

normal peripheral B-cell numbers associated with normal antibody responses. With the exception of low isoagglutinins, this patient's humoral immune system was intact initially and underwent a slow but progressive deterioration. It seems likely that different mutations in the *BTK* gene result in physicochemical differences in the enzyme, which account for variability in the time of onset, clinical severity, and different laboratory parameters⁴; however, with the exception of certain premature termination mutations, no consistent genotype-phenotype correlations can be identified. The variable expression of *BTK* deficiency reflects the complexities of development of the B-cell compartment and role of compensating mechanisms in humoral immunity. Bruton's original patient with XLA was noted to have adenoidal and tonsillar tissue similar to that of this patient, and Bruton's patient should be studied once again with definitive molecular methods, such as those used in this case, to determine whether that patient had CVID or XLA.

Patients with varying degrees of immunoglobulin deficiencies will require intensive investigation at the genetic level to distinguish accurately be-

tween clinical syndromes that, in the past, have been diagnosed on a phenotypic basis. In addition, investigations in this area will undoubtedly help to elucidate the complex interactions that are responsible for the development, maintenance, and function of the B-cell system.

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Elevated serum tryptase in exercise-induced anaphylaxis

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Exercise-induced anaphylaxis (EIA) is a unique medical emergency in that it derives from a physical allergy.¹⁻³ Sheffer et al.² believe EIA to be distinct from asthma, cholinergic urticaria, and angioedema, which can occur in some individuals who exercise. Several studies have suggested the role of mast cells in this disease^{3,4} as judged by biopsy and plasma histamine studies.

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Abbreviation used

EIA: Exercise-induced anaphylaxis

The opportunity to evaluate a young man with EIA in whom striking elevation of serum tryptase was demonstrated during an acute episode recently arose and is described below.

CASE REPORT

K.Z., an 18-year-old male high school football player was seen in consultation; he was complaining of acute skin rashes and hives associated with exercise. He also stated that he could at times experience wheezing and

TABLE I. Spirometric results

	Predicted	Baseline	After exercise	Percent change
FVC (L)	4.86	5.83	5.03	-14
FEV ₁ (L)	4.19	4.98	3.44	-31
REF ₂₅₋₇₅ (L/sec)	4.66	5.52	2.45	-56

FVC, Forced vital capacity; FEV₁, forced expiratory volume in 1 second; REF₂₅₋₇₅, maximum mid-expiratory flow rate.

TABLE II. Laboratory values

	Patients	Normal range
WBC count (cells/mm ³)	14,100	3.5-11,000
Hemoglobin (gm/dl)	19.4	12.0-16.0
Hematocrit (%)	60.1	36-49
Tryptase (ng/ml)	8	<1
Histamine (ng/ml)	11	0.-0.43

WBC, White blood cell.

dyspnea when the hives developed. However, not every outbreak of hives was associated with dyspnea, and at times, he noted that dyspnea could develop without hives. The hives could last up to 60 minutes after cessation of exercise, and dyspnea could last 30 to 45 minutes. This problem developed suddenly and recently, despite heavy athletic activity all through his teens. Exposure to temperature extremes could also cause symptoms. The level of exercise necessary to trigger an attack was not necessarily strenuous according to his experience. None of the attacks occurred after meals or snacks. The patient had no history of allergic disease from infancy to the present. He was a nonsmoker. The family history for atopic disease was negative. Results of physical examination were entirely normal. Results of allergy skin testing by the prick method were negative in response to a wide variety of inhalants including tree, grass, and weed pollens; fungi; pets; and house dust mite. Results of baseline spirometry were normal. The patient was asked to go jogging around the medical facility and to return to the office when he experienced any suggestive symptoms. He returned within 10 minutes, complaining of breathlessness, at which time physical examination revealed a blood pressure of 60/40 mm Hg, diffuse hives, angioedema, and wheezing. The hives were typical of urticaria rather than cholinergic in variety. Spirometry revealed airway obstruction (Table I). Blood samples were drawn for assay, and he was given 0.2 ml of subcutaneous epinephrine 1/1000 and nasal oxygen and was watched closely for the next 90 minutes during which he received another dose of 0.2 ml of epinephrine. All symptoms resolved, and physical findings returned to normal. Blood was drawn during the height of the attack and revealed leukocytosis and hemoconcentration (Table II). The serum tryptase level was elevated to 8 ng/ml (normal <1

ng/ml), and the plasma histamine level was elevated to 11 ng/ml (normal, 0 to 0.43 ng/ml).

After full recovery, the patient was advised regarding exercise curtailment and the use of autoinjectors of epinephrine, antihistamines, cromolyn sodium, and inhaled bronchodilators to deal with any symptoms that might develop when medical attention was not available. He has been followed up since this episode and has done well with this revised program of activity, without need for epinephrine. He has declined any further test challenges in which more detailed results could be obtained.

DISCUSSION

This case report clearly and dramatically demonstrates the role of mast cells in EIA. The elevated plasma histamine levels mirror those previously reported, and the elevated serum tryptase levels further document mast cell involvement in an attack triggered by mild exercise at a medical care facility. Elevations in plasma histamine have previously been reported.^{3,5,6} Furthermore, alterations in tissue mast cells in skin biopsy specimens of patients with EIA have been described.^{4,7} A loss of electron density, loss of internal substructure of granules, and fusion of granule membranes with mast cell membranes—all of which were suggestive of mast cell activation—were noted in skin biopsy specimens of patients.⁷

In this case, we had merely planned a mild exercise challenge to document the patient's history of exercise-induced urticaria. We had no reason to expect EIA or exercise-induced asthma. As a result, no control blood samples for histamine or tryptase determinations were obtained.

Tryptase has been clearly shown to be a mediator of human mast cells and has been widely used as a marker of mast cell involvement in atopic patients with asthma and in patients with Hymenoptera venom-induced anaphylaxis.⁸⁻¹⁰

This case report may be the first in vivo demonstration of tryptase involvement in EIA. The eventual development of more potent mast cell-stabilizing drugs may be of great clinical utility in preventing EIA episodes in patients subject to this disease. Furthermore, it would be of interest to

assess other patients with exercise-induced asthma and anaphylaxis to evaluate the frequency with which these phenomena occur.

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