

Diagnostic Evaluation and Classification of Mastocytosis

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Mast cells: relevant biologic features

Mast cells (MCs) are hematopoietic cells with unique biologic properties and a unique spectrum of mediators and cell surface antigens [1,2]. In contrast to blood basophils or other granulocytes, MCs are long-lived cells, with an estimated life span of several months. Mature MCs reside in diverse organs, often in vicinity to smaller or larger blood vessels [1,2]. Histologically, MCs can readily be identified by their content of metachromatic granules and dye-staining properties as well as by their content of proteolytic (chymotryptic) enzymes [1,2]. Thus, within these granules, MCs store various proteoglycans and enzymes as well as vasoactive and proinflammatory mediators [1–3]. Some of these mediators, such as histamine, are stored and released from MCs after cross-linking of high-affinity IgE receptors or activation by complement [1–3]. Other compounds, such as α -protryptase, are constitutively produced and constitutively secreted by MCs. Therefore, baseline total tryptase levels can be used as a marker of MCs (roughly indicating the total MC mass) in normal subjects as well as in patients with mastocytosis (see the article by Schwartz elsewhere in this issue) [4–6].

A well-established concept is that MCs are derived from bone marrow progenitor cells [7–11]. Precommitted and MC-committed progenitors are also circulating in the peripheral blood. These cells have the capacity to undergo differentiation and MC maturation after entering the tissues [12]. Several factors are considered to contribute to growth and differentiation of MCs. The most important cytokine is stem cell factor (SCF). This cytokine induces the differentiation of MCs from their progenitors [8–15]. MC

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progenitors, in turn, express a specific tyrosine kinase receptor for SCF (KIT) which is encoded by the *KIT* proto-oncogene [10,12,16]. Both KIT and the KIT ligand SCF are considered important for survival and differentiation of MCs. In line with this assumption, defects in the *kit* or *scf* genes in mice lead to a profound deficiency in MCs [17,18]. By contrast, “gain-of-function mutations” in *KIT* are associated with enhanced survival and autonomous growth of MCs [19,20]. Such mutations, particularly *KIT* D816V, are often detected in patients with systemic mastocytosis (SM) [21–26].

Pathogenesis of mastocytosis: current status

So far, little is known about the pathogenesis of mastocytosis and factors contributing to disease progression [27–31]. Likewise, it is not known which factors contribute to the abnormal accumulation and distribution of MCs in the skin in cutaneous mastocytosis (CM), as only a subgroup of patients with CM displays a *KIT* mutation. It also remains unknown whether patients in whom a D816V *KIT* mutation is present may later all develop systemic disease (ie, SM) [23,24,31].

In SM, the histologic feature common to all categories of SM is the focal accumulation (clustering) of MCs in visceral organs [27–30]. Depending on the variant of SM, MCs and/or their progenitors may also show enhanced proliferation compared with normal cells [27–30]. A generally accepted hypothesis is that MCs usually are monoclonal cells in SM [32–34]. This assumption is primarily based on the *KIT* point mutation D816V, which is detectable in most patients (>80%) with SM [20–26,35]. Therefore, the D816V mutation of *KIT* is considered to represent an important “hit” contributing to MC differentiation and MC cluster formation in SM [19,20]. By contrast, this mutation alone may be unable to act as a proliferation-enhancing oncogene [36]. In fact, *KIT* D816V is detectable in patients with completely indolent SM with a normal life expectancy as well as in patients with a highly aggressive disease course, including aggressive systemic mastocytosis (ASM) and mast cell leukemia (MCL) [27–30,32,33]. In these patients, additional defects (so far undefined) are likely to contribute to uncontrolled and aggressive growth of MCs and their progenitors.

Apart from D816V, other *KIT* mutations have also been detected in SM (Table 1) [37–39]. In addition, chromosomal defects, gene defects, and gene polymorphisms have been described [40–44]. Many of these defects are detected in patients who have an associated (clonal) hematologic non-mast cell lineage disease (AHNMD), and most of the defects have been linked to distinct myeloid neoplasms. One example is the *FIP1L1/PDGFR*A fusion gene that has recently been associated with chronic eosinophilic leukemia (CEL). Such defects are thus indicative of an AHNMD in SM but must not be judged as a marker of SM. Thus, the presence of eosinophilia plus *FIP1L1/PDGFR*A in a patient with SM leads to the diagnosis of SM with

Table 1

Gene defects in systemic mastocytosis with or without an associated (clonal) hematologic non-mast cell lineage disease

