Mastocytoses

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1 Classification of Mastocytosis

Mastocytosis comprises a group of diseases characterized by an increase in the number of mast cells in one or more organs. It is divided into cutaneous and systemic forms (Table 1). Cutaneous mastocytosis often occurs in early childhood and is usually characterized by benign progression and spontaneous remission. In contrast, systemic mastocytosis occurs more frequently in adulthood and shows a persistent course.

2 Basics

Mast cells are crucial in triggering IgE-mediated allergic reactions and natural immune responses. They express the high-affinity IgE receptor FcεRI and KIT, the receptor for stem cell factor (SCF). Mast cells produce a large number of mediators, such as histamine, proteoglycans, proteases and cytokines, which are stored in cytoplasmic granules and released by degranulation. These cytoplasmic granules exhibit metachromasia after staining with toluidine blue or Giemsa. This was described in 1877 by Paul Ehrlich, who also introduced the term "mast cells" (Ehrlich 1877).

Mast cells are particularly frequent at interfaces of the body, i.e., in the skin, the respiratory tract, and the gastrointestinal tract. In the skin, mast cells are predominantly located in the papillary dermis and near blood and lymph vessels, sensory nerves, and adnexal structures. The colocalization of mast cells and vessels is functionally important: after activation, mast cells lead to vasodilation, extravasation, and subsequently to the recruitment of proinflammatory cells. The proximity to sensory nerves also has functional relevance: mast cells can be activated by neuropeptides such as substance P or vasoactive intestinal peptide (VIP) and in turn lead to the activation of skin nerves and the release of neuropeptides through the release of mediators such as histamine and tryptase.

Mast cells are derived from CD34-positive progenitor cells. The mast cell precursor cells pass through the blood vessels into the mucous membranes and connective tissue of their terminal organs, including the skin (Dahlin and Hallgren 2015). Under the influence of local growth factors, in particular SCF, they differentiate into mature mast cells. SCF is the most important growth and differentiation factor for mast cells, and these effects of SCF require the activation of the tyrosine kinase receptor KIT (Gurish and Boyce 2006). Mutations that lead to a defect of SCF or KIT result in mast cell deficiency, whereas mutations that lead to an activation of KIT, as found in mastocytosis patients, lead to increased proliferation and accumulation of mast cells (Theoharides et al. 2015).

Mast cells produce and secrete a large array of different mediators, which are divided into two groups:

- Preformed mediators
- De novo produced mediators

The most important **preformed mediators** include biogenic amines (mainly histamine), various proteases (tryptase, chymase, carboxypeptidase, and others), proteoglycans (especially heparin) and various cytokines including tumor necrosis factor. These mediators are stored in cytoplasmic granules and their release occurs after mast cell activation by signals leading to their degranulation. The **de novo produced mast cell mediators** include arachidonic acid-dependent products such as leukotriene C4 and prostaglandin E2 as well as various cytokines, chemokines, and growth factors. The spectrum, kinetics, and extent of the released mediators dependent on the mast cell-activating signal. Mast cells can be activated by many different signals. The best-known mechanism of mast cell activation is the cross-linking of

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FcεRI-bound IgE by an allergen. This leads to the degranulation of mast cells and the release of de novo synthesized mediators. IgE/FcεRI-mediated activation of mast cells is crucial for triggering allergic reactions. In addition, mast cells also play an important role in numerous other biological processes: dermal mast cells can induce and coordinate natural immune responses against various pathogens and contribute to homeostasis and wound healing of the skin. IgE- and FcεRI-independent activation mechanisms play an important role in these processes (Metz and Maurer 2007).

Signals that lead to a non-allergic activation of mast cells are often referred to as histamine liberators or mast cell secretagogues. These include physical factors (heat, cold, pressure, friction, vibration, ultraviolet [UV] radiation) and a wide range of endogenous and environmental factors, such as toxins (snake and insect toxins, bacterial toxins), neuropeptides (substance P, endothelin-1), hormones (estrogen, gastrin), complement factors (C3a and C5a), and alcohol. Many drugs can also lead to mast cell activation, for example, codeine, morphine, acetylsalicylic acid, and other nonsteroidal anti-inflammatory drugs, contrast agents, and anesthetics.

