# Mastocytosis and related entities : a practical roadmap

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**Mastocytosis and related entities: a practical roadmap**

List of abbreviations

| | |
|---|---|
| AdvSM | Advanced systemic mastocytosis |
| ASM | Aggressive systemic mastocytosis |
| aST | acute serum tryptase |
| BM | Bone marrow |
| BMM | Bone marrow mastocytosis |
| bST | baseline serum tryptase |
| CM | Cutaneous mastocytosis |
| DCM | Diffuse cutaneous mastocytosis |
| HVA | Hymenoptera venom allergy |
| HaT | Hereditary alpha tryptasemia |
| ISM | Indolent systemic mastocytosis |
| MC | Mast cell |
| MCA | Mast cell activation |
| MCAS | Mast cell activation syndrome |
| MCL | Mast cell leukemia |
| MIS | Mastocytosis in the skin |
| MMAS | Monoclonal mast cell activation syndrome |
| MPCM | Maculopapular cutaneous mastocytosis |
| SM | Systemic mastocytosis |
| SM-AHN | Systemic mastocytosis with associated hematological neoplasm |
| SSM | Smouldering systemic mastocytosis |
| VIT | Venom immunotherapy |

Introduction

Mastocytosis, is a complex heterogenous multisystem disorder that is characterized by a pathologic activation or accumulation of neoplastic mast cells (MCs) in one or more organs. This clonal MC expansion is often associated with a somatic gain-of-function mutation (D816V in most of the cases) in the *KIT* gene, encoding for the MC surface receptor *KIT* (CD117), a stem cell growth factor receptor (1). Mastocytosis is a term used for a heterogenous group of

conditions. Based on clinical and biochemical criteria, the World Health Organization (WHO) divided mastocytosis into different subclasses (2). The exact prevalence of mastocytosis remains elusive, but it is estimated that the disease affects approximately 1 in 10,000 persons (3). Familial cases of mastocytosis with a germline mutation have an estimated occurrence of 1.5% of all mastocytosis patients (4).

The clinical presentation of mastocytosis varies significantly, ranging from asymptomatic patients to a life-threatening disease with multiple organ involvement, potentially leading to cytopenia, malabsorption, hepatosplenomegaly, lymphadenopathy, ascites or osteolytic bone lesions with pathological fractures (5). Patients with mastocytosis may experience symptoms related to release of MC mediators, such as flushing or diarrhea or even more severe symptoms such as anaphylaxis (6).

Recently, a new genetic trait, hereditary alpha tryptasemia (H$\alpha$T), was described which involves a copy number variation in the *TPSAB1*-gene (7, 8). Its role as standalone multisystem syndrome is heavily debated (9, 10). There is emerging evidence suggesting there might be a link between H$\alpha$T and mastocytosis due to the increased prevalence of H$\alpha$T in patients with SM (11, 12).

The aim of this review is to provide a practical roadmap for diagnosis and management of mastocytosis and its associated entities, since there are still many misconceptions about these topics.

## Classification

As mentioned in the introduction, mastocytosis comprises multiple variants as defined by the WHO (13). As shown in table 1, mastocytosis is classified into four main categories: cutaneous mastocytosis (CM), a generally benign skin-limited disease, MC sarcoma, extracutaneous mastocytoma and systemic mastocytosis (SM) with distinct grades of aggressiveness, *viz.* bone marrow mastocytosis (BMM), indolent systemic mastocytosis (ISM), smouldering systemic mastocytosis (SSM), aggressive systemic mastocytosis (ASM) and mast cell leukemia (MCL) all of which might be accompanied with another hematologic non-mast cell lineage neoplasm which results in another distinctive subclassification. In CM, systemic involvement is absent.

CM is further subdivided into three variants based on clinical findings. If systemic involvement is confirmed, SM is further subdivided into five different variants based on clinical and biochemical findings. An overview of all variants is presented in table 1.

| **Variant** | | **Subclassification** | **Features** |
|---|---|---|---|
| Cutaneous mastocytosis | | MPCM | Is subdivided into polymorphic and monomorphic. |
| | | DCM | Most severe form of CM. Presents with generalized erythema with pachydermia (thickening of the skin) and hyperpigmentation. |
| | | Cutaneous Mastocytoma | Solitary elevated brown or yellowish lesion. More lesions are possible with a maximum of three solitary lesions. |
| Systemic mastocytosis | Non-Adv SM | BMM | Fulfils criteria for SM, no B- or C-findings, no skin lesions and low disease burden |
| | | ISM | Most common form of SM. Maximum 1 B-finding and no C-findings are present. |
| | | SSM | SM with at least 2 B-findings, no C-findings. There is a higher risk for transformation to AdvSM. |
| | Adv SM | SM-AHN | SM with diagnosis of non-MC-lineage hematologic malignancy. |
| | | ASM | SM with presence of one or more C-findings and thus organ dysfunction. |
| | | MCL | Rare. Highest mortality and most difficult to treat. Even more rare variant is aleukemic MCL. |
| Mast cell sarcoma | | | Rare. High-grade MC tumor, with destructive growth pattern. No signs of SM. |
| Extracutaneous mastocytoma | | | Rare. Low-grade MC tumor, with non-destructive growth pattern. No signs of SM, nor skin involvement. |

*Table 1: WHO-classification of mastocytosis (13).*

*MPCM: maculopapular cutaneous mastocytosis; DCM: diffuse cutaneous mastocytosis; AdvSM: advanced systemic mastocytosis; BMM: Bone marrow mastocytosis; ISM: indolent systemic mastocytosis; SSM: smouldering systemic mastocytosis; SM-AHN: systemic mastocytosis with associated hematologic neoplasm; ASM: aggressive systemic mastocytosis; MCL: mast cell leukemia; B-findings: markers of mast cell burden; C-findings: signs of organ dysfunction. More on B- and C-findings (table 5) in section 'patient has SM: next steps'*

The diagnosis of SM relies on bone marrow investigation and fulfilling of specific criteria (see paragraph 'Bone marrow investigation: diagnostic criteria'). In the following paragraphs specific situations will be outlined in which scenarios SM could be suspected and when BM investigation is recommended. Findings that should rise suspicion are shown in box 1.

