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Updated Diagnostic Criteria and Classification of Mast Cell Disorders: A Consensus Proposal

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Abstract

Mastocytosis is a hematologic neoplasm characterized by expansion and focal accumulation of neoplastic mast cells (MC) in diverse organs, including the skin, bone marrow (BM), spleen, liver, and gastrointestinal tract. The World Health Organization classification divides the disease into prognostically distinct variants of cutaneous mastocytosis (CM) and systemic mastocytosis (SM). Although this classification remains valid, recent developments in the field and the advent of new diagnostic and prognostic parameters created a need to update and refine definitions and diagnostic criteria in MC neoplasms. In addition, MC activation syndromes (MCAS) and genetic features predisposing to SM and MCAS have been identified. To discuss these developments and refinements in the classification, we organized a Working Conference comprised of experts from Europe and the United States in August 2020. This article reports on outcomes from this conference. Of particular note, we propose adjustments in the classification of CM and SM, refinements in diagnostic criteria of SM variants, including smoldering SM and BM mastocytosis (BMM), and updated criteria for MCAS and other conditions involving MC. CD30 expression in MC now qualifies as a minor SM criterion, and BMM is now defined by SM criteria, absence of skin lesions and absence of B- and C-findings. A basal serum tryptase level exceeding 20 ng/mL remains a minor SM criterion, with recognition that hereditary alpha-tryptasemia and various myeloid neoplasms may also cause elevations in tryptase. Our updated proposal will support diagnostic evaluations and prognostication in daily practice and the conduct of clinical trials in MC disorders.

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Introduction

Mastocytosis is a hematologic neoplasm defined by expansion and accumulation of neoplastic mast cells (MC) in the skin and/or in internal organs, such as the bone marrow (BM), spleen, lymph nodes, liver, and gastrointestinal tract.[1–5] The classification of the World Health Organization (WHO) delineates mastocytosis into cutaneous mastocytosis (CM), systemic mastocytosis (SM) and MC sarcoma (MCS) (Supplemental Digital Content, Table S1, http://links.lww.com/HS/A201).[6–10] Based on disease-specific features, SM is further divided into indolent SM (ISM), smoldering SM (SSM), aggressive SM (ASM), SM with an associated hematopoietic neoplasm (SM-AHN), and MC leukemia (MCL).[6–10] MCS is a rare, localized, aggressive MC tumor that usually progresses to MCL within a short time.[11–14] The prognosis in advanced SM (ASM, SM-AHN, MCL) and MCS is unfavorable (Supplemental Digital Content, Table S1, http://links.lww.com/HS/A201). Without successful therapy, the estimated median survival time in these patients is less than 3 years.

In a vast majority of all patients with SM, the disease-driving *KIT* mutation D816V is expressed in neoplastic cells.[15–19] In some SM patients, including those with well-differentiated (WD) MC morphology, other or no *KIT* mutations are detected, and in true MCS, neoplastic cells usually lack *KIT* D816V.[12–14,18] In childhood CM, several different *KIT* mutations have been described, including *KIT* D816V.[18,20]

Patients with MC disorders frequently suffer from mediator-related symptoms.[21–26] Depending on genetic variables, comorbidities, and efficacy of prophylactic therapy, the symptoms may be mild, severe, or even life-threatening.[21–26] However, there are also patients with CM or SM who do not develop any mediator-related symptoms over years. In those with severe recurrent symptoms (anaphylaxis), serum tryptase levels usually increase substantially above the individual's baseline during an attack, and a MC activation syndrome (MCAS) may be diagnosed.[24,26–29] A genetic variable that may influence the frequency and severity of mediator-induced symptoms in SM is hereditary alpha-tryptasemia (HαT), a recently described autosomal dominant trait defined by an increased copy number of the *TPSAB1* gene encoding alpha tryptase.[30–33] Most HαT carriers present with an elevated basal serum tryptase level. Patients with SM who carry HαT may suffer from recurrent severe episodes of anaphylaxis and thereby qualify as a MCAS, especially when a concomitant allergy is present.[29,33] Indeed, IgE-dependent allergies are relevant comorbidities in SM.[21,22,25,29] Another relevant condition associated with SM is osteopathy which may manifest as osteosclerosis, osteopenia, osteoporosis, or osteolysis with the potential for pathologic fractures.[34–38]

With regard to survival and progression, prognostically relevant pathologies are concomitant myeloid neoplasms (AHN), including chronic myelomonocytic leukemia, myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), MDS/MPN overlap-neoplasms, chronic eosinophilic leukemia, and acute myeloid leukemia (AML).[39–43] In these patients, neoplastic cells (MC, AHN cells, or both) may display chromosomal abnormalities and additional somatic defects, including mutations in *ASXL1*, *SRSF2*, *TET2*, *JAK2*, *RUNX1*, or *RAS*.[43–51] The prognosis in these patients is unfavorable and is usually dictated by the aggressiveness of the AHN.

