

Editorial

Mastocytosis: from Nettleship and Darier to Metcalfe and Valent

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In 1869, Nettleship and Tay described a unique cutaneous disease that showed a symmetrical spread with pigmented maculopapular lesions and an urticaria-like response to rubbing or scratching.¹ The disease was termed urticaria pigmentosa (UP) by Sangster in 1878.² Soon after the discovery of the mast cell by Paul Ehrlich in 1879, the lesions were found to contain focal accumulations of mast cells.³ For a long time, it was assumed that such pathological accumulation of mast cells, called mastocytosis (MC), is restricted to skin. However, in 1949, Ellis described a systemic form of mastocytosis with involvement of visceral organs.⁴ In 1905, Darier⁵ wrote an article about UP and its pathognomonic sign and the clinical test was associated with Darier.

Mastocytosis (MC) is a proliferation of mast cells and their subsequent accumulation in one or more organ systems. Mast cell disease can be limited to the skin, which is referred to as cutaneous mastocytosis (CM), or involve extracutaneous tissue, which is called systemic mastocytosis (SM). The diagnosis of cutaneous mastocytosis (CM) is

based on typical clinical and histological skin lesions and absence of criteria of systemic involvement. Most patients with CM are children and present with urticaria pigmentosa. Other less frequent forms of CM are diffuse cutaneous mastocytosis (DCM) and mastocytoma of skin. Systemic mastocytosis (SM) is commonly seen in adults and defined by multifocal histological lesions in the bone marrow (affected almost invariably) or other extracutaneous organs (major criteria) together with cytological and biochemical signs (minor criteria) of systemic disease (SM-criteria). SM is further divided into the following categories: indolent systemic mastocytosis (ISM), SM with an associated clonal hematologic non-mast cell lineage disease (AHNMD), aggressive systemic mastocytosis (ASM), and mast cell leukemia (MCL).⁶

In September, 2000, the World's leading experts in MC met to discuss and present data at the "Year 2000 Working Conference on Mastocytosis," held in Vienna, Austria. Valent *et al.*⁶ presented a uniform classification system for MC at the conference.

Symptoms of MC occur when pharmacologic or physical stimuli cause mast cell degranulation and release of histamine, prostaglandins, leukotrienes and other chemical mediators. These episodic

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Table 1 Classification of mastocytosis by Valent *et al.* [6]

Cutaneous mastocytosis (criteria for systemic mastocytosis not fulfilled)		
Maculopapular cutaneous mastocytosis		
Typical urticaria pigmentosa		
Plaque form		
Nodular		
Telangiectasia	macularis	eruptiva
perstans		
Diffuse cutaneous mastocytosis		
Mastocytoma of the skin		
Indolent systemic mastocytosis		
Systemic mastocytosis with AHNMD		
Aggressive systemic mastocytosis		
Mast cell leukemia		
Mast cell sarcoma		
Extracutaneous mastocytoma		

attacks can be manifested by flushing, urticaria or, in extreme cases, by life-threatening vascular collapse.⁷

Mast cells originate from bone marrow progenitor cells and are distributed throughout the connective tissues. They are concentrated in the skin around the peripheral nerves and adjacent to blood and lymphatic vessels. When activated by IgE or other stimuli, mast cells release preformed mediators of inflammation (**Table 3**). These mediators initiate a leukocyte-cytokine cascade that contributes to the acute and delayed hypersensitivity reactions and the various cutaneous and systemic manifestations of MC.

There has been a progressive evolution in the understanding of the biologic role of mast cells over the last 30 years. Key discoveries include the description of mast cell growth factors, documentation that mast cells are derived from CD 34+ pluripotential stem cells, recognition of the expression of key adhesion molecules on mast cells, description of mast cell apoptosis, discovery

Table 2 Stimuli and substances that can cause degranulation of the mast cells [7]

Emotional stress
Physical stimuli (e.g., heat, cold, friction, exercise, sunlight, sexual intercourse)
Bacterial toxins
Venoms (bee sting)
Biologic polypeptides (e.g., lobster, crayfish, jellyfish, <i>Ascaris</i>)
Polymeric eye drops (containing dextran)
Immunologic stimuli (e.g., IgE)
Complement-derived anaphylotoxins
Drugs
Acetylsalicylic acid (aspirin)
Amphotericin B (Fungizone)
d-Tubocurarine
Dextromethorphan
Ethanol
Gallium (Ganite)
Narcotics (e.g., morphine, meperidine [Demerol], codeine)
Nonsteroidal anti-inflammatory drugs
Polymyxin B (Aerosporin)
Quinine
Radiographic contrast containing iodine
Reserpine
Scopolomine (Transderm Scop)

of the leukotrienes, and the recognition that mast cells produce cytokines.