AHNMD gene defect(s)	Detected in SM without AHNMD (frequency*)	Detected in SM-AHNMD (frequency*)
<i>KIT</i> D816V (+)	ISM (+), SSM (+) ASM (+), MCL (+/–)	CMMML (+), atypical CML (+), AML (–)
Other <i>KIT</i> mutations		
<i>KIT</i> D816Y, <i>KIT</i> D816F	—	—
<i>KIT</i> D816H, <i>KIT</i> D816F	—	—
<i>KIT</i> D820G, <i>KIT</i> F522C	—	—
<i>KIT</i> V530I, <i>KIT</i> V560G	—	—
<i>KIT</i> D816F, <i>KIT</i> K509I	—	—
BCR/ABL	n.r.	CML and atypical CML (–)
JAK2V617F	n.r.	MPD (?)
FIP1L1/PDGFRα	n.r.	CEL (+)
AML1/ETO	n.r.	AML-M2 (+) ^a
Other AML-related fusion genes	n.r.	—
Monoclonal Ig	+ ^b	NHL/myeloma (+)

Abbreviations: AML, acute myeloid leukemia; ASM, aggressive systemic mastocytosis; CEL, chronic eosinophilic leukemia; CML, chronic myeloid leukemia; CMMML, chronic myelomonocytic leukemia; Ig, immunoglobulin; ISM, indolent systemic mastocytosis; MCL, mast cell leukemia; MPD, myeloproliferative disorder; NHL, Non-Hodgkin's lymphoma; n.r., not reported so far; PDGFRα, platelet-derived growth factor receptor-α; SM, systemic mastocytosis; SM-AHNMD, SM with an associated hematologic clonal non-mast cell lineage disease; SSM, smoldering systemic mastocytosis; ?, not known so far.

^a AML with t(8;21) according to the World Health Organization.

^b In approximately 20% to 30% of all cases of SM, a monoclonal gammopathy with undefined significance (MGUS) is detectable.

* Score: +, detected in most cases; +/-, detected in a subset of cases; –, detected only rarely.

associated CEL (SM-CEL), a special subvariant of SM-AHNMD. Table 1 provides a summary of common defects that can be identified in patients with SM.

A second important aspect in the pathogenesis of SM is the abnormal expression of cell surface adhesion antigens on neoplastic MCs [45–47]. Several of these antigens, such as CD2 or CD25, are specifically detectable on neoplastic MCs in SM. CD2 (LFA-2) is of special interest, because this antigen is involved in cell–cell adhesion. Thus, MCs also express CD58 (LFA-3), the natural ligand of CD2. An attractive hypothesis is that CD2-CD58-induced aggregation of MCs in SM may contribute to abnormal cluster formation [46]. MCs in SM also express other cell–cell adhesion molecules, however [48–50]. Whether these molecules, especially CD2, indeed play a pathogenetic role in SM remains unknown at present. It is also unknown whether the *KIT* mutation D816V or another defect is responsible for abnormal expression of CD2 (or other adhesion-related molecules) on MCs in patients with SM.

Diagnostic criteria and World Health Organization classification

Traditionally, mastocytosis can be divided into CM and SM [27–30]. Localized MC tumors (mastocytomas and MC sarcoma) are rare [27,28]. CM is usually diagnosed in early childhood [51]. By contrast, most adult patients have SM. In adults, the diagnosis is usually established by a bone marrow examination [52,53], whereas in most children, a bone marrow examination is not required. Apart from the bone marrow, other organs, such as the liver or the gastrointestinal tract, may be affected in SM [54–58]. In contrast to SM, CM shows spontaneous regression in a significant number of cases, mostly during or shortly before or after puberty [59].

SM is a persistent disease in which the *KIT* mutation D816V is detected as a recurrent and frequent defect [20–26]. In some patients, this mutation is not only found in MCs but also in non-MC lineage (myeloid) cells [25,26,60–64]. Based on such data, SM is now accepted to be a myeloproliferative disorder (MPD) [32–34]. This concept is consistent with the observation that MCs derive from multipotent myeloid progenitor cells [7–11] and with the relatively high incidence of AHNMDs, including secondary leukemias, that occur in these patients [65–68].

During the past decade, substantial progress has been made in the morphologic, phenotypic, and genetic characterization of neoplastic MCs [32–35]. Based on these advances, an updated consensus classification for mastocytosis and disease-related criteria has been developed and adopted by the World Health Organization (WHO) [69,70]. This new WHO classification is thus able to differentiate between SM and CM, between SM and myelomastocytic disorders, and between SM and a reactive increase in MCs through defined and generally accepted criteria [69,70]. These criteria have been called SM criteria and are divided into major SM criteria and minor SM criteria (Table 2). If at least one major criterion and one minor criterion or at least three minor criteria are fulfilled, the final diagnosis is SM (see Table 2).

