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Serum Tryptase Levels in Patients with Mastocytosis: Correlation with Mast Cell Burden and Implication for Defining the Category of Disease

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Key Words
Mast cells · Mastocytosis · Tryptase · Classification · Disease criteria

Abstract

Background: The serum tryptase level is used as a diagnostic marker in mastocytosis and is considered to reflect the burden of (neoplastic) mast cells (MC). ***Methods:*** In the present study, serum tryptase levels were measured in patients with mastocytosis by fluoroenzyme immunoassay and compared with the extent of infiltration of the bone marrow (BM) by neoplastic MC, determined by tryptase immunohistochemistry. Sixteen patients with cutaneous mastocytosis (CM) and 43 patients with systemic mastocytosis (SM) were examined. ***Results:*** In most patients with CM (defined by the absence of dense compact MC infiltrates in tryptase-stained BM sections), normal or near-normal serum tryptase levels (median 10 ng/ml, range 2–23 ng/ml) were measured. By contrast, in the vast majority of patients with SM, elevated serum tryptase levels (median 67 ng/ml) were found. In addition, there was a significant correlation between the grade of infiltration of the BM by neoplastic MC and tryptase levels in patients with SM ($r = 0.8$). Moreover, enzyme levels differed significantly among the groups of patients with different types of SM. The highest levels (>900 ng/ml) were detected in the patient with MC leukemia, 2 patients with slowly progressing SM and high MC burden (smoldering SM) and 1 patient with indolent SM. In contrast, in all 3 patients with isolated BM mastocytosis (no skin lesions and no signs of multiorgan involvement), serum tryptase levels were <20 ng/ml. ***Conclusions:*** In summary, our data suggest that the measurement of serum tryptase is a reliable noninvasive diagnostic approach to estimate the burden of MC in patients with mastocytosis and to distinguish between categories of disease.

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Introduction

The term mastocytosis denotes a group of disorders characterized by abnormal growth and accumulation of mast cells (MC) in one or more organs [1–4]. Cutaneous and systemic variants of the disease have been described [1–7]. Cutaneous mastocytosis (CM) typically manifests as urticaria pigmentosa and shows a benign course [7]. The involvement of extracutaneous organs is not detectable in these patients. Systemic mastocytosis (SM) is characterized by multiorgan involvement [1–6] and may develop at any age. The spectrum of SM ranges from an indolent clinical course to aggressive forms with rapid progression of the disease [1–6, 8–11]. Based on the histology of the organ(s) involved, impairment of organ function and biochemical markers, diagnostic criteria and an updated consensus classification for mastocytosis have recently been proposed [12].

During the past few years, it has been found that most if not all variants of SM represent clonal neoplastic disorders. In particular, recurring transforming point mutations of *c-kit* as well as consistent disease-related abnormalities in the phenotype of MC have been described in SM. Of particular interest is the abnormal (diagnostic) expression of CD2 and CD25 on bone marrow (BM) MC [13–22]. Recently, serum tryptase was introduced as an additional diagnostic marker of the disease [23]. In particular, it was found that almost all patients with typical urticaria pigmentosa (UP) have normal tryptase levels, whereas in the majority of cases with SM, enhanced tryptase levels were measured. Moreover, it has been hypothesized that the level of serum tryptase reflects the total burden of MC in patients with mastocytosis [23–26]. However, so far this hypothesis has not been tested formally.

In the present study, we attempted to correlate serum tryptase levels with the grade of infiltration of the BM by tryptase-positive (neoplastic) MC in patients with mastocytosis.

Patients and Methods

Patients

A total number of 59 patients (29 females, 30 males) with mastocytosis were analyzed retrospectively in a multicenter study (Universities of Innsbruck, Madrid, Tübingen and Vienna). The median age was 40 years (range 5–77 years, mean ± SD 43 ± 14 years). Sixteen patients presented with CM and 43 patients had SM. According to recently established criteria [12], patients with SM were classified as having indolent SM (ISM; n = 31), (isolated) BM mastocytosis (BMM; n = 3), smoldering SM (SSM; n = 3), aggressive SM (ASM; n = 5) and MC leukemia (MCL; n = 1). Patients with an associated clonal hematologic non-MC lineage disease were excluded because patients with myeloid neoplasms without mastocytosis (i.e. a subgroup of acute myeloid leukemia, but also other myeloid neoplasms) are known to exhibit elevated levels of serum tryptase [27, 28]. The characteristics of the patients included in this study are shown in table 1.

