Myelodysplastic/Myeloproliferative Neoplasms

Kathryn Foucar, MD

Key Words: Myelodysplasia; Myeloproliferative; Myeloid neoplasm, WHO classification

Abstract

Myelodysplastic/myeloproliferative neoplasms (MDS/MPNs) are rare de novo myeloid neoplasms that exhibit hybrid dysplastic and proliferative features at presentation. By definition, the CBC shows a variable combination of cytopenias and cytoses with dysplasia of at least 1 lineage. The bone marrow of patients with MDS/MPNs is characteristically hypercellular and shows dysplastic and proliferative features as predicted from the peripheral blood. By definition, the percentage of blasts in the blood and the bone marrow must be less than 20%. Four subtypes of MDS/MPNs have been identified, including chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), atypical chronic myeloid leukemia, BCR-ABL1+ (aCML), MDS/MPNs unclassifiable (MDS/MPN-U), along with a provisional category, refractory anemia with ringed sideroblasts and thrombocytosis (RARS-T). The 2008 World Health Organization (WHO) classification system criteria for these subtypes of MDS/MPN are delineated in Table 1.1-17

Although abnormalities in the regulation of the RAS pathway are common in various types of MDS/MPN, aside from JMML, distinctive genetic features vital to the subclassification of MDS/MPNs have not yet been delineated.9,18 Indeed, the newly proposed 2008 WHO classification of MDS/MPNs shows little change from the 2001 classification, reflecting the general lack of new biologic and genetic insights into this distinctive hybrid group of disorders. Cases of CMML with eosinophilia and PDGFRB rearrangement have been removed from the MDS/MPN category and placed in a new genetically defined category.1

Chronic Myelomonocytic Leukemia

Five workshop cases were ultimately concluded to fulfill the diagnostic criteria for prototypic CMML. As
with all MDS/MPN subtypes, the diagnosis of CMML is problematic, and several specific controversial issues were identified in this subgroup.\textsuperscript{3,4,6} One significant problem area is the distinction between CMML and acute myeloid leukemia (AML) based on the percentage of promonocytes. Promonocytes are defined as immature monocytic cells with nuclear features of immaturity, especially nucleoli. Because promonocytes are considered as “blast equivalents,” cases with significant promonocytes will fulfill criteria for AML even if actual morphologic blasts do not exceed 20% in the blood or bone marrow Image 2\textbf{I}, Image 3\textbf{I}, and Image 4\textbf{I}.

Workshop cases 111 and 138 highlighted the challenge in distinguishing CMML from evolving AML. Another challenging differential diagnostic issue was highlighted by case 139 in which the distinction between aCML and CMML was problematic Image 5\textbf{I} and Image 6\textbf{I}. In this case, monocytes, although accounting for only 4% (0.04) of total WBCs, were absolutely increased at a level of 1,800/µL (1.8 × 10\textsuperscript{9}/L). Thus, this absolute monocyte count could be used to classify this case as CMML, while aCML was the preferred diagnosis of the panel based on the striking predominance of the granulocytic cells in the peripheral blood and bone marrow.

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\textbf{Table 1}

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<tr>
<th>Disorder</th>
<th>Blood</th>
<th>Bone Marrow</th>
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<tr>
<td>CMML</td>
<td>Persistent monocytosis, &gt;1 × 10\textsuperscript{9}/L; dysplasia, ≥1 lineages present; neutrophilia, usually present; &lt;20% blasts</td>
<td>&lt;20% blasts; usually hypercellular; dysplasia in ≥1 lineages; 2 subtypes based on blast percentage</td>
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<td>JMML</td>
<td>Persistent monocytosis, &gt;1 × 10\textsuperscript{9}/L; &lt;20% blasts; minor criteria: WBC count, &gt;10,000/µL (10 × 10\textsuperscript{9}/L); increased hemoglobin F level; left shift; GM-CSF hypersensitivity in culture; clonal cytogenetic abnormality</td>
<td>&lt;20% blasts; usually hypercellular</td>
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<td>aCML (BCR-ABL\textsuperscript{1}−)</td>
<td>Neutrophilia with left shift; prominent dysgranuloipoiesis; left shift ≥10% of WBCs; &lt;20% blasts; minimal to absent basophilia and monocytosis; monocytes generally &lt;10%</td>
<td>&lt;20% blasts; hypercellular with granulocytic expansion with dysplasia; variable dysplasia of other lineages</td>
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<td>MDS/MPN, unclassifiable</td>
<td>Hybrid dysplastic/proliferative features; &lt;20% blasts</td>
<td>&lt;20% blasts; usually hypercellular</td>
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<td>Provisional RARS-T</td>
<td>Hybrid dysplastic/proliferative features with sustained thrombocytosis (platelet count, ≥450 × 10\textsuperscript{9}/L [450 × 10\textsuperscript{9}/L]); &lt;20% blasts</td>
<td>&lt;20% blasts; ≥15% of erythroid precursors are ringed sideroblasts</td>
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aCML, atypical CML, BCR-ABL\textsuperscript{1}−; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; CMPN, chronic myeloproliferative neoplasm; GM-CSF, granulocyte-macrophage colony-stimulating factor; JMML, juvenile myelomonocytic leukemia; MDS/MPN, myelodysplastic/myeloproliferative neoplasms; RARS-T, refractory anemia with ringed sideroblasts and thrombocytosis.
The bone marrow in CMML is typically hypercellular with a predominance of granulocytic and monocytic cells; the monocytic component can be highlighted by cytochemical staining (Image 6B) Image 7. The usefulness of bone marrow core biopsy sections, especially in conjunction with immunohistochemical stains, in the diagnosis of CMML has been emphasized recently.5,11 These core biopsy features include hypercellularity, a predominance of myelocytic/monocytic cells, abnormal localization of immature precursors, and dysplastic megakaryocytes.6