- Typical cutaneous skin lesions (in adults). See figure 1
- Severe anaphylaxis without muco-cutaneous symptoms
- Reoccurrence of anaphylaxis due to HVA after discontinuation of VIT
- Unprovoked anaphylaxis
- Unexplained osteoporosis or fragility fractures especially of lumbar spine
- Recurrent mast cell mediator related symptoms (e.g., diarrhea, flushing) with no other explanation

*Box 1: When to think of mastocytosis?*

*HVA: Hymenoptera venom allergy; VIT: venom immunotherapy*

<u>Cutaneous lesions of mastocytosis: when to marrow?</u>

Cutaneous involvement is the most common sign of mastocytosis (14) and is termed mastocytosis in skin (MIS). It should not be confused with CM, since MIS is a provisional entity that is reserved for cases with cutaneous involvement but in whom systemic involvement has not been ruled out yet. In contrast with SM, CM has no extracutaneous infiltration of MCs and is further divided into three different entities: maculopapular CM (MPCM) (figure 1), diffuse CM (DCM) and mastocytoma of the skin. MPCM can be subdivided into monomorphic and polymorphic, dependent on the type of rash. Monomorphic lesions are small symmetrical distributed oval red-brown macules or papules. Most of these lesions locate on the trunk and

usually palms, soles, face and head are spared. Polymorphic lesions are generally larger with variable size, shape and color (14).

The diagnosis of CM relies mainly on recognition of (typical) skin lesions. A positive Darier's sign serves as a major criterium. This involves a local wheal and flare reaction when lesions are stroked at moderate pressure. Darier's sign differs from dermographism, since the latter also applies to nonlesional skin. Obviously, intake of antihistamines might result in a false negative Darier's sign. It is dissuaded to test Darier's sign in patients with mastocytoma or the nodular variant of polymorphic MPCM as this can provoke flushing or even hypotension. However, this sign can be negative in adults with (cutaneous) mastocytosis but will often be positive in children (14). The first two minor criteria are based on the skin biopsy. The first being an increased number (four- to eightfold) of MCs on histology. It is of note that the normal range value of MCs in skin is highly dependent on the site of biopsy and that some patients with CM do not have an increased number of MCs in the skin (15). The second minor criterion is the presence of an (activating) *KIT* mutation in lesional skin tissue.

Children with MPCM can present with heterogenous skin lesions, most often polymorphic lesions. The onset of CM usually occurs in the first 6 months of life, when skin lesions can be prone to blistering, particularly if located on the head. Baseline serum tryptase (bST) levels are in most cases within normal range and if elevated, they usually normalize within the first years after diagnosis. In most cases, the skin lesions regress spontaneously upon adolescence. However, in a minority of patients, skin lesions persist into adulthood, especially children with monomorphic lesions. These patients are far more likely to have systemic involvement (16).
If a child presents with typical cutaneous lesions of mastocytosis one should obtain a thorough history and perform a complete physical examination. Laboratory tests include a complete blood count, serum electrolytes, transaminases and measurement of bST. Furthermore, an abdominal ultrasound should be performed. A bone densitometry is only recommended in selected cases (e.g., a child with unexplained bone pain). If a child with suspicious skin lesions presents with - (a) clinically significant abnormalities in cytology or biochemistry, (b) a bST > 100 ng/mL or a rapidly rising bST or (c) obvious organomegaly - a BM biopsy should be obtained. The prevalence of SM in children with MIS is unclear, mostly because children undergo a bone marrow only when signs and symptoms suggest the presence of an

advanced/progressive neoplasm. Detection of *KIT* (D816V) in peripheral blood and the morphology (e.g. monomorphic lesions) of skin lesions might be suggestive of systemic disease and might represent an indication for BM examination (17). On the other hand, if no abnormalities are found, we suggest a watchful waiting approach in these patients, because of the invasive nature of a BM examination.

In most adults with cutaneous involvement, SM is diagnosed. Rarely, no systemic involvement can be found in adult patients. Very rarely, adults present with polymorphic lesions. An adult presenting with suspicious skin lesions always requires further workup for SM including a thorough clinical history, physical examination, laboratory examinations (complete blood count, electrolytes, transaminases, bST) and an abdominal ultrasound. Moreover, a BM biopsy should be performed, regardless of symptoms or bST level (16).

Anaphylaxis: when to marrow?