3 Cutaneous Mastocytosis

Etiopathogenesis

Cutaneous mastocytosis is characterized by an accumulation of mast cells in the skin. In all forms of cutaneous mastocytosis, by definition, the skin is the only organ in which an increased number of mast cells is found. The pathogenesis of cutaneous mastocytosis is still largely unclear. Activating KIT mutations, which play a decisive role in systemic mastocytosis, are also found in skin mastocytosis. Although adults carry the typical KIT mutation (D816V) in exon 17, about half of children have mutations in other regions, primarily in exons 8, 9, and 11. Even though cutaneous mastocytosis is divided into different subtypes, there are smooth transitions between a single lesion (mastocytoma), hundreds of maculopapular lesions, and diffuse skin infiltration with mast cells (Table 1). In the majority of cases, cutaneous mastocytosis is a childhood disease (Hartmann and Metcalfe 2000; Siebenhaar et al. 2012).

Some forms, such as nodular cutaneous mastocytosis and bullous cutaneous mastocytosis, occur almost exclusively in children, whereas a telangiectatic variant (formerly known as telangiectasia macularis eruptiva perstans [TMEP], see below) occurs only in adults.

Diagnostic Procedures

In patients with a typical skin appearance, the suspicion of cutaneous mastocytosis should be confirmed by triggering of **Darier's sign** (urticarial transformation of a lesion after mechanical stimulation with a spatula) (Darier 1905) and a skin biopsy. All patients with cutaneous mastocytosis should be examined for an increase in serum tryptase, as this correlates with the total number of mast cells (Schwartz 2006). Serum tryptase values in cutaneous mastocytosis are within the normal range (<15 μg/l) or only slightly increased. It is estimated that about 80% of adult patients with mastocytosis in the skin are affected by systemic mastocytosis. Annual monitoring and exclusion of secondary osteoporosis in these patients is recommended. In symptomatic patients with elevated serum tryptase or detection of the D816V mutation in the peripheral blood, the suspicion of systemic mastocytosis should be clarified by examination of the bone marrow and peripheral blood counts.

Therapy

All patients are informed about possible trigger factors for the activation of mast cells. These include physical exercise, stress, general anesthesia, physical factors such as heat and

Table 1 Classification of mastocytosis (Hartmann et al. 2016)

Mastocytosis	Age groups	Frequency[a]	Prognosis	Clinical course
CM				
Maculopapular CM	Children (frequent)	+++	Good	Mostly remission
	Adults (rare)[b]	+	Good	Chronic and stable
Diffuse CM	Children	+	Good	Chronic and stable
Cutaneous mastocytoma	Mostly children	++++	Good	Mostly remission
SM				
ISM	Mostly adults	+++	Good	Chronic and stable
Smoldering SM	Mostly adults	++	Variable	Chronic or progressive
SM-AHN	Mostly adults	++	Variable	Progressive
ASM	Mostly adults	+	Variable	Progressive
MCL	Mostly adults	+[c]	Infaust	Progressive
MCS[c]				

CM cutaneous mastocytosis, *SM* systemic mastocytosis, *ISM* indolent systemic mastocytosis, *SM-AHN* systemic mastocytosis with associated hematological neoplasia, *ASM* aggressive systemic mastocytosis, *MCL* mast cell leukemia, *MCS* mast cell sarcoma

[a]The index shows the frequency of the subform within the group

[b]Typical maculopapular lesions in adults are often associated with systemic mastocytosis

[c]Mast cell leukemia and mast cell sarcoma are rarities compared with other forms of mastocytosis

cold, UV radiation, and insect bites and stings. Relevant trigger factors must be avoided (Brockow 2014). Mastocytosis patients should receive a mastocytosis passport and, if there is a risk of anaphylactic reactions, an emergency kit. Treatment with beta blockers should be avoided. Mastocytosis patients in whom anaphylactic reactions have occurred as a result of insect bites should receive specific immunotherapy (chapter "▶ Bee and Wasp Venom Allergy").

In patients with cutaneous mastocytosis, the therapy depends on the existing symptoms. In asymptomatic patients no therapy is necessary and patients should be informed that there are currently no curative therapeutic options. In patients with symptoms, second-generation H1 antihistamines are used to control itching and urticarial reactions. In the case of gastrointestinal symptoms, H2 blockers, cromoglycate, and proton pump inhibitors may also be used. Therapy-resistant patients with severe skin symptoms may be recommended to undergo UV therapy (psoralen ultraviolet light A therapy) and/or short-term topical treatment with glucocorticoids, either by occlusion or intralesional injection (mastocytoma). This treatment leads not only to a reduction of symptoms by stabilizing mast cells but also to a temporary reduction in the number of mast cells (Siebenhaar et al. 2014).

