



## Letters

## Serum tryptase levels in pediatric mastocytosis and association with systemic symptoms

Mastocytosis is characterized by clonal expansion of mast cells. When diagnosed in children, mastocytosis is usually limited to the skin, which is termed cutaneous mastocytosis (CM). According to its clinical presentation, CM can be classified into mastocytoma (20% of cases), maculopapular CM (MPCM, 75%; previously urticaria pigmentosa), and diffuse cutaneous mastocytosis (DCM; 5%).<sup>1,2</sup> Contrary to adult-onset mastocytosis, complete or partial resolution is often noted by adolescence.<sup>3</sup> Serum tryptase level is a marker of mast cell burden. It is widely available and used to assess risk of systemic involvement. Other causes of elevated basal tryptase levels include chronic eosinophilic leukemia, renal disease, and hereditary  $\alpha$ -tryptasemia.<sup>4</sup>

For most clinical laboratories, the reference range of serum tryptase is 0 to 11 ng/mL. Current guidelines indicate that a level above 20 ng/mL is a minor diagnostic criterion for systemic mastocytosis (SM); therefore, bone marrow biopsy and other investigations are considered for patients with elevated serum tryptase levels.<sup>4,5</sup> This recommendation is still discussed for pediatric CM, considering the characteristic benign clinical course of disease. Bone marrow biopsy is considered an invasive procedure and may require general anesthesia in children. We examined serum tryptase levels in pediatric patients with CM to determine its range in our pediatric cohort and its association with systemic symptoms.

We conducted a retrospective review of serum tryptase levels and clinical progression of all patients with diagnosis of mast cell disorders examined at our hospital outpatient allergy clinics from January 2006 to August 2017. A positive Darier sign was required for CM diagnosis. General symptoms, such as flushing, generalized pruritus, abdominal pain, diarrhea, or anaphylaxis, were recorded. This study was conducted with approval from our institutional review board.

From 3,159,616 pediatric patients examined in our hospital during that time, we identified 114 patients with CM (60 males and 54 females; median age, 4 years; age range, 5 months to 17 years). Pediatric mastocytosis was classified according to clinical features. Abdominal imaging to assess organomegaly was not indicated for most patients. Patients with diagnosis of urticaria pigmentosa were classified under MPCM. Monomorphic and polymorphic forms were not separately reported. A total of 100 patients (89%) received a diagnosis of MPCM, 10 (8.7%) of mastocytoma and 4 (3.5%) of DCM. None of the patients received a diagnosis of SM during the study period. Tryptase levels were not obtained in 16 patients with MPCM and 4 patients with mastocytoma. The patients with MPCM and mastocytoma had a median tryptase level

of 5.6 ng/mL (range, 2–65 ng/mL), and values for the 4 patients with DCM were 18, 75, 160, and 283 ng/mL (Fig 1). A total of 2 patients with DCM experienced systemic symptoms, including flushing and diarrhea that improved over time.

The serum tryptase level was elevated in 10 patients with MPCM, and 3 of these patients had levels above 20 ng/mL (32, 33, and 65 ng/mL). Notably, 12 patients (10.7%) with MPCM and mastocytoma had systemic symptoms. Only 3 of the 12 patients who experienced general symptoms had elevated tryptase levels, and 2 patients with mastocytoma and normal tryptase levels had episodes of idiopathic anaphylaxis. The odds ratio of presenting with general symptoms when serum tryptase level was elevated was 2.52 (95% confidence interval, 0.73–8.68). Bone marrow biopsy was performed in 1 patient with DCM with a serum tryptase level of 283 ng/mL, and results were normal. Skin biopsy confirmed mastocytosis in the 3 patients in whom it was performed. All 3 had the MPCM form. In 1 patient who presented with general symptoms and a serum tryptase level of 3 ng/mL, *cKIT* mutation c.1255\_1257del (p.D419del) was reported on skin biopsy. Genetic studies were not indicated in other patients.

Our data confirmed the association of DCM, the CM form with the highest mast cell burden, and elevated serum tryptase levels, which were significantly different from those obtained in patients with mastocytoma and MPCM ( $P < .001$ ). A relatively low value of serum tryptase at 18 ng/mL was observed in 1 patient with DCM. This finding was unexpected and a reminder of the imperfect role of this marker in the diagnosis and classification of CM forms. There was an association of elevated serum tryptase levels and presence of general symptoms, although it was not statistically significant.

Limitations of our study included the retrospective nature and the lack of patients with SM. Prospective studies that included diagnostic methods to rule out SM would be necessary to increase level of confidence on the absence of systemic disease.