The diagnosis can be more challenging in patients presenting without skin lesions as in this group of patients screening for *KIT*-mutations in peripheral blood has low negative predictive value (18). One should suspect mastocytosis in patients with recurrent, unexplained or severe anaphylaxis, especially those with severe hypotension, in whom mucocutaneous manifestations such as urticaria, pruritus or angio-edema are absent. If a patient presents with anaphylaxis, a useful tool to identify patients at risk for mastocytosis is the Red Española of Mastocitosis (REMA)-score (19). This score was developed by the Spanish Network of Mastocytosis and is based on a set of variables to help to identify mast cell activation syndrome (MCAS) or systemic mastocytosis. The REMA-score can help identifying patients in whom a BM biopsy should be performed (20). The scoring system has a sensitivity of 0.92, a positive predictive value of 0.89, a specificity of 0.81 and negative predictive value of 0.87. Another useful tool used to determine the risk of mastocytosis in case of severe unprovoked anaphylaxis is the NIH Idiopathic Clonal Anaphylaxis Score (NICAS) with a sensitivity and specificity of 0.75 and 1.00, respectively (21). A score of 2 or more is highly suspicious for clonal MC disease. Both scoring systems are shown in table 2. A NICAS- or REMA-score $\geq 2$ is suggestive for clonal MC disease and a BM biopsy should be performed. Of note, if a *KIT*-mutation is detected in peripheral blood, one should always proceed to a BM biopsy because of the high positive predictive value.

| REMA | | |
|---|---|---|
| Variable | | Score |
| Gender | Male | +1 |
| | Female | -1 |
| Clinical symptoms | Absence of urticaria, pruritus and angioedema | +1 |
| | Urticaria, pruritus and/or angioedema | -2 |
| | Presyncope and/or syncope | +2 |
| Baseline serum tryptase | < 15 ng/mL | -1 |
| | > 25 ng/mL | +1 |
| **NICAS** | | |
| Variable | | Score |
| Gender | Male | +1 |
| | Female | -1 |
| Clinical symptoms | Absence of angioedema | +1 |
| | Flushing | -1 |
| | Urticaria | +1 |
| | Syncope | +3 |
| Baseline serum tryptase | <11.4 ng/mL | -1 |
| | >11.4 ng/mL | +2 |
| Allele specific PCR (*KIT* mutation) | Negative | -1 |
| | Positive | +3 |

*Table 2. Scoring systems used in patients with anaphylaxis to evaluate risk of clonal mast cell disease. A score < 2 makes primary mast cell disease very unlikely. NICAS is used in patients with idiopathic anaphylaxis.*

Elevated baseline serum tryptase: always mastocytosis?

Serum tryptase is the sum of monomeric pro-tryptase, which is secreted constitutively, and mature tetrameric tryptase, which is released by MCs during degranulation (e.g., during an allergic reaction). In patients with mastocytosis, bST is often elevated (>11.4 ng/mL), mainly due to the increased release of the pro-tryptase. (22). A bST < 11.4 ng/mL is less suggestive for mastocytosis, but it cannot be ruled out. In fact, many patients with SM have normal

ranges of serum tryptase, especially in HVA with and without MIS (18, 23). An elevated bST can also be seen in other conditions. In fact, it is estimated that 6% of the general population has an elevated bST (>11.4 ng/mL and is mostly caused by HαT (91%) followed by chronic kidney disease (7%) and clonal disease including mastocytosis, but also by other hematologic malignancies (1%) and obesity (24). Other causes are rare genetic conditions (pathogenic *GATA2* and *PLCG2* variants) or acquired causes such as helminthic infections (22). The most common conditions associated with elevated bST are shown in table 3.

| |
|---|
| Healthy individuals |
| Obesity |
| Administration of SCF |
| Chronic eosinophilic leukemia |
| Acute myeloid leukemia |
| Myelodysplastic syndromes |
| Myeloproliferative neoplasm |
| Myelomastocytic leukemia |
| Mastocytosis |
| Chronic worm infections |
| Kidney failure |
| Atopy |
| Hereditary α tryptasemia |
| False positive result |

*Table 3: Causes of elevated baseline serum tryptase adapted from Valent et al. (25)*

*SCF: stem cell factor*

HαT is a genetic trait which may modify the expression of multifactorial allergic diseases rather than directly cause specific phenotypes (9). Whether it might manifest itself as a multisystem syndrome with a clinical phenotype comparable with SM (e.g., abdominal cramps, headache, etc.) is debatable. HαT has an autosomal dominant pattern of inheritance (7). Therefore, if an individual presents with suggestive symptoms and bST is more than 8 ng/mL, bST in first degree family members should be measured. Note that the cut-off is slightly

lower compared to the criteria for SM. If multiple family members have this trait, HαT can be suspected. Confirmation is possible through the detection of copy number variation in the *TPSAB1*-gene. Generally, the higher the number of copies, the higher the bST. In contrast, bST values do not corelate well with the clinical phenotype (9). The highest number of copies currently reported is a quintuplication, which is a very rare finding (12). Giannetti et al. hypothesized that HαT might be associated with MC abnormalities and might contribute to the development of SM and MCAS based on atypical MCs found in a subset of patients with MCAS as well as with SM (26). Furthermore, several studies show that an increased prevalence of HαT-carriers was found among patients with SM, especially in patients with ISM. This subset of patients exhibited higher levels of bST, a significant lower *KIT* D816V allele burden and an increased number of severe mediator related symptoms (10). Increased number of alpha copies of the *TPSAB1* gene is now considered as an additional biomarker in the risk-assessment of severe anaphylaxis in patients with SM (27, 28). However, the exact link between the two, as well as the underlying pathophysiologic mechanism behind them needs to be further elucidated.

Besides tryptase, other biomarkers have been proposed to evaluate for mast cell activation (MCA). Prostaglandin $D_2$, like tryptase, is specific for MCs. Another potential marker is histamine. Consequently, a significant increase in histamine metabolites and prostaglandin $D_2$ metabolites in urine compared to baseline can be used to demonstrate MCA. However, histamine is released in equal amounts by basophils and MCs and is therefore less accurate to detect MCA. Plasma histamine, diamine oxidase and soluble IgE-receptor alpha chain are potentially useful markers. However, these tests are not widely available, and consensus concerning the cut-off for positivity, has not been reached yet. Biomarkers that are currently not recommended are heparin, chymase, bradykinin, stem cell factor, interleukins, chemokines, basogranulin and platelet activating factor (29).

