

## Telangiectasia macularis eruptiva perstans: more than skin deep

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### Abstract

Systemic mastocytosis is a rare disease involving the infiltration and accumulation of active mast cells within any organ system. By far, the most common organ affected is the skin. Cutaneous manifestations of mastocytosis, including Urticaria Pigmentosa (UP), cutaneous mastocytoma or telangiectasia macularis eruptiva perstans (TMEP), may indicate a more serious and potentially life-threatening underlying disease. The presence of either UP or TMEP in a patient with anaphylactic symptoms should suggest the likelihood of systemic mastocytosis, with the caveat that systemic complications are more likely to occur in patients with UP. TMEP can usually be identified by the typical morphology, but a skin biopsy is confirmative. In patients with elevated tryptase levels or those with frequent systemic manifestations, a bone marrow biopsy is essential in order to demonstrate mast cell infiltration. Further genetic testing for mutations of *c-kit* gene or the *FIP1L1* gene may help with disease classification and/or therapeutic approaches. Rarely, TMEP has been described with malignancy, radiation therapy, and myeloproliferative disorders. A few familial cases have also been described. In this review, we discuss the clinical features, diagnosis and management of patients with TMEP. We also discuss the possible molecular pathogenesis and the role of genetics in disease classification and treatment.

### Introduction

Cutaneous eruptions can occasionally provide significant insight to underlying disease.

A case in point is systemic mastocytosis, which can present with a plethora of dermatological manifestations. TMEP is a rare form of cutaneous mastocytosis (CM) that can occasionally be associated with an underlying systemic mastocytosis (SM).<sup>1,3</sup> Patients who present with this rare cutaneous disease should undergo routine testing to search for systemic disease. Development of additional morbidities, such as reactions to bee stings, systemic anaphylaxis, osteoporosis or bleeding secondary to heparin release from mast cells, may occur and may complicate the diagnosis, unless suspected.<sup>4,8</sup> On occasion, the disease may evolve into a hematological malignancy, making early diagnosis, classification and monitoring an essential aspect of disease management.<sup>9</sup>

This review will discuss the diagnosis, pathology, pathogenesis and mast cell biology as well as the management of TMEP, complicated by systemic mastocytosis.

### Case Report

A 43-year-old female was referred to the Allergy and Immunology Clinic by her primary care physician for evaluation of a persistent skin eruption. Worsening diffuse, erythematous skin eruptions that originated predominantly on the thighs and trunk region had been present for over a year. The lesions were described as itchy and raised at times but often appeared as merely discolorations of the skin. The rash waxed and waned periodically but had continued to spread and become generalized. The patient was evaluated by a dermatologist one year prior and a biopsy of the skin at that time was reported as benign. Twice daily loratadine was also started at that time with no change in the rash. Local treatments with steroid injections temporarily helped to alleviate the symptoms but the rash returned soon after. The patient could not pinpoint a single etiology. She had tried changing many environmental factors, including foods and detergents, to no avail. The patient had developed several episodes of systemic anaphylaxis associated with angioedema and flushing, but denied wheezing or syncope. She has otherwise been in good health with the exception of seasonal allergic rhinoconjunctivitis with sensitivity to dust, mold and pollen as well as a few instances of bronchitis and sinusitis.

Physical exam of the skin reveals a diffuse erythematous macular eruption with overlying dilated capillaries located on the thighs, upper extremities and back (Figure 1A, 1B). The patient was also found to have a very weakly positive Darier's sign (rubbing of the skin produces wheal and flare reaction with localized erythema, pruritis and edema).<sup>10,11</sup> These exam findings were consistent with a diagno-

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sis of TMEP. Further work-up included a skin biopsy, complete blood count with differential, comprehensive chemistry panel, thyroid stimulating hormone levels, anti-nuclear antibody, rheumatoid factor, erythrocyte sedimentation rate, C reactive protein as well as serum tryptase and 24-hour urine histamine levels. In addition, allergy testing (Radioallergosorbent testing or RAST for specific IgE), levels of complement components (C3, C4) and serum immunoglobulins (immunoglobulins G, A, M and E) were obtained. Flow cytometry for T- and B- lymphocyte subsets (CD4, CD8, NK-cells and CD19 positive B cells) was performed and plasma levels of interleukins 4, 5 and 6 were analyzed with particular attention paid to interleukin 6 which correlates with mast cell burden. A bone marrow biopsy was performed to look for evidence of systemic mastocytosis. A bone density test was also scheduled to rule out osteoporosis which is commonly associated with mastocytosis.

