Mastocytosis and Mast Cell Disorders

**Synonym: systemic mast cell disease (SMCD)**

Mast cells are found in the perivascular spaces of most tissues and contain pro-inflammatory and vasoactive mediators. These mediators are released after IgE receptor cross-linking induced by allergens or other stimuli. Mast cell disorders may involve either of the following:

- Excessive proliferation of mast cells (mastocytosis).
- Normal numbers of cells but abnormal reactivity.

The excess release of mediators can cause clinical features such as pruritus, flushing, nausea, vomiting, diarrhoea, abdominal pain, vascular instability and anaphylaxis. Also, complications may arise when mast cells accumulate in the skin, gastrointestinal tract, bone marrow, liver, spleen, and lymph nodes. The clinical features of systemic mastocytosis are caused by accumulation of clonally derived mast cells in different tissues, including bone marrow, skin, gastrointestinal tract, liver and spleen. Systemic mastocytosis is now classified as a myeloproliferative neoplasm.

**Classification of mast cell disorders**

**Mastocytosis**

The World Health Organization (WHO) classification (simplified here) is:

- Cutaneous mastocytosis - usually children:
  - Urticaria pigmentosa (maculopapular cutaneous mastocytosis) - the most common type.
  - Diffuse cutaneous mastocytosis (very rare).
  - Mastocytoma of skin.

- Systemic mastocytosis:
  - Indolent systemic mastocytosis.
  - Systemic mastocytosis with associated haematological non-mast cell lineage disease (SM-AHNMD).
  - Aggressive systemic mastocytosis.
  - Mast cell leukaemia (very rare).

- Localised mast cell proliferations (very rare):
  - Extracutaneous mastocytoma.
  - Extracutaneous mast cell sarcoma.

Telangiectasia macularis eruptiva perstans (TMEP) is a rare form of cutaneous mastocytosis, in which telangiectases occur together with the rash.

**Mast cell activation syndrome (MCAS)**

- MCAS - synonym: mast cell activation disorder (MCAD) - is characterised by the accumulation of genetically altered mast cells and/or abnormal release of mast cell mediators, affecting functions in potentially every organ system, particularly the skin, the gastrointestinal tract and the cardiovascular and nervous systems.
- Patients experience many of the same symptoms as with mastocytosis. Chronic MCAS can be difficult to diagnose, especially when symptoms are mild or atypical.
- The use of antihistamines and mast cell membrane-stabilising drugs with symptomatic treatment is often effective.

More recently, an attempt has been made to draw up international consensus criteria for the diagnosis of MCAS, as follows:

- Recurrent or chronic symptoms of mast cell activation.
- Laboratory results showing evidence of mast cell activation (e.g., a transient rise in serum tryptase (>15 ng/mL but <20 ng/mL) or urinary N-methyl histamine, or the histamine metabolites prostaglandin D2 and prostaglandin F2-alpha.
- Response of clinical symptoms to anti-mediator therapy.

**Aetiology**

The cause is unknown but is probably multifactorial. A mutation of the oncogene C-KIT D816V is found in many (but not all) cases.

**Epidemiology**
This is a rare and heterogeneous group of disorders, of which urticaria pigmentosa is the most common manifestation. It affects under 1 in 1,000 patients attending dermatology clinics. Estimated incidence is 1 in 150,000.

**Possible triggers for mastocytosis symptoms**

- Physical stimuli - eg, heat, cold, friction, sunlight, fatigue, exercise or fever.
- Emotional stimuli - eg, stress.
- Certain foods - eg, cheese, spices, shellfish, food preservatives, flavourings and colourings, monosodium glutamate.
- Environmental toxins - eg, perfumes, pesticides.
- Insect bites, jelly fish stings, snake bites.
- Infection (bacterial, fungal or viral).
- Drugs - eg, alcohol, anaesthetic agents, dextran, aspirin and non-steroidal anti-inflammatory drugs (NSAIDS), antibiotics, opioids, thiamine, quinine, gallamine, procaine, some radiographic dyes, polymyxin B, scopolamine and tubocurarine.

**Presentation**

**Cutaneous mastocytosis**

**Urticaria pigmentosa**

- The rash comprises light brown, itchy, raised patches - on any part of the body.
- The lesions blister when rubbed (Darier's sign) and become red, swollen and itchy. This confirms the presence of mastocytosis.
- Rarely, anaphylactic reactions can occur after mechanical/thermal stimulation of skin lesions.
- Dermatographism may be found on unaffected skin.
- It usually affects infants from a few months of age. The lesions can persist and gradually increase in number for several months or years.
- Symptoms gradually improve as the child gets older; the condition usually disappears by puberty. The younger the patient and the smaller the number of the lesions, the higher the probability of spontaneous remission. An adult onset increases the risk of systemic involvement and persistence.

