Pediatric Myelodysplastic Syndromes: They Do Exist!

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Summary: One of the most common hematologic malignancies in adults, myelodysplastic syndrome (MDS) is a heterogeneous group of clonal disorders characterized by peripheral cytopenia(s) and normal or hypercellular bone marrow with dysplasia in ≥1 blood cell lineages. MDS frequently evolves to secondary acute myeloid leukemia with poor prognosis. Although uncommon among pediatric hematologic malignancies, both de novo and secondary MDS occur in children and may be the first presentation of an inherited bone marrow failure syndrome. Unlike its adult counterpart, pediatric MDS is more frequently associated with hypocellular bone marrow and monosomy 7. Refractory cytopenia is more typical than refractory anemia, as seen in the elderly. Its recognition and management can be quite challenging and requires the expertise of an experienced hematopathologist. In this review, we describe the epidemiology, genetics, and clinical spectrum of pediatric MDS along with its diagnostic and therapeutic challenges. We also compare and contrast pediatric and adult MDS.

Key Words: myelodysplastic syndromes, bone marrow failure syndromes, aplastic anemia, myeloid leukemia (J Pediatr Hematol Oncol 2014;36:1–7)

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal disorders characterized by peripheral cytopenia(s) and normal or hypercellular bone marrow with dysplasia in ≥1 blood cell lineages. Some are well-recognized distinct entities, for example, refractory anemia with ring sideroblasts, del (5q), and therapy related. MDS frequently evolves to secondary acute myeloid leukemia (AML) with poor prognosis. Its pathobiology is still not well understood, which has hampered the advancement of diagnostic and therapeutic strategies. Recent drug approvals for MDS include lenalidomide for del (5q) syndrome and the hypomethylating agents azacitidine and decitabine. Although MDS is one of the most common hematopoietic malignancies in older adults with a median age of 70 years at diagnosis, it is less frequently diagnosed in pediatrics (for a comparison of features see Table 1). In children and adolescents, MDS occurs in both de novo and secondary forms, but often presents a unique diagnostic challenge for the clinician. Secondary MDS follows either after genotoxic therapy or inherited bone marrow failure syndromes (IBMFS). Juvenile myelomonocytic leukemia (JMML) represents a special form of myelodysplastic and myeloproliferative disorder. Pediatric MDS may be under-diagnosed due to lack of validated, pediatric-specific diagnostic criteria or understanding of the natural history of refractory cytopenias. As little is known about the natural history of MDS in pediatrics, the decision when to transplant may be difficult.

EPIDEMIOLOGY

Although the true incidence of pediatric MDS has been difficult to ascertain, best estimates come from large population-based studies in Europe and Canada. The estimated incidence is approximately 1.8 to 4 cases per million per year, with the lower end of the range estimated from exclusion of patients with Down syndrome.1,2 Data published from the United Kingdom suggest a lower annual incidence of 0.8 cases per million, but included only primary MDS.3 In contrast, the incidence of AML and ALL is approximately 6 and 42 cases per million, respectively. The median age at presentation of pediatric MDS is 6.8 years and seems to be equally distributed among males and females.1–7 In the only large published series of advanced or high-risk pediatric MDS, the median age was higher at 10.7 years with a 2:1 male predominance.8

Secondary pediatric MDS is strongly associated with IBMFS, such as Fanconi anemia, Shwachman-Diamond syndrome, severe congenital neutropenia, dyskeratosis congenita, and MonoMAC syndrome.1,9–20 Other genetic conditions associated with MDS include paroxysmal nocturnal hemoglobinuria (PNH), monosomy 7 syndrome, Down syndrome, neurofibromatosis, Bloom syndrome, and Li-Fraumeni syndrome.1,9–20 Some will display MDS as the first presenting sign of that disorder. As our recognition and genetic-based diagnosis of these rare genetic disorders advance, it is likely that this number will increase and the corresponding incidence of purported de novo pediatric MDS will decrease, respectively. In addition, acquired severe aplastic anemia (SAA) infrequently evolves into secondary MDS. However, resolving the distinction between SAA and MDS significantly reduces the number of secondary MDS and AML after immunosuppressive therapy (IST) for SAA.21,22

