# The potential clinical utility of serum α-protryptase levels

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**Background: Because biopsy criteria for diagnosing systemic mastocytosis are not precise, the value of serum α-protryptase levels in the work-up of suspected systemic mastocytosis should be considered.**

**Objective: A retrospective analysis was performed on subjects with total tryptase serum levels that were high (≥20 ng/mL), while β-tryptase serum levels were normal (<1 ng/mL) or modestly elevated (1 to 5 ng/mL).**

**Methods: Over a 3.5-year period, 52 qualifying specimens were identified from 1369 consecutive samples. The corresponding subjects were divided into those with suspected mastocytosis and those with suspected anaphylaxis. Subjects with suspected mastocytosis were subdivided into 3 subgroups on the basis of biopsy results (positive, negative, or not available). Subjects with suspected anaphylaxis were subdivided into living and deceased subgroups.**

**Results: Among the 15 subjects who underwent biopsy, α-protryptase serum levels (the difference between directly-measured levels of serum total tryptase and β-tryptase), when greater than 75 ng/mL (n = 9), were always associated with a positive biopsy result for systemic mastocytosis; levels from 20 to 75 ng/mL (n = 6) were associated with a positive biopsy result in 50% of subjects. α-Protryptase serum levels may be a more sensitive screening test than a bone marrow biopsy for this disorder. Also, elevated α-protryptase serum levels in some adult patients return to normal over time, suggesting that mast cell hyperplasia resolved in these patients. Finally, a high α-protryptase level may reveal anaphylaxis to be a presenting manifestation of systemic mastocytosis or mast cell hyperplasia.**

**Conclusion: Levels of serum α-protryptase, relative to those of β-tryptase, appear to be useful in the diagnostic work-up and follow-up of subjects with suspected systemic mastocytosis. (J Allergy Clin Immunol 1999;103:1092-9.)**

***Key words:*** *Mastocytosis, anaphylaxis, tryptase, mast cell*

Two principal classes of human tryptase have been reported, the products of α-tryptase (α-preprotryptase protein) and β-tryptase (β-preprotryptase protein) genes.[1] β-Preprotryptase is processed to β-tryptase, which forms active tetramers that are stored in mast cell secretory granules and are secreted from mast cells during degranulation.[2,3] In contrast, α-preprotryptase appears to be processed only to α-protryptase, an inactive monomer, which is constitutively secreted by mast cells at rest.[4] Consequently, circulating levels of α-protryptase reflect the total body burden of mast cells, whereas levels of β-tryptase, which are usually undetectable in serum at baseline, increase to reflect the magnitude of mast cell activation. To measure primarily β-tryptase, the G5 mAb is used either for capture or detection.[5] To measure α-protryptase, total tryptase is measured with mAbs that detect both α-protryptase and β-tryptase,[6] and the value for β-tryptase is subtracted to calculate the level of α-protryptase.

During experimental insect sting–induced systemic anaphylaxis, the serum level of β-tryptase (normal value, <1 ng/mL) correlates with clinical severity as measured by the drop in mean arterial pressure.[7] During such reactions, serum levels of β-tryptase peak 30 to 60 minutes after the onset of symptoms and then decline, with a half-time of about 2 hours.[8] In one study of tryptase levels in insect sting–induced systemic anaphylaxis, the ratios of total tryptase to β-tryptase were less than 6 in 16 of 17 subjects and 23 in the 1 outlier.[6]

In a study of tryptase levels in subjects with mastocytosis, most subjects (35 of 42) with systemic mastocytosis indicated by a bone marrow biopsy had levels of α-protryptase greater than 20 ng/mL and ratios of total tryptase to β-tryptase greater than 20.[4] Normal subjects (n = 55) had α-protryptase levels of less than 14 ng/mL.[6] This suggested a specificity greater than 98% and a sensitivity of 83% for α-protryptase levels when compared to a bone marrow biopsy. However, among the 7 subjects with systemic mastocytosis and a serum α-protryptase level below 20 ng/mL, all had α-protryptase levels between 10 and 20 ng/mL, 3 had ambiguous bone marrow readings, and another had the bone marrow biopsy performed 5 years before the serum sample was collected. Most subjects with local cutaneous mast cell disease (10 of 13) had levels similar to those of normal control subjects (1 to 11 ng/mL, ratios ≤11). Among the 3 subjects with serum α-protryptase levels above this range, one was an infant with diffuse cutaneous mastocytosis, and another had no bone marrow biopsy performed.