**Diffuse cutaneous mastocytosis**

- This usually occurs in the first year of life.
- The rash is very itchy, with generalised yellowish, thickened skin.
- Blisters are large and sometimes haemorrhagic; they occur spontaneously or following mild trauma.
- With more extensive skin involvement, systemic symptoms are more likely. These include flushing, headache, palpitations, abdominal pain, diarrhoea, dyspepsia, wheezing, syncope, hypotensive shock and death.
- Early onset of blisters worsens the prognosis.

**Mastocytoma of skin**

This is a macular, papular or nodular lesion of yellow, brown or reddish colour.

**Systemic mastocytosis**

Patients may present with 'inexplicable' symptoms related to mast cell mediator release, such as vascular instability, anaphylactic shock, flushing, diarrhoea and headache (sometimes without skin lesions). There is a wide range of symptoms and a variety of triggers (see box). The condition may be unmasked by an anaphylactoid response to a stinging insect. Possible symptoms and signs of systemic mastocytosis are:

- **Skin:**
  - Facial flushing (may be pruritic or burning).
  - Urticaria pigmentosa (as above).

- **Gastrointestinal:**
  - Abdominal pain.
  - Diarrhoea or steatorrhoea (due to malabsorption or altered motility).
  - Nausea and vomiting.
  - Hyperacidity, dyspepsia and peptic ulcers.
  - Hepatomegaly and splenomegaly.

- **Cardiovascular:**
  - Syncope, hypotension or anaphylactic shock.
Haematological and bones:
- Anaemia or other cytopenias (if bone marrow involvement).
- Hypersplenism.
- Lymphadenopathy.
- Fractures (if bone marrow involved).
- Rarely, a bleeding disorder due to heparin-like anticoagulant (case report).\[15\]

Respiratory:
- Bronchospasm.
- Nasal congestion and upper pharyngeal symptoms are also reported.\[14, 18\]

Neurological:
- Headaches.
- Peripheral neuropathy.

Localised mastocytosis\[10\]
- Mastocytoma is a benign tumour with uniform growth.
- Mast cell sarcoma is a locally destructive tumour.

Investigations\[1\]
- Skin biopsy (with analysis of C-KIT D816V).
- Blood tests:
  - FBC (anaemia, thrombocytopenia, and leukocytosis), clotting studies, renal function tests and LFTs.
  - Serum tryptase - almost all patients with systemic mastocytosis have serum tryptase >20 ng/mL.\[15\]
- Urinary histamine metabolite levels (eg, 11β-prostaglandinF2α or N-methyl histamine) may be elevated.\[19\]
- If there is suspected systemic involvement (including most adults with suspected mast cell disorders) then complete staging is needed. This includes:
  - CXR (or chest CT scan) for lymphadenopathy.
  - Gastrointestinal investigations - eg, endoscopy and ultrasound of abdomen.
  - Bone density scan and skeletal X-rays.
  - Bone marrow biopsy/aspirate.
- Other tests include:
  - Chromosomal analysis: 20% of patients with systemic mastocytosis have an abnormal karyotype.
  - Molecular testing for KIT D816V mutation is always positive but JAK2 V617F is rarely positive.
  - The mast cell clone is CD-117 positive and CD-2 and/or CD-25. Expression of CD-25 on mast cells is seen in systemic mastocytosis but not in reactive states of mast cell hyperplasia.

Diagnosis
There is a suggested diagnostic protocol. The diagnostic criteria are:\[1\]

- Major criteria:
  - Biopsy finding of multiple dense accumulations of mast cells in bone marrow or in other non-skin tissue.

- Minor criteria:
  - In bone marrow biopsy, more than 25% of the mast cells are spindle-shaped; or in bone marrow smears, more than 25% of the mast cells are atypical mast cells.
  - Detection of a point mutation at codon 816 in the KIT receptor gene. This may be found in bone marrow or blood or other internal organs.
  - Mast cells in bone marrow, blood, or other internal organs are found to have on their surface the KIT receptor plus CD2 and/or CD25.
  - Serum total tryptase level persistently greater than 20 ng/mL. This criterion cannot be used if the patient has a clonal non-mast cell associated haematological disorder.

- The diagnosis of systemic mastocytosis may be made if one major and one minor criterion are present, or if three minor criteria are fulfilled.

