

MOST COMMON CLINICAL PRESENTATIONS OF CUTANEOUS MASTOCYTOSIS

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SUMMARY – The term mastocytosis is referred to as an array of uncommon, usually sporadic, heterogeneous clinical illnesses that result from the hyperplasia of tissue mast cells. It comprises many different clinical manifestations varying from indolent cutaneous forms to systemic and malignant conditions. The characteristic presentation of mastocytosis consists of cutaneous manifestations: either a solitary mastocytoma, urticaria pigmentosa, or less commonly, diffuse cutaneous mastocytosis. Urticaria pigmentosa is the most common manifestation of cutaneous mastocytosis that manifests as a generalized eruption of round or oval erythematous macules, papules and plaques with variable amounts of brown pigment, usually on the trunk, but may also occur in all regions of the body including face and mucous membranes. Pruritus, dermographism and Darier's sign are additional features of these eruptions. Mastocytosis may also be manifested as mastocytoma, a rare, benign, pediatric tumor that results from hyperplasia of mast cells in papillary dermis in the first few weeks of life. The clinical course of mastocytosis is variable. The prognosis for the majority of pediatric patients with urticaria pigmentosa is extremely good, and over half of cases clear completely by adolescence, while those with aggressive systemic mastocytosis or mast cell leukemia show a progressive course, usually with a fatal outcome.

Key words: *Mastocytosis, cutaneous – diagnosis; Mastocytosis, cutaneous – pathology; Mastocytosis, cutaneous – therapy; Mast cells – pathology; Skin – pathology*

Introduction

The term mastocytosis comprises a group of uncommon, usually sporadic, heterogeneous clinical diseases that result from hyperplasia of tissue mast cells. There are many different clinical manifestations varying from indolent cutaneous forms to systemic and malignant conditions¹. One of the most common presentations of cutaneous mastocytosis is urticaria pigmentosa, a benign condition that results from hyperplasia of mast cells in papillary dermis. The crucial characteristic of mastocytosis is hyperplasia of mast cells within various tissues. Mast cells originate from a pluripotent CD34+ stem cell derived from bone marrow. Initially, mast cells were thought to be tissue equivalents of basophils in periph-

eral circulation, but recently they have been found to be distinct from basophils. Mast cells are usually round, typically between 9 and 12 microns in diameter, they are larger than basophils and have a cytoplasm containing numerous intracellular granules which stain characteristically with toluidine or alcian dye to the color of violet to reddish purple²⁻⁴. Mast cells do not stain with hematoxylin-eosin, whereas basophils possess a multi-lobular nucleus and are stained with hematoxylin-eosin.

Humans have two kinds of mast cells: those that secrete the neutral protease tryptase (designated MC_T) and those that secrete other enzymes, primarily carboxypeptidase, cathepsin G, and chymase (designated MC_{TC}). Both forms of human mast cells contain similar amounts of histamine. MC_T cells are predominantly found in gastrointestinal submucosa, skin, and vascular structures, whereas MC_{TC} cells are more commonly found in the connective tissue of the lung, upper respiratory tract, and small intestine²⁻⁴.

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Mastocytosis generally occurs in childhood. Therefore the onset of urticaria pigmentosa occurs between birth and 2 years of age in approximately 55% of cases; an additional 10% develop the disease before the age of 15 years. Mastocytosis in these age groups differs in many respects from mastocytosis that has its onset in adulthood. Typical presentation of pediatric-onset mastocytosis consists of cutaneous manifestations: either a solitary mastocytoma, urticaria pigmentosa, or less commonly, diffuse cutaneous mastocytosis. Particularly in infants, bullous eruptions may occur. Mastocytosis in infants and children may involve internal organs, including bone marrow and gastrointestinal tract, although such manifestations appear to be less common in children than in adults. The diagnosis of cutaneous mastocytosis is based on clinical features, histopathologic analysis, and absence of systemic mastocytosis criteria^{5,6}.

Plasma histamine levels may be elevated in pediatric-onset mastocytosis. Treatment usually involves the use of H1 and H2 antihistamines to control itching and hypersecretion of gastric acid that may occur. The prognosis in children with mast cell disease is variable; approximately half of the children with urticaria pigmentosa may experience resolution of lesions and symptoms by adolescence^{5,6}.