The gold standard for the diagnosis of mastocytosis is a tissue biopsy showing a pathologic increase in the number of mast cells. However, in skin there is no precise mast cell concentration that defines cutaneous mastocytosis. In bone marrow biopsy specimens, paratrabecular collections of spindle-shaped mast cells intermixed with fibroblasts, mononuclear cells, and eosinophils are char-

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acteristic of systemic mastocytosis.[9,10] However, such lesions are not always evident. Also, tryptase immunostaining may provide a more sensitive and specific marker of mastocytosis in bone marrow biopsy specimens than classical histochemical or histoenzymatic stains,[11] suggesting false-negative readings in some cases subjected to a standard analysis of the biopsy specimen. There is no precise mast cell concentration in bone marrow biopsy specimens or aspirates now in use to distinguish mastocytosis from normal tissue. Because biopsy criteria for diagnosing systemic mastocytosis are not precise and a biopsy could miss disease present at other sites, the relative value of α-protryptase levels in the work-up of suspected systemic mastocytosis should be considered. This study is a retrospective analysis of the clinical value of an elevated level of α-protryptase (≥20 ng/mL) with a normal or slightly elevated (≤5 ng/mL) level of β-tryptase using samples received in our diagnostic immunology laboratory over a 3.5-year period.

## METHODS

### Immunoassays

To measure total tryptase, the B12 mAb was used for capture, and biotinylated G4 and G3 mAbs were used for detection as described.[4,6] The lower limit of sensitivity for the total tryptase assay is 0.4 ng/mL. A comparable assay is offered by Pharmacia-Upjohn Diagnostics and is performed by many reference laboratories. To measure β-tryptase, the B12 mAb was used for capture, and biotinylated G5 mAb was used for detection.[4] The lower limit of sensitivity for the β-tryptase assay is 1 ng/mL. In both cases purified human lung–derived tryptase (essentially all β-tryptase) was used as a standard. When the β-tryptase level was less than 1 ng/mL, a value of 1 was used to calculate the ratio of total tryptase to β-tryptase.

### Samples

The study was approved by the Human Studies Internal Review Board of Virginia Commonwealth University. Clinical information relating to the blood samples sent to our diagnostic laboratory for measurement of tryptase levels between January 1993 and June 1996 were retrospectively obtained. Inclusion criteria included samples with a markedly elevated serum total tryptase level (≥20 ng/mL) and a β-tryptase level that was normal (<1 ng/mL) or modestly elevated (≤5 ng/mL). Exclusion criteria were specimens from previously diagnosed cases of mastocytosis of which we were aware and those sent from institutions known to have ongoing mastocytosis studies. Questionnaires were formulated and sent to referring physicians to ascertain specific clinical symptoms and signs experienced by each patient and any laboratory or biopsy results. A total of 1369 blood specimens were sent to our diagnostic laboratory for analysis of tryptase levels during this period; 104 specimens had tryptase levels within the required range, and 79 of these qualified for our study.

## RESULTS

Of the 52 returned questionnaires, clinical diagnoses were suspected anaphylaxis in 30 and suspected mastocytosis in 22. These 2 groups will be discussed separately. Demographic data are shown in Table I in which subjects were divided according to their clinical diagnosis and subdivided according to biopsy results for the mastocytosis group and into deceased or living subgroups for the anaphylaxis group. However, all subgroups exhibited a similar age distribution, with female and white subjects predominating.

**TABLE I.** Demographic data

| Clinical diagnosis | Median age, y (range) | Sex, M/F | Race |
|---|---|---|---|
| Suspected mastocytosis | | | |
| Biopsy$^+$ (n = 12) | 43 (30-73) | 4/8 | 12 white |
| Biopsy$^-$ (n = 3) | 34 (21-41) | 1/2 | 3 white |
| No biopsy (n = 7) | 42 (35-60) | 1/7 | 6 white, 1 black |
| Suspected anaphylaxis | | | |
| Living subjects (n = 19) | 39 (19-55) | 9/10 | 17 white, 1 black, 1 Indian |
| Deceased subjects (n = 11) | 37 (19-49) | 2/9 | 7 white, 2 black, 2 Hispanic |

