Advances in the diagnosis and classification of myelodysplastic syndromes

Robert P Hasserjian

Abstract

The diagnosis and classification of myelodysplastic syndromes (MDS) present unique challenges, particularly in the distinction from benign conditions that can cause cytopenia. The diagnostician must effectively incorporate information from several morphologic modalities (trephine biopsy, aspirate smear, and peripheral blood smear) as well as a myriad of ancillary testing results, such as flow cytometry, cytogenetics, and, increasingly, molecular genetic testing results. Our understanding of the pathogenesis of MDS has evolved rapidly in recent years, largely due to advances in molecular genetic technology and more complete characterization of genetic aberrations and gene expression patterns. The 2008 WHO Classification is currently being updated to incorporate this new information. In this review, the principles of bone marrow interpretation with respect to the diagnosis and classification of MDS in the current era will be reviewed, including accurate morphologic interpretation, use of flow cytometry and immunohistochemistry, appropriate use of cytogenetics, and the emerging role of molecular genetics.

Keywords bone marrow; myelodysplastic syndrome; myeloid; pathology

Introduction

Myelodysplastic syndromes (MDS) encompass a group of clonal haematopoietic stem cell neoplasms characterized by ineffective haematopoiesis. MDS manifests as morphologic dysplasia in haematopoietic elements and by peripheral cytopenias. Most MDS cases exhibit progressive disease with worsening cytopenias over time and often an increase in myeloblasts. The biologic course is highly variable, being prolonged and indolent in some patients and rapidly progressive with evolution to acute myeloid leukaemia (AML) in others. The main challenges facing the diagnostician are to distinguish MDS from neoplastic and non-neoplastic mimics and to accurately classify MDS once a diagnosis has been made. In recent years, our understanding of MDS biology and clinically relevant prognostic factors has increased: there are now multiple tools in the diagnostician's armamentarium to aid in correct diagnosis and classification. These tools include an important role for morphology as well as ancillary studies such as flow cytometry, cytogenetics, and molecular genetic analysis. This review will discuss the appropriate application of the various diagnostic testing modalities to correctly diagnose and classify MDS in adults; this review will not cover MDS in the paediatric population.

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Diagnosis of myelodysplastic syndrome: a minefield of mimickers

Clinical history

Some degree of cytopenia (anaemia, neutropenia, or thrombocytopenia below the normal threshold for each institution) is a prerequisite for the diagnosis of MDS. However, there are many non-MDS conditions that may cause cytopenia. Cytopenia is the most common indication for bone marrow biopsy and many elderly patients in whom a diagnosis of MDS is being considered have co-morbidities that can also be associated with cytopenia. The extent of screening prior to bone marrow biopsy varies among practitioners and it cannot necessarily be assumed that the haematologist has always taken a careful history and performed necessary laboratory testing to exclude secondary causes of anaemia or other cytopenias. Thus, the diagnostician must be aware of the myriad possible non-neoplastic causes of cytopenias and should be able to interrogate the clinical record to determine if these possibilities have been properly evaluated. Knowledge of the duration of cytopenia is also helpful, as many non-neoplastic causes of cytopenia are transient in nature. The diagnostician should be aware of the presence of any splenomegaly, which can itself cause cytopenia by sequestration and would be an unusual finding in MDS, and lymphadenopathy, which might suggest a lymphoma or lymphoid leukaemia. Finally, any history of prior cytotoxic chemotherapy or radiation therapy must be elicited to determine if MDS is therapy-related. Most cases of therapy-related MDS behave aggressively due to their high prevalence of adverse genetic features such as *TP53* mutation and complex karyotype. Therapy-related MDS may resemble any of the MDS subtypes discussed below and thus will not be discussed as a specific entity in this review. In these situations, it is prudent to provide the diagnosis of therapy-related MDS, but also give the specific WHO morphologic category.

Morphology

As mentioned above, morphology is a critical aspect of MDS diagnosis: excellent morphology is absolute prerequisite to ensure accurate diagnosis of all myeloid neoplasms. Evaluation of bone marrow morphology should include examination of a peripheral smear and a bone marrow aspirate smear (stained with May-Grunwald-Giemsa or Wright-Giemsa) as well as an adequate bone marrow trephine biopsy specimen, optimally at least 1.5 cm in length. The biopsy core(s) should be adequately fixed and should undergo gentle decalcification to preserve cellular morphology and antigenicity in case immunostains are required.[1] Thin sectioning of the trephine specimen (at 2–3 microns) optimizes morphologic interpretation.