### Juvenile Myelomonocytic Leukemia

Two cases were submitted to the workshop with a diagnosis of JMML that was supported by panel review Image 8.

Both of these cases illustrated the usefulness of confirming hypersensitivity to granulocyte-macrophage colony-stimulating factor in bone marrow culture studies as a criterion for establishing the diagnosis of JMML.3,7-11 Unlike the other subtypes of MDS/MPN, JMML frequently affects children, and even very young children are affected. In 1 workshop case (case 205), the patient showed striking leukocytosis at birth and survived only 18 days. The other workshop case (016) was a 28-month-old girl in whom JMML had been diagnosed when she was 19 months old.

Because of its predilection for the pediatric age group and because of the association with neurofibromatosis-1 (NF-1), JMML is unique among the MDS/MPNs. The pathogenesis of JMML is complex, and defects in the RAS signaling pathway have been documented, which are linked...
to granulocyte-macrophage colony-stimulating factor hypersensitivity confirmed in the majority of cases. These RAS signaling pathway defects include inactivation of the NF1 tumor suppressor gene or oncogenic mutations of the NRAS, KRAS2, or PTPN11 gene. An important consideration in this disease is the distinction between JMML and congenital AML as highlighted by case 205. Genetic testing is essential in making the distinction between JMML (frequently associated with monosomy 7) and other potential types of congenital leukemia, such as 11q23-associated congenital acute monocytic and lymphoblastic leukemias. As with CMML, the distinction between JMML and AML is based on the percentage of blasts...
and promonocytes, which cannot exceed 20% in blood or bone marrow. The bone marrow aspirate is usually hypercellular with prominent granulocytic and monocytic components. Although immature cells are present, the percentage of blasts and promonocytes is less than 20%.

**Atypical Chronic Myeloid Leukemia BCR-ABL1–**

Criteria for aCML are challenging in that a variety of morphologic and genetic criteria need to be met. Obviously, the exclusion of BCR-ABL1-related disease is essential. In addition, a requirement for neutrophilia with left shift and prominent dysgranulopoiesis has been established by WHO criteria. Although left shift is required, the percentage of blasts cannot exceed 20% in blood or bone marrow. Finally, although basophilia and monocytosis (≤10%) are typically absent, mild basophilia and monocytosis do not exclude a diagnosis of aCML (Table 1). Consequently, cases with striking leukocytosis and a modest percentage of monocytes will actually exceed 1,000/µL (1 × 10⁹/L), which is used as the major criterion for CMML. This dilemma is apparent for one of the cases submitted as aCML (case 015) and one of the cases initially submitted as CMML (case 139). Consequently, cases that most clearly fulfill criteria for aCML are those in which there is marked leukocytosis with a striking predominance of granulocytic cells showing marked dysplasia and modest left shift. Neither basophilia nor monocytosis should be striking, and even if the absolute monocyte count exceeds 1,000/µL (1 × 10⁹/L), a diagnosis of aCML is still appropriate. Similarly, the bone marrow should show granulocytic expansion with dysplasia without a dominant monocytic component; the granulocytic predominance can be highlighted by cytochemical or immunohistochemical stains. As with all MDS/MPN cases, genetic testing is essential in excluding BCR-ABL1-related disease and cases with AML-defining translocations.

**Myelodysplastic/Myeloproliferative Neoplasms, Unclassifiable**

Seven cases were recommended by the panel for a diagnosis of MDS/MPN-U, and this group of cases highlights many challenging aspects of this diagnosis. Several cases ultimately diagnosed as MDS/MPN-U actually had mild monocytosis or basophilia (cases 015 and 098) and 1 case had striking bone marrow fibrosis (case 189). Cytogenetic abnormalities in this group of cases included del(20)q (case 098), del(5)q (case 193), and trisomy 8 (case 153). Aside from the hybrid myeloproliferative/myelodysplastic features that are a requirement for this category of myeloid neoplasm, the blood features are relatively nondescript. The bone marrow features included consistent hypercellularity, granulocytic lineage expansion, and frequent dysplastic megakaryocytes and.