### Suspected mastocytosis

Among those with a suspected diagnosis of systemic mastocytosis, 2 subjects were classified as having mastocytosis with an associated hematologic disorder (Type II mastocytosis); one had anemia, thrombocytopenia, and early forms of myelocytes in the peripheral smear, and the other had anemia, eosinophilia, and a myeloproliferative disorder. The remaining subjects were classified as having indolent mastocytosis. Clinical manifestations were cutaneous lesions (flushing, hives, cutaneous eruption, bulla, pruritus, and/or angioedema) in 10 subjects (6 with classical urticaria pigmentosa), gastrointestinal symptoms in 8 subjects (abdominal cramps, nausea, vomiting, and/or diarrhea), cardiovascular symptoms in 5 subjects (syncope, palpitation, and/or hypotension), skeletal symptoms in 5 subjects (bone pain with or without abnormal x-ray findings), and respiratory symptoms in 4 subjects (dyspnea, shortness of breath, and/or wheezing).

Among those subjects with suspected mastocytosis, as defined by the inclusion criteria, all subjects had total tryptase levels greater than 20 ng/mL (22 to 700 ng/mL) measured during an asymptomatic period as shown in Fig 1. Also, the ratio of total tryptase to β-tryptase was greater than 20 in all of these patients, ranging from 22 to 600. Fifteen subjects underwent further evaluation by tissue biopsy, and 7 did not. Bone marrow biopsy was performed in 13 subjects, skin biopsy in 2 subjects, and gastric biopsy in 2 subjects. Mastocytosis was diagnosed by bone marrow biopsy in 11 subjects, 2 of whom had an associated hematologic disorder, and by gastric biopsy alone in 1 subject. One subject underwent bone marrow, skin, and gastric biopsy procedures; each was read as mastocytosis (total tryptase, 199 ng/mL). Two subjects had negative bone marrow biopsy results (total tryptase levels of 23 and 75 ng/mL, each having recurrent episodes of flushing, dizziness, diarrhea, crampy abdom-

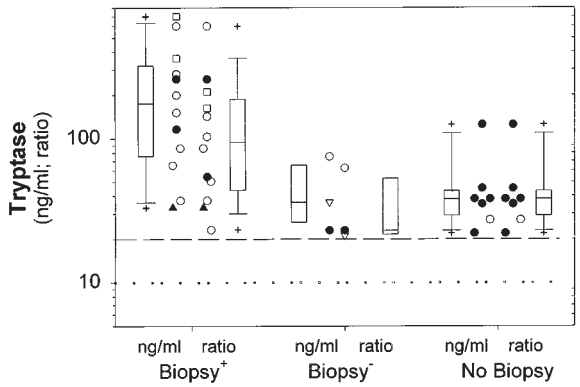


**FIG 1.** Suspected mastocytosis. Total tryptase values (ng/mL) and the total tryptase/β-tryptase ratios are shown for subjects with suspected mastocytosis who were subdivided into those with positive biopsy results *(biopsy+),* those with negative biopsy results *(biopsy–),* and those not undergoing biopsy. *Filled symbols* represent those samples in which β-tryptase was 1 ng/mL or less, giving a ratio that was numerically equivalent to the total tryptase value. Mastocytosis with an associated hematologic disorder *(open squares),* mastocytosis diagnosed by gastric biopsy alone *(open traingles),* and the sample corresponding to a negative skin biopsy alone *(open inverted triangles)* are shown as indicated. Box and whisker plots show median, 25th and 75th percentiles *(rectangles),* 10th and 90th percentiles *(whiskers),* and outliers *(+).* A horizontal dashed line is shown at the 20 ng/mL cutoff for total tryptase.

inal pain, and vomiting), and one had a negative skin biopsy result alone (total tryptase level of 36 ng/mL, with recurrent flushing, diarrhea, vomiting, and crampy abdominal pain but no hyperpigmented skin lesions).

The respective median values for total tryptase level and total tryptase/β-tryptase ratio were 175 ng/mL and 95 in the group with positive biopsy results, 36 ng/mL and 23 in the group with negative biopsy results, and 38 ng/mL and 38 in the group not undergoing biopsy (Fig 1). The median total tryptase level was significantly higher in the group with positive biopsy results than the other groups ($P = .015$, Kruskal-Wallis 1-way ANOVA of positive biopsy result, negative biopsy result, and no biopsy groups), suggesting the bone marrow biopsy is more likely to be positive in subjects with a higher systemic mast cell burden, as measured by total tryptase level.