<u>Bone marrow investigation: diagnostic criteria</u>

In patients with suspicion of mastocytosis, an extensive history and physical examination should be carried out with special attention to skin lesions and presence of Darier's sign (see section on CM). Laboratory work up involves cytology and biochemistry, including measurement of bST and vitamin D. If eosinophilia is present, *FIP1L1 – PDGFRA* (FIP1 like 1-

platelet derived growth factor receptor alpha) fusion gene should be determined. If enough arguments are gathered, one should proceed to a BM biopsy with flowcytometric research to look for aberrant MC markers (CD2, CD25 and/or CD30), pathologic investigation for evaluation of dense MC infiltrates and genetics for *KIT* D816V analysis using high sensitive polymerase chain reaction (PCR) assay needs to be performed (30) to evaluate for SM. High sensitive PCR is preferred over Sanger sequencing and next-generation sequencing (NGS) since these latter techniques have significant risk of false negative results. High sensitive PCR allows the physician to identify virtually all patients with *KIT* D816V mutation (31). The criteria for SM are listed in table 4 and shown in figure 2. The diagnosis is confirmed if the major and at least one minor criterion are fulfilled or if at least three minor criteria are fulfilled (2).

| **Major criterion** |
|---|
| Multifocal dense infiltrates of MC (>15 cells in aggregates) detected in BM AND/OR in sections of other extracutaneous organs |
| **Minor criteria** |
| >25% of all MCs are atypical or spindle shaped in sections of extracutaneous organs |
| *KIT* point mutation at codon 816 in BM or another extracutaneous organ |
| Expression of CD2, CD25 and/or CD30 in mast cells in peripheral blood, BM OR any extracutaneous organ |
| Baseline serum tryptase level >20 ng/mL (with exception of patients with unrelated myeloid neoplasm) |

*Table 4: Diagnostic criteria for systemic mastocytosis according to the WHO. See figure 2.*
*MC: mast cell; BM: bone marrow*

<u>Patient has SM: next steps</u>

*Determination of the WHO category*

Once a diagnosis of SM is established, the WHO classification should be defined (figure 3). This classification is based on the number of MCs found in a BM smear, presence of non-MC-hematologic malignancy and B- and C-findings (see table 5) indicating organ dysfunction due to MC infiltration and is evaluated through peripheral blood examination (cytology, biochemistry), abdominal ultrasound and BM biopsy.

When less than 25% MCs are found in the BM smear in a patient who fulfills the criteria for SM, an indolent form of SM (ISM) can be diagnosed on the condition that there are no B- or C-findings nor signs of a hematologic malignancy are found. The clinical phenotype is mainly dominated by symptoms related to MCA and/or anaphylaxis. These patients have a normal life expectancy and very low risk of developing ASM (32). Although the main clinical characteristic of aggressive forms of mastocytosis (ASM or MCL) is organ dysfunction due to MC infiltration and uncontrolled accumulation (33), these patients can experience symptoms due to MC degranulation as well. MCs can accumulate in various organs and tissues, potentially leading to a variety of signs and symptoms, such as cytopenia, liver dysfunction, ascites, pleural effusion, osteolytic bone lesions, pathologic weight loss, etc. ASM can present as a slowly progressive disease, but also as a rapidly progressive disease that might progress to MCL.

Another variant of SM is smoldering SM (SSM). This entity lies in between ISM and ASM in the clinical spectrum of mastocytosis. SSM meets all criteria for ISM, except in this variant B-findings are present, which is indicative for a high MC-burden. Generally, these patients have higher incidence of constitutional symptoms. Since the risk of disease progression and leukemic transformation may be higher in these groups (32), a more frequent follow-up is indicated.

Some patients with SM present with synchronous hematologic non-MC malignancy according to WHO-criteria or develop a hematologic malignancy along the way. Patients with SM and associated hematologic neoplasm (SM-AHN) can conceptually be further divided into ISM-AHN, SSM-AHN, ASM-AHN or ML-AHN. Generally, these patients have less complaints of MC mediator release and are more likely to experience constitutional symptoms (32). In most cases the associated hematologic neoplasm is myeloid in origin, usually a myeloproliferative neoplasm or myelodysplastic syndrome although other forms have been described (e.g., acute myeloid leukemia, (non)-Hodgkin lymphoma, multiple myeloma) (34).

| **B-findings** |
| --- |
| ≥ 30% infiltration (focal, dense aggregates) of MCs in BM ± bST > 200 ng/mL ± *KIT* D816V VAF ≥ 10% in BM of PB leukocytes |
| Signs of dysplasia or myeloproliferation in non-MC-lineage, but insufficient criteria for hematologic malignancy with normal or slightly abnormal cytology |
| Hepatomegaly without liver dysfunction ± splenomegaly without hypersplenism ± clinical or radiological lymphadenopathy |
| **C-findings** |
| BM dysfunction manifested by at least one cytopenia (ANC < 1.0 x $10^9$/L, Hgb < 10 g/dL or platelets < 100 x $10^9$/L), but no obvious (non-MC-lineage) hematologic malignancy |
| Ascites and elevated liver enzymes ± hepatomegaly or cirrhotic liver ± portal hypertension |
| Palpable splenomegaly with hypersplenism ± weight loss ± hypalbuminemia |
| Skeletal involvement with large osteolytic bone lesions (≥2cm) with pathological fractures ± bone pain |
| Malabsorption with hypoalbuminemia ± weight loss due to gastro-intestinal MC-infiltrates |

