

Cutaneous Mastocytosis in Childhood: An Update from the Literature

Öner Özdemir,¹ Süreyya Savaşan^{2,3}

¹Division of Allergy and Immunology, Department of Pediatrics, Sakarya University Faculty of Medicine, Training and Research Hospital, Sakarya, Türkiye

²Department of Pediatrics, Central Michigan University College of Medicine, Mt Pleasant, Michigan, USA

³Division of Hematology-Oncology, Pediatric Blood and Marrow Transplant Program, Children's Hospital of Michigan, Barbara Ann Karmanos Cancer Center, Detroit, Michigan, USA

ABSTRACT

Mastocytosis is an uncommon disease characterized by clonal infiltration of mast cell (MC) in different tissues. Cutaneous mastocytosis (CM) is the most frequent type observed during childhood and is characterized by MC accumulation limited to the skin. In adults, systemic mastocytosis is the most common type, characterized by MC proliferation in various organs such as the bone marrow, lymph nodes, liver, and spleen. Genetic alterations, primarily the *KIT* D816V mutation, play a pivotal role in the pathogenesis of CM, stimulating MC growth and mobilization, leading to tissue and organ infiltration. CM can be classified into three types: solitary mastocytoma, maculopapular CM, and diffuse CM. While cutaneous lesions in most CM cases naturally regress around puberty, the disorder is not always self-limiting. Even though systemic mastocytosis cases are rare, follow-up is necessary for all children diagnosed with CM. Patients with mastocytosis often experience symptoms associated with MC mediators, with itching being the most common, typically triggered by stimuli applied to the lesions. The treatment approach for CM primarily focuses on avoiding triggers. The use of H1 and H2 antihistamines during symptom flare-ups and the availability of adrenaline autoinjectors for severe systemic reactions constitute the mainstay of CM management.

Keywords: Mastocytosis, cutaneous mastocytosis, children, mast cells, urticaria pigmentosa.



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Address for correspondence:

Öner Özdemir.
Sakarya University Faculty of Medicine, Training and Research Hospital, Department of Pediatrics, Division of Allergy and Immunology, Sakarya, Türkiye
Phone: +90 264 444 54 00
E-mail:
ozdemir_oner@hotmail.com

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INTRODUCTION

Mastocytosis is a systemic disorder characterized by the accumulation of clonal mast cells (MCs) in the dermis and/or various organs.¹ This article discusses the cutaneous forms observed in children based on current literature.

History

The terminology “mast cell pathology” was first used by Nettleship and Tay² in 1869 when they reported the first pediatric patient with dermal involvement. In 1878, Sangster³ coined the term “urticaria pigmentosa” (UP) to describe dermal lesions, while the term “cutaneous mastocytosis” (CM) was first introduced by Sezary and Chauvillon⁴ in 1936. The discovery and understanding of the pathogenesis of CM were outlined by Ellis⁵ in 1949 when he observed MC infiltration in the dermis and other organs such as the liver, spleen, bone marrow, and lymph nodes.



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Table 1. Triggers of mast cell activation

Environmental	Human body	Drugs	Nutritional	Emotional
Heat	Exercise	Analgesics/NSAIDs	Alcohol	Stress
Cold	Teething	Opioid/narcotics	Caffeine	Anxiety
Pressure	Fever	Muscle relaxant	Spices	
Friction	Infection	Contrast media	Fermented food	
Sunlight	Endoscopy	Antibiotics	Bacterial toxins	
Allergens	GIS operation	Vaccinations		
Venom, pollen, molds, mite, food, etc.		Cough suppressants IFN- α 2b		

Epidemiology of CM in Childhood

Incidence/Prevalence

Although there is no definitive data on the incidence of mastocytosis, the number of new cases has been reported to range from 5 to 10/10⁶ individuals in the population.⁶ The estimated prevalence of mastocytosis cases admitted per year is between 1 in 50,000 and 1 in 150,000.⁷

