years were 11% and 51% for subjects presenting with AML and MDS, respectively. Bone marrow surveillance had been conducted in 33% of AML subjects and 46% of MDS subjects. Individuals monitored with bone marrow surveillance before MDS/AML diagnosis had a 3-year OS of 62% compared with 28% without surveillance ($P = .13$). Several patients developed MDS in the setting of stable blood counts (n = 6). A rising MCV was present in 4 of 15 cases before diagnosis. Taken together, these data support (but do not prove) the value of surveillance bone marrow examinations in addition to blood counts and the need for review of morphology by a pathologist with experience in SDS.

Telomere disorders (dyskeratosis congenita)

Recent advances in genetic diagnosis, in particular NGS gene panels, have widened the phenotype of telomere disorders beyond the classical clinical triad of oral leukoplakia, reticular rash, and nail dysplasia typically considered diagnostic of dyskeratosis congenita (DC). DC is a cancer-prone IBMFS caused by germline mutations in key telomere biology genes that result in extremely short telomeres.[21] All modes of inheritance have been reported in DC, and de novo mutations are common. Broad phenotypic heterogeneity occurs within DC, with some patients having limited manifestations of disease until midadulthood. Clinically severe variants of DC include Hoyeraal–Hreidarsson syndrome associated with significant immune deficiency and often, cerebellar hypoplasia and Revesz syndrome (exudative retinopathy in addition to other manifestations of DC). Subsets of apparently isolated idiopathic aplastic anemia or familial MDS/AML without overt syndromic features diagnosed in childhood or adulthood carry germline mutations in the same telomere biology genes implicated in DC.[22] Clinically significant bone marrow failure occurred in half of patients with DC by age 50 years old in 1 prospective cohort.[23] Patients with DC have increased risks of MDS (>500 times) and AML (>73 times) compared with the general population.[24] These high frequencies justify screening blood counts and bone marrow examinations, although some children with DC and severe immune deficiency will warrant transplant to restore resistance to infection before development of marrow failure or MDS/AML. Lifetime screening in persons with milder phenotypes is logistically challenging, but apprising affected persons of the risk and possible screening strategies so that an informed decision can be made is essential. Androgens have been reported to have some benefit in improving marrow function in DC, which can be valuable in persons with too much comorbidity for transplantation; however, benefits are likely temporary, and side effects can be significant (liver toxicity or virilization).[25,26]

Patients with DC are typically fragile and tolerate chemotherapy and radiation poorly. In particular, later lung fibrosis is frequent and commonly lethal, increasing enthusiasm for avoiding toxic treatments, such as busulfan and radiation.[27] Children with DC often have both immune deficiency and marrow aplasia, and therefore, they have relatively little resistance to engraftment; reports over the last decade have detailed progressive reductions in the amount of preparative therapy used to engraftment allogeneic marrow. A series of reports has described efficacy of reduced intensity preparative regimens in children with DC.[27-32] These data were followed by a report of successful transplantation after fludarabine and antithymocyte globulin alone with no myeloablation (no alkylating agent and no radiation).[33] This promising report is now extended to an initially single-center study and now ongoing multicenter study investigating the use of alemtuzumab and fludarabine alone in DC, and early reports indicate that this very low-toxicity regimen is sufficient to achieve engraftment in most cases.

Clinical case: part 2

IgG replacement was well tolerated, but there was no improvement in interstitial lung disease and no return to high school athletics. The patient was readmitted with recurrent fevers and worsened chest imaging. *Mycobacterium kansasii* was cultured from a bronchoalveolar lavage, and antimycobacterial therapy was started. The combination of monocytopenia and mycobacterial infection lead to consideration of GATA2 deficiency, and a mutation in *GATA2* was identified (c.1186C>T [Arg396Trp]). Bone marrow examination showed moderate hypocellularity with absent monocyte precursors and reduced B- and T-cell numbers. There were no clonal chromosomal abnormalities and no morphologic dysplasia.

GATA2 deficiency

In 2011, 4 clinical syndromes were united by a common genetic diagnosis of heterozygous germline or sporadic mutations in *GATA2*.[34-38] The clinical syndromes all approached the disorder from a different clinical perspective, resulting in 4 different names for the same genetic abnormality: autosomal dominant and sporadic monocytopenia and *Mycobacterium avium* complex (Monomac); dendritic-cell, monocyte, B, and natural killer (NK) lymphoid deficiency; Emberger syndrome (lymphedema, congenital deafness, and monosomy 7); and familial MDS/AML. The phenotypic diversity of GATA2 deficiency makes clinical diagnosis difficult, and a high level of awareness to proceed to genetic testing is necessary. Infectious complications are common in GATA2 deficiency, such as in the clinical case described in this report, and result from the frequent deficiency of monocytes, NK cells, and B lymphocytes.[36] Hematologic manifestations of GATA2 deficiency are usually progressive cytopenias, with progression from a normocellular marrow to hypocellular MDS and then, in some instances, to AML, CMML, or myeloproliferative neoplasm. The overall prevalence of myeloid malignancy (MDS and AML) is high (~75%), with a median age of onset of about 20 years old. Common acquired somatic chromosomal abnormalities include monosomy 7 and trisomy 8 karyotypes and mutations in *SETBP1* and *ASXL1* genes.[39] The high risk for progression to advanced myeloid neoplasia and life-threatening infectious complications guide decision making toward timely stem cell transplantation.