Follow-up serum tryptase levels were obtained in 8 of these subjects. As shown in Fig 2, total tryptase levels increased over a 6- to 12-month period in 2 subjects (*A* and *F*), of which 1 had a positive biopsy result and the other did not undergo biopsy. Total tryptase levels declined in one subject with a positive biopsy result **(***C***)** but remained well above 20 ng/mL over a 5-year time span. This subject had a hypotensive episode at the 45-month time point in which β-tryptase rose to 4 ng/mL, which was reflected in a higher total tryptase level and lower ratio than surrounding time points. Surprisingly, in 5 subjects (*B, D, E, G,* and *H*), including both subjects with a negative bone marrow biopsy result (*D* and *E*), tryptase levels returned to below 20 ng/mL over 3- to 26-month time spans. These observations raise the possibility that systemic mastocytosis may be reversible or transient in some subjects.

## Suspected anaphylaxis

Among specimens from those 30 subjects with the diagnosis of anaphylaxis or suspected anaphylaxis, 11 were postmortem specimens, and 19 specimens were taken from living subjects when symptomatic (Table I). The agents listed as possible causes of these anaphylactic events were intravenous iron dextran in 2 postmortem specimens; nonsteroidal anti-inflammatory drugs in 3 subjects; intravenous penicillin in 1 subject, which resulted in fatality; possible food suspected in 4 subjects of which 3 ended in fatality (peanut allergy in 1); latex exposure in 2 subjects; exercise in 2 subjects; insect sting in 1 subject; and unidentified etiology in 15 subjects (5 fatalities).

*Living subjects.* In 18 of the living subjects, skin or gastrointestinal manifestations were associated with hypotension or respiratory compromise. The living subject group had median values for total tryptase, β-tryptase, and total tryptase/β-tryptase ratio (35, 1.6, and 24, respectively) (Fig 3). One living subject exhibited only cutaneous lesions, associated with a total tryptase level of 33 ng/mL and a β-tryptase level of 1 ng/mL. Although total tryptase levels failed to distinguish any subgroups within the living subjects, analysis of total tryptase/β-tryptase ratios revealed 2 subgroups, 6 with a ratio below 12 and 13 with a ratio above 19. The lower ratio subgroup contained subjects with serum β-tryptase levels of at least 3 and no more than 5 ng/mL. The biphasic distribution of total tryptase/β-tryptase ratios suggested 2 distinct disease patterns, with low ratios being associated with systemic anaphylaxis and higher ratios suggesting underlying systemic mastocytosis as a predisposing factor to systemic anaphylaxis.

In 10 of these 19 subjects, the putative time of sample collection after onset of signs and symptoms was provided by the corresponding physicians and ranged from 20 minutes to 12 hours. However, there was no apparent correlation between times of blood collection and either the total tryptase values, β-tryptase values, or total tryptase/β-tryptase ratios. This may relate in part to the absence of precise information on the severity of the clinical events, a principal determinant of the peak β-tryptase value during anaphylaxis, and the precipitating factor.

Follow-up specimens were obtained from 5 of the 19 living subjects with suspected systemic anaphylaxis as shown in Fig 4. The time after the initial presentation is shown in the upper right corner of each panel. Note that in each case the total tryptase/β-tryptase ratio and total tryptase value converged after the initial specimen because β-tryptase levels became 1 ng/mL or less. Follow-up total tryptase levels remained above 20 ng/mL in 2 subjects (*A* and *B*), fell to between 10 and 20 ng/mL in 2 subjects (*C* and *D*), and fell to between 1 and 10 ng/mL in 1 subject **(***E***)**. The total tryptase values remained above 20 ng/mL in only 2 (*A* and *B*) of these subjects, suggesting systemic mastocytosis. A normal total tryptase level