A study at the National Institutes of Health examined patients with pediatric mastocytosis, including 66% of patients with MPCM, 14% with DCM, 6% with mastocytoma, and 14% with indolent SM. Although 7 of the 14 patients with DCM underwent bone marrow biopsy, none reported abnormal findings. All 19 patients who received a diagnosis of organomegaly, by their results of ultrasonography, had abnormal findings in bone marrow biopsy, which was the best predictor of SM.<sup>3</sup> All 34 patients without the diagnosis of organomegaly had normal bone marrow biopsy findings. The same group reported the association of the *cKIT* D816V mutation in peripheral blood in children with SM; however, this finding had less sensitivity than the presence of organomegaly.<sup>6</sup>

A Polish cohort of 102 children with mastocytosis was reported with a distribution of CM similar to our patient group, with 89% of patients having MPCM, 7% having DCM, and 4% having

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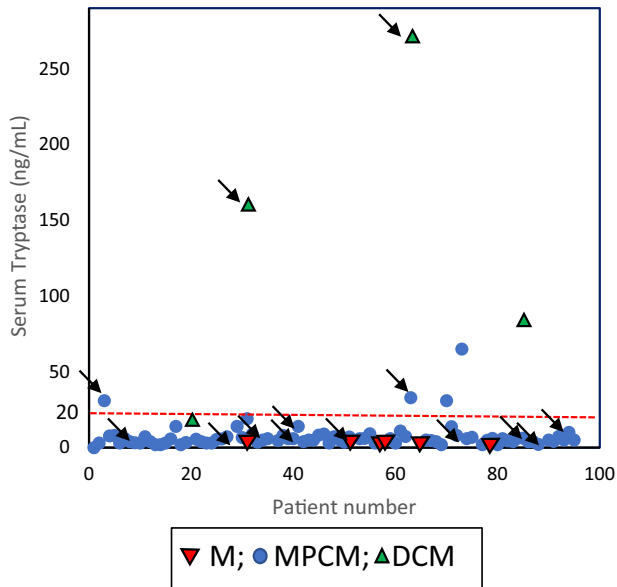


**Figure 1.** Serum tryptase levels from pediatric patients who received a diagnosis of diffuse cutaneous mastocytosis (DCM) (n = 4), mastocytoma (n = 6), and maculopapular cutaneous mastocytosis (MPCM) (n = 74) at diagnosis. Arrows indicate patients with general symptoms. DCM, diffuse cutaneous mastocytosis; MPCN, maculopapular cutaneous mastocytosis.

mastocytoma.<sup>7</sup> The investigators described 7 patients with DCM and only 6 with MPCM with serum tryptase levels greater than 20 ng/mL and none presenting with systemic symptoms; 2 patients with MPCM with normal serum tryptase levels presented with anaphylaxis episodes. Furthermore, 3 of the patients with CM with serum tryptase levels greater than 20 ng/mL underwent bone marrow biopsies, which all had normal results. The Italian Mastocytosis Registry reported serum tryptase levels (median, 5.4 ng/mL; range, 1.6–195 ng/mL) in 54 of 200 children and adolescents with mastocytosis, including 3 (tryptase levels, 16.9, 25, and 100 ng/mL) of 4 with SM.<sup>8</sup> A review of all serum tryptase levels recorded in a pediatric hospital identified 11 patients with CM during 2 years. Only 3 had elevated serum tryptase levels, and none presented with systemic involvement.<sup>9</sup>

The data from our cohort were consistent with previous reports that suggested that pediatric mastocytosis is largely limited to cutaneous disease. We found an association of serum tryptase levels with DCM but not with the risk of presenting with general symptoms, which had been previously suggested.<sup>10</sup> Bone marrow biopsies in children with CM to look for systemic disease may not be indicated based only on elevated serum tryptase levels,

and other clinical data, such as organomegaly and hereditary  $\alpha$ -tryptasemia, should be considered in this clinical decision.

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Neha Seth, MD<sup>\*,†</sup>  
 Karen T. Tuano, MD<sup>\*,†</sup>  
 Maria Buheis, MD<sup>\*,†</sup>  
 Audrey Chan, MD<sup>†,‡</sup>  
 Javier Chinen, MD, PhD<sup>\*,†</sup>  
<sup>\*</sup>Section of Allergy and Immunology  
 Department of Pediatrics  
 Baylor College of Medicine  
 Houston, Texas  
<sup>†</sup>Texas Children's Hospital  
 Houston and The Woodlands  
 Texas  
<sup>‡</sup>Section of Dermatology  
 Department of Medicine  
 Baylor College of Medicine  
 Houston, Texas  
 jchinen@bcm.edu

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