Table 1. Patient characteristics

Mastocytosis (subtype)	n	Median age years	Presence of UP-like skin lesions	Median serum tryptase level ng/ml
CM	16	36 (5–76)	16	10.3 (2–23)
ISM	31	42 (18–71)	30	51.5 (15–938)
ISM/BMM	3	57 (47–63)	0	7.2 (6–11)
SSM	3	47 (40–48)	3	940 (148–970)
ASM	5	44 (21–77)	1	290 (72–477)
MCL	1	34	0	970

Figures in parentheses represent range.

Immunohistochemistry

BM biopsies were obtained from the iliac crest after informed consent was given. The BM biopsy specimens were fixed in 7.5% neutral buffered formalin (overnight), decalcified in EDTA and embedded in paraffin. Sections of 2 μm were cut, dewaxed and treated with 0.3% methanol-H_2O_2 (v/v) (30 min) or 0.3% TBS-H_2O_2 to block endogenous peroxidase activity. After each step, sections were rinsed twice in 0.05 *M* Tris-buffered saline (TBS; pH 7.5). Immunohistochemical staining was performed according to published techniques [29, 30]. In brief, sections were incubated with antitryptase monoclonal antibody (mAb) G3 (Chemicon, Temecula, Calif., USA) for 1 h at room temperature (RT), washed in TBS, incubated with biotin-labeled horse anti-mouse antibody (30 min, RT), washed and then exposed to avidin-biotin-peroxidase complex (30 min, RT). Antibody binding was made visible using 3-amino-9-ethylcarbazole. Sections were counterstained with Mayer's haemalaun and mounted in Aquatex. Control slides were treated similarly, with the primary antibody being omitted. Tryptase-stained BM sections were examined to establish the diagnosis and to estimate the grade of infiltration of the BM by neoplastic MC (percentage of dense infiltrates). According to recently established consensus criteria, the 'minimal' diagnostic infiltrate is defined as a dense, usually sharply demarcated histologic lesion consisting of at least 15 MC per infiltrate with a considerable number of spindle-shaped cells [12].

Measurement of Tryptase

Total serum tryptase (α-pro- + β-types) concentrations were measured by a commercial fluoroimmunoenzyme assay (Pharmacia, Uppsala, Sweden) [31]. The detection limit of this assay was 1 ng/ml. No cross-reactivities with histamine, heparin or cytokines were found [32].

Statistical Analysis

In order to analyze the significance of differences in serum tryptase levels and the grade of BM infiltration by dense tryptase-positive infiltrates among the different groups of patients with mastocytosis,

the Kruskal-Wallis test (variance analysis for nonparametric data) was applied. Differences were considered to be significant when the p value was <0.05. Linear regression analysis was done to evaluate the correlation between concentrations of serum tryptase and the infiltration grade of neoplastic MC in the BM.

Results

Immunohistochemistry

The diagnosis of mastocytosis is traditionally based on histological and cytomorphological examinations of MC in tissue (BM) sections. We performed immunohistochemistry using the antitryptase mAb G3 on BM biopsy specimens in order to diagnose mastocytosis and to determine the percentage of infiltration of the BM by neoplastic MC. In each case, the entire area of the BM section was examined (range 10–250 mm^2). In line with previous data [30], the mAb G3 was found to produce a clear staining reaction with MC. In patients with CM, only a few, if any, loosely scattered tryptase-positive cells were detectable, but no dense infiltrates. In SM, marked differences in the infiltration patterns were observed, ranging from a few 'diagnostic' infiltrates up to large multifocal dense infiltrates with additionally increased numbers of loosely scattered MC. In typical ISM, the percentage of BM infiltration with neoplastic MC ranged between 1 and 65% (median 14%). In BMM, BM infiltration was less than 10% in all 3 cases. By definition, cases with SSM showed a high infiltration grade (25, 50 and 70%). Moreover, discrete signs of myeloproliferation (not fulfilling criteria for an associated clonal hematologic non-MC lineage disease) were found in 2 cases with SSM. In ASM, the median infiltration grade of the BM was 25% (range 5–70%). In the patient with MCL, the grade of MC infiltration was 85%. Figure 1 shows the grade of BM infiltration in the different categories of SM. As assessed by Kruskal-Wallis test (for comparing multiple groups with nonparametric distribution), these differences were found to be significant ($p < 0.005$). The 'group' MCL was not included in our statistics, as only 1 patient had MCL.

