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Pediatric-onset Mastocytosis: A Long term Clinical follow-up and correlation with Bone Marrow Histopathology

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Abstract

Background—Pediatric onset mastocytosis usually presents as urticaria pigmentosa; and less often as diffuse cutaneous mastocytosis. While the literature indicates that disease often resolves, there has been a move to more aggressive therapy for mastocytosis early in life. We addressed the long term prognosis of pediatric-onset disease by examining 17 children with mastocytosis which we had reported on in 1989.[1]

Procedure—We successfully contacted 15 of these patients and data was collected regarding their clinical status. Original bone marrow specimens were re-stained, re-examined, and correlated with disease outcome using consensus criteria. Three of five patients with persistent disease underwent repeat bone marrow biopsies.

Results—There was complete regression of disease as defined by cutaneous findings and symptoms (clinical disease severity) in 10 of 15 patients (67%). Three patients had major (20%) and two had partial regression of disease (13%). Repeat marrow examinations on three patients with persistent disease documented systemic mastocytosis based on marrow findings in one patient who had partial regression of disease and was the only patient with initial morphologic evidence of systemic disease. Of the remaining two patients, one demonstrated partial regression and the other major regression of disease; and neither had evidence of systemic mastocytosis.

Conclusion—This study demonstrates that initial bone marrow biopsies were prognostic in that those without evidence of systemic disease experienced disease regression; and that the long term prognosis for children managed symptomatically with mastocytosis is highly encouraging.

Keywords

Cutaneous mastocytosis; pediatric mastocytosis; urticaria pigmentosa; serum tryptase; bone marrow; KIT

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Introduction

Mastocytosis encompasses a disease spectrum that is characterized by a pathologic increase in mast cells in cutaneous tissue and extracutaneous organs such as the bone marrow, liver, spleen and lymph nodes. The disease usually presents in two age-related patterns: pediatric-onset mastocytosis and adult-onset mastocytosis, which may differ in their clinical manifestations and disease course. Pediatric-onset mastocytosis commonly is diagnosed prior to 2 years of age, and usually consists of cutaneous disease, with urticaria pigmentosa (UP) the most common sub-variant.[1–5] The course of pediatric-onset mastocytosis is variable in contrast to adult onset disease which usually presents with systemic disease and persists.

The data concerning the natural history of pediatric disease comes from studies where each analysis depended in part or in total on retrospective chart reviews and where conclusions were largely based on skin examinations. In one such retrospective-prospective pediatric report where records and follow-up examinations were available for 25 children with UP, and an average follow-up was approximately 5 years, 76 % improved, 16 % remained unchanged, one had complete disease resolution, and one was worse.[5] In a second prospective study, 55 children with UP were followed for at least two years after initial examination, during which time 9% had involution of all lesions. In this study, where the average follow-up was 4.1 years, 36% had shown improvement over 6.1 years, and in 55% disease remained unchanged.[6] In a third retrospective study, records of mastocytosis patients seen in an ambulatory clinic were available to assess disease outcome over a 1–15 year period. Thirty-five of 62 patients with UP (56%) showed complete disease resolution.[3] In a fourth retrospective-prospective study, of 72 cases of UP, 20% cleared disease over an average of 13 years, while 50% improved, 18% were no different, and 10% were worse.[4] In these largely retrospective studies, no sequential bone marrow examinations were performed nor was prognosis related to bone marrow findings. The only comments relating to predicted disease course and long term prognosis related to statements that prognosis improved in patients with UP who presented without other abnormal findings[3] or when UP had its onset in infancy or early childhood.[4]

To better understand the natural history of pediatric mastocytosis, we decided to pursue a follow-up study of 17 children who were reported in a novel article published in 1989 from the then Mast Cell Biology Section of the Laboratory of Clinical Investigation within the NIH. The original study described the symptomatology and bone marrow histopathology of 17 children with pediatric mastocytosis.[1]

We were able to contact 15 of the original patients whose data was collected from 1986–1988. At the time of data re-analysis, these patients were 18 to 26 years in age. The original data was re-evaluated and patients classified into the following variants of mastocytosis: UP, diffuse cutaneous mastocytosis (DCM) and indolent systemic mastocytosis (ISM) based on the WHO criteria formulated by a consensus panel in 2001.[7] This approach thus offered a unique opportunity to examine pediatric patients followed over approximately 20 years and where initial correlative histopathology was available for analysis.

