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# Telangiectasia macularis eruptiva perstans: an old terminology, still frequently used

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## Abstract

The term telangiectasia macularis eruptiva perstans (TMEP) was originally used to describe a rare form of cutaneous mastocytosis (CM) that was limited to the skin with lesions consisting of irregular, telangiectatic macules ranging in color from red to brown. Recent guidelines, however, recommended that the sole presence of telangiectasias should not form the basis of a distinct variant of CM. We conducted a review of the literature from 1930 to 2017 and found 76 cases that were reported as TMEP. Owing to a general misconception about diagnosis of CM and SM, there is a need for further discussion and awareness of the newly proposed World Health Organization (WHO) guidelines.

*Keywords: TMEP: telangiectasia macularis eruptiva perstans; CM: cutaneous mastocytosis; SM: systemic mastocytosis;WHO: World Heatlh Organization; MPN: myeloproliferative neoplasms; MC: mast cells; MPCM: maculopapular cutaneous mastocytosis; UP: urticaria pigmentosa; DCM: diffuse cutaneous mastocytosis; ISM: indolent SM; SSM: smoldering systemic mastocytosis; AHN: systemic mastocytosis with associated hematologic neoplasm; ASM: aggressive systemic mastocytosis; MCL: mast cell leukemia MCS: mast cell sarcoma; MIS: mastocytosis in the skin*

## Introduction

Mastocytosis represents a wide variety of disorders with an abnormal proliferation of mast cells that release histamine and inflammatory mediators [1]. These mediators are associated with pruritus, flushing, nausea, vomiting, abdominal pain, diarrhea, vascular instability, and headache [1]. The clinical presentation of mastocytosis is heterogeneous, ranging from disease limited to the skin that spontaneously resolves, often seen in pediatric cases, to more ominous variants with extracutaneous involvement associated with multiorgan failure and shortened lifespan, more commonly found in adult patients [2]. Cutaneous lesions are usually red or brown and monomorphic in adults with similar color, size, and shape, whereas the lesions in children are frequently polymorphic [3]. Darier sign, characterized by reddening and whealing of lesions upon mechanical stroking or rubbing, is often negative in adults, but commonly positive in children [3].

Historically, mastocytosis was subdivided into cutaneous mastocytosis (CM) and systemic mastocytosis (SM). Telangiectasia macularis eruptiva perstans (TMEP) represented a rare form of CM characterized by small, irregular, reddish, telangiectatic, and maculopapular skin lesions with a background color of light to dark brown, in addition to an abnormal infiltration of mast cells in the superficial dermis [4, 5]. Histologically, diagnosis was made by detection of increased amounts of mast cells around dilated venous plexus capillaries and venules of the upper third of the dermis [5]. No guidelines were established as to whether systemic testing should be performed, given the suspected diagnosis of TMEP. Furthermore, there was a lack of evidence demonstrating that TMEP was a separate subtype of CM, as it could have simply represented a highly vascularized form of maculopapular CM with dilated vessels [6]. Owing to an increasing

number of variants in clinical presentation and prognosis, the criteria for diagnosis of CM and SM evolved [1]. In 2016, an international task force of experts from various medical specialties proposed a revised definition of CM that would remove TMEP as a diagnosis because of overlap with urticaria pigmentosa (UP), [3]. Consequently, the term TMEP should no longer be used as a diagnosis, even if the predominant clinical feature is telangiectasia. The World Health Organization (WHO) refined its classification and diagnostic criteria for mastocytosis in 2016, and an understanding of these updates are essential for correct disease management.