Solitary mastocytomas often do not require therapy and may respond well to local glucocorticoid treatment or may be excised if persistent.

Course and Prognosis

Skin mastocytosis usually develops in early childhood and rarely occurs without systemic involvement in adults. The prognosis is good and childhood-onset cutaneous mastocytosis often shows spontaneous remission.

3.1 Maculopapular Cutaneous Mastocytosis

(Nettleship 1869; Sangster 1878)

Synonym

Urticaria pigmentosa (historical)

Epidemiology

Childhood-onset mastocytosis usually begins within the first 6 months of life; adult-onset mastocytosis may start at any time after adolescence.

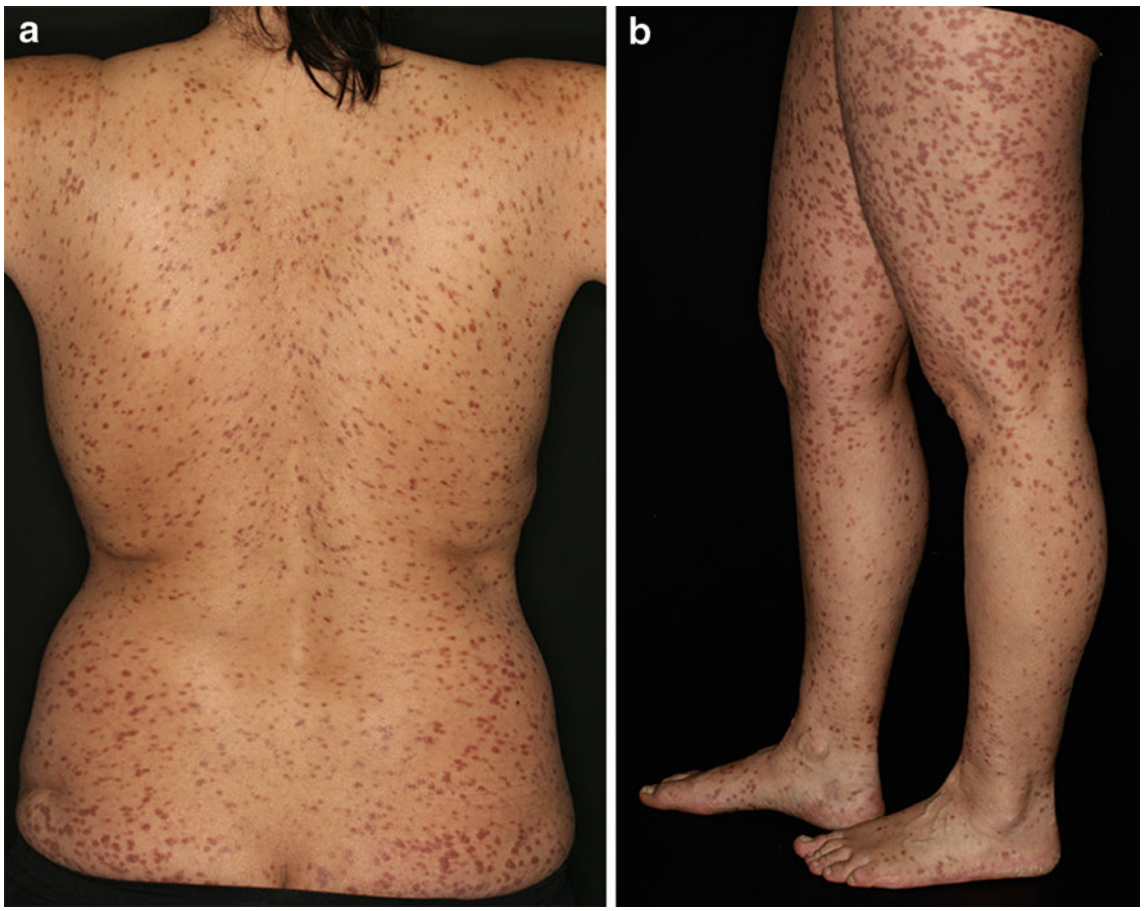

Fig. 1 (**a**, **b**) Maculopapular cutaneous mastocytosis in adulthood

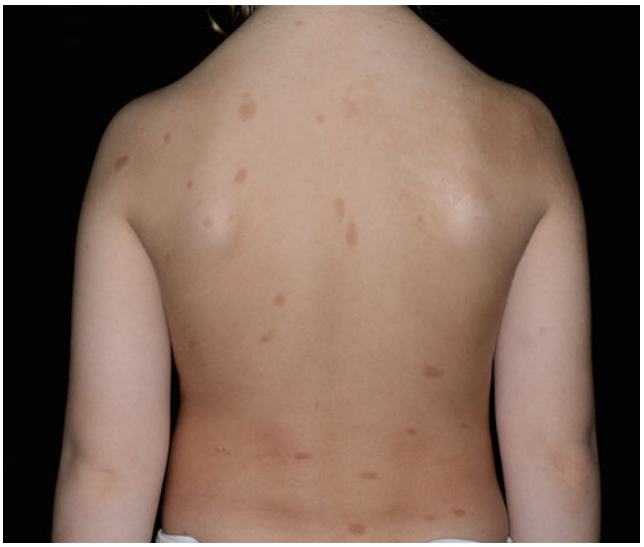

Fig. 2 Childhood maculopapular cutaneous mastocytosis

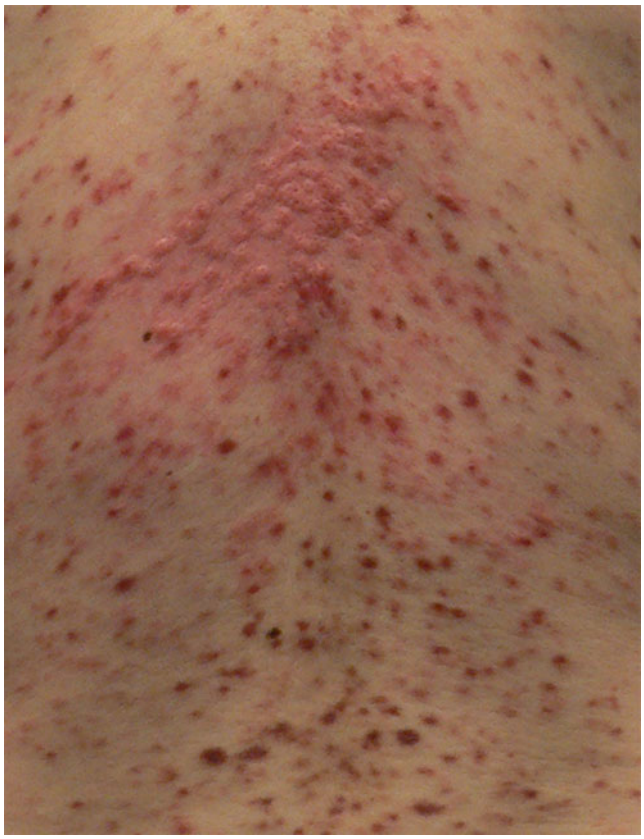

Fig. 3 Darier's sign

Clinical Features

In adult-onset mastocytosis there are numerous, up to hundreds of characteristic, reddish-brown, monomorphic maculopapular lesions (Fig. 1). Children usually have larger lesions than adults (Fig. 2) and affected skin areas can have blisters, especially in early childhood. The size and shape of skin lesions in children vary and have a more polymorphic character (macular, plaque-like, nodular, xanthelasmoid). After irritation, a urticarial reaction (wheals, flare, itch) occurs. The induction of such urticarial changes is called **Darier's sign** (Fig. 3). Predilection sites of cutaneous mastocytosis in adulthood are the proximal extremities with transition to the trunk, whereas the palms of the hands, soles of the feet, and the face are usually omitted. The clinical picture ranges from a few isolated lesions to large-scale confluent skin lesions that can affect more than 50% of the integument, which can be associated with advanced forms of systemic mastocytosis (Fig. 4).

In some adults, there are telangiectatic forms of the cutaneous lesions that are preferentially located on the upper trunk. This variant, formerly known as TMEP (Fig. 5) (Weber and Rast 1935) is described in older classifications as a subtype of cutaneous mastocytosis. However, because other typical maculopapular skin lesions are frequently found in other areas in some patients in addition to telangiectatic lesions, the term TMEP as an independent subtype of cutaneous mastocytosis has been omitted from the updated classification.