Cutaneous mastocytosis is a relatively common disorder in pediatric dermatology clinics. Sagher and Even-Paz⁸ demonstrated that its prevalence varied from 1: 1,000 to 1: 8,000 dermatological cases in the USA, while Torreló et al.⁹ reported 5.4 cases per 1,000 pediatric dermatology cases in Spain. It was also noted to occur in 1: 500 first-time pediatric dermatology cases.¹⁰ In another study conducted at a Turkish dermatology clinic, the rate of childhood CM was found to be 1: 234 among newly presented patients at the clinic.¹¹ Furthermore, Beare and Minor estimated the prevalence of CM as 1: 800 among first-time pediatric patients in Northern Ireland.¹²

Other Features of Clinical Presentation

Mastocytosis can onset at birth or develop at any time until late adulthood. The incidence of CM declines until school age and then increases again after the age of 15. Delayed onset of the disease during childhood is associated with an increased risk of developing systemic mastocytosis (SM), while cases of aggressive neonatal mastocytosis are exceptionally rare.^{10,13}

Cutaneous mastocytosis exhibits a bimodal distribution, with 55% of cases occurring from birth to 2 years of age, 10% in pediatric cases under 15 years old, and 35% in cases over the age of 15.¹⁴ Urticaria pigmentosa (UP), also known as maculopapular CM (MPCM), typically presents in infants around one year of age and is usually diagnosed before the age of two. Several studies, ranging from 17 to 180 cases, have reported disease onset before the age of 2 in frequencies ranging from 78% to 98%.¹⁵ Conversely, mastocytomas are relatively more common in children over 15 years of age.¹⁶

Although most pediatric cases do not have a family history of CM, familial cases have been occasionally observed. Familial cases, involving at least one first-degree family member, have been reported in 2% to 4% of patients, with the majority associated with c-kit germline mutations.¹⁷ Cutaneous mastocytosis affects individuals of all races and does not show gender predilections.

Pathophysiology of Cutaneous Mastocytosis in Childhood

Mast cells originate from the bone marrow and migrate to connective tissue in a precursor form, where they play various roles. While some rare familial cases have been reported, pediatric mastocytosis is generally considered a sporadic disease. Despite some progress, the exact pathogenesis is still not fully understood.^{13,17,18}

In adult cases, mutations in the cell surface membrane receptor tyrosine kinase (c-Kit, CD117) on mast cells are typically observed. This receptor codes for a receptor for stem cell factor, and the stimulation of this receptor leads to the proliferation and maturation of mast cell precursors.¹⁶

c-KIT and Other Mutations

Pediatric mastocytosis was previously considered nonclonal and believed to be a self-resolving disease. However, it has been found that approximately 90% of adults with systemic mastocytosis (SM) have a point mutation in codon 816 (D816V) of the c-Kit gene in exon 17. In comparison, this mutation is detected in about 40% of patients with CM and has been reported to range from 0% to 83%.¹⁶ One study demonstrated c-Kit mutations in 43% of dermal biopsies from pediatric cases with CM. The most common mutation is a gain-of-function mutation in codon 816, resulting in the replacement of amino acid aspartic acid (D) with valine (V), known as D816V. Gain-of-function mutations also occur at codons 816 and 820, while loss-of-function mutations occur at codon 839. Missense activating mutations at codon 816 (Asp816Val and Asp816Phe)

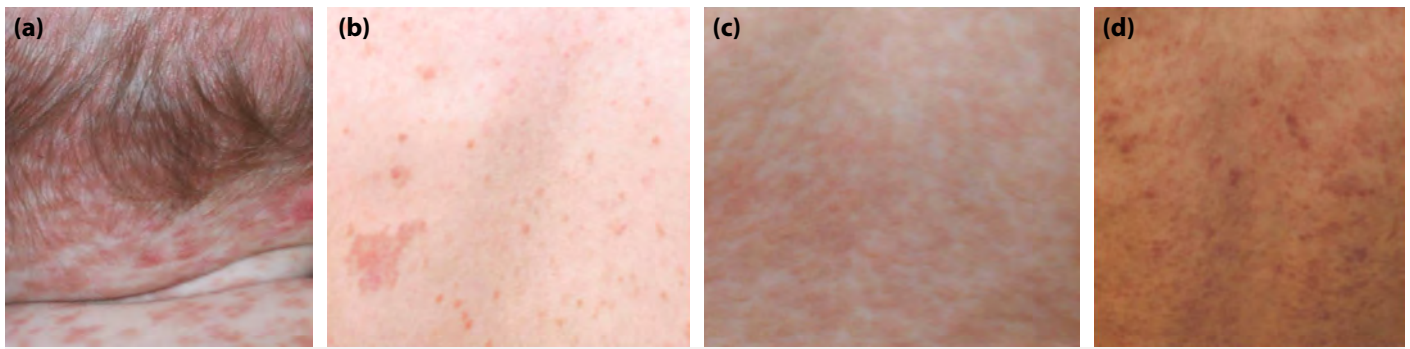


Figure 1. (a–d) Polymorphic maculopapular cutaneous mastocytosis in four different patients.

