

Severity of Cutaneous Findings Predict the Presence of Systemic Symptoms in Pediatric Maculopapular Cutaneous Mastocytosis

Meredith Barnes, B.A., Livia Van, M.D., Laura DeLong, M.D., M.P.H., and
Leslie P. Lawley, M.D.

Department of Dermatology, School of Medicine, Emory University, Atlanta, Georgia

Abstract: Although the prognosis of maculopapular cutaneous mastocytosis (MPCM), also referred to as urticaria pigmentosa, is often benign, clinicians lack evidence to reliably predict those at risk of associated systemic manifestations. We sought to elucidate clinical markers of disease severity to provide better treatment and prognostic information for individuals with MPCM. A retrospective chart review querying characteristics of children diagnosed with MPCM in the Emory Dermatology Clinic was performed. Follow-up was obtained through a clinical encounter or telephone interview. Linear regression was used to determine predictors of the number of MPCM-related systemic symptoms. Of 67 subjects, 57% were male, and the mean age of onset was 4.5 months. The maximum number of MPCM lesions was 1 to 10 in 16%, 11 to 30 in 33%, 31 to 50 in 25%, 51 to 100 in 6%, and more than 100 in 20% of subjects. For their MPCM lesions, 46% of subjects reported itching, 34% flushing, and 25% blistering. Reported systemic symptoms included diarrhea (22%), abdominal pain (15%), wheezing or dyspnea (13%), vomiting (10%), bone pain (10%), headaches (8%), cough (10%), rhinorrhea (8%), irritability (6%), and anaphylaxis (1.5%). In a multivariate linear regression analysis, the maximum number of MPCM lesions ($p = 0.02$) and the number of skin symptoms ($p < 0.01$) were statistically significant predictors of the number of systemic symptoms, controlling for age of onset, body sites involved, and sex. The correlation between cutaneous findings and symptomatology could aid clinicians in identifying individuals with MPCM who might warrant systemic evaluation and therapy.

Maculopapular cutaneous mastocytosis (MPCM) is one of three subsets of cutaneous mastocytosis according to the World Health Organization (1).

Although we lack adequate terminology for pediatric mastocytosis, a consensus conference has proposed that MPCM can be used interchangeably with

Address correspondence to Leslie P. Lawley, M.D., Department of Dermatology, Dermatology Clinical and Outcomes Research Unit, Emory University School of Medicine, 1525 Clifton Road, 3rd Floor, Atlanta, GA 30322, or e-mail: Leslie.Lawley@emory.edu.

urticaria pigmentosa (UP) (1), although UP often includes other morphologies such as nodules and plaques. In past studies, UP has accounted for 70% to 90% of pediatric mastocytosis (2). The other two defined forms of pediatric mastocytosis are mastocytoma and diffuse cutaneous mastocytosis (3). This article focuses on patients with MPCM who in the past may have been labeled with UP. Although mast cell involvement is usually limited to the skin, patients with MPCM often experience cutaneous and systemic symptoms, including blistering, pruritus, diarrhea, shortness of breath, and even anaphylaxis (4). Attributed to the release of mast cell mediators that act locally and remotely, these symptoms not only affect quality of life, but also may cause significant morbidity and infrequently mortality (2,5).

Several prior studies have delineated the benign nature of pediatric MPCM in contrast to adult mastocytosis, which often has persistent, systemic involvement due to mast cell infiltration of other organ systems (2,6,7). Although pediatric MPCM often has a favorable prognosis and resolves by adolescence, clinicians lack data to support the use of noninvasive tools to assess a patient's risk for persistent symptoms. Furthermore, clinicians are unable to accurately predict the small proportion of pediatric cases that will progress to systemic involvement.

Various tools have been created to gauge the risk of severe systemic symptoms, including anaphylaxis, and the risk of disease progression (8–10). Tryptase levels have been shown to correlate with mast cell burden and have therefore been a marker that can be used to risk stratify MPCM patients. A recent study of children with mastocytosis revealed that median serum baseline total tryptase levels were statistically significantly higher in children with extensive skin involvement (>90% of body surface area). Tryptase levels also correlated with the severity of systemic symptoms, and levels were calculated to predict the likelihood of requiring daily antimediator therapy, hospitalization, and management in an intensive care unit (ICU) (8).