CLINICAL PRESENTATION

About 20% of pediatric MDS is found incidentally on routine laboratory evaluation7 or during evaluation for a suspected bone marrow failure syndrome. More commonly, it presents with symptoms related to the cytopenias(s), such as fatigue, fever, infection, and bleeding.7 In contrast to adults, pediatric MDS often presents with bilineage cytopenias and very rarely with isolated anemia (ie, neutropenia and/or thrombocytopenia, with/without macrocytic anemia).7,23 Isolated 5q− or del (5q) syndrome common in
adults, is almost never seen in children. These findings are collectively reflected in the current World Health Organization (WHO) nomenclature of “refractory cytopenia of childhood” (RCC), as opposed to “refractory anemia.” RCC is the most common subtype of pediatric MDS, accounting for approximately 50% of cases, with the remaining being indistinguishable from “adult-type” refractory anemia with excess blast (RAEB) or RAEB-T.

**GENETICS**

Clonal analyses of karyotype and gene mutations revealed that pediatric MDS differs from adult MDS. Karyotype abnormalities are common, occurring in 30% to 50% of pediatric MDS, with the majority consisting of copy number variations in all or part of the chromosome. In contrast to abnormalities involving chromosome 5 in adult MDS, monosomy 7 is the most common cytogenetic abnormality in pediatric MDS and occurs in about 30% of patients. Other less common but recurrent cytogenetic abnormalities are trisomies 8 and 21 (which may be constitutional, mosaic, or somatically acquired), and the loss of part of chromosome 20 (eg, 20q→). Complex karyotypes tend to signify a high-risk population. Development and refinement of single-nucleotide polymorphism arrays have allowed the identification of additional microdeletions below the resolution of standard cytogenetic assays, and can reveal previously undetectable regions of copy number—neutral loss of heterozygosity, or uniparental disomy.

Understanding noncoding regions of DNA, identification of noncoding RNA, and description of global methylation and histone modification changes (epigenetics) are adding to the complexity of an emerging story for MDS in adults. Recurrent mutations affecting genes that regulate DNA methylation (DNMT3A, IDH1/IDH2, and TET2), histone function (EZH2 and ASXL1), and splicing machinery (U2AF35, ZRSR2, SRSF2, and SF3B1) have been identified in adult patients with MDS. Interestingly, these mutations are rare in pediatric de novo or secondary MDS. Several studies have found splicing factor mutations in only 1 of 187 pediatric MDS patients who had RAEB-T and in none of 28 patients with MDS, after excluding JMML which accounted for an additional 3 of 142 total JMML patients (combined data). However, even in the identified cases, the SRSF2 mutation did not seem to serve as a driver. It was always accompanied by other known oncogenic driver mutations (PTPN11 or NRAS), disappeared during disease progression, and was not present at the time of multiple relapses. To date, mutations in genes that regulate DNA methylation and histone function have not yet been established in pediatric MDS. Exactly how these genetic and epigenetic changes lead to disease have yet to be elucidated, but is an area of active research.

### Rare Yet Novel MDS Genes and Associated Syndromes (RUNX1, CEBPA, and GATA2)

Although very rare, familial forms of nonsyndromic MDS and AML have been described and 2 genes identified: RUNX1/AML1 in familial platelet disorder with a predisposition to acute myelogenous leukemia and CEBPA in familial AML. Recently, germline missense mutations in GATA2 were identified in 4 distinct families with multigenerational early-onset MDS/AML in an autosomal dominant manner. These mutations result in a dominant-negative loss of function through disruption of protein interactions necessary for DNA binding and activation of target genes. In these patients, the MDS subtype and clinical course were variable.