Over the past 15 years, a number of additional prognostic variables have been identified and validated in adult patients with SM. Moreover, multiparametric scoring systems have been established through which overall and progression-free survival can be predicted.[52–56] In addition, a number of novel treatment concepts have been established in the past 2 decades, including KIT D816V-targeting tyrosine kinase inhibitors, allogeneic hematopoietic stem cell transplantation (SCT), immunotherapies, and IgE-targeting approaches.[26,57–67] These treatments have greatly improved prognosis, survival, and the quality of life in patients.[26,57–67] Therefore, it is of utmost importance to establish the correct diagnosis and to base treatment decisions on disease- and patient-related parameters, following the principles of personalized medicine.[5,10,24,26,29,66]

To provide contemporary standards, it is also important to adjust disease-related criteria to new developments. In fact, although the diagnostic criteria and classification defined between 2001 and 2017 are still valid, recent developments in the field and the advent of new markers have created a need to refine and update diagnostic criteria for MC disorders.

To address these issues, a Working Conference was organized in 2020. The current article provides a summary of discussions and outcomes of this conference.

Historical overview: criteria and classification of mastocytosis 2000–2020

Between 1991 and 2000, criteria to diagnose CM and SM were discussed, validated, and prepared in a series of clinical studies, workshops, and conferences.[5,6,68] The resulting diagnostic criteria and classification of CM and SM were presented in the Year 2000 Working Conference and were adopted by the WHO in 2001.[6,7] The WHO classification of MC disorders was subsequently refined in 2008[8] and 2017.[9,10] To assist the WHO, our Europe (EU)/US consensus group organized Working Conferences in 2000,[6] 2005,[69] 2010,[24] 2012,[70] 2015,[5,10] and 2020 (Supplemental Digital Content, Table S2, http://links.lww.com/HS/A201). Moreover, competence networks have been established in the EU and the United States, namely the European Competence Network on Mastocytosis[71] and the American Initiative in Mast Cell Diseases,[72] with the shared goals of improving patient management, to fostering research, and supporting the development of diagnostic criteria and standards of care in MC disorders.

Working conference, consensus discussion, and preparation of consensus statements

The year 2020 Working Conference on MC disorders was organized from August 30 to September 1, 2020. The related consensus discussions took place from February 2020 to January

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2021. Because of the coronavirus (SARS-CoV-2) pandemic, the Working Conference was organized as a hybrid (combined on-site and web-based) meeting. The consensus-forming procedure and the development of consensus statements are described in the supplement. As in 2010,[24] we also invited patients and their representatives to support the consensus group by formulating and forwarding important open issues, questions, and suggestions to the scientific community (Supplemental Digital Content, Table S3, http://links.lww.com/HS/A201). Details are described in the Supplemental Digital Content, http://links.lww.com/HS/A201.

CM and skin involvement in SM: proposed modifications

In the diagnostic algorithm, a first essential step is to define whether the patient is suffering from CM or SM.[5–10,73] It is important to note that most patients with CM are children, whereas SM is usually diagnosed in adulthood.[5–10,73] Still, most adult patients with SM present with skin lesions. In contrast to children, adults always undergo a complete staging, including a BM investigation (histology and aspirate), to confirm or exclude SM by applying SM criteria.[5–10,69] In contrast, a BM examination is usually not recommended in children, unless clear signs for an advanced SM or another hematologic neoplasm are found.[69,73]

