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This study was funded by the Vancouver Coastal Health Research Institute. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure of potential conflict of interest: E. Fung is employed by the University of British Columbia. The rest of the authors declare that they have no relevant conflicts of interest.

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Available online August 13, 2014.
http://dx.doi.org/10.1016/j.jaci.2014.06.037

Familial hypertryptasemia with associated mast cell activation syndrome

To the Editor:

Diagnostic criteria and a classification of systemic mastocytosis (SM) have been proposed by the World Health Organization.[1]

Patients with SM frequently experience symptoms caused by mast cell activation (MCA), such as flushing, urticaria, gastrointestinal cramping, and sometimes even life-threatening anaphylaxis. In these cases the term mast cell activation syndrome (MCAS) is appropriate.[2-4] MCAS is defined by the clinical signs of MCA confirmed by biochemical measurements (ie, increase in serum tryptase level exceeding 20% of baseline value plus absolute 2 ng/mL) and by a response of MCA symptoms to antimediator or mast cell–stabilizing agents.[3]

However, MCAS can also develop in the absence of SM. When only 1 or 2 minor criteria of SM are fulfilled, thereby indicating the presence of monoclonal mast cells without definitive evidence of overt SM, the diagnosis is still primary (monoclonal) MCAS.[2,4,5] In other patients an underlying allergy or another reactive condition is found.[2,4] However, there are also cases without underlying conditions. These patients are classified as idiopathic MCAS.

Usually SM and MCAS behave as nonheritable conditions. We present a 3-generation family in whom 4 affected relatives have had recurrent episodes of abdominal cramping and diarrhea for several years. One of the family members (patient II-5) was referred to our outpatient clinic. Diagnostic evaluations disclosed a basal serum tryptase level of 29 ng/mL (normal value, <15 ng/mL) and an increase of greater than 20% plus 2 ng/mL recorded repeatedly at the time symptoms occurred (Fig 1, *A*). Symptoms improved with mast cell stabilizers (oral cromolyn) and H_1- and H_2-anthistamines but relapsed with their cessation. On the basis of these findings, the diagnosis of MCAS was established.[4]

MCAS was also diagnosed in 3 other family members (patients II-3, II-4, and II-6), who also showed evidence for MCA and responded to oral cromolyn and antihistamines (Table I).

Interestingly, hypertryptasemia, with basal tryptase levels of greater than 20 ng/mL (median, 37 ng/mL; range, 25.5-62.7 ng/mL), was found in 7 relatives in 3 consecutive generations, suggesting a monogenic form of hypertryptasemia with autosomal dominant inheritance (Fig 1, *B*).

All patients, except III-3 and III-6, underwent a bone marrow (BM) examination. Patients II-3, II-4, II-5, and II-6 underwent gastrointestinal tract biopsies. Table E1 in this article's Online Repository at www.jacionline.org contains a list of applied antibodies for flow cytometric analyses of BM aspirates and for immunohistochemical analyses of BM and gastrointestinal biopsy specimens.

Abdominal ultrasound and measurement of bone mineral density by using dual-energy x-ray absorptiometry were also included in the clinical evaluation.

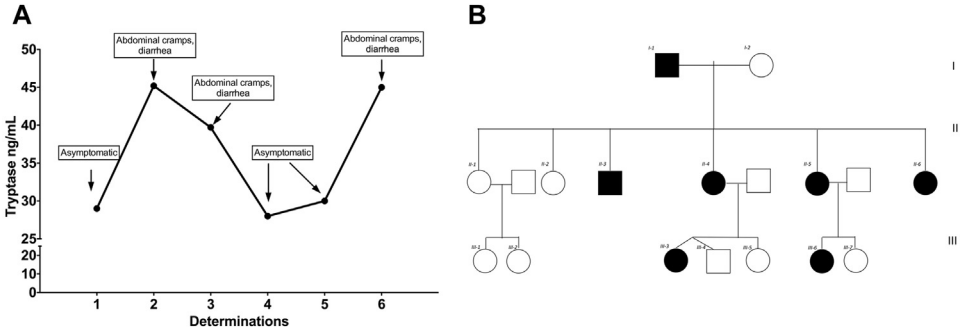

FIG 1. A, Measurements of serum tryptase levels in the asymptomatic phase and during gastrointestinal symptoms in one family member (subject II-5). From these measurements, it is evident an elevated basal tryptase level (constantly >20 ng/mL) and a significant increase (>20% of baseline plus 2 ng/mL) in concomitance of symptoms. **B,** Genealogical tree indicating familial occurrence of MCA/hypertryptasemia and showing a pattern compatible with dominant inheritance.