Differential diagnosis
- Other pruritic rashes - eg, other forms of urticaria.
- Other causes of flushing:\[20\]
  - Carcinoid syndrome.
  - Phaeochromocytoma.
  - Other causes of anaphylaxis.
  - Rarely, medullary carcinoma of the thyroid, pancreatic cell tumour, renal cancer.
Other causes of abdominal pain, peptic ulceration or liver disease, including:

- Inflammatory bowel disease.
- Irritable bowel syndrome.
- Malabsorption syndromes.
- Zollinger-Ellison syndrome.
- Other types of hepatitis or cirrhosis.
- Other haematological or myeloproliferative disorders.

Management\[^{10}\]

This is concerned mainly with symptom control, as there is currently no cure. Systemic mastocytosis is usually managed by haematologists.

**Acute anaphylaxis**\[^{16}\]

- Those prone to acute severe symptoms should avoid trigger factors where possible, wear a medical emergency identification bracelet or similar and carry written treatment protocols from their specialist.
- Acute anaphylaxis is treated with intramuscular adrenaline (epinephrine), antihistamines (H\(_1\) and H\(_2\) receptor blockers), fluids and pressor agents.\[^{18}\]
- Patients with recurrent anaphylactoid reactions should carry injectable adrenaline (epinephrine) in pen format for emergency use.
- Consider immunotherapy against insect venom.

**Skin and vascular symptoms**

- For pruritus, weals and flushing - H\(_1\) and H\(_2\) receptor antagonists such as chlorphenamine, ketotifen and cimetidine.
- Mast cell stabilisers - sodium cromoglicate, nedocromil and ketotifen.
- Local corticosteroids for skin lesions. Intraleisonal steroid injection is sometimes used.
- Psoralen in combination with ultraviolet A (PUVA) treatment - gives temporary benefit for skin lesions.

**Bronchospasm**

Inhaled bronchodilators - eg, salbutamol.

**Gastrointestinal symptoms**

- H\(_2\) receptor antagonists or proton pump inhibitors for peptic ulceration.
- Oral sodium cromoglicate for diarrhoea and abdominal pain.\[^{21}\]
- Anticholinergics for diarrhoea.

**Other possible systemic treatments**\[^{22}\]

- Leukotriene inhibitors have been used in the treatment of systemic mastocytosis.
- Systemic corticosteroids may be helpful for malabsorption, ascites and bone pain, to prevent anaphylaxis and for severe skin disease.\[^{18}\]
- Low-dose aspirin may be helpful for symptoms resistant to H\(_1\) and H\(_2\) antagonists alone but must be started cautiously under supervision.\[^{23}\]

**Bone pain**

- Oral sodium cromoglicate may help.\[^{21}\]
- Osteoporosis prevention/treatment - calcium, vitamin D, and bisphosphonates.\[^{11}\]

**Drugs to avoid**\[^{24}\]

- Beta-blockers are contra-indicated in patients with systemic mastocytosis undergoing surgery - these drugs may counteract endogenous adrenaline (epinephrine) and may precipitate anaphylaxis.
- Avoid alpha-blockers and cholinergic antagonists.

**Aggressive disease**\[^{2}\]

- Splenectomy may be helpful for patients with significant hypersplenism or portal hypertension (it may reduce the mast cell burden and improve cytopenias).
- Aggressive systemic forms of mastocytosis may be treated with interferon alfa, with or without corticosteroids, or cladribine. In some cases, more intensive treatments such as imatinib, or drug combinations, may be considered.\[^{22}\]
- Bone marrow transplantation may be considered in some extreme cases.\[^{25}\]
- Haematopoietic stem cell transplant is being explored.\[^{26}\]
- For patients with mast cell sarcoma, surgical excision with consecutive radiation and/or high-dose chemotherapy has been used.\[^{27}\]
- More latterly, stem cell therapy has been used.\[^{24}\]

**Children**

A protocol for management in children is available.\[^{28}\]
Prognosis

Cutaneous mastocytosis
- Childhood cases of urticaria pigmentosa and mastocytoma often resolve spontaneously. Adults are more likely to develop the systemic form of the disease.

Systemic mastocytosis
- This has no known cure and tends to be progressive.
- Prognosis depends on the degree of haematological and organ involvement, as the classification (above) suggests.
- Indolent systemic mastocytosis has a relatively good prognosis — decades of life, using mainly symptomatic treatment, although life-threatening problems can occur.
- In SM-AHNMD, the prognosis depends on the course of the associated haematological disorder.
- Agressive systemic mastocytosis and mast cell leukaemia have a poorer prognosis. The median survival for aggressive systemic mastocytosis is 41 months and for mast cell leukaemia it is less than 6 months. [29, 30]

Localised mastocytosis [10]
- Mastocytoma is a benign tumour with a good prognosis.
- Mast cell sarcoma is locally destructive and usually has a poor prognosis.

Further reading & references
- Metcalfe DD; DermNet NZ.