have been detected in various forms of mastocytosis, including UP, mastocytomas, and diffuse cutaneous mastocytosis (DCM). Cases with the Asp816Phe mutation tend to develop the disorder at earlier ages compared to those with Asp816Val mutations.¹⁹

When *c-KIT* sequencing was performed, a high frequency of mutations (44%) located outside the common exon 17 was identified, indicating that pediatric mastocytosis can also be a clonal disease.²⁰ *c-KIT* mutations are more commonly detected in other exons, such as exons 8, 9, and 11, in up to 25% of children with mastocytosis.²¹ Among patients without codon 816 (D816V, D816Y, and D816I) mutations, other mutations, including those in exons 8, 9, 11, and 13 were observed in 44% through whole *c-KIT* sequencing. Therefore, in the absence of the *c-KIT* D816V mutation, sequencing the complete *c-KIT* gene is advised in cases of CM.^{20–22}

Patients with mastocytosis who also present with food allergies have been shown to have increased expression of *TRAF4*, a component of the tumor necrosis factor receptor-associated factor family gene. Allergies to insect venom have been associated with the expression of *B3GAT1* (Table 1), which encodes the enzyme 3-beta-glucuronosyltransferase 1, whose enzymatic activity is associated with CD57 epitope expression.¹⁶ Furthermore, the induction of melanocytes play a role in hyperpigmentation, IL-31 plays a role in pruritus, and IL-6 is associated with disease severity.¹⁶ Serum tryptase levels in DCM cases are elevated during the early days of infancy but tend to decrease around 9–12 months. There appears to be a relationship among the Scoring index of Mastocytosis (SCORMA), treatment, and follow-up.¹⁶

Histopathology

While UP can be easily recognized based on clinical grounds, a skin biopsy is necessary to confirm the diagnosis. The histologic hallmark of UP is the increased density of MC in the skin. Cutaneous lesions can have up to a 40-fold higher MC presence than normal dermis, with more rounded or cuboidal shapes. The diag-

nosis is supported by the increased frequency and morphology of MCs, and the presence of aggregates with more than 15 MCs per cluster or monomorphic buildup with >20 MCs per microscopic high-power field (HPF).²³ Mast cells can be identified through staining with toluidine blue, Leder, Giemsa, tryptase, and CD117.

Bone marrow biopsies show significant features such as hyperplasia, eosinophils, MCs, and early myeloid cells. Mast cell collections can be observed around blood vessels and throughout the skin in children.^{15,23,24} Initial bone marrow biopsy has been shown to be prognostic, as patients without signs of SM showed improvement in long-term clinical follow-up studies of CM.¹⁵

Clinical Appearance Of Cutaneous Mastocytosis in Childhood

After a general classification of mastocytosis, the clinical appearance and progression of CM are discussed below.

Classification

Mastocytosis is broadly categorized into two main classes: CM and SM. In children, CM is the most common form. The latest classification by the World Health Organization (WHO) in 2019 included the following categories: CM; SM associated with a clonal hematological neoplasm mechanism; aggressive SM; indolent SM; smoldering SM; MC sarcoma; and MC leukemia.¹⁶

Cutaneous mastocytosis is limited to the dermis and has a good prognosis. It almost exclusively occurs in children. The WHO divides CM into three main categories: maculopapular cutaneous mastocytosis (MPCM), diffuse cutaneous mastocytosis (DCM), and solitary skin mastocytoma (Table 2). If CM includes three or fewer lesions, they are named mastocytomas, whereas MPCM is characterized by 4 to 100 lesions. The DCM category involves diffuse cutaneous involvement (Fig. 1–3).^{16,25,26}