Materials and Methods

Patient population

Between 1986 and 1989, fourteen males and 3 females were referred to the NIH for confirmation of the diagnosis of cutaneous mastocytosis. Age at evaluation varied between 3 months and 8 years (median: 2.5 years), with disease onset from birth to 3 years. These individuals were evaluated as part of National Institute of Allergy and Infectious Diseases (NIAID) Institutional Review Board (IRB)-approved research protocols. All parents gave

written informed consent to participate in the studies. Patients underwent a bone marrow biopsy and aspirate during the initial evaluation and the findings were reported.[1]

By late 2007, a follow up of these individuals, now with an age range of 20 to 28 years, was completed. Contact was established with 15 of the 17 individuals, of which 12 were evaluated during a follow-up visit at the NIH. Informed consent was again obtained. Follow-up information was obtained by telephone from three individuals. A bone marrow aspiration and biopsy was performed on three of five subjects with continued symptoms. The two remaining patients declined the request for a repeat bone marrow procedure.

Disease Assessment

Disease severity at follow up was determined utilizing a grading system for mastocytosis developed by a consensus panel that defined diagnostic criteria, set forth treatment recommendations and agreed on response criteria to use in the evaluation of responses to therapy.[8] In that document, the scoring system included criteria to score skin involvement and skin specific symptoms, response to therapy, and constitutional and mediator-related symptoms. For our purposes, skin-specific symptoms included flushing, pruritus, and blistering. Constitutional or mediator-specific symptoms consisted of nausea, headache, diarrhea, syncope, abdominal pain, vomiting, musculoskeletal pain, and systemic hypotension. Total serum tryptase was determined using the commercial fluoroenzyme Immunoassay (Pharmacia Immuno CAP), the reference value being 0.00 – 11.50 ng/ml. The highest limit of detection of this assay is 500 ng/ ml (Mayo Clinic Laboratories, Rochester, MN).

Bone Marrow Preparation and Analysis

Bone marrow trephine biopsies were fixed either in B-5 fixative (original specimens) or B-Plus fixative (follow-up specimens), embedded in paraffin and processed for morphologic evaluation using standard procedures.[9] Immunohistochemical studies with anti-tryptase, anti-CD117 (Cell Marque, Hot Springs, AR), and anti-CD25 antibodies (Vision BioSystems, Norwell, MA) were performed using immunoperoxidase staining procedures and an automated immunostainer (Ventana Medical System, Tucson, AZ) according to the manufacturer's instructions. We recommend the tryptase immunohistochemical stain because it highlights morphology of mast cells and small mast cell aggregates, which can be missed on H&E sections. Images were obtained using an Olympus DP12 digital camera system. Bone marrow biopsies were inspected and scored in a blinded fashion by a single pathologist. Multi-parameter flow cytometry was performed after bone marrow aspirates were processed and stained with antibodies for CD2, CD25, CD45 and CD117. The CellQuest program was used for data analysis as described.[9] The detection of the KIT D816V mutation was performed by RT-PCR/RFLP analysis. The targeted gene area was amplified and the PCR products subjected to restriction enzymes in order to obtain fragments for analysis as described.[9]

Results

Disease severity at follow-up

At initial evaluation reported in 1989[1] (Table I), the diagnosis of UP in 15 patients and DCM in two patients was assigned based on gross inspection and histologic examination of lesional skin. The initial clinical assessment revealed the occurrence of cutaneous symptoms including pruritus (88%) and flushing (65%), and presence of bullae/vesicles (53%). In addition, subjects reported abdominal pain (41%), musculoskeletal pain (bone pain) (18%), and headache (12%) (Supplemental Table I). The only published follow-up of any of the children in this group was within a subsequent general review of hematologic aspects of mastocytosis which referred to an 18 month follow-up bone marrow evaluation on two of these patients instituted when abnormalities appeared in the CBC. [10] In the first patient, the marrow was unchanged (patient

11). However, the second patient's marrow revealed new lesions typical of adult-onset disease (patient 14 in our studies, listed as patient 16 in reference 10). This patient had partial regression of disease and continues to have systemic mastocytosis based on bone marrow pathology.

Data for the current study was collected approximately 20 years after the initial report, with 12 patients returning for a visit at the NIH. Three additional patients were contacted by phone. Disease severity at follow up was determined utilizing a grading system for mastocytosis developed by a consensus panel that refined diagnostic criteria, set forth treatment recommendations and agreed on response criteria to use in the evaluation of responses to therapy.[8] Using these criteria, ten patients (67%) had a complete regression of skin lesions as well as skin-specific and constitutional symptoms which categorized them as complete regression. Three patients (patients 1, 4 and 5) (20%) had major regression of their disease documented by greater than 50% resolution of skin lesions (Supplemental Figure 1 and Supplemental Figure 2). A partial regression was seen in two patients (patients 11 and 14) (13%) demonstrated by 10–50% regression of skin lesions and a similar reduction in skin-specific and constitutional symptoms. In one of these two remaining individuals, DCM persisted (patient 11). In the other remaining patient (patient 14) where the diagnosis of indolent systemic mastocytosis (ISM) was rendered after re-evaluation of the original marrow biopsy, utilizing the current WHO criteria, a repeat bone marrow biopsy, as will be discussed later, showed persistence of ISM. Therefore, in 13/15 individuals (87%), there was complete or major clinical regression of the disease.

