

CUTANEOUS MANIFESTATIONS OF MASTOCYTOSIS

Ahmed Ismail Manjra

Paediatric Allergologist, Westville Hospital, Durban

Email | manjra@mweb.co.za

CLINICAL VIGNETTE

JH – 12 years of age – was first seen in 2014 for a skin rash that was present from six months of age. At about three years of age he experienced severe blistering of the skin which resolved spontaneously. On examination, a severe diffuse rash over his entire body was noticed which had a *peau d'orange* appearance. He also had pachydermia of the skin (see Figures 1, 2, 3). A biopsy of the skin confirmed mastocytosis and his mast-cell tryptase level was 22.4 ug/L. The type of cutaneous mastocytosis that JH has is diffuse mastocytosis. He has been seen regularly for the past five years. His skin has improved with time (see Figure 3).

HISTORY OF MAST-CELL DISCOVERY

In 1863, a German pathologist, Friedrich von Recklinghausen, was the first to describe mast cells in frog mesentery. In 1875, a German anatomist, Wilhelm Waldeyer, reported finding mast cells in a tissue spread of rat dura mater and named these cells 'embryonal' or 'plasma' cells. Two years later, Waldeyer's medical student, Paul Ehrlich, described the discovery in human connective tissues of these same cells in his dissertation. He termed these *mastzellen* or well-nourished cells, due to their rich granular content evident from unique metachromatic-staining properties with aniline-positive. Paul Ehrlich was awarded the Nobel Prize for medicine in 1908 for this discovery.¹

PHYSIOLOGY OF MAST CELLS

Mast cells are involved in inflammation, coagulation, adaptive immunity and allergic responses. They are involved in the early allergic reactions in asthma, allergic rhinitis (AR) and anaphylaxis. They mediate their reaction through degranulation. Mast cells are non-proliferating sedentary cells with a long lifespan.^{2,3,4,5,6} They differentiate in the bone marrow from common myeloid-precursor cells in response to stem-cell factor (KIT ligand), which is the ligand of the CD117 transmembrane tyrosine kinase receptor, encoded by *KIT*. CD117 regulates the growth, migration, survival and effector functions of mast cells and then rapidly migrates to epithelial tissues which are in contact with the external environment, that is, the skin, the respiratory tract and the gastrointestinal tract. The mast cells also reside in perivascular spaces and connective tissue surrounding nerves and then differentiate into non-proliferating mature mast cells. These then express secretory granules.

Mast cells are activated primarily by IgE-dependent mechanisms (allergen, anti-IgE) but also by IgE-independent mechanisms

(IgG, bacterial and viral components, complement fragments (C3a, C5a)) cytokines, chemokines, drugs, physical stimuli and hormones. Activated mast cells release inflammatory mediators from storage granules and also form new mediators from de novo synthesis. The mediators in storage granules are histamine, tryptase, chymase and carboxypeptidase. Those derived from phospholipid membrane metabolism are platelet-activating factor, leukotrienes and prostaglandins. Those derived after de novo synthesis are cytokines and chemokines.

There are sub-groups of mast cells: MC_{TC} expressing tryptase, chymase, carboxypeptidase and cathepsin populate mainly connective tissue and skin, and MC_T that express mainly tryptase predominate in the lungs. Interconversion between these sub-types occurs depending on the microenvironment.⁷

HISTORY OF MASTOCYTOSIS

In 1869, an English dermatologist, Edward Nettleship, and an English ophthalmologist, Warren Tay, in the *British Medical Journal* described a rare urticarial skin disease: a symmetric distribution of pigmented maculopapular lesions.⁸ A decade later, this disease was termed urticaria pigmentosa (UP) by another London dermatologist, Alfred Sangster,⁹ and another decade later, German dermatologist Paul Gerson Unna was the first to associate mast cells with human disease, noting the presence of these cells in the lesions of urticaria pigmentosa.¹⁰