Metcalfe is well known for his highly cited work in allergic diseases, particularly his work in the role of mast cells in allergic inflammation. In his studies of patients with mast cell disorders, Metcalfe has characterized the spectrum of the diseases associated with mastocytosis, and has developed the currently accepted treatment programs for this disease. His basic laboratory research focuses on the growth and differentiation of mast cells, employing molecular biologic techniques. His work has led to the current appreciation of the spectrum of mast cell phenotypes, the growth factors regulating mast cell

Table 3 Mast cell products and their clinically significant activity

Mast cell product	Clinically significant activity
<i>Preformed secretary granule-associated mediators</i>	
Histamine	Vasodilatation, erythema, edema, pruritus, urticaria, bronchoconstriction, increased gastric acid, intestinal cramping, further degranulation of mast cells, leukocyte activation
Proteoglycans	
Heparin	Osteoporosis, inhibition of localized clotting; rarely, prolonged partial thromboplastin time
Neutral proteases	
Trypsin	Inhibition of coagulation locally, bronchoconstriction, osteoporosis
Chymase	Inhibition of coagulation locally, activation of mast cells, blistering (?)
Cathepsin G and carboxypeptidase	Kinin generation, hepatic fibrosis (?)
Acid hydrolases	Bone lesions, osteoporosis
<i>Lipid mediators</i>	
Leukotrienes	Bronchoconstriction, increased vascular permeability and contractility
Prostaglandin D2	Pruritus, pain, rhinorrhea, hypotension, flushing, osteoporosis

differentiation, and interactions between mast cells and tissue matrix.

Metcalf⁸ classified mastocytosis as indolent disease confined to skin, indolent systemic disease with or without cutaneous involvement, mastocytosis with an associated hematologic disorder, aggressive lymphadenopathic mastocytosis with eosinophilia and mastocytic leukemia.

Although the exact pathogenicity of mastocytosis is still unclear but, recent studies have suggested that activating mutations of *c-kit*, a proto-oncogene encoding for the receptor (*kit*) of stem cell factor, are a possible cause of some forms of mastocytosis. The type III receptor tyrosine kinase (*kit*) is critical to the development and survival of mast cells and melanocytes. A mutation of the receptor causes it to remain in the "on" position. The ligand for *kit* can stimulate mast cell development, proliferation, and mediator release, as well as melanocyte proliferation and pigment production.⁹ The induction of melanocytes explains the hyperpigmentation that is commonly associated with cutaneous mast cell lesions.

Table 4 Metcalfe classification of mastocytosis (Produced with permission from Dr. Dean Metcalfe (NIH, NIAID) for JPAD)

Category IA	Indolent disease confined to skin
Category IB	Indolent systemic disease with or without cutaneous involvement
Category II	Mastocytosis with an associated hematologic disorder
Category III	Aggressive lymphadenopathic mastocytosis with eosinophilia
Category IV	Mastocytic leukemia

Systemic mastocytosis is diagnosed if one major and one minor criterion are met, or three minor criteria are fulfilled.⁶ The major criterion is multifocal dense infiltrates of mast cells (>15 MC aggregating) detected in sections of bone marrow and/or other extracutaneous organ(s) by tryptase-immunohistochemistry or other stains. Minor criteria are:

- In mast cell infiltrates detected in sections of bone marrow or other extracutaneous organs, >25% of mast cells are spindle shaped or, in bone marrow smears, atypical mast cells compose >25% of all mast cells.
- Detection of a *c-kit* point mutation at codon 816 in bone marrow or blood or other extracutaneous organ(s).
- Kit mast cells in bone marrow or blood or other extracutaneous organ(s) co-express CD2 and/or CD25.
- Serum total tryptase concentration >20 ng/ml (in case of an AHNMD, this is not valid).⁶

Despite significant advances in research on mastocytosis, curative treatment is not yet available. Current management is based on avoidance of mediator-releasing triggers and symptomatic treatment.¹⁰

References

1. Nettleship E. Rare forms of urticaria. *Br Med J* 1869; **2**: 323-4.
2. Sangster A. Urticaria pigmentosa. *Lancet* 1878; **I**: 683.
3. Ehrlich P. Beiträge zur Kenntnis der granulierten Bindegewebszellen und der eosinophilen Leukozyten. *Arch Anat Physiol* 1879; **3**: 166-9.
4. Ellis JM. Urticaria pigmentosa. A report of a case with autopsy. *AMA Arch Pathol* 1949; **48**: 426-9.
5. Darier JF. Quelques remarques sur l'urticaire pigmentaire. *Ann Dermatol Syphiligr* 1905; **6**: 339-44.
6. Valent P, Horny HP, Escribano L *et al.* Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res* 2001; **25**: 603-25.
7. Longley J, Duffy TP, Kohn S. The mast cell and mast cell disease. *J Am Acad Dermatol* 1995; **32**: 545-61 [Published erratum in *J Am Acad Dermatol* 1995; **33**:52].
8. Metcalfe DD. Classification and diagnosis of mastocytosis: current status. *J Invest Dermatol* 1991; **96**: 2S-4S.
9. Longley BJ, Tyrrell L, Lu SZ *et al.* Somatic c-kit activating mutations in urticaria pigmentosa and aggressive mastocytosis: establishment of clonality in a human mast cell neoplasm. *Nat Genet* 1996; **12**: 312-4.
10. Hartmann K, Bruns SB, Henz BM. Mastocytosis: review of clinical and experimental aspects. *J Invest Dermatol Symp Proc* 2001; **6**: 143-7.