*Table 5. Refined B and C-findings, adapted from Valent et al. (2)*

*MC: mast cell; BM: bone marrow; bST: baseline serum tryptase; VAF: variant allele frequency, PB: peripheral blood; ANC: absolute neutrophil count; Hgb: hemoglobin*

*Prevention of anaphylaxis in mastocytosis*

If mastocytosis is diagnosed, it is mandatory to educate the patient to recognize signs of anaphylaxis since their risk of anaphylaxis is higher, particularly in patients without skin lesions (35). Patients should always carry two epinephrine auto-injectors and be instructed when/how to use these correctly. Triggers for anaphylaxis should be avoided (see table 6) with attention to augmenting factors (e.g., alcohol, infections, exercise, stress). To reduce the risk of anaphylaxis, patients with SM in need of surgery or procedures involving iodinated contrast media, should always undergo a thorough pre-procedural evaluation (36) and, if the intervention were to be scheduled, one can consider a second-generation H1-antihistamine three days prior to the procedure and continue this up until three days after the procedure.

Moreover, patients should receive corticosteroids (80 mg methylprednisolone) 24h and 1h in advance of the procedure. It is of note that alternative protocols are used worldwide and data concerning efficacy is lacking (37) and one should always remain cautious in these patients. Adrenaline should always be within reach. Finally, if an IgE-mediated HVA is present, lifelong VIT is indicated (38).

| **Class** | **Recommended to avoid** | **Suggested alternative** |
|---|---|---|
| Opioid | Morphine, codeine, buprenorphine | Tramadol, fentanyl, remifentanil |
| NMBA | All if possible | Cis-atracurium |
| Antihypertensive drugs | Beta-blockers | |
| | ACE-inhibitors | Sartans |
| Iodinated contrast media | High osmolar preparate | Low osmolar preparate |
| NSAID | Strong COX-1 inhibitors (if no previous exposure *) | Selective COX-2 inhibitors |

*Table 6: Non exhaustive list of drugs that should be avoided or used with caution in patients with SM. Adapted from De Wachter et al. (37) and Pardanani et al. (39).*

*NMBA: neuromuscular blocking agent; ACE: angiotensin converting enzyme; NSAID: non-steroidal anti-inflammatory drug; COX: cyclo-oxygenase*

** Consider challenge if no previous exposure*

*How to tackle mediator related symptoms?*

MC-mediator related symptoms should be addressed in a stepwise manner. According to the affected organ system and severity, different kinds of drugs can be used. H1- (and H2-) histamine receptor antagonists are the first line treatment. They are effective in patients with pruritus, flushing, urticaria but also in abdominal pain and cramping, pyrosis and diarrhea. If abdominal symptoms persist, proton pump inhibitors can be added. In case of refractory abdominal symptoms despite adequate therapy, sodium cromolyn can be considered as a third line therapy. Persistent cutaneous symptoms can be treated with a leukotriene receptor antagonist in second line. If patients do not benefit from this, aspirin can be considered, especially in patients with flushing (40). One must take into account that NSAIDs have the

potential to trigger anaphylaxis. The first dose of strong COX-1 inhibitors should be administered in monitored setting, if no previous exposure is known.

Omalizumab is an option in persistent mediator related complaints. If symptoms are severe or uncontrollable with conventional therapy, cytoreductive agents can be considered (31, 39, 41). In cases where rapid debulking is indicated, cladibrine is commonly used. Interferon-alpha can be indicated if there are uncontrolled mediator related symptoms, especially if there is skeletal involvement. Other drugs are more targeted to the *KIT* receptor. Imatinib should not be used in patients with *KIT* D816V mutation, since they are resistant to it. Other *KIT* genotypes (e.g., K509I, V560G, F522C) can respond to treatment with imatinib (42). In contrast, midostaurine can be used in patients with *KIT* D816V mutation and has fair results. Other drugs such as masitinib, avapritinib, ripretinib and sarilumab are currently under investigation (43).

Whereas focus mainly lies on symptom control in patients with ISM and SSM, a different approach is needed in patients with AdvSM. These patients typically have less mediator related symptoms but suffer more from organ dysfunction due to MC infiltration. Therefore, cytoreductive therapy has a central role in this entity. The details are beyond the scope of this review but are discussed elsewhere (31, 43). In highly aggressive AdvSM, hemapoetic stem cell transplantation should be considered.

*Osteopenia and osteoporosis*

Bone disease is an important comorbidity in patients with SM. Therefore, a DEXA-scan is mandatory in the evaluation of a patient with SM, including a vertebral fracture assessment (VFA). Although very common (found in up to 50% of patients), most patients have asymptomatic bone disease (44). The risk is relatively higher in men than women with mastocytosis, with a prevalence of 46% and 18%, respectively, in a cohort <50 years of age (45). The most common manifestation is osteoporosis, but lytic bone lesions, osteopenia and osteosclerosis can also be found. Vitamin D and calcium should be substituted adequately. If bone involvement Is confirmed, one should consider bisphosphonates or a RANKL-inhibitor (46).