The term 'mastocytosis' was first used only in 1936: it is caused by the clonal expansion and accumulation of mast cells in different organs and tissues. The clonal nature of the disease can be established by the demonstration of activating mutations of the c-kit gene in most patients. This requires sophisticated genetic testing. The c-kit gene encodes for a receptor in the membrane of mast cells called KIT, a tyrosine-kinase protein that regulates the growth and differentiation of these cells. In mastocytosis, KIT mutations induce a ligand-independent hyperactivation state of the receptor that leads to an increased survival of mast cells, resulting in their accumulation in tissues.¹¹

CLASSIFICATION

There are two main forms of mastocytosis, depending in which organs mast cells accumulate:

- Cutaneous mastocytosis (CM), when the skin is the only tissue in which mast cells accumulate.
- Systemic mastocytosis (SM), where mast cells accumulate in extracutaneous organs, mostly in the bone marrow, with or without skin involvement.



Figure 1: Diffuse mastocytosis (patient JH)



Figure 2: Close-up photo of patient JH with diffuse mastocytosis



Figure 3: Resolving diffuse mastocytosis (patient JH)



Figure 4: Female adult with smouldering systemic mastocytosis and maculopapular cutaneous lesions, monomorphic type associated with this disease (formerly known as urticaria pigmentosa or UP)*



Figure 5: Female adult athlete with maculopapular cutaneous lesions, monomorphic type (formerly known as urticaria pigmentosa or UP), during a flare when the lesions are swelling*



Figure 6: Female adult with smouldering systemic mastocytosis (SSM) and typical maculopapular, cutaneous lesions, monomorphic type (formerly called urticaria pigmentosa or UP) during a flare*



Figure 7: Adult female with maculopapular, cutaneous lesions, monomorphic type during a flare*



Figure 8: Male child with cutaneous mastocytosis, characterised by maculopapular cutaneous lesions, polymorphic type (formerly known as urticaria pigmentosa or UP). Note that in some children, during a flare in response to a trigger, lesions may become bullous or blistered*



Figure 9: Male child with cutaneous mastocytosis during flare causing blisters in his maculopapular cutaneous lesions*



Figure 10: Male child with the maculopapular cutaneous lesions, polymorphic type, consistent with cutaneous mastocytosis (formerly called urticaria pigmentosa or UP)*



Figure 11: Male child with cutaneous mastocytosis with polymorphic lesions and other rashes



Figure 12: Cutaneous mastocytoma, normal and inflamed

The first classification (in the early 1900s) recognised three main forms of UP, based on their morphological appearance:¹²

- macular
- nodular
- mixed type.

With time, rarer forms of UP were described, such as bullous UP, telangiectasia macularis eruptive perstans and diffuse erythrodermic mastocytosis.

In 1963 and 1965, Caplan proposed a new classification of UP, according to the number of skin lesions and age of onset:¹³

- solitary (group 1)
- multiple lesions appearing in infancy and early childhood (group 2)
- multiple lesions appearing in late childhood, adolescence, and adulthood (group 3).

In 1979, Lennert and Parwaresch developed a new classification in which CM and SM were incorporated:¹⁴

- benign mast-cell neoplasms, which included mastocytoma, CM (diffuse or localised variants) and SM with skin involvement;
- malignant (systemic) mast-cell neoplasms, which included malignant mastocytosis (also called mast-cell reticulosis), mast-cell sarcoma and mast-cell leukaemia.

In the early 1990s, a new classification was agreed on by consensus between the Mayo Clinic and the National Institutes of Health (NIH) in the United States:¹⁵

- Category I (indolent mastocytosis)
- Category II (mastocytosis associated with a haematological disorder)
- Category III (aggressive mastocytosis)
- Category IV (mastocytic leukaemia).

In the ensuing years many advances were made in the understanding of CM and SM. The World Health Organisation (WHO) proposed a new classification for CM and SM in 2000 which was subsequently revised in 2016. The new 2016 WHO classification is – after many revisions – as follows:^{16,17,18,19}

- Cutaneous mastocytosis (CM)
 - maculopapular CM = UP
 - diffuse CM
 - mastocytoma of skin
- Systemic mastocytosis (SM)
 - indolent SM
 - smouldering SM
 - SM with associated hematological neoplasma
 - aggressive SM
 - mast-cell leukaemia.

