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Asfandyar attended medical school at the University of Ottawa graduating in 2017. He then completed his dermatology residency at the University of Toronto in 2022. During his residency, he also completed the Master of Science in Community Health (Health Practitioner Teacher Education) at the University of Toronto. He was awarded the Women's College Hospital F.M. Hill Resident Mentorship Award, PARO Trust Fund Resident Teacher Award for the University of Toronto, and the Canadian Dermatology Association Resident Teacher Award in his final year of residency. His clinical and research interests include medical dermatology, therapeutics, wound care, immunobullous disorders and cutaneous lymphomas. He has published numerous peer-reviewed manuscripts and has a mixed academic-community practice, working at Sunnybrook Health Sciences Centre and medical dermatology clinics in the GTA.

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MANAGEMENT OF CUTANEOUS MASTOCYTOSIS

Overview

The mastocytoses are a group of mast cell proliferation disorders that can result in both cutaneous and systemic symptoms.[1] Mastocytosis can initiate at birth or may appear at any point thereafter, even in late adulthood. Mastocytosis with a childhood onset is described as beginning prior to puberty. Most frequently, adult-onset mastocytosis appears in the third or fourth decade of life.[1] Mastocytosis affects individuals of all racial and gender identities. The majority of patients with mastocytosis have no family history of the condition; however, familial cases have been reported in the literature.[2]

The World Health Organization (WHO) has classified mastocytosis into a number of categories: 1) Cutaneous mastocytosis (CM); 2) Indolent systemic mastocytosis (ISM); 3) Systemic mastocytosis with a nonmast-cell clonal hematologic disorder (SM-AHNMD); 4) Aggressive systemic mastocytosis (ASM); 5) Mast cell leukaemia (MCL); 6) Mast cell sarcoma; and 7) Extracutaneous mastocytoma (**Table 1**).[3] The most frequent site of organ involvement in individuals with mastocytosis is the skin and this will be the focus of this article.[2]

Pathogenesis

Although the precise etiology of this group of disorders is not entirely understood, it is believed to be caused by an activation mutation in the gene that codes the stem cell factor (KIT) receptor on the surface of mast cells.[4] Mast cell tumours develop in

WHO CLASSIFICATION OF MASTOCYTOSIS	
Variants	**Subvariants**
Cutaneous mastocytosis (CM)	Urticaria pigmentosa (maculopapular), diffuse, mastocytoma
Indolent systemic mastocytosis (ISM)	Smoldering systemic mastocytosis (SSM), isolated bone marrow mastocytosis
Systemic mastocytosis with associated clonal hematological non-mast cell-lineage disease (SM-AHNMD)	Associated with myeloproliferative disorder, CMML, myelodysplastic disorder, AML, non-Hodgkin lymphoma, HES†
Aggressive systemic mastocytosis (ASM)	Lymphadenopathic with eosinophilia‡
Mast cell leukemia (MCL)	Aleukemic
Mast cell sarcoma (e.g., larynx, colon, brain)	
Extracutaneous mastocytoma (e.g., lung)	

Table 1. *WHO classification of mastocytosis.*[2,3]
†HES: Hypereosinophlic syndrome
‡ A rare form of systemic mastocytosis affecting the lymph nodes with eosinophilia

AGE OF ONSET	
Childhood	**Adulthood**
1. Urticaria pigmentosa (most common)	1. Urticaria pigmentosa (red to tan macules and papules)
2. Mastocytoma (common)	2. Telangiectasia macularis eruptiva perstans (TMEP)
3. Diffuse cutaneous mastocytosis (rare)	3. Nodular mastocytosis (rare)
	4. No skin manifestations (systemic involvement more likely)

Table 2. *Childhood and adult mastocytosis clinical variants.*[2,5]

the skin as a result of these mutations, leading to activation and replication of mast cells.

Clinical Presentation

Children and adults are generally asymptomatic, unless there is extracutaneous involvement. When symptoms do manifest, they are brought on by the actions of mediators generated by mast cells, including histamine, eicosanoids and cytokines.[5] These symptoms and findings can include pruritus, flushing, diarrhea, abdominal pain, palpitations, light headedness, and syncope. Pulmonary symptoms typically are absent in mastocytosis. Extracutaneous involvement is frequently indicated by complaints of fever, night sweats, malaise, weight loss, bone pain, epigastric pain, and cognitive disorganization.[5]

Exercise, heat or local irritation to skin lesions can aggravate the symptoms of mastocytosis. Substances that have been associated with triggering mastocytosis symptoms include alcohol, opioids, salicylates, and other nonsteroidal anti-inflammatory drugs (NSAIDs), as well as polymyxin B, and anticholinergic drugs.[6] Additional possible triggers are anaphylaxis following stings from the Hymenoptera species; in light of this, patients should have access to an epinephrine autoinjector at all times.