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**Image 9** (Case 016) Bone marrow aspirate in juvenile myelomonocytic leukemia shows a predominance of myelomonocytic cells confirmed by cytochemical stain (A, Wright; B, naphthyl butyrate esterase). Contributed by C.H. Dunphy.

**Image 10** A and B, Marked leukocytosis with left-shift and dysplasia is evident in this blood sample from an elderly patient with atypical chronic myeloid leukemia (A and B, Wright).
Provisional Category: Refractory Anemia With Ringed Sideroblasts and Thrombocytosis

Seven cases of the provisional RARS-T subtype of MDS/MPN-U were submitted. This group of cases was particularly problematic because, in many cases, the bone marrow core biopsy sample showed striking features suggestive of a chronic myeloproliferative neoplasm rather than a hybrid MDS/MPN. Indeed, enlarged, hyperlobulated megakaryocytes were frequently encountered in cases that were submitted as RARS-T, raising the possibility that these cases could be more optimally classified as a chronic myeloid neoplasm with associated ringed sideroblasts. Further evidence supporting a diagnosis of a chronic myeloproliferative neoplasm included the identification of...
JAK2 mutations in several of the cases.\textsuperscript{15,16} As with other types of MDS/MPN, the lack of a specific genetic marker for this disorder makes diagnosis challenging and controversial. If myeloproliferative features predominate in the bone marrow and especially if a JAK2 mutation is identified, consideration of a chronic myeloproliferative neoplasm is clearly warranted (Image 16). However, a recent study suggests that cases fulfilling criteria for RARS-T have a unique biology with median survival times greater than in other MDS/MPN disorders but less than in essential thrombocytemia.\textsuperscript{17} The role of JAK2 mutations in this biology is not clear because the frequency of JAK2 mutations was similar in cases of RARS-T and MDS/MPN-U. Other factors that seem to have prognostic significance in RARS-T compared with MDS/MPN-U, regardless of JAK2 mutation status, include conventional karyotype and platelet count.\textsuperscript{17}

**Conclusions and Recommendations**

MDS/MPNs were among the most challenging and controversial groups of diseases evaluated at the SHP/EAHP Workshop. Reasons for the difficulty in reaching consensus in this category of cases relate to the relatively subjective morphologic criteria in blood and bone marrow and, more

**Image 15** (Case 128) This composite illustrates blood, ringed sideroblasts, thrombocytosis, and hyperlobulated megakaryocytes in a case with features of refractory anemia with ringed sideroblasts and thrombocytosis, but the core biopsy was suggestive of a chronic myeloproliferative neoplasm (A, blood sample, Wright; B, aspirate, Prussian blue; C, blood sample, Wright; D, core biopsy sample, H&E). Contributed by R.F. McClure.
important, to the absence of distinctive biologic and genetic features of disorders with hybrid myelodysplastic/myeloproliferative features. General recommendations include careful attention to the identification of promonocytes because these “blast equivalent” cells can clearly impact the distinction between CMML and JMML at one end of the spectrum and AML at the other. Even if morphologic blasts are not numerous, abundant promonocytes may “shift” a case of possible MDS/MPN into AML. Careful attention must also be given to the morphologic features of megakaryocytes on bone marrow core biopsy sections because cases in which the megakaryocytes show dominant myeloproliferative features may have JAK2 positivity and, thus, be better considered as

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<th>Table 2</th>
<th>Recommendations for Myelodysplastic/Myeloproliferative Neoplasms</th>
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<td>Diagnosis of exclusion without defining cytogenetic features</td>
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<td>Hybrid dysplastic or proliferative features at initial diagnosis</td>
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<td>CBC should demonstrate cytopenias and cytoses</td>
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<td>Delineation of promonocytes is essential; blast equivalents</td>
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<td>Blasts/blast equivalents &lt;20% in blood and bone marrow</td>
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<td>If JAK2 mutation identified, consider chronic myeloproliferative neoplasm</td>
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<tr>
<td>Genetic testing essential to exclude BCR-ABL1-related neoplasms, PDGFR(\alpha)/B, FGFR1, isolated del5q, and low-blast-count AML-defining translocations</td>
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AML, acute myeloid leukemia.

Image 16 This composite of bone marrow core biopsy specimens from cases 126 (A), 128 (B), 168 (C), and 195 (D) highlights the spectrum of megakaryocyte morphologic features in problematic cases submitted as refractory anemia with ringed sideroblasts and thrombocytosis (A-D, H&E). Contributed by Y.R. Orduz, R.F. McClure, L.C. Contis, and D. Gratzinger.
a type of chronic myeloproliferative neoplasm. Even though a distinctive genetic “marker” for MDS/MPNs has not yet been identified, genetic testing must always be performed on these cases to exclude the possibility of a BCR-ABL1-related disorder or some other translocation such as t(8;21) that would favor a diagnosis of low-blast-count AML.

References


