

# A Case of Cutaneous Indolent Mastocytosis

Dr. W. K. Tang

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## CASE SUMMARY

### History

HT was a five-year-old girl who enjoyed good past health and an unremarkable birth history. Her mother noticed that there was a brownish plaque on her left inner thigh. The lesion slowly increased in size over the past few years. The child experienced episodic redness involving the face, trunk and limbs, lasting for 1-2 hours. The last episode occurred two months ago. There was no known precipitating factor for the attack. She also experienced recurrent urticaria that occurred about once a week, from the age of one to three. This was precipitated by hot weather. There was no associated

shortness of breath or any other systemic upset. There was no family history of similar problem.

### Physical examination

There was a well-defined 2.5x1.2 cm<sup>2</sup> brownish-red plaque over the left inner thigh (Figure 1). There was no demographism and no Darier's sign associated with the lesion. No organomegaly or lymphadenopathy was found.

### Differential diagnosis

The differential diagnoses included mastocytosis, juvenile xanthogranuloma and lymphocytoma cutis.

### Investigations and diagnosis

Skin biopsy showed large amount of mast cells in the dermis. This was consistent with a diagnosis of cutaneous indolent mastocytosis in a five-year-old girl with no systemic symptoms or signs.



Figure 1: A well-defined brownish red plaque over the left inner thigh

## REVIEW OF MASTOCYTOSIS

### Definition

Mastocytosis is a rare disorder characterized by abnormal growth and accumulation of mast cells in skin, visceral organs such as bone marrow, gastrointestinal tract, liver, spleen and lymph nodes.

### Pathogenesis

The etiology is unknown. But evidence shows that it is related to deregulation or abnormalities of the *c-kit* receptor (mutation of codon 816 gene) or excessive production of its ligand. There is also increased production of mast-cell growth factor.

There is a debate on whether the disease is a reactive or neoplastic disorder. Traditionally it is regarded as a reactive process especially with respect to the benign course in pediatric group. But there is evidence suggesting its neoplastic nature.<sup>1</sup> Firstly, by using the human androgen receptor gene (HUMARA),<sup>2</sup> mast cells in mastocytosis were shown to derived from a clonal proliferation of pluripotent haemopoietic stem cell. Secondly, there is association with myeloproliferative and myelodysplastic disorders; in fact, some patients with mastocytosis could progress into acute leukaemia.

### Classification (Metcalf in 1991)

Mastocytosis is classified according to the clinical courses. There are four main categories.

#### 1. Indolent

Patients in this category may have only cutaneous involvement or with systemic mast cells infiltration. Cutaneous lesions such as solitary mastocytoma, urticaria pigmentosa, bullous mastocytosis and diffuse erythrodermic mastocytosis are commonly found in children, while telangiectasia macularis eruptiva perstans (TMEP) is mainly seen in adult. When urticaria pigmentosa occurs in adult, it tends to be more persistent and have more systemic involvement.

The prognosis of this group of disease is usually very good. For urticaria pigmentosa in children, 50% will disappear before puberty and the others usually show significant improvement. Even for the diffuse

erythrodermic mastocytosis, spontaneous resolution is the rule, although there is a risk of persistence and systemic involvement extending into adulthood.

#### 2. Mastocytosis with haematological disorders

Dysmyelopoietic disorders, malignant lymphoma, chronic neutropenia could be found in this group of patients. The prognosis depends on the underlying haematological disorder.

#### 3. Lymphadenopathy mastocytosis with eosinophilia (Aggressive, with or without skin involvement)

The disease usually progresses rapidly in this group of patients. Mast-cell proliferation occurs in the bone marrow, then the gastrointestinal tract, and the other organs. The prognosis is much guarded. It should be noted that 26-58% of patients with systemic mastocytosis have peripheral lymphadenopathy, and they are not classified under this category of mastocytosis.<sup>1</sup>

#### 4. Mastocytic leukemia

It is the rarest form of mastocytosis, which occurs most commonly in adult. Patients have grave prognosis and usually die several months after the initial diagnosis.

### Clinical manifestations

Clinical symptoms occur as a result of direct organ infiltration and chemical mediators released from the mast cells. The latter is subdivided into three groups:

- A. Preformed secretory granule-associated mediators
  - Histamine, heparin, protease
- B. Lipid mediators
  - Leukotriene, prostaglandin D<sub>2</sub>, platelet activating factor
- C. Cytokines
  - Tumor necrosis factor, interleukins

The symptoms ranged from itchy skin lesions, flushing to anaphylaxis and even death (Table 1).

### Investigations and diagnosis

Darier's sign is not pathognomonic of urticaria pigmentosa, and may rarely occur with juvenile xanthogranuloma, histiocytosis X, leukaemia cutis, and cutaneous T- and B-cell lymphoma.

