

Cutaneous Mastocytosis in Adults and Children

New Classification and Prognostic Factors



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KEYWORDS

- Mastocytosis • Mast cell • Cutaneous mastocytosis • Urticaria pigmentosa
- Classification • Prognosis • WHO

KEY POINTS

- Cutaneous mastocytosis is a highly heterogeneous subtype of mastocytosis. Heterogeneity mainly depends on the age at disease onset and the clinical form of presentation.
- The classification of cutaneous mastocytosis has recently been redefined by the World Health Organization and an international consensus task force.
- A subset of children with mastocytosis shows persistence of the disease into adulthood, usually as the classic indolent systemic mastocytosis or as well-differentiated systemic mastocytosis.

INTRODUCTION

Mastocytosis is a heterogeneous disease characterized by the clonal expansion and accumulation of mast cells (MCs) in different organs and tissues.^{1–3} The clonal nature of the disease can be established by the demonstration of activating mutations of the c-kit gene in most patients, provided that highly sensitive diagnostic methods are used.^{4–7} This proto-oncogene encodes for a receptor in the membrane of MCs called *KIT*, a tyrosine-kinase protein that regulates growth and differentiation of MCs. In mastocytosis, *KIT* mutations induce a ligand-independent hyperactivation state of the receptor that leads to an increased survival of MCs, resulting in their accumulation in tissues.

Depending on the sites of organ involvement, 2 main forms of mastocytosis are recognized: (1) cutaneous mastocytosis (CM), when the skin is the only tissue affected, and (2) systemic mastocytosis (SM), characterized by MC infiltrates in

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extracutaneous organs, mostly the bone marrow (BM), with or without concomitant skin involvement.^{1,8–10} The heterogeneity of mastocytosis is evidenced by the fact that the disease can develop both in children, supposedly as CM that tends to spontaneously regress by adolescence, and in adults, in whom mastocytosis is often systemic and shows a chronic course. More rarely, mastocytosis can exhibit an aggressive behavior with high cell proliferation rates and shortened survival.

In this article, we focus on the dermatologic aspects of mastocytosis, including a brief review through the different terminologies, concepts, and classification approaches that have been used along the history, with special emphasis on the most modern vision of the disease.

HISTORIC OVERVIEW

In 1869, Nettleship and Tay¹¹ described the case of a 2-year-old girl who presented with what looked like a rare form of chronic urticaria leaving brownish stains, which is widely thought to be the first case of mastocytosis reported in the literature, 10 years before the discovery of MCs by Paul Ehrlich.¹² The term *urticaria pigmentosa* (UP) was coined in 1878 by Sangster¹³ to refer to a skin eruption found in a child that was described as “an anomalous mottled rash accompanied by pruritus, factitious urticaria and pigmentation.” Nine years later, Unna¹⁴ documented the presence of MCs in skin lesions of UP, but it was not until 1936 when the term mastocytosis was first used.¹⁵

Early attempts for classification of CM date from the first quarter of the twentieth century. At that time, 3 main forms of UP were already distinguished:

1. Macular
2. Nodular (xanthelasmoid form)
3. Mixed type (maculonodular)^{16,17}

Later, more uncommon forms of UP with peculiar characteristics, such as bullous UP,^{18,19} diffuse erythrodermic mastocytosis,^{20,21} and *telangiectasia macularis eruptiva perstans* (TMEP)²² were described, becoming rapidly recognized as novel cutaneous variants of UP.

By the mid-twentieth century, the systemic nature of mastocytosis was first established on the basis of histopathological findings in an autopsy carried out in a fatal case of UP that showed MC infiltrates not only in the skin but also in internal organs.²³ Within the following years, the concept of mastocytosis as a systemic disease in nature was rapidly spread out in parallel to increasing numbers of reports showing extracutaneous involvement,^{24–29} but also cases purely restricted to the skin were described.^{24,25} a dual vision of the disease that still remains today.

In the 1960s, Caplan^{26,27} proposed to classify UP cases into 3 categories according to the number of skin lesions and the age at disease onset:

1. Solitary lesion (group I)
2. Multiple lesions appearing in infancy and early childhood (group II)
3. Multiple lesions appearing in late childhood, adolescence, and adulthood (group III)

Noteworthy, this classification provided pioneer information in terms of prognosis of the different categories of the disease. Thus, whereas solitary lesions tended to involute completely with time, some cases in group II and most cases in group III seemed to persist indefinitely; moreover, a correlation was found between late onset of skin lesions (group III) and the existence of a systemic MC disease.