Histology and immunohistochemistry (major criterion)

The most important step in the diagnostic workup of adult patients is a thorough examination of the bone marrow (biopsy and aspirate) [27–30,52,53,71]. The major SM criterion is the presence of compact, dense, multifocal MC infiltrates within a bone marrow biopsy section. The most suitable marker for MC detection in such biopsies is tryptase [71–74]. Thus, antibodies against tryptase detect even small-sized (compact or diffuse) MC infiltrates [71–74]. Compact MC infiltrates are diagnostic and may also be detectable in extramedullary visceral organs [53–58].

Apart from compact and sharply demarcated MC infiltrates, other types of MC infiltrates have been described [52,53]. In more advanced MC disorders (eg, ASM, MCL), MC infiltrates may show a diffuse or mixed (compact

Table 2
World Health Organization criteria for systemic mastocytosis

Major ^a	Multifocal dense infiltrates of MCs (> 15 MCs in aggregate) in tryptase-stained biopsy sections of the bone marrow or of another extracutaneous organ
Minor ^a	More than 25% of MCs in bone marrow or other extracutaneous organ(s) show abnormal morphology (i.e, are atypical MC type I or are spindle-shaped MCs) in multifocal lesions in histologic examination <i>KIT</i> mutation at codon 816 ^b in extracutaneous organ(s) (in most cases, bone marrow cells are examined) <i>KIT</i> + MCs in bone marrow show aberrant expression of CD2 and/or CD25 Serum total tryptase > 20 ng/mL (does not count in patients who have AHNMD-type disease)

Abbreviations: AHNMD, associated (clonal) hematologic non-mast cell lineage disease; MCs, mast cells.

^a If at least one major criterion and one minor criterion or at least three minor criteria are fulfilled, the diagnosis SM can be established [69,70].

^b Activating mutations at codon 816, in most cases, *KIT* D816V.

infiltrate with diffuse component) infiltration pattern [52,53]. In patients with ASM or MCL, the remaining bone marrow architecture is often altered by the MC infiltrate, whereas this is not the case in typical indolent systemic mastocytosis (ISM). Here, the MC infiltrate does not lead to an alteration in the architecture of the remaining (surrounding) normal bone marrow even if MCs are diffusely spread in these areas [52,53].

Minor diagnostic criteria for systemic mastocytosis

Minor SM criteria relate to the morphology of MCs (eg, spindle-shaped, atypical MC type I), their phenotype (eg, CD2, CD25), elevated serum tryptase, and demonstration of codon 816 mutations of *KIT* [69,70]. The application of such criteria is often crucial in the diagnostic workup, because MCs may also increase and even form focal infiltrates in reactive MC hyperplasia or in myelomastocytic disorders [75–78]. Major and minor SM criteria are listed in Table 2. Box 1 shows differential diagnoses to be considered in suspected SM.

Morphology of mast cells in bone marrow smears

The bone marrow smear in suspected SM may show an increased percentage of MCs; abnormal morphology of MCs; or additional cytomorphologic abnormalities, such as myelodysplasia, eosinophilia, or an increase in blasts, which must always raise the suspicion of an AHNMD [69,70,79]. In normal bone marrow, the percentage of MCs is low (<0.05%). In patients with SM, the percentage is usually higher [79]. An MC percentage of greater than 10% in bone marrow smears is associated with a poor prognosis and often is indicative of aggressive disease [79]. If the percentage exceeds

Box 1. Differential diagnosis of systemic mastocytosis^a

- A. Systemic disorders mimicking MC mediator effects
 - Vascular diseases (with hypotension and shock)
 - Endocrinologic disorders (eg, diabetes, adrenal tumors, VIPoma)
 - Neurologic and psychiatric disorders (eg, encephalopathy, neuritis)
 - Gastrointestinal disorders (eg, Crohn's disease, ulcerative colitis)
 - Infectious diseases (eg, parasitic infections, hepatitis)
- B. Benign disorders associated with MC activation
 - Allergies, atopic disorders
 - Benign cutaneous flushing
 - Idiopathic anaphylaxis
 - Chronic urticaria
 - Drug effects on MCs
- C. Local MC hyperplasia
 - Immunocytoma with reactive focal increase in MCs
 - Cutaneous tumors (eg, melanomas, basal cell carcinoma)
 - Chronic inflammation (eg, autoimmune disorders, intestinal ulcer)
 - Treatment with recombinant SCF
- D. Myelomastocytic overlap syndromes
 - Myelomastocytic leukemia (myeloid neoplasm with increase in MCs but criteria to diagnose SM not fulfilled)
 - Tryptase-positive acute myeloid leukemia (AML)
 - KIT-positive AML with blast cells expressing CD2 (FAB AML-M4eo, some M3)
 - AML with aberrant expression of *KIT* point mutations at codon 816
 - Chronic myeloid leukemia with accumulation of tryptase-positive cells
 - Idiopathic myelofibrosis with focal accumulation of MCs
 - Acute or chronic basophilic leukemia

