



EDUCATIONAL OBJECTIVE: Readers will include myelodysplastic syndromes in the differential diagnosis in patients who have unexplained infections, bleeding, or cytopenias

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Myelodysplastic syndromes: A practical approach to diagnosis and treatment

ABSTRACT

The myelodysplastic syndromes (MDS) are clonal bone marrow disorders that lead to underproduction of normal blood cells. The consequent cytopenias result in infections and bleeding complications. MDS transform to acute myeloid leukemia in one-third of patients. The number of diagnoses has exploded in the past decade as a result of increased recognition and understanding of the disease and the aging of the population. New therapies can extend life. MDS are now considered the most common form of leukemia, and in some cases deserve immediate intervention. This review describes common presentations of MDS, optimal diagnostic approaches, and therapies for lower- and higher-risk disease.

KEY POINTS

Multilineage cytopenia almost always suggests abnormal bone marrow function and can be the reason for referral to a hematologist-oncologist.

Factors that make MDS more difficult to manage and that worsen the prognosis are older age at diagnosis and comorbidities such as coronary artery disease, chronic obstructive pulmonary disease, and chronic kidney disease.

Patients with lower-risk disease can continue follow-up with their primary care provider once the treatment goals and plans are established.

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MYELODYSPLASTIC SYNDROMES (MDS) are a heterogeneous group of disorders of blood cell production in the bone marrow that can transform into acute myeloid leukemia (AML).^{1,2} They are diagnosed most often in the elderly.

Primary care physicians and geriatricians tend to be the first to identify the problem, as they recognize that cytopenias are not simply a normal consequence of aging.

MDS are considered to be cancers, akin to chronic leukemia or acute leukemia, with epidemiologic data tracked by national cancer registries and the US Centers for Disease Control and Prevention, under the auspices of the Surveillance, Epidemiology, and End Results (SEER) program.³

In this article, we briefly review the classification of MDS, current epidemiologic data, key diagnostic features, and current management options.

WHEN TO SUSPECT MDS

In many patients, MDS are asymptomatic and appear as an abnormality on a routine complete blood cell count (CBC) or as part of a workup for anemia. Symptoms develop as the bone marrow's ability to produce normal-functioning blood cells is more and more compromised. The range of symptoms depends on the bone marrow cell type affected.

Patients with MDS typically have some degree of anemia, often detected incidentally on a routine CBC, or they have symptoms stemming from anemia or thrombocytopenia, or have recurrent infections.

Subtypes of MDS have different pathologic and clinical presentations and different prognoses. They are often categorized as lower-risk or higher-risk, depending on the likelihood of transforming to AML. Patients with lower-risk MDS survive a median of 3 to 7 years. Higher-risk types are pathobiologically similar to AML in older adults, and patients either develop AML or die of complications of MDS, on average within 1.5 years.

Several classification schemes and prognostic models guide the selection of the most appropriate therapy.

Older age and comorbidities such as coronary artery disease, chronic obstructive pulmonary disease, and chronic kidney disease make MDS more difficult to manage and worsen the prognosis.⁴

■ MOST PATIENTS ARE OLDER

Only since 2001, when MDS became reportable to SEER,^{3,5} has the epidemiology of MDS been reported in the United States.

MDS are currently diagnosed in an estimated 3.4 per 100,000 US citizens yearly.

The incidence rate increased from 3.28 per 100,000 per year in 2001 to 3.56 per 100,000 in 2004.⁵ The increase has been attributed to enhanced awareness of the disease and to the aging of the population, with the number of people age 65 or older in the United States expected to double from the year 2000 to 2030. Another factor is that effective therapies are now available, possibly making hematologists and oncologists more likely to pursue the diagnosis.

These numbers translate to 10,000 to 15,000 new cases annually, and given the life expectancy of patients affected by this disease (and the life-extending treatments for it), an estimated 30,000 to 60,000 Americans living with MDS.^{6,7}

Even though MDS can occur at any age, most patients are older. The median age at diagnosis is 71 years,^{3,5,8} and 72% of patients are age 70 or older.³ The prevalence increases with age, to a rate of 36 per 100,000 in those age 80 and older.⁹ However, in areas of East Asia, it occurs at ages almost 2 decades younger than in the rest of the world.⁵

MDS are more common in men than in

women and in whites than in blacks. Smoking appears to increase the risk, but alcohol consumption does not.¹⁰

About 10% of cases of MDS are secondary, most often due to radiation treatment or chemotherapy (particularly with alkylating agents and topoisomerase inhibitors) for cancer. The time from treatment of a primary malignancy (most often prostate, breast, bladder, lung, or non-Hodgkin lymphoma) to the development of MDS is about 5 years.⁵ A small number of cases are due to occupational exposure to radiation or benzene or other organic solvents, as might occur in the rubber industry (see below). Secondary MDS have a worse prognosis than primary (de novo) MDS.