In children, CM is defined by typical skin lesions, a positive Darier's sign, and the absence of clinical signs of systemic involvement (Supplemental Digital Content, Table S4, http://links.lww.com/HS/A201).[69,73] In adults, CM is defined by typical skin lesions, the Darier's sign, and/or a positive skin histology and absence of criteria sufficient to diagnose SM in staging examinations.[69,73] An important point is that the discrimination between CM and SM in adults is of prognostic significance as patients with CM exhibit better progression-free survival.[74] Another important point is that in patients with CM, systemic involvement with clonal MC (eg, 1 or 2 minor SM criteria detected) is not sufficient for the diagnosis of SM unless the full spectrum of SM criteria is fulfilled.[5–10] In adults with skin lesions who did not (yet) undergo a complete staging with BM analyses, the provisional diagnosis of "mastocytosis in the skin" (MIS) is appropriate (Supplemental Digital Content, Table S4, http://links.lww.com/HS/A201).[69,73,74] In children, the provisional diagnosis of MIS does not apply unless (i) serum tryptase levels exceed 100 ng/mL and/or (ii) clear signs for a systemic hematologic disease (eg, unexplained splenomegaly) are found and (iii) no BM studies were performed (Supplemental Digital Content, Table S4, http://links.lww.com/HS/A201).[69,75] Otherwise, the diagnosis in children is CM.[69]

Once diagnosed, CM should be subclassified into maculopapular CM (MPCM), diffuse CM, and cutaneous mastocytoma.[5–10,69,73] Diagnostic criteria for these variants are shown in Table 1. Most children with CM and almost all adults with CM exhibit MPCM. In many children, cutaneous lesions disappear spontaneously before or during adolescence. Two distinct forms of childhood MPCM have been recognized: a variant characterized by monomorphic small-sized lesions, and a second form defined by polymorphic (often larger) lesions.[73,76] Only the monomorphic form is also found in adults, suggesting that only this variant is likely to persist into adulthood, whereas polymorphic lesions usually disappear which is in line with clinical observations.[73,74,76] Therefore, childhood MPCM is further divided (subclassified) into the monomorphic form and polymorphic form (Table 1).

Refinements of major and minor SM criteria

In general, major and minor diagnostic criteria and the resulting definition of SM remain unchanged compared with previous proposals.[5–10] The diagnosis of SM can be established when at least 1 major and 1 minor or 3 minor SM criteria are fulfilled

Table 1.

Proposed Classification and Criteria of CM.

Variant and Subvariant(s)	Abbreviation	Features/Criteria
Maculopapular cutaneous mastocytosis	MPCM	Positive Darier's sign[a]
		Typical pigmented skin lesions
Urticaria pigmentosa	UP	Positive histology[b]
		KIT mutation in lesional skin
Monomorphic variant	MPCM-m	Monomorphic skin lesions[c]
Polymorphic variant	MPCM-p	Polymorphic skin lesions[c]
		No signs/criteria of SM[d]
Diffuse cutaneous mastocytosis	DCM	Positive Darier's sign[a]
		Diffuse involvement of the entire skin
		Positive histology[b]
		Criteria for SM not fulfilled[d]
Cutaneous mastocytoma		Positive Darier's sign[a]
		Positive histology[b]
Isolated mastocytoma		One single lesion
Multilocalized mastocytomas		Two or 3 lesions
		No signs/criteria of SM[d]

[a]Whereas the Darier´s sign and typical skin lesions serve as major diagnostic criteria (in both the monomorphic and polymorphic variant), a positive histology and the presence of an activating *KIT* mutation serve as minor diagnostic criteria. In the case of atypical lesions or a negative Darier's sign, the diagnosis of mastocytosis can still be established provided that minor criteria are fulfilled. In young children with typical mastocytoma, testing for the Darier's sign is often avoided because of the risk to provoke systemic reactions. Testing for the Darier's sign should always be done gently and only when needed for diagnosis.

[b]Histologic examination includes standard stains and immunohistochemistry using antibodies against tryptase and KIT regardless of the variant (monomorphic or polymorphic). The numbers of KIT$^+$/tryptase$^+$ mast cells is usually elevated in lesional skin in patients with mastocytosis and skin involvement.

[c]The monomorphic variant is found in children and adults. When found in children, the likelihood that the lesions will persist into adulthood is high. Polymorphic skin lesions are detected in childhood MPCM but usually not in adults with CM or systemic mastocytosis. When detected in children, the likelihood that the polymorphic skin lesions will spontaneously disappear at or shortly after puberty (in adolescence) is high.

[d]In all adult patients, SM has to be excluded by staging investigations including bone marrow studies. In children, bone marrow studies are only performed when clinical signs and symptoms and/or laboratory findings are indicative of an advanced hematologic disease.

