Cytogenetic Diagnosis of Myelodysplastic Syndromes

Harold J. Olney, Michelle M. Le Beau

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6.1 Introduction

The cytogenetic evaluation of bone marrow samples from patients with a myelodysplastic syndrome (MDS) has become an integral part of clinical care. A cytogenetic analysis not only confirms the diagnosis but is invaluable in defining the prognosis and expected survival, as well as the risk for progression to an acute myeloid leukemia (AML). On a more fundamental level, cytogenetic analysis has been instrumental in establishing the clonality of these syndromes as well as providing hints at the pathobiology of these entities. Here we will review the most frequently encountered abnormalities, exploring their clinical and genetic features, as well as the techniques of cytogenetic analysis and their applications in MDS.

6.2 Diagnosis

The diagnosis of all hematological malignancies, including MDS, begins with the appropriate clinical evaluation combined with expert pathological and genetic analysis. An accurate diagnosis is crucial in management decisions. Dysplasia identified in bone marrow samples may be found in a number of benign and congenital conditions including nutritional disorders, toxic exposures and infectious states, as well in MDS and acute leukemias (Jaffe et al. 2001). In highly dysplastic cases of MDS, or when the blast count is elevated, the diagnosis of MDS is relatively straightforward and is characterized by typical laboratory findings discussed earlier in this volume. Given the varied pathological and clinical picture of MDS, however, more sophisticated testing can be useful in establishing the diagnosis.

The key distinguishing feature of these syndromes is the clonal nature of the dysplasia. Initial work with X chromosome inactivation patterns in females, based on isozymes of the enzyme glucose-6-phosphate dehydrogenase, suggested that MDS was a clonal disorder (Prchal et al. 1978). This technique, however, is limited to females, and it can be difficult to interpret in cases with random imbalances in X inactivation (skewing) (Busque and Gilliland 1998). Amplification of a polymorphic short tandem repeat in the human androgen receptor gene (HUMARA) on the X chromosome with polymerase chain reaction techniques is an extension of this approach (Okamoto et al. 1998). The most widely available and standardized technique for identifying clonality in MDS is classic cytogenetic analysis. In fact, the World Health Organization (WHO) has included recurring cytogenetic abnormalities in the classification of several subtypes of MDS with distinct clinical presentations and natural histories as discussed below (Jaffe et al. 2001). Other techniques more suited for research rather than clinical application include the analysis of restriction fragment length polymorphisms, and mutated oncogenes or tumor suppressor genes, which have also confirmed the clonal nature of MDS (Weimar et al. 1994). Aberrant in vitro growth patterns of stem cells can be characteristic of MDS (Spitzer et al. 1979), yet this evaluation is restricted to laboratories with expertise in this technique and is not routinely available. Immunophenotyping protocols (Wells et al. 2003) and microarray techniques, including array comparative genomic hybridization (Walker et al. 2002) hold potential future clinical diagnostic and prognostic promise.

6.2.1 Cytogenetic Analysis

The value of cytogenetic analysis in predicting survival and risk of leukemic transformation during a patient’s clinical course has been well established (Jotterand and Parlier 1996; Morel et al. 1993; Sole et al. 2000; Toyama et al. 1993). Among the few independent variables identified that predict clinical outcomes in MDS, cytogenetic findings form the cornerstone of successful prognostic scoring systems (Table 6.1) (Greenberg et al. 1997). At the time of diagnosis, recurring chromosomal abnormalities are found in 40–70% of patients with primary MDS and in 95% of patients with therapy-related MDS (t-MDS) (Vallespi et al. 1998). The frequency of cytogenetic abnormalities increases with the severity of disease, as does the risk of leukemic transformation. Clonal chromosome abnormalities can be detected in marrow cells of 25% of patients with refractory anemia (RA), 10% of patients with refractory anemia with ringed sideroblasts (RARS), 50% of patients with refractory cytopenias with multilineage dysplasia (RCMD), 50–70% of patients with refractory anemia with excess blasts 1, 2 (RAEB-1,2), and 100% of patients with MDS with isolated del(5q) [5q–].

Most recurring cytogenetic abnormalities found in MDS are unbalanced, most commonly the result of the loss of a whole chromosome or a deletion of part of a chromosome, but unbalanced translocations and more complex derivative (rearranged) chromosomes