### TABLE 1. Comparison of Common Features of Adult and Pediatric MDS

<table>
<thead>
<tr>
<th></th>
<th>Adult MDS</th>
<th>Pediatric MDS</th>
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<tr>
<td>Incidence (cases per million)</td>
<td>3-5/10^6</td>
<td>1.8-4/10^6</td>
</tr>
<tr>
<td>Median age (y)</td>
<td>&gt; 20/10^5 in those &gt; 70 y</td>
<td>7</td>
</tr>
<tr>
<td>Presentation</td>
<td>Isolated, transfusion-dependent anemia, with/ without neutropenia and/or thrombocytopenia</td>
<td>Bilineage cytopenias most common; refractory thrombocytopenia &gt; neutropenia and/or anemia</td>
</tr>
<tr>
<td>Etiology</td>
<td>Primary (de novo) most common</td>
<td>Secondary or therapy related most common</td>
</tr>
<tr>
<td>BM cellularity</td>
<td>Hypercellular or normocellular; hypocellular is rare</td>
<td>Variable; hypocellular is most common</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>5q− or 7/q− most common</td>
<td>Monosomy 7/q− ≥ trisomy 8</td>
</tr>
<tr>
<td>Genetics</td>
<td>Mutations in DNMT3a, ASXL1, TET2, SF3B1, U2AF35; methylation changes</td>
<td>FANC members, SBDS, DKC, TERT, TERC, ELANE, HAX1, WAS, GATA-2 (related to IBMFS)</td>
</tr>
<tr>
<td>Physical findings</td>
<td>None</td>
<td>Skeletal, cutaneous, genitourinary, cardiovascular, and gastrointestinal anomalies (related to IBMFS)</td>
</tr>
<tr>
<td>Therapeutic options</td>
<td>RBC and platelet transfusions</td>
<td>Monitoring</td>
</tr>
</tbody>
</table>

HSCT indicates hematopoietic stem cell transplant; IBMFS, inherited bone marrow failure syndromes; IST, immunosuppressive therapy; MDS, myelodysplastic syndrome; RARS, refractory anemia with ring sideroblasts; RBC, red blood cells; RCC, refractory cytopenia of childhood; ?, unknown efficacy.
In addition, recurrent germline mutations in GATA2 have also been described in syndromic forms of familial and sporadic MDS. The MonoMAC syndrome is an immunodeficiency syndrome characterized by marked monocytopenia, and B-cell and NK-cell lymphopenia, with resultant susceptibility to mycobacterial infections, human papillomavirus, and other opportunistic viral and fungal infections. The constellation of features also includes a predisposition to MDS/AML, and/or pulmonary alveolar proteinosis. In Emberger syndrome, GATA2 mutations are associated with lymphedema and MDS/AML. As more patients are sequenced for GATA2 mutations, we will learn more about the range of GATA2 mutations and their associated MDS phenotypes.

**DIAGNOSTIC CHALLENGE**

Consideration of pediatric MDS should occur when thrombocytopenia, neutropenia, and/or anemia has persisted for 3 months in an otherwise healthy child or adolescent. Closer inspection might reveal the physical anomalies associated with Fanconi anemia, Shwachman-Diamond syndrome, or dyskeratosis congenita. The presence of warts might suggest Mono-Mac syndrome. Subtle clues also include the presence of macrocytic anemia with normal vitamin B12 and folate levels. Dysplastic granules or abnormal nuclear segmentation in circulating neutrophils would also raise suspicion. Diagnosis depends greatly on bone marrow aspirate and biopsy. MDS is largely a diagnosis of morphology and thus subject to interpretation, interobserver variability in diagnosis, and sampling error if significant hypocellularity exists.

Morphologic evaluations of peripheral blood and of bone marrow are important components in the evaluation of pediatric myelodysplasia. The overall spectrum of morphologic change found in pediatric MDS is similar to that of adult MDS, but the frequency and clinical significance of specific abnormalities can differ.

