Large maculopapular cutaneous lesions are associated with favorable outcome in childhood-onset mastocytosis

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Background: Mastocytosis, characterized by pathologic accumulation of mast cells, can manifest itself in adulthood or childhood. Pediatric patients usually have cutaneous mastocytosis (CM) with mast cell infiltrates limited to the skin and spontaneous improvement of skin lesions after several years. However, there are some patients with persistent disease resembling adulthood-onset mastocytosis.

Objective: The current classification of CM differentiates between 3 subforms. In clinical practice we noticed that different variants of these subforms might exist, particularly in patients with childhood-onset mastocytosis. Therefore, in the present study, we aimed to investigate whether specific cutaneous lesions in patients with childhood-onset mastocytosis are associated with other disease parameters.

Methods: We analyzed 144 patients with a disease onset of less than age 17 years using a systematic dermatologic approach.

Results: One hundred twenty-two patients presented with maculopapular cutaneous mastocytosis (MPCM), 12 patients presented with diffuse CM, and 10 patients presented with solitary mastocytoma of the skin. Patients with MPCM showed particularly heterogeneous cutaneous lesions and were therefore grouped into 3 variants presenting either with small lesions (MPCM-small, skin lesions <1 cm in diameter; n = 19), large lesions (MPCM-large, skin lesions ≥1 cm in diameter; n = 89), or atypical lesions (MPCM-other, n = 14). Patients with MPCM-large lesions, compared with those with MPCM-small lesions, were characterized by significantly lower tryptase levels, shorter disease duration, and earlier disease onset. In addition, more patients with MPCM-large lesions exhibited spontaneous regression of cutaneous lesions.

Conclusion: Our data show that patients with MPCM-large lesions compared with those with MPCM-small lesions have a more favorable disease course and suggest exploring the size of cutaneous lesions as a prognostic parameter in childhood-onset MPCM. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

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Mastocytosis is characterized by pathologic accumulation of mast cells (MCs) in tissues.[1,2] The organ most frequently affected is the skin, followed by bone marrow and the gastrointestinal tract. The current World Health Organization classification includes cutaneous mastocytosis (CM), which is defined by MC infiltrates confined to the skin, and various categories of systemic mastocytosis (SM), which are defined by accumulation of MCs in at least 1 extracutaneous organ, often combined with skin involvement.[2-6] Because of the increased release of MC mediators, patients with mastocytosis can experience pruritus, flushing, headache, abdominal cramping, diarrhea, and anaphylaxis.

Onset of mastocytosis can occur in adulthood or childhood.[7-14] Recent studies revealed several differences between adulthood- and childhood-onset mastocytosis.[10] For example, adult patients usually carry the activating mutation *KIT* D816V located in exon 17 of the *KIT* gene, whereas children express diverse *KIT* mutations affecting either exon 8, 9, 10, 11, or 17.[15-22] Most adults exhibit SM, whereas most pediatric patients have CM. Anaphylaxis is a frequent symptom in adults but only rarely concerns children.[23] Moreover, adult patients usually experience a chronic course, and children often show a transient course with spontaneous regression after several years.[24-30]

Patients with MC infiltrates in the skin exhibit heterogeneous cutaneous lesions.[31-37] The current classification of CM differentiates between 3 subforms, namely maculopapular cutaneous mastocytosis (MPCM)/urticaria pigmentosa, diffuse cutaneous mastocytosis (DCM), and solitary mastocytoma of the skin (mastocytoma).[2,4,5] However, in clinical practice we noticed that different variants of these subforms might exist, particularly in childhood-onset mastocytosis. Therefore in the present study we sought to investigate whether specific cutaneous lesions in patients with childhood-onset mastocytosis are associated with other disease parameters. Using a systematic dermatologic approach, we found that patients with large MPCM lesions compared with those with small lesions are characterized by lower tryptase levels, shorter disease duration, and more frequent spontaneous improvement.

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Abbreviations used
CM: Cutaneous mastocytosis
DCM: Diffuse cutaneous mastocytosis
MC: Mast cell
MPCM: Maculopapular cutaneous mastocytosis
SM: Systemic mastocytosis

METHODS

Patients

Our study includes 144 patients with childhood-onset mastocytosis who regularly attended the Mastocytosis Clinic of the Department of Dermatology, University of Cologne, Cologne, Germany, between 1999 and 2012 (Table I). Inclusion criteria were the presence of CM lesions and a disease onset of less than age 17 years (mean ± SD, 18.8 ± 42.1 months; range, 0-192 months). At initial presentation, age ranged from 0 to 61 years (mean ± SD, 10.6 ± 14.2 years). Patients were given diagnoses and classified into different disease categories according to established criteria.[2,4,5] Measurement of serum tryptase levels was performed at the patient's first visit by using a fluoroimmunoenzyme assay (ImmunoCAP Tryptase; Thermo Fisher Scientific, Uppsala, Sweden; mean ± SD, 23.6 ± 46.6 μg/L; range, 1.4-293.0 μg/L). In agreement with current recommendations, a bone marrow biopsy was only performed in adult patients.[4]

Characterization of CM lesions

CM lesions of all patients were assessed by an experienced dermatologist (K.H.) and a resident (T.W.) using photographic images that were routinely taken by photographers of the Photo Department, University Hospital Cologne, Cologne, Germany, at initial presentation and at follow-up visits after achieving written informed consent. Additionally, patients were asked to provide previous pictures of themselves (eg, from their beach holidays during childhood).

