Bone Marrow Dysplasia
A Continuing Diagnostic Challenge

Dysplasia of hematopoietic tissue, or myelodysplasia, has moved, in the last 15 years, from a position of relative obscurity to one of central importance in hematology. This shift occurred largely as a result of the French-American-British (FAB) Cooperative Group’s series of definitive publications on the criteria for acute leukemia and myelodysplastic syndromes (MDS).1,2,3 The FAB classifications have brought order and reproducibility to the diagnosis of acute leukemia and MDS. Furthermore, the FAB criteria have survived by proving to be flexible enough to incorporate change as new diagnostic categories, such as acute megakaryoblastic leukemia (also called FAB M7), are needed.

In this issue of the American Journal of Clinical Pathology, Menke and colleagues4 direct our attention to an area of MDS diagnosis that may warrant further refinement. This is the category defined by the FAB as the lowest grade, or most minimal, of the MDS syndromes, refractory anemia. Although refractory anemia, according to its original definition, may be associated with a single cytopenia of any lineage, in practice its name has led to its virtual restriction to cases showing anemia, with or without associated neutropenia and thrombocytopenia. Refractory anemia is often difficult to identify when the hallmarks of dysplasia are subtle, and the diagnosis may become one of exclusion, aided by the passage of time.

The significance of the study by Menke and colleagues4 is in drawing more interest to the problem of another cytopenia as a sign of low-grade MDS: isolated, refractory thrombocytopenia. Clearly, this subset of patients exists but it is not well recognized; in fact, it is so infrequently recognized that many patients are thought to have idiopathic thrombocytopenic purpura and are subjected to unwarranted therapies with adverse side effects.4,5 The delay in recognition of refractory thrombocytopenia is probably related to the relatively slow progress of our understanding of normal megakaryopoiesis and thrombocytopenia, compared to other hematopoietic cell lines, and the concomitant slow progress in quantitative assessment of megakaryocyte and platelet characteristics.

A number of questions that arise from the current study press for answers, and some of them are addressed below.

How should refractory thrombocytopenia be defined? Menke and colleagues1 accepted patients with platelet counts as high as 159 × 10^9/L, whereas Najean and LeCompte5 based their study on patients with thrombocytopenia and a normal platelet life span, thus documenting a platelet production defect; most cases lacked dysmegakaryopoiesis, and no cytogenetic studies were done. Tricot and associates6 based their study on dysmegakaryopoiesis; all their patients had clonal cytogenetic abnormalities and shortened platelet life spans. (The conflicting platelet life span results between the latter two studies may be a moot point because such studies are rarely done in this country.) Thus we are still working to develop basic criteria to establish the diagnosis.

How should dysmegakaryopoiesis be defined? This criterion should perhaps be the sine qua non of refractory thrombocytopenia, yet the wide disparity among studies shows that it is far from a universally accepted minimum criterion. This may be due to a real absence of dysplasia in megakaryocytes in some cases, but is probably a reflection of the difficulty even experienced morphologists have in recognizing abnormal megakaryocytes. The problem extends to the identification of abnormal platelets. Well-documented standards are still evolving for normal megakaryocyte number, size, nuclear and cytoplasmic features, and ploidy distribution. Recent morphologic and ultrastructural studies have documented increased numbers of “denuded” megakaryocyte nuclei and peculiar cytoplasmic changes in the setting of human immunodeficiency virus infection,8 but much remains to be done to develop objective and reproducible criteria for megakaryocyte morphology and function. The situation is not significantly better for platelets: even a straightforward criterion such as “thrombocytopenia” is uncertain. Menke and colleagues4 accepted patients with platelet counts as high as 159 × 10^9/L, whereas Najean and LeCompte5 and Tricot and associates6 confined their studies to those with platelet counts less than 100 × 10^9/L. Not only do authors’ requirements for thrombocytopenia differ but the very methods used in most laboratories...
to count platelets have unacceptably high coefficients of variations. Accurate measurement of other platelet parameters, including size and function, is even more difficult to achieve.

