Australasian Journal of Dermatology

Australasian Journal of Dermatology (2020) ••, ••–•• doi: 10.1111/ajd.13443

REVIEW ARTICLE

Cutaneous mastocytosis: A dermatological perspective

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ABSTRACT

Mastocytosis is a rare disease characterised by expansion and collection of clonal mast cells in various organs including the skin, bone marrow, spleen, lymph nodes and gastrointestinal tract. The prevalence of mastocytosis has been estimated to be one in 10 000, while the estimated incidence is one per 100 000 people per year. Cutaneous mastocytosis is classified into (i) maculopapular cutaneous mastocytosis, also known as urticaria pigmentosa; (ii) diffuse cutaneous mastocytosis; and (iii) mastocytoma of the skin. In adults, cutaneous lesions are usually associated with indolent systemic mastocytosis and have a chronic evolution. Paediatric patients, on the contrary, have often cutaneous manifestations without systemic involvement and usually experience a spontaneous regression. Diagnosis of cutaneous mastocytosis may be challenging due to the rarity of the disease and the overlap of cutaneous manifestations. This short review describes pathogenesis and clinical aspects of cutaneous mastocytosis with a focus on diagnosis and currently available therapies.

Key words: cutaneous mastocytosis, mastocytosis, cutaneous malignancies, urticaria pigmentosa.

INTRODUCTION

Mastocytosis is a rare disease characterised by expansion and collection of clonal mast cells in various organs including the skin, bone marrow, spleen, lymph nodes and gastrointestinal tract.

The prevalence of mastocytosis has been estimated to be one in 10 000, while the estimated incidence is one per 100 000 people per year.[1] Mastocytosis occurs more frequently in children (65%). Among adult patients, the onset is most commonly observed between 20 and 40 years of age.[2]

According to the WHO, mastocytosis can be classified into non-advanced or advanced systemic disease.[3] Non-advanced mastocytosis includes patients with cutaneous mastocytosis, indolent systemic mastocytosis and smouldering systemic mastocytosis. In contrast, advanced systemic mastocytosis includes patients with aggressive systemic mastocytosis, systemic mastocytosis with an associated haematological malignancy and mast cell leukaemia. While patients with non-advanced mastocytosis have an excellent prognosis, those with advanced disease have a much worse outcome.[4]

In cutaneous mastocytosis (CM), the skin is the only tissue affected. It is the most common form seen in childhood and usually has an auto-resolving course with only a few cases persisting into adulthood.[5]

According to the World Health Organization, CM is divided into (i) maculopapular cutaneous mastocytosis, also known as urticaria pigmentosa; (ii) diffuse cutaneous mastocytosis; and (iii) mastocytoma of the skin.[6] A European Union–US consensus group have defined the inclusion criteria for cutaneous involvement in patients with mastocytosis.[7]

PATHOGENESIS AND GENETIC

Mast cells normally constitute <0.1% of marrow cellularity and are identified by coexpression of CD117 and FcεRI. They derive from CD34+ pluripotent progenitor cells that from the bone marrow migrate to peripheral tissues where they reach full maturation.[8]

Mature mast cells usually are found within vascular tissues and have heterogeneous morphology, biochemical

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Financial support: None.

Conflict of interest: none.

Submitted 25 April 2020; revised 14 July 2020; accepted 20 July 2020.

and functional characteristics. These differences depend on the anatomic location, causing specific clinical signs and symptoms when having an aberrant proliferation.

Researchers identified stem cell factor that acts through the activation of the receptor KIT, as the leading factor to mast cell proliferation. The constitutive activation of KIT in mastocytosis is also associated with aberrant expression of CD25 and CD2.[8]

CD30 expression, a member of the tumour necrosis factor family, has been demonstrated in 11 of 27 (41%) patients with CM but it did not correlate with an aggressive disease.[9]

Conventionally, tissue mast cells are classified as either mucosal or connective tissue mast cells. Connective tissue mast cells are usually localised adjacent to the epithelial surface of the skin and contain tryptase and a chymotryptase. Furthermore, human mast cell granules contain biologically active molecules, including tumour necrosis factor-α, histamine, acid hydrolases, cathepsin G and carboxypeptidase.[10] After being activated, mast cells release granule-associated mediators and produce lipid-derived substances that induce immediate allergic responses such as pruritus, flushing, palpitations and abdominal cramping.[11]

Many different drugs, toxins and physical stimuli can be responsible foe mast cell activation.