The first comprehensive classification of mastocytosis in which both CM and SM were incorporated together was developed by Lennert and Parwaresch in 1979.²⁸

The investigators divided MC neoplasms into 2 main categories: (1) benign MC neoplasms, which included mastocytoma, CM (diffuse or localized variants), and SM with skin involvement, and (2) malignant (systemic) MC neoplasms, which included malignant mastocytosis (also called MC reticulosis), MC sarcoma, and MC leukemia. Here, the investigators emphasized the poor prognosis in terms of survival of patients with malignant MC tumors.

In early 1990s, a consensus classification of mastocytosis was agreed on at an interdisciplinary meeting.²⁹ The new classification was adapted from previous classification schemes developed at the Mayo Clinic³⁰ and at the National Institutes of Health,³¹ and recognized 4 categories of the disease:

1. Category I (indolent mastocytosis)
2. Category II (mastocytosis associated with a hematologic disorder)
3. Category III (aggressive mastocytosis)
4. Category IV (mastocytic leukemia)

In this revised classification, cutaneous lesions of mastocytosis, including UP, mastocytoma, diffuse and erythrodermic mastocytosis, and TMPE, were grouped under the general term of “cutaneous disease” and included within the category of indolent mastocytosis together with other manifestations, such as syncope, ulcer disease, malabsorption, BM MC aggregates, skeletal involvement, hepatosplenomegaly, and lymphadenopathy.²⁹

Over the following decade, major advances were made in the understanding of MC physiopathology that contributed to provide more specific diagnostic criteria for SM. Such criteria were used as a basis for a new consensus classification of mastocytosis formulated in the year 2000,³² which was adopted by the World Health Organization (WHO) in 2001.³³ In this classification, CM was considered as a separate entity defined by the presence of skin lesions (with histologic demonstration of MC infiltrates in the dermis) in the absence of diagnostic criteria for SM, and included 3 main variants:

1. UP
2. Diffuse CM (DCM)
3. Mastocytoma of skin

Within the UP variant, for which the investigators proposed also the term “maculopapular CM (MPCM),” several subvariants were recognized, including a plaque form, a nodular form, and a telangiectatic subvariant (also referred to as TMPE). However, other investigators were aligned with the idea of considering the subvariants of UP as separate entities of CM on the basis of their different macroscopic appearance and prognosis; accordingly, a modified classification of CM including 5 variants also was proposed:

1. MPCM
2. Plaque-type CM
3. Nodular CM/mastocytoma (solitary or multiple)
4. DCM
5. Telangiectatic CM³⁴

The 2001 WHO classification of mastocytosis remained substantially unchanged in terms of CM variants in the updated versions of the WHO classification in 2008¹ and 2016.^{8,9} However, an international task force involving experts from Europe (EU) and the United States has recently recommended that MPCM/UP should be subdivided into 2 variants: (1) monomorphic variant, characterized by small maculopapular lesions that typically arise in the adulthood, and (2) polymorphic variant, which shows

large and heterogeneous lesions that can be macular, plaque-type, or nodular and is almost exclusively seen in children.¹⁰ The rationale for this proposal is a potential prognostic impact in terms of duration of the disease in children, because polymorphic lesions tend to spontaneously regress by adolescence, whereas in children with the monomorphic variant of MPCM, mastocytosis frequently persists into adulthood usually as a systemic disease. Other recommendations supported by the EU/US consensus group are to consider a maximum of 3 cutaneous lesions under the term mastocytoma, which should be no longer referred to as solitary mastocytoma, and to remove TMEP from the classification of CM.¹⁰

THE SKIN IN MASTOCYTOSIS

The skin is the most frequently affected tissue in patients with mastocytosis. Overall, virtually all children and more than 80% of adult patients with mastocytosis show cutaneous lesions, but their macroscopic and microscopic characteristics as well as their localization and distribution strongly differ from one patient to another.