Children show a more truncal distribution and the lesions can include the face as well as palms and soles. The most common symptoms of cutaneous mastocytosis are flush reactions and itching, both of which can be severe. Less common complaints include diarrhea, vomiting, tachycardia, fatigue, headaches, weight loss, and respiratory problems. These are primarily due to the mediators released by skin mast cells after activation (Hartmann and Metcalfe 2000).

Differential Diagnoses

Multiple leiomyomas can lead to a clinically similar picture and the activation of the smooth musculature can result in a pseudo-Darier's sign, which, however, lacks the erythema. Also, leukemic infiltrates, lymphomas, and various adnexal tumors, such as eruptive syringomas, can be clinically similar, but do not show any urticarial changes.

Histopathology

The skin lesions are characterized by an increase in mast cells, which are restricted to the affected skin. The mast cell infiltrates are compact and predominantly perivascular. The correlate of hyperpigmentation is epidermal basal increased melanin. Staining with Giemsa or toluidine blue or by antitryptase antibodies can be used for quantifying the number of skin mast cells. Immunohistological staining for CD117 (KIT) is also suitable.

Course

The prognosis of skin mastocytosis is good. In the majority of affected children, skin lesions recede spontaneously before or

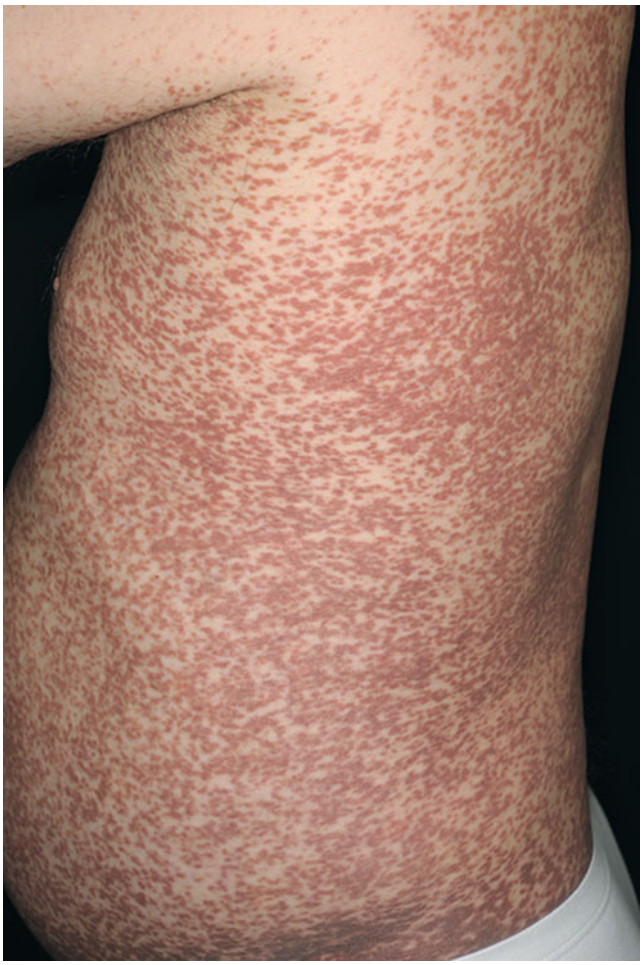

Fig. 4 Pronounced maculopapular cutaneous mastocytosis in adulthood

during puberty, often over several years. In contrast, cutaneous mastocytosis, which occurred in adulthood, shows a persistent course and may be the beginning of systemic mastocytosis.

3.2 Diffuse Cutaneous Mastocytosis

Epidemiology
Diffuse cutaneous mastocytosis is a disease of early childhood.

Clinical Features
The skin often has a yellowish-red coloring and can appear edematous and thickened. Hyperpigmentation of intertriginous areas often occurs. All patients suffer from itching, which is often severe. Rubbing or scratching can lead to blisters and also to systemic complaints, including shortness of breath and diarrhea. In the case of severe forms, large-area blisters may occur (Fig. 6).