MAST-CELL SARCOMA

This classification divided SM and CM into two separate entities. Following a proposal that the UP variant be divided into various sub-types, these sub-types were proposed:²⁰

- MPCM (maculopapular CM)
- plaque-type CM

- nodular CM/mastocytoma (solitary or multiple)
- DCM (diffuse CM)
- telangiectatic CM (TMEP).

In 2016, a task force comprising the European Competence Network on Mastocytosis (ECNM), the American Academy of Allergy, Asthma & Immunology (AAAAI), and the European Academy of Allergology and Clinical Immunology (EAACI) published a consensus report. They discarded the above classification and adopted a modified one, proposing that CM be divided as follows:²¹

- MPCM (urticaria pigmentosa)
- DCM
- mastocytoma.

The task force recommended that MPCM/UP should be subdivided into two variants. First, a *monomorphic variant*, characterised by small maculopapular lesions that typically arise in adulthood and, secondly, the *polymorphic variant*, which shows large, heterogeneous lesions that can be macular, plaque-type, or nodular and is almost exclusively seen in children.

This proposal has prognostic implications in terms of the duration of the disease in children, because polymorphic lesions tend to regress spontaneously by adolescence, whereas in children the monomorphic variant of MPCM frequently persists into adulthood, usually as a systemic disease.

The other recommendation of the EU/US consensus group was to consider a maximum of three 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.

CLINICAL PRESENTATION OF CUTANEOUS INVOLVEMENT IN PATIENTS WITH MASTOCYTOSIS

The cutaneous manifestation of mastocytosis affects almost all children and approximately 80% of affected adults. The macroscopic and microscopic appearance of the lesions, their morphology and distribution vary between adults and children and also differ from patient to patient.

ADULT-ONSET MASTOCYTOSIS²²

The majority of adult patients develop mastocytosis between 20 to 35 years of age; however, onset can occur at any age.

Adult patients with cutaneous involvement present with characteristic small, round, brown or red monomorphic lesions (see Figures 4, 5, 6, 7). The lesions can range from a few to covering the entire body. The extent of cutaneous involvement correlates with the severity of systemic disease and the tryptase level. The lesions can affect the entire body and usually start on the thigh or in the armpit (axilla) and then spread to the entire body except the face.

The majority of patients with SM have bone-marrow involvement; however, some may have only the cutaneous manifestation without bone-marrow involvement.

A proportion of patients may have telangiectatic or fixed red-macular lesions, particularly on the chest, shoulders, neck and upper back. These patients usually also have maculopapular lesions at other body sites. The task force was of the opinion that the presence of telangiectasias should not form the basis of a separate variant of CM.²⁰ Accordingly, telangiectasia macularis eruptiva perstans, which has been proposed as a separate variant of CM in previous classifications, is no longer diagnosed as a separate entity.

The other cutaneous variants of mastocytosis seen commonly in children are very rare in adults. Mastocytomas almost never occur in adults.

CHILDHOOD-ONSET MASTOCYTOSIS

All children with mastocytosis have skin involvement. The cutaneous manifestation of mastocytosis in children is much more varied than in adults. All the three variants (MPCM, DM and mastocytoma) occur in children²¹ (onset can be from birth but usually starts at six months of age):