■ GENETIC AND ENVIRONMENTAL FACTORS

The cause of de novo MDS is not known. Genetic and environmental factors probably both play a role. The lower median age at diagnosis in Eastern countries such as Japan than in the United States suggests that environmental factors¹¹ such as smoking, ionizing radiation, and benzene exposure play a role.^{12,13} Some epidemiologic evidence suggests a higher incidence of MDS after exposure to solvents, hair dyes, and pesticides.¹³

Congenital conditions such as Down syndrome, Fanconi anemia, and Bloom syndrome are associated with MDS. Those affected usually present at an earlier age,¹³ suggesting a “multiple-hit” mechanism of cancer development with genetic and environmental factors. MDS rarely run in families.

■ SYMPTOMS ARE OFTEN NONSPECIFIC

Symptoms of MDS are often vague and nonspecific, and the diagnosis is often made during a workup for anemia, thrombocytopenia, or neutropenia discovered on a CBC. If present, signs and symptoms depend on the blood and bone marrow cell types that are affected.

When erythrocytes are affected (the most common situation), patients present with signs of anemia, including pallor, pale conjunctiva, tachycardia, hypotension, fatigue, headache, and exercise intolerance, or with signs and symptoms of a worsening underlying condi-

Primary care physicians and geriatricians tend to be the first to identify MDS

tion such as angina pectoris, heart failure, or emphysema.

When platelets or neutrophils are affected. Fewer than 20% of patients present with symptoms of isolated thrombocytopenia such as minor bleeding (eg, mucosal bleeding, petechiae, easy bruising, epistaxis) or major bleeding (eg, gastrointestinal bleeding, intracranial hemorrhage) or of isolated neutropenia (eg, fatigue, frequent bacterial infections of different organs systems).

Splenomegaly and lymphadenopathy are uncommon in MDS and, if detected, should raise suspicion of a myeloproliferative or lymphoproliferative neoplasm.

LABORATORY TESTS NEEDED

Complete blood cell count

Once the common causes of patient's symptoms are evaluated, a CBC is needed to look for a hematologic cause. If a patient is ultimately determined to have MDS, anemia is the most common finding on the CBC: about 80% of patients with MDS are anemic at presentation.⁶

Anemia associated with MDS can be microcytic, normocytic, or, most commonly, macrocytic.¹⁴ Thrombocytopenia and neutropenia can be solitary or associated with anemia, and they are seen in about 40% of patients at the time of diagnosis.⁶ As the disease progresses, the degree of cytopenia worsens and, in most cases, preserved cell lineages are eventually affected.

Once cytopenia is discovered, a workup for the cause is needed. We emphasize a workup first for anemia, as it is the most common form of cytopenia in MDS. A workup for isolated thrombocytopenia or neutropenia usually requires a bone marrow examination earlier in the course, and we will discuss it only briefly here. Multilineage cytopenia almost always suggests abnormal bone marrow function and can be the basis for referral to a hematologist or oncologist.

Evaluation of anemia

If anemia is detected, it is reasonable to look for nonhematologic causes such as gastrointestinal bleeding, a cardiac cause, or a nutritional deficiency.

TABLE 1

Common causes of anemia based on red blood cell morphology

Microcytic anemia

Iron deficiency
Thalassemia
Lead toxicity

Macrocytic anemia

Low vitamin B₁₂, folate, copper levels
History of alcohol abuse
Medications
Hemolytic anemias
Myelodysplastic syndromes

Normocytic anemia

Chronic kidney disease
Thyroid disorders
Human immunodeficiency virus infection,
other viral infections
Rheumatologic disorders

Anemia has a variety of possible hematologic causes, as shown in a study in the United States.¹⁵ When blood samples were collected from more than 2,000 people age 65 and older, 10.6% were found to have anemia, categorized as follows:

- Nutrient-deficiency anemia, related to low levels of vitamin B₁₂, folate, or more commonly iron
- Anemia of chronic inflammation (formerly anemia of chronic disease, associated with a major medical disorder)
- Unexplained anemia (of those with unexplained anemia, 17.4% had blood findings compatible with MDS).¹⁵

Depending on the red blood cell morphology (TABLE 1), tests that are reasonable for the workup of anemia before MDS are suspected include the following:

- Tests for nutrient deficiencies such as iron, vitamin B₁₂, and folate levels. Subsequent tests can include assessment for copper deficiencies. Vitamin B₁₂ and copper deficiency can mimic MDS.
- Fecal occult blood testing, and, if positive, further evaluation for a source of gastrointestinal bleeding.
- Liver function tests, renal function tests,

Cytopenias are not simply a normal consequence of aging

TABLE 2

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and tests for endocrine disorders, such as thyroid function tests.

