

# Elevated Serum Tryptase in Non-Anaphylaxis Cases: A Concise Review

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## Keywords

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## Abstract

One of the most important blood tests in the field of allergy, mast cell tryptase has numerous diagnostic uses, particularly for anaphylactic reactions and for the diagnosis of mastocytosis. However, there are numerous other non-anaphylactic conditions where clinicians may see elevated serum tryptase (hypertryptasemia) and the practicing clinician ought to be aware of these important differential diagnoses. Such conditions include systemic mastocytosis, hematological malignancies, and chronic kidney disease. This article provides a comprehensive, updated summary on the variety of non-anaphylactic conditions where hypertryptasemia may be seen.

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## Introduction

One of the most important blood tests in the field of allergy, mast cell (MC) tryptase has numerous diagnostic uses, particularly for anaphylactic reactions and for the diagnosis of mastocytosis. Tryptase is secreted from preformed granules when MCs are activated, with several

isoforms of tryptase existing encoded by five loci on chromosome 16p [1]. The dominant isoforms are  $\alpha$ - and  $\beta$ -tryptase, and  $\alpha$ - and  $\beta$ -protryptase are continuously secreted by cells [2]. In healthy individuals, these protryptases reflect constitutive total serum tryptase [2]. By contrast, mature  $\beta$ -tryptase is preformed and stored in MC granules and is released upon MC degranulation such as in anaphylaxis [3]. The primary functions of tryptase remain elusive but it is thought to promote inflammation, chemotaxis, and fibroblast proliferation [1, 4].

The ImmunoCAP tryptase assay (Phadia) is a commercially available fluoroenzyme sandwich assay that measures tryptase on an automated platform. This measures both  $\alpha$ - and  $\beta$ -tryptase isoforms as total tryptase [5]. Other assays available include the enzyme-linked immunosorbent assay (ELISA).

A raised serum tryptase (hypertryptasemia) has numerous diagnostic uses. The main use is in the diagnosis of anaphylactic reactions; however, it does not distinguish between IgE-mediated versus non-IgE-mediated reactions. Serum tryptase level is positively correlated with degree of anaphylaxis severity and tends to be higher in drug and insect venom anaphylaxes rather than food

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anaphylaxis [6, 7]. It peaks at 1–2 h post anaphylactic trigger [8]. However, elevated MC tryptase has poor sensitivity and patients may have normal tryptase levels during anaphylaxis. In one study, around a third of anaphylactic patients had a normal serum tryptase during the event; however, only 3% of the enrolled patients had hymenoptera anaphylaxis, possibly biasing the overall frequency of normal tryptases [6].

Curiously, tryptase tends to increase with age, even after correcting for other medical comorbidities and is higher in males than females [7, 9]. Regression analysis reveals a rise in baseline tryptase of 0.28 µg/L per decade of life in patients with normal (<11.4 µg/L) tryptase [10]. Despite the role for MCs in allergic disorders, it is generally not elevated (>11.4 µg/L) in atopic conditions [11]. With MCs found in numerous organs [12], raised tryptase has significance in other diseases and clinical settings other than anaphylaxis. It is hence important for physicians to be aware of these conditions and the following review will concisely summarize the differential diagnoses of hypertryptasemia in non-anaphylaxis cases.

## MC Activation Disorders

Disorders that are associated with MC activation can be classified as primary disorders (clonal MC disorders such as mastocytosis), secondary (non-clonal disorders such as chronic autoimmune urticaria), and idiopathic [13].

### *Mastocytosis*

A serum tryptase >20 µg/L is a diagnostic criteria for systemic mastocytosis; however, values in the normal range do not reliably exclude this condition [14]. The total tryptase in mastocytosis patients is not affected by the number of α- and β-tryptase alleles [15]; though, patients with mastocytosis often have a greater elevated α-tryptase form over β-tryptase [3].

Total serum tryptase is a reliable indicator of bone marrow MC burden in mastocytosis and can help distinguish subtypes [16]. Patients with systemic mastocytosis tend to have higher total serum tryptase than those with cutaneous mastocytosis [16]. Furthermore, within the latter group, those with more extensive disease (diffuse cutaneous mastocytosis), have higher tryptase levels than more limited disease (mastocytoma, maculopapular cutaneous mastocytosis) [17, 18]. Children with cutaneous mastocytosis were more likely to have flushing symptoms and bullous skin lesions with hypertryptasemia [19].