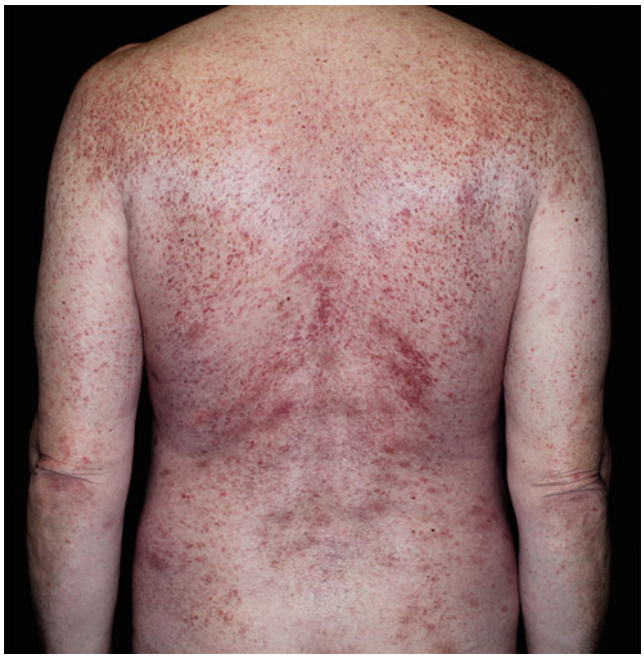

Fig. 5 Maculopapular cutaneous mastocytosis with telangiectasia

Differential Diagnosis
Blister-forming autoimmune dermatoses should be ruled out in the case of pronounced blisters.

Histopathology
There is a pronounced mast cell infiltrate with edema, occasionally subepidermal blisters, and often dermal fibrosis.

Course
Diffuse cutaneous mastocytosis, like other cutaneous forms of childhood mastocytosis, usually shows a benign course, but may be less prone to spontaneous regression.

3.3 Mastocytoma

(Fox 1883)

Synonyms
Mast cell nevus (historical); Xanthelasmoidea (historical) (Fox 1877)

Epidemiology
Mastocytoma usually occurs before the age of 2 years, often at birth or shortly thereafter. However, mastocytomas can also occur in older children, rarely even in adults.

Clinical Features
Reddish-brown nodules or plaques that show a positive Darier's sign after mechanical stimulation (Fig. 7). Blisters

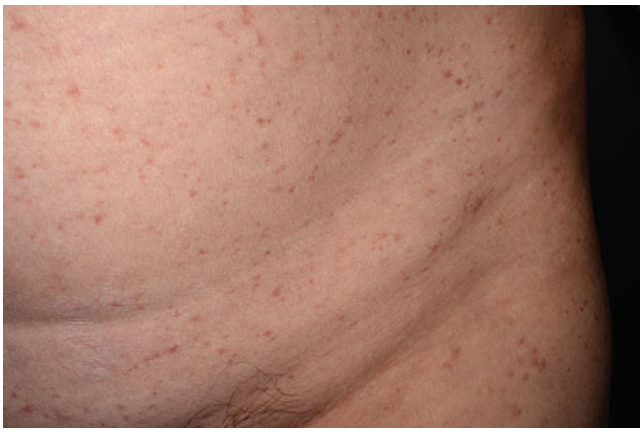

Fig. 6 Diffuse cutaneous mastocytosis in childhood

or crusts are rarely seen. Systemic complaints due to the release of mast cell mediators are possible.

Differential Diagnosis
Differential diagnoses of reddish-brown nodules in childhood include the mastocytoma, the pointed nevus, and the juvenile xanthogranuloma. Occasionally, insect bites or stings can also produce a similar picture if there is pronounced edema or blisters. Rarely, is there a resemblance to a xanthoma.

Histopathology
The dermis shows dense mast cell infiltrates.

Course
As a rule, spontaneous remission occurs over months to years with rare exceptions.

4 Systemic Mastocytosis

Etiopathogenesis
Systemic mastocytosis is a heterogeneous group of diseases resulting in mast cell accumulation in extracutaneous organs. In most cases, the cause is an activating mutation of the SCF receptor KIT, most often the somatic mutation Asp816Val (D816V) in exon 17. The subtypes of systemic mastocytosis differ considerably in prevalence, clinical picture, course, prognosis, and treatment (Carter et al. 2014).