The purpose of morphologic assessment in MDS is to accurately enumerate the relative proportion of haematopoietic cell types and to identify specific deviations from normal cytology that represent dysplasia, a hallmark of the disease. The most important cell to recognize and accurately enumerate is the myeloblast: a precise myeloblast percentage in both the blood and bone marrow aspirate smear is critical in separating MDS from AML and can also help distinguish MDS from reactive conditions, which generally do not show increased (≥5%) bone marrow blasts. Morphologic dysplastic features observed in MDS in peripheral blood and bone marrow are listed in Table 1 and

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Dysplastic features observed in MDS

Lineage	Peripheral blood	Bone marrow
Erythroid	Anisocytosis and poikilocytosis	Lobulated nuclei and nuclear budding
	Basophilic stippling	Megaloblastoid change
		Multinuclearity
		Vacuolated pronormoblasts
		Pyknotic nuclei
		Irregular hemoglobinization
		Ring sideroblasts
Myeloid	Pelger-Huët (bilobed) nuclear anomaly	Hypogranularity
	Unilobate nuclei	Myeloperoxidase deficiency
	Nuclear hypersegmentation	Pseudo—Chédiak-Higashi granules
	Ring-shaped nuclei	
	Hypogranularity	
Megakaryocytes	Large, vacuolated, or hypogranular platelets	Small mononuclear or binuclear megakaryocytes
		Micromegakaryocytes (mononucleated forms with a diameter of 7—10 μm)
		Large megakaryocytes with multiple small separated, rounded nuclei

(From references 2, 3.)

Table 1

typical dysplastic morphologic features are illustrated in Figure 1. The 2008 WHO Classification suggests that at least 10% of cells in a given lineage must show one or more of the listed features in Table 1 in order to consider that lineage to be dysplastic; depending on the number of lineages with ≥10% dysplastic cells, MDS cases may have single lineage or multilineage (bilineage or trilineage) dysplasia. However, just as many non-MDS conditions may cause cytopenia, significant dysplasia also may be observed in many conditions that are not MDS; examples are illustrated in Figure 1 and are listed below.

1) Drugs and toxins, especially recent (<6 months) cytotoxic chemotherapy and heavy alcohol intake
2) Metabolic deficiencies, particularly Vitamin B_{12}, folate, and copper
3) Stress erythropoiesis due to inherited haemoglobinopathies or acquired haemolytic anaemias
4) Systemic infections, especially HIV and hepatitis C
5) Autoimmune diseases
6) Concurrent neoplasms infiltrating the marrow, especially hairy cell leukaemia, plasma cell myeloma, and hepatosplenic T-cell lymphoma.

Because these conditions can cause significant secondary dysplasia, the current threshold of 10% to define a lineage as dysplastic may result in overcalling of dysplasia in non-MDS cases. Moreover, significant dysplasia in two lineages has been reported to occur in up to a quarter of normal individuals.[4] Some studies suggest that applying more restricted features of dysplasia (micromegakaryocytes, Pelger-Huet neutrophils, and neutrophil hypogranularity) and ignoring less specific findings, such as erythroid cytoplasmic vacuolization or irregular hemoglobinization, may improve on the specificity of morphologic dysplasia for MDS.[2,5,6] For the megakaryocyte lineage in particular, a higher threshold of 30% or 40% appears to provide greater specificity in identifying MDS, without significantly sacrificing sensitivity.[2,6]

Conversely, some patients may harbour persistent, unexplained cytopenia yet show no significant dysplasia or MDS-defining cytogenetic abnormalities (see below). These cases have been termed *idiopathic cytopenia of undetermined significance* (ICUS). Patients with ICUS should followed clinically but should not be diagnosed as MDS. A subset of ICUS patients will eventually be diagnosed with MDS on follow up.[7]

Immunohistochemistry and additional stains

Provided a good bone marrow aspirate and peripheral smear are obtained and reviewed, immunohistochemistry is usually not required to diagnose and classify MDS. However, in some situations, immunohistochemistry on the bone marrow core or a clot section may be helpful:

1) In fibrotic bone marrow, cells may be crushed and difficult to identify. In such cases, staining for lineage-specific markers (such as CD71/glycophorin/haemoglobin for erythroid cells, MPO/lysozyme/CD33 for myeloid cells and CD61/CD42b/Factor VIII for megakaryocytes) and CD34 can help identify cell types and quantify blasts. Myeloblasts in the vast majority of MDS cases are CD34 positive and this stain is preferred over CD117, which also stains promyelocytes, early erythroid elements and mast cells, rendering myeloblast enumeration difficult (Figure 2).
2) A stain for CD34 helps highlights the presence of clusters of blasts away from bone trabeculae (abnormal localization of immature precursors, ALIP), a phenomenon associated with an adverse prognosis in MDS.
3) Micromegakaryocytes, which are quite specific for MDS, may be difficult to distinguish from early erythroid cells or even plasma cells in bone marrow trephine sections. Staining with a megakaryocyte marker such as CD61, CD42b or CD31 can help reveal these small dysplastic megakaryocyte forms.
4) In some cases of lymphoma (which often mimic MDS by cytopenic presentation), the lymphoma cells may infiltrate

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