Curiously, in one study [20], systemic mastocytosis patients who had at least one episode of anaphylaxis have lower baseline tryptases than those who had not, indicating that MC burden by itself is not a risk factor for anaphylaxis. Furthermore, the anaphylaxis risk appeared to be bell-shaped with rising tryptase level. Up to a tryptase level of 40 µg/L, the anaphylaxis risk seems to increase, which decreases with tryptases greater than 40 µg/L [21].

### *MC Activation Syndrome*

MC activation syndrome (MCAS) is one form of MC activation disorder characterized by excess MC mediator release without evidence of MC clonal disease. These heterogeneous conditions are often associated with biochemical evidence of MC activation, but total tryptase may be normal. In one study, only a third of patients had hypertryptasemia [22]. It is important that in these patients, other causes of hypertryptasemia are investigated and excluded such as mastocytosis. Patients often complain of a constellation of episodic symptoms such as abdominal pain, flushing, and poor concentration, and consistent with MC activation disorder, they typically respond well to MC mediator inhibitors [23].

### *Urticaria/Angioedema*

Basal total serum tryptase tends to be higher in patients with chronic urticaria over atopic and non-atopic healthy controls, likely due to increased MC burden and/or greater release of tryptase per MC [24]. Other studies have found tryptase ≥15 µg/L in 12% of patients with urticaria/angioedema without anaphylaxis [25]. Hypertryptasemia was seen between 3 and 9% of patients with chronic spontaneous urticaria (CSU) [26, 27]. As expected, this hypertryptasemic CSU cohort was older than the normotryptasemic CSU patients, and 44% consented to bone marrow biopsies which excluded systemic mastocytosis [27].

## Familial Hypertryptasemia

The tryptase locus contains five tryptase-encoding genes: *TPSG1*, *TPSB2*, *TPSAB1*, *TPSD1*, and *TPSE1* which are found on chromosome 16p [1, 28]. Lyons et al. [29] described familial cohorts that had elevated baseline tryptases via increased copy number α-tryptase-encoding regions on *TPSAB1*. These patients have a baseline tryptase of >8 µg/L and commonly have complaints of arthralgias, gastroesophageal reflux disease, flushing, urticaria, hypermobility, postural orthostatic tachycardia syndrome, increased risk of anaphylaxis to stinging in-

sects, and irritable bowel syndrome [29]. Furthermore, duplications and triplications of the  $\alpha$ -tryptase-encoding regions on *TPSAB1* were associated with higher basal tryptase levels (mean  $15 \pm 5$  and  $24 \pm 6$   $\mu\text{g/L}$ , respectively) which correlate with increasing symptoms [28].

The mechanism of this appears to be through increased secretion of pro-tryptase from MCs and basophils; though curiously, total tryptase within these cells does not appear to be increased [28]. These patients were determined to have the autosomal dominant condition termed familial hypertryptasemia (FHT) or hereditary  $\alpha$ -tryptasemia. MCs from these patients do not appear to be more prone to degranulation, indicating the problem is not a disorder of MC activation [29]. A recent study found that in these patients,  $\alpha$ -tryptase forms tetramers with  $\beta$ -tryptase in MCs and mediates the biological activity and hence symptoms of hereditary  $\alpha$ -tryptasemia [30].

There are variable responses to treatment which consists of high-dose H1 and H2 antihistamines, and cromolyn sodium [28]. A patient with sclerotic bone lesions from gene duplication FHT received partial symptomatic relief with zoledronic acid [31]. In a preliminary investigation, some of these symptoms responded to omalizumab, which may be, in part, attributed to the downregulation of Fc $\epsilon$ RI on MCs [32].

Other cases of FHT have been described with associated MCAS and have an uncertain genetic basis [33]. A curious and rare case also exists of a family with five  $\alpha$ -tryptase-encoding genes and a mean baseline tryptase of around 35  $\mu\text{g/L}$  [34]. As a recently described entity, further case experiences of FHT are required to further our understanding of this condition.

