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Review

Cutaneous Mastocytosis

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Abstract

Background: Mastocytosis is a heterogeneous group of rare diseases characterized by the proliferation and accumulation of mast cells in body tissues. It usually presents in the skin, but may affect other tissues, especially the bone marrow, liver, spleen, and gastrointestinal tract. Cutaneous mastocytosis may be associated with both local and systemic symptoms, including flushing, blistering, pruritus, shortness of breath, asthma exacerbation, hypotension, and gastrointestinal upset, including acid reflux, peptic ulcer, or diarrhea. Symptomatic treatment is used in cutaneous mastocytosis. The majority of pediatric patients experience spontaneous remission of mastocytosis. This article presents a current overview for a better understanding of the symptoms associated with mastocytosis, to describe recent advances in its pathophysiology and treatment.

Mastocytosis is a haematopoietic disorder which is usually seen sporadically and characterised by increased number and the accumulation of mast cells in one or more organs [**1**]. Despite the most common location is the skin, it may also occur in the liver, spleen, bone marrow, lymph nodes, lungs and gastrointestinal tract [**2, 3**]. It can be divided into cutaneous mastocytosis and systemic mastocytosis [**4, 5, 6, 7**]. Cutaneous mastocytosis usually affects the patients in early childhood and the disease often regresses spontaneously [**1, 8**]. However systemic mastocytosis frequently occurs in adult patients and tends to resist permanently [**9**].

Bone marrow-derived mast cells differentiate and maturate in peripheral tissues [**10**]. Effects of stem cell factor (known as mast cell growth factor or KIT ligand) on the mast cells and mast cell progenitors occur as a result of interaction through KIT receptor [**10, 11**]. KIT protein is a receptor which is encoded by c-kit proto-oncogene and the structure of the tyrosine kinase for stem cell factor [**10, 12**]. Activating KIT point mutations at codon 816 leads to excessive improvement of mast cells and mast cell progenitors [**10, 13, 14**].

Some mediators such as histamine, tryptase, TNF-α, leukotriens, prostaglandins, platelet activating factor (PAF), heparin, IL-8 are excreted from mast cells and thus some local and systemic symptoms such as flushing, bullae, pruritus, dyspnea, exacerbation of asthma, low blood pressure, gastroesophageal reflux, peptic ulcer or diarrheae may occur. The most important mediator causing all of these symptoms is histamine [**6, 8, 10, 11, 14, 15, 16, 17, 18**].

The incidence is not exactly known but 5 to 10 new cases per million have been estimated on a yearly basis [**14**].

Four distinct clinical variants of cutaneous mastocytosis are published by WHO in 2001:

1- Urticaria pigmentosa

Table 1. Factors Available Aggrevating the Urticaria Pigmentosa

Drugs	
	Aspirin
	NSAID
	Ethyl alcohol
	Amphotericin B
	D- tubocurarine
	Scopolamine
	Polymyxin B
	Quinine
	Reserpine
	Thiamine
	Procaine
Physical stimulus	
	Excessive exercise
	Sun light
	Compression
	Friction
	Extreme hot/cold
Emotional stress	
Insect bites	
Radiographic contrast agents	
General anesthesia	

2- Isolated mastocytoma (solitary mastocytoma)

3- Diffuse cutaneous mastocytosis

4- Telangiectasia macularis eruptiva perstans (TMEP) [**14**].

In 2008, in the updated WHO classification in principle of classification of the subtypes of mastocytosis was retained, but disease group was assigned to the myeloproliferative neoplasias. Here, cutaneous mastocytosis are divided into three different main subtypes, but telangiectasia macularis eruptiva perstans (TMEP) is classified as a special form of maculopapular cutaneous mastocytosis.

1- Maculopapular cutaneous mastocytosis (urticaria pigmentosa, UP)

a. Special form: plaque form

b. Special form: nodular form

c. Special form: telangiectasia macularis eruptiva perstans (TMEP)

2- Diffuse cutaneous mastocytosis

3- Solitary mastocytoma [**14**].

Urticaria Pigmentosa

Urticaria pigmentosa, also known as maculopapular mastocytosis, was first described by *Nettelship* and *Tay* in 1869 [**19, 20**]. This form of cutaneous mastocytosis is the most common form (70-90%), whose incidence is 1/1000-8000. It is seen in both sexes with equal frequency [**6, 13, 20, 21**]. It occurs more often in infants and children when comparing to adults. Clinical findings appear usually within the first two years of life [**20**].

The disease clinically appears with oval or round hyperpigmented macules, papules or patches coloured brown-red-yellow and 2-4 mm in diameter (**Figure 1, 2**) [**6, 20, 22**]. Blister formation can be seen especially in infants. These lesions can be swollen by manipulation (e.g rubbing) or spontaneously. This reaction is known as *Darier* sign and occurs in 50% of patients [**8, 23**]. Lesions are larger in adults than infants and children [**14**]. The most predilection sites are chest and dorsal areas on the body, while the palms, soles and face are not usually affected [**8, 24**]. The most common systemic or local symptom and finding is flushing (17-36%) [**6**]. The other systemic symptoms includes diarrhea, vomiting, tachycardia, headache, weight loss and respiratory system symptoms [**25, 26, 27**].