Myeloid dysplasia with progressive cytopenias and new cytogenetic changes in the bone marrow prompted HSCT in approximately half of patients with the GATA2 deficiency in a recent study.[40,41] HSCT is the only curative therapy for GATA2 deficiency. However, HSCT can be challenging because of comorbidities often related to immune deficiency, such as disseminated *M. avium* complex infections and pulmonary alveolar proteinosis. Optimal transplant strategies have not yet been defined, although nonmyeloablative conditioning seems acceptable in those with early or no MDS, and comorbidities may limit feasibility of a full myeloablative preparative regimen that might be desirable in those with more aggressive malignancy.

Clinical case: part 3

The patient improved clinically with treatment of *Mycobacterium*. A surveillance marrow 6 months later showed a low level of monosomy 8 with minimal morphological dysplasia, with granulomas suggestive of incomplete clearance of mycobacteria. The marrow was repeated 3 months later and showed persistence of trisomy 8 and reduced cellularity. The patient's sibling was identified as HLA matched and negative for the GATA2 mutation. A successful bone marrow transplant was performed using a reduced intensity preparative regimen (busulfan/fludarabine) with full recovery. Physical activity is now normal, and the patient has returned to collegiate sports, although there remains lung scarring with a mild restrictive defect on formal testing.

Germline mutations in RUNX1

Heterozygous germline *RUNX1* mutations were first described in 6 families, each carrying a different mutation and transmitted in an autosomal dominant manner in 1999.[42] Expressivity is variable, and individuals carrying germline *RUNX1* may be asymptomatic throughout their lifetime or develop familial platelet disorder with myeloid malignancies, including mild to moderate thrombocytopenia, functional platelet defects leading to prolonged bleeding, and an increased risk of MDS, AML, or T-cell acute lymphoblastic leukemia (T-ALL). Leukemia or AML can occur in childhood or adulthood, and median age of onset of MDS/AML is 33 years old, with a wide age range, although T-ALL usually develops at a younger age. Risk of malignant transformation is estimated at 30% to 40%, although it should be remembered that experience with this disorder is currently limited but growing quickly, and these data may change with longer follow-up. Patients carrying *RUNX1* mutations with a dominant negative effect seem to have a higher risk of malignant transformation than patients carrying haplo-insufficient *RUNX1* mutations.[43,44] Clonal hematopoiesis occurs in more than two-thirds of young asymptomatic germline *RUNX1* mutation carriers and seems to be a precursor of myeloid malignancies, which require additional secondary mutations. Germline *RUNX1* mutations are associated with chromosome aberrations typical for MDS and AML, including del(5q), del(7q), +8, or –Y. MDS or AML in persons with a germline *RUNX1* mutation in general can be treated in the same manner as in persons without a germline mutation, because tolerance of therapy is not expected to be different in such cases.

Identification of a case of germline RUNX1 deficiency is typically followed by a family genetic study, which will often identify a number of additional affected but asymptomatic persons. Family studies can illustrate the phenotypes of disease that have already occurred in any family but will not reliably predict clinical course for any 1 individual within that family. For example, Ripperger et al[45] described a single family in which father and daughter carried the same *RUNX1* mutation; the father developed MDS at 47 years old, and the daughter developed MDS at 13 years old. The wide range of clinical expression, spanning decades, make surveillance somewhat challenging. However, the frequency of malignancy is sufficiently high that surveillance blood counts and bone marrow examinations should be offered and discussed with all affected persons.

Less frequent mutations conferring genetic susceptibility to MDS

Mutation in the 5′ untranslated region of the gene *ANKRD26* is associated with heritable thrombocytopenia and susceptibility to MDS.[1] *DDX41* germline mutations, located on chromosome 5q, are associated with autosomal dominant familial MDS/AML. Only a small number of pedigrees have been described so far, and latency is long, with an average age at diagnosis of MDS in the 60s, a typical age of onset in the general population; it might easily be mistakenly regarded as sporadic, and therefore, frequencies may be higher than suspected. Missense mutations in the gene *ETV6* located on chromosome 12p seem to be dominant negative function, disrupting the nuclear localization of the *ETV6* protein, resulting in reduced expression of platelet-associated genes, and leading to familial thrombocytopenia. Individuals with germline *ETV6* mutations are reported to be at increased risk for all hematologic malignancies, including MDS, AML, CMML, B-lymphoblastic leukemia, and plasma cell myeloma. Mutations in *SRP72* have been identified as a rare cause of familial MDS and bone marrow failure. Two pedigrees with autosomal dominant MDS and aplastic anemia have been reported. In both families, MDS developed in adulthood, and little is yet known about prevalence. In all of these rare families, discussion and risk assessment are needed to plan surveillance for asymptomatic gene carriers. Moreover, genetic screening of potential family member bone marrow donors is essential.

Conclusions

Clinical experience and data (although limited) support careful surveillance with bone marrow examinations in persons with FA, SDS, or DC who are at very high risk of hematological malignancy. Transplant is reasonably successful for MDS in these disorders, but outcomes are very poor for those with AML, further supporting surveillance to allow transplant before transformation to AML. Careful attention must be paid to host susceptibility to DNA damage in planning the transplant strategy.

GATA2 and *RUNX1* germline mutations can be diagnosed in childhood or adulthood and are associated with a great degree of clinical heterogeneity. Consideration should be given to hematological surveillance in individual consultation with each affected family member. Treatment of MDS and AML can typically be similar to treatments offered to those without genetic susceptibility, although comorbidities related to immune deficiency can be an issue in GATA2 deficiency. Accurate diagnosis of any germline abnormality is critical when family donors are being considered as potential bone marrow donors, a particular concern in *GATA2* and *RUNX1*, because an affected person may be asymptomatic well into adulthood.

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