CM = cutaneous mastocytosis; SM = systemic mastocytosis.

Table 2.

Proposed Refined Major and Minor SM Criteria.

Major criterion:	Multifocal dense infiltrates of mast cells (≥15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s)
Minor criteria:	a. ≥25% of all mast cells are atypical cells (type I or type II) on bone marrow smears or are spindle-shaped in mast cell infiltrates detected in sections of bone marrow or other extracutanous organs[a]
	b. KIT-activating *KIT* point mutation(s) at codon 816 or in other critical regions of *KIT*[b] in bone marrow or another extracutaneous organ
	c. Mast cells in bone marrow, blood, or another extracutaneous organ express one or more of: CD2 and/or CD25 and/or CD30[c]
	d. Baseline serum tryptase concentration >20 ng/mL (in the case of an unrelated myeloid neoplasm, an elevated tryptase does not count as an SM criterion. In the case of a known HαT, the tryptase level should be adjusted[d]
	If at least 1 major and 1 minor or 3 minor criteria are fulfilled → the diagnosis is SM

[a]In tissue sections, an abnormal mast cell morphology counts in both a compact infiltrate and a diffuse (or mixed diffuse + compact) mast cell infiltrate. However, the spindle-shaped form does not count as an SM criterion when mast cells are lining vascular cells, fat cells, nerve cells, or the endosteal-lining cell layer. In the bone marrow smear, an atypical morphology of mast cells does not count as SM criterion when mast cells are located in or adjacent to bone marrow particles. Morphologic criteria of atypical mast cells have been described previously.[6]

[b]Any type of *KIT* mutation counts as minor SM criterion when published solid evidence for its transforming behavior is available. A list of such *KIT* mutations (including variants in *KIT* codons 417, 501–509, 522, 557–560, 642, 654, 799, 816, 820, 822) is provided in Supplemental Digital Content, Table S6, http://links.lww.com/HS/A201 (KIT-activating mutations are labeled in bold).

[c]All 3 markers fulfill this minor SM criterion when expression in mast cells can be confirmed by either flow cytometry or by immunohistochemistry or by both techniques.

[d]Although the optimal way of adjustment may still need to be defined, one way is to divide the basal tryptase level by 1 plus the extra copy numbers of the alpha tryptase gene. Example, when the tryptase level is 30 and 2 extra copies of the alpha tryptase gene are found in a patient with HαT, the HαT-corrected tryptase level is 10 (30/3 = 10) and thus is not a minor SM criterion.

HαT = hereditary alpha-tryptasemia; SM = systemic mastocytosis.

(Table 2).[5–10] The major criterion is the multifocal infiltrate of MC forming compact aggregates of at least 15 MC in the BM or another extracutaneous organ system.[5–10] Sometimes, MC infiltrates may be distorted or even masked by AHN cell infiltrates. In these patients, the diagnosis SM (SM-AHN) can sometimes only be established after successful cytoreduction.[43,77] Therefore, we recommend that all SM criteria are applied again in all patients with a *KIT* D816V-mutated myeloid neoplasm after (successful) cytoreductive therapy.

The abnormal morphology of MC (atypical spindle-shaped cells with hypogranulated cytoplasm and oval nucleus) is the first minor SM criterion.[5–10] At least 25% of all MC must exhibit these morphologic features in BM smears or BM sections to qualify as a minor SM criterion.[5–10] Even if MC form only diffuse infiltrates without compact aggregates in BM sections, the abnormal MC morphology (≥25%) counts as a minor SM criterion (Table 2). However, the spindle-shaped morphology criterion does not include MC that are adjacent to (lining) blood vessels, endosteal surfaces, nerve cells, or fat cells.