Many authors have demonstrated that patients with mastocytosis have an increased plasma activities of phospholipase A2 and phospholipase C, as well as elevated diacylglycerols and palmitoylethanolamide concentrations, and decreased levels of anandamide. All these factors have the capacity to influence the mast cell biological activity by either directly activating mast cells or promoting the production/degradation of other molecules.[12] Phospholipase C together with phospholipase D is a crucial element for mast cell activation and degranulation.

Hydrolysis of phosphatidylinositol 4,5-bisphosphate by phospholipase C, and of phosphatidylcholine by phospholipase D, produces diacylglycerols, which activate effector enzymes (such as protein kinase C) and regulate multiple cellular processes of several cells including mast cells (Fig. 1).[13]

Moreover, plasma levels of phospholipases, diacylglycerols and some N-acylethanolamines are altered in patients with mastocytosis and phospholipase C activity is further increased in patients with symptomatic and aggressive forms of disease.[14]

Genetic alterations seem to play an important role in the development and progression of the disease. Almost 80% of the cases have a somatic gain-of-function D816V mutation of KIT receptor; it has been demonstrated that cells carrying mutated KIT have an increased chemotactic response towards stem cell factor.[15] Bodemer and colleagues analysed the coding sequence of KIT from cutaneous lesions of 50 children and reported that 86% of the patients had mutations in KIT.[16] In contrast, Fradet demonstrated that only 28% of adult patients with CM had mutations in KIT.[17] An E839K mutation has been described in the skin lesions of children with mastocytosis.[18]

Additional somatic genetic alterations may also drive some disease features. For example, the Fip1-like-1–platelet-derived growth factor receptor-α (FIP1L1-PDGFRA), fusion oncogene that results from a deletion of chromosome 4q12, has been described in a subset of patients with associated eosinophilia.[19]

Among germline mutations, a polymorphism in the gene for the IL-4 receptor α-chain has been shown to be

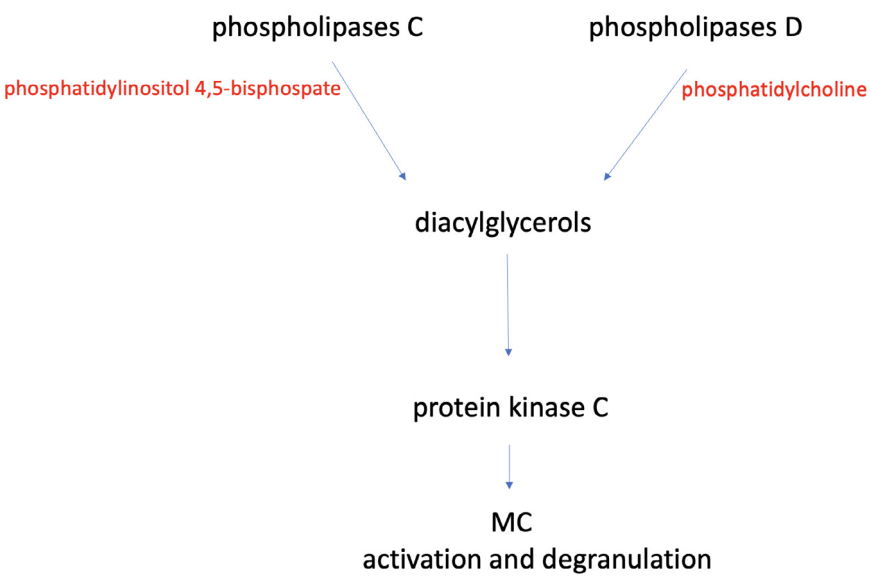

Figure 1 Phospholipases C and Phospholipases D pathway and activity. Hydrolysis of phosphatidylinositol 4,5-bisphosphate by Phospholipases C, and of phosphatidylcholine by Phospholipases D, produces diacylglycerols, which activate effector enzymes [such as protein kinase C (PKC)] and regulate multiple cellular processes of several cells including mast cells (MC).

associated with less extensive mast cell involvement in mastocytosis limited to the skin.[20]

In addition, patients with advanced systemic mastocytosis may also have mutated genes, including TET2, SRSF2, ASXL1, RUNX1 and JAK2.[21] In conclusion, the different mutation burden between non-advanced and advanced mastocytosis appears to be the key which may explain the differences in presentation and clinical course (Figs 2 and 3).