Blast cell numbers are a critical morphologic parameter for identifying and classifying MDS. For both adults and children, a blast percentage of at least 5% (but < 20%) in the bone marrow or ≥ 2%, but < 20%, in the peripheral blood are defining features of the high-grade MDS, RAEB. The WHO classification further subdivides RAEB based on the blast count, with a threshold of 10% blasts in the bone marrow or 5% blasts in the peripheral blood separating RAEB-2 from RAEB-1. In adults this distinction has been shown to have significant prognostic and therapeutic implications. This subclassification is also applied to cases of pediatric RAEB, although its prognostic significance in children is still unclear.

The peripheral blood and bone marrow are also evaluated for dysplastic change. Morphologic features of MDS at all ages include dysmegakaryopoiesis, with dysplastic forms showing nuclear hypolobation or multinucleation, and often decreased size; micromegakaryocytes, characterized by small size and a nonlobated nucleus are a particularly characteristic finding (arrowhead, Fig. 1). Myeloid and erythroid lineages may show megaloblastic maturation. Additional abnormalities of erythroid precursors include nuclear budding and bridging, as well as multinucleation, whereas dysplastic neutrophils are characterized by nuclear hyposegmentation and cytoplasmic hypogranulation (arrow, Fig. 1). In adult MDS, the most common pattern of disease is unilineage erythroid dysplasia (dyserthropoiesis) with anemia. In pediatric myelodysplasia, however, the myeloid and megakaryocytic lineages are more often affected, and multilineage disease is common at presentation. The WHO classification mandates that cases with cytopenia and multilineage dysplasia are diagnosed as refractory cytopenia with multilineage dysplasia (RCMD). The category of RCMD was introduced in the 2001 WHO classification because of studies showing that, even without increased blasts, the presence of multilineage as opposed to unilineage dysplasia was associated with poorer prognosis. However, it was not clear that this classification scheme was optimal for pediatric MDS. In particular it was uncertain whether multilineage dysplasia

**TABLE 2. WHO Classification of Pediatric MDS**

<table>
<thead>
<tr>
<th>Pediatric MDS: 2008</th>
<th>Blast Count (%)</th>
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<tr>
<td></td>
<td>Peripheral Blood</td>
</tr>
<tr>
<td>Refractory cytopenia of childhood</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>RAEB</td>
<td>2-19</td>
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<tr>
<td>RAEB in transformation (RAEB-T)†</td>
<td>20-29</td>
</tr>
<tr>
<td>MDS/MPN</td>
<td>Juvenile myelomonocytic leukemia</td>
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<tr>
<td>BCR-ABL negative chronic myeloid leukemia (Ph-CML)</td>
<td></td>
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<tr>
<td>Down syndrome-related myeloid disorders</td>
<td>Transient abnormal myelopoiesis</td>
</tr>
<tr>
<td>Down syndrome-related myeloid disorders</td>
<td>MDS/AML</td>
</tr>
</tbody>
</table>

*The MDS/MPN and Down syndrome-associated myeloid diseases have been removed from the MDS classification and are each considered distinct biological entities.

†Without disease-defining characteristics of AML.

AML indicates acute myeloid leukemia; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasms; RAEB, refractory anemia with excess blasts; WHO, World Health Organization.
in pediatric MDS without increased blasts was indicative of poorer prognosis.\textsuperscript{23,43} The current WHO classification (Table 2) has therefore added a provisional diagnostic category: RCC, as an alternative to the division of pediatric MDS cases between the original categories of refractory anemia, and RMCD.\textsuperscript{40,60} Although morphologic evaluation can identify dysplastic changes supporting a diagnosis of MDS, they lack specificity for neoplastic disease, and exclusion of the many alternative etiologies for the dysplastic features may be necessary for definitive diagnosis of pediatric MDS.