- Review of drugs that can cause megaloblastoid erythropoiesis, such as methotrexate (Trexall), valproic acid (Depakote), phenytoin (Dilantin), phenobarbital (Luminal), sulfasalazine (Sulfazine), and zidovudine (Retrovir).
- Assessment of the responsiveness of the bone marrow to anemia, via a reticulocyte count or an erythropoietin level, or both, prior to any blood transfusion.
- Screening for relevant infections, including human immunodeficiency virus (HIV), hepatitis, or, in rare cases, parvovirus.
- Screening for lifestyle factors that may re-

sult in bone marrow suppression, such as excessive alcohol intake.

Evaluation of other cytopenias

In cases of isolated thrombocytopenia or combined bicytopenia (eg, anemia and thrombocytopenia), abdominal ultrasonography should be done to evaluate for splenomegaly.

Blood tests to evaluate for immune-mediated cytopenias, including idiopathic thrombocytopenic purpura and hemolytic anemia, include the direct and indirect Coombs antiglobulin tests, the lactate dehydrogenase level, the reticulocyte count, and the haptoglobin level. Other immune-mediated causes of cytopenia include connective tissue disorders

TABLE 3

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and vasculitides, and an antinuclear antibody titer and rheumatoid factor level can also be considered.

Referral if tests are negative

If all these tests are negative, the next step is referral to a hematologist-oncologist for further workup, which may include a review of the peripheral blood smear; bone marrow aspiration and biopsy for evaluation of iron stores and bone marrow cellularity; and specialized tests such as assessment of antiplatelet antibodies, protein electrophoresis, or fluorescence in situ hybridization to evaluate for specific clonal disorders. The purpose of bone marrow aspiration and biopsy in MDS is to evaluate the morphology of the bone marrow and the patient's cytogenetic profile. Each has its prognostic and therapeutic implications.

■ SCORING SYSTEMS FOR MDS, RATHER THAN STAGING SYSTEMS

The purpose of classification systems for any medical condition is to uniformly evaluate and group patients with a disease subtype to compare patient populations similarly

throughout the world, to predict prognosis, and to dictate therapeutic directions.

MDS have two main classification systems, the FAB (French-American-British) and the WHO (World Health Organization). Revised in 2008,¹⁶ the WHO classification (TABLE 2)¹⁷ is widely accepted because it incorporates morphologic and cytogenetic factors and correlates with prognosis.¹⁸ The categories are distinguished by specific characteristics of peripheral blood and bone marrow.

Unlike many other cancers, MDS are not “staged.” Rather, prognostic systems have been devised to predict the risk of transformation to AML and to predict overall survival. These systems are based on:

- The number of myeloblasts in the bone marrow (the higher the count, the worse the prognosis)
- The number or degree of cytopenias
- Cytogenetic abnormalities (acquired genetic abnormalities in the neoplastic clone), found in about half of patients with MDS.¹⁹

The most widely used prognostic systems are the International Prognostic Scoring System (TABLE 3)² and the WPSS (WHO Classi-

Older age at diagnosis and comorbidities make management more difficult and worsen the prognosis

fication-based Prognostic Scoring System¹). The latter system incorporates transfusion burden.

SUPPORTIVE CARE

Supportive care includes transfusion of blood products to minimize complications of cytopenias and to improve quality of life, as well as antibiotics to treat active infections.

Transfusions

Almost all patients with MDS need red cell transfusions at some point, while fewer need platelets. The frequency of transfusion depends on the extent of the disease and on comorbidities.

Red blood cells typically are given when the hemoglobin level falls below 8.5 g/dL, and platelets are given when the platelet count is below $100 \times 10^9/L$, in the absence of symptoms. Patients with symptomatic anemia should receive transfusion to relieve their symptoms. Some patients need transfusions occasionally, while others are transfusion-dependent.

Iron chelation

Blood product transfusions can lead to iron overload, particularly with a lifetime administration of more than 20 units, or with a year of continuous transfusions, and this is associated with diminished survival.²⁰

However, considering the short survival of patients with MDS, the benefit of iron chelation is debatable. This intervention should be reserved for patients with lower-risk disease who are expected to survive more than 1 year and who have received more than 25 units of packed red blood cells.²¹

Antibiotics

Neutropenia is defined as an absolute neutrophil count less than $1.5 \times 10^9/L$. The risk of infection, particularly bacterial infection, is significantly increased when the neutrophil count is below $0.5 \times 10^9/L$. Fever (temperature $> 100.4^\circ F$ or $38.0^\circ C$) in neutropenic patients is an emergency, requiring hospitalization and immediate initiation of broad-spectrum antibiotics along with a workup for the cause of the fever.²² Prophylactic antibiotics have no proven role in MDS patients with neutropenia.