*Evaluation for disease progression*

As mentioned earlier, patients with ISM are at risk to evolve to AdvSM. Since the risk of transition is very low (32), patients should be evaluated at least yearly with a complete blood count, biochemistry and bST. *KIT* mutation burden can be monitored in patients with high mast cell burden. If all these values remain stable, no further action is required. If severe biochemical abnormalities with no other explanation are observed, it is advised to repeat BM examination and to revise the presence of B- and C-findings. Evaluation is summarized in box 2. The follow up of patients with AdvSM is beyond the scope of this review (31).

| **Suspicion of SM** |
| --- |
| • History and physical examination (inspection of skin, Darier's sign, hepatosplenomegaly, lymphadenopathy)<br>  ○ Lab: cytology, biochemistry, baseline serum tryptase, vitamin D, *KIT* D816V analysis using highly sensitive PCR assay<br>  ○ If eosinophilia: *FIP1L1 - PDGFRA*<br>• Bone marrow biopsy<br>  ○ Pathology: MC invasion?<br>  ○ Flowcytometric research: CD2/CD25/CD30 expression of MC<br>  ○ Genetics: *KIT* D816V analysis using highly sensitive PCR assay<br>• Skin biopsy<br>  ○ Pathology: MC invasion?<br>  ○ Genetics: *KIT* D816V analysis using highly sensitive PCR assay |
| **SM has been confirmed** |
| • Determine subtype<br>• Measures to prevent anaphylaxis<br>• Treat mediator related symptoms<br>• Screen for bone involvement: DEXA-scan. Repeat every two years<br>• Yearly follow up<br>  ○ Clinical: evolution of skin lesions if present<br>  ○ Lab: cytology, biochemistry, baseline serum tryptase, vitamin D |

- Genetics: *KIT* D816V analysis using highly sensitive PCR assay in patients with high mast cell burden
- Bone marrow biopsy: only in patients with NonAdv-SM in patients with significant changes in baseline serum tryptase, development of B- or C-findings (restaging)

*Box 2: Evaluation for suspected SM and work-up for confirmed SM*

*PCR: polymerase chain reaction; MC: mast cell; DEXA: Dual Energy X-ray Absorptiometry; NonAdv-SM: non advanced systemic mastocytosis; B-findings: markers of mast cell burden; C-findings: signs of organ dysfunction.*

Only a few criteria for SM are fulfilled, what now?

The approach for patients with signs of clonal MC pathology and aberrant MCs is mainly the same as patients with SM. One could classify this entity as pre-systemic mastocytosis. The same measures should be considered in this group of patients: prevention of anaphylaxis, treatment of mediator related symptoms, evaluation for bone disease and evaluation for disease progression (47).

Although no definite diagnosis of SM can be made in these patients, severe symptoms can be present and the risk of anaphylaxis is increased. Patients can also present with symptoms compatible with mast cell activation syndrome (MCAS) including bone disease (i.e.: bone pain, osteopenia, osteoporosis with fractures, osteolytic bone lesions or osteosclerosis) (46), cardiovascular symptoms (palpitations, hypotension, syncope), respiratory, cutaneous (flushing, urticaria, angioedema), gastro-intestinal (chronic diarrhea, cramping, ulcerative disease), neuropsychiatric or systemic symptoms (fatigue).

MCAS

MCAS can be found in SM. Symptoms arise from MC released mediators (such as: histamine, heparin, tryptase, leukotrienes, multifunctional cytokines) and are mostly flushing, pruritus, blistering, diarrhea, abdominal pain, vomiting, headache, bone pain, hypotension and syncope (48). These symptoms are often very aspecific and can arise from several other etiologies (e.g., cardiac, gastro-enterologic, endocrinologic, infectious, neurologic, cutaneous and drug toxicity). A complete overview of differential diagnosis is mentioned elsewhere (25).

MCAS is not a diagnosis of exclusion, and in order to prevent over-diagnosis, patients must fulfill strict diagnostic criteria (see table 7).

| | |
|---|---|
| Criteria A: Symptoms | Typical clinical signs of recurrent or severe MCA with involvement of at least 2 organs systems |
| Criteria B: MC markers | Proof of MCA through consensus formula of aST and bST (increase of 20% + 2 ng/mL) or other biomarkers such as histamine, prostaglandins, leukotrienes, and metabolites |
| Criteria C: Response to therapy | Response to drugs that stabilize MCs, drugs directed against MC mediator production or drugs inhibiting MC mediator release or inhibit MC mediator effects |

*Table 7. Diagnostic criteria for MCAS. All criteria must be fulfilled.*
*MCA: mast cell activation; aST: acute serum tryptase; bST: baseline serum tryptase; MC: mast cell*

If a patient is likely to have MCAS and fulfills the diagnostic criteria, one should determine whether it is a primary, secondary or idiopathic MCAS. Therefore, evaluating the presence of aberrant (clonal) MCs through screening for SM is advised. In addition, if based on the history of the patient a consequent trigger is identified, evaluation of underlying IgE-mediated hypersensitivity should be initiated. A primary MCAS can be diagnosed if clonal MCs are observed and many of these patients will have concurrent mastocytosis. However, some patients with primary MCAS do not meet sufficient criteria for the diagnosis of SM. In this subset of patients, the term monoclonal MCAS (MMAS) is sometimes used, because of the presence of monoclonal MCs (25).

Secondary MCAS refers to patients without clonal MCs, but with an underlying condition or allergy that explains excessive MCA. Many of these patients will have an underlying IgE-dependent allergy. If there are no arguments for an underlying allergy, auto-immune disorders, chronic infections and malignancy should be excluded, since these entities are able to trigger MCA in some cases. Notably, a patient can have concurrent primary and secondary MCAS (e.g., a patient with SM with symptoms due to MC mediator release and an HVA. Patients with combined MCAS are at high risk of severe anaphylaxis and usually require specific therapy (38).

Idiopathic MCAS comprises the group of patients who fulfill all diagnostic criteria, but the underlying reason remains unclear. Aberrant MCs, an underlying allergy or other underlying conditions are absent.