Frequency of Types

Cutaneous mastocytomas are observed in 15% to 50% of cases, UP in 45% to 75% of cases, and diffuse skin involvement in less than 5% to 10% of childhood CM.^{16,20,26–28} Torrelo et al.,⁹ Azaña et al.,¹⁷ and Stein reported that MPCM is the most fre-

quent type, accounting for up to 90% of cases, followed by mastocytoma in up to 40% of cases, while Hannaford et al.²⁷ showed that 51% of patients had mastocytoma. In the largest pediatric series of 172 patients,⁹ only three patients were reported to have DCM (2%). Another study with 71 patients found that 53 cases (75%) had UP, 12 (17%) had mastocytoma, and six (8%) had DCM.¹⁰

Maculopapular Cutaneous Mastocytosis (Urticaria Pigmentosa)

Maculopapular cutaneous mastocytosis, also known as urticaria pigmentosa, is characterized by well-defined lesions of maculopapular, plaque, nodule, or bulla nature. These lesions range in size from millimeters to centimeters and have a yellow-brownish or red-brown color. They can be found on the scalp, face, trunk, and extremities, and typically exhibit an asymmetric distribution. The lesions classically spare the face, palms, and soles (Fig. 1a–d). They are typically pruritic, and the number of lesions can vary from less than 10 to around 100.^{13,16,26}

A monomorphic variant with an adult-type pattern is characterized by multiple small, round, mostly flat, brown, or red maculopapular skin lesions. This variant typically shows a central or truncal area and a symmetrical distribution. It only occurs in toddlers and school-age children. These small lesions become visible after the age of 2, and their disappearance may take longer than 8 years compared to larger lesions. In some patients with monomorphic cutaneous lesions, SM may develop in the long term.²⁹

The more common polymorphic type, characterized by slightly larger lesions of varying size and shape, is usually observed in children. The polymorphic type often presents within the first few weeks or before seven months of age and has a better prognosis. A characteristic feature of the polymorphic type of MPCM in children, unlike in adults, is the presence of lesions on the head, particularly on both sides of the forehead, neck, and extremities. Childhood-onset polymorphic type is associated with lower serum tryptase levels, a shorter disease duration, more frequent spontaneous remission of dermal lesions, and an overall more favorable outcome compared to the monomorphic variant.²⁹ Maculopapular cutaneous mastocytosis lesions can also change their forms throughout childhood, transitioning from maculopapular to plaque/nodular shapes.

Although telangiectatic CM (telangiectasia macularis eruptiva perstans, TMEP) is not recognized in the WHO 2019 classification, some consider it a type of MPCM. This condition is exceptionally rare in children and primarily occurs in adults. The skin eruption consists of red, telangiectatic macules on a tan-to-brown background.^{16,21,30}

Yellowish plaques of MPCM were previously referred to as xanthelasmoid mastocytosis in the literature.³¹

Mastocytomas (Nodular Mastocytosis)

Cutaneous mastocytomas are either congenital or develop during the third month of infancy. They are characterized by up to three trunk

Table 2. Features of types of cutaneous mastocytosis

Types of CM	Features of CM								
	Frequency	Numbers	Skin appearance	Size	Localization	Symptoms	Systemic	Tryptase	Prognosis
Urticaria pigmentosa (MPCM)	70–90%	Multiple	Maculopapular, plaques, nodules	>1 cm	Asymmetric, trunk, neck, palmar-plantar	Pruritus, flushing, diarrhea	Rare	↑, sometimes ↔	Good, regression
Polymorphic				<1 cm	Symmetric, trunk, arm				
Monomorphic									
Mastocytoma	10–30%	≤3	Nodules, plaques, macule, blistering	≥1 cm	Asymmetric	Rare	Very rare	↔	Very good
Diffuse cutaneous mastocytosis	1–3%	Diffuse (multiple)	Erythroderma, pachyderma (leathery), blistering	>1 cm (large/diffuse)	Asymmetric and extensive	Pruritus, flushing, diarrhea, anemia	Frequent	↑	Fair