TREATMENT OF LOWER-RISK DISEASE

Erythropoiesis-stimulating agents

Once a patient starts to require red blood cell transfusions, an erythropoiesis-stimulating agent (EPA) can be considered.^{23,24} These include recombinant agents such as erythropoietin (Procrit) and darbepoetin alfa (Aranesp).

Response is measured as an improvement in hemoglobin or as independence from transfusions in those previously dependent on them. Patients most likely to respond are those whose pretransfusion erythropoietin level is below 100 IU/L and who have minimal transfusion needs.^{25,26} Addition of a colony-stimulating factor can be considered for patients with neutropenia. On average, about 40% of patients ultimately respond to an EPA, but those who respond eventually develop resistance to the agent. Retrospective data indicate that use of EPAs may improve survival in MDS.^{23,24}

The recommended threshold hemoglobin level for starting an EPA is less than 10 g/dL. Patients need to be monitored with a CBC every time they receive treatment. The agent should be stopped once the hemoglobin level reaches 12 g/dL. A number of studies have shown lower survival rates when ESAs are used in nonhematologic malignancies, particularly if the malignancy is advanced and when the ESA is used to achieve a goal hemoglobin above 12 g/dL. There are no data to suggest a higher death rate in patients with hematologic malignancies who take ESAs. The use of ESAs in MDS patients should be judicious, however, and titrated to a goal hemoglobin level no higher than 12 g/dL.²⁷

Other treatments

If ESA treatment is ineffective, other treatments may be considered, usually initiated by a hematologist or medical oncologist.

Immunosuppressive therapy with antithymocyte globulin (Thymoglobulin)²⁸ is an option for patients with hypocellular or immune-mediated MDS. This treatment may decrease the need for transfusion and may improve the blood count.

Lenalidomide (Revlimid) for MDS with isolated chromosome 5q deletion²⁹ can decrease the need for blood transfusion in approximately two-thirds of these patients.

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Azacitidine (Vidaza) or decitabine (Dacogen), in patients with more advanced subtypes of MDS (eg, those with excess blasts) or with pancytopenia unresponsive to other therapies, can induce hematologic improvement and decrease transfusion dependence, as well as prolong survival.

Stem cell transplantation, for patients with more advanced subtypes of MDS and who have an appropriately matched donor, has the potential of being curative.

Experimental treatments are available in clinical trials.

■ TREATMENT OF HIGHER-RISK DISEASE

About 25% of patients with newly diagnosed MDS and 15% to 20% of patients with established MDS have higher-risk disease.³⁰ These patients should almost always be followed by a hematologist or medical oncologist, with therapy initiated immediately, regardless of blood counts, given the high likelihood of transformation to AML or death within 1.5 years.

The treatment options for higher-risk disease include:

- Methyltransferase inhibitors such as azacitidine and decitabine^{31–34}
- Cytotoxic chemotherapy (similar to treatment of acute myeloid leukemia)
- Bone marrow-hematopoietic stem cell transplantation^{35,36}
- Experimental treatments in clinical trials.

As mentioned earlier, outside of transplantation, only azacitidine has been shown to improve overall survival (with a doubling of survival at 2 years, to 50%), and no drug therapy is curative. Managing patient expectations for treatment outcome is thus crucial in higher-risk disease, and ongoing assessments of quality of life, both on or off therapy, should be considered obligatory.

Stem cell transplantation cures MDS

MDS are complex and heterogeneous, so treatment options range from supportive care

to chemotherapy and allogeneic stem cell transplantation.⁶ The choice depends on the severity of disease, ie, lower-risk or higher-risk (**TABLE 3**), as well as on the prognosis, the availability of therapeutic options, and the patient's expectations.

Hematopoietic stem cell transplantation is the only curative treatment for MDS. However, it is performed in fewer than 5% of patients,³⁰ usually younger patients with few comorbidities, because the rate of transplant-related death is high. Therefore, most treatments are palliative, aimed at improving the quality of life and prolonging survival.

The balance between risks and benefits of these treatments must be justifiable.³⁰ Further, patients who have no symptoms or who have lower-risk disease need no treatment and may not for years. However, they do need close follow-up, because their symptoms will worsen and will eventually require treatment.

■ TAKE-HOME POINTS

- Myelodysplastic syndromes are more prevalent than previously realized. Mainly a disease of older adults, they should be suspected in any patient with unexplained cytopenia.
- Life expectancy at the time of diagnosis depends on the types of cells affected.
- Supportive and disease-altering options are available.
- Prompt referral to a hematologist or oncologist is important for confirmation of the diagnosis and initiation of an appropriate treatment plan. Patients with lower-risk disease can continue follow-up with their primary care provider once treatment goals and plans are established.

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Symptoms depend on which blood and marrow cell types are affected

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