^a SM criteria are sufficient to discriminate SM from these differential diagnoses.

20%, MCL is diagnosed provided that SM criteria are met [79]. Based on an established proposal, four stages of MC maturation can be recorded: nongranulated (tryptase-positive) blast, metachromatically granulated blast (metachromatic blast), promastocyte (atypical MC type II or MCs with bi- or multilobed nuclei), and mature MC (typical mononuclear MCs) (Table 3) [69,70,79]. Immature MCs are frequently detectable in patients with ASM or MCL [79]. In ISM, bone marrow MCs are more mature, albeit they do show characteristic morphologic abnormalities, including cytoplasmic extensions, oval nuclei, and a hypogranulated cytoplasm [79]. Such MCs are called “atypical MC type I” and are detected in most patients with ISM [79].

Abnormal immunophenotype of mast cells in systemic mastocytosis

MCs exhibit a characteristic cell surface antigen phenotype in normal tissues as well as in SM [32,45–50]. Thus, in patients with SM, a number of CD antigens are usually overexpressed on bone marrow MCs compared with normal MCs [45–47]. MCs in patients with SM usually coexpress CD2 and CD25, two surface antigens that are not expressed in normal MCs [45–47]. Therefore, abnormal expression of at least one of these two antigens on MCs is a minor SM criterion [69,70]. Expression of CD2 and CD25 in bone marrow MCs is usually investigated by flow cytometry [45–47] (see the article by Escribano and colleagues elsewhere in this issue). An alternative is immunohistochemistry [80,81]. In both instances, CD25 is the more sensitive parameter.

Serum tryptase measurement

Tryptase is a well-established and important disease-related marker that should be determined in patients with suspected mastocytosis [4–6]. In healthy individuals, serum tryptase levels range between less than 1 and 15 ng/mL [4–6]. In patients with CM, tryptase levels are normal to slightly elevated [4–6]. This is

Table 3
Mast cell subtypes defined by morphologic criteria

Cell type	Morphologic features
Metachromatic blast	Blast-like, few or several metachromatic granules Special tests (phenotyping) is applied to confirm MC lineage involvement (to exclude basophils)
Promastocyte or atypical MC type II	Mostly immature MCs with bi- or multi-lobed nuclei, often hypogranulated
Atypical MC type I	MCs in which two of the three following morphologic aspects are found: Cytoplasmic extensions (spindle shape) Hypogranulated cytoplasm Oval decentralized nucleus
Mature MC or typical tissue MC	Round cell with round central nucleus and well-granulated cytoplasm

Abbreviation: MC, mast cell.

also observed in cases with “isolated” bone marrow mastocytosis (BMM) [6]. Higher tryptase values are recorded in SM. Thus, in most patients with SM, total serum tryptase levels exceed 20 ng/mL, which serves as a minor SM criterion (see the article by Schwartz elsewhere in this issue) [4–6]. Moreover, tryptase levels in SM are believed to correlate with the burden of neoplastic MCs [5,6]. Elevated tryptase levels are also seen in other myeloid neoplasms, however, especially acute and chronic myeloid leukemias and myelodysplastic syndromes (MDS) without mastocytosis [82–85]. Moreover, total tryptase levels may transiently increase during a severe allergic reaction [85,86]. Thus, MC tryptase alone cannot be regarded as a disease-specific and diagnostic marker of SM. Based on these limitations, a persistently elevated serum total tryptase level of greater than 20 ng/mL is used as a minor criterion of SM provided that an AHNMD has been excluded [69]. All in all, tryptase is a valuable first (and preinvasive) screen marker and a useful diagnostic test in suspected SM, and it should be applied in all patients with recognition of its potential limitations [4–6,87].