CLINICAL FEATURES AND HISTOPATHOLOGY

Cutaneous manifestations of mastocytosis are various and differ according to the age of onset.

In adults, cutaneous lesions are usually associated with indolent systemic mastocytosis and have a chronic evolution.[22] Paediatric patients, on the contrary, often just have cutaneous manifestations without systemic involvement and usually experience a spontaneous regression.[23]

Maculopapular cutaneous mastocytosis/Urticaria pigmentosa is the most common variant of CM; it usually presents as 0.5–1 cm yellowish to red-brown macules or papules. Trunk and extremities are the most affected areas, whereas face, scalp, palms and soles are usually spared. These lesions often show positivity for the Darier sign, pathognomonic of mastocytosis.[24] Two different variants of maculopapular CM have been described: monomorphic and polymorphic. The monomorphic variant appears as small maculopapular lesions where all lesions are similar in shape, colour and size, affecting mostly adult patients, whereas polymorphic variant presents with lesions of different size and shape seen in predominantly children.[7] In children, the monomorphic variant tends to persist until adulthood, whereas the polymorphic form usually

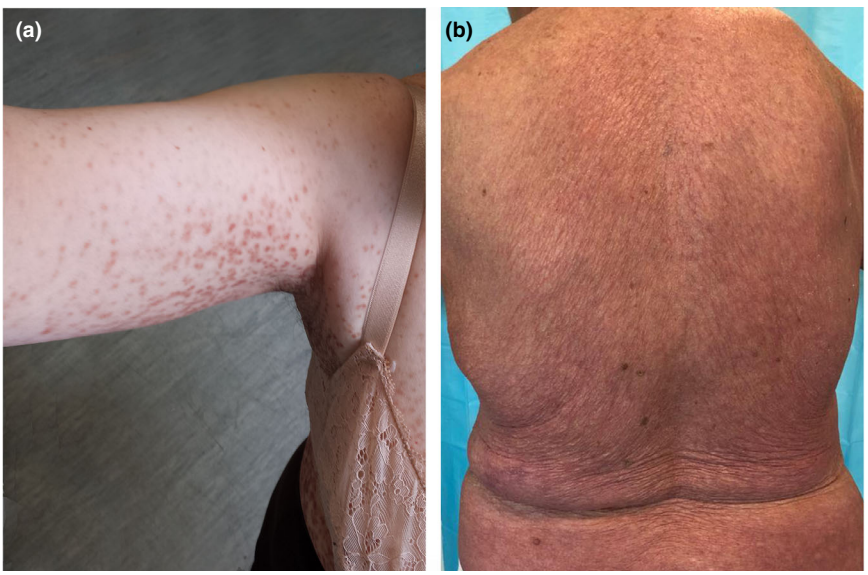

Figure 2 Clinical features. (a) Patient with maculopapular cutaneous mastocytosis/urticaria pigmentosa presenting with red-brown macules and papules on trunk and extremities. (b) Patient with diffuse erythrodermic mastocytosis presenting with generalised erythema and thickened skin.

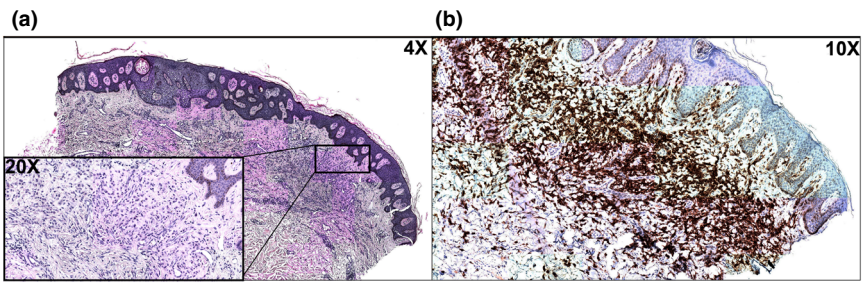

Figure 3 Histopathologic features. (a) Hyperplastic epidermis with hyperpigmented basal layer associated with diffuse infiltration of loosely arranged mast cells in the superficial dermis, at times also in proximity to the dermoepidermal junction. Some scattered dilated vascular channels are also observed (HE, x4). High-power magnification reveals the cuboidal or spindle shape of the neoplastic mast cells, which are characterised by abundant granular cytoplasm and little, whether present, cytological atypia (HE, x20). (b) Strong and diffuse cytoplasmic stain for CD117 in neoplastic mast cells (CD117, x10).