### **Chronic Kidney Disease and End-Stage Kidney Disease**

Tryptase may be raised in patients with chronic kidney disease (CKD), accounting for around 7% of all elevated tryptase samples in one laboratory's retrospective review of elevated tryptases [35]. It tends to be elevated with more severe CKD, correlating with other markers of CKD including creatinine and proteinuria [36]. Hence, the majority of patients on chronic hemodialysis have hypertryptasemia with a mean level of 17.3  $\mu\text{g/L}$  in one study [37]. Correspondingly, serum tryptase is also an independent risk factor for the progression of CKD to end-stage kidney disease [38].

It is likely that hypertryptasemia is a secondary phenomenon of renal inflammation. MCs are found in the

renal interstitium and are involved in the pathogenesis of renal injury, inflammation, and fibrosis [39–41]. Increased circulating serum stem cell factor, which promotes growth of MCs, has been observed in CKD and may be another mechanism for hypertryptasemia [42]. Furthermore, total tryptase was not detected in the urine of mastocytosis patients by ELISA, indicating that reduced renal clearance is unlikely a mechanism for hypertryptasemia [43]. Of course, if tryptase is degraded into other metabolites, this may be missed in this study; however, the metabolism of serum tryptase is not currently known.

### **Hematological Malignancies**

Tryptase expression by myeloblasts has been found using flow cytometric and histological techniques [44]. It has become a useful surrogate diagnostic and prognostic marker in a range of hematological malignancies [45]. Consequently, a fifth of myelodysplastic syndromes, myeloid neoplasms, and myeloproliferative disorders typically have raised serum tryptase levels [46, 47]. In acute myeloid leukemia, persistently elevated tryptase is associated with increased risk of clinical relapse [48].

Although lymphoid neoplasms are thought not to increase serum tryptase, MCs may be associated with some B cell neoplasms [49], and at least one case report exists of a patient who had hypertryptasemia and acquired angioedema to non-Hodgkin's lymphoma, both of which resolved upon treatment and remission of the cancer [50]. Non-MC clonal diseases such as B cell lymphomas can be a rare complication of systemic mastocytosis [51].

MC leukemias may accompany other myeloid hematological malignancies and generally have poor prognoses. Expectedly, these cases have hypertryptasemia which reflects MC burden and symptoms similar to mastocytosis patients [52, 53]. MC sarcoma is a rare and aggressive clonal MC disorder that commonly affects bone. One systematic analysis of 23 cases found a markedly elevated median tryptase of 236  $\mu\text{g/L}$  [54].

By extension, the myeloproliferative form of the hypereosinophilic syndrome also has hypertryptasemia as a feature. The hypertryptasemic subset of patients with this feature had features of splenomegaly, fibrosis (e.g., endomyocardial fibrosis), and increased bone marrow MC dysplasia over the non-hypertryptasemic hypereosinophilic syndrome patients [55]. These patients can also be identified by the presence of the fusion gene of Fip1-like 1 (*FIP1L1*) to platelet-derived growth factor receptor  $\alpha$

(*PDGFRA*) and helps distinguish patients from those who have systemic mastocytosis with eosinophilia, which is a distinct pathological entity [56].

### Cardiovascular Disease

The observation that baseline tryptase is positively correlated with the degree of coronary artery disease suggests either a role for MCs in the pathogenesis of coronary artery disease or activation as a bystander process [57]. MCs found in cardiac tissue are increasingly being recognized in the pathophysiology of various cardiac disorders [58].

Consistent with this, higher serum levels of tryptase are noted in patients who have suffered an acute coronary syndrome (ACS) compared to healthy controls [59, 60]. This finding persisted even up to 3 months post ACS event [59]. Tryptase levels also have prognostic powers in determining future risk of major adverse cardiovascular events. In patients who had an ST segment elevation myocardial infarction, post percutaneous intervention tryptase negatively correlated with myocardial reperfusion and left ventricular ejection fraction [61]. Hence, patients who experienced major adverse cardiovascular events 2 years post ACS had higher baseline and discharged tryptase levels than those who did not [62, 63]. This finding was independent of troponin and C-reactive protein levels [63].

MCs are also found in blood vessels and play a role in surveillance of the blood for IgE molecules and the pathogenesis of aneurysmal formation [64, 65]. Consequently, there have been two case reports of patients, with a history of hymenoptera anaphylaxis, who had markedly elevated baseline tryptases in the setting of abdomen aortic aneurysms. Following their repairs, the tryptases largely normalized [66].