Recent data suggest that CD30 expression in MC is strongly associated with SM but is not found in other myeloid neoplasms.[78–81] CD30 is detectable in neoplastic MC in a majority of patients with ISM and advanced SM by flow cytometry and immunohistochemistry (Figure 1; Supplemental Digital Content, Table S5, http://links.lww.com/HS/A201).[78–81] Even in patients with a WD morphology, where MC often lack CD2 and/or CD25, neoplastic MC usually display CD30.[80] Therefore, CD30 is proposed as a new addition to the existing minor SM criterion. The refined definition of this minor criterion is: MC express one or more of the 3 aberrantly expressed antigens: CD2, CD25, and CD30 (Table 2). It is important to note that all 3 markers may be detected by flow cytometry and/or immunohistochemistry. Initial data had reported a rough correlation between strong cytoplasmic expression of CD30 and advanced SM.[78] However, subsequent validation did not show a clear-cut delineation.[79–81] Therefore, our faculty concludes that CD30 does not qualify as a grading marker in SM. Another question was whether CD2 should be replaced by CD30. However, although CD2 is less frequently and less abundantly expressed in neoplastic MC compared with CD25, CD2 was not eliminated as criterion because of its specificity in SM, whereas CD25 is rarely detected also in MC in reactive states.

A number of different *KIT* variants can be detected in SM.[18] The most prevalent mutation is D816V. This mutation is found in around 90% of all adult patients with nonadvanced SM. However, other KIT-activating and thus disease-driving mutations may also be present, especially in cases with advanced SM.[18] Therefore, any *KIT* mutation that is known to cause ligand-independent activation of KIT should count as a minor SM criterion. A list of all relevant *KIT* mutations is provided in Supplemental Digital Content, Table S6, http://links.lww.com/HS/A201.

The basal serum level of tryptase is elevated in most SM patients.[82–85] Therefore, a clearly elevated basal serum tryptase is a minor SM criterion.[5–10] The consensus threshold is 20 ng/mL. However, apart from SM, a number of other conditions and pathologies are associated with an elevated tryptase level. Therefore, the following restrictions are proposed: (1) only the basal serum tryptase level (measured in a symptom-free interval) can qualify as a minor SM criterion; (2) the basal serum tryptase level does not qualify as a SM criterion when an AHN is also diagnosed (AHN cells may produce tryptase), and (3) in patients with known HαT, the basal tryptase level should be corrected for the presence of HαT. One suggested approach discussed in the conference was to correct for HαT by dividing the basal tryptase level by one plus the number of extra alpha tryptase gene-copies. Details are described in the Supplemental Digital Content, http://links.lww.com/HS/A201.

In patients with unknown *TPSAB1* status, the old definition of this SM criterion should apply. It is worth noting that testing for *TPSAB1* copy numbers is not yet available in all centers.

Proposed criteria for BM mastocytosis and separation from ISM and SSM

The separation between BM mastocytosis (BMM) and other forms of SM is of crucial importance for several reasons. One is that the absence of skin lesions is often observed in advanced SM.[5–10] Second, recent data suggest that patients with BMM with low disease burden (defined as no B-findings and a tryptase level <125 ng/mL) have a better prognosis than patients with typical ISM, SSM, and "BMM" with higher MC burden (high-risk BMM).[86] Therefore, we propose that BMM be defined as a separate SM variant where no B-finding is detectable and the basal tryptase level is below 125 ng/mL (ie, exclusion of high-risk BMM patients). As soon as one B-finding is detected and/or serum tryptase levels exceed 125 ng/mL, the patient should be diagnosed as ISM without skin lesions but not as BMM. The same holds true when dense infiltrates of atypical MC (major SM criterion) are detected in an extramedullary organ which also changes the diagnosis to ISM. Table 3 shows adjusted diagnostic criteria proposed for BMM, typical ISM (with or without skin lesions), and SSM. Since patients with advanced SM often present without skin lesions, it is of crucial importance to exclude the presence of C-findings and MCL in all patients with BMM (Table 3).