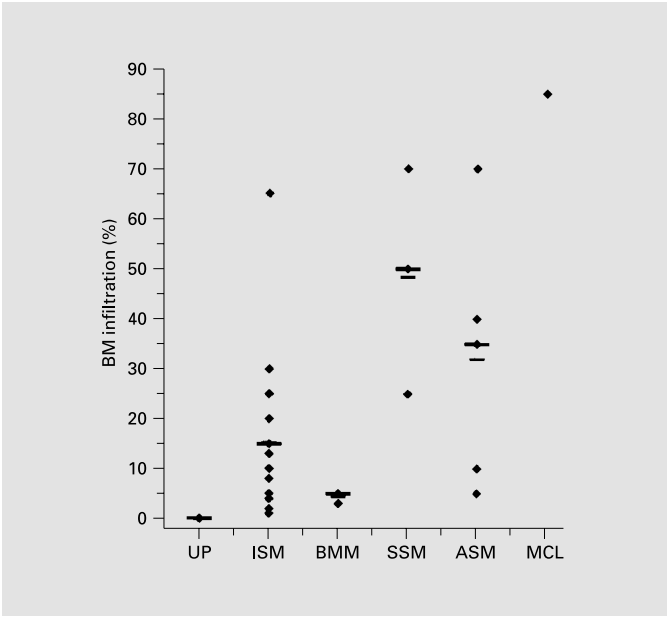

Fig. 1. Percentage of BM infiltration with dense infiltrates of MC in various categories of mastocytosis. The grade of MC infiltration was determined by tryptase immunohistochemistry. The median percentages (thick horizontal bars) and mean percentages (thin horizontal bars) for each group are also shown. Differences among disease categories were found to be significant ($p < 0.005$).

Serum Tryptase Levels in Patients with Mastocytosis

The vast majority of patients with CM (87%) had serum tryptase levels <20 ng/ml with a median of 10 ng/ml (range 2–23 ng/ml). Only 2 patients (13%) had slightly elevated levels, with 22 and 23 ng/ml, respectively. In contrast, 35 out of all 43 patients with SM (81%) had serum tryptase levels >20 ng/ml. The median serum tryptase level in the whole SM group was 67 ng/ml (range 6–970 ng/ml). However, the median serum tryptase values and the percentages of cases with serum tryptase >20 ng/ml differed greatly among the various categories of SM. In fact, a serum tryptase level >20 ng/ml was found in 26 of 31 patients with typical ISM (84%), 3 of 3 patients with SSM (100%) and 5 of 5 patients with ASM (100%). The 3 cases with BMM (a subgroup of ISM) had normal serum tryptase levels (6, 8 and 11 ng/ml). The highest serum tryptase levels were found in 2 patients with SSM (940 and 970 ng/ml), the patient with MCL (970 ng/ml) and 1 patient with ISM (938 ng/ml). The median tryptase level in the ASM group was 290 ng/ml (range 72–477 ng/ml). In patients with typical ISM, the serum tryptase levels varied greatly and ranged from 15 to 938 ng/ml with a median of 52 ng/ml. Figure 2 shows a comparison of tryptase levels in different disease categories. In a subset of patients ($n = 6$), serum tryptase levels were determined serially over a longer time period (>1 year) and showed a constant range without major changes (data not shown).

Correlation between Serum Tryptase and BM Infiltration by Neoplastic MC

As visible in figure 3, a significant correlation ($r = 0.8$) was found between serum tryptase levels and the BM