**Table 1. Clinical manifestations of mastocytosis**

Cutaneous manifestations	
Pruritus, urticaria, urticaria pigmentosa, diffuse infiltrative papules and plaques, dermographism	
Mast-cell mediator-related	
Common	<ul style="list-style-type: none"> <li>• Flushing</li> <li>• Intermittent gastrointestinal complaints, such as diarrhoea, abdominal pain, nausea and vomiting. Palpitations/tachycardia</li> </ul>
Uncommon	<ul style="list-style-type: none"> <li>• Altered cognitive functions</li> <li>• Hypotension</li> <li>• Respiratory symptoms</li> <li>• Peptic ulcer, gastritis, duodenitis, malabsorption</li> <li>• Syncope, anaphylaxis</li> </ul>
Constitutional symptoms (may indicate systemic involvement)	
Weakness, fatigue, malaise, fever, weight loss	
Organ infiltration (in systemic mastocytosis)	
<ul style="list-style-type: none"> <li>• Hepatomegaly, splenomegaly</li> <li>• Skeletal lesions, arthralgia</li> <li>• Bone-marrow infiltration</li> <li>• Lymphadenopathy</li> </ul>	

In general, the diagnosis of mastocytosis can be made clinically and further supported by skin biopsy. The numbers of mast cell are much higher (15-20 folds) in lesional skin of patients with systemic mastocytosis. Whereas there are only scanty mast cell in the lesional skin in patient with TMEP. However, the absolute numbers of mast cell in the skin are not helpful in differentiating different categories of mastocytosis.

When systemic involvement is suspected, either one of the following should be obtained:<sup>3</sup>

- i. Histological evidence of mast-cell hyperplasia in at least one tissue other than skin
- ii. Increased histamine or N-methylhistamine in the urine. Routine 24-hour urine collection to measure histamine is a convenient first test. But concurrent genitourinary tract bacteria can lead to artificially high concentration of histamine. Since the histamine concentration is briefly raised after an attack. A more

sensitive method is to collect a separate serial collection of urine after an episode, which showed an increase followed by a decrease in urinary histamine excretion immediately after an attack.

- iii. Unexplained hepatomegaly  
Since mastocytosis in pediatric group usually has an excellent prognosis, conservative approach is recommended. On the contrary, for older patients aggressive investigations are justifiable for there is higher chance of having systemic involvement or even malignancies (Table 2).

**Management<sup>4</sup>**

Treatment should be aimed at relieving symptoms and does not alter the course of the diseases. Patients and their relatives should be taught the signs of anaphylaxis and methods of emergency treatment and support. Patients should also be taught to avoid physical or biochemical factors, which may trigger the attack such as emotional

**Table 2. Diagnostic tests and investigations for mastocytosis<sup>6,7</sup>**

Children		Adult OR Suspected systemic involvement	Elderly
Age <5	Age >5		
		<ul style="list-style-type: none"> <li>• Skin biopsy</li> </ul>	
	<ul style="list-style-type: none"> <li>• Complete blood count and differential</li> <li>• 24-hour urine for methyl-histamine</li> <li>• Bone scan/skeletal survey</li> <li>• Upper GI tract endoscopy</li> </ul>		<ul style="list-style-type: none"> <li>• Bone marrow biopsy</li> <li>• CT scan</li> </ul>

stress, extreme temperature, sun light exposures, lobster, crayfish, alcohol, insect bite and medication (for example aspirin, narcotics, amphotericin B, scopolamine etc).

For solitary mastocytoma with its clinically benign nature, patient can actually be managed conservatively. Topical or intralesional steroid, surgical excision and cryotherapy can be used to induce remission.

When systemic and/or generalized cutaneous involvement occurs, H-1 receptor blocker with or without H-2 receptor blockers is used to decrease the histamine effects. Sodium cromoglycate is found to be useful in reducing diarrhoea and abdominal pain in patients who are unresponsive to other treatments. Systemic steroids and phototherapy such as PUVA can be tried in resistant cases. Aspirin and other NSAID should generally be avoided, but paradoxically judicious use of them can reduce systemic symptoms by the inhibition of PG-D2 production by mast cells. High doses of aspirin to achieve plasma salicylate concentrations of 1.45-2.17 mmol/L are necessary to achieve this effect. However it is important to combine aspirin with antihistamine.

$\alpha$ -Interferon has anti-secretory and anti-proliferative influence on mast cells. It may control the signs & symptoms of widespread systemic mastocytosis. But since there are only limited case reports mentioned its use so further investigation is required.

### Prognosis

Children with indolent cutaneous disease usually remit by puberty, therefore reassurance of their parent is all that is needed.

Poor prognostic factors have been suggested by Travis et al.<sup>5</sup> as follows:

1. Constitutional symptoms
2. Anaemia
3. Thrombocytopenia
4. Abnormal liver function
5. Lobulated mast-cell nuclei
6. Low percentage of fat cells in the bone marrow
7. Presence of haematological disorder

For older patients with hepatosplenomegaly, lymphadenopathy and severe haematological abnormalities, the presence of mast cell leukaemia is likely and should be looked out for.<sup>8</sup>

### Learning points:

*Mastocytosis is a rare cutaneous disorder. Haematological abnormalities and malignancies should be looked for when it occurs in adult or when there is associated organomegaly.*

### References

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