Subtypes of Mastocytosis in the Skin/Cutaneous Mastocytosis

The WHO currently recognizes 3 main subforms of CM, which include MPCM/UP, DCM, and mastocytoma of skin.^{8,9}

In the MPCM subform, skin lesions are typically brownish to reddish oval or round macules and papules, but in some cases large plaques or nodules can coexist or even predominate. According to the EU/US consensus group, MPCM can be divided into 2 variants¹⁰:

1. Monomorphic MPCM, characterized by homogeneous, small skin lesions that are highly variable in number and usually show a central body distribution with centrifugal spread (Fig. 1A).
2. Polymorphic MPCM, in which the skin lesions are heterogeneous and show different shapes and sizes, but are generally larger than those from the monomorphic variant (Fig. 1B).

Overall, the monomorphic MPCM variant is more commonly seen in adult-onset mastocytosis, in which the skin involvement usually coexists with SM. By contrast,

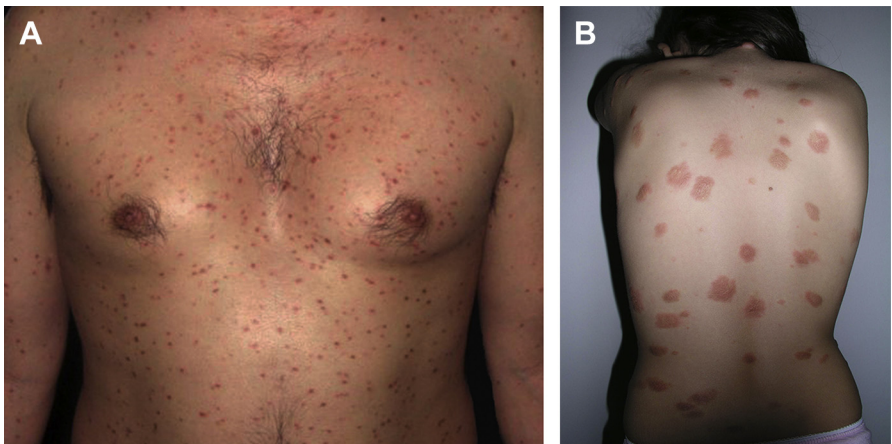


Fig. 1. MPCM. (A) MPCM monomorphic variant (EU/US consensus classification). (B) MPCM polymorphic variant (EU/US consensus classification).

polymorphic MPCM typically occurs in children in whom the disease is generally restricted to the skin and tends to show spontaneous regression by puberty in most cases.

DCM is defined by a generalized thickening of almost the entire skin in the absence of individual hyperpigmented cutaneous lesions.¹⁰ Although as per definition the term DCM implies an extensive cutaneous involvement, it should be emphasized that not all patients showing extensive cutaneous disease correspond to DCM.³⁵ The typical macroscopic appearance of the skin in DCM has been traditionally referred to as “peau d’orange,” “crocodile-like pachydermia,” or “elephant skin” (Fig. 2A). Overall, this subform of CM is rare and generally develops at birth or shortly after.¹⁰ Children with DCM usually show recurrent episodes of generalized blistering (Fig. 2B) often associated with systemic symptoms, such as flushing, gastrointestinal symptoms, and, in most severe cases, hypotension requiring epinephrine or other life-threatening complications.^{36–38} Elevated serum tryptase (sT) levels (frequently higher than 100 µg/L) are typically detected at early stages of the disease, as a reflection of both the high MC burden in the skin and an increased MC-mediator releasability, but generally decline over time in parallel with gradual improvement of MC-mediator release symptoms.^{10,37,39} Because of the high density of skin MCs that characterize DCM, it is not recommended to perform the Darier sign in these cases, to avoid a potentially massive MC degranulation that could result in severe symptoms. Despite the extent of cutaneous involvement and the severity of clinical symptoms at onset, DCM usually resolves by adolescence, frequently leaving a *cutis laxa*-like residual appearance of the skin, although in some patients the disease persists into adulthood. In many of these later cases, the BM is infiltrated by round, fully granulated MCs in the absence of aberrant expression of CD25 and CD2 and frequently lacking *KIT* mutations or carrying germline mutations located at exons 8 or 9 of *KIT* (eg, del D419, K509I); altogether, these findings are consistent with the diagnosis of well-differentiated SM.^{40–43}