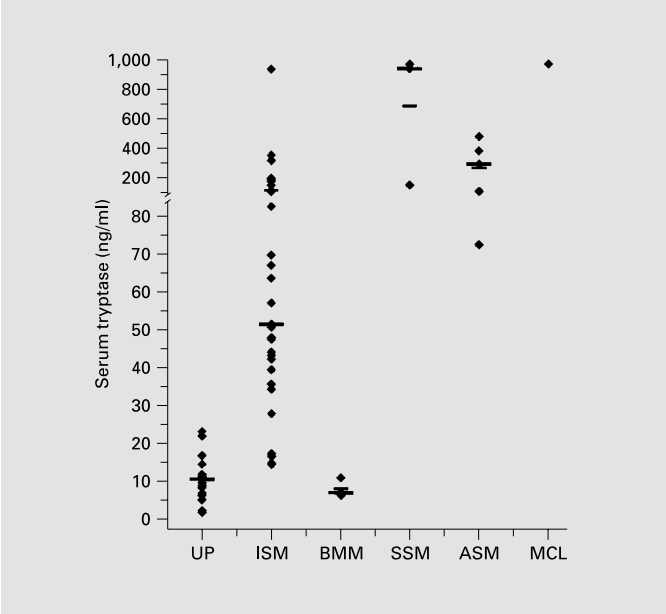

Fig. 2. Serum tryptase levels in various groups of patients with mastocytosis. Serum tryptase levels were measured by fluoroimmunoenzyme assay. The median (thick horizontal bars) and mean (thin horizontal bars) serum tryptase levels in each category of mastocytosis are also shown. Differences in serum tryptase levels found among categories of disease were found to be significant ($p < 0.005$).

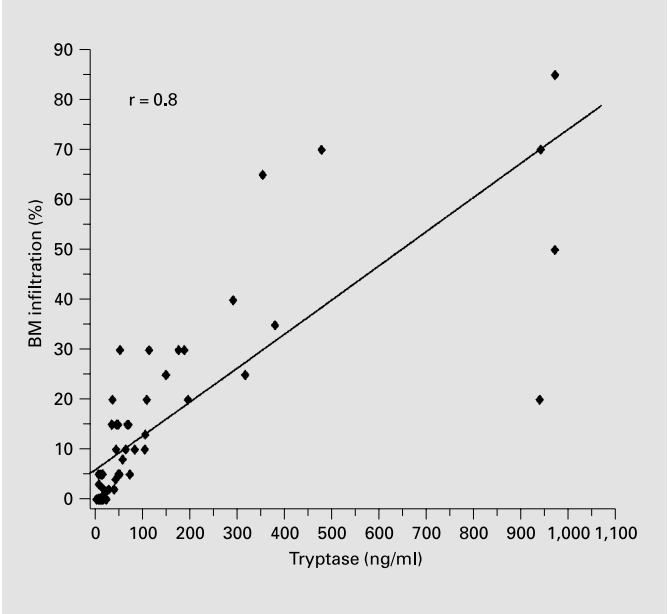

Fig. 3. Correlation between serum tryptase levels and BM infiltration grade in SM. Serum tryptase levels and the grade of BM infiltration by neoplastic MC were correlated. The grade of infiltration by dense MC infiltrates was assessed by tryptase immunohistochemistry using the antitryptase mAb G3. A significant correlation between the enzyme level and infiltration grade was found ($r = 0.8$).

infiltration grade assessed by tryptase immunohistochemistry. In cases with a BM infiltration grade exceeding 5%, the serum tryptase level was always higher than 20 ng/ml. Only 1 patient with a relatively low BM infiltration grade (20%) had a very high serum tryptase level (938 ng/ml). This could be explained by an infiltration of organs other than the skin or BM. All in all, the serum tryptase levels appeared to correlate well with the MC burden (visualized in BM sections) in patients with SM.

Discussion

In the present study, serum tryptase levels and the percentage of infiltration of the BM by neoplastic MC were analyzed in 59 patients with mastocytosis. In the majority of patients with CM, the serum tryptase level was less than 20 ng/ml, whereas almost all cases with SM had tryptase levels higher than 20 ng/ml. A significant correlation was found between the serum tryptase levels and the percentage of dense infiltrates of MC in the BM. The highest enzyme levels were detected in patients with SSM and MCL. Interestingly, all 3 patients with BMM expressed a normal tryptase level. All in all, serum tryptase measurement seems to be an important noninvasive diagnostic approach for the estimation of the MC burden in patients with SM.

The diagnosis of mastocytosis is traditionally based on histologic examination of involved tissue [1, 2]. In almost all cases of SM, the BM is affected and has to be examined to establish the diagnosis. Thus, the presence of focal accumulations of MC with typical histological and cytomorphological properties [1, 2, 8, 33–35] is still the major diagnostic criterion for SM. In the past, BM sections stained with Giemsa, toluidine blue or chloroacetate esterase were used for the diagnosis of SM [1, 2]. However, recently it has been shown that the use of mAbs against MC tryptase is always superior in screening for diagnostic histological lesions [33, 34]. Therefore, in this study, the diagnosis of SM was based on tryptase staining of BM sections, and only patients without immunohistochemically detectable (tryptase-positive) BM infiltrates were classified as having CM. The grade of infiltration of the BM by MC in SM was also established on the basis of tryptase immunohistochemistry.