- **Polymorphic variant:**²² This variety is seen exclusively in children. It spontaneously regresses by puberty but may persist into adulthood. Most children display a variant with brown or red and often oval lesions of different sizes. The majority of lesions are clearly larger than those found in patients with adulthood-onset mastocytosis. The margins of the lesions can be either sharp or indistinct and can be either elevated or flat. Some of the lesions may be plaques or nodules but not papules or macules (see Figures 8, 9, 10, 11). In the past, this variety was termed 'plaque' or 'nodular'. Children usually show largely homogeneous lesions of a certain type; however, with time the type can vary.
- In some children nodules present during infancy may transform into plaques at the age of around five to ten years and into macules after the age of ten years before the lesions finally regress around puberty in many (but not all) patients. The lesions in children are usually symmetrical and generalised and they can involve the head, neck and extremities. As in other variants of CM in paediatric patients, the polymorphic skin lesions can undergo blistering upon irritation until the patient is two to three years of age. The serum tryptase levels are normal in these patients but may be elevated for 1–2 years in those with severe cutaneous involvement.²³
- **Diffuse mastocytosis (DM):**²² This form is extremely rare. This is the variant had our patient JH has. These patients have diffuse thickening and erythema of the skin. Their skin resembles a *peau d'orange* or pachydermia of the skin (see Figures 1, 2, 3). They have extensive skin involvement. The lesion usually develops at birth or shortly after. They experience generalised blistering of the skin often associated with systemic symptoms, such as flushing, gastrointestinal symptoms and, in most severe cases, hypotension requiring epinephrine, or other life-threatening complications. They have elevated tryptase levels. The lesions usually resolve by adolescence, but may persist into adulthood.
- **Cutaneous mastocytoma (CM):**²¹ These patients have solitary brown to yellowish nodular lesion that frequently involves the trunk or extremities, although any part of the body

can be affected (see Figure 12). In the EU/US task force's consensus report, it was agreed to consider under the term 'mastocytoma' all those cases showing a maximum of three cutaneous lesions, whereas patients with four or more lesions would be categorised as MPCM. In most cases, cutaneous mastocytoma is often already present at birth or it develops within the first months. The lesions always regress by adulthood and the tryptase levels are normal in these patients.

- Some patients with mastocytosis show skin lesions that do not fit perfectly with any of the currently accepted sub-forms and variants. More rarely, patients can present with skin lesions confined to a segment or area of the body. These cases may represent a mosaic manifestation of the disease (i.e. type 1 mosaicism) in which the mutational event would be limited to the part of the body affected.

DIAGNOSIS

MAJOR CRITERIA FOR THE DIAGNOSIS OF CM²⁴

Darier's sign is an important clinical feature of CM.²⁵ It is elicited by stroking a CM lesion around five times with a tongue spatula using moderate pressure. Within a few minutes, a wheal-and-flare reaction of the lesion (not or hardly seen in the surrounding skin) will develop. Therefore Darier's sign differs from dermographism, which also affects non-lesional skin. The EU/US task force points out that a clearly positive Darier's sign is an important diagnostic finding in patients with mastocytosis.²¹ It is not always positive in adult patients but is usually positive in paediatric patients. In this regard, it is noteworthy that antihistamines can decrease the wheal-and-flare reaction. Darier's sign is often not elicited correctly, resulting in either false-negative or false-positive results.

It is recommended not to illicit Darier's sign in very young patients or in those with polymorphic MPCM or DM, since it could provoke massive histamine and tryptase release, resulting in unwanted side-effects such as flushing and hypotension.

MINOR CRITERIA FOR THE DIAGNOSIS OF CM

The two minor criteria are identified via skin-lesion biopsy: increased mast-cell numbers and the presence of an (activating) *KIT* mutation.

In most cases, the cutaneous forms of mastocytosis are recognisable by inspection of the skin. A skin biopsy is therefore not essential, particularly if the clinician is familiar with the appearance of CM. However, a 3 mm punch biopsy of lesional skin can be performed when the diagnosis of CM is in doubt. However, skin biopsy does not provide information about systemic involvement. A bone-marrow examination will be necessary to exclude SM in adults.

CONCLUSION

The classification of the cutaneous manifestations of mastocytosis has undergone many changes in the last decade. As our understanding of this condition improves with time, and with the introduction of international registries for this condition, many more changes in the classification can be expected in the future.

* Figure 1-3 are used with the kind permission of the patient and his parents.

* Figures 4–12 are used with the kind permission of the Mastocytosis Society (<https://tmsforacure.org/>).

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest.

This article has been peer reviewed.