The clinical spectrum of mastocytosis can be classified by age of onset (**Table 2**).[2,5,7]

Three prominent clinical manifestations of childhood-onset mastocytosis, which almost always affects the skin, are: 1) Solitary or few, referred to as "mastocytomas," accounts for 15%-50% of cases; 2) Multiple lesions (<10 to >100), referred to as "urticaria pigmentosa" or "maculopapular mastocytosis," accounting for 45%-75% of cases; and 3) Diffuse cutaneous involvement, accounting for less than 5%-10% of patients.[8,9,10]

A mastocytoma manifests as a plaque or nodule that ranges in colour from tan to yellow-tan to brown, may only be marginally raised, and typically has a leathery texture. These lesions have a distal predilection and may be congenital or appear during infancy. There are two major variants that have been described in the literature: small, monomorphic tan to brown macules, or large, polymorphic yellow-tan to brown plaques or nodules. Urticaria pigmentosa may present as a combination of these morphologies, with variable numbers and sizes of macules and papulonodules.[11] Diffuse cutaneous mastocytosis manifests as leathery, thicker skin with varied hyperpigmentation in a broad distribution. Frequently, systemic involvement is absent and spontaneous remission usually takes place.[2]

In adult-onset mastocytosis, the most common lesions are small (<1 cm), monomorphic, reddish-brown macules and papules (urticaria pigmentosa); in patients with skin type I, they may also be pink to red in hue. The trunk and proximal extremities are the most common locations for these lesions; the face, distal extremities, palms and soles typically are spared. Although individual lesions may disappear, typically their overall number increases over time. Variable hyperpigmentation and small telangiectasias are visible under close inspection. Telangiectasia macularis eruptiva perstans (TMEP), a rare type of adult cutaneous mastocytosis, is characterized by macules and patches comprised of telangiectasias without extensive hyperpigmentation. Mastocytomas in adulthood are uncommon.

Initial Evaluation of a Patient with Cutaneous Mastocytosis

When evaluating a patient with cutaneous mastocytosis, it is important to inquire about constitutional symptoms on history. A thorough review of systems should be performed with particular attention to the central nervous system (headache, cognitive disorganization, fatigue); gastrointestinal system (epigastric pain, diarrhea, cramping); cardiovascular system (chest pain, palpitations, dyspnea); and endocrine system (bone pain and history of fractures). Appropriate investigations such as endoscopy or bone scan can be guided by clinical history.[2,3,5]

Physical examination should include assessment for lymphadenopathy and hepatosplenomegaly. Depending on the examination, ultrasound or other imaging modalities may be used to further investigate abnormalities.[2,3,5] The Darier's sign, which appears as an urticaria-like wheal when skin lesions are stroked or rubbed, is diagnostic and results from the release of mast cell mediators. In children, especially those with nodular lesions, Darier's sign is easily seen, and it may be accompanied by systemic symptoms. Darier's sign tends to be more subtle in adult mastocytosis than in childhood mastocytosis.

A skin biopsy should be obtained in all individuals with cutaneous mastocytosis to confirm diagnosis. A complete blood count (CBC), liver function tests (LFTs) and serum tryptase levels should also be done in adult patients to rule out systemic involvement.[2,3,5] Laboratory studies usually are not necessary in children, particularly if they present with solitary mastocytoma or are asymptomatic. Abnormal CBC, LFTs and tryptase may require additional investigations such as a bone marrow biopsy and imaging. In the case that an eosinophilia is present, a peripheral blood screen and bone marrow sample should be considered.

Management

There is no known cure for mastocytosis and, in consideration of this, treatment for patients with this condition focuses primarily on symptom relief. Many cutaneous mastocytosis exhibit little, if any, symptoms and therefore require minimal to no treatment. Patients with mastocytosis need to be advised to stay away from potential mast cell degranulating substances and environmental triggers. **Table 3** lists potential triggers that have been directly or indirectly linked to inciting anaphylactoid responses in mastocytosis patients.

Antihistamines are frequently useful in managing the symptoms of mastocytosis.[12] Due to their longer half-lives and more targeted inhibition of the H1 receptor, the second-generation antihistamines cetirizine, loratadine and fexofenadine are often favoured (**Table 3**). For symptom control, the use of numerous medications and greater than usual doses is frequently necessary: for instance, taking cetirizine at night, in addition to fexofenadine in the morning, to treat histamine-related symptoms in adults.[2] In some cases, including in patients with gastric acid hypersecretion, the use of an H2 antagonist (such as cimetidine, ranitidine, famotidine, or nizatidine) may be advantageous.[13]

Mastocytosis-related gastrointestinal signs and (to a lesser extent) cutaneous and CNS symptoms may be relieved by taking oral cromolyn sodium (disodium cromoglycate; 400–800 mg/day), a mast cell stabilizer with poor oral absorption.[14] It has also been reported