Serum tryptase related to residual disease

Serum tryptase measurements were not available at the time of the study reported in 1989. On follow-up, serum tryptase levels were obtained for 12 patients and ranged from 2–126 ng/ml (Supplemental Table I). In the majority of patients, levels were below 20 ng/ml. The exceptions occurred to two patients with partial regression of disease, one with DCM (patient 11:126 ng/ml) and one with ISM (patient 14: 82 ng/ml) (Supplemental Table I). Patients 1, 4, 5, and 11 had mild persistent symptoms with tryptases of 4, 4, 8 and 12 ng/ml respectively; and required only as needed medications. By contrast, patient 14 with a serum tryptase of 82 ng/ml required chronic H1 and H2 antihistamines; and proton pump inhibitor therapy.

Bone marrow re-analysis

We have re-reviewed available original bone marrow biopsy specimens from 13 of 17 patients (biopsies from patients 2 and 3 were inadequate for re-review; those for patients 4 and 9 could not be located). These biopsies were scored according to the current WHO criteria for diagnosis of systemic mastocytosis and are described in Table II. In order to better assess mast cell numbers and morphology, we also performed immunohistochemical staining with anti-tryptase, anti-CD117 and anti-CD25 antibodies, which were not available at the time of the original bone marrow biopsy evaluation. Unfortunately, CD25 staining on slides cut from archived tissue blocks was technically unsuccessful, attributed to the differences in fixation and processing of the bone marrow specimens 20 years ago and the time in storage.

When original bone marrow biopsies from the 1989 study were immunostained with tryptase and CD117, patients 5, 11, 14, 15 and 16 were found to have increased scattered mast cells (Table II). Patient 14 also had mast cell aggregates (defined by WHO criteria as more than 15 mast cells) in the marrow specimen, and so fulfilled the major WHO criterion for diagnosis of systemic mastocytosis. In the 1989 study [1], patient 14 had been diagnosed as having only UP based on criteria existing at that time (Table I). Patients 14, 15, and 16 revealed the presence of more than 25% spindle shaped mast cells within the mast cell compartment in their bone marrow biopsies, which is a minor WHO criterion for diagnosis of systemic mastocytosis.

[7] However, these latter patients did not have other criteria for the diagnosis of systemic disease.

Examples of re-stained original bone marrow biopsy specimens are shown in Figure 1. In patient 5, who had persistent UP, there was an increase in mast cells without large mast cell aggregates or spindle shaped mast cells (Figures 1A, B) and these findings did not meet criteria for systemic disease. The original bone marrow biopsy of patient 11 (DCM) revealed increased scattered mast cells, but no mast cell aggregates of > 15 mast cells. All mast cells were round and no spindle-shaped mast cells were seen (Figures 1C, D). Based on the absence of mast cell aggregates, the original bone marrow again did not meet the WHO criteria for the diagnosis of SM. Patient 14's bone marrow specimen contained large mast cell aggregates (>15 mast cells) associated with lymphocytes and eosinophils, classically found in patients with SM (Figures 1E, F). In addition, more than 25% of mast cells were spindle-shaped fulfilling current WHO criteria for diagnosis of SM and agreeing with the original interpretation of this marrow.

Current bone marrow and analysis

Three of the patients with continued symptoms and skin lesions (5, 11, and 14) agreed to undergo a repeat bone marrow examination in order to determine their disease status. In addition to histomorphologic analysis, these bone marrow specimens were also studied by flow cytometry. Analysis of *c-kit* for the D816V activating mutation, recognized in 1995 to be commonly associated with systemic disease [11], was also performed.