Abnormalities noted from the extensive work-up included elevated serum tryptase level which was found to be 89.7 µg/L (reference range 0.4-19.9 µg/L) and an elevated 24-hour urinary histamine level of 79 ng/24 hours (reference range, 13-62 ng/24 hours). A 3-mm punch biopsy of the right thigh showed superficial perivascular chronic inflammation. A

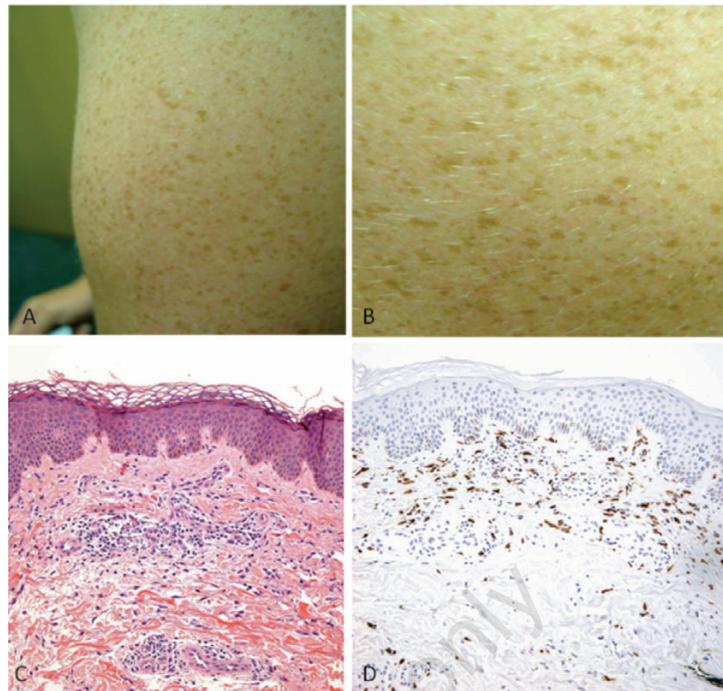
mast cell tryptase immunohistochemical stain was used to identify mast cells (Figure 1C, 1D). Greater than 15 mast cells per perivascular high power field were observed. These findings are consistent with, and support the clinical diagnosis of, TMEP.

Bone marrow aspiration and core biopsy revealed 5-10% infiltration by mast cells, confirming the diagnosis of indolent systemic mastocytosis (ISM). Many of the mast cells within the aspirate were reported as hypogranular and some were spindle-shaped. Mast cell infiltrates were identified from ill-defined nodules within the bone marrow interstitium. CD117/c-KIT/Asp816Val mutation analysis of the bone marrow by polymerase chain reaction (PCR) was strongly positive. Fluorescent in situ hybridization (FISH) testing of CHIC2/PDGFR $\alpha$ /FIP1L1 gene regions was found to be within normal limits. No diagnostic features of an associated myeloproliferative neoplasm or myelodysplastic syndrome were identified. A mutated (and an unmutated) form of c-kit was detected in the patient by flow cytometry (Figure 2).

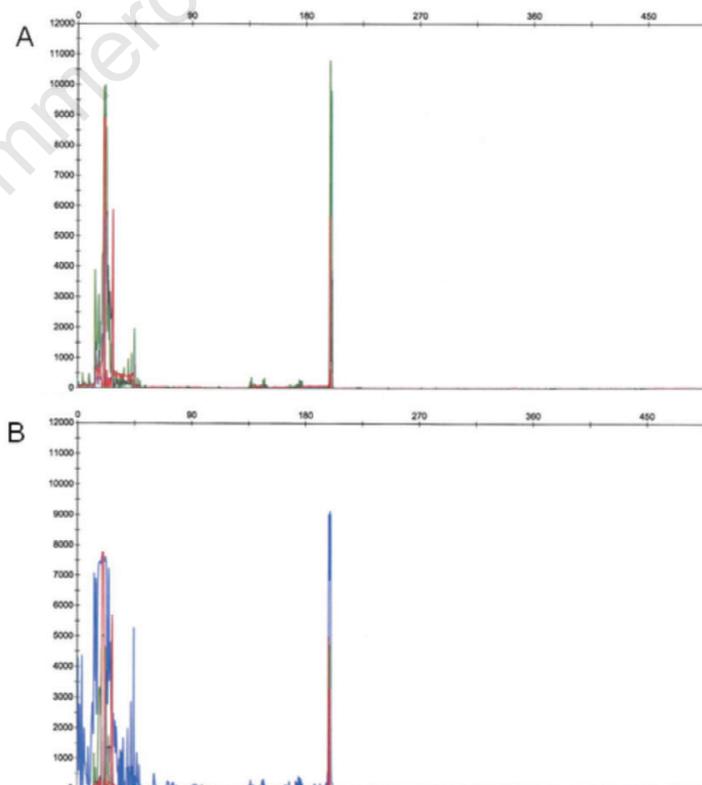
The patient was subsequently referred back to dermatology for psoralen plus ultraviolet A (PUVA) light therapy which alleviated cutaneous symptoms to some extent. The antihistamines loratadine, cetirizine and famotidine were all prescribed to the patient for daily use. A dual-emission x-ray absorptiometry (DEXA) was performed to look for signs of osteoporosis or other bone involvement. The patient was also instructed to follow Patterson protocol for IV contrast prophylaxis with any future contrast imaging studies. Two injectable epinephrine pens were also administered to the patient for prophylactic use with an anaphylactic episode. She has had two breakthrough anaphylactic episodes since the original diagnosis. At last follow up, the patient was seemingly doing well without anaphylactic reactions, but with persistent skin involvement.