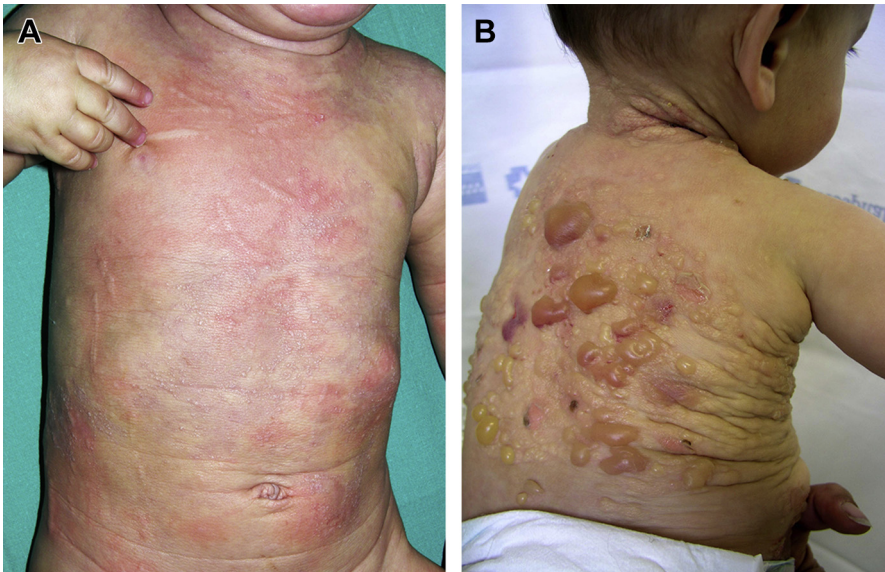


Fig. 2. DCM. (A) A child with DCM in between episodes of blistering showing “peau d’orange” skin and dermatographism. (B) A child with DCM suffering an episode of extensive blistering.

Cutaneous mastocytoma usually consists of a solitary brown to yellowish nodular lesion that frequently involves the trunk or extremities, although any part of the body can be affected (**Fig. 3**). In the last consensus report by the EU/US task force, it was agreed to consider under the term mastocytoma all those cases showing a maximum of 3 cutaneous lesions, whereas patients with 4 or more lesions would be categorized as MPCM.¹⁰ In most cases, cutaneous mastocytoma is often already present at birth or develops within the first months of life, and is extremely rare in adults. The histologic picture of mastocytoma is often undistinguishable from that found in DCM, with a massive MC infiltration occupying the whole dermis⁴⁴; therefore, the Darier sign should not be elicited in such cases either. An important feature of mastocytoma is the dynamic pattern of the skin lesion/s, which initially may increase in size (but not in number) to further develop into other types of lesion (eg, nodule into papule) and finally regressing after variable periods of time.^{45,46} In clinical daily practice, mastocytoma is often diagnosed exclusively on the basis of its characteristic clinical features, skin biopsy being not necessary in most cases.

It should be noted that some patients with mastocytosis show skin lesions that do not perfectly fit with any of the currently accepted subforms and variants. More rarely, patients can present with skin lesions confined to a segment or area of the body^{47,48}; these cases might represent a mosaic manifestation of the disease (ie, type 1 mosaicism) in which the mutational event, albeit unconfirmed, would be limited to the part of the body affected.⁴⁹

Diagnosis of Cutaneous Mastocytosis

At present, CM is defined by the presence of skin lesions resulting from the accumulation of MCs within the dermis in the absence of criteria for SM.^{1,2,8–10} This means that BM examination would become necessary for the distinction between CM and SM, both entities being mutually exclusive, although many patients with SM can present with cutaneous involvement. For this reason, the concept of “mastocytosis in the skin” (MIS) has emerged in recent years as a provisional diagnosis for patients with mastocytosis skin lesions in the absence of a BM study that, when done, will provide the definitive diagnosis (eg, CM or SM).² As a general rule, the prediagnostic check-point MIS should be established in all adult patients and in children with persistently increased sT levels, until the BM study is performed. By contrast, it is generally accepted that in children with sT <20 µg/L, the diagnosis of CM can be assumed without BM examination.²



Fig. 3. Mastocytoma of the skin.