All three bone marrow specimens showed an increase in mast cells (Table III, Figure 2) after immunostaining with tryptase and CD117 antibodies. In patient 5, morphologically, mast cells remained similar to the mast cells in the original bone marrow biopsies obtained 20 years earlier (Figures 2A–C, Table III). Mast cells remained round, with no increase in spindle-shaped forms. Small mast cell aggregates (>15 mast cells) were observed, but mast cells were negative for CD25, a marker found in more than 95% of patients with systemic mastocytosis. Thus again this patient did not meet the WHO criteria for ISM. Patient 11 (Figures 2D–F, Table III), despite an increase in round mast cells, did not have any mast cell aggregates of >15 mast cells, nor any spindle-shaped mast cells. CD25 staining was negative in mast cells. Thus, this patient did not fulfill the WHO morphologic criteria for diagnosis of systemic mastocytosis. The marrow findings in patient 14 (Figures 2G–I, Table III) were similar to his original marrow findings 20 years previously. There were small mast cells aggregates and an increase in spindle-shaped mast cells. CD 25 positive mast cells were present in this specimen, thus fulfilling both major and minor WHO morphologic criteria for diagnosis of systemic mastocytosis.

The repeat bone marrow aspirations performed on patients 5, 11 and 14 were also analyzed by flow cytometry for the aberrant expression of CD25 on mast cells and for the presence of the KIT D816V mutation. Only patient 14, who met the diagnostic criteria for systemic mastocytosis, was positive both for KIT D816V and CD25.

Discussion

Pediatric-onset mastocytosis is an uncommon disease. Although the resolution of disease is often stated to be approximately 50%, there are only a small number of studies on which this general conclusion is based.[3–6] The present study represents the longest duration of follow-up in a pediatric population with cutaneous disease and in which the initial study included a bone marrow analysis.

The results of our study are highly encouraging for those dealing with children with cutaneous mastocytosis. In this follow-up study, 10 of 15 of patients had complete resolution of cutaneous disease and symptoms at follow-up approximately 20 years later (Table I). This resolution of

disease, based on cutaneous findings and symptom scores, occurred in the absence of use of topical or systemic steroids, PUVA or cytoreductive agents including imatinib. Thus reports, such as one recently published reporting cutaneous improvement after administration of imatinib[12] should be viewed with caution, as the natural history of disease is improvement. This conclusion is reinforced by our observation that the remaining 5 patients in our study experienced a major or partial regression of disease on conservative therapy.

The bone marrow examination performed when children were first entered into the study was highly predictive of outcome. All patients who experienced disease resolution or major regression had essentially normal original pediatric marrow biopsies upon re-evaluation. Two patients had partial regression. One of these patients had DCM at original evaluation and this persisted and was present on follow-up. The initial marrow examination revealed some increase in mast cells which persisted and was present on repeat biopsy. However, no disease progression on repeat examination was found. The second patient had UP and a bone marrow examination was compatible with ISM at the time of the initial evaluation. A repeat marrow biopsy during the follow-up examination reported in this paper again revealed evidence of ISM; and the marrow findings appeared relatively unchanged from the initial bone marrow. Thus if an initial marrow did not show evidence of systemic disease, no evidence of systemic disease was found an average of 20 years later. If a marrow was positive for ISM, the disease persisted. We continue, based on this data, to recommend bone marrow studies only on children with evidence of systemic disease including organomegaly, elevated tryptase, or unexplained peripheral blood abnormalities.

The KIT D816V mutation is one of the minor diagnostic criteria for systemic disease.[7,8] The one patient with persistent systemic disease was positive for this mutation. We do not know if other mutations [13] were present in other individuals in this study, but if they were present, they did not prevent disease resolution.

Tryptase levels were not available in the late 1980's, as the tryptase assay was reported and evaluated somewhat later for both the diagnosis of mastocytosis and anaphylaxis.[14–17] However, on the follow-up repeat examinations, only two patients had tryptase levels above 20 ng/. One patient had persistent DCM, and it is known that such patients with extensive cutaneous disease may have elevated tryptase levels.[17] The second patient was the patient with persistent ISM, whose tryptase level could be expected to be elevated.

The age of inception of pediatric-onset cutaneous mastocytosis has been reported to have prognostic implications. In previous studies, skin lesions characterized as hyperpigmented red brown macules or papules typically were reported to appear prior to two years of age. In five such studies with 180, 112, 71, 55 and 17 patients, disease-onset prior to age 2 years was seen in 78, 92, 98, 92, and 82%, respectively.[1–5] In the majority of patients, these lesions were reported to fade or resolve by late adolescence or early adulthood. Fading or resolution of UP is also reported in some adults (around 20%), although bone marrow disease persisted.[18] Similarly, patients entered into our study had disease onset by age 2 and most had disease resolution or improvement as discussed above.