An additional tool called the SCORing Mastocytosis (SCORMA) index was developed to provide a clinical score based on the activity and extent of cutaneous lesions and subjective symptoms. Researchers found that the SCORMA index correlated with serum tryptase levels and proposed using the score in lieu of serial blood tests (9). A study by Brockow et al (10) compared the extent of cutaneous involvement with symptom extent and severity in children and adults with MPCM. The study revealed a

correlation in adults but failed to demonstrate a relationship in the pediatric cohort.

Considering the varying reports of the utility of correlating cutaneous findings with disease severity in children, we sought to further investigate potential clinical markers of pediatric disease severity to provide better treatment and prognostic information for children with MPCM and families.

PATIENTS AND METHODS

After receiving institutional review board approval, patients seen at the Emory Pediatric Dermatology Clinic within the last 25 years were recruited. Potential subjects were identified by initially searching for *International Classification of Diseases, Ninth Edition* diagnosis code 757.33 (congenital skin pigment anomaly). Patients newly diagnosed with MPCM in the last 5 years were also recruited. Inclusion criteria were a diagnosis of MPCM before age 15 years with five or more individual lesions, with the majority specifically described as macules and papules. Diagnosis was made according to the presence of a Darier's sign or compatible skin histopathology. The Darier's test was performed on lesional and nonlesional skin for negative control. Exclusion criteria included a diagnosis of diffuse cutaneous mast cell disease or an initial MPCM diagnosis after age 15 years.

Upon enrollment after informed consent, the patient's age, sex, race, family history of mastocytosis, review of systems (itch, flushing, abdominal pain, nausea, vomiting, diarrhea, bone pain, headache, dyspnea, irritability, syncope, palpitations, reactions to bee stings, anaphylaxis), and age of MPCM onset were documented. The frequency of positive review of symptoms per month was recorded. For patients enrolled during a clinic visit, a physical examination including cutaneous, abdominal, and lymph node assessment was completed. The approximate number and distribution of lesions was noted. If the enrollment questionnaire was performed over the telephone, the same queries were recorded from clinic visit notes. Evidence of systemic involvement, including hepatomegaly, splenomegaly, or lymphadenopathy on examination and tryptase levels and complete blood counts, were recorded if available. Subjects who agree will be followed prospectively with annual follow-up questionnaires. Results reported here were acquired from the retrospective arm of the study.

Statistical analysis was performed using the Student *t*-test to compare continuous variables. Pearson correlation coefficients were used to determine the correlation between the number of skin lesions and

systemic symptoms. Linear regression was used to determine predictors of the number of MPCM-related systemic symptoms. A p-value less than 0.05 was considered statistically significant.

RESULTS

Of the 67 individuals with MPCM identified, 38 (57%) were male (Table 1); 61% were Caucasian, 10% African American, 10% Asian, and 3% Hispanic. The mean age of onset was 4.5 months (0.37 yrs), with onset ranging from birth to 4 years of age. Mean follow-up time was 5.57 years (range 1–19 yrs), with 20 subjects being followed up for longer than 5 years. Sixteen percent of subjects had fewer than 10 lesions, 33% had 10 to 30, 25% had 31 to 50, 6% had 51 to 100, and 20% had more than 100. Ninety-three percent of MPCM lesions were on the trunk, followed by 78% on the head and neck, 69% on the lower extremities, and 60% on the upper extremities. One body site was involved in 8% of subjects, two in 20%, three in 29%, and four in 43%.

Of their MPCM lesions, 46% of subjects reported itching, 25% blistering, and 34% flushing (Table 2). Heat was the most common trigger of cutaneous symptoms reported; others included stress, friction on the skin, and a wide variety of foods, including dairy products, citrus fruits, strawberries, peanuts, chocolate, and eggs. Seventy percent of patients had a positive Darier's sign. Biopsy was performed to confirm the diagnosis of cutaneous mastocytosis in 17 patients (25%).

Systemic symptoms reported are listed in Table 2, the two most common being diarrhea (22%) and abdominal pain (15%). Thirty-six percent of subjects reported the presence of at least one systemic symptom at any time, with 20% of subjects experiencing three or more systemic symptoms. Fifteen patients had tryptase levels checked at some point during their disease course, which ranged from 3 to 37 µg/L (mean 8.4 µg/L, normal 0.3–11.5 µg/L).