Etiology and Pathogenesis

The etiology of mastocytosis is unknown, but mutations in the *c-kit* gene may play a role. The *c-kit* gene is a proto-oncogene expressed on mast cells, hematopoietic stem cells, germ cells and melanocytes, and has a role in the control of their proliferation. Various mutations in *c-kit* gene have been described in children with mastocytosis, but their prognostic value is still unclear⁷. Most cases of pediatric mastocytosis either do not have *c-kit* mutations or have a dominant negative loss of function mutation. A small subset of patients with childhood onset of mastocytosis do have activating *c-kit* mutations and they tend to have a very extensive disease that may persist to adulthood and be associated with systemic involvement⁸. It is well-known that *c-kit* is a type III transmembrane tyrosine receptor with an extracellular domain that binds to the mast cell growth factor (stem cell growth factor), which is responsible for growth, function and survival of mast cells⁹.

Whether mastocytosis is a hyperplastic reaction to an unknown stimulus or it is a neoplastic condition, remains unknown. Increased local concentrations of solu-

ble mast cell growth factor in the lesions of cutaneous mastocytosis are believed to stimulate mast cell proliferation, melanocyte proliferation, and melanin pigment production. The induction of melanocytes explains the hyperpigmentation that is commonly associated with cutaneous mast cell lesions. Impaired mast cell apoptosis has been postulated to be involved, as evidenced by up-regulation of the apoptosis-preventing protein BCL-2 demonstrated in patients with mastocytosis. Activating mutations of the proto-oncogene *c-kit* have been identified but do not explain the initiation of the disease. Recently, interleukin 6 levels have been shown to be elevated and correlated with disease severity, indicating interleukin 6 to be involved in the pathophysiology of mastocytosis⁴.

Associated systemic manifestations are believed to reflect the release of mast cell-derived mediators such as histamine, prostaglandins, heparin, neutral proteases, and acid hydrolases. Symptoms and signs induced by mediators may include headache, flushing, dizziness, tachycardia, hypotension, syncope, anorexia, nausea, vomiting, abdominal pain, and diarrhea. The skeletal, hematopoietic, gastrointestinal, cardiopulmonary, and central nervous systems may be involved either directly *via* mast cell infiltration, or indirectly *via* mast cell mediator release⁴.

Clinical Features

Most signs and symptoms of mastocytosis, including life-threatening conditions, are caused by both preformed and newly generated mediators released from mast cells^{10,11}. Histamine is the most common preformed mast cell mediator, its clinical effects on the skin being pruritus, wheal and flare response, and hives^{2,3,8,11}.

The skin is the most commonly involved organ in mastocytosis. Cutaneous mastocytosis can generally be classified into three groups: solitary mastocytoma, disseminated (disseminated mastocytomas, urticaria pigmentosa, telangiectasia macularis eruptiva perstans) and diffuse mastocytosis (diffuse, bullous and erythrodermic mastocytosis)^{8,11} (Fig. 1).

Mastocytoma is the most common presentation of cutaneous mastocytosis. Mastocytoma is an uncommon, benign, pediatric tumor that results from hyperplasia of mast cells in papillary dermis. It may be present at birth or develop within the first few weeks of life^{1,8}. Mastocytomas are either solitary or very few in number and present as brownish or orange-yellow plaques or nod-

ules, larger than 1 cm in diameter, sharply defined. Lesions may have a *peau d'orange* surface. Multiple nodular lesions are very rare^{8,9}. It usually presents on the skin of

distal extremities, but may also occur on the face, scalp and trunk, but not on the palms and soles. Skin lesions will urticate (Darier's sign) or even blister upon strok-