Five patients had increased mast cells and three patients had spindle shaped mast cells on the initial bone marrow biopsy. One of these patients (patient 15) had complete resolution of clinical and constitutional symptoms at follow-up. Three of the remaining four patients were re-evaluated. One of these was the patient with continued systemic disease (patient 14), one had persistent DCM (patient 11) and one had continued UP. However, two other patients with continued UP (patients 1 and 4) had neither an increase in mast cells nor spindle shaped mast cells noted on original bone marrow examination. Thus, while the presence of increased mast

cells and of spindle-shaped mast cells was more often observed in those with persistent disease, the association was not sufficient to predict outcome.

The etiology of most cases of pediatric cutaneous mastocytosis remains unknown. Such cases have, by association, been attributed to mutations and polymorphisms in KIT. But if or how such genetic rearrangements would cause disease that often resolves is unknown. This leaves open the possibility that some cases of cutaneous mastocytosis could involve a mechanism independent of KIT mediated signaling.

This study makes the important observations that patients with pediatric-onset mastocytosis often experience disease resolution by adulthood; and that a bone marrow examination, if read as positive for evidence of systemic disease, should lead to the possibility that disease may persist. This further documentation of the natural history of mastocytosis combined with evidence of the predictive nature of a bone marrow examination should help in counseling those dealing with childhood onset cutaneous mastocytosis; and help prevent the unwarranted use of more aggressive agents directed toward ablating the mast cell compartment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Morphological and immunohistochemical re-analysis of original bone marrow biopsies. (A,B) Patient 5, (C,D) Patient 11, and (E,F) Patient 14. Bone marrow biopsy sections. (A,C,E) Hematoxylin and eosin stain (H&E) and (B,D,F) anti-CD117 antibody. Magnification 100x. Representative samples of mast cell morphology, Inserts (B,D,F). Magnification 1000x.

Figure 2. Morphological and immunohistochemical analysis of follow-up bone marrow biopsies. (A–C) patient 5, (D–F) patient 11, and (G–I) patient 14. Bone marrow biopsy sections. (A,D,G) Hematoxylin and eosin stain (H&E), (B,E,H) anti-CD117 antibody, and (C,F,I) anti-CD25 antibody. Magnification 100x

Table 1

Demographics

Age of onset	Gender	Age at initial evaluation	Age (yrs) at most recent evaluation	At diagnosis	Disease variant At follow up	Clinical outcome
16m	F	3y	24	UP	UP	Major regression
23m	M	11m	21	UP	Resolved	Complete regression
36m	M	3y	23*	UP	Resolved	Complete regression
43m	F	3y	19	UP	UP	Major regression
52y	F	8y	26	UP	UP	Major regression
62y	M	5y	NF	UP	Unknown	Unknown
71m	M	2y	23*	UP	Resolved	Complete regression
84d	M	1y	21	UP	Resolved	Complete regression
93m	M	3m	21	DCM	Resolved	Complete regression
101y	M	3y	17	UP	Resolved	Complete regression
11birth	M	5m	18	DCM	DCM	Partial regression
126w	M	4y	24*	UP	Resolved	Complete regression
132m	M	6m	20	UP	Resolved	Complete regression
14birth	M	6m	20	UP	UP/ISM	Complete regression [†]
153m	M	3y	18	UP	Resolved	Complete regression
164m	M	7m	NF	UP	Unknown	Unknown
17birth	M	3y	19	UP	Resolved	Complete regression

d-days, w-weeks, m-months, y-years; UP-Urticaria Pigmentosa, NF-no follow up, DCM-Diffuse Cutaneous Mastocytosis, and ISM-Indolent Systemic Mastocytosis

* Contacted by phone only

[†] Patient's initial marrow re-read as diagnostic of indolent systemic mastocytosis

Table II

Original Bone Marrow Biopsies (re-stained)

Number	Cellularity (%)	Increased MC	MC Aggregates	Spindle shaped MC
1	50–60	no	no	no
2	IS	–	–	–
3	IS	–	–	–
4	NA	–	–	–
5	30–60	yes	<15 MC	no
6	40–70	no	no	no
7	50–60	no	no	no
8	80–90	no	no	no
9	NA	–	–	–
10	50–60	no	no	no
11	100	yes	yes	no
12	40	no	no	no
13	80–90	no	no	no
14	70–90	yes	yes	yes
15	60	yes	no	yes
16	80	yes	no	yes
17	40–70	no	no	no

MC indicates mast cell(s); IS, inadequate specimen; NA, not available.

Table III

Follow up Bone Marrow Biopsies

Number	Cellularity (%)	Increased MC	MC Aggregates	Spindle shaped MC	CD25+ MC	c-kit mutation (D816V)
5	40	yes	small	no	no	no
11	70	yes	no	no	no	no
14	40-50	yes	small	yes	yes	yes

MC indicates mast cell(s)