(termed nuocytes, natural helper cells, or group 2 innate lymphoid cells) can generate large quantities of IL-5 and IL-13 during antihelminth responses, are prominent in nasal polyps from humans, and could well contribute to inflammation in allergic diseases.

ANAPHYLAXIS

DEFINITION

Life-threatening anaphylactic responses of sensitized humans occur within minutes after systemic exposure to specific antigen. They are manifested by respiratory distress due to laryngeal edema and/or intense bronchospasm, often followed by vascular collapse, or by shock without antecedent respiratory difficulty. Cutaneous manifestations exemplified by pruritus and urticaria with or without angioedema are characteristic of such systemic anaphylactic reactions. Gastrointestinal manifestations include nausea, vomiting, crampy abdominal pain, and diarrhea.

PREDISPOSING FACTORS AND ETIOLOGY

There is no convincing evidence that age, sex, race, or geographic location predisposes a human to anaphylaxis except through exposure to specific immunogens. According to most studies, atopy does not predispose individuals to anaphylaxis from penicillin therapy or venom of a stinging insect but is a risk factor for allergens in food or latex. Risk factors for a poor outcome, however, include older age, use of beta blockers, and the presence of preexisting asthma. Severe hymenoptera anaphylaxis (generally with prominent hypotension) can be a presenting feature of underlying systemic mastocytosis. Additionally, some individuals suffering from recurrent episodes of idiopathic anaphylaxis possess morphologically aberrant mast cells in their bone marrow that express a mutant, constitutively active form of c-*kit*, even without evidence of frank mastocytosis.

The materials capable of eliciting the systemic anaphylactic reaction in humans include the following: heterologous proteins in the form of hormones (insulin, vasopressin, parathormone); enzymes (trypsin, chymotrypsin, penicillinase, streptokinase); pollen extracts (ragweed, grass, trees); nonpollen allergen extracts (dust mites, dander of cats, dogs, horses, and laboratory animals); food (peanuts, milk, eggs, seafood, nuts, grains, beans, gelatin in capsules); monoclonal antibodies; occupation-related products (latex rubber products); Hymenoptera venom (yellow jacket, yellow and white-faced hornets, paper wasp, honey bee, imported fire ants); polysaccharides such as dextran and thiomersal as a vaccine preservative; drugs such as protamine; antibiotics (penicillins, cephalosporins, amphotericin B, nitrofurantoin, quinolones); chemotherapy agents (carboplatin, paclitaxel, doxorubicin); local anesthetics (procaine, lidocaine); muscle relaxants (suxamethonium, gallamine, pancuronium); vitamins (thiamine, folic acid); diagnostic agents (sodium dehydrocholate, sulfobromophthalein); biologics (omalizumab, rituximab, etanercept); and occupation-related chemicals (ethylene oxide). Drugs function as haptens that form immunogenic conjugates with host proteins. The conjugating hapten may be the parent compound, a nonenzymatically derived storage product, or a metabolite formed in the host. Recombinant biologics can also induce the formation of IgE against the proteins or against glycosylated structures that serve as immunogens. Most recently, outbreaks of anaphylaxis to the anti-epidermal growth factor antibody cetuximab were reported in association with elevated titers of serum IgE to alpha-1,3-galactose, an oligosaccharide found on certain nonprimate proteins. Alpha-galactose antibodies also account for some episodes of delayed anaphylaxis to beef, lamb, and pork.

PATHOPHYSIOLOGY AND MANIFESTATIONS

Individuals differ in the time of appearance of symptoms and signs, but the hallmark of the anaphylactic reaction is the onset of some manifestation within seconds to minutes after introduction of the antigen (with the exception of alpha-galactose allergy), generally by injection or less commonly by ingestion. There may be upper or lower airway obstruction or both. Laryngeal edema may be experienced as a "lump" in the throat, hoarseness, or stridor, whereas bronchial obstruction is associated with a feeling of tightness in the chest and/or audible wheezing. Patients with asthma are predisposed to severe involvement of the lower airways and increased mortality. Flushing with diffuse erythema and a feeling of warmth may occur. A characteristic feature is the eruption of well-circumscribed, discrete cutaneous wheals with erythematous, raised, serpiginous borders and blanched centers. These urticarial eruptions are intensely pruritic and may be localized or disseminated. They may coalesce to form giant hives, and they seldom persist beyond 48 h. A localized, nonpitting, deeper edematous cutaneous process, angioedema, may also be present. It may be asymptomatic or cause a burning or stinging sensation. Angioedema of the bowel wall may cause sufficient intravascular volume depletion to precipitate cardiovascular collapse.

In fatal cases with clinical bronchial obstruction, the lungs show marked hyperinflation on gross and microscopic examination. The microscopic findings in the bronchi, however, are limited to luminal secretions, peribronchial congestion, submucosal edema, and eosinophilic infiltration, and the acute emphysema is attributed to intractable bronchospasm that subsides with death. The angioedema resulting in death by mechanical obstruction occurs in the epiglottis and larynx, but the process also is evident in the hypopharynx and to some extent in the trachea. On microscopic examination, there is wide separation of the collagen fibers and the glandular elements; vascular congestion and eosinophilic infiltration also are present. Patients dying of vascular collapse without antecedent hypoxia from respiratory insufficiency have visceral congestion with a presumptive loss of intravascular fluid volume. The associated electrocardiographic abnormalities, with or without infarction, in some patients may reflect a primary cardiac event mediated by mast cells (which are prominent near the coronary vessels) or may be secondary to a critical reduction in blood volume.

The angioedematous and urticarial manifestations of anaphylaxis have been attributed to the release of endogenous histamine. A role for the cysteinyl leukotrienes in causing marked bronchiolar constriction seems likely. Vascular collapse without respiratory distress in response to experimental challenge with the sting of a hymenopteran was associated with marked and prolonged elevations in blood histamine and intravascular coagulation and kinin generation. The finding that patients with systemic mastocytosis and episodic vascular collapse excrete large amounts of PGD_2 metabolites in addition to histamine suggests that PGD_2 is also of importance in the hypotensive anaphylactic reactions. As noted, serum PAF levels correlate with severity of anaphylaxis and are inversely proportional to the constitutive level of the acetylhydrolase involved in PAF inactivation. The actions of the array of mast cell–derived mediators are likely additive or synergistic at the target tissues.

DIAGNOSIS

The diagnosis of an anaphylactic reaction depends on a history revealing the onset of symptoms and signs within minutes after the responsible material is encountered. It is appropriate to rule out a complement-mediated immune complex reaction, an idiosyncratic response to a nonsteroidal anti-inflammatory drug (NSAID), or the direct effect of certain drugs or diagnostic agents on mast cells. Intravenous administration of a chemical mast cell–degranulating agent, including opiate derivatives and radiographic contrast media, may elicit generalized urticaria, angioedema, and a sensation of retrosternal oppression with or without clinically detectable bronchoconstriction or hypotension. In the transfusion anaphylactic reaction that occurs in patients with IgA deficiency, the responsible specificity resides in IgG or IgE anti-IgA; the mechanism of the reaction mediated by IgG anti-IgA is presumed to be complement activation with secondary mast cell participation.

The presence of specific IgE in the blood of patients with systemic anaphylaxis was demonstrated historically by passive transfer of the serum intradermally into a normal recipient, followed 24 h later by antigen challenge into the same site, with subsequent development of a wheal and flare (the *Prausnitz-Küstner reaction*). In current clinical practice, immunoassays using purified or recombinant antigens can demonstrate the presence of specific IgE in the serum of patients with