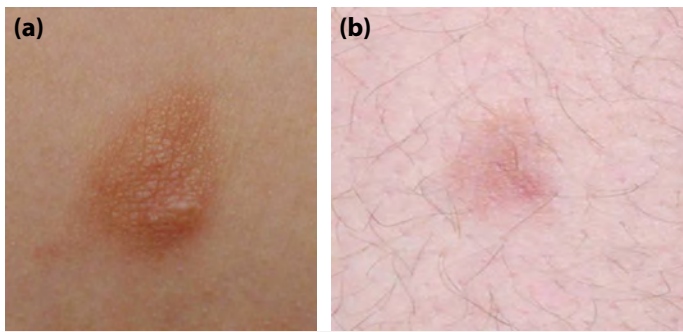


Figure 2. (a, b) Solitary nodular (plaque) type cutaneous mastocytosis in two different patients.

or limb lesions that are brown or yellow in color (Fig. 2a, b). If there are more than three lesions, a diagnosis of MPCM should be considered. Mastocytomas occur less frequently than UP in children (10–35%).

Typically, a mastocytoma appears as a single brown, red, or yellow macule or nodule that is sharply demarcated and usually measures between 1 cm to 10 cm in diameter. The yellow-brownish papules or plaques with a leathery pattern are typically noticed in the first months of infancy, occasionally with blistering and subsequent crusting. Mastocytomas may cause arterial hypotension or flushing. They can occasionally increase in size and change in morphology and usually regress by puberty. In the majority of cases, there is no systemic involvement.^{13,16,26}

Diffuse Cutaneous Mastocytosis (DCM)

Diffuse cutaneous mastocytosis (DCM), which often manifests in the first few months of infancy or is present at birth, accounts for 1–13% of CM cases and is known to progress to fatal MC leukemia in some patients.¹⁰ Characteristic lesions in DCM can be maculopapular, nodular, bullous, or generalized erythrodermic, and they appear yellow to orange in color (Fig. 3). The affected skin may exhibit exaggeration of normal skin markings, a leather-like or orange-peel-like texture, or thickening. Over time, hyperpigmentation and dermographism may develop.^{13,16,26,10} This condition has a good chance of remission at five years. However, a high fatality rate of up to 24% has been observed, primarily due to anaphylactic shock and gastrointestinal bleeding. The true incidence of anaphylactic shock or progression to SM in DCM is not known. Rare cases have demonstrated MC infiltration in visceral organs, leading to specific dysfunctions such as hypovolemic shock, anemia, diarrhea, intestinal bleeding, malnutrition, or an associated myeloproliferative disorder. Many symptoms are related to the release of MC mediators and their local and systemic effects.^{29,32}



Figure 3. Diffuse cutaneous mastocytosis in one of our patients.

Evaluation of Pediatric Patients with CM

Clinical examination of the skin lesions is crucial for distinguishing between different forms of CM, such as MPCM/UP, DCM, and mastocytoma. The presence of lymphadenopathy, hepatosplenomegaly, or abnormal blood tests may suggest SM and require further investigations, such as abdominal ultrasound or CT scans, as well as a bone marrow biopsy. In such cases, comprehensive laboratory examinations including hemogram, hepatic and renal function tests, and serum tryptase should be considered.^{16,25}

Searching for systemic symptoms, such as flushing, pruritus, palpitations, dizziness, syncope, abdominal pain, and diarrhea, is necessary. Twenty-five percent of cases with UP may experience digestive system symptoms.²⁵ In a study conducted by the National Institutes of Health, pruritus was reported in 83% of cases, flushing in 65%, vesicles in 53%, abdominal pain in 41%, bone pain in 18%, and headaches in 12%.¹⁴

The Darier sign, characterized by the development of a wheal upon patting or friction of cutaneous lesions, is a highly specific marker in CM. This wheal becomes erythematous, edematous, and pruritic within 15–30 minutes.¹³ It is secondary to the release of MC mediators, which can also cause systemic symptoms upon physical stimulation. In some cases, blister-

Table 3. Diagnostic approach in childhood mastocytosis (modified form various literature)**Suspected CM lesion (single or multiple)**

Skin biopsy (3 mm punch): histology, genetic study

Laboratory tests

CBC with differentials, routine biochemistry, baseline serum tryptase

Studies could be repeated routinely every 6-8 months. In the case of MC mediator-related symptoms, these studies are repeated more frequently

Abdominal ultrasound

Organomegaly suspected or with

Severe systemic mast cell mediator-related symptoms (GI, flushing, syncope, pre-syncope, cyanotic spells)