Concluding remarks

Patients with mastocytosis can present in three different ways: with typical skin lesions, severe anaphylaxis or recurrent mediator related symptoms. In children with skin lesions compatible with mastocytosis, a watchful waiting policy can be justified in the absence of certain red flags. However typical skin lesions in adults should always give rise to a full workup. Second, in case of anaphylaxis both the NICAS and REMA-score are useful tools to check if MC disease should be suspected. In case of an anaphylaxis, determination of acute and baseline serum tryptase is absolutely crucial. Also, an elevated baseline serum tryptase with compatible symptoms could lead one to the diagnosis of mastocytosis, although the most common cause is H$\alpha$T. Of note, patients with SM can have concurrent H$\alpha$T and are consequently at great risk of anaphylaxis. To conclude, mastocytosis is a rare disease, but due to its clinical implications a diagnosis should not be missed. Key messages are summarized in box 3.

| | |
|---|---|
| General | • Mastocytosis comprises a heterogenous group of diseases in which there is abnormal function or accumulation of mast cells.<br>• Hereditary alpha tryptasemia is the most common cause for an elevated baseline tryptase.<br>• Mastocytosis can be concurrent with hereditary alpha tryptasemia. These patients have a significant increased risk of anaphylaxis. |
| Diagnosis | • Monomorphic maculopapular lesions in adults are highly suspicious of SM, even with normal baseline serum tryptase.<br>• Severe anaphylaxis (often due to Hymenoptera) without mucocutaneus symptoms is highly suspicious of SM.<br>• In case of unprovoked anaphylaxis in a patient, mastocytosis is suspected.<br>• Young patients with unexplained osteoporosis.<br>• The indication for BM relies on a combination of clinics (anaphylaxis, cutaneous lesions) and biochemical signs (*KIT* in peripheral blood, baseline serum tryptase). |
| Management | • Preventive measures should be applied in patients with SM: provide 2 auto-injectors with adrenaline, certain drugs should be avoided and if HVA is present lifelong VIT is advised.<br>• Mediator related symptoms should be treated in first line with antihistamines, PPI, leukotriene receptor antagonist, omalizumab or TKI (under investigation) if refractory symptoms.<br>• Be aware of increased risk of osteoporosis and screen using DEXA-scan every two years.<br>• Foresee yearly follow up (cytology, biochemistry, vitamin D and baseline serum tryptase). |

*Box 3: Key messages*

*SM: systemic mastocytosis; BM: bone marrow; HVA: Hymenoptera venom allergy; VIT: venom immunotherapy; PPI: proton pump inhibitor; TKI: tyrosine kinase inhibitor; DEXA: Dual Energy X-ray Absorptiometry*

*Figures*

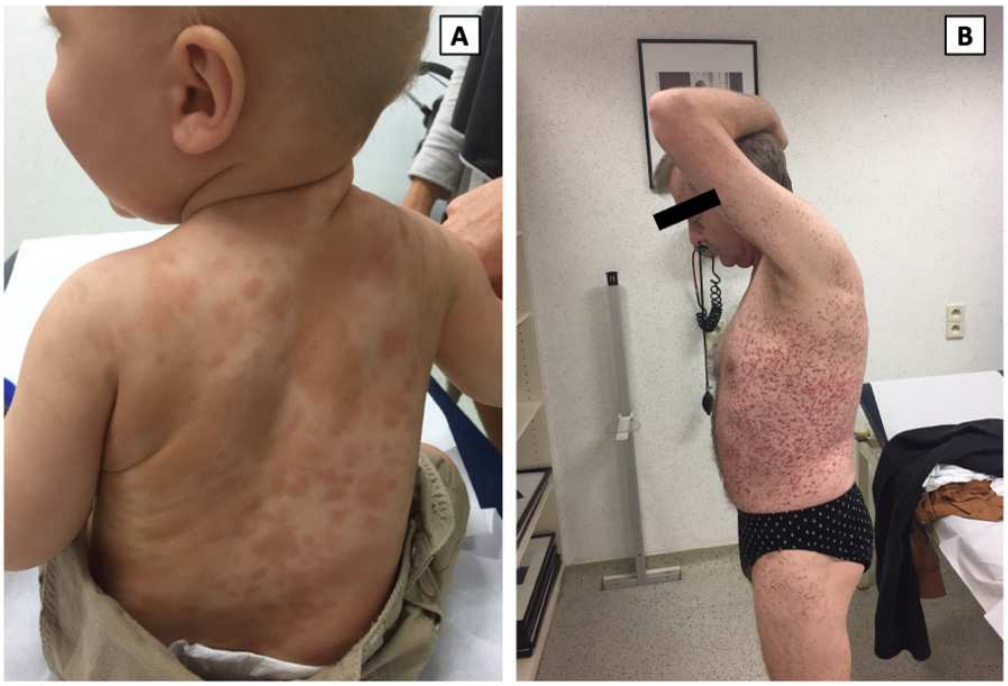


*Figure 1: Different cutaneous lesions seen in patients with mastocytosis.*
*A: polymorphic maculopapular cutaneous mastocytosis (MPCM), usually found in children and tend to disappear upon adolescence.*
*B: monomorphic maculopapular cutaneous mastocytosis (MPCM), usually found in adults and suggest underlying systemic mastocytosis*