Causes of secondary dysplasia must be excluded. Other nonhematologic, systemic conditions can cause secondary myelodysplasia and may mimic RCC. These include viral infections (especially EBV, CMV, Parvovirus, HSV, and HIV) medications (antinepileptics, antipsychotics, antimitabolites, etc), metabolic diseases (eg, mevalonate kinase deficiency), mitochondrial diseases (Pearson syndrome), rheumatic diseases (juvenile idiopathic arthritis), and nutritional deficiencies (vitamin B\textsubscript{12}, folate, vitamin E, or copper deficiencies)\textsuperscript{45–50}.

MDS are primarily defined by their morphologic features in peripheral blood and bone marrow aspirate smears, but the bone marrow core biopsy can also show distinctive morphologic findings, and some differences between pediatric and adult MDS. In adults, evaluation of marrow cellularity in the biopsy can be useful as adult MDS often shows increased cellularity though peripheral blood counts are low. However, the majority of cases of pediatric MDS show a hypocellular marrow.\textsuperscript{7} When the decrease is marked, hypocellular MDS can be difficult to distinguish from SAA. As RCC is the most common pediatric subtype, it is important to note that about 80% of patients with RCC have markedly hypocellular bone marrow at presentation making it difficult to distinguish RCC from aplastic anemia, especially if no MDS-related cytogenetic abnormality is detected. If present, MDS-related cytogenetic abnormalities also help to differentiate between RCC and aplastic anemia but may not distinguish primary MDS from secondary MDS arising from an IBMFS. In addition, RCC must be distinguished from PNH, which may present without the classic PNH phenotype.\textsuperscript{51–53} Classically, the bone marrow in acquired aplastic anemia is largely occupied by fat with scattered myeloid cells and without erythroid islands, erythroid hyperplasia, micromegakaryocytes, or dysplastic granulocytes. However, if the hypocellularity leaves only few evaluable cells, it may be exceedingly difficult to discern the 2. Furthermore, other than identification of one of the known mutations involved in classic IBMFS or other previously described syndromes, there is a lack of specific disease-defining genetic markers (exceptions include identification of 5q\textsuperscript{–} or monosomy 7 in the proper clinical context).

Features of the bone marrow biopsy have been proposed as useful markers to help distinguish aplastic anemia from MDS. Baumann et al\textsuperscript{41} reported that the presence of patchy cellularity in the core biopsy due to foci of residual hematopoiesis, usually composed of erythroid precursors, showing increased immaturity allowed them to identify reliably a hypocellular MDS from aplastic anemia. Immunohistochemical studies of the biopsy may also be useful, allowing the identification of specific cell types or detection of cell cycle markers.\textsuperscript{54} Antibodies to CD34, to CD61 or CD41, and to E-cadherin can be useful in the identification of blasts, megakaryocytes and immature erythroid precursors, respectively. Dysplastic features such as small megakaryocytes, may be demonstrated and an approximate blast percentage obtained.

**TREATMENT OPTIONS**

The only curative therapy is hematopoietic stem cell transplantation (HSCT), but the decision when to pursue this can be difficult. For adult MDS patients, the international prognostic scoring system has been useful to guide therapy (Table 3), but it has not been validated in pediatric MDS and has limited utility.\textsuperscript{56} Particularly for pediatric patients with primary MDS, the natural history is largely unclear, and the timing and need for HSCT remain contentious. For example, RCC is often associated with a more indolent, stable course and low risk for leukemic transformation, but may progress, whereas other MDS subtypes may be much more aggressive with high rates of leukemic transformation and poor prognosis. Optimization of management requires better understanding of disease pathogenesis, pediatric-specific subtypes, and their prognostic implications.

Standard supportive care with transfusions and broad-spectrum antibiotics for fever and neutropenia is essential to prevent and treat complications of the disease. Although supportive therapy alone may be a reasonable option in the elderly, treatment for pediatric patients is with curative intent and HSCT is the treatment of choice for most. Outcomes for HSCT in pediatric MDS are best when considered early and before disease progression.\textsuperscript{57,58} Careful observation with routine bone marrow surveillance may be acceptable in patients with mild cytopenias, without transfusion requirements or infections, and without monosomy 7 or complex cytogenetics.