Persistence of skin lesions after puberty

Clinical changes suggestive of systemic involvement

Bone marrow biopsy

Severe systemic mast cell mediator-related symptoms (GI, flushing, syncope, pre-syncope, cyanotic spells)

Organomegaly or significant lymphadenopathy

Persistence of skin lesions after puberty

Clinical changes suggestive of systemic involvement

ing of the lesions may also be observed. Darier's sign is more prominent in children due to the higher MC density in their skin lesions.¹⁶ Darier's sign can be seen in 88–92% of affected patients. A negative Darier's sign may not exclude CM, so it is highly specific but not fully sensitive.^{10,25}

Skin Biopsy

Although rarely necessary in clinical practice, a skin biopsy may be performed for confirmation purposes.²⁶ Correlating the biopsy results with laboratory tests is crucial to distinguish CM from SM, and these tests should be repeated for follow-up every 6–12 months.¹⁶ When a dermal biopsy is required, a 3 mm punch should be used. The patient should have discontinued the use of H1 antihistamine medication before the biopsy. Histopathological findings include perivascular (papillary and upper dermis), interstitial, and nodular sheet-like infiltration of mast cells. In UP, MCs have irregular shapes and may be accompanied by bi-lobular polymorphonuclear infiltrating eosinophils. Immunohistochemical staining for tryptase and c-KIT may also be useful in skin lesion biopsy samples.¹⁶

Serum Tryptase

Serum tryptase is a useful marker in distinguishing between SM and CM since it is typically within the normal range in CM. Blood sampling should be done in a basal state, and normal levels range from 1–11.4 ng/mL. However, normal values are not well-established in younger children. In infants, toddlers, and school children without additional symptoms such as hepatomegaly and failure to thrive, bone marrow aspiration, which is the usual diagnostic procedure in adults, is not necessary, even if serum tryptase levels are elevated (Table 3).

In adults, if serum tryptase is above 20 ng/mL, further diagnostic studies should be considered. One marrow involvement or involvement of organs other than the skin is very rare in children with CM.²⁶ However, it is important to note that almost all cases of adult-onset CM persist and may progress to SM.³³

High tryptase levels in CM patients are also rarely reported. Children with extensive skin lesions, such as those seen in DCM, may have higher serum tryptase levels in early childhood and experience more severe symptoms associated with MC mediators, including systemic allergic reactions and anaphylaxis. However, tryptase levels usually decline over time.²⁹ It is essential to remember that high serum tryptase levels can be observed in other disorders, such as hereditary alpha trypsinemia, chronic eosinophilic leukemia, and certain nephropathies. An elevated tryptase level itself, without other systemic findings, should not automatically require a bone marrow assessment, as emphasized above.¹³

Serum Histamine Levels

Serum histamine concentration in DCM cases is elevated during the first two months of infancy but tends to decline by 9–12 months of age. Cases of mastocytosis with higher histamine levels are associated with more severe bone involvement and elevated baseline gastric acid levels.¹³

Other Laboratory Tests

Generally, basic tests are within normal levels in CM, although mild eosinophilia may sometimes be observed. In one study, eosinophilia was found in 10.7% of cases, anemia in 21.4%, and thrombocytopenia in 3.5%.¹⁰

Serum Cytokine Levels

Elevated levels of interleukin-31 (IL-31) have been found to be associated with pruritus, and higher levels of IL-6 are recognized as an indicator of CM severity.¹³

Diagnosis and Clinical Features of CM in Childhood

Cutaneous mastocytosis is generally diagnosed by visualizing characteristic dermal lesions, primarily in children. Furthermore, CM diagnosis can be established based on the characteristic appearance of the three different forms described before: UP, mastocytomas, and DCM, with a positive Darier sign and skin biopsy showing MC infiltrates in cases with questionable clinical manifestations. Hematoxylin-eosin and other staining methods are used for histological identification of MCs. However, histological confirmation is not necessary since the clinical presentation is usually clear, with distinctive morphology and dissemination of cutaneous lesions, onset during infancy, and the presence of the pathognomonic Darier sign in the majority of pediatric cases.^{16,26}