Two patients with more than 100 cutaneous lesions reported emergency department visits because of nonanaphylaxis MPCM-related events, including

TABLE 1. Demographic Characteristics and Years of Follow-Up of Patients with Maculopapular Cutaneous Mastocytosis

Factor	Value
Male, <i>n</i> (%)	38 (57)
Caucasian, <i>n</i> (%)	41 (61)
Age of onset, years, mean ± SD	0.37 ± 0.64
Follow-up, years, mean ± SD	5.57 ± 4.189

TABLE 2. Prevalence of Cutaneous and Systemic Symptoms in Patients with Maculopapular Cutaneous Mastocytosis (*n* = 67)

Signs and symptoms	<i>n</i> (%)
Cutaneous	
Positive Darier's sign	47 (70)
Itching	31 (46)
Blistering	17 (25)
Flushing	23 (34)
Systemic	
Diarrhea	15 (22)
Abdominal pain	10 (15)
Wheezing or dyspnea	9 (13)
Vomiting	7 (10)
Bone pain	7 (10)
Cough	7 (10)
Headaches	5 (8)
Rhinorrhea	5 (8)
Irritability	4 (6)
Anaphylaxis	1 (1.5)

intense itching that responded to oral corticosteroid treatments. The sole patient with reported anaphylaxis was due to a reaction to midazolam given as an inpatient for a procedure.

In univariate linear regression analysis, the maximum number of skin lesions ($p = 0.004$) and the number of skin symptoms ($p = 0.002$) were statistically significant predictors of the number of systemic symptoms. The number of body sites involved, age of onset, sex, and race were not significant predictors of the number of systemic symptoms. In multivariate linear regression analysis (Table 3) that controlled for age of onset, sex, and body sites involved, the maximum number of skin lesions ($p = 0.02$) and number of skin symptoms ($p = 0.005$) remained statistically significant predictors of the number of systemic symptoms.

DISCUSSION

Our study focused on establishing a database of children with MPCM that could be used to identify

TABLE 3. Multivariate Linear Regression of the Number of Systemic Symptoms in Patients with Maculopapular Cutaneous Mastocytosis

Variable	Coefficient	p-Value
Number of lesions	0.329	0.02
Number of skin symptoms	0.386	0.005
Age of onset	−0.737	0.46
Sex	0.053	0.70
Number of sites involved	−0.131	0.38

After controlling for age of onset, sex, and body sites involved, the number of skin lesions and the number of skin symptoms remained statistically significant predictors of the number of systemic symptoms.

clinical factors associated with worse prognosis, including severe systemic symptoms and prolonged MPCM involvement. We found that a greater number of skin lesions and cutaneous symptoms were independent predictors of systemic symptoms. The number of skin lesions may help predict who is more likely to develop systemic symptoms in the future and therefore require closer long-term follow-up.

Itching was the most common skin-related symptom, experienced by almost half of the children with MPCM. Although the Darier's sign is classically considered to be pathognomonic for MPCM, only 70% of our patients had a positive Darier's sign on examination, which was lower than expected. Azana et al (2) found a positive Darier's sign in nearly 90% of their study population. Considering that the Darier's sign is frequently used to diagnose MPCM clinically, it is important not to preclude the diagnosis in its absence or be too dependent on results since interrater reproducibility can vary. The literature lacks clear directions on performing a Darier's test, which probably explains in part the variability of results. In the authors' experience, demonstration of a Darier's sign involves rubbing a representative lesion firmly for 30 seconds and then waiting several minutes for the wheal to develop. Normal skin should be rubbed similarly as a negative control. As a note of caution, children tend to have a higher concentration of mast cells in lesions, so blistering and flushing response can occur.

Gastrointestinal (GI) symptoms were the most common systemic manifestation, followed by respiratory complaints and bone pain. GI symptoms including diarrhea and abdominal pain were also the most common systemic symptoms reported in the Alvarez-Twose et al (8) MPCM population. GI symptoms were less commonly seen in the Ben-Amitai et al (6) study, but 26.5% of their MPCM study population experienced associated systemic symptoms. Neuropsychiatric symptoms have been reported in patients with mastocytosis, but our retrospective cohort did not describe such conditions, including attention disorders and hyperactivity. Twenty percent of our study population experienced three or more systemic symptoms, underscoring the importance of proper symptom management with antihistamines and mast cell stabilizers.