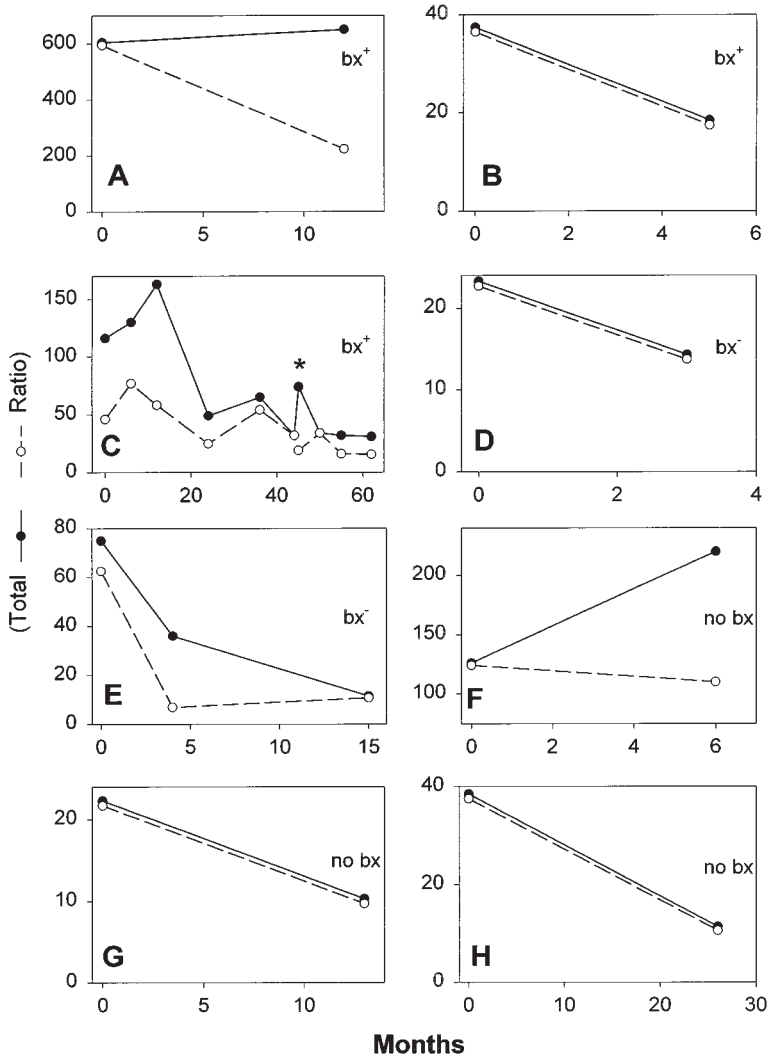


**FIG 2.** Follow-up tryptase values in suspected mastocytosis. Follow-up tryptase values were obtained in 8 subjects with suspected mastocytosis. *Filled circles* are total tryptase values; *open circles* are total tryptase/β-tryptase ratios. *Acutely symptomatic.

approximately 1 month after the initial specimen was collected in one subject **(*E*)** indicates anaphylaxis without underlying systemic mastocytosis. Subjects reflected in panels *C* and *D* had follow-up total tryptase levels in serum between 10 and 20 ng/mL, which are consistent with a modestly elevated mast cell burden but not in the range typical of systemic mastocytosis.

*Postmortem specimens.* Among the 11 postmortem specimens from subjects with suspected anaphylaxis, median values for total tryptase levels, β-tryptase levels, and the total tryptase/β-tryptase ratio were 43 ng/mL, 2.5 ng/mL, and 30, respectively. Individual data points are shown in Fig 3. Prominent angioedema with respiratory compromise was reported in 7 subjects, whereas syncope and/or profound hypotension were reported in 2 subjects. One subject had a seizure after receiving a local anesthetic in a dental office. Another was found 3 days after apparently receiving an injection of depomedroxyprogesterone acetate. Three subjects had β-tryptase levels of less than 1 ng/mL, including one with a food-induced anaphylactic reaction while receiving propranolol therapy and one with acute myelocytic leukemia and sepsis who had hypotension while receiving cytarabine. Unfortunately, precise information on the relationship between onset of signs and symptoms, time of death, and time of sample collection were not available. Nevertheless, the data suggest an underlying increase in the mast cell burden in this group of subjects, raising the possibility that systemic mastocytosis was an underlying condition, perhaps predisposing these individuals to systemic anaphylaxis.