Treatment with hypomethylating agents likely play a role in MDS in those patients with cytopenias and hypocellular bone marrow.\textsuperscript{59} This has led to the application of IST in MDS. IST with cyclosporine (CSA) and/or antithymocyte globulin, similar to the regimens used for SAA, has been modestly successful in a small subset of adult MDS, particularly those of younger age (below 60 y) with low-risk, hypocellular MDS and associated with HLA-DR15.\textsuperscript{60–62} IST may also be useful in RCC. Hematologic response rates range from 63% to 76%. Overall and failure-free survival rates at 3 to 5 years are about 88% to 90% and 57% to 63%, respectively, with fewer adverse events than seen in adults.\textsuperscript{63,64} The presence of minor PNH clones in RCC may also predict a response to IST.\textsuperscript{65} Although promising, long-term efficacy data are still lacking. More importantly, efficacy and durability of response to IST are inherently related to the degree in which autoimmunity contributes to disease pathogenesis and the mechanisms that allow for clonal evolution.

Recent drug approvals for adult MDS include the immunomodulating agent lenalidomide for del (5q) syndrome and the hypomethylating agents azacitidine and decitabine; however, these latter agents continue to show relatively low response rates (< 20%). In pediatrics, experience with hypomethylating agents and demonstration of safety comes from treatment of solid tumors such as neuroblastoma\textsuperscript{66} and with limited, albeit promising, experience in JMML.\textsuperscript{67} There is a small body of literature to suggest that pediatric patients with high-risk MDS (RAEB or RAEB-T) or JMML demonstrate abnormal methylation patterns that are associated with a poor prognosis.\textsuperscript{68,69}
However, more studies are needed to better characterize these patterns in pediatric MDS to assess the clinical utility of these agents as a therapeutic strategy. Furthermore, the likelihood of these agents providing lifelong durability of response will need to be weighed against the curative intent of HSCT.

CONCLUSIONS

The incidence of pediatric MDS is underestimated and diagnosis requires index of suspicion and an experienced hematopathologist. All pediatric patients with suspected MDS or aplastic anemia should have a bone marrow evaluation with routine cytogenetics, in addition to FISH for common MDS-associated cytogenetic anomalies as these 2 modalities are complimentary. In addition, these patients should have a workup to rule out occult PNH or IBMFS (Fanconi anemia, Shwachman-Diamond syndrome, dyskeratosis congenita, etc.) that may have MDS or aplastic anemia as its first presentation. The high rates of MDS/AML in associated congenital syndromes, including pediatric IBMFS, may provide meaningful insights into MDS/AML in associated congenital syndromes, including IBMFS (Fanconi anemia, Shwachman-Diamond syndrome, dyskeratosis congenita, etc.) that may have MDS or aplastic anemia as its first presentation. The high rates of MDS/AML in associated congenital syndromes, including pediatric IBMFS, may provide meaningful insights into MDS/AML in associated congenital syndromes, including IBMFS (Fanconi anemia, Shwachman-Diamond syndrome, dyskeratosis congenita, etc.) that may have MDS or aplastic anemia as its first presentation. The high rates of MDS/AML in associated congenital syndromes, including pediatric IBMFS, may provide meaningful insights into MDS/AML in associated congenital syndromes, including IBMFS (Fanconi anemia, Shwachman-Diamond syndrome, dyskeratosis congenita, etc.) that may have MDS or aplastic anemia as its first presentation. The high rates of MDS/AML in associated congenital syndromes, including pediatric IBMFS, may provide meaningful insights into MDS/AML in associated congenital syndromes, including IBMFS (Fanconi anemia, Shwachman-Diamond syndrome, dyskeratosis congenita, etc.) that may have MDS or aplastic anemia as its first presentation.

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