Anaphylaxis was rare, with the sole anaphylaxis episode occurring after exposure to midazolam. Rare reports exist of anesthetics causing anaphylaxis in individuals with MPCM, but there have not been any reports of events attributed to midazolam (11–14).

This subject had extensive skin involvement (>100 lesions) and had seven MPCM-related systemic symptoms. Treated at an outside hospital, the anaphylaxis event was based solely on a caregiver's report and may have been pseudo-anaphylaxis. Brockow et al (15) previously reported that children with mastocytosis experience anaphylaxis less often than adults, which may explain the paucity of such events in this young cohort. Two patients reported emergency department visits because of extreme pruritus. One had evidence of slight hepatosplenomegaly on ultrasound, and some white blood cell differential abnormalities, including high absolute eosinophil and metamyelocyte levels despite a normal tryptase level (7.2 µg/L). In the Alvarez-Twose et al (8) study, 2 patients with extensive cutaneous disease of a total of 80 subjects with MPCM required hospitalization for severe adverse events, including pruritus.

No consensus exists regarding the best way to predict potentially severe systemic symptoms in children with MPCM or the most appropriate way to monitor these patients. After controlling for the number of body sites involved, age of onset, sex, and race, our study demonstrated a positive correlation between the number of MPCM skin lesions and the number of systemic symptoms. We also found a statistically significant correlation between the number of skin symptoms reported, including blistering, itching, and flushing, and the number of systemic symptoms that children with MPCM experienced after controlling for the same parameters. Patients who had emergency department visits or hospitalizations from MPCM-related systemic symptoms all had more than 100 cutaneous lesions.

An article that Alvarez-Twose et al (8) recently published demonstrated a correlation between tryptase and the extent of skin disease, as well as calculated cutoff values for serum baseline tryptase levels likely to predict the need for antimediator therapy (6.6 µg/L), hospitalization (15.5 µg/L), and management in the ICU (30.8 µg/L) for individuals with MPCM. Our data regarding tryptase levels in individuals with MPCM are limited, considering a majority of subjects did not have tryptase levels drawn. Of the 15 patients with available tryptase levels, the patient with the highest tryptase level (37 µg/L) developed multiple macules, papules, and plaques that eventually became nearly confluent. Although she was given antimediator therapy, she had not required hospitalization at the time of analysis, and her parents refused further examination for systemic mastocytosis. Her evolving skin morphology highlights our need for better

terminology to classify pediatric mastocytosis. One patient with a slightly elevated tryptase level (14.5 µg/L; normal range 1–11.5 µg/L) and normal complete blood count was later discovered to have systemic involvement with mast cell infiltration of the colon and bone marrow several months later. Although the focus of the Alvarez-Twose et al (8) study was using serum baseline tryptase levels to predict symptomatology, not predicting the likelihood of systemic disease, this particular patient may represent an outlier.

In contrast to Brockow et al (10), our study demonstrated a positive correlation between the number of skin lesions and systemic symptoms, as well as between the number of skin symptoms and systemic symptoms in children with MPCM. Heide et al (9) suggested that the SCORMA index may be useful in detecting a change in severity at separate time points. Our study supports the emphasis on skin symptoms in that index. Clinicians may estimate a patient's risk of severe systemic symptoms simply by performing a good history and skin examination instead of serial blood draws. Furthermore, because symptoms may follow after the development of additional skin lesions, a thorough skin examination may help clinicians determine how closely to follow an individual with MPCM. It may also be reasonable to draw a one-time serum baseline tryptase level at diagnosis to risk stratifying individuals with MPCM.

Study limitations include its retrospective nature, reliance on caregiver reports of symptoms, small number of subjects, lack of tryptase data, and short follow-up. Although symptoms associated with MPCM (e.g., cough or rhinorrhea) are also commonly seen from infectious etiologies in children, we attempted to limit confounding by surveying the frequency with which patients exhibited these symptoms on average each month. Additionally, all subjects enrolled in the study were from a single institution, which limits the external generalizability of our results. We will continue to follow current patients with MPCM every 1 to 2 years with a clinic visit or questionnaire until resolution of their MPCM symptoms. We also hope to continue to enroll patients prospectively to address these limitations.

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