Molecular and cytogenetic tests

The examination of the bone marrow in suspected SM should include analysis of *KIT* for codon 816 mutations. A sensitive routine test is restriction fragment length polymorphism (RFLP) analysis [35]. In patients with suspected SM, the mutation should always be sought in bone marrow cells. If the test result is negative in a bone marrow sample, sequence analysis to screen for other *KIT* mutations may be performed. Any sequence analysis may yield false-negative results because of low sensitivity, however [35]. By contrast, a false-negative RFLP result is unusual unless MC infiltrates in the bone marrow are extremely small (as in BMM) or MCs are outnumbered by D816V-negative leukemic cells. In such patients, the mutation may only be detected when enriched (sorted or microdissected) MCs are analyzed.

In patients with (suspected) AHNMD, bone marrow cells should not only be examined for the presence of *KIT* mutations but subjected to molecular analyses seeking specific fusion genes or specific chromosomal defects related to a hematopoietic neoplasm [34]. Likewise, in patients with coexisting eosinophilia, bone marrow or blood cells should be examined for the presence of a *CHIC-2* deletion and for the *FIP1L1/PDGFRA* fusion gene [33]. In SM-AML, the t(8;21) is often detected (see Table 1). Apart from molecular markers and chromosomes, it may sometimes be appropriate to measure the numbers of colony-forming progenitor cells in patients with suspected SM-AHNMD [34,88].

Categories and subvariants of mastocytosis

The delineation of subcategories of CM is based on macroscopic inspection and biopsy of lesional skin [51,89–91]. Based on these aspects, three

major subvariants of CM have been defined by the WHO: maculopapular cutaneous mastocytosis (MPCM) or urticaria pigmentosa (UP), diffuse CM, and solitary mastocytoma of skin [51,69,70,89–91].

In patients with suspected SM, a number of staging investigations are required to define the exact subtype of disease. Aggressive SM is characterized by progressive infiltration of diverse organs by MCs, with resulting impairment of organ function; respective findings are called C-Findings [69,70,92]. MC infiltration with associated organomegaly should not be regarded as organopathy (C-Finding) unless accompanied by signs of impaired organ function [69,92]. Thus, organomegaly is also found in patients with an indolent or uncertain (smoldering) course [60–64] and is then regarded as a B-Finding [69]. B- and C-Findings are listed in [Box 2](#). In patients with a suspected AHNMD [65–68], WHO criteria (for SM and AHNMD) are used to define the subvariant of the AHNMD (see [Table 1](#)) [69]. It may sometimes

Box 2. B- and C-Findings

B-Findings: indication of high burden of MCs and expansion of the genetic defect into various myeloid lineages

1. Infiltration grade (MCs) in greater than 30% in bone marrow in histology and serum total tryptase levels greater than 200 ng/mL
2. Hypercellular marrow with loss of fat cells, discrete signs of dysmyelopoiesis without substantial cytopenias or WHO criteria for an MDS or MPD
3. Organomegaly: palpable hepatomegaly, splenomegaly, or lymphadenopathy (on CT or ultrasound) greater than 2 cm without impaired organ function

C-Findings: indication of impaired organ function attributable to MC infiltration (has to be confirmed by biopsy in most cases)

1. Cytopenia(s): ANC less than 1000 per μL , hemoglobin less than 10 g/dL, or platelets less than 100,000 per μL
2. Hepatomegaly with ascites and impaired liver function
3. Palpable splenomegaly with hypersplenism
4. Malabsorption with hypalbuminemia and weight loss
5. Skeletal lesions: large-sized osteolyses and/or severe osteoporosis causing pathologic fractures
6. Life-threatening organopathy in other organ systems that is definitively caused by an infiltration of the tissue by neoplastic MCs

be difficult to discriminate between SM-AML, MCL, and a myelomastocytic leukemia [75,76,78]. MCL is a rare subentity of SM, where SM criteria are fulfilled and there is a diffuse leukemic infiltration of hematopoietic tissues by highly atypical MCs [27–30,69,70,92–94]. In contrast to ISM, patients with MCL (and most with ASM) lack UP-like skin lesions [27–30,69,70,92–94]. Table 4 provides a summary of variants of mastocytosis recognized by the WHO.

An important aspect of mastocytosis is the frequent occurrence of mediator-related symptoms. These symptoms may be mild but may also be severe or even life-threatening [95–97]. It is important to be aware that such severe symptoms can occur in any subvariant of mastocytosis (CM or SM) and that the symptoms are not by themselves diagnostic of aggressive disease (not regarded as C-Findings). In all patients with mediator-related symptoms (requiring therapy), it is appropriate to document the aspect by adding the subscript SY to the final diagnosis (eg, SM_{SY}, CM_{SY}).

The following sections provide a brief overview of variants and subvariants of mastocytosis recognized by the WHO, with special reference to diagnostic criteria.