By defining the morphology and distribution of skin lesions, patients were first classified into 3 groups presenting with either MPCM, DCM, or mastocytoma (Fig 1). Cutaneous lesions of all patients with MPCM were then further defined as being small (skin lesions <1 cm in diameter), large (skin lesions ≥ 1 cm in diameter), or other (atypical lesions that could not be clearly described as being small or large) by defining diameter as the largest possible distance between 2 points along the border of the skin lesion. Moreover, MPCM lesions were categorized as being flat or elevated, showing a sharp or indistinct margination, round or polycyclic shape, and confluent or not confluent arrangement (see Fig E1 in this article's Online Repository at www.jacionline.org).

Mutational analysis

The presence of *KIT* codon 816 mutations was investigated in formalin-fixed and paraffin-embedded skin biopsy specimens, as previously described.[31] Briefly, total genomic DNA was extracted from paraffin-embedded sections by using the QIAamp DNA Micro kit (Qiagen, Hilden, Germany). Total DNA was used for *KIT* mutation analyses performed by using melting point analysis of amplification products with the LightCycler System (Roche Molecular Systems, Mannheim, Germany). Amplicons to be genotyped were generated by means of nested PCR and locked nucleic acid–mediated PCR clamping to increase diagnostic sensitivity.

Histologic analysis

Skin biopsy specimens were fixed in 4% neutral-buffered formalin and embedded in paraffin. Immunohistochemical investigations were performed with antibodies against MC tryptase (1:1200; clone AA-1; Diagnostic BioSystems, Pleasanton, Calif) and CD25 (1:50; clone 4C9; Novocastra, Newcastle, United Kingdom) by using the avidin-biotin immunoperoxidase staining technique. In tryptase-stained sections MC density, MC localization within the dermis, MC infiltration pattern, MC morphology, and percentage of spindle-shaped MCs were determined.

TABLE I. Clinical characteristics of patients with childhood-onset mastocytosis and skin lesions participating in the study

Parameters	All	MPCM	DCM	Mastocytoma
All, no. (%)	144 (100)	122 (84.7)	12 (8.3)	10 (6.9)
Sex				
No.	144	122	12	10
Male, no. (%)	71 (49.3)	59 (48.4)	6 (50.0)	6 (60.0)
Female, no. (%)	73 (50.7)	63 (51.6)	6 (50.0)	4 (40.0)
Disease onset (mo)				
No.	142	120	12	10
Mean ± SD	18.8 ± 42.1	21.6 ± 45.2	2.8 ± 2.3	5.2 ± 8.2
Range	0-192	0-192	0-6	0-25
Disease duration (y)				
No.	144	122	12	10
Mean ± SD	10.0 ± 12.5	9.5 ± 11.1	19.2 ± 23.4	5.1 ± 4.6
Range	0-71	0-70	1-71	0-13
Tryptase (μg/L)*				
No.	109	93	11	5
Mean ± SD	23.6 ± 46.6	**16.5 ± 35.8**	**90.2 ± 78.5**	**9.3 ± 4.7**
Range	1.4-293.0	1.4-265.0	35.4-293.0	4.9-16.0

Statistically significant differences are shown in boldface.
*Tryptase: MPCM and DCM, $P < .0001$; DCM and mastocytoma, $P = .0022$.

Statistical analysis

Statistical analysis was performed by using GraphPad Prism software (version 5.01; GraphPad Software, La Jolla, Calif) with the nonparametric Mann-Whitney *U* test. Correlation analysis was performed with Spearman rank order correlation. A *P* value of less than .05 was considered statistically significant.

RESULTS

Study population

To investigate whether specific CM lesions are associated with other disease parameters in patients with childhood-onset mastocytosis, we retrospectively analyzed 144 patients who presented with skin lesions and had mastocytosis onset at less than 17 years of age (Table I). Of these 144 patients, 122 (84.7%) were given a diagnosis of MPCM, 12 (8.3%) were given a diagnosis of DCM, and 10 (6.9%) were given a diagnosis of solitary mastocytoma (Fig 1). Serum tryptase levels at initial presentation were significantly increased in patients with DCM compared with those in patients with MPCM or mastocytoma (Table I; mean ± SD: MPCM, 16.5 ± 35.8 μg/L; DCM, 90.2 ± 78.5 μg/L; mastocytoma, 9.3 ± 4.7 μg/L). There was no significant difference in sex, disease onset, and disease duration between those with MPCM, DCM, or mastocytoma.

Characteristics of cutaneous lesions in childhood-onset mastocytosis

Cutaneous lesions were next defined in more detail by using dermatologic terms of morphology and distribution (Fig 1 and Table II). Patients with DCM and mastocytoma showed rather homogeneous skin lesions typical for DCM and mastocytoma, respectively, whereas patients with MPCM presented with heterogeneous lesions, which differed from patient to patient in, for example, size, margination, and distribution (Fig 1).