regresses around puberty.[11] Rare forms of maculopapular CM include a *bullous variant* (often in the first weeks of life), a *plaque form*, a *nodular form, diffuse erythrodermic mastocytosis* and *telangiectasia macularis eruptiva perstans* (TEMP) with multiple hyperpigmented maculae often associated with erythema and telangiectasias.[25] However, this has recently been challenged, as the presence of telangiectasias should not form the basis of a separate variant of CM, and should no longer be diagnosed.[7] Histopathologically, maculopapular CM is represented by an assemblage of neoplastic mast cells within the papillary dermis mainly located around blood vessels and skin appendages, sometimes with extension to the reticular dermis and into the subcutaneous fat. The increase in lesional skin of dermal mast cells, detected with anti-tryptase antibody, is four to eight times that of normal skin, even though the number of dermal mast cells varies from patient to patient, and there is even an overlap between mastocytosis and healthy skin.[26]

In cutaneous mastocytosis, in contrast with bone marrow in systemic mastocytosis, there is no specific or aberrantly expressed marker of clonality. In particular, staining of cutaneous mast cells for CD25 or CD2 often produces a negative result.[27] Mast cells in lesional skin can be spindle-shaped in the monomorphic maculopapular variant, whereas they tend to be spherical (round) in polymorphic lesions.[7] Some authors suggest that the paediatric polymorphic variant of maculopapular CM shows a higher number of mast cells compared to the monomorphic variant.[7]

Diffuse cutaneous mastocytosis is a rare variant of cutaneous mastocytosis, presenting in about 1–5% of all cases. Onset of diffuse CM is usually at birth or during early infancy.[24]

Diffuse CM is often characterised in children by generalised erythema, usually with thickened skin (pachydermia), sometimes papules and a marked dermographism.[28] In adults, it appears usually as extensive bullae (sometimes haemorrhagic), mainly localised on the trunk, scalp and extremities with a conspicuous dermographism, which can progress to erosions and desquamation of the skin and result in hyperpigmentation.[28]

In these patients, it is important to avoid inducing the Darier sign, to minimise the potential massive release of mediators from the high number of mast cells infiltrating the skin.

Most paediatric patients with CM have a normal serum tryptase. Elevated serum tryptase levels (frequently higher than 100 mg/L) are usually found at early stages of the disease, as a reflection of both the high mast cell burden in the skin and an increased mast cell-mediator release, but generally regress with gradual improvement of mast cell-mediator release symptoms.[7]

However, in diffuse CM tryptase levels may be elevated with or without systemic involvement.

Histopathologically, diffuse CM is characterised by a diffuse mast cell infiltration of the dermis and a particularly increased number of mast cells that usually involve entirely the skin layers.[28]

Cutaneous mastocytoma is common in children while it is rarely seen in adult patients. It presents at birth or more commonly within the first 3 months of life, with spontaneous resolution during childhood.[29]

Usually, mastocytoma is a single elevated brown or yellow macule, plaque or nodule on the extremities but may involve the palms or soles. Sometimes patients can develop more than 1 lesion. When only 1 lesion is observed, the disease is classified as solitary mastocytoma, while with 4 or more lesions, the patient should be classified as having maculopapular CM.[7]

Histopathology mast cells infiltrate the papillary and reticular dermis and extend to the subcutis. The mast cells present a marked nuclear pleomorphism with bilobed or multilobed (up to 5) nuclei. A small number of eosinophils with flame figures may be present throughout the dermis.[30]

Systemic symptoms, due to the release of histamine and other mediators, may include pruritus, blistering, flushing, dyspnoea and hypotension. Blistering is seen mostly in paediatric patients, in particular in children <2 years with a wide cutaneous involvement. Extended blistering has been linked to a massive release of mast cell factors and could be considered as a predictor of complications in children with mast cell.[31] Another common symptom among patients with mast cell is flushing. Although flushing is considered a skin limited symptom, it could represent a life-threatening complication. Since flushing is related to an increased blood flow in the skin, caused by vasoactive mast cell's mediators, it can lead to a hypotensive collapse.[31]

Excess flushing can also also be seen in carcinoid syndrome. Clinical features of both these conditions can overlap, and both seem to respond to somatostatin analogue treatment. Nevertheless, negative imaging, bone marrow biopsy and high levels of serum tryptase can simplify the differential diagnosis.[32]

