TABLE 376-3 DIAGNOSTIC CRITERIA FOR SYSTEMIC MASTOCYTOSIS[a]

Major: Multifocal dense infiltrates of mast cells in bone marrow or other extracutaneous tissues with confirmation by immunodetection of tryptase or metachromasia
Minor: Abnormal mast cell morphology with a spindle shape and/or multilobed or eccentric nucleus
Aberrant mast cell surface phenotype with expression of CD25 (IL-2 receptor) and CD2 in addition to C117 (c-*kit*)
Detection of codon 816 mutation in peripheral blood cells, bone marrow cells, or lesional tissue
Total serum tryptase >20 ng/mL

[a]Diagnosis requires either the major criterion and one minor criterion or three minor criteria.

and/or a 24-h urine collection for measurement of histamine, histamine metabolites, or metabolites of PGD_2 are noninvasive approaches to consider before bone marrow biopsy. The pro-β and α forms of tryptase are elevated in more than one-half of patients with systemic mastocytosis and provide a minor criterion; the fully processed ("mature") β form is increased in patients undergoing an anaphylactic reaction. Additional studies directed by the presentation include a bone densitometry, bone scan, or skeletal survey; contrast studies of the upper gastrointestinal tract with small-bowel follow-through, computed tomography scan, or endoscopy; and a neuropsychiatric evaluation. Osteoporosis is increased in mastocytosis and may lead to pathologic fractures.

The differential diagnosis requires the exclusion of other flushing disorders. The 24-h urine assessment of 5-hydroxy-indoleacetic acid and metanephrines should exclude a carcinoid tumor or a pheochromocytoma. Some patients presenting with recurrent mast cell activation symptoms without an obvious increase in mast cell burden in skin or bone marrow have been shown to carry aberrant mast cells with clonality markers of D816C c-*kit* mutation or surface CD25 expression. Most patients with recurrent anaphylaxis, including the idiopathic group, present with angioedema and/or wheezing, which are not manifestations of systemic mastocytosis.

TREATMENT SYSTEMIC MASTOCYTOSIS

The management of systemic mastocytosis uses a stepwise and symptom/sign–directed approach that includes an H_1 antihistamine for flushing and pruritus, an H_2 antihistamine or proton pump inhibitor for gastric acid hypersecretion, oral cromolyn sodium for diarrhea and abdominal pain, and aspirin for severe flushing with or without associated vascular collapse, despite use of H_1 and H_2 antihistamines, to block biosynthesis of PGD_2. Systemic glucocorticoids appear to alleviate the malabsorption. Mast cell cytoreductive therapy consisting of IFN-α or cladribine is generally reserved for advanced, nonindolent variants of systemic mastocytosis. Their efficacy in ASM is variable, perhaps because of dosage limitations due to side effects. Chemotherapy is appropriate for the frank leukemias. A self-injectable epinephrine prescription is recommended for most patients due to increased incidence of anaphylaxis. Although c-*kit* is a receptor tyrosine kinase, the gain-in-function mutation of codon 816 is not susceptible to inhibition by imatinib mesylate.

ALLERGIC RHINITIS

DEFINITION

Allergic rhinitis is characterized by sneezing; rhinorrhea; obstruction of the nasal passages; conjunctival, nasal, and pharyngeal itching; and lacrimation, all occurring in a temporal relationship to allergen exposure. Although commonly seasonal due to elicitation by airborne pollens, it can be perennial in an environment of chronic exposure to house dust mites, animal danders, or insect products. In North America, the incidence of allergic rhinitis is about 7%. The overall prevalence in North America is nearly 20%, with the peak prevalence of nearly 40% occurring in childhood and adolescence.

PREDISPOSING FACTORS AND ETIOLOGY

Allergic rhinitis generally occurs in atopic individuals, often in association with atopic dermatitis, food allergy, urticaria, and/or asthma (Chap. 309). Up to 40% of patients with rhinitis manifest asthma, whereas ~70% of individuals with asthma experience rhinitis. Symptoms generally appear before the fourth decade of life and tend to diminish gradually with aging, although complete spontaneous remissions are uncommon. A relatively small number of weeds that depend on wind rather than insects for pollination, as well as grasses and some trees, produce sufficient quantities of pollen suitable for wide distribution by air currents to elicit seasonal allergic rhinitis. The dates of pollination of these species generally vary little from year to year in a particular locale but may be quite different in another climate. In the temperate areas of North America, trees typically pollinate from March through May, grasses in June and early July, and ragweed from mid-August to early October. Molds, which are widespread in nature because they occur in soil or decaying organic matter, propagate spores in a pattern that depends on climatic conditions. Perennial allergic rhinitis occurs in response to allergens that are present throughout the year, including animal dander, cockroach-derived proteins, mold spores, or dust mites such as *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*. Dust mites are scavengers of human skin and excrete cysteine protease allergens in their feces. In up to one-half of patients with perennial rhinitis, no clear-cut allergen can be demonstrated as causative. The ability of many allergens to cause rhinitis rather than lower respiratory tract symptoms (particularly pollens) may be attributed to their large size, 10–100 μm, and retention within the nose.

PATHOPHYSIOLOGY AND MANIFESTATIONS

Episodic rhinorrhea, sneezing, obstruction of the nasal passages with lacrimation, and pruritus of the conjunctiva, nasal mucosa, and oropharynx are the hallmarks of allergic rhinitis. The nasal mucosa is pale and boggy, the conjunctiva congested and edematous, and the pharynx generally unremarkable. Swelling of the turbinates and mucous membranes with obstruction of the sinus ostia and eustachian tubes precipitates secondary infections of the sinuses and middle ear, respectively. Nasal polyps, representing mucosal protrusions containing edema fluid with variable numbers of eosinophils and degranulated mast cells, can increase obstructive symptoms and can concurrently arise within the nasopharynx or sinuses. However, atopy is not a risk factor for nasal polyps, which instead may occur in the setting of the aspirin-intolerant triad of rhinosinusitis and asthma and in patients with chronic staphylococcal colonization, which produces superantigens leading to an intense T_H2 inflammatory response.

The nose presents a large mucosal surface area through the folds of the turbinates and serves to adjust the temperature and moisture content of inhaled air and to filter out particulate materials >10 μm in size by impingement in a mucous blanket; ciliary action moves the entrapped particles toward the pharynx. Entrapment of pollen and digestion of the outer coat by mucosal enzymes such as lysozymes release protein allergens generally of 10,000–40,000 molecular weight. The initial interaction occurs between the allergen and intraepithelial mast cells and then proceeds to involve deeper perivenular mast cells, both of which are sensitized with specific IgE. During the symptomatic season when the mucosae are already swollen and hyperemic, there is enhanced adverse reactivity to the seasonal pollen. Biopsy specimens of nasal mucosa during seasonal rhinitis show submucosal edema with infiltration by eosinophils, along with some basophils and neutrophils.

The mucosal surface fluid contains IgA that is present because of its secretory piece and also IgE, which apparently arrives by diffusion from plasma cells in proximity to mucosal surfaces. IgE fixes to mucosal and submucosal mast cells, and the intensity of the clinical response to inhaled allergens is quantitatively related to the naturally occurring pollen dose. In sensitive individuals, the introduction of allergen into the nose is associated with sneezing, "stuffiness," and discharge, and the fluid contains histamine, PGD_2, and leukotrienes. Thus the mast cells of the nasal mucosa and submucosa generate and release mediators