## Materials and Methods

Review of the medical records provided information about history, skin punch biopsies and histological examination, serum tryptase levels, 24-hour urinary histamine, extensive autoimmune testing, Radioallergosorbent (RAST) testing and bone marrow biopsy. Cells obtained from bone marrow biopsy were tested for CD117/c-KIT/Asp816Val and FIP1L1/PDGFR $\alpha$  mutations. A thorough review of the literature was performed using PubMed/MeSH Database search. Available case reports and current review articles were investigated to provide up-to-date information about mastocytosis and TMEP. This case report has been approved by the East Tennessee State



**Figure 1.** (A) Spontaneous telangiectasia macularis eruptiva perstans macular eruption. (B) Magnified view of the skin manifestations with small tan macules and red brown streaking. Images are produced with permission of the patient. (C) A cellular infiltrate is concentrated around superficial dermal blood vessels. Hematoxylin and eosin stain. 200x magnification. (D) The infiltrate demonstrates a substantial mast cell component (>15 per perivascular high power field). Many more mast cells are present than could be appreciated on the H&E-stained section. Mast cell tryptase immunohistochemical stain. 200x magnification.



**Figure 2.** Flow cytometry used to detect c-kit mutation. Both non-mutated peaks (A) and mutated peaks (B) were present in the patient. All patients with the c-kit mutation associated with mastocytosis should have some unmutated DNA present. These figures were kindly provided by Dr. Rebecca F. McClure of Mayo Clinic, Rochester, Minnesota.

University (ETSU) and ETSU/Veterans Affairs Institutional Review Board. Patient consent was obtained for photographs and appropriate clinical procedures.

## Discussion

Mastocytosis is a rare disease caused by an abnormal accumulation of mast cells in one or more organ systems. The most common organ affected by mastocytosis is the skin.<sup>12,13</sup> Mastocytosis has a bimodal distribution with the majority of cases occurring in childhood and then peaking again at age 30-50 years. Men and women are affected equally but the Caucasian population is reported to be affected more commonly than any other race.<sup>8,11</sup> The true incidence and prevalence of mastocytosis is unknown. Studies suggest there are between 1/50,000 and 1/150,000 patients who present with mastocytosis per year.<sup>11,14</sup>

Mastocytosis encompasses a wide spectrum of disease processes ranging from purely cutaneous to indolent or aggressive systemic disease to malignancy or hematological disease.<sup>15</sup> More than 1 out of 4 adult patients with systemic disease also have cutaneous findings, therefore, recognizing the cutaneous manifestations of mastocytosis is an essential skill for clinicians.<sup>11,16</sup> Systemic mastocytosis is diagnosed according to major and minor criteria. The single major criteria is multifocal dense aggregates of mast cells (>15 MCs in aggregate) in bone marrow or another organ. The four minor criteria include abnormal morphology seen in >25% of mast cells, *c-kit* mutation D816V, bone marrow mast cell expression of CD2 or CD25 and tryptase levels >20 ng/mL.<sup>17</sup> The presence of either one major and one minor criteria or three minor criteria is required for diagnosis. The various forms of SM include Indolent Systemic Mastocytosis (ISM), Systemic Mastocytosis with an Associated Clonal Hematologic Non-Mast Cell Lineage Disease (SM-AHNMD), Aggressive Systemic Mastocytosis (ASM), Mast Cell Leukemia (MCL), Mast Cell Sarcoma (MCS) and Extracutaneous Mastocytoma (Table 1). ISM is the most common and was the form of SM observed in the patient presented in this report. Bone marrow is involved in nearly all cases of ISM, however, mast cell infiltrates are typically low (<30%).<sup>1</sup> ISM affects younger patients and has a good prognosis. Survival times are comparable to patients not affected by SM.<sup>17,18</sup>