According to the recommendations of the EU/US consensus group, the diagnosis of MIS would require the presence of typical skin lesions (major criterion) together with at least 1 of the following minor criteria:

1. Increased MC numbers in a biopsy from lesional skin
2. Activating *KIT* mutations in lesional skin tissue¹⁰

Neoplastic infiltrates of dermal MCs can be identified by immunohistochemistry using specific stains (eg, tryptase or c-kit –CD117–) as spindle-shaped or spherical/cuboidal cells that may show different histologic patterns:

1. Perivascular
2. Interstitial
3. Nodular
4. Diffuse (sheetlike)⁴⁴

In addition, recent studies have suggested that the aberrant expression of CD25 on skin MCs in patients with MIS might indicate a higher risk of having a systemic MC disease.^{50–52}

Similar to BM MCs in patients with SM, the clonal neoplastic nature of MCs in MIS/CM can be established in most cases by the demonstration of activating *KIT* mutations in skin biopsies, with remarkable differences between adults and children. Thus, the *KIT* D816V mutation can be detected in virtually all adult patients using a sensitive polymerase chain reaction technique,⁵³ but only in 27% to 36% of children^{54,55}; by contrast, other mutant variants involving codon 816 of *KIT* or mutations in regions of the *KIT* receptor other than codon 816 are detected in up to 50% of patients with childhood-onset mastocytosis.⁵⁵ Altogether, these findings support the notion that pediatric MIS is a clonal disease associated with *KIT* mutations that are often different from the classic D816V *KIT* mutation. Despite this, the identification of *KIT* mutations in children with MIS does not necessarily result into an increased risk for persistence of the disease into adulthood, as demonstrated by a previous study showing spontaneous regression of skin lesions in several children who carried the D816V *KIT* mutation.⁵⁴

PROGNOSTIC FACTORS IN CUTANEOUS MASTOCYTOSIS

The clinical significance of the presence of MIS differs according to the age of the patients at disease onset. In most children, MIS emerges during the first 2 years of life, frequently within the first 6 months, and some patients show skin lesions already at birth.^{10,37,56} In adults with MIS, although the peak of disease onset occurs at ages between 20 and 50 years,^{10,57} cases evolving from pediatric-onset MIS also can be occasionally observed.^{40,41,43,58–61} According to the current 2016 WHO classification of mastocytosis,^{8,9} the most frequent subtype of MIS found in children is MPCM (~40%–75%), followed by cutaneous mastocytoma (~20%–50%), and DCM (~3%–8%),^{10,37,44,62,63} whereas in adults, the vast majority of patients (eg, >95%) who present with skin involvement show the MPCM subform, mastocytoma and DCM being extremely rare in adulthood.¹⁰ Interestingly, skin biopsies from patients with the polymorphic variant of pediatric MPCM often show findings highly suggestive of the so-called well-differentiated CM. These histologic findings consist of a variable degree of abnormally increased numbers of dermal MCs with a predominantly round or polygonal shape and fully granulated cytoplasm, frequently coexisting with dermal binucleated or polynucleated promastocytes, which tend to be disposed forming strands or rows between collagen bundles.⁴⁰ This same histologic picture of mature-appearing MCs infiltrating the skin also can be seen in mastocytoma and in

some cases of DCM, where MC numbers are particularly increased and usually show a sheetlike pattern involving the whole dermis and eventually extending deep into the subcutaneous cellular tissue. In contrast to polymorphic MPCM lesions, MCs in skin lesions of patients with the monomorphic MPCM variant tend to be spindle shaped and their numbers appear to be lower.¹⁰