The precise criteria by the EU/US working group include the absence of findings or conditions of SM, the presence of distinctive cutaneous lesions of mastocytosis and the related Darier's sign as a major criterion for CM, and one or two of the following minor criteria: MC infiltration in the tissue with clusters of more than 15 MCs per cluster or scattered MCs with more than 20 per high-power field (HPF), and detection of c-KIT mutation at codon 816 and other codons in the involved dermal tissue.^{29,34}

In addition to obtaining a detailed medical history and observing characteristic skin lesions, physical examination should include the assessment of lymphadenopathy and hepatosplenomegaly. If there is a possibility of a visceral organ or bone marrow involvement, imaging studies such as liver ultrasound or CT scans may be performed. Hemograms, serum tryptase levels, liver function tests, and evaluation of the c-KIT gene can be conducted in certain pediatric cases. If abnormal findings are present, a bone marrow biopsy may be warranted, although bone marrow involvement is extremely rare in pediatric CM. Gastrointestinal symptoms may require a barium study and/or endoscopy, and a radiographic skeletal assessment or bone scan might be indicated in cases of bone pain or a history of fractures.²⁵

Other Manifestations of CM

It is critical to remember that CM cases can lead to symptoms associated with MC mediators, both locally and/or systemically. Flushing is a common symptom, while arterial hypotension, cyanosis, respiratory arrest, and anaphylactic reactions are less common in MPCM. Additionally, CM cases may present with digestive symptoms, including diarrhea, abdominal pain, hyperacidity, or peptic ulcers.¹⁶

In children with MPCM who present as early as their first few months of infancy, outbreaks of flushing are occasionally detected, particularly with deeply infiltrated lesions or prominent cutaneous involvement. Occasionally, fluctuations in consciousness secondary to arterial hypotension may occur. In (solitary) mastocytomas or polymorphic MPCM with plaque or nodular dermal lesions, blistering can rarely occur in the early years of childhood, especially in association with mechanical irritation, but it usually heals without scarring.²⁶

In DCM, larger affected skin areas with a higher degree of infiltration are involved, and patients present with prominent urticarial dermographism of the thickened skin, especially during infancy and toddler years. Dermographic urticaria is more frequently present in DCM than in monomorphic MPCM. In cases of suspicion of DCM, Darier's sign should be carefully examined because flushing and even hypotension can be triggered secondary to immense MC stimulation in young children, particularly when there is prominent dermal involvement.²⁶

Risk Factors and Triggers for MC Activation (Systemic Symptoms) and Anaphylaxis in CM

Although anaphylaxis and systemic involvement are rare in pediatric CM, symptoms associated with MC mediators are frequent in DCM. Risk factors for anaphylaxis and/or systemic symptoms include high serum tryptase levels, the presence of DCM, and extensive dermal lesions. Additionally, children with MPCM, who have greater skin involvement and higher serum tryptase levels, are more likely to experience systemic symptoms. For uncomplicated polymorphic MPCM of moderate severity, the risk of anaphylaxis is not significantly increased compared to the general population.^{26,28}

In adult cases of mastocytosis, the triggers for anaphylaxis differ from those in pediatric CM. In two-thirds of pediatric patients, no specific trigger can be identified, resulting in idiopathic anaphylaxis. Food allergies are reported in 10–20% of cases, drugs in less than 10%, and venoms do not appear to be major triggers of anaphylactic reactions in children, unlike in adults with mastocytosis.²⁶ Since some medications used in general anesthesia can trigger MC degranulation, it is generally recommended to select anesthetic agents carefully and often administer antihistamine therapy before and after surgeries (Table 1).¹³

A marginally elevated risk of side effects following the first vaccination in children with CM, up to 3–6% more than the general population, has been reported.¹³ For subsequent vaccinations, no relapse risk has been identified, and any side effects were mild, if any. In patients with marked cutaneous involvement, bullous skin lesion development, flushing, or DCM, a two-hour clinical observation after the first vaccination is appropriate.¹³

Therefore, the authors recommend the use of single-vaccine regimens, if possible, and post-vaccination monitoring in pediatric CM. However, childhood/mandatory vaccines should still be administered to the routine schedule in those with other forms of CM.^{13,26}