## DISCUSSION

This retrospective analysis of subjects with elevated levels of total tryptase (≥20 ng/mL) relative to β-tryptase (≤5 ng/mL) identifies 3 hypotheses of potential clinical value. First, α-protryptase serum levels may be a better reflection of the total mast cell burden than focal tissue

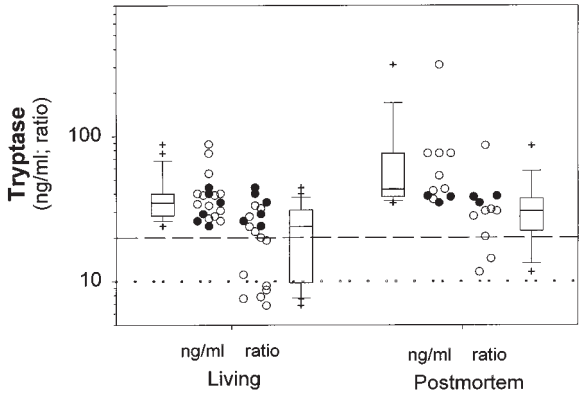


**FIG 3.** Suspected anaphylaxis. Total tryptase values (ng/mL) and the total tryptase/β-tryptase ratios are shown for subjects with suspected anaphylaxis who were subdivided into living and deceased groups. Closed symbols represent those samples in which β-tryptase was 1 ng/mL or less, giving a ratio that was numerically equivalent to the total tryptase value. Box and whisker plots are as described in Fig 1. A horizontal dashed line is shown at 20 ng/mL, and a dotted line is shown at 10 ng/mL.

biopsy specimens and thereby serve as a more sensitive and specific screening test for systemic mastocytosis. Second, an elevated body burden of mast cells may spontaneously reverse, suggesting that follow-up α-protryptase levels may have prognostic value. Third, anaphylaxis may be a presenting manifestation of systemic mastocytosis or mast cell hyperplasia. Limitations of the current study result from its retrospective nature, a lack of clinical information corresponding to the 1265 samples with total tryptase levels of less than 20 ng/mL and β-tryptase levels of greater than 5 ng/mL, potential bias in the study population, and follow-up data in a limited number of subjects. However, mastocytosis is an uncommon condition, and α-protryptase levels have not been systematically evaluated in a population with suspected mastocytosis, justifying in part the analysis of data as presented.

Among the 15 subjects with suspected systemic mastocytosis who underwent biopsy, the 3 with negative biopsy results had total tryptase levels from 20 to 75 ng/mL. Among those with positive biopsy results, 3 had levels from 20 to 75 ng/mL, and 9 had levels above 75 ng/mL. The 2 with an associated hematologic disorder had total tryptase levels of greater than 75 ng/mL, which is consistent with a previous report of high levels in such subjects.[4] Consequently, the specificity of a total tryptase level of greater than 75 ng/mL appears to be quite high for systemic mastocytosis with a positive biopsy result. On the other hand, a level of 20 to 75 ng/mL yielded a positive biopsy result in 3 of 6 subjects, with one of the subjects with a negative biopsy result having only a biopsy of nonlesional skin that flushed during anaphylactic attacks. Thus the likelihood of a positive biopsy result increases at higher total tryptase levels. However, a total tryptase level of 20 ng/mL or greater associated with a ratio of total tryptase to β-tryptase of greater than 10 may be a more specific and sensitive indicator of systemic mast cell disease than a focal biopsy alone.

Whether those subjects with a tryptase level from 20 to 75 ng/mL and a negative biopsy result truly had systemic mastocytosis that was missed by a focal biopsy bears further consideration. One possibility is that total tryptase levels in this range may not always reflect an elevated mast cell burden. For example, if the output of α-protryptase per mast cell increases or the rate of removal of α-protryptase from the circulation diminishes, higher levels of total tryptase would result. However, whether either of these 2 scenarios is biologically relevant remains to be clarified. Another possibility is that markedly elevated levels of basophils could lead to elevated levels of total tryptase. α-Tryptase mRNA is the predominant tryptase transcript in normal peripheral blood basophils, although tryptase mRNA and protein levels in basophils are much lower than in mast cells.[12,13] At present, the primary determinant of α-protryptase levels appears to be the total body burden of mast cells.