Table 4
World Health Organization classification of mastocytosis^a

Variant term	Abbreviation	Subvariants
Cutaneous mastocytosis	CM	Urticaria pigmentosa (UP) Maculopapular CM (MPCM) Diffuse CM (DCM) Mastocytoma of skin
Indolent systemic mastocytosis	ISM	Smouldering systemic mastocytosis (SSM) ^b Isolated bone marrow mastocytosis (BMM) ^b
Systemic mastocytosis with an associated (clonal) hematologic non-mast cell lineage disease	SM-AHNMD	SM-AML SM-MDS SM-MPD SM-CEL, SM-HES SM-CMML SM-NHL
Aggressive systemic mastocytosis	ASM	Lymphadenopathic SM with eosinophilia
Mast cell leukemia	MCL	Aleukemic MCL
Mast cell sarcoma	MCS	
Extracutaneous mastocytoma		

Abbreviations: AML, acute myeloid leukemia; CEL, chronic eosinophilic leukemia; CMML, chronic myelomonocytic leukemia; HES; hyper easinophilic syndrome; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder.

^a For details of the World Health Organization classification of mastocytosis, see references 69 and 70.

^b Provisional subentities.

Cutaneous mastocytosis

CM preferentially develops in early childhood [51,90]. Diagnostic MC infiltrates are confined to the skin by definition [51,69]. To prevent confusion with SM, the obsolete term *CM with systemic involvement* should be avoided. In most patients with SM, a characteristic macular or maculopapular rash is observed [51,89,90]. In a smaller group, skin lesions are diffuse or nodular [51]. A positive Darier's sign is a typical finding. Blistering of the skin may also be observed but is a rare event. The diagnosis of CM is based on typical skin lesions, demonstration of characteristic infiltrates of MCs in the histology of lesional skin, and lack of SM criteria [51,69]. The serum tryptase level in CM is less than 20 ng/mL in most cases [4–6,69].

As mentioned previously, three categories of CM have been defined by the WHO: (1) MPCM (UP), (2) diffuse cutaneous mastocytosis (DCM), and (3) mastocytoma of skin [51,69,70]. MPCM (UP) is the most frequent type of CM [89,90]. A number of (rare) subvariants of MPCM or UP have been described, including a plaque form, a nodular form, and a telangiectatic subvariant (telangiectasia macularis eruptiva perstans [TMEP]) [51,90,98,99]. The prognosis of MPCM (UP) is favorable. In many children, skin lesions regress during or shortly before puberty. By contrast, in adults, the disease frequently persists and often turns out to be (convert to) SM. In some patients with CM, skin lesions are extensive or accompanied by severe mediator-related symptoms (CM_{SV}) requiring therapy. A reasonable approach in such cases is to offer mediator-targeting drugs or to consider psoralen–UV-A (PUVA) therapy [51,90,100]. In severe cases, glucocorticoids may be required as well. DCM is less frequently diagnosed [51,90,91,101]. In contrast to UP, a diffuse erythrodermic rash is seen [102]. The prognosis in DCM is variable, and the condition may persist into adulthood. Solitary mastocytoma of the skin is usually seen in early childhood [51,90,103]. In many cases, the tumor resolves spontaneously. Otherwise (persistent nodules), excision is recommended [103].

Indolent systemic mastocytosis

ISM is the most frequently diagnosed variant of SM. ISM is associated with SM criteria, the presence of typical skin lesions, and an indolent course with a normal life expectancy [69,70,95]. Mediator-related symptoms are often recorded [95,96]. The bone marrow is invariably affected and displays multifocal dense MC infiltrates [52,53]. In typical cases, the infiltration grade is low [52,53]. In the bone marrow smear, there are less than 5% MCs, which are usually atypical MC type I (see Table 3) [79]. Apart from the marrow, MC infiltrates may be detected in other organs, including the liver, spleen, and the gastrointestinal tract [53–58]. MCs usually coexpress CD2 and CD25 with KIT and contain the *KIT* mutation D816V [20–23,45,69]. In most patients, the serum tryptase concentration exceeds

20 ng/mL [4–6,85,86]. Depending on the symptoms recorded, patients with ISM may require treatment with “mediator-targeting” drugs, including antihistamines, but are not treated with cytoreductive agents (Table 5) [29,30,34,95,97,104]. Skin lesions in ISM may also require treatment. In most cases, transient responses are seen with PUVA therapy [105].