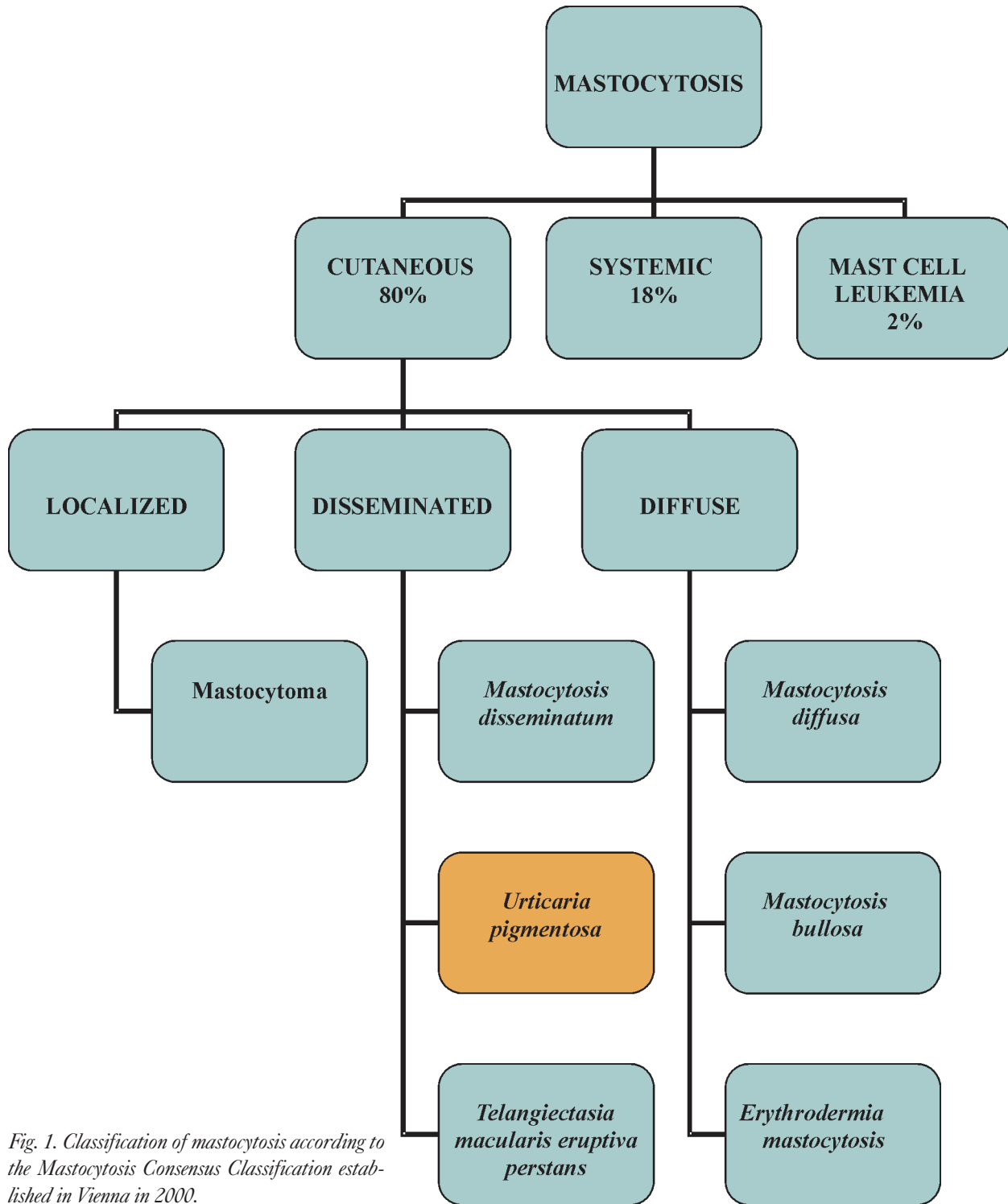


Fig. 1. Classification of mastocytosis according to the Mastocytosis Consensus Classification established in Vienna in 2000.

ing. There may be associated local pruritus. Mastocytomas usually involute spontaneously before puberty, but persistence of lesions has been described. Mastocytoma may resemble xanthoma, juvenile xanthogranuloma, bite reaction, *café-au-lait* macule or nevus of Spitz. Sometimes it may be clinically impossible to distinguish a mastocytoma from amelanotic melanoma^{1,8,9}.

Bullous lesions can occur in all forms of cutaneous mastocytosis due to not well-developed dermoepidermal junction in infants¹¹. Hyperpigmentation can occur in all forms of cutaneous mastocytosis due to increased epidermal melanin pigment^{6,8,9,11}. Patients with cutaneous mastocytosis may have extracutaneous symptoms such as itching, flushing, palpitation, nausea, vomiting, abdominal pain, hypotension, cyanosis and bone pain^{6,9}.

Urticaria pigmentosa is the most common manifestation of cutaneous mastocytosis in infants, with the onset before 6 months of age in more than half of cases. The incidence is 1 *per* 1000 to 1 *per* 8000 live births. It may be present at birth or develop within the first few weeks of life^{8,9,12}. It presents as generalized eruption of round or oval erythematous macules, papules and plaques with variable amounts of brown pigment, usually on the trunk. All regions of the body including face and mucous membranes may be involved, but the palms, soles and scalp are often spared. Pruritus, dermographism and Darier's sign are additional features of these eruptions (Fig. 2). Diascopy shows light-brown persistent pigment in the lesions of urticaria pigmentosa^{9,12}. In the majority of pediatric patients with urticaria pigmentosa the prognosis is extremely good and over half of cases



Fig. 2. Typical reddish-brown macules and papules of urticaria pigmentosa (with positive Darier's signs – arrows) in an adult.

clear completely by adolescence. Most of the remaining pediatric patients will have only lightly pigmented, asymptomatic residual macules¹¹.