Recently, the serum tryptase level was introduced as a diagnostic marker for SM. Moreover, it has been assumed

that the enzyme level reflects the total burden of MC in SM [24, 25]. However, so far, this hypothesis has not been confirmed by solid data comparing enzyme levels and a quantitative histological parameter. In the present study, we were able to demonstrate a significant correlation between the percentage of dense infiltrates with neoplastic MC in the BM and the level of serum tryptase in SM. In fact, in almost all patients with a high infiltration grade, serum tryptase levels were also in the upper range. In a few patients, however, especially in those with ISM, serum tryptase levels were higher than would have been expected from immunohistochemical findings. This may be due to a significant involvement (MC infiltration) of extracutaneous organs other than the BM in these patients. Another possibility would be a higher rate of constitutive (or induced) secretion of tryptase compared to other patients. In fact, the pro-α type of tryptase is constitutively released by normal and neoplastic MC and is the predominant form measurable in the serum of patients with SM [26]. A third possible explanation for the divergent results obtained from immunostaining of BM and serum enzyme measurements in some patients with SM could be that apart from dense infiltrates, a variable amount of loosely scattered MC were also present in the BM. These cells are easily detectable by staining with an antitryptase antibody, but were not included in the estimation of the MC infiltration of the BM in our mastocytosis patients [34, 35]. These loosely scattered MC, however, may also contribute to the MC burden and thus to the level of serum tryptase. Overall, in the whole group of patients with SM, a high MC burden was reflective of a markedly enhanced serum tryptase level.

Patients with CM usually have serum tryptase levels of less than 20 ng/ml. However, in the present study, 2 out of 16 patients with CM had slightly elevated serum tryptase levels. This may be due to the fact that a few small-sized MC lesions could have developed in the BM (or in other organs), but were not present (or detected) in the biopsy material obtained. Another possibility would be that the MC burden in the skin (or the enzyme secretion rate in skin MC) was sufficient to cause an elevated serum tryptase level in these patients.

In both ISM and ASM, a subgroup of patients presented with very high serum tryptase levels as well as a high grade of BM infiltration by neoplastic MC. On the other hand, not all patients with ASM had a high amount of BM MC or very high tryptase levels. One of our patients with ASM presented with a low grade of BM MC infiltrates (5%) and a rather low serum tryptase level (72 ng/ml). Thus, the serum tryptase level and BM infiltration grade per se do not seem to be absolutely indicative of the aggressiveness of the disease. In line with this notion, some patients with ISM had tryptase levels over 200 ng/ml and a very high grade of MC infiltration in the BM without any symptoms or signs of aggressiveness. This coincidence of high levels of disease-related markers, i.e. high serum tryptase levels and a high grade of BM infiltration, and no or only mild disease-related symptoms is characteristic of SMM. This entity has therefore been proposed as a provisional subcategory of ISM [12].

The second provisional subentity of ISM is (isolated) BMM [12]. Until now, BMM was primarily known by pathologists, since an infiltration of extramedullary organs except the skin cannot be excluded without extensive staging biopsies (which is not practicable in indolent cases). Thus, by definition, in patients with BMM, only one organ, i.e. the BM, should be involved, and the burden of MC is low. In the present study, a subgroup of (indolent) patients with dense MC infiltrates (low infiltration grade) in the BM, but without skin lesions, had normal serum tryptase levels. These findings argue against a high MC burden or involvement of multiple organs. In fact, we believe that the presence of small-sized BM MC infiltrates without skin lesions together with a normal serum tryptase level provides evidence for the presence of BMM. Of particular importance in this regard is the notion that the majority of patients with aggressive MC disease (ASM, MCL) also present with BM infiltration without skin lesions, similar to patients with BMM. However, in contrast to BMM, tryptase levels are always elevated in these cases, indicating a high MC burden with infiltration of multiple organs. Thus, together with other disease-related parameters (e.g. the absence of skin lesions), the measurement of serum tryptase seems of great importance in the staging of mastocytosis and the differentiation between prognostically different categories of the disease.

Taken together, our results show that the measurement of serum tryptase levels is an important diagnostic approach in patients with mastocytosis and is helpful for the estimation of the burden of neoplastic MC and for the delineation of subgroups of patients.

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