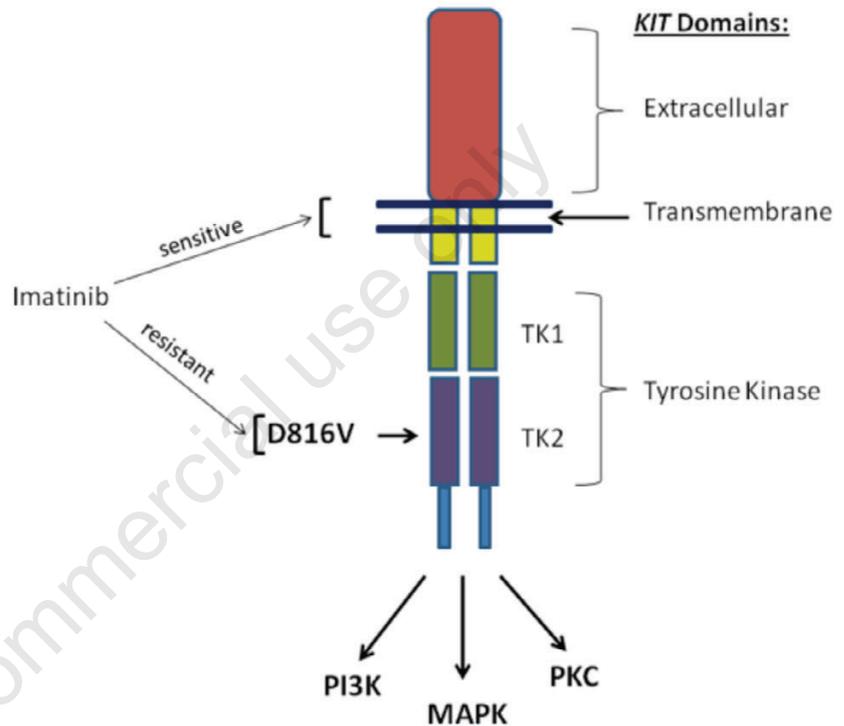
## Systemic mastocytosis

Mastocytosis, often presenting as dermatological disease, is classified according to the World Health Organization (WHO) Criteria released in 2001.<sup>17,19</sup> There are six main cate-

gories of mastocytosis which will be discussed in this article (Table 1). The diagnosis of CM, made by clinical observation and skin biopsy, is an indication for further evaluation of the patient to rule out SM. Serum tryptase levels and 24-hour urinary histamine levels are two common, non-invasive methods of looking for systemic involvement. A bone marrow biopsy is ultimately indicated to look for proliferation of mast cells and specific cytogenetic mutations. A specific mutation of the *c-kit* receptor on mast cells, referred to as Asp816Val or D816V, is the most common genetic mutation associated with mastocytosis (Figure 3). The bone

marrow is probably the most common site of systemic involvement in the disease.<sup>20</sup> This may be attributed to the fact that mast cell progenitor cells originate in the bone marrow. Other organs may also be examined for systemic involvement, especially if organomegaly is present.

Yearly complete blood count, comprehensive metabolic panel, serum tryptase levels and 24-hour urinary histamine levels should be obtained to follow disease progression. There is a possibility of transformation to mast cell leukemia or other hematological malignancy in all patients with mastocytosis.



**Figure 3. Schematic diagram of c-kit tyrosine kinase receptor. The most common mutations, particularly the D816V mutation, that result in mastocytosis affect this specific protein on mast cells.**

**Table 1. WHO Classification of Mastocytosis. The official WHO classification system which is based on the consensus classification for mastocytosis proposed in 2001.<sup>19</sup> This classification system and its criteria enable differentiation among the multiple forms of mastocytosis. Common abbreviations are also listed for reference. \*Most common manifestation.**

|   |          |
|---|----------|
| Cutaneous Mastocytosis  | CM       |
| Maculopapular cutaneous mastocytosis  |          |
| Urticaria pigmentosa*   | UP/MPCP  |
| Telangiectasia macularis eruptiva perstans  | TMEP     |
| Diffuse cutaneous mastocytosis  | DCM      |
| Mastocytoma of the skin   |          |
| Indolent systemic mastocytosis  | ISM      |
| Smoldering mastocytosis   |          |
| Isolated bone marrow mastocytosis   |          |
| Systemic mastocytosis with an associated clonal hematologic non-mast cell lineage disease | SM-AHNMD |
| Aggressive systemic mastocytosis  | ASM      |
| Mast cell leukemia  | MCL      |
| Mast cell sarcoma   | MCS      |
| Extracutaneous mastocytoma  |          |

## Cutaneous mastocytosis

According to the World Health Organization (WHO) classification, CM is divided into urticaria pigmentosa or maculopapular cutaneous mastocytosis (UP/MPCM), diffuse cutaneous mastocytosis (DCM), and mastocytoma of the skin (Table 2). UP/MPCM is present in the vast majority of CM cases. It presents with a maculopapular rash and positive Darier's sign. The three subvariants of UP/MPCM are a plaque form, a nodular form and a telangiectatic form known as TMEP.<sup>1,17,21</sup> DCM presents with a diffuse erythrodermic rash and the skin may be diffusely thickened. Mastocytomas are usually solitary or few, less than 1 cm in diameter and reddish or yellow in color. By definition, CM is restricted to the skin so wherever extracutaneous involvement exists, the diagnosis is SM. Pure CM is most common in children. Many adults with cutaneous disease actually have an underlying SM.

## Telangiectasia macularis eruptiva perstans

TMEP is a very rare cutaneous finding seen in less than one percent of patients with mastocytosis.<sup>16,22-24</sup> It was first described in the 1930s by Parks Weber.<sup>25</sup> The lesions of TMEP typically appear as small, irregular reddish-brown telangiectatic macules overlying tan to brown background. Individual lesions are usually between 2 and 4 mm in diameter.<sup>16</sup> The telangiectatic lesions will classically blanch on diascopy. One study discussed the use of dermatoscopy to identify telangiectatic vessels arranged in a reticular pattern; these findings are considered unique to and characteristic of TMEP.<sup>21</sup> Lesions are typically located on the trunk and proximal extremities in a symmetrical pattern and are non-pruritic. Palms, soles and face are spared in most cases. Darier's sign, a common finding of UP/MPCM, is typi-

cally negative or slight in patients with TMEP due to the relatively smaller number of mast cells involved.<sup>8,16</sup> Diagnosis is usually based on clinical exam and confirmed by skin biopsy with histological examination.