TREATMENT LADDER FOR MASTOCYTOSIS	
Avoidance of mast cell degranualtors	Physical: Friction, heat (hot bath), cold (swimming), exercise Diet: Alcohol, hot beverages, spicy foods Medications (partial list): Aspirin, NSAIDS, narcotics (codeine, morphine), anticholinergics, polymyxin B, dextromethorphan, systemic anaesthetics. Local injection of lidocaine is generally safe.
Local therapy for symptom control	Potent topical corticosteroids Topical calcineurin inhibitors Intralesional corticosteroids
Systemic therapy for symptom control	Oral antihistamines Oral cromolyn sodium Omalizumab Light therapy (PUVA or nbUVB) Oral corticosteroids Pre-measured EpiPen
Systemic therapy for aggressive/severe mastocytosis (not discussed in this article)	Imatinib mesylate Interferon alpha Cladribine

Table 3. *Treatment ladder for mastocytosis.*[2,5]

in the literature that topical cromolyn may be used to treat cutaneous mastocytosis. Omalizumab, a humanized murine monoclonal antibody to IgE that is authorized for the treatment of chronic urticaria and asthma, has also been shown to be effective for symptomatic adult-onset mastocytosis that is resistant to antihistamine therapy.[15]

In patients with mastocytosis, psoralen with UVA (PUVA) or narrowband ultraviolet B therapy administered up to four times per week may help manage pruritus and cutaneous wheezing.[16] While phototherapy can lower the histamine content of cutaneous mast cells, it is unable to completely eliminate mast cell infiltrates.

Strong topical corticosteroids, particularly when used under occlusion for six weeks or longer, may stop cutaneous whealing and pruritus, as well as reduce the number of lesional skin mast cells; however, they can also cause skin atrophy.[2,17] Triamcinolone acetonide intralesional injections have also been effective in removing mast cell infiltrates from the skin of patients with mastocytosis.[18] Additionally, according to case reports, topical calcineurin inhibitor treatment improves cutaneous mastocytomas. Prednisone alone or in combination with cyclosporine has been reported to relieve gastrointestinal and cutaneous symptoms in patients with systemic mastocytosis.[19]

For emergency use, a premeasured epinephrine (adrenaline) preparation (such as an EpiPen® [Pfizer Canada, Kirkland, Quebec] or Auvi-Q® [Kaleo, Richmond, Virginia]) should be given to those individuals with severe mastocytosis who frequently have life-threatening episodes of hypotension following mast cell mediator release.[20] Within hours of the original occurrence, these patients may occasionally have subsequent, comparable episodes; prednisone 20-40 mg/day for 2-4 days may suppress these recurring reactions.

Conclusion

Mastocytosis may result in both cutaneous and systemic symptoms. It is believed to be caused by an activation mutation in the gene that codes the stem cell factor (KIT) receptor on the surface of mast cells. Although there is no cure for mastocytosis, symptom relief can be achieved through the use of a variety of therapeutic agents.

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Financial Disclosures:
None

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INDICATION AND CLINICAL USE:

DUOBRII is indicated for improving the signs and symptoms of plaque psoriasis in adult patients with moderate to severe plaque psoriasis.

DUOBRII is not indicated for patients under the age of 18 years.

Clinical trials with DUOBRII did not include sufficient patients aged 65 and older to establish efficacy and safety in geriatric patients.

CONTRAINDICATIONS:

- Hypersensitivity to the drug, any medicinal or non-medicinal ingredient in the formulation, any component of the container, or other corticosteroids or retinoic compounds.
- Viral lesions of the skin, bacterial or fungal skin infections, parasitic infections, skin manifestations relating to tuberculosis or syphilis, or eruptions following vaccinations.
- Seborrheic dermatitis.
- Women who are pregnant or may become pregnant.

RELEVANT WARNINGS AND PRECAUTIONS:

- Patients with skin diseases with impaired circulation
- Patients with chronic leg ulcers
- HPA axis suppression
- Patients with hepatic impairment
- Patients with impaired immune system function
- Patients with concomitant skin infection
- Patients with renal impairment
- Allergic contact dermatitis
- Patients with glaucoma
- Striae, telangiectasias, folliculitis, or skin atrophy
- Conditions where the skin barrier may be impaired
- Wind or cold weather
- Exposure to excessive sunlight or sunlamps, or to photosensitizing drugs
- Breastfeeding women
- DUOBRII should be used with caution as topical corticosteroid use may lead to rebound relapses, development of tolerance, risk of generalized pustular psoriasis and development of local or systemic toxicity
- Conditions that augment systemic absorption

FOR MORE INFORMATION:

Please see the Product Monograph at https://health-products.canada.ca/dpd-bdpp/index-eng.jsp for important information on adverse reactions, drug interactions, and dosing not discussed in this piece. The Product Monograph is also available by calling 1-800-361-4261.

† Based on a prospective, multicentre, randomized, double-blind, phase III clinical trial, comparing DUOBRII lotion to the vehicle lotion, in 215 patients 18 years and older with moderate to severe plaque psoriasis.

REFERENCE:

1. Gold LS, Lebwohl MG, Sugarman JL, et al. Safety and efficacy of a fixed combination of halobetasol and tazarotene in the treatment of moderate-to-severe plaque psoriasis: Results of 2 phase 3 randomized controlled trials. *Journal of the American Academy of Dermatology.* 2018;79(2):287–93.

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