Another consideration is whether an elevated mast cell burden, reflected by an elevated serum level of α-protryptase, is a permanent condition. Many, if not all, adult subjects diagnosed with systemic mastocytosis reportedly carry somatic mutations in Kit,[14-17] a proto-oncogene critically involved in the development and survival of human mast cells. Once such a mutation forms in an appropriate hematopoietic cell, one could predict that mast cell development and survival would increase,[18] leading to a chronically increased mast cell burden. Indeed, excessive stimulation of normal Kit by exogenously administered stem cell factor (Kit ligand) leads to an increase in the number of mast cells and the total serum tryptase level.[19] However, in the latter case, withdrawal of exogenous stem cell factor permits the total tryptase level, and presumably the mast cell burden, to return to baseline. Another example of inducible mast cell hyperplasia, this time in rodent lungs, is one in which mast cell hyperplasia is associated with virus infection.[20-22] Children with urticaria pigmentosa often experience spontaneous remission of their skin lesions with time. Thus it is possible that transient elevations of stem cell factor or of other putative mast cell growth factors could lead to a transient mast cell hyperplasia without involving somatic mutations of Kit. In this light, it is of interest to note that total tryptase levels declined to below 20 ng/mL in 5 of the 8 subjects with suspected mastocytosis who had follow-up levels 3 to 26 months later, one of whom had biopsy-proven disease and 2 of whom had a negative bone marrow biopsy result, suggesting a corresponding decrease in the mast cell burden. An alternative consideration might be that the output of α-protryptase per mast cell decreased. Nevertheless, a predictive marker for persistence or remission would be clinically useful. Whether the respective presence or absence of the somatic Kit mutations associated with systemic mastocytosis[23,24] might serve this role is an issue for future research. Also, clinical trials aimed at reducing the mast cell burden need appropriate placebo control arms to take

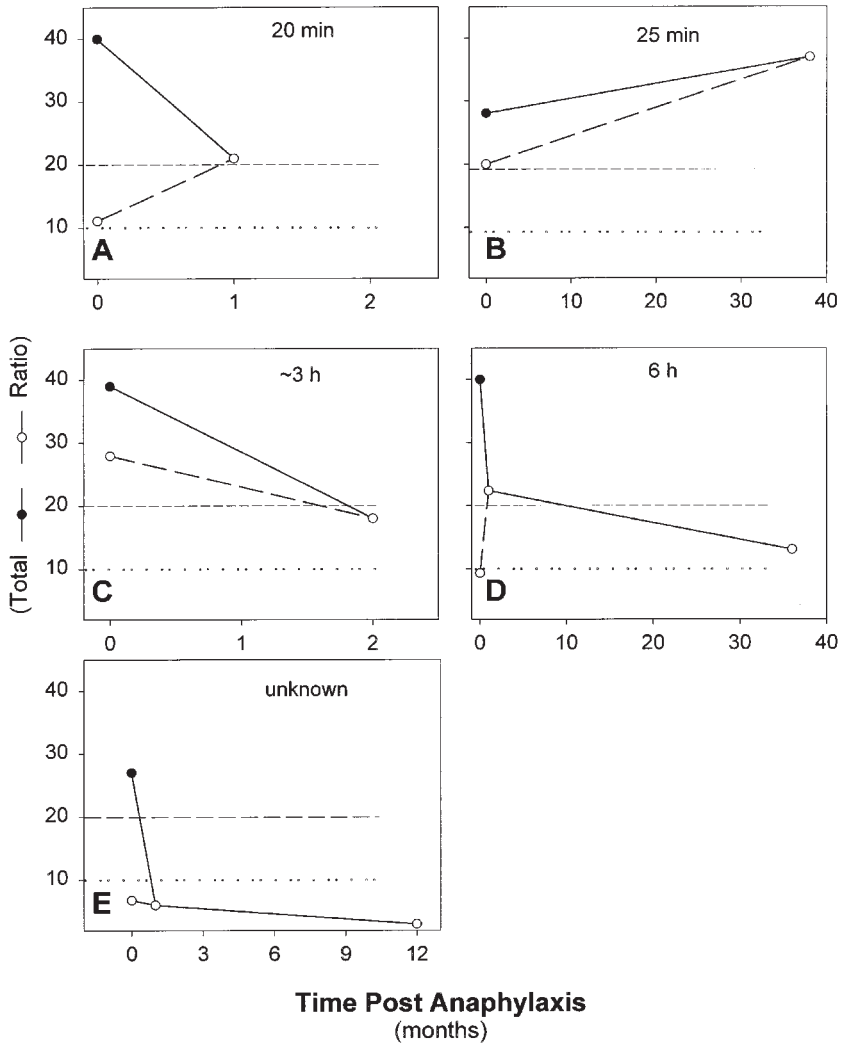


**FIG 4.** Follow-up tryptase values in suspected anaphylaxis. Follow-up tryptase values were obtained in 5 subjects with suspected anaphylaxis. *Filled circles* are total tryptase values; *open circles* are total tryptase/β-tryptase ratios. A horizontal dashed line is shown at 20 ng/mL, and a dotted line is shown at 10 ng/mL.

into account that even in adults an elevated mast cell burden in some cases may spontaneously decline.