TABLE I. Patients' clinical and laboratory features

Features	Patients						
	I-1	II-3	II-4	II-5	II-6	III-3	III-6
Age (y)	54	19	24	21	16	0.4	3
Basal tryptase (ng/mL)	62.7	37.0	25.5	29	26.1	41.8	39.2
Symptoms indicating presence of MCAS*	Asymptomatic	Abdominal cramps and diarrhea* with response to antimediator therapy	Abdominal cramps and diarrhea* with response to antimediator therapy	Abdominal cramps and diarrhea* with response to antimediator therapy	Abdominal cramps and diarrhea* with response to antimediator therapy	Asymptomatic	Asymptomatic
CBC	Normal	Eosinophils: 750 cells/μL	Normal	Normal	Normal	Normal	Normal
Total IgE (kU/L)	24	38	54	14	106	NP	10
Screening for underlying atopic/allergic disorder†	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Liver function test results	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Renal function test result	Normal	Normal	Normal	Normal	Normal	Normal	Normal
BM	Normal trilinear hematopoiesis; no mast cell aggregates; no mast cells with atypical morphology; CD25-CD30 negative	Normal trilinear hematopoiesis; no mast cell aggregates; no mast cells with atypical morphology; CD25-CD30 negative; smear eosinophils, 5.4%	Normal trilinear hematopoiesis; no mast cell aggregates; no mast cells with atypical morphology; CCD25-CD30 negative	Normal trilinear hematopoiesis; no mast cell aggregates; no mast cells with atypical morphology; CD25-CD30 negative	Normal trilinear hematopoiesis; no mast cell aggregates; no mast cells with atypical morphology; CD25-CD30 negative; smear: eosinophils, 8%	NP	NP
Gastrointestinal biopsy	NP	No mast cell aggregates; no mast cells with atypical morphology; CD2-CD25-CD30 negative	No mast cell aggregates; no mast cells with atypical morphology; CD2-CD25-CD30 negative	No mast cell aggregates; no mast cells with atypical morphology; CD2-CD25-CD30 negative	No mast cell aggregates; no mast cells with atypical morphology; CD2-CD25-CD30 negative	NP	NP
Abdominal ultra sound	Normal	Mild hepatomegaly (15.5 cm); borderline splenic volume (12.2 cm)	Normal	Normal	Normal	Normal	Normal
DEXA densitometry	Normal	Normal	Normal	Normal	Normal	NP	NP
KIT mutation	Negative	Asp816Val	Negative	Negative	Negative	Negative	Negative
FIPL1/PGDFRA fusion	NP	Negative	NP	NP	Negative	NP	NP
Other possible symptoms related to MCA	Apathy, migraine	Apathy, migraine	Apathy	Apathy	Apathy	None	None

DEXA, Dual-energy x-ray absorptiometry; *NP*, not performed.
*During these symptoms, an acute tryptase level increase to 20% of baseline plus an additional 2 ng/mL was found.
†Includes measurement of specific IgE for house dust mite; birch, grass, and mugwort pollen; cat and dog dander; *Hevea* species latex; cow's milk; egg whites; and peanut and for the recombinant panallergens Bet v 1 *(Betula verrucosa)*, Bet v 2 *(B verrucosa)*, Pru p 3 *(Prunus persica)*, tropomyosin from shrimp, and parvalbumin from cod.

Sanger sequencing was applied to detect *KIT* mutations, *PDFRA* mutations, or both (patients II-3 and II-6), and a DNA linkage analysis was performed. For details, see DNA linkage analysis in the Methods section in this article's Online Repository at www.jacionline.org. Table I summarizes demographics, clinical, and laboratory results.

Analysis of the *KIT* gene in BM samples revealed a classic Asp816Val mutation in 1 family member (patient II-3). In this patient we also detected splenomegaly but did not find any other signs of SM (Table I). In light of only 2 minor SM criteria, we were not able to establish the diagnosis of SM in this case. We then repeated the *KIT* mutation analysis with BM cells in all family members. However, again, no other family member with the *KIT* D816V mutation was detected.

According to the current classification of MCAS, most of our family members would fit within the classification of idiopathic MCAS. In fact, the major other differential diagnosis is a primary (monoclonal) MCAS.[4-7] Indeed, an increased tryptase