Isolated BMM is a special (provisional) subvariant of ISM. BMM is characterized by the absence of skin lesions, lack of multiorgan involvement, and a low or normal serum tryptase level [6,27,28,69]. It is important to separate BMM from ASM or MCL, where skin lesions are also absent but baseline serum tryptase levels are usually (extremely) high. Patients with BMM may (or may not) have mediator-related symptoms. In symptomatic patients, antimediator-type therapy is recommended.

Smoldering systemic mastocytosis (SSM) is another provisional subentity of ISM [60–64,69]. In contrast to typical ISM, two or three B-Findings can be recorded (see Box 2). These B-findings reflect a high burden of MCs and the extension of the clonal disease process to several myeloid lineages

Table 5
Cytoreductive treatment options for patients with systemic mastocytosis

Disease variant	Treatment options
Typical indolent systemic mastocytosis (ISM)	No cytoreductive treatment required (exception: consider IFN- α 2b for severe osteoporosis even if no histology documenting ASM is available)
Smouldering systemic mastocytosis (SSM)	Watch and wait in most cases; however, in select cases (eg, rapidly progressive B-findings), IFN- α 2b with or without glucocorticoids can be considered
SM-AHNMD	Treat AHNMD as if no SM is present and also treat SM as if no AHNMD was found; if splenomegaly and hypersplenism prohibit therapy, consider splenectomy
SM-CEL + FIPL1/PDGFRA	Imatinib (STI571)
SM-AML	Curative chemotherapy with or without SCT, or supportive/palliative drugs
SM-MDS	Palliative in most cases
Aggressive systemic mastocytosis (ASM) with slow progression	IFN- α 2b with glucocorticoids or 2CdA; in patients without detectable <i>KIT</i> D816V, imatinib (STI571) can be considered
ASM with rapid progression and patients who do not respond to IFN- α 2b	Polychemotherapy ($\pm$ IFN- α 2b); consider SCT in select cases (after debulking); for select cases, 2CdA or other cytoreductive drugs can be considered; consider hydroxyurea as palliative drug
Mast cell leukemia (MCL)	Polychemotherapy ($\pm$ 2CdA, $\pm$ IFN- α 2b); consider SCT after successful debulking; consider hydroxyurea as palliative drug

Abbreviations: AML, acute myeloid leukemia; CEL, chronic eosinophilic leukemia; IFN, interferon; MDS, myelodysplastic syndrome; PDGFRA, platelet-derived growth factor receptor- α ; SCT, stem cell transplantation; SM-AHNMD, systemic mastocytosis with an associated (clonal) non-mast-cell lineage disease.

[64,69]. Clinically, the smoldering state has an uncertain prognosis and a variable clinical course. In some instances, the clinical course is long-lasting and silent. In other patients, an AHNMD or ASM develops after a certain latency period. Typically, patients with SSM have a bone marrow infiltration grade greater than 30% (dense infiltrates), serum tryptase levels greater than 200 ng/mL, signs of myelodysplasia or myeloproliferation in their bone marrow, and palpable organomegaly (hepato-, spleno-, or lymphadenopathy) [64,69]. These B-Findings are attributable to organ infiltration by MCs or by other myeloid (neoplastic) cells. Impairment of organ function (C-Findings) is not observed, however. The bone marrow in SSM typically contains mixed infiltrates (dense focal with an additional diffuse component) of MCs [52,53]. These MCs may be quite immature. The *KIT* mutation D816V is detectable in most cases [60–64]. In most instances, the mutation is also detected in other myeloid lineages, and thus in unfractionated blood leukocytes [60–64]. The treatment of SSM is identical to that in patients with ISM; however, patients with SSM should be observed closely for signs of progression or occurrence of an AHNMD or ASM.

Systemic mastocytosis with an associated clonal hematologic non-mast cell lineage disease

In a group of patients with SM, an AHNMD may be diagnosed [65–70]. In these cases, criteria to diagnose an AHNMD as well as SM criteria are met [69]. Patients with SM-AHNMD are categorized according to the AHNMD and the type of SM. In most cases, a myeloid neoplasm, such as an MPD (eg, idiopathic myelofibrosis [IMF], CEL), or an acute myeloid leukemia (AML) develops [65–70]. MDS/MPD-overlap syndromes may also be diagnosed in patients with SM-AHNMD. In contrast, the occurrence of a lymphoid neoplasm is a relatively rare event. In all patients, separate treatment plans for SM and the AHNMD component of the disease should be established. In these patients, SM should be treated as if no AHNMD is present and AHNMD should be treated as if no SM had been diagnosed (see Table 5). Likewise, in patients with SM and associated CEL with the *FIP1L1/PDGFRA* fusion gene, imatinib (STI571) has recently been shown to produce reasonable responses similar to those seen in CEL without coexisting SM [106,107]. In patients with SM-AML, polychemotherapy (which would be given in patients with AML without SM) may induce complete hematologic remission of AML, although the SM component of the disease may not respond to this therapy [67,108]. An important aspect in SM-AHNMD is that the SM component may present as ISM or ASM, which, in turn, has implications for determining the treatment plan. In some patients, cytoreductive drugs may show beneficial effects for both disease components.