Forms of Systemic Mastocytosis
The most common systemic form of mastocytosis is **indolent systemic mastocytosis**, which is characterized by mast cell infiltrates of the bone marrow and/or other organs such as the gastrointestinal tract. Most patients with indolent systemic mastocytosis also have maculopapular skin lesions (Fig. 1). The symptoms of indolent systemic mastocytosis are caused by mediators released by mast cells and can cause flushing

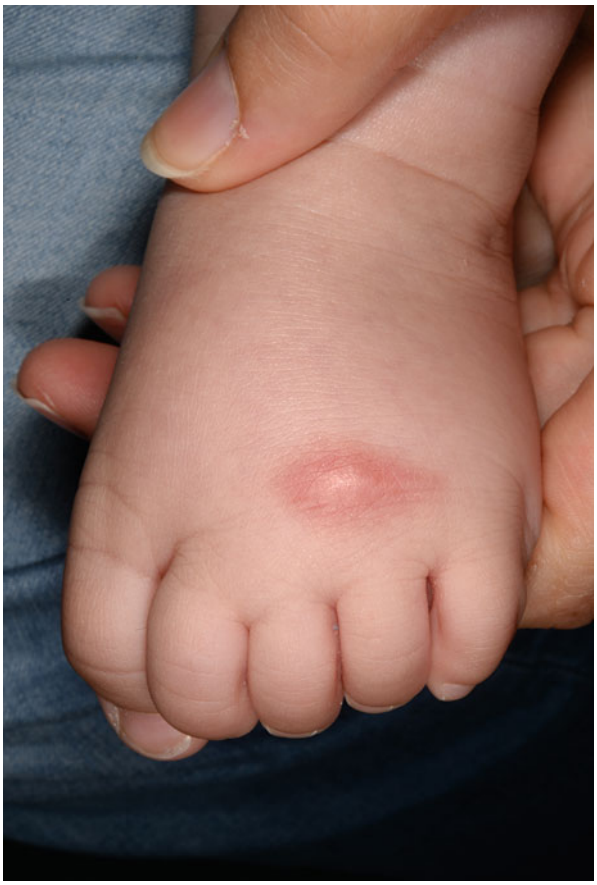

Fig. 7 Mastocytoma

reactions and itching, diarrhea, vomiting, tachycardia, fatigue, headaches, weight loss, and respiratory problems. In contrast to the advanced forms of systemic mastocytosis, organomegaly and a restriction of organ functions by mast cell infiltrates are not observed. The prognosis of indolent systemic mastocytosis is good and the course is usually chronic and stable or very slowly progressive. In the majority of patients, elevated serum tryptase levels are measured, which should be monitored regularly to detect possible progression of systemic mastocytosis.

S**moldering systemic mastocytosis** is characterized by a high mast cell count (bone marrow infiltration >30%), serum tryptase values >200 µg/l and/or organomegaly without dysfunction. It is assumed that there is an increased risk of a transition to an aggressive form, which is why these patients should be subjected to regular monitoring.

The advanced forms of systemic mastocytosis, **aggressive systemic mastocytosis** and **mast cell leukemia** are rare. The complaints are caused by the restricted function of organs as a result of neoplastic mast cell infiltrates. Involvement of the liver, spleen, bones, and lymphatic system is common, whereas the skin is rarely affected. Progress of aggressive systemic mastocytosis can be slow or fast, and patients

usually require cytoreductive therapy. Mast cell leukemia, the most aggressive form of systemic mastocytosis, is very rare and characterized by highly elevated numbers of atypical mast cells in the bone marrow and peripheral blood leading to multiorgan failure.

Up to one third of patients with indolent or aggressive systemic mastocytosis are at risk for developing an associated myeloproliferative or other hematological disease. This form of progress is called **systemic mastocytosis with associated hematological neoplasm**. The course and prognosis of this form of mastocytosis are primarily determined by the associated hematological disease.

Diagnostic Procedure

In symptomatic patients with typical skin appearance and elevated serum tryptase values >15 μg/l), systemic mastocytosis should be suspected and clarified in accordance with the WHO-criteria (Valent et al. 2016) by bone marrow and blood count examination. The proof of the typical Kit-D816V mutation by highly sensitive quantitative PCR of the blood, which correlates very well with bone marrow findings, may be helpful for the diagnosis. In patients with systemic mastocytosis, in addition to bone marrow analyses and depending on the symptoms, the clarification of a possible organ infestation such as by upper abdominal sonography or colonoscopy including histology is recommended. Owing to accompanying secondary osteopenia and osteoporosis in about half of the patients, osteodensitometry is recommended (Valent et al. 2014).