Although systemic symptoms are more frequently seen in adult patients as a consequence of the presumably systemic progression of the disease, in children there is a higher risk of anaphylaxis due to the massive release of mast cells mediators.[22]

The incidence and severity of anaphylaxis are 4 to 6 times higher in patients with mastocytosis compared with that in the general population. Triggers of anaphylaxis in include *Hymenoptera* venom, drugs and food. Idiopathic anaphylaxis can also occur.[33]

In children with mastocytosis, vaccination can potentially induce anaphylaxis and exacerbate mediator-derived symptoms, such as generalised flushing, pruritus, urticaria/angioedema, bullous lesions or gastrointestinal symptoms.[33]

It has been demonstrated that the level of serum tryptase correlates with the risk of anaphylaxis and extension of skin involvement in children with CM, while in adults the extent of cutaneous lesions seems to correlate with flushing and pruritus but not with the risk of anaphylaxis.[34]

For this reason, the SCORMA index has been created to evaluate the severity of cutaneous mastocytosis. This score evaluates: the extension of cutaneous involvement, the

intensity of lesions (pigmentation, vesiculation, elevation, Darier sign) and the subjective symptoms (flushing, diarrhoea, pruritus).[35]

DIAGNOSIS

The diagnosis of cutaneous mastocytosis may be challenging due to the rarity of the disease and the overlap of cutaneous manifestations that sometimes make difficult defining and identifying them, causing delay in the correct diagnosis. Criteria of cutaneous involvement in patients with mastocytosis are summarised in Table 1.[7] The first step in determining the diagnosis is represented by the identification of the characteristic clinical findings, history and physical examination. Darier sign is nearly always positive in paediatric patients and in most adult patients.[7] A skin biopsy is critical for confirmation of the disease and to exclude an increase in mast cells related to other disorders.

Neoplastic infiltrates of dermal mast cells can be identified by immunohistochemistry using specific stains (e.g. tryptase or c-kit CD117) as spindle-shaped or spherical/cuboidal cells. Moreover, recent studies have suggested that the aberrant expression of CD25 on skin mast cells in patients with CM might indicate a higher risk of having a systemic mast cell disease.[27]

A full blood count with peripheral smear is mandatory to rule out a systemic involvement or other associated haematological diseases. In those cases that are highly suspicious for a systemic involvement, bone marrow biopsy should be performed. Furthermore, dosing plasma histamine levels is a key factor in determining systemic involvement. Histamine metabolites 1-methyl-4-imidazole acetic acid, N-methylhistamine, prostaglandin D2, the thromboxane metabolite 11-dihydroxy-thromboxane B2 and α-protryptase seem to be elevated in the majority of mastocytosis patients. The α-protryptase is also used for the follow-up of patients with systemic mastocytosis.[36]

High levels of alkaline phosphatase in patients with indolent mastocytosis can predict systemic involvement due to mast cell mediated organ involvement of bones and liver.[37]

The goal for the diagnosis is to identify true cutaneous mastocytosis excluding any systemic involvement, thus avoiding over treatment

It has been estimated that 95% of patients with indolent systemic mastocytosis have maculopapular skin lesions compared to 50% of patients with advanced systemic mastocytosis. Skin lesions appear in less than 50% of patients with mast cell leukaemia.[38]

Table 1 Criteria for cutaneous mastocytosis

Major criteria
• Typical skin lesions of mastocytosis
• Darier sign
Minor criteria
• Increased numbers of mast cells in biopsy sections of lesional skin (at least 4-fold)
• (Activating) KIT mutation in lesional skin tissue

PROGNOSIS

It is important to emphasise that cutaneous mastocytosis is a complete different disease than advanced systemic mastocytosis in terms of biology and prognosis.

In patients with CM, the risk of disease progression to systemic mastocytosis is not high and the main focus of the treatment is improvement in quality of life. Nevertheless, it is important to identify those cases that have a higher risk of progression.[39]

Recently, an international prognostic scoring system has been developed based on independent prognostic variables. For patients with non-advanced mastocytosis, the variables are age and alkaline phosphatase while for advanced systemic mastocytosis they are tryptase, blood counts and absence of skin involvement. Levels of alkaline phosphatase 100 U/L or higher and age of 60 years of older were the two major independent predictors of survival in patients with non-advanced mastocytosis. In particular, a rise in phosphatase alkaline level could indicate a disease progression, since it reflects mast cell organ involvement and damage.[40]