Postmortem tryptase has also been noted to be increased in patients who have died from ACS or acute dissecting aneurysms, with median values of 17.2 and 19.0  $\mu\text{g/L}$ , respectively, compared to 74.2  $\mu\text{g/L}$  for anaphylactic shock [67].

### Eosinophilic Gastrointestinal Disorders

MCs are playing an increasingly recognized role in various gastrointestinal disorders such as irritable bowel syndrome [68]. It is therefore no surprise that raised tryptase may be seen in a subset of gastrointestinal diseases. A pooled total of 27.2% patients with eosinophilic esophagitis (EoE) have hypertryptasemia [69, 70], in line

with the finding that EoE biopsies have increased numbers of tryptase-positive MCs over control gastroesophageal reflux disease patients [71]. These EoE patients tend to have more abdominal pain, asthma, urticaria, and arthralgias than patients with normal tryptase, with no increase in allergic manifestations or diarrhea [69, 70]. Tryptase was not correlated with eosinophil count on biopsies [70], and it is unclear whether tryptase correlates with disease activity. Hypertryptasemia has also been found in eosinophilic gastroenteritis [55].

### Parasitic Infections

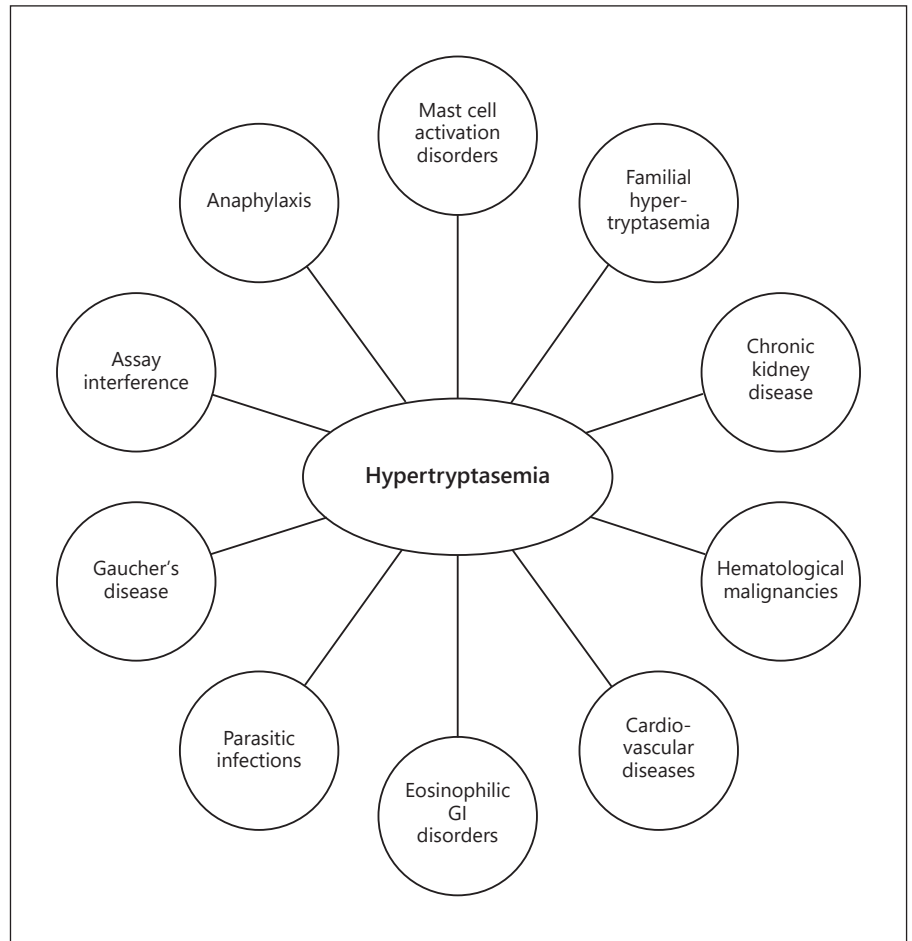
MCs and tryptase play a significant role in parasitic infections [72], so it is of no surprise that serum tryptase can be elevated in these infections. Despite this, only one disease example of this could be found in the literature. Onchocerciasis (river blindness) is caused by the parasitic worm *Onchocerca volvulus*. This condition causes devastating cutaneous lesions and blindness. As part of the treatment of this disease with ivermectin, MC infiltration follows shortly which concomitant rise in serum total tryptase levels above reference range [73], and MC infiltration in nodules [74]. This reflects the T helper 2 cell-driven anti-parasitic immune response indicating that serum tryptase may act as a monitoring biomarker.