What is the mechanism of thrombocytopenia in these patients? It is tempting to assume that the megakaryocytes are, in fact, dysplastic (whether visibly so or not) and that they either fail to produce platelets or produce defective platelets that are lost through "ineffective thrombopoiesis." Although this is probably the case in many patients, the production and biologic fate of platelets is difficult to assess. Data on anti-platelet antibodies in refractory thrombocytopenia are incomplete and conflicting. Autoimmune and possibly phagocytic mechanisms may contribute to thrombocytopenia, even in patients with clear evidence of myelodysplasia. Decreased marrow megakaryocytes often are cited as evidence of decreased platelet production, and increased megakaryocytes are cited as evidence of increased platelet sequestration/destruction. But even this simple relationship has not held up in patients with thrombocytopenia and autoimmune disorders. Perhaps other sites of thrombopoiesis, such as the lungs, need to be studied more closely to clarify this issue.

What is the relationship of refractory thrombocytopenia to similar familial or constitutional genetic disorders? The diagnosis of MDS in children and adults with inherited disorders is still difficult. These are rare and sometimes complex problems requiring extensive clinical and laboratory investigation. A large study of children and young adults with isolated chronic thrombocytopenia and normal megakaryocyte counts showed apparent autosomal-dominant transmission of a genetic disorder. Of particular concern in this study was the development of acute leukemia in 7% of 54 young patients, who had otherwise suffered few clinical effects of their disorder. In another recent study, a consanguineous kindred yielded three cases of a new autosomal-recessive disorder characterized by dysmegakaryopoiesis, micromegakaryocytes (documented quantitatively), and abnormal megakaryocyte ploidy. Case reports continue to accumulate on the problem of chronic thrombocytopenia, dysplasia, and chromosomal abnormalities in children. In all these studies, the subjects were considered to have idiopathic thrombocytopenia purpura and were treated accordingly, which treatment included splenectomy despite normal levels of anti-platelet antibodies. Much needs to be done to define MDS in children and broaden the definition, as in adults, to include refractory thrombocytopenia.

Why is it important to recognize refractory thrombocytopenia as a myelodysplastic syndrome? There are two reasons: (1) to improve understanding of the natural history, including the increased risk of acute leukemia, and (2) to avoid harmful or ineffective therapy and focus on potentially beneficial therapies. Regarding the first reason, many patients with refractory thrombocytopenia progress to multiple cytopenias and more overt MDS (64% in the current study and 38% in another) and even acute myeloid leukemia (45% in the current study and 7% and 19% in two others). The 5-year probability of patient survival in the current study was only 45%. This disorder eventually may prove to be worse than refractory anemia in severity of clinical symptoms, risk of acute myeloid leukemia, and expected long-term survival. Second, it is clear from Menke and colleagues' study and other studies that many of these patients were misdiagnosed as having idiopathic thrombocytopenic purpura and received corticosteroids, followed by aseptic necrosis of the hip, and splenectomy. These treatments and their serious complications can be avoided in patients with refractory thrombocytopenia. Rather, therapies may be explored that have shown some early promising results in increasing platelet counts in MDS, such as granulocyte–monocyte colony-stimulating factor, erythropoietin, danazol, and interleukin-3.

Where do we go from here? Refractory anemia should be redefined and joined by its counterparts, refractory thrombocytopenia and refractory neutropenia, in the ranks of recognized myelodysplastic syndromes. Indeed, isolated refractory neutropenia is four times more common than isolated thrombocytopenia, according to one survey of refractory anemia. Like isolated refractory thrombocytopenia, it deserves to be studied more fully rather than being included in the ménage of mono-, bi-, and pan cytopenias that now characterizes refractory anemia. (Can refractory monocytopenia, eosinopenia, and basopenia be far behind?)

These are but a sample of the questions and tasks ahead. Far from being outstripped by our surgical pathology colleagues in their increasing quest for dysplasia (witness CIN, VIN, MIN, VAIN, PIN, and so on), the students of hematopoietic dysplasia have their work cut out for them for many years.

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REFERENCES


