ET can also evolve into PMF, but whether this is a feature of ET or represents PMF presenting initially with isolated thrombocytosis is unknown.

TREATMENT ESSENTIAL THROMBOCYTOSIS

Survival of patients with ET is not different than for the general population. An elevated platelet count in an asymptomatic patient without cardiovascular risk factors requires no therapy. Indeed, before any therapy is initiated in a patient with thrombocytosis, the cause of symptoms must be clearly identified as due to the elevated platelet count. When the platelet count rises above 1×10^6/μL, a substantial quantity of high-molecular-weight von Willebrand multimers are removed from the circulation and destroyed by the enlarged platelet mass, resulting in an acquired form of von Willebrand's disease. This can be identified by a reduction in ristocetin cofactor activity. In this situation, aspirin could promote hemorrhage. Bleeding in this situation usually responds to ε-aminocaproic acid, which can be given prophylactically before and after elective surgery. Plateletpheresis is at best a temporary and inefficient remedy that is rarely required. Importantly, ET patients treated with ^{32}P or alkylating agents are at risk of developing acute leukemia without any proof of benefit; combining either therapy with hydroxyurea increases this risk. If platelet reduction is deemed necessary on the basis of symptoms refractory to salicylates alone, pegylated IFN-α, the quinazoline derivative, anagrelide, or hydroxyurea can be used to reduce the platelet count, but none of these is uniformly effective or without significant side effects. Hydroxyurea and aspirin are more effective than anagrelide and aspirin for prevention of TIAs but not more effective for the prevention of other types of arterial thrombosis and are actually less effective for venous thrombosis. The effectiveness of hydroxyurea in preventing TIAs is because it is an NO donor. Normalizing the platelet count also does not prevent either arterial or venous thrombosis. The risk of gastrointestinal bleeding is also higher when aspirin is combined with anagrelide.

As more clinical experience is acquired, ET appears more benign than previously thought. Evolution to acute leukemia is more likely to be a consequence of therapy than of the disease itself. In managing patients with thrombocytosis, the physician's first obligation is to do no harm.

132 Acute Myeloid Leukemia

Guido Marcucci, Clara D. Bloomfield

INCIDENCE

Acute myeloid leukemia (AML) is a neoplastic disease characterized by infiltration of the blood, bone marrow, and other tissues by proliferative, clonal undifferentiated cells of the hematopoietic system. These leukemias comprise a spectrum of malignancies that, untreated, range from rapidly fatal to slowly growing. In 2013, the estimated number of new AML cases in the United States was 14,590. The incidence of AML is ~3.5 per 100,000 people per year, and the age-adjusted incidence is higher in men than in women (4.5 vs 3.1). AML incidence increases with age; it is 1.7 in individuals age <65 years and 15.9 in those age >65 years. The median age at diagnosis is 67 years.

ETIOLOGY

Heredity, radiation, chemical and other occupational exposures, and drugs have been implicated in the development of AML. No direct evidence suggests a viral etiology.

Heredity Certain syndromes with somatic cell chromosome aneuploidy, such as trisomy 21 noted in Down syndrome, are associated with an increased incidence of AML. Inherited diseases with defective DNA repair, e.g., Fanconi anemia, Bloom syndrome, and ataxia-telangiectasia, are also associated with AML. Congenital neutropenia (Kostmann syndrome) is a disease with mutations in the genes encoding the granulocyte colony-stimulating factor (G-CSF) receptor and, often, neutrophil elastase that may evolve into AML. Germline mutations of CCAAT/enhancer-binding protein α (*CEBPA*), runt-related transcription factor 1 (*RUNX1*), and tumor protein p53 (*TP53*) have also been associated with a higher predisposition to AML in some series.

Radiation High-dose radiation, like that experienced by survivors of the atomic bombs in Japan or nuclear reactor accidents, increases the risk of myeloid leukemias that peaks 5–7 years after exposure. Therapeutic radiation alone seems to add little risk of AML but can increase the risk in people also exposed to alkylating agents.

Chemical and Other Exposures Exposure to benzene, a solvent used in the chemical, plastic, rubber, and pharmaceutical industries, is associated with an increased incidence of AML. Smoking and exposure to petroleum products, paint, embalming fluids, ethylene oxide, herbicides, and pesticides have also been associated with an increased risk of AML.

Drugs Anticancer drugs are the leading cause of therapy-associated AML. Alkylating agent–associated leukemias occur on average 4–6 years after exposure, and affected individuals have aberrations in chromosomes 5 and 7. Topoisomerase II inhibitor–associated leukemias occur 1–3 years after exposure, and affected individuals often have aberrations involving chromosome 11q23. Newer agents for treatment of other hematopoietic malignancies and solid tumors are also under scrutiny for increased risk of AML. Chloramphenicol, phenylbutazone, and, less commonly, chloroquine and methoxypsoralen can result in bone marrow failure that may evolve into AML.

CLASSIFICATION

The current categorization of AML uses the World Health Organization (WHO) classification (Table 132-1), which includes different biologically distinct groups based on clinical features and cytogenetic and molecular abnormalities in addition to morphology. In contrast to the previously used French-American-British (FAB) schema, the WHO classification places limited reliance on cytochemistry. A major difference between the WHO and the FAB systems is the blast cutoff for a diagnosis of AML as opposed to myelodysplastic syndrome (MDS); it is 20% in the WHO classification and 30% in the FAB. However, within the WHO classification, specific chromosomal rearrangements, i.e., t(8;21)(q22;q22), inv(16)(p13.1q22), t(16;16)(p13.1;q22), and t(15;17)(q22;q12), define AML even with <20% blasts.

Immunophenotype and Relevance to the WHO Classification The immunophenotype of human leukemia cells can be studied by multiparameter flow cytometry after the cells are labeled with monoclonal antibodies to cell-surface antigens. This can be important for separating AML from acute lymphoblastic leukemia (ALL) and identifying some subtypes of AML. For example, AML with minimal differentiation that is characterized by immature morphology and no lineage-specific cytochemical reactions may be diagnosed by flow-cytometric demonstration of the myeloid-specific antigens cluster designation (CD) 13 and/or 117. Similarly, acute megakaryoblastic leukemia can often be diagnosed only by expression of the platelet-specific antigens CD41 and/or CD61. Although flow cytometry is useful, widely used, and in some cases essential for the diagnosis of AML, it is supportive only in establishing the different subtypes of AML through the WHO classification.

Clinical Features and Relevance to the WHO Classification The WHO classification also considers clinical features in subdividing AML. For example, it identifies therapy-related AML as a separate entity that develops following prior therapy (e.g., alkylating agents, topoisomerase II inhibitors, ionizing radiation). It also identifies AML with