Follow-Up of Children with CM

The SCORMA index is essential and useful in the management and monitoring of children with CM. This index consists of three parts: Part A assesses the extent of the lesions, part B evaluates the activity (intensity) of the lesions, and part C captures subjective symptoms. A visual analog scale is used, ranging from 0 to 10, and if the patient is under five years old, it is completed by parents. The SCORMA index is calculated using the formula $A5 + 5B + 2C5$. The index score ranges between 5.2 and 100 points.^{16,35}

Prognosis

The prognosis of childhood CM is excellent, particularly when the disease begins in the first two years of infancy. In cases manifesting in early childhood, spontaneous remissions or regressions tend to occur by adolescence in up to 50–80% of cases.^{16,26}

New studies on the likely course of pediatric mastocytosis suggest that complete resolution of dermal lesions is typically observed in cases with solitary mastocytoma and MPCM.³⁶ In most patients with polymorphic MPCM, clinical findings no longer exist in adulthood. The course over the years is characterized by a flattening of the cutaneous lesions. Marked forms, particularly monomorphic MPCM that presents later, from school age onwards, can progress into SM types; therefore, monitoring serum tryptase levels may be useful.^{26,37}

The prognosis of mastocytomas is outstanding, even though a positive Darier's sign may be observed for several years and localized blistering frequently occurs. Solitary mastocytoma spontaneously improves by adolescence in most patients, and there is no transition into SM.^{26,36}

Determining the prognosis for DCM is somewhat difficult since severe, life-threatening MC mediator-linked symptoms may occur even in infancy. Additionally, there is a low propensity for complete improvement of cutaneous lesions, and it is challenging to predict the likelihood of SM development due to the rarity of DCM.²⁹ In DCM, serum tryptase concentrations are typically high, while there is no bone marrow involvement or SM development. Nonetheless, the prognosis is promising in these patients as well, with a widespread improvement of dermal lesions and a reduction in serum tryptase by adolescence. Spontaneous decrease in cutaneous lesions was observed in five out of 12 cases with DCM.³⁸ Only a small percentage of

DCM, particularly familial types, progress into SM due to c-KIT germline mutations. Persistently increased tryptase levels, along with hepatomegaly or splenomegaly, can be markers of this progression in these patients.²⁶

Are There Any Predictive Factors for Spontaneous Regression?

In 1963, Caplan demonstrated that spontaneous regression occurs in most pediatric mastocytosis patients, and no prognostic factors have been identified.³⁹ In a study with 32 cases, it was shown that certain medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), beta-lactams, nifedipine, and levothyroxine, and/or chronic tobacco exposure during pregnancy, negatively affected the spontaneous resolution of the disorder during childhood.²¹ Unexpectedly, it was found that patients who achieved complete improvement of the disorder had an allergic disease, generally asthma or atopic dermatitis, before or after the diagnosis of CM.¹³ These atopic patients achieved complete improvement, possibly because they were given medications to treat their dysreactive conditions, which might have benefited CM.

Monitoring for Systemic Involvement

All cases should be assessed for systemic disease, especially in the presence of other risk factors, including the monomorphic type of CM, persistent cutaneous lesions after puberty, late onset of cutaneous lesions appearing after two years of age, clinical examination findings such as lymphadenopathy or hepatosplenomegaly, and abnormal laboratory results such as anemia, leukopenia, leukocytosis, and the presence of circulating and/or immature MCs in the bone marrow.¹⁶

Differential Diagnosis of CM in Childhood

The differential diagnosis includes several cutaneous and/or systemic pathologies, such as atopic dermatitis, bullous impetigo, urticaria, angioedema, juvenile xanthogranuloma, toxic shock syndrome, drug-related eruptions, post-inflammatory hyperpigmentation, pigmented nevus, arthropod stings, autoimmune bullous diseases, leukemia, and hemophagocytic lymphohistiocytosis in infancy.^{16,25,34}

Associated Disorders/Syndromes of CM in Childhood

One of the associated syndromes of CM is Nager syndrome, which involves multiple congenital malformations, including short stature, microcephaly, dysmorphic facies, conductive hearing loss, skeletal deformities, and CM.^{29,40}

Some associated disorders of CM were reported in a study involving 28 children with CM, showing a relation with a simultaneous diagnosis of autism spectrum disorder, with up to a ten-fold increased prevalence, and pervasive neurodevelopmental disorder when compared to the general population.⁴¹

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