Histologically, TMEP typically involves only a slight increase in mast cells with infiltration of the superficial dermis and epidermal hyperpigmentation.<sup>16</sup> Mast cells are primarily located around dilated capillaries and venules of the superficial venous plexus found in the upper third of the dermis.<sup>21,22,26,27</sup> Giemsa and toluidine-blue stains highlight the metachromatic intracytoplasmic granules and are good for recognizing mast cells.<sup>20</sup> Immunohistochemical staining for *c-kit* and/or tryptase is more sensitive and may also be used to confirm the diagnosis (Figure 1D).<sup>22</sup>

Unlike the other forms of CM, TMEP most commonly manifests in adulthood. There have been reports of TMEP in children, infants and familial cases but these are extremely rare.<sup>27,28</sup> TMEP is traditionally thought to be restricted to the skin, however, it has been reported in association with SM.<sup>10,29</sup> Bone marrow, gastrointestinal tract, liver, spleen and lymph node involvement have all been described in patients with TMEP.<sup>22</sup> Systemic involvement should always be suspected if symptoms such as flushing, diarrhea, dyspnea, tachycardia, pruritis, syncope or signs of anaphylaxis are present in addition to the characteristic skin lesions.<sup>26</sup> One study suggests bone marrow biopsy and aspirates should be routine in all adult patients with CM for baseline staging purposes.<sup>30</sup> CM is commonly restricted to the skin in children and adolescents. It is not necessary to perform bone marrow biopsy in these patients without symptomatic indications or abnormal tests. Serum tryptase and 24-hour urine histamine are good preliminary tests to investigate for systemic involvement.<sup>17</sup>

Some cases of TMEP have been described as familial, with a clustering within families.<sup>27,31</sup>

There have been rare cases described in patients undergoing radiation, in patients with breast or renal carcinoma,<sup>32</sup> malignant melanoma,<sup>33</sup> or in patients with Sjogrens syndrome.<sup>34</sup> Other cases have been described in patients with multiple myeloma,<sup>35</sup> myeloproliferative disorders (such as Polycythemia Rubra Vera)<sup>36</sup> and in association with leukemia or myelofibrosis.<sup>9,37,38</sup> Coexistence of UP and TMEP has also been described in rare cases.<sup>37,39-41</sup> On occasion, TMEP may present as unexplained pruritis.<sup>42</sup> Some cases of TMEP may present in atypical locations such as unilaterally on the face<sup>43,44</sup> and/or localized to the upper arms.<sup>26</sup> Neurological complications such as prolonged loss of consciousness or the *Kounis-like* phenomenon have also been described.<sup>45</sup>

## Diagnosis and evaluation

Due to the range of organs that can be affected as well as the esoteric nature of the symptoms of systemic disease, the diagnosis may be missed for years. Delay in diagnosis may put patients at risk for life-threatening events including anaphylaxis and histamine-mediated vascular collapse.<sup>7,12,13,46</sup> Skin findings suggestive of cutaneous mastocytosis should be biopsied to confirm clinical suspicions. Avoid the use of local anesthetic containing epinephrine during skin biopsy due to the ability of epinephrine to stimulate mast cell degranulation. Adults who present with cutaneous forms of mastocytosis should also be carefully considered for further investigation into an underlying systemic disease.<sup>17,30</sup> Systemic symptoms of mastocytosis may occasionally mimic carcinoid syndrome, which should be considered in the differential diagnosis. Strategies for diagnosing mastocytosis are discussed in Table 3.

Tryptase, the main protein component of the secretory granules found within mast cells, is a good indicator of total mast cell burden.<sup>15</sup> In

**Table 2. Telangiectasia macularis eruptiva perstans and other cutaneous mastocytoses. A brief summary of the prominent clinical, histopathological and demographic descriptors of telangiectasia macularis eruptiva perstans as well as the other forms of cutaneous mastocytosis.**

| CM          | Clinical findings   | Pathological findings   | Demographics  |
|-------------|---|---|---|
| TMEP        | Red-brown, maculo-papular, telangiectatic, irregular, 2-6 mm. Located on trunk & extremities. Darier's sign negative or slight. | Subtle increase in MC, perivascular location, upper 1/3 of dermis, dilated superficial capillaries. | Almost exclusively in adults. Seen in <1% of patients with mastocytosis.                          |
| UP          | Red-brown, maculo-papular rash, 0.5-3.5 mm, flushing, pruritis, positive Darier's sign, dermatographism.                        | Increased number of mature MC.  | Presents at any age, peak incidence in childhood and again in 3rd decade of life. Most common CM. |
| Mastocytoma | Red-brown nodules or plaques, usually <1 cm, positive Darier's sign.  | Large, solitary collection of densely packed MC.  | Most appear in first 3 months of life. Rare in adults.  |
| DCM*        | Thickened red-brown edematous skin, orange-peel texture, positive Darier's sign, dermatographism.                               | Diffuse, generalized band-like infiltration of MC.  | Present before age 3.   |

