along with systemic glucocorticoids. Cyclosporine can be efficacious for patients with chronic idiopathic or chronic autoimmune urticaria that is severe and poorly responsive to other modalities and/or where a glucocorticoid requirement is excessive. For chronic urticaria induced by autoantibody activation of mast cells and basophils or cold urticaria, monoclonal anti-IgE antibodies such as omalizumab may be considered.

The therapy of inborn C1INH deficiency has been simplified by the finding that attenuated androgens correct the biochemical defect and afford prophylactic protection; their efficacy is attributed to production by the normal gene of an amount of functional C1INH sufficient to control the spontaneous activation of C1. The antifibrinolytic agent ε-aminocaproic acid may be used for preoperative prophylaxis but is contraindicated in patients with thrombotic tendencies or ischemia due to arterial atherosclerosis. Infusion of isolated C1INH protein may be used for prophylaxis or treatment of an acute attack; a bradykinin 2 receptor antagonist and ecallantide, a kallikrein inhibitor, which are administered SC, are each being assessed for amelioration of attacks. Treatment of the underlying hematologic malignancy is indicated for acquired C1INH deficiency.

SYSTEMIC MASTOCYTOSIS

DEFINITION

Systemic mastocytosis is defined by a clonal expansion of mast cells that in most instances is indolent and nonmalignant. The mast cell expansion is generally recognized only in bone marrow and in the normal peripheral distribution sites of the cells, such as skin, gastrointestinal mucosa, liver, and spleen. Mastocytosis occurs at any age and has a slight preponderance in males. The prevalence of systemic mastocytosis is not known, a familial occurrence is rare, and atopy is not increased.

CLASSIFICATION AND PATHOPHYSIOLOGY

A consensus classification for mastocytosis recognizes cutaneous mastocytosis with variants and four systemic forms (Table 376-2). Cutaneous mastocytosis is the most common diagnosis in children, whereas the form designated as *indolent systemic mastocytosis* (ISM) accounts for the majority of adult patients; it implies that there is no evidence of an associated hematologic disorder, liver disease, or lymphadenopathy and is not known to alter life expectancy. In *systemic mastocytosis associated with clonal hematologic non–mast cell lineage disease* (SM-AHNMD), the prognosis is determined by the nature of the associated disorder, which can range from dysmyelopoiesis to leukemia. In *aggressive systemic mastocytosis* (ASM), mast cell infiltration/proliferation in multiple organs such as liver, spleen, gut, and/or bone results in a poor prognosis; a subset of patients with this form has prominent eosinophilia with hepatosplenomegaly and lymphadenopathy. *Mast cell leukemia* (MCL) is the rarest form of the disease and is invariably fatal at present; the peripheral blood contains circulating, metachromatically staining, atypical mast cells. An aleukemic form of MCL is recognized without circulating mast cells when the percentage of high-grade immature mast cells in bone marrow smears exceeds 20% in a nonspicular area. Mast cell sarcoma and extracutaneous mastocytomas are rare solid mast cell tumors with malignant and benign features, respectively.

TABLE 376-2 CLASSIFICATION OF MASTOCYTOSIS

Cutaneous mastocytosis (CM)
Urticaria pigmentosa (UP)/maculopapular cutaneous mastocytosis (MPCM)
Variants: plaque form, nodular form; telangiectasia macularis eruptiva perstans (TMEP)
Solitary mastocytoma of skin
Diffuse cutaneous mastocytosis
Indolent systemic mastocytosis (ISM)
Systemic mastocytosis with an associated clonal hematologic non–mast cell lineage disease (SM-AHNMD)
Aggressive systemic mastocytosis (ASM)
Mast cell leukemia (MCL)
Mast cell sarcoma (MCS)
Extracutaneous mastocytoma

Source: Modified from SH Swerdlow et al (eds): *World Health Organization Classification of Tumors: Pathology and Genetics in Tumors of Hematopoietic and Lymphoid Tissues.* Lyon, IARC Press, 2008.

A point mutation of A to T at codon 816 of c-*kit* that causes an aspartic acid to valine substitution is found in multiple cell lineages in patients with mastocytosis, resulting in a somatic gain-in-function mutation. This substitution, as well as other rare mutations of c-*kit*, is characteristic of patients with all forms of systemic mastocytosis but is also present in some children with cutaneous mastocytosis, as might be anticipated because mast cells are of bone marrow lineage. The prognosis for patients with cutaneous mastocytosis and for almost all with ISM is a normal life expectancy, whereas that for patients with SM-AHNMD is determined by a non–mast cell component. ASM and MCL carry a poorer prognosis. In infants and children with cutaneous manifestations, namely, urticaria pigmentosa or bullous lesions, visceral involvement is usually lacking, and resolution is common.

CLINICAL MANIFESTATIONS

The clinical manifestations of systemic mastocytosis, distinct from a leukemic complication, are due to tissue occupancy by the mast cell mass, the tissue response to that mass, and the release of bioactive substances acting at both local and distal sites. The pharmacologically induced manifestations are pruritus, flushing, palpitations and vascular collapse, gastric distress, lower abdominal crampy pain, and recurrent headache. The increase in local cell burden is evidenced by the lesions of urticaria pigmentosa at skin sites and may be a direct local cause of bone pain and/or malabsorption. Mast cell–mediated fibrotic changes occur in liver, spleen, and bone marrow but not in gastrointestinal tissue or skin. Immunofluorescent analysis of bone marrow and skin lesions in ISM and of spleen, lymph node, and skin in ASM has revealed only one mast cell phenotype, namely, scroll-poor cells expressing tryptase, chymase, and CPA.

The cutaneous lesions of urticaria pigmentosa are reddish-brown macules or papules that respond to trauma with urtication and erythema (Darier's sign). The apparent incidence of these lesions is ≥80% in patients with ISM and <50% in those with SM-AHNMD or ASM. Approximately 1% of patients with ISM have skin lesions that appear as tan-brown macules with striking patchy erythema and associated telangiectasia (telangiectasia macularis eruptiva perstans). In the upper gastrointestinal tract, gastritis and peptic ulcer are significant problems. In the lower intestinal tract, the occurrence of diarrhea and abdominal pain is attributed to increased motility due to mast cell mediators; this problem can be aggravated by malabsorption, which can also cause secondary nutritional insufficiency and osteomalacia. The periportal fibrosis associated with mast cell infiltration and a prominence of eosinophils may lead to portal hypertension and ascites. In some patients, flushing and recurrent vascular collapse are markedly aggravated by an idiosyncratic response to a minimal dosage of NSAIDs. The neuropsychiatric disturbances are clinically most evident as impaired recent memory, decreased attention span, and "migraine-like" headaches. Patients may experience exacerbation of a specific clinical sign or symptom with alcohol ingestion, temperature changes, stress, use of mast cell–interactive narcotics, or ingestion of NSAIDs.

DIAGNOSIS

Although the diagnosis of mastocytosis is generally suspected on the basis of the clinical history and physical findings, and can be supported by laboratory procedures, it can be established only by a tissue diagnosis. By convention, the diagnosis of systemic mastocytosis depends heavily on bone marrow biopsy to meet the criteria of one major plus one minor or three minor findings (Table 376-3). The bone marrow provides the major criterion by revealing aggregates of mast cells, often in paratrabecular and perivascular locations with lymphocytes and eosinophils, as well as the minor criteria of an abnormal mast cell morphology, an aberrant mast cell membrane immunophenotype, or a codon 816 mutation in any cell type. A serum total tryptase level