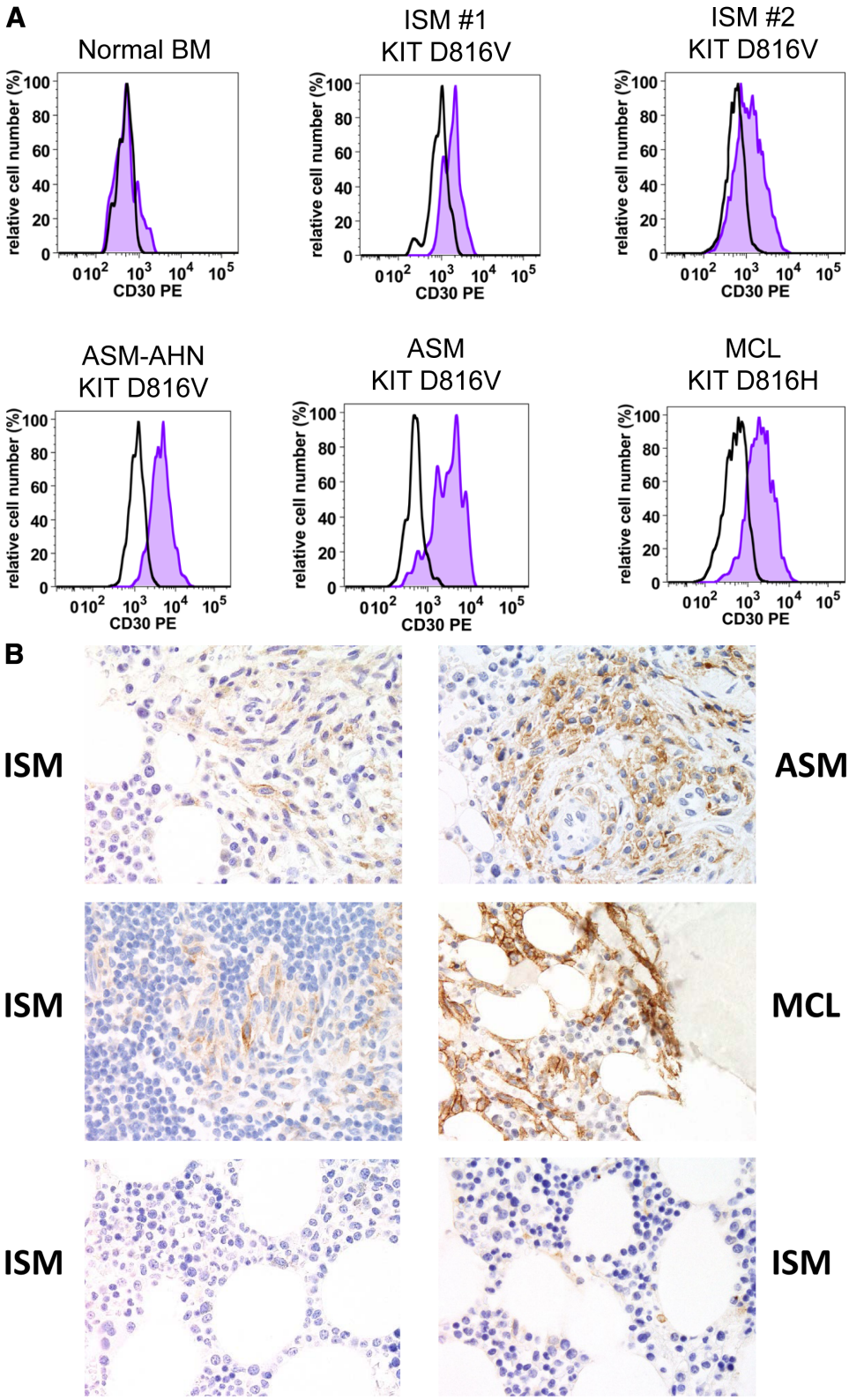

Figure 1. Expression of CD30 in neoplastic mast cells in systemic mastocytosis. (A), Flow cytometric detection of CD30 on neoplastic MC in patients with SM. BM cells were obtained from a control patient (no known BM disease; upper left image), patients with indolent SM (ISM: upper middle and right panels), and patients with advanced SM, namely 1 with ASM with an AHN (ASM-AHN: lower left image), 1 with ASM (lower middle histogram), and 1 with MCL by multicolor flow cytometry on a FACSCanto (Becton Dickinson). MC were identified as $CD117^{++}/CD45^{+}/CD34^{-}$ cells and stained with a phycoerythrin-labeled monoclonal antibody against CD30 (BerH8 from BD Biosciences; blue histograms). The isotype-matched control antibody (black open histogram) is also shown. (B), Immunohistochemical detection of CD30 in neoplastic MC. BM biopsy sections from patients with ISM, ASM, and MCL (as indicated) were stained with a monoclonal antibody against CD30 (Ber-H2 from Dako, Glostrup, Denmark) by an indirect immunoperoxidase staining technique as reported.[81] The 2 images at the bottom show the nonaffected BM in 2 patients with ISM (control). Images were prepared using an Olympus DP21 camera connected to an Olympus BX50 microscope equipped with 60×/0.90 UPlan-Apo objective lens (Olympus, Hamburg, Germany) and processed with Adobe Photoshop CS2 software version 9.0 (Adobe Systems, San Jose, CA) as described.[81] All patients gave written informed consent before BM samples were obtained and analyzed. AHN = associated hematologic neoplasm; ASM = aggressive SM; BM = bone marrow; ISM = MC = mast cells; MCL = MC leukemia; SM = systemic mastocytosis.