Anaphylactic or anaphylactoid reactions may be a presenting manifestation of systemic mastocytosis. For example, in subjects who experienced anaphylaxis to insect stings but were later found to be without venom-specific IgE, elevated total tryptase levels were found that suggested underlying mastocytosis was present and predisposed them to these anaphylactoid reactions.[25,26] A previous report of tryptase levels in experimental insect sting–induced anaphylaxis found a total tryptase level of greater than 10 ng/mL before the sting challenge in 5 of the 17 subjects in whom severe anaphylactic reactions with higher acute levels of β-tryptase later developed.[6] These elevated baseline levels varied from 11 to 18 ng/mL. During anaphylaxis, only one subject with a baseline level of 12 ng/mL total tryptase exhibited a total tryptase/β-tryptase ratio of greater than 10 (24); all others had ratios ranging from 1 to 6, showing that underlying mast cell hyperplasia was not present in most subjects with anaphylaxis to an insect sting.

The current study identified 19 living subjects whose clinical diagnosis was anaphylaxis. Although none had β-tryptase levels of greater than 5 ng/mL because of the inclusion criteria of our study, the clinical severity of the attack and the timing of blood collection were not precisely known, even though both are critical parameters for a full analysis of a β-tryptase level. Nevertheless, reportedly acute samples could be subdivided on the basis of the total tryptase/β-tryptase ratios, which were less than 12 in 6 of these subjects and greater than 19 in the remaining 13 subjects. One would like to know whether a high ratio at or near the time of anaphylaxis suggests underlying mastocytosis and whether a low level suggests anaphylaxis alone. Nonacute follow-up levels were obtained in 3 members of the low-ratio group

and in 2 members of the high-ratio group. In all cases β-tryptase levels returned to normal (<1 ng/mL), which is consistent with mast cell degranulation occurring during the acute event. Among the 3 low-ratio subjects, total tryptase levels returned to normal in 1 subject 1 month later, fell in another subject from 40 to 22 in 1 month and to 13 3 years later, and in the third subject fell from 40 to 21 in 1 month. These data suggest that an increased mast cell burden was present at the time of anaphylaxis in 2 of these 3 subjects, but each exhibited a decline in total tryptase levels over time, suggesting a possible spontaneous resolution of the mast cell hyperplasia. Among the 2 high-ratio subjects, total tryptase levels decreased from 39 to 18 2 months later in 1 subject but increased from 28 to 37 38 months later in the other. These data suggest long-term mastocytosis in the latter subject and possible resolving disease in the former subject. We conclude that nonacute follow-up samples are needed to best assess whether there is underlying mastocytosis and whether this condition may spontaneously remit.

Elevated levels of β-tryptase in postmortem sera have been used as an indicator of anaphylaxis[27-29] but occasionally are found to be elevated when anaphylaxis was not expected.[30,31] In cases of sudden infant death syndrome, elevated levels of β-tryptase were found more often in such subjects than in control deaths in 2 studies[32,33] but not in a third study.[34] Retrospective analysis of a portion of the cases from the initial study[33] did not reveal elevated levels of total tryptase either in the experimental or control groups (unpublished data), suggesting that an elevated mast cell burden did not predispose these infants to anaphylaxis. In the current study all 11 postmortem samples had total tryptase/β-tryptase ratios above 10, and 9 had levels above 20, suggesting an elevated mast cell burden may have been present at the time of death. These data suggest that mastocytosis or mast cell hyperplasia might be first seen as fatal anaphylaxis in some subjects. In summary, α-protryptase levels estimated from measurements of total tryptase and β-tryptase should be considered as a potential screening test for systemic mastocytosis or systemic mast cell hyperplasia. These conditions may be underrecognized, particularly in subjects with severe or fatal anaphylactic reactions.

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