## Mastocytosis: Diagnosis and Classification

The WHO now classifies mastocytosis as one of eight subcategories of myeloproliferative neoplasms (MPN), [2]. Infiltration of neoplastic, clonal proliferation of mast cells (MC) that are morphologically and immunophenotypically abnormal into one or more organs causes mastocytosis [2]. Mastocytosis can be characterized by cutaneous mastocytosis (CM), systemic mastocytosis (SM), or a localized mast cell tumor (**Table 1**), [6]. CM is defined by an increased number of mast cells in the skin without involvement of extracutaneous tissues, whereas SM is defined by the proliferation and accumulation of mast cells in the bone marrow (BM) and/or other extracutaneous organs, with or without skin involvement [7]. CM is divided into maculopapular CM (MPCM), which is equivalent to urticarial pigmentosa (UP), diffuse cutaneous mastocytosis (DCM), and solitary mastocytosis of the skin [8]. SM is divided into indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SM), systemic mastocytosis with associated hematologic neoplasm (AHN), and mast cell leukemia (MCL), [8]. Regardless of the subtype of SM, the bone marrow (BM) is involved in nearly all cases [9]. Mast cell sarcoma (MCS) is a separate subtype of mastocytosis [8].

The diagnosis and classification of mastocytosis is determined by morphologic, molecular, and immunophenotypic WHO criteria [2]. Mastocytosis in the skin (MIS) describes patients with skin lesions typical of mastocytosis who have not had full work-up for systemic involvement, including BM biopsy. In patients with clinical signs and symptoms of MIS, first obtain a skin biopsy with histology [7]. If MIS is confirmed, WHO criteria for SM include screening for serum tryptase level, BM histology (tryptase and/or KIT (CD117) immunostaining), MC immunophenotyping (CD25 and CD2 expression), KITD816V mutation screening in the BM, blood, or extracutaneous specimen, and FIP1L1-PDGFRA screening in the BM and blood if eosinophilia is present [7]. These patients have a different prognosis than those with SM, so a BM biopsy is necessary and suggested for all adult patients with MIS. If at least one major and two minor or three minor criteria

**Table 1.** *WHO mastocytosis classification 2016.*

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| **Cutaneous mastocytosis (CM)** |
| Maculopapular CM (MPCM)/urticaria pigmentosa (UP) |
| Diffuse CM (DCM) |
| Solitary mastocytoma of skin |
| **Systemic mastocytosis** |
| Indolent SM (ISM) |
| Smoldering SM (SSM) |
| SM with associated hematologic neoplasm (AHN) |
| Aggressive SM (ASM) |
| Mast cell leukemia (MCL) |
| **Mast cell sarcoma (MCS)** |

**Table 2.** *SM criteria defined by the WHO and updated in 2016.*

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| **Major SM criterion** |
| Multifocal dense infiltrates of MCs (≥15 MCs in aggregates) in BM biopsies and/or biopsies of extracutaneous organs |
| **Minor SM criterion** |
| >25% of MCs are atypical on BM aspirate smears or are spindle-shaped in MC infiltrates detected on sections of visceral organs |
| Activating KIT point mutation at codon 816 in BM, blood, or other extracutaneous organ |
| MCs in BM, blood, or other extracutaneous organ express CD2 and/or CD25 in addition to normal mast cell markers |
| Baseline serum total tryptase level >20 ng/mL |

are met, SM is confirmed (**Table 2**), [2, 7]. The major criterion includes multifocal dense infiltrates of MCs in aggregates on BM or other extracutaneous organ biopsy. Tryptase is a vasoactive immunoregulatory mediator found in mast cell granules, and elevated serum total tryptase levels >20 ng/mL is a minor criterion for the diagnosis of SM owing to its elevation in most patients with SM [1, 2, 4]. A positive KIT mutation represents a minor diagnostic criterion of mastocytosis, since the catalytic domain of c-kit can lead to unregulated growth and differentiation of mast cells and has been associated with a large number of adults with mastocytosis [1]. FIP1L1-PDGFRA screening in the presence of eosinophilia distinguish chronic eosinophilic leukemia from SM [7]. Neoplastic cells are characterized by abnormal morphology and immunoreactivity to CD2 and CD25 [7]. After systemic investigation, >95% of adults with mastocytosis are diagnosed with SM [2]. If SM is confirmed, screening for B and C findings should be performed to assess for SSM and ASM (**Table 3**), [7]. SSM requires two or more B-findings and no C-findings whereas ASM requires one C-finding and documentation of local mast cell infiltration [2, 7]. Criteria for associated hematologic neoplasms should also be checked [2, 7]. Nevertheless, some patients have only CM; systemic testing was performed and negative [2]. If SM is not found, follow up should be done with a blood count, serum tryptase level, and observation of clinical symptoms [7]. Although adult-onset mastocytosis tends to be a chronic disease, pediatric mastocytosis in the skin has been reported to spontaneously remit in 70-80% by their teenage years [6]. Therefore, systemic testing is not necessary in children and the diagnosis of CM is accepted [6].