Adult onset urticaria pigmentosa has a high association with systemic involvement and there is no tendency of spontaneous resolution⁹. Urticaria pigmentosa can easily be overlooked due to its resemblance to chronic urticaria with postinflammatory hyperpigmentation. In addition, urticaria pigmentosa sometimes may mimic multiple leiomyomas, leukemic infiltrates, lymphomas and multiple adnexal tumors.

Telangiectasia macularis eruptiva perstans (TMEP) is the rarest form of cutaneous mastocytosis and can be observed in one percent of all patients with mastocytosis that usually occurs in adults. It is characterized by generalized, reddish-brown telangiectatic macules, 2-4 mm in diameter, irregularly defined, usually involving the trunk. Darier's sign is not always demonstrated in adult-onset TMEP due to lower number of mast cells *per* vascular unit (TMEP 3.3; normal skin 1.5; urticaria pigmentosa 6.4). Systemic involvement is rare; however, 10% of all cases may have systemic involvement, and may include episodic flushing, palpitation, syncope, headaches and gastrointestinal complaints. Skin biopsy shows infiltrates of mast cells, mainly in the upper dermis and clustered around dilated capillaries and venules. Metachromatic granules of mast cells can be identified by special stains such as Giemsa or toluidine blue. Some cases may be self-limited. The course is chronic^{8,12}.

Diffuse cutaneous mastocytosis is an extremely rare form of cutaneous mastocytosis that usually presents as erythroderma involving almost the entire skin of infants. Diffuse edema and thickening with a doughy consistency is observed. Diffuse cutaneous mastocytosis exclusively presents in infancy and usually resolves spontaneously before the third and fifth year of life. Due to the widespread and heavy mast cell load in the skin, these children have flushing, hypotension, shock and may have diarrhea and gastrointestinal bleeding⁹. Although diffuse cutaneous mastocytosis may resolve spontaneously by the time of puberty, these patients are at a higher risk of the disease persisting into adulthood, systemic involvement and severe complications¹¹.

Systemic mastocytosis criteria include one major criterion (multifocal dense infiltrates of mast cells (>15 cells aggregating) detected in sections of bone marrow and/or other extracutaneous organ(s)) and four minor criteria: 1) prominent spindling of mast cells (>25% of

all mast cells are spindle-shaped, or atypical mast cells comprise 25% of all mast cells in bone-marrow smears); 2) atypical immunophenotype of mast cell with co-expression of CD2 and/or CD25 (antigens which have not been found to be expressed on normal/reactive mast cell); 3) activating (somatic) point mutations of the *c-kit* proto-oncogene usually involving exon 17, with the imatinib-resistant type D816V being most frequent; and 4) persistently elevated serum tryptase level (>20 ng/mL). Normal plasma tryptase level is in the range of 2-14 ng/mL⁷. The diagnosis of systemic mastocytosis is established with fulfillment of one major and one minor criteria, or three minor criteria^{7,13}.

Aggressive systemic mastocytosis is characterized by organ impairment due to infiltration of mast cells⁷.

The presence of more than 10% of circulating abnormal mast cells supports the diagnosis of mast cell leukemia. The average time of survival is approximately 6 months^{7,11}.

It is generally accepted that systemic involvement is more likely to occur in adults with cutaneous mastocytosis, and it is commonly known to have a good prognosis in childhood. Therefore, in pediatric patients, a bone marrow examination is not required unless organomegaly or significant peripheral blood abnormalities are present. There is a tendency for spontaneous resolution before puberty; however, 15%-30% of children whose disease persists into adulthood will develop systemic mastocytosis⁶. Cutaneous mastocytosis in children has a low incidence of systemic involvement, whereas systemic mastocytosis occurs in $>25\%$ of cutaneous mastocytosis in adults⁶.

Treatment

Solitary mastocytoma resolves spontaneously and no treatment is required. For those patients that have associated severe local or systemic symptoms, surgical excision of mastocytoma is curative¹⁴.

Several triggering factors that patients with mastocytosis should avoid include trauma, physical stimuli, warm and cold water baths, hot drinks, the ingestion of alcohol, spicy foods and medications such as salicylates and other non-steroidal anti-inflammatory drugs, procaine, codeine, morphine, polymyxin B sulfate, thiamine and contrast media, since they may cause excessive degranulation of mast cells¹⁵.