CM, cutaneous mastocytosis, TMEP, telangiectasia macularis eruptiva perstans, UP, urticaria pigmentosa (also referred to as maculopapular cutaneous mastocytosis), DCM, diffuse cutaneous mastocytosis. \*Two variants have been described: i) Diffuse erythrodermic cutaneous mastocytosis (dermatographia, blistering and systemic disease are common) and ii) pseudoxanthomatous mastocytosis, or xanthelasma (lasting through adult life).<sup>2</sup>

general, most patients with pure CM exhibit normal serum tryptase levels. Tryptase levels > 20 µg/L are typically seen with SM.<sup>20,47</sup> Elevated 24-hour urinary histamine is another common finding associated with systemic mastocytosis but is non-specific. The metabolite of histamine, N-methylhistamine, is a more sensitive test and should be used when possible.<sup>15</sup>

A practical tool for the evaluation of CM is the SCORMA (SCORing MASTocytosis) Index (Table 4). It consists of three parts: (A) the extent of skin affected expressed as a percent, (B) the intensity of the skin abnormality based on pigmentation/erythema, vesiculation, elevation and Darier's sign and (C) five subjective symptoms which include triggers, flushing, diarrhea, pruritis and bone pain. These parts are each scored and applied to a formula to calculate the final SCORMA Index. This clinical tool may be useful to initially evaluate severity. It is considered comparable to serum

tryptase levels in predicting systemic involvement. SCORMA Index is also an excellent method for monitoring disease progression and treatment efficacy.<sup>47</sup>

In general, patients with cutaneous lesions have a good prognosis despite involvement of other organs.<sup>11</sup> This fact may be attributed to tendency for earlier diagnosis if skin lesions are present and predilection of skin disease with ISM, which in itself has a better prognosis than the other types of SM. ISM has a prolonged clinical course with survival times estimated at two decades and more if transformation into another disease category does not occur.<sup>20</sup>

**Cytogenetics and molecular aspects**

Essential aspects of mast cell biology and the role of these cells in the immune-inflammatory response has been reviewed by us.<sup>48-50</sup> The relationship between mast cells and T cells, fibroblasts and eosinophils have impor-

tant implications for disease pathogenesis.<sup>51-53</sup> Mast cells can be activated by a variety of processes, including antigens (such as venom stings or food allergens), cytokines as well as by some bacteria.<sup>54-57</sup> The involvement of mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) pathway in signaling may explain the efficacy of drugs such as the glucocorticoids in some complications. These aspects may also explain the complications of bee stings or drug/food reactions in patients with mastocytosis, and the resultant recommendation of avoidance of contact with some of these triggers.<sup>4,8,46</sup> A list of triggers in SM is provided in Table 5.

An important genetic component of mastocytosis involves a mutation in the type III transmembrane tyrosine kinase receptor *c-kit* (Figure 3). This receptor has an extracellular domain that binds to mast cell growth factor which functions to promote growth and functionality of mast cells.<sup>16</sup> The most common type of mutation occurs within codon 816 (known as D816V) and causes constitutive activation of the *c-kit* receptor.<sup>10</sup> Testing for the D816V mutation can be done on bone marrow biopsy, as was performed in the case described, or on skin biopsy. This mutation does not differentiate cutaneous and extracutaneous involvement but is found in nearly all adult cases of systemic mastocytosis.<sup>10,15</sup> Many promising drugs that specifically target mast cells and the *c-kit* receptor are currently under investigation, including PKC412, AMN107 and dasa-

**Table 3. Diagnostic strategies in telangiectasia macularis eruptiva perstans and/or suspected mastocytosis. Summary of diagnostic strategies that may be employed when mastocytosis is suspected.**

|  |
|--|
| <b>For patients with TMEP or UP</b>                |
| Skin biopsy  |
| Complete blood count and differential              |
| Comprehensive chemistry                            |
| Serum tryptase level                               |
| Bone marrow biopsy with evaluations for mutations* |

|   |
|---|
| <b>For patients with suspected systemic mastocytosis</b>  |
| Urine collection for biochemical testing  |
| Bone scan   |
| DEXA study/bone mineral density   |
| Gastrointestinal endoscopy (for GI tract symptoms or diarrhea)                                    |
| Tissue biopsy (for involved sites such as liver or GI mucosa)                                     |
| Computed tomography of the abdomen, chest and/or pelvis   |
| Exclude other disease presenting in a similar fashion (flushing, diarrhea, wheezing, hypotension) |
| Carcinoid syndrome (Urine 5-HIAA)   |

TMEP, telangiectasia macularis eruptiva perstans; UP, urticaria mastocytosis; DEXA, Dual-energy X-ray absorptiometry; GI, gastrointestinal; 5-HIAA, 5-hydroxyindoleacetic acid. \*Mutations including *c-kit* (D816V) and FIP1L1.