REFERENCES

1. Nobel Foundation. All Nobel Laureates in Physiology or Medicine. Available at http://www.nobelprize.org/nobel_prizes/medicine/laureates/ (accessed 16 December 2012).
2. Dahlin JS, Hallgren J. Mast cell progenitors: Origin, development and migration to tissues. *Mol Immunol* 2015;63:9–17.
3. Weller C, Collington SJ, Williams T, Lamb JR. Mast cells in health and disease. *Clin Sci* 2011;120:473–484.
4. Wilcock A, Bahri R, Bulfone-Paus S, Arkwright PD. Mast cell disorders from infancy to maturity. *Allergy* 2019;74:53–63.
5. Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. *N Engl J Med* 2015;373(19):1885–1886.
6. Renkea J, Kędzierska-Mieszkowska S, Langec M, Nedoszytkoc B, et al. Mast cells in mastocytosis and allergy – important player in metabolic and immunological homeostasis. *Adv Med Sci* 2019;64:124–130.
7. Irani AA, Schechter NM, Craig SS, DeBlois G, Schwartz LB. Two types of human mast cells that have distinct neutral protease compositions. *Proc Natl Acad Sci USA*. 1986;83:4464–4468.
8. Nettleship E, Tay W. Rare forms of urticaria. *Brit Med J* 1869;2:323–330.
9. Sangster A. An anomalous mottled rash, accompanied by pruritus, factitious urticaria and pigmentation, 'urticaria pigmentosa'? *Trans Clin Soc London* 1878;11:161–163.
10. Unna P. Beiträge zur Anatomie und Pathogenese der urticaria simplex und pigmentosa. *Monatschrift der praktischen Dermatologie* 1887;6:9–18.
11. Chan EC, Bai Y, Kirshenbaum AS, Fischer ER, et al. Mastocytosis associated with a rare germline KIT K509I mutation displays a well-differentiated mast cell phenotype. *J Allergy Clin Immunol* 2014;134(1):178–187.
12. Finnerud CW. Urticaria pigmentosa (nodular type) with a summary of the literature: report of a case. *Arch Dermatol Syphilol* 1923;8(3):344–358.
13. Caplan RM. Urticaria Pigmentosa and systemic mastocytosis. *JAMA* 1965;194,10:1077–1080.
14. Lennert P, Pawarwesch MR. Mast cells and mast cell neoplasia. *Histopathology* 1979;3(5):349–365.
15. Metcalfe DD. Classification and diagnosis of mastocytosis: Current status. *J Invest Dermatol* 1991;96(3):2S–4S.
16. Valent P, Horny HP, Escribano L, Longley BJ, et al. Diagnostic criteria and classification of mastocytosis: A consensus proposal. *Leuk Res* 2001;25(7):603–625.
17. Valent P, Horny HP, Li CY, et al. Mastocytosis. In: Jaffe ES, Harris NL, Stein H, et al, editors. World Health Organisation (WHO) classification of tumours pathology and genetics tumours of haematopoietic and lymphoid tissues. Lyon (France): IARC Press; 2001:291–302.
18. Valent P, Horny HP, Escribano L, Longley BJ, et al. Diagnostic criteria and classification of mastocytosis: A consensus proposal. *Leuk Res* 2001;25:603–625.
19. Arber DA, Orazi A, Hasserjian R, Thiele J, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016;127(20):2391–2405.
20. Akin C, Valent P. Diagnostic criteria and classification of mastocytosis in 2014. *Immunol Allergy Clin North Am* 2014;34:207–218.
21. Hartmann K, Escribano L, Grattan C, Brockow K, et al. Cutaneous manifestations in patients with mastocytosis: Consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology. *J Allergy Clin Immunol* 2016;137(1):35–45.
22. Matito A, Azaña JM, Torrelo A, Alvarez-Twose I. Cutaneous Mastocytosis in adults and children. New classification and prognostic factors. *Immunol Allergy Clin N Am* 2018;38:351–363.
23. Alvarez-Twose I, Vano-Galvan S, Sanchez-Munoz L, Morgado JM, et al. Increased serum baseline tryptase levels and extensive skin involvement are predictors for the severity of mast cell activation episodes in children with mastocytosis. *Allergy* 2012;67:813–821.
24. Valent P, Akin C, Escribano L, Fodinger M, et al. Standards and standardization in mastocytosis: Consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 2007;37(6):435–453.
25. Galen BT, Rose MG. Darier's sign in mastocytosis. *Blood* 2014;123:1127.