Sperr and colleagues demonstrated that adult and paediatric patients with CM had an improved overall survival compared to patients with indolent systemic mastocytosis.[37] Furthermore, patients with indolent systemic mastocytosis had a higher risk of progression to advanced mastocytosis compared to patients with cutaneous mastocytosis. Lastly, patients with advanced systemic mastocytosis sometimes did not show any cutaneous involvement; in particular, skin lesions are usually absent in patients with advanced systemic mastocytosis and mast cell leukaemia.[3]

TREATMENT

Identifying the appropriate therapeutic strategies for treatment of CM has always been challenging due to the rarity of these conditions and the lack of prospective controlled or multicenter studies. The main goal of treatment in CM is to control skin lesions and systemic symptoms related to the massive release of mast cells mediators.

First-line treatments suggested are antihistamines (both H1 and H2) and corticosteroids. In particular, the H1 class show a remarkable improvement in urticaria pigmentosa and diffuse CM as well as in controlling symptoms of pruritus and flushing. Patients with high risk of anaphylactoid reactions should take H1 and H2 antihistamines as prophylaxis on a regular basis. H2 antihistamines are more efficient in controlling gastrointestinal symptoms such as abdominal pain, cramping and diarrhoea.[41] Recently, the safety and efficacy of the H1 antagonist rupatadine has been demonstrated in controlling mediator-related symptoms.[42] In children with mastocytomas, good results have been acheived with surgery and intralesional corticosteroids, with significant regression of cutaneous lesions.[26]

Pimecrolimus, a topical inhibitor of calcineurin, has also shown some efficacy in localised CM.[43]

Solitary mast cells lesions can also be treated with pulsed dye laser therapy, resulting in cosmetic improvement and reduction in the urticarial reaction.[44]

In extensive urticaria pigmentosa and diffuse CM, both oral psoralen with ultraviolet light (PUVA) and natural sunlight have been shown to be effective.[45] Second-line treatment options for more aggressive forms of CM are imatinib, a tyrosine kinase inhibitor and omalizumab, a humanised IgG1 monoclonal antibody against IgE.[46,47,48]

Imatinib has been shown to reduce pruritus and bullous lesions in both urticaria pigmentosa and diffuse CM.[49]

Masatinib, a new highly selective tyrosine kinase inhibitor, has shown promising results in a phase 2 study in both systemic mastocytosis and CM patients, regardless of their *KIT* mutation status.[50]

A promising treatment option in CM seems to be the raft modulator miltefosine.[51]

Tyrosine kinase inhibitors such as midostaurin (PKC412), dasatinib and nilotinib have shown promising results in the treatment of systemic mastocytosis.[52]

Another important aspect in the management of patients with mastocytosis is the avoidance or control of factors that could trigger type I hypersensitivity reactions, namely alcohol and nonsteroidal anti-inflammatory agents in sensitive patients.[53]

Further studies are needed to provide a consensus and generate appropriate guidelines in the treatment of patients with cutaneous mastocytotis that could help physicians managing patients in daily clinical practice.

THE ROLE OF THE DERMATOLOGIST

The clinical course of mastocytosis is extremely variable and can be influenced by the age of onset, type of cutaneous manifestation, possible various organs involvement and comorbidities. In this perspective, the role of the dermatologist, as first physician to approach the disease, is crucial. Little is known about aspects of the disease such as epidemiology, prognostic factors and compliance to therapies. For this purpose, the European Competence Network on Mastocytosis (ECNM) has been established,[54] as well as American Initiative for Mast Cell Disorders. Together, they have developed and defined diagnostic criteria and approaches for the diagnosis, classification and management of mastocytosis that were adopted by the World Health Organization (WHO).[3] An Italian registry has also been created.[55]

It is hoped that an increasing awareness of this disease together with greater knowledge on a biological level and the development and use of new effective drugs, especially in systemic forms, will lead to the development of a greater number of cooperative groups that can better define, in a real-life scenario, the true incidence and prevalence of mastocytosis together with an increasingly better defined diagnostic and prognostic framework.

CONCLUSIONS

Cutaneous mastocytosis is a rare disease characterised by expansion and collection of clonal mast cells in the skin.

Diagnosis may be challenging due to the rarity of the disease and the overlap of cutaneous manifestations, and for this reason, the role of the dermatologist is crucial as the first physician to approach the disease as well as part of a multidisciplinary team involving different specialists.

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