The histopathological features are as follows:

1. Tryptase positive, spindle-shaped mast cell infiltration on the skin.

2. A large number of mast cells localized around vessels within the skin.

3. Increased melanin pigmentation in the basal cell layer.

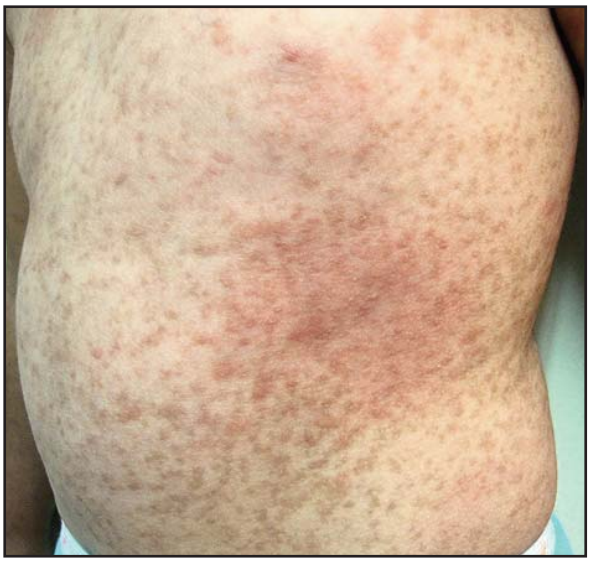

Figure 1. Oval or round hyperpigmented macules, and papules located on the trunk of a child.

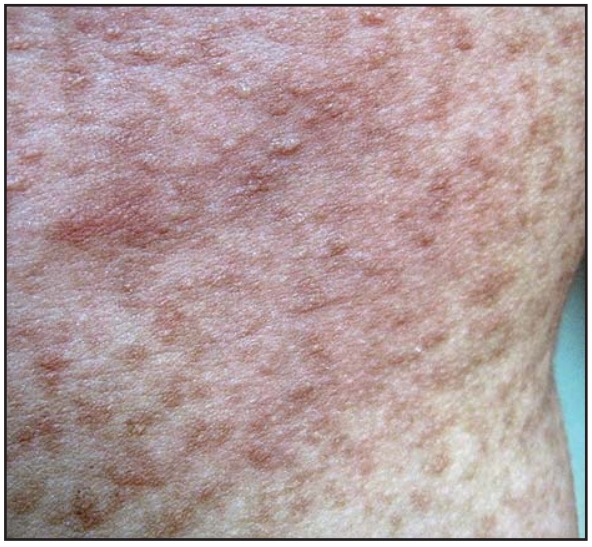

Figure 2. Closer view of the lesions

4. Mast cells stained with Haematoxylin-Eosin, Giemsa, Toluidin Blue and/or Tryptase,

and also Kit (CD117) are positive immunohistochemically [**6, 14, 26, 28**].

When a biopsy is planned in a patient with suspicious cutaneous mastocytosis, the use of adrenaline containing local anesthetics should be avoided due to their secretory effects on granules within mast cells. Injections should be done over the surface or periphery of the lesions [**28, 29**].

From all patients diagnosed as urticaria pigmentosa; complete blood count, routine biochemistry tests, liver function tests and basal serum tryptase levels must be done. If the patient is an infant or a child and, has an abnormal blood count, enlarged liver, spleen or lymph nodes and elevated serum tryptase levels (>20 ng/ml), all necessary tests such as abdominal ultrasound and CT, gastrointestinal system endoscopy, bone radiographs, scans and, even bone marrow biopsy should be done exactly [**24, 30, 31, 32**]. However, if the patient is an adult diagnosed as urticaria pigmentosa, bone marrow examination must be done absolutely [**24, 33**]. Medical history, clinical findings, *Darier* sign and histopathological examination are all necessary for the correct diagnosis [**14, 20**].

The management of urticaria pigmentosa is divided into five categories:

1- Patient education; if the patient is a child, parent education.

2- Avoidance of the factors that trigger the release of mediators.

3- Treatment of acute mast cell mediator release.

4- Treatment of chronic mast cell mediator release.

5- Treatment of organ infiltration [**14**].

Many of the factors that may cause exacerbation of the disease are described in **Table 1** [**6, 14, 17**].

Antihistamines, such as H_1 or H_2 antihistamines or combination of both, are the first step medications among systemic treatment options. H_1 antihistamines prevent itching, flushing and urticaria while H_2 antihistamines control gastric acidity. Doxepin is an other alternative drug which inhibits H_1 and H_2 receptors. The mast cell stabilisers like sodium cromolyn and ketotifen are also used in patients with urticaria pigmentosa. Topical corticosteroids can be used and also intralesional triamcinolone acetonide injection is available for localized lesions [8, 26]. Systemic PUVA therapy is preferable alternative therapy modality for patients who do not respond to standart treatments. Patients with chronic and widespread involvement should keep adrenaline and wristband [**26**].