### Gaucher's Disease

Gaucher's disease is a rare genetic disorder caused by the deficiency of  $\beta$ -glucocerebrosidase, an enzyme for the catabolism of glucocerebroside, a component of cell membranes. Therapy involves enzyme replacement therapy for which immediate hypersensitivity reactions are possible. A single case report exists of an 18-month-old boy who had an immediate hypersensitivity to imiglucerase enzyme replacement and an elevated baseline tryptase of 63.2  $\mu\text{g/L}$ . Bone marrow examination excluded systemic mastocytosis and the authors wondered about the possibility of intrinsic MC or myeloid lineage perturbations contributing to the hypertryptasemia [75].

### Assay Interference

Immunoassays such as the fluoroenzyme immunoassay are subject to interference from the sample and can falsely elevate the value of the analyte being measured.



**Fig. 1.** Causes of hypertryptasemia. GI, gastrointestinal.

Heterophilic antibodies (e.g., human anti-mouse antibodies) can interfere with the tryptase assay by non-specifically binding onto capture or detector antibodies and causing false elevations in the analyte [77, 78]. In one study, 14 samples with elevated tryptase were treated with heterophile antibody blocking tubes (HBTs) and normalized tryptases in 8/14 (57.1%) cases [77]. Although IgM rheumatoid factors may cause false positives in some assays, one study did not substantiate their interference with the fluoroenzyme immunoassay [79]. The authors found no correlation between the amount of IgM rheumatoid factors present and the reduction in tryptase after HBT treatment [79].

However, others argue against the significance of heterophile antibodies in causing artificially raised tryptase. Tryptase was seen to increase with age, which was not significantly affected by HBT treatment [9]. The authors opined that heterophile antibodies increase naturally with age and they appear to be of minimal relevance in

assay interference [9]. This study, however, looked at a general clinic population with only 4.1% of patients with a tryptase greater than 11.4 µg/L.

### Conclusion

Widely available and rapid tryptase testing in busy healthcare facilities has enabled quick diagnosis and confirmation of anaphylaxis. However, poor specificity for anaphylaxis or MC-mediated immediate hypersensitivities means a myriad of other diagnoses need to be considered for a raised serum tryptase level such as hematological malignancies. This phenomenon relates to the systemic distribution of MCs in the body and numerous triggers for their degranulation (Fig. 1). Accordingly, hypertryptasemia can be thought of as a product of increased numbers of MCs, increased MC degranulation, increased gene copies, or possibly artefactual from assay interference.

Despite the non-specificity, serum tryptase remains a robust biomarker and is one of the most important tests in diagnosing anaphylaxis and in the field of allergy [80]. Other tests for anaphylaxis, such as plasma histamine, have their limitations in that they have a narrow window period for which blood can be sampled or are only established in a research setting [81]. Certainly, point-of-care tryptase testing would be a useful venture in the future to quickly assist physicians in the diagnosis of anaphylaxis and/or when there is doubt as to the diagnosis.

The astute clinician needs to be cognizant of the myriad of differential diagnoses when considering hypertryptasemia and care must be exercised when evaluating the patient. Persistent evaluation of baseline tryptase that cannot be explained by common medical conditions (e.g., CKD) should prompt evaluation for rarer, yet important, diagnoses including mastocytosis. Testing for the sensitive D816V *KIT* mutation and/or bone marrow biopsy is warranted for hypertryptasemia and a clinical presentation compatible with hematological malignancy or mastocytosis [82].

It is also possible that some of the aforementioned hypertryptasemic conditions ascribed to secondary causes (e.g., CKD, urticaria/angioedema) may have undiag-

nosed FHT or increased copy numbers of  $\alpha$ -tryptase-encoding sequences on *TPSAB1* which, until recently, remained unknown. Around 6% of the general patient population may have hypertryptasemia and it is unclear how many of these have copy number variations of  $\alpha$ -tryptase-encoding genes [10]. This serves as a timely reminder to investigate appropriately to rule these conditions out, which can have important implications for patient symptomatology and management.

### Disclosure Statement

The authors have no conflicts of interest to declare.

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### Author Contributions

A.Y.S.L. contributed to concept design and wrote the manuscript.

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