**Table 4. SCORMA Index. The clinical components of the SCORMA Index. The severity of cutaneous mastocytosis can be evaluated using the listed criteria. It may also be used as a tool for disease surveillance.**<sup>47</sup>

|                                |   |   |
|--------------------------------|---|---|
| Part A                         | Extent of skin abnormality present on physical examination.                                   | Measured as percent body surface area involved.   |
| Part B                         | 1. Pigmentation/erythema<br>2. Vesiculation<br>3. Elevation<br>4. Positive Darier's sign      | Measured according to examiners' observation. Absent = 0, mild = 1, moderate = 2, severe = 3. |
| Part C                         | 1. Provoking Factor(s)<br>2. Flushing<br>3. Diarrhea<br>4. Pruritis<br>5. Localized bone pain | Subjective severity of symptoms reported by the patient on a scale of 1-10.                   |
| SCORMA Index = A/4 + 5B + 2C/5 |   | Scores range from 5.2 to 100  |

**Table 5. Triggers that can activate mast cells. Physical stimuli and substances that can activate mast cells. These may be considered triggers for systemic symptoms or anaphylaxis in patients with mastocytosis.**

|   |
|---|
| Alcohol   |
| Bacterial toxins                                |
| Emotional stress                                |
| Exercise  |
| Food allergens (e.g., shellfish, peanuts)       |
| Immunologic stimuli (e.g., IgE)                 |
| Sunlight  |
| Temperature extremes                            |
| Venoms (e.g., hymenoptera)                      |
| Pharmaceutical agents                           |
| Acetylsalicylic acid                            |
| Amphotericin B                                  |
| d-Tubocurarine                                  |
| Dextromethorphan                                |
| Gallium   |
| Narcotics (e.g., morphine, meperidine, codeine) |
| Nonsteroidal anti-inflammatory drugs            |
| Polymyxin B                                     |
| Polymeric eye drops                             |
| Quinine   |
| Radiographic contrast containing iodine         |
| Reserpine                                       |
| Scopolamine                                     |

tinib.<sup>20</sup> A less common mutation located in the Fip1-like 1 gene (FIP1L1) is routinely tested for in patients with SM because it is a good indicator of response to treatment with the targeted tyrosine kinase inhibitor Imatinib.<sup>7</sup>

Constitutive signaling resulting from any mutation leads to uncontrolled proliferation of mast cells. Increased release of the *c-kit* ligand, known as mast cell growth factor (MCGF) or stem cell factor (SCF), may also contribute by acting locally to cause mast cell proliferation. Additionally, MCGF has been shown to cause melanocyte proliferation with increased production of melanin pigment. This likely accounts for the hyperpigmentation typical of UP/MPCM lesions.<sup>21</sup> Subsequent localized release of mast cell mediators and angiogenic factors from the activated mast cells can cause permanent vasodilation. This mechanism is responsible for the telangiectasias and erythematous nature of the lesions seen with TMEP.<sup>26</sup> Systemic release of excess mast cell mediators causes the clinical signs and symptoms of mastocytosis.

Some of the main mast cell mediators include histamine, heparin, tryptase, leukotrienes and interleukins. Histamine causes vasodilation, erythema, edema, pruritis and increased gastric acid.<sup>13</sup> Heparin and tryptase are both thought to be involved in the premature development of osteoporosis in patients with SM. These two factors are also responsible for inhibition of coagulation and possible increased bleeding risk. Leukotrienes are involved in bronchoconstriction and increased vascular permeability.<sup>13</sup> Treatment at this time most commonly consists of modulating the effects of these mast cell mediators.

## Treatment

There is no established first-line therapy for TMEP or systemic mastocytosis and much of treatment is focused on symptomatic relief. The literature suggests a combination of avoidance of triggers, limiting release of mast cell mediators and blocking the effects of these mediators.<sup>58</sup> The more aggressive forms, including ASM and MCL, may require a more intensive therapeutic regimen. Cyto-reductive and chemotherapeutic agents may be required in such cases.

Common triggers for patients with mastocytosis (Table 5) include alcohol, exercise, extreme temperatures, venoms, aspirin, nonsteroidal anti-inflammatory drugs, anesthesia and narcotics.<sup>7,13</sup> Patients should be educated about exposure to triggers and should be managed on an individual basis.