## Treatment

A review of all treatments of mastocytosis is outside the scope of this article. There is no gold-standard treatment for patients with mastocytosis, but the individual patient's symptoms, organ involvement, and clinical presentation should guide treatment [6]. The mediators released from mast cells found in all subtypes of mastocytosis require a broad approach to the treatment of systemic symptoms [1]. Treatment currently includes H1 antihistamines, H2 antihistamines, proton pump inhibitors, anti-leukotriene agents, and injectable epinephrine to improve symptoms [1]. Topical corticosteroids may be effective acutely for CM, and psoralen-ultraviolet A therapy can be used in severe cases [1]. Patients should avoid known triggers that stimulate mast cell degradation, such as exposure to certain foods, sunlight, heat, cold, alcohol, and drugs [4]. In patients with SM, corticosteroids, ketotifen, cromolyn sodium, or leukotriene antagonists may be used [8]. Immunotherapy or IgE-depleting agents can be used for patients with SM and severe symptoms from allergy to bee or wasp venom [8]. Drugs targeting mutant KIT forms are in development and may be a novel therapeutic treatment for SM in addition to allogeneic stem cell transplant for refractory cases [8].

## Discussion

Reports on the epidemiological aspects of mastocytosis are few. The prevalence of mastocytosis in the pediatric population is not known. The disease is likely to be underdiagnosed or misdiagnosed

**Table 3.** *WHO "B- and C-" findings in SM.*

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| **B findings** | |
| | BM biopsy with >30% infiltration by MCs and total serum tryptase >200 ng/mL |
| | Signs of dysplasia or myeloproliferation in non-MC lineage, but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm, with normal or slightly abnormal blood counts |
| | Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging |
| **C findings** | |
| | Bone marrow dysfunction manifested by one or more cytopenia, but no obvious non-MC hematopoietic malignancy |
| | Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension |
| | Skeletal involvement with large osteolytic lesions and/or pathological fractures |
| | Palpable splenomegaly with hypersplenism |
| | Malabsorption with weight loss due to gastrointestinal MC infiltrates |

owing to the complicated symptoms, varying systemic involvement, and a lack of awareness among medical professionals. The prevalence of disease will likely increase with greater awareness of updated diagnostic recommendations.

We conducted a search of the literature on PubMed from 1930 to 2017 and identified 61 relevant articles (with 76 reported single cases) in 8 different languages (English, Spanish, German, French, Dutch, Italian, Hungarian, and Portuguese) describing patients with a diagnosis of TMEP [10-70]. The median age at diagnosis was 46, ranging from 0.5 to 86 years, and a female to male ratio of 1.1:1. Systemic testing was only done in 26 out of 76 subjects (34.2%) and was positive in 6 (23.1%). Of the 26 cases with systemic testing done, none were children. These findings demonstrate the need for increased awareness and usage of WHO guidelines so that patient survival and quality of life can be greatly improved.

## Conclusion

Mastocytosis is a rare, but complex disease with many subtypes and clinical variants. Owing to the difference in prognosis, ranging from no symptoms with a normal life expectancy to severe symptoms and death within weeks, a thorough understanding of the disease and correct diagnostic algorithm is needed. Additionally, an increasing number of patients seek information about their disease on the internet, and they may encounter outdated, incorrect, or irrelevant information that may raise unnecessary concerns. Increased acceptance and awareness of WHO diagnostic criteria for patients with signs and symptoms of mastocytosis can lead to earlier diagnosis and treatment, which produces better health outcomes.

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