Itch and redness of skin lesions are common local MC-mediator symptoms in both adults and children with MIS. By contrast, blistering is restricted to pediatric patients, and it is particularly frequent in children with early disease onset (eg, <2 years) who present with extensive cutaneous involvement (eg, DCM)^{36,37,56,64}; moreover, extensive blistering disease is an indicator of massive MC activation and has been regarded as a predictor of severe complications in children with mastocytosis.³⁵ Blisters also can be frequently observed in children with large skin lesions (eg, nodular lesions), especially when affecting the scalp or body sites exposed to repeated friction or pressure.³⁷ Flushing is another symptom that often occurs in patients with MIS. Although it has been classically considered as a cutaneous manifestation in patients with mastocytosis, flushing actually results from increased blood flow through the skin caused by vasoactive substances released from MCs (eg, histamine), and it can precede the development of hypotensive collapse; for this reason, the presence of flushing in a patient with mastocytosis should alert about the potential development of serious, life-threatening complications.³⁵ Patients with MIS also can suffer from a wide range of other (systemic) symptoms, including abdominal cramping, diarrhea, bone pain, dyspnea, headache, and anaphylaxis, among others.^{37,56,63} Although systemic symptoms are more frequently observed in adults as a consequence of the presumably systemic nature of the disease,⁶⁵ systemic symptoms also can occur in pediatric mastocytosis, in which the disease is mostly restricted to the skin; in these latter cases, systemic symptoms result from the effect of a wide variety of mediators massively produced by huge numbers of cutaneous MCs that are released into the bloodstream; accordingly, systemic symptoms in pediatric mastocytosis are particularly common in patients with DCM and in those with very extensive MPCM.^{37,38,65–67} The most common triggers of symptoms in patients with MIS are skin rubbing and exposition to extreme temperatures (eg, heat and/or hot water, more rarely cold).³⁷ Other frequent elicitors are stress, some drugs, insect venoms, and premenstrual stages in adults, and fever, irritability, teething, and vaccines among children, especially those with extended cutaneous involvement.^{37,66,68}

Some features have been identified as potential predictors for the severity of MC-mediator release symptoms in patients with MIS. Total sT levels have been shown to correlate quite well with the burden of neoplastic MCs in patients with mastocytosis,^{69,70} and also with the extent of skin involvement and the risk for severe MC activation events, including anaphylaxis in pediatric mastocytosis.^{37,66,71} In contrast to children, the extent of cutaneous involvement in adult patients with MIS seems to correlate with the presence of pruritus and flushing,³⁶ but not with the risk for anaphylaxis.⁶⁶ The extent and the activity of mastocytosis cutaneous lesions together with the assessment of subjective symptoms have been incorporated into a scoring model called the SCORMA Index, which has shown to be useful as a tool for evaluating the severity of the disease in both adults and children with MIS.^{71–73}

The current consensus classification, which divides MPCM into monomorphic and polymorphic variants, has been suggested to show prognostic impact, because most (but not all) children with the polymorphic MPCM variant usually display normal sT levels and show spontaneous regression by puberty, whereas those with the monomorphic MPCM variant more frequently have increased sT levels and higher probability of persistence of the disease in adulthood.^{10,74} Other factors that have been strongly associated

with disease resolution in pediatric-onset mastocytosis include a lower age at onset (eg, <2 years),^{75,76} a lower extent of skin affected,⁷⁶ and a normal BM examination.⁷⁵

By contrast, the potential persistence of childhood-onset MIS beyond adolescence is closely related to the presence of concomitant (underlying) systemic involvement^{75,77} that can be demonstrated on the basis of BM findings. However, it should be noted that the probability of SM in children with MIS is low, particularly if sT levels are lower than 20 µg/L. However, a recent study including 105 patients with childhood-onset mastocytosis has shown that 19 of 53 patients who were selected for BM examination had SM, the presence of organomegalies being the best predictor of SM in this pediatric population, especially when increased sT levels were also detected.³⁹

THE NEED FOR FURTHER CLASSIFICATION OF MASTOCYTOSIS

The current classification and categories of CM are not fully satisfactory. Some old-fashioned terms are now outdated, but others, such as “urticaria pigmentosa” are still used and need to be reevaluated. Other terms, such as “maculo-papular” or “nodular” are being inaccurately used according to their definition in dermatologic terminology. In children, the precise incidence of systemic involvement has not been established and, thus, a classification based on the number of lesions is not useful in terms of disease severity or prognosis. Regarding solitary lesions, also named mastocytomas, their clinical appearance is heterogeneous and it remains not clear if patients with 2 or 3 lesions should be included in this category.

Despite the great relevance of the 2016 WHO classification of mastocytosis and the recent consensus classification of CM by the EU/US task force in showing the heterogeneity of skin lesions in mastocytosis, a more accurate classification of the different patterns of cutaneous involvement in mastocytosis, probably incorporating histopathological and genetic profiles of the disease that could have prognostic impact, is warranted in the near future.

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