For cutaneous manifestations, oral psoralen plus UVA photochemotherapy, high-dose UVA-1 and narrow-band ultraviolet B phototherapy (UVB) have all proven beneficial both cosmetically and symptomatically.<sup>22,59,60</sup> Surgery with

**Table 6. Treatment of telangiectasia macularis eruptiva perstans and systemic mastocytosis. Mast cell components that cause typical symptoms of mastocytosis and how to treat based on symptomatology.**

| Component               | Symptom                             | Treatment  |
|-------------------------|-------------------------------------|--|
| Mast cell               | Plethora                            | Cromoglycate   |
| Histamine               | Vasodilation<br>Excess gastric acid | H <sub>1</sub> receptor antagonists<br>H <sub>2</sub> receptor antagonists |
| Tyrosine kinase         | Mast cell proliferation             | Imatinib and congeners   |
| NF-κB                   | Inflammation                        | Glucocorticoids  |
| LTC4                    | Inflammation                        | Leukotriene inhibitors   |
| Multiple mediators      | Hypotension                         | Epinephrine/autoinjectors  |
| Mast cell proliferation | Systemic disease                    | Biological agents<br>(e.g., interferon α)                                  |
| Mast cell infiltration  | UP/TMEP<br>Mastocytoma              | PUVA (phototherapy)<br>Excision  |

TMEP, telangiectasia macularis eruptiva perstans; SM, systemic mastocytosis; NF-κB, nuclear factor kappa B; LTC4, leukotriene C4; UP, urticaria pigmentosa; PUVA, psoralens and ultraviolet A.

585 nm flashlamp-pumped dye laser is also thought to improve cutaneous symptoms.<sup>61</sup> In nearly all cases, the symptom relief was transient and therapy had to be repeated. If pure CM is diagnosed, observation and conservative management of skin lesions is reasonable. With underlying SM, treatment of systemic disease is reported to provide relief of cutaneous symptoms as well.

Antihistamines are a well-established option for symptoms of SM. H1-histamine-receptor antagonists are used for pruritis and urticaria and H2 antagonists for excess gastric acid secretion.<sup>62,63</sup> The anti-mediator drug ketotifen may also be used to relieve pruritis, urticaria, flushing and bone pain.<sup>1,10</sup> Additionally, leukotriene receptor antagonists have proven successful for short-term control of mediator-induced symptoms.<sup>58,64</sup> Agents that stabilize mast cells, such as oral disodium cromoglycate, are used to block the release of mediators and decrease pruritis and flushing. Oral cromolyn sodium appears to work particularly well for gastrointestinal symptoms.<sup>65-67</sup> Corticosteroids, both intravenous and topical, have also been used and may be beneficial in patients with frequent hypotensive episodes.<sup>20</sup> Topical steroids may help to alleviate skin symptoms. Table 6 demonstrates treatment options with respect to mediator-related symptoms. Interferon-α, immunosuppressants and other cyto-reductive agents have been reported as possible treatments for more severe and aggressive forms of mastocytosis.<sup>20,68,69</sup>

Prophylactic measures should also be taken in patients with SM. Patients should be educated about common triggers, risks with surgery and using the Patterson Protocol for procedures involving IV contrast due to the increased risk of anaphylaxis. Providing patients with epinephrine injections for emergency use in cases of anaphylaxis or episodes of hypotension is highly recommended.<sup>5</sup> DEXA scans should also be obtained due to the high-

er risk of osteopenia and osteoporosis in these patients. Also encourage careful follow-up with yearly monitoring of CBC, serum tryptase and 24-hour urinary histamine for disease surveillance.

Investigation into the cytogenetics of mastocytosis continues to reveal encouraging treatment targets. Imatinib may be used as treatment for SM, however, the D816V mutation is an indicator of poor response to this therapy.<sup>7</sup> Only patients with the FIP1L1 mutation have been shown to have a good response to Imatinib therapy.<sup>7</sup> Increasing knowledge of the genetics of mastocytosis enables progression of treatment options. The most promising agents appear to be those that specifically target the *c-kit* kinase receptor on mast cells. Therapies targeting the specific cytogenetics of mastocytosis have potential to be the first and only curative modality. Further research and development in this field is needed.

## Conclusions

Characteristic skin findings can sometimes indicate the need for a high index of suspicion for an underlying systemic illness. It is essential to recognize and investigate cutaneous manifestations of diseases, especially those that may prove potentially fatal. Mastocytosis is a rare disease that most commonly presents with cutaneous manifestations. The symptoms of mastocytosis are caused by release of mediators from mast cells that may cause, in severe cases, anaphylaxis or histamine-mediated vascular collapse.

Progressing, eruptive erythematous lesions with reddish-brown macules and telangiectasias of the trunk and extremities are seen with telangiectasia macularis eruptiva perstans (TMEP), a rare form of maculopapular cutaneous mastocytosis. Further work-up

should be initiated, especially in adult patients with new-onset skin manifestations of mastocytosis, in order to look for systemic involvement.

Treatment options include but are not limited to phototherapy (PUVA and UVB), antihistamines (H<sub>1</sub> and H<sub>2</sub> blockers) and injectable epinephrine due to the increased risk for anaphylaxis. Yearly complete blood count, comprehensive metabolic panel, serum tryptase levels, 24-hour urine histamine and SCORMA Index are excellent options for disease surveillance and monitoring response to treatment. Patients should be followed closely due to the possibility of transformation to mast cell leukemia or other hematological malignancy. Due to the prevalence of the D816V mutation in adults with mastocytosis, further investigation into cytogenetics and targeted therapy is promising.

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