The diagnosis of MDS may be a challenge, because sometimes subtle clinical and pathologic features must be distinguished and precise diagnostic categorization requires a hematopathologist knowledgeable in the latest classification scheme. Nonetheless, it is important that the internist and primary care physician be sufficiently familiar with MDS to expedite referral to a hematologist, both because many new therapies are now available to improve hematopoietic function and the judicious use of supportive care can improve the patient's quality of life.

EPIDEMIOLOGY

Idiopathic MDS is a disease of the elderly; the mean age at onset is older than 70 years. There is a slight male preponderance. MDS is a relatively common form of bone marrow failure, with reported incidence rates of 35 to >100 per million persons in the general population and 120 to >500 per million in the older adult. MDS is rare in children, but monocytic leukemia can be seen. Secondary or therapy-related MDS is not age related. Rates of MDS have increased over time, due to better recognition of the syndrome by physicians and an aging population.

ETIOLOGY AND PATHOPHYSIOLOGY

MDS is associated with environmental exposures such as radiation and benzene; other risk factors have been reported inconsistently. Secondary MDS occurs as a late toxicity of cancer treatment, usually a combination of radiation and the radiomimetic alkylating agents such as busulfan, nitrosourea, or procarbazine (with a latent period of 5–7 years) or the DNA topoisomerase inhibitors (2-year latency). Acquired aplastic anemia, Fanconi anemia, and other constitutional marrow failure diseases can evolve into MDS. However, the typical MDS patient does not have a suggestive environmental exposure history or a preceding hematologic disease. MDS is a disease of aging, suggesting random cumulative intrinsic and environmental damage to marrow cells.

MDS is a clonal hematopoietic stem cell disorder characterized by disordered cell proliferation and impaired differentiation, resulting in cytopenias and risk of progression to leukemia. Both chromosomal and genetic instability have been implicated, and both are likely aging-related. Cytogenetic abnormalities are found in approximately one-half of patients, and some of the same specific lesions are also seen in frank leukemia; aneuploidy (chromosome loss or gain) is more frequent than translocations. More sensitive assays, such as comparative genomic hybridization and single nucleotide polymorphism arrays, reveal chromosomal abnormalities in a large proportion of patients with normal conventional cytogenetics. Accelerated telomere attrition may destabilize the genome in marrow failure and predispose to acquisition of chromosomal lesions. Cytogenetic abnormalities are not random (loss of all or part of 5, 7, and 20, trisomy of 8) and may be related to etiology (11q23 following topoisomerase II inhibitors). The type and number of cytogenetic abnormalities strongly correlate with the probability of leukemic transformation and survival.

Genomics has illuminated the role of point mutations in the pathophysiology of MDS. Recurrent somatic mutations, acquired in the abnormal marrow cells and absent in the germline, have been identified in almost 100 genes. Many of the same genes are also mutated in AML without MDS, whereas others are distinctive in subtypes of MDS. A prominent example of the latter is the discovery of mutations in genes of the RNA splicing machinery, especially *SF3B1*, which strongly associate with sideroblastic anemia. Some mutations correlate with prognosis: spliceosome defects with favorable outcome, and mutations in *EZH2, TP53, RUNX1*, and *ASXL1* with poor outcome. Mutations and cytogenetic abnormalities are not independent: *TP53* mutations associate with complex cytogenetic abnormalities and *TET2* mutations with normal cytogenetics. Correlation and exclusion in the pattern of mutations indicate a functional genomic architecture. Analysis of deep sequencing results in patients whose MDS evolved to AML has shown evidence of clonal succession, with founder clones acquiring further mutations that allow clonal dominance. Furthermore, the prevalence of abnormal cells by morphology underestimates bone marrow involvement by MDS clones, as cells normal in appearance are apparently derived from the abnormal clones. Both presenting and evolving hematologic manifestations result from the accumulation of multiple genetic lesions: loss of tumor-suppressor genes, activating oncogene mutations, epigenetic pathways that affect mRNA processing and methylation status, or other harmful alterations. Pathophysiology has been linked to mutations and chromosome abnormalities in some specific MDS syndromes. The 5q– deletion leads to heterozygous loss of a ribosomal protein gene that is also mutant in Diamond-Blackfan anemia, and both are characterized by deficient erythropoiesis. An immune pathophysiology may underlie trisomy 8 MDS, in which patients often experience improved blood counts after immunosuppressive therapy; there is T cell activity directed to hematopoietic progenitors, which the cytogenetically aberrant clone resists. However, in general for MDS, the role of the immune system and its cells and cytokines; the role of the hematopoietic stem cell niche, the microenvironment, and cell-cell interactions; the fate of normal cells in the Darwinian competitive environment of the dysplastic marrow; and how mutant cells produce marrow failure in MDS are not well understood.

CLINICAL FEATURES

Anemia dominates the early course. Most symptomatic patients complain of the gradual onset of fatigue and weakness, dyspnea, and pallor, but at least one-half the patients are asymptomatic, and their MDS is discovered only incidentally on routine blood counts. Previous chemotherapy or radiation exposure is an important historic fact. Fever and weight loss should point to a myeloproliferative rather than myelodysplastic process. MDS in childhood is rare and, when diagnosed, increases the likelihood of an underlying genetic disease. Children with Down syndrome are susceptible to MDS, and a family history may indicate a hereditary form of sideroblastic anemia, Fanconi anemia, or a telomeropathy. Inherited *GATA2* mutations, as in the MonoMAC syndrome (with increased susceptibility to viral, mycobacteria, and fungal infections, as well as deficient numbers of monocytes, natural killer cells, and B lymphocytes), also cause MDS in young patients.

The physical examination is remarkable for signs of anemia; approximately 20% of patients have splenomegaly. Some unusual skin lesions, including Sweet syndrome (febrile neutrophilic dermatosis), occur with MDS. Accompanying autoimmune syndromes are not infrequent. In the younger patient, stereotypical anomalies point to a constitutional syndrome (short stature, abnormal thumbs in Fanconi anemia; early graying in the telomeropathies; cutaneous warts in *GATA2* deficiency).

LABORATORY STUDIES

Blood Anemia is present in most cases, either alone or as part of bi- or pancytopenia; isolated neutropenia or thrombocytopenia is more unusual. Macrocytosis is common, and the smear may be dimorphic with a distinctive population of large red blood cells. Platelets are also large and lack granules. In functional studies, they may show marked abnormalities, and patients may have bleeding symptoms despite seemingly adequate numbers. Neutrophils are hypogranulated; have hyposegmented, ringed, or abnormally segmented nuclei; contain Döhle bodies; and may be functionally deficient. Circulating myeloblasts usually correlate with marrow blast numbers, and their quantity is important for classification and prognosis. The total white blood cell count (WBC) is usually normal or low, except in chronic myelomonocytic leukemia. As in aplastic anemia, MDS can be associated with a clonal population of PNH cells. Genetic testing is commercially available for constitutional syndromes.

Bone Marrow The bone marrow is usually normal or hypercellular, but in about 20% of cases, it is sufficiently hypocellular to be confused with aplasia. No single characteristic feature of marrow morphology distinguishes MDS, but the following are commonly observed: dyserythropoietic changes (especially nuclear abnormalities) and ringed sideroblasts in the erythroid lineage; hypogranulation and hyposegmentation in granulocytic precursors, with an increase in myeloblasts; and megakaryocytes showing reduced numbers of or disorganized