Treatment is directed at inhibiting both the local and systemic effects of released mast cell mediators¹⁴.

Treatment usually involves the use of H1 and H2 antihistamines to control itching and hypersecretion of gastric acid that may occur⁵. If symptoms persist, small doses of aspirin as an inhibitor of prostaglandin D₂ synthesis (40 mg/day in adults) can be used, and in the absence of worsening clinical symptoms the dosage may be gradually increased until plasma salicylate levels rise to 20-30 mg/dL (approximately 3.9 to 5.2 g/day of aspirin in adults)¹⁴.

Oral administration of disodium cromoglycate (400-800 mg/day) has been reported to alleviate the gastrointestinal, cutaneous and central nervous system symptoms associated with mastocytosis. It has proved effective in controlling pruritus and blister formation in infants with mastocytosis. Treatment aim is symptomatic relief¹⁴.

Psoralen and ultraviolet radiation (PUVA) may be efficacious in reducing pruritus, but improvement requires 4 to 10 weeks of treatment and most patients experience recurrence of their cutaneous symptoms following therapy cessation¹⁴.

Recurrent, life-threatening episodes of hypotension following degranulation of mast cells have been reversed by early administration of subcutaneous epinephrine (EpiPen)^{8,14}.

A number of antineoplastic agents, including methotrexate, chlorambucil, vinblastine, and 6-mercaptopurine, have been used to treat malignant systemic mastocytosis. Unfortunately, no significant clinical responses have been observed. Recently, the use of interferon α -2b has been reported effective in controlling the signs and symptoms of mastocytosis in patients with widespread systemic disease¹⁴. There is a concern about side effects of spastic diplegia in infants treated with interferon α -2b¹⁶.

Tyrosine kinase inhibitors such as imatinib have been shown to cause mast-cell apoptosis in some adults with systemic mastocytosis. There are no reports on their use in children.

Vincristine has been shown to induce apoptosis and inhibition of mast-cell proliferation, but management of systemic mastocytosis in pediatric population was unsuccessful^{7,17}.

Conclusion

The clinical course of mastocytosis is variable. In the majority of pediatric patients with urticaria pigmentosa as the most common variant of mastocytosis the prognosis is extremely good and over half of cases clear com-

pletely by adolescence. Most patients, in particular those with cutaneous mastocytosis, remain in an indolent stage for years and decades, whereas those with aggressive systemic mastocytosis or mast cell leukemia show a progressive course, usually with fatal outcome.

Although childhood cutaneous mastocytosis has a favorable course in general, the subset of children with congenital bullous mastocytosis are at a higher risk of sudden death and a more guarded prognosis should be given.

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Sažetak

NAJČEŠĆI KLINIČKI OBLICI MASTOCITOZA KOŽE

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Pojam mastocitoza predstavlja skupinu rijetkih, uglavnom sporadičnih i klinički heterogenih bolesti koje nastaju uslijed hiperplazije mastocita u tkivima. Bolest se očituje kroz nekoliko kliničkih slika: od indolentnog kožnog do sistemskog i malignog oblika. Mastocitoza se očituje na koži kao mastocitom, *urticaria pigmentosa* i rijetko kao difuzna mastocitoza kože. *Urticaria pigmentosa* je najčešći oblik mastocitoze; klinički je obilježena generaliziranim erupcijom okruglih i ovalnih eritematoznih makula, papula i plakova s različitim količinom smeđkastog pigmenta, najčešće na trupu. Javlja se i na drugim dijelovima tijela kao što su lice i sluznice, dok su dlanovi, tabani i vlasište uvijek nepromijenjeni. Drugi simptomi bolesti uključuju svrbež, dermatografizam i Darierov znak. Mastocitoza se očituje i kao mastocitom, rijedak dobroćudni tumor dječje dobi koji nastaje zbog hiperplazije mastocita u papilarnom dermisu u prvim tjednima života. Klinički tijek mastocitoze je različit. Prognoza mastocitoze dječje dobi je uglavnom povoljna i u više od polovice slučajeva promjene se povlače do adolescencije, iako u mnogih bolesnika promjene kože mogu trajati nekoliko desetljeća. Kod bolesnika s agresivnom sistemskom mastocitozom ili mastocitnom leukemijom bolest ima progresivan tijek i uglavnom završava smrću.

Ključne riječi: Mastocitoza, kožna – dijagnostika; Mastocitoza, kožna – patologija; Mastocitoza, kožna – liječenje; Mastociti – patologija; Koža – patologija