dose-dependent marrow suppression, although its more ominous complication is the rare idiosyncratic reaction that gives rise to marrow aplasia. Drugs that are most commonly associated with neutropenia include clozapine, sulfasalazine, ticlopidine, and the thionamide antithyroid agents. Most drug-induced neutropenias respond rapidly to discontinuation of the offending agent. The administration of G-CSF speeds recovery.

Autoimmune neutropenia may be seen as a primary disease or as a secondary manifestation of systemic autoimmune disease or lymphoproliferative disease. Primary autoimmune neutropenia is a disorder of infants and young children that resolves spontaneously in more than 90% of patients within 2 years. Secondary autoimmune neutropenia is a common accompaniment to systemic lupus erythematosus. Although not usually clinically severe, neutropenia is often a marker of disease activity.

Neutropenia in rheumatoid arthritis is associated with splenomegaly (i.e., Felty's syndrome) and is part of the spectrum of large granular lymphocyte (LGL) leukemia. LGL leukemia is a clonal expansion of suppressor T cells. Patients who develop LGL in association with rheumatoid arthritis share a common HLA-DR4 haplotype with patients with Felty's syndrome, suggesting that they are in a common spectrum of disease. LGL is also a relatively common cause of acquired neutropenia in elderly patients in the absence of rheumatoid arthritis. Recent data have linked LGL to mutations in the *STAT3* gene.

Laboratory Evaluation

Unless the diagnosis of benign or cyclic neutropenia is likely, the evaluation of the patient with neutropenia should include stopping all potentially offending drugs and performing serologic studies to rule out collagen vascular disease. Unlike the evaluation of patients with leukocytosis, bone marrow examination is indicated early for those with neutropenia and is frequently diagnostic. Neutropenia often reflects primary hematologic disease, and bone marrow examination enables the physician to diagnose marrow failure syndromes, leukemia, and myelodysplasia. In the absence of bone marrow failure, other causes of neutropenia may give a characteristic bone marrow picture. All patients undergoing bone marrow examination should have cytogenetic studies performed to aid in the diagnosis of myelodysplasia.

Sudden onset of agranulocytosis that does not affect platelets or erythrocytes typically is attributable to drug or toxin exposure. Bone marrow examination is rarely necessary. If performed, drug-induced neutropenia produces a characteristic maturation arrest of myeloid cells. Rather than actual inhibition of neutrophil maturation, this feature reflects the immune destruction of myeloid precursors that leaves only the earliest cells behind.

Treatment

The therapeutic approach to patients with neutropenia depends on the degree of depression of the neutrophil count. Neutrophil counts between 1000 and 1500 cells/μL are not usually associated with significant impairment of the host response to bacterial infection and require no intervention beyond that demanded for diagnosis and treatment of the underlying cause. Patients with neutrophil counts between 500 and 1000 cells/μL should be alerted to their slightly increased risk of infection, although serious problems are rarely encountered in patients with functional neutrophils and counts higher than 500 cells/μL.

Patients with neutrophil counts lower than 500 cells/μL are at significant risk for infection. They should be instructed to notify the physician at the first sign of infection or fever, and they must be managed aggressively with intravenous antibiotics regardless of the documentation of a source or infecting organism. Patients with a significantly depressed neutrophil count may exhibit few signs of infection because much of the inflammatory response at the site of infection is generated by the neutrophils themselves.

In patients with severe immune-mediated neutropenia, steroids and intravenous immunoglobulin may be helpful in elevating the neutrophil count and in preventing infectious complications. G-CSF may increase the peripheral white cell count and may help resolve infections in neutropenia induced by drugs, including chemotherapy. It has been efficacious for some patients with immune-mediated neutropenia and those with myelodysplasia.

For a deeper discussion of these topics, please see Chapter 167, "Leukocytosis and Leukopenia" in Goldman-Cecil Medicine, *25th Edition.*

PROSPECTUS FOR THE FUTURE

Significant progress has been made in elucidating the molecular pathogenesis of severe congenital neutropenia and cyclic neutropenia. Compounds that modulate the unfolded protein response may play a role in the treatment of these disorders. Other studies of the molecular basis of myeloid differentiation are establishing the importance of transcription factor function in neutrophil maturation and are providing insights into the pathogenesis of leukemia and myelodysplasia. Their findings may delineate pathways with entry points for therapeutic intervention in myeloid malignancies.

SUGGESTED READINGS

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