Aggressive systemic mastocytosis

This rare subvariant of SM is characterized by organ damage caused by aggressive or even devastating infiltration of MCs into various organs [27–30,69,70,92]. In contrast to MCL, the bone marrow smear shows less than 20% MCs [69,92]. In contrast to ISM or SSM, C-Findings indicating impaired organ function (organ damage) attributable to MC infiltration are detectable (see Box 2). These patients show one of the following: (1) significant cytopenia(s); (2) impairment of liver function attributable to MC infiltration, often with ascites; (3) osteolyses with pathologic fractures; (4) malabsorption with weight loss; (5) splenomegaly with hypersplenism; or (6) life-threatening impairment of organ function in other organ systems [69,70,92]. The most commonly affected organs are the liver, bone marrow, and skeletal system. UP-like skin lesions are usually absent [69,70,92]. The histology of the bone marrow in ASM shows a variable degree of infiltration with mixed (ie, dense focal plus diffuse) MC infiltrates [52,53]. The cytology may disclose major cell atypia, with occurrence of promastocytes and metachromatic blasts [69,79]. Patients with ASM are candidates for treatment with cytoreductive or experimental (targeted) drugs (see Table 5). Patients with relatively slow progression are usually treated with glucocorticoids (prednisone) and interferon- α (IFN α ; initial standard dose of 3 million IU administered subcutaneously three times a week) [92,109–113]. Prednisone (50–75 mg administered orally daily) should be started a few days before IFN α [34,92,97,113]. During the first days of treatment, the patient should be hospitalized. After a few weeks, the IFN α dose can usually be escalated to 3 to 5 million IU/d and the prednisone can be tapered to a low maintenance dose (12.5 mg/d or less). In patients with osteopenia or osteoporosis, glucocorticoids should always be combined with a bisphosphonate [92,97]. Patients with ASM with rapid disease progression (to MCL or AML) or failure to respond to IFN α are candidates for 2CdA or polychemotherapy (see Table 5) [34,92,94,114–116]. The use of targeted drugs in ASM has also been considered. Imatinib (STI571) has been described to be effective in some of these patients. In fact, several patients with SM with wild-type KIT or KIT mutations other than D816V seem to respond to imatinib [38,107]. Most patients with SM exhibit KIT D816V, however, which apparently confers resistance against imatinib [117,118]. Therefore, imatinib is not recommended for patients with ASM or MCL in whom KIT D816V is detectable. More recent data suggest that some of the novel tyrosine kinase inhibitors, including PKC412, BMS354825, and AMN107, may act cytoreductive on MCs even if these cells display KIT D816V.

Mast cell leukemia

MCL is a rare neoplasm defined by increased numbers of highly atypical MCs in bone marrow smears ($\geq 20\%$) and in the peripheral blood

[27–30,92–94]. Patients typically experience rapidly progressive organopathy involving the liver, bone marrow, and other organs (C-Findings). The bone marrow typically shows a diffuse and dense infiltration pattern with highly abnormal MCs [69,70,79,92–94]. MCs often show a blast-like morphology and/or have polylobed nuclei (promastocytes) [69,79]. In typical cases, MCs account for more than 10% of circulating blood leukocytes [69,79,94]. In a smaller group of patients, in which MCs account for less than 10%, the diagnosis of aleukemic MCL is established [69,79,94]. In many patients, MCs express CD2 and CD25. The *KIT* mutation D816V may be detected (not in all cases). The prognosis in MCL is poor. Most patients survive less than 1 year and respond poorly to cytoreductive drugs or chemotherapy [69,79,92,94]. A curative approach for MCL is not available (see Table 5) [94]. A highly experimental option is stem cell transplantation, which may be considered for young patients who enter remission in response to polychemotherapy or in response to a targeted drug.

Summary

During the past few years, mastocytosis research has reached important milestones, including the formulation of diagnostic criteria, definition of markers, and targeting of mutated KIT. Important aims for the future are to standardize diagnostic assays and techniques, and to achieve harmonization among centers as a basis for the design of multicenter clinical trials in SM, including the rare ASM and MCL subvariants.

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