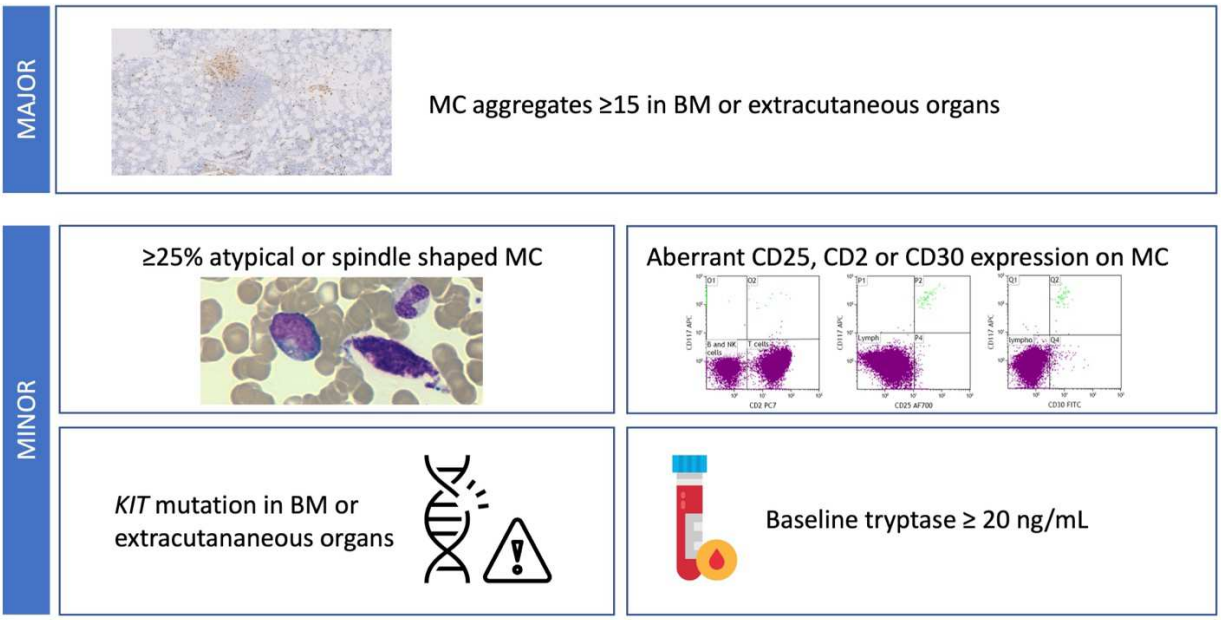


*Figure 2: diagnostic criteria for systemic mastocytosis*

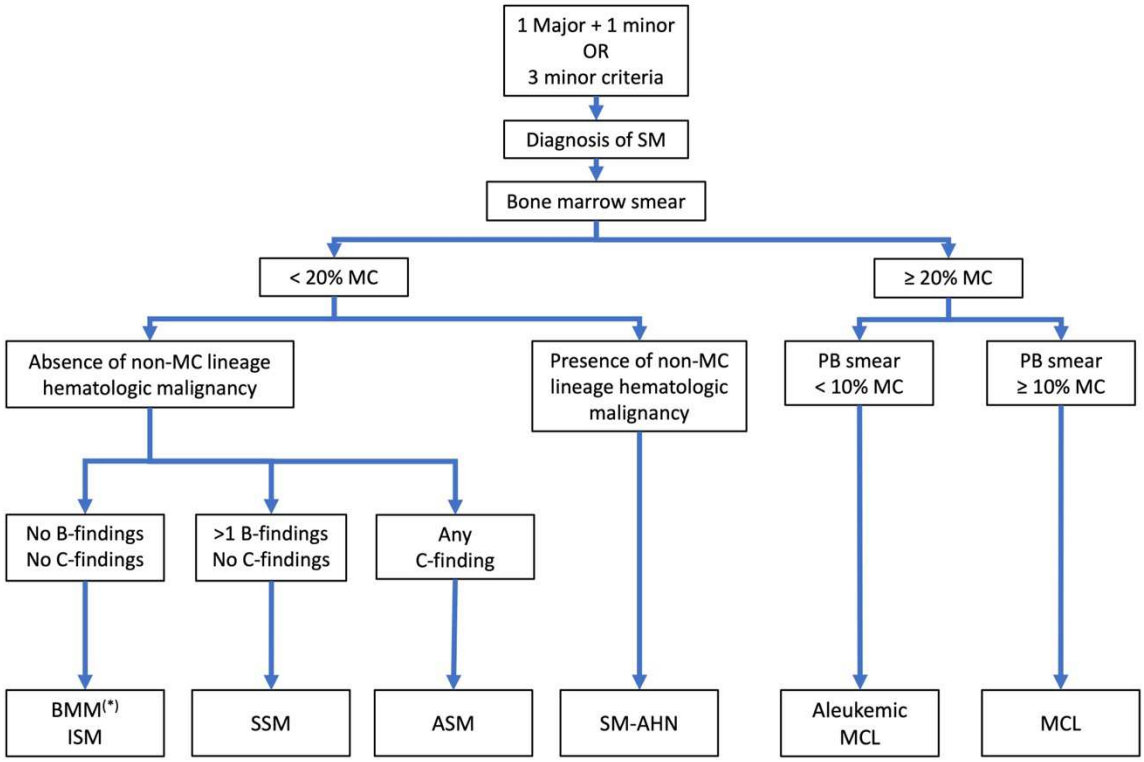


*Figure 3: Subclassification of SM. Adapted from Valent et al. (49)*

*SM: systemic mastocytosis; MC: mast cell; BMM: bone marrow mastocytosis; ISM: indolent systemic mastocytosis; SSM: smouldering systemic mastocytosis; ASM: aggressive systemic mastocytosis; SM-AHN: systemic mastocytosis with associated hematologic neoplasm; MCL: mast cell leukemia; PB: peripheral blood*

*(*) In BMM, no skin lesions are present and serum tryptase is < 125 µg/L*

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