Therapy

The aim of the treatment of patients with systemic mastocytosis is to control the symptoms. Antihistamines, used at doses of up to four-fold the standard dose if needed, as well as H2 blockers and cromoglycate for gastrointestinal symptoms show efficacy in many patients (Siebenhaar et al. 2014). Associated osteoporosis and anaphylaxis require therapy in an interdisciplinary approach. The recommendations described for trigger factors and anaphylaxis in Sect. 3 also apply to systemic mastocytosis.

There are currently a number of novel therapeutic options under investigation in clinical trials, including more selective tyrosine kinase inhibitors and mast cell-targeting antibodies (Gotlib 2006; Arock et al. 2015).

In patients with aggressive systemic forms of mastocytosis, the aim of the therapy is to reduce the number of mast cells. Most recently, tyrosine kinase inhibitors have become available for the treatment of systemic mastocytosis. Other approaches, including interferon-α, cladribine (purine nucleoside analog), imatinib (kinase inhibitor, in patients without the Kit-D816V mutation), and, as ultima ratio, classical chemotherapeutics (doxorubicin, daunorubicin, vincristine), however, have had very limited success.

References

Mast Cells

Dahlin JS, Hallgren J (2015) Mast cell progenitors: origin, development and migration to tissues. Mol Immunol 63:9–17

Gurish MF, Boyce JA (2006) Mast cells: ontogeny, homing, and recruitment of a unique innate effector cell. J Allergy Clin Immunol 117:1285–1291

Metz M, Maurer M (2007) Mast cells – key effector cells in immune responses. Trends Immunol 28:234–241

Theoharides TC, Valent P, Akin C (2015) Mast cells, mastocytosis, and related disorders. N Engl J Med 373:163–172

Mastocytosis

Arock M, Akin C, Hermine O et al (2015) Current treatment options in patients with mastocytosis: status in 2015 and future perspectives. Eur J Haematol 94:474–490

Brockow K (2014) Epidemiology, prognosis, and risk factors in mastocytosis. Immunol Allergy Clin N Am 34:283–295

Carter MC, Metcalfe DD, Komarow HD (2014) Mastocytosis. Immunol Allergy Clin N Am 34:181–196

Gotlib J (2006) KIT mutations in mastocytosis and their potential as therapeutic targets. Immunol Allergy Clin N Am 26:575–592

Hartmann K, Metcalfe DD (2000) Pediatric mastocytosis. Hematol Oncol Clin North Am 14:625–640

Hartmann K, Escribano L, Grattan C et al (2016) 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 137:35–45

Schwartz LB (2006) Diagnostic value of tryptase in anaphylaxis and mastocytosis. Immunol Allergy Clin N Am 26:451–463

Siebenhaar F, Weller K, Blume-Peytavi U (2012) Childhood-onset mastocytosis. Dermatologist 63:104–109

Siebenhaar F, Akin C, Bindslev-Jensen C (2014) Treatment strategies in mastocytosis. Immunol Allergy Clin N Am 34:433–447

Valent P, Escribano L, Broesby-Olsen S et al (2014) Proposed diagnostic algorithm for patients with suspected mastocytosis: a proposal of the European Competence Network on Mastocytosis. Allergy 69:1267–1274

Valent P, Akin C, Metcalfe DD (2016) Mastocytosis 2016: updated WHO classification and novel emerging treatment concepts. Blood 129:1420–1427

First Describer

Darier J (1905) Quelques remarques sur l'urticaire pigmentaire. 4 ^{e} Série, tome VI. Ann Dermatol Syphiligr 7:339–344

Ehrlich P (1877) Beiträge zur Kenntnis der Anilinfärbungen und ihrer Verwendung in der mikroskopischen Technik. Arch Mikrosk Anat 13:263–264

Fox WT (1877) Atlas of skin diseases. Consisting of a series of coloured illustrations together with a descriptive text and notes upon treatment. Churchill, London. Plate LXIII Xanthelasmoidea

Fox WT (1883) On urticaria pigmentosa or xanthelasmoidea. Med Chir Trans 66:329–347

Nettleship E (1869) Chronic urticae leaving brown stains: nearly two years' duration. Br Med J II:323–324

Sangster A (1878) Anomalous mottled rash accompanied by pruritus, factitious urticaria and pigmentation, "urticaria pigmentosa?". Trans Clin Soc Lond 11:161–163

Weber FP, Rast H (1935) Telangiectasia macularis eruptiva perstans: a telangiectatic and relatively pigmentless variety of urticaria pigmentosa of adults. Acta Derm Venereol 16:216–224