Other typical features of BMM are a relatively high prevalence of severe IgE-mediated allergies to bee and/or wasp venom (often with MCAS) and osteoporosis.[21,22,86–88] In most cases, the *KIT* D816V allele burden in the blood and MC infiltration grade in the BM are low. Sometimes, a WD MC morphology is detected. Regarding progression to advanced SM, the prognosis of BMM is favorable.[86]

Proposed modifications in B-findings and C-findings

B-findings are indicative of a high MC burden, expansion of SM in various organ-systems, and involvement of multiple myeloid lineages, without organ damage.[5–10] By contrast, C-findings are indicative of SM-induced organ damage.[5–10,89,90] It is important to note that organ damage caused by an AHN or by other etiologies (such as infection or therapy-induced) does not count as a C-finding. In addition, it is important to note that the causative impact of the local SM infiltrate (aggressive growth pattern) should be demonstrated by biopsy whenever possible to document the presence of a C-finding.[5–10,90,91] In patients with SM-AHN, it may sometimes be difficult to define the relative impact of the SM infiltrate and that of the AHN, especially when both disease components present as advanced malignancies (eg, ASM-AML). In these cases, both disorders may cause marked organ damage (eg, cytopenia).

Table 3.

Proposed Revised Criteria for BMM, Typical ISM, ISM Without Skin Involvement, and SSM.

Variant	Criteria
BMM	SM criteria fulfilled
	No skin lesions
	No B-finding(s)
	No C-finding(s)
	Basal serum tryptase <125 ng/mL
	No dense SM infiltrates in an extramedullary organ
	No signs/criteria for MCL
	No signs/criteria for an AHN
(Typical) ISM	SM criteria fulfilled
	Typical skin lesions
	No or one B-finding
	No C-finding
	No signs/criteria for MCL
	No signs/criteria for an AHN
ISM without skin lesions	SM criteria fulfilled
	No skin lesions
	No or one B-finding[a] and/or:
	Basal serum tryptase ≥125 ng/mL and/or:
	Dense SM infiltrates in an extramedullary organ
	No C-finding
	No signs/criteria for MCL
	No signs/criteria for an AHN
SSM	SM criteria fulfilled
	Two or 3 B-findings
	No C-finding
	No signs/criteria for MCL
	No signs/criteria for an AHN[b]

[a]Serum tryptase levels may exceed 200 ng/mL (if no other B-finding is detected) or below 200 ng/mL (in which case 1 B-finding may be detected).

[b]Additional mutations in other (driver) genes, such as *TET2*, may be detected by next generation sequencing. However, when new gene variants occur or the variant allele frequency increases over time, a re-examination of the bone marrow is required to exclude SM-AHN.

AHN = associated hematologic neoplasm; BMM = bone marrow mastocytosis; ISM = indolent SM; MCL = mast cell leukemia; SM = systemic mastocytosis; SSM = smoldering SM.

Our faculty also discussed whether new molecular and/or immunological parameters may qualify as indicators of a huge burden of MC and/or multilineage involvement and thus as B-findings. After a thorough discussion, our faculty agreed that a high variant allele frequency (VAF) of *KIT* D816V in aspirated BM cells or peripheral blood (PB) leukocytes (>10%) should qualify as indicator of a high burden of MC or a surrogate for multilineage involvement in SM and thus as B-finding (Table 4). In addition, multilineage involvement with *KIT* D816V as determined by quantitative polymerase chain reaction in sorted myeloid BM or PB leukocytes is indicative for (confirms the presence of) a B-finding and thus SSM. However, cell sorting is not routinely applied in daily practice in most centers. Finally, the presence of additional mutations (in other driver-genes such as *SRSF2* or *ASXL1*) in SSM was discussed. However, although clearly being indicative of a huge burden of clonal cells, our faculty concluded that such additional mutations are more commonly expressed in AHN subclones and thus support the diagnosis SM-AHN rather than SSM. Whereas in the original definition, B-findings should not be accompanied by major blood count abnormalities, our faculty is of the opinion that marked leukocytosis (persistent neutrophilia, monocytosis, and/or eosinophilia) and thrombocytosis may well be detected and even count as indication of myeloproliferation and thus confirmation of a B-finding, unless leukocytosis/thrombocytosis are caused by a reactive process or the diagnostic criteria for an overt MPN or MDS/MPN are fulfilled—in which case, the diagnosis changes to SM-MPN. Refined B-findings are shown in Table 4.