Isolated Mastocytoma

Isolated mastocytoma, also known as nodular mastocytosis, is the second most common clinical variant of cutaneous mastocytosis after urticaria pigmantosa [**21, 34**]. The true incidence is unknown but is estimated to be between 10-15% [**8, 35**]. It often occurs at birth or within the first few months but may be rarely seen later [**21, 36, 37**]. It usually presents 1cm to 4cm in diameter, round or oval shaped, red to brown or yellow-pinkish color, smooth or view of orange peel, infiltrated single macule, nodule or plaque-like lesion. It generally appears on the trunk or extremities but may be seen anywhere on the skin [**11, 21, 35, 38**].

The pathogenesis is unknown but is suspected of being reactive rather than neoplastic. There are reports declaring that it could occur as post-traumatic and post-vaccination case (e.g. Hepatitis B vaccination). There is no kit mutation [**39**].

Histopathological features include increased number of mast cells with normal cytological appearance, increased melanin production, therefore hyperpigmentation, and increased dermal fibroblasts. These mast cells are stained by Haematoxylin-Eosin and Toluidin blue [**39**].

Clinical symptoms range from asymptomatic disease to severe itching. Patients may complain of flushing which presents suddenly on the face and upper trunk and improves spontaneously within 10 to 30 minutes [**11**]. However, urticaria, blistering, respiratory distress, low blood pressure and gastrointestinal symptoms may also occur in patients with isolated mastocytoma [**8, 35, 39**]. Dissemination of the disease is rare, but if it happens, it occurs within 2 to 3 months from the onset of the lesion. *Darier* sign is positive [**11**].

Differential diagnosis includes various conditions such as pigmented nevi, xanthoma, juvenile xanthogranuloma, neurofibroma, hemangioma, granuloma annulare [**11, 35, 37, 40**].

Isolated mastocytoma has a benign clinical course and heals spontaneously in childhood without leaving any scarring. Dissemination of the disease is a rare condition theoretically but there is no case report in the literature [**11, 37**].

Treatment options are as follows:

I. Symptomatic therapy

a. Antihistamines

b. Ketotifen

c. Aspirin

II. PUVA

III. Topical steroids

IV. Intralesional steroid injections [**35, 37**].

Diffuse Cutaneous Mastocytosis

This rare form is seen 1.74% ratio among all cutaneous mastocytosis [**15**]. There is mast cell infiltration in all over the skin. The disease begins within the first three years of life, improves spontaneously between the ages of 15 months and 5 years [**4**]. There is a red-brown coloured appearance and orange peel view, especially on flexural locations of the body [**9, 19**]. Systemic symptoms are more severe than other types of cutaneous mastocytosis. Generalized erythroderma and prolonged bleeding may be associated with the disease. These severe symtoms gradually decrease by time, but the patients should be closely monitored [**8**]. Severe dermographism is a distinctive feature for this form [**9**]. Linear or grouped-shaped bullous lesions are most commonly seen in diffuse cutaneous mastocytosis and often occur over the trunk, scalp and extremities. It may be associated with indolent systemic mastocytosis. The presence of bullae is a sign of poor prognosis [**4, 15**]. Histopathological features are multifocal mast cell clusters in the dermis, especially perivascular distribution is determined. The diagnosis is made by both clinically and histopathologically [**9**].

Treatment options are as follows:

I. Avoidance of the triggering factors which cause mediator release

II. H_1/H_2 antihistamines

III. Chromolyn sodium

IV. Ketotifen

V. PUVA

VI. If there are bullous lesions, avoidance of secondary infections [**4, 41**].

Telangiectasia Macularis Eruptiva Perstans

Telangiectasia macularis eruptiva perstans was first described by *Moynahan* in 1949 [**42**]. This condition is the rarest form (<1%), even some autors think that it is a variant of urticaria pigmentosa [**43, 44**]. This form is usually seen in adults, it is rare in child. Clinical features are round or oval shaped, 2-6mm in diameter, reticular telangiectatic macules and hyperpigmented plaques [**24, 42, 43**]. It usually occurs over the trunk and extremities and rarely over the face [42]. The lesions are located generally on the skin but systemic involvement is possible, as well [**43, 44**]. *Darier* sign is usually negative. The diagnosis should be confirmed by biopsy. Spindle-shaped mast cells are determined in the upper dermis and around the capillary veins. CD68 tryptase immunperoxidase positivity is helpful in the diagnosis [**42, 44**].

Treatment options are as follows:

I. Avoidance of the factors that trigger the release of mediators

II. H1/H2 antihistamines

III. Chromolyn sodium

IV. Ketotifen

V. PUVA

VI. Doxepin

VII. Topical/intralesional/systemic corticosteroid

VIII. Topical pimecrolimus

IX. Systemic interferon

X. 585nm laser treatment

XI. Electron beam therapy [**42, 43, 44, 45**].

Telangiectasia macularis eruptiva perstans may be associated with some disorders such as systemic mastocytosis, multiple myeloma, myelofibrosis, polycythemia vera, thrombocythemia, renal cell cancer and malignant melanoma [**43**].

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