Refinements of C-findings were also discussed in our Working Conference. First, weight loss was removed as an independent C-finding but is now added as a confirming feature to both malabsorption and splenomegaly. In fact, the presence of weight loss per se, although clinically relevant, is problematic for several reasons, one being that weight loss is difficult to define in patients with, for example, concomitant ascites. Therefore, when present, weight loss confirms the organ-damaging impact of SM-induced organopathy but is per se no longer required as a defining feature of a C-finding. The second change in C-findings relates to osteolyses. In fact, only huge osteolyses (>2 cm in diameter) with clear clinical impact (eg, fractures) and confirmed histology, count as a C-finding. Smaller osteolyses and osteoporosis, even when associated with (pathological) fractures, do not count as C-finding (Table 4). Finally, it should be noted that organomegaly without organ damage does not count as C-finding, even when organomegaly is associated with constitutional symptoms.

Updated criteria for SSM

In general, the basic definition for SSM should remain the same: when SM criteria are fulfilled and 2 or 3 B-findings can be documented, but no (not a single) C-finding(s), no signs/criteria for MCL and no signs/criteria for an AHN are found, the final diagnosis is SSM (Table 3).[5–10] The updated B-findings described earlier should be applied in these patients. Since SSM may be associated with a less favorable prognosis compared with typical ISM or BMM,[41,53] it is important and standard to follow these patients closely to detect signs of progression as early as possible.[69] Re-evaluation and restaging should be performed when signs of advanced SM or AHN are detected.[69,91] Useful follow-up parameters are the basal tryptase level, alkaline phosphatase, and *KIT* D816V VAF in PB.[92–95] When these parameters change over time, C-findings occur, or blast cells or MC are detectable in differential counts, a re-examination of the BM is performed.[5,69,91,96] The same holds true for patients in whom new molecular lesions or expansion of a mutated subclone is detectable by next generation sequencing (suspected AHN). Patients with SSM may progress to ASM, SM-AHN, or MCL.[5,39,50,53,96,97]

Table 4.

Proposed Refined B-findings and C-findings.

B-findings	C-findings (SM-induced Organ Damage)
High MC burden: Infiltration grade (MC) in BM ≥30% in histology (IHC) and/or serum tryptase ≥200 ng/mL[a] and/or *KIT* D816V VAF ≥10% in BM or PB leukocytes	-
Signs of myeloproliferation and/or myelodysplasia[b]: Hypercellular BM with loss of fat cells and prominent myelopoiesis ± left shift and eosinophilia ± leukocytosis and eosinophilia and/or discrete signs of myelodysplasia (<10% neutrophils, erythrocytes, and megakaryocytes)	Cytopenia/s: ANC < 1 × 10^9/L Hb < 10 g/dL PLT < 100 × 10^9/L (one or more found)
Organomegaly: Palpable hepatomegaly without ascites or other signs of organ damage or/and palpable splenomegaly without hypersplenism and without weight loss or/and lymphadenopathy palpable or visceral LN-enlargement found in ULS or CT (>2 cm)	Hepatopathy: Ascites and elevated liver enzymes[c] ± hepatomegaly or cirrhotic liver ± portal hypertension Spleen: Palpable splenomegaly with hypersplenism ± weight loss ± hypalbuminemia GI tract: Malabsorption with hypoalbuminemia ± weight loss Bone: Large-sized osteolysis (≥2 cm) with pathologic fracture ± bone pain

[a]In the case of a known HαT, the basal serum tryptase level should be adjusted. Although the optimal way of adjustment still needs to be defined, one way is to divide the basal tryptase level by 1 plus the extra copy numbers of the alpha tryptase gene. Example, when the tryptase level is 300 and 2 extra copies of the alpha tryptase gene are found in a patient with HαT, the HαT-corrected tryptase level is 100 (300/3 = 100) and would thus not qualify as a B-finding.

[b]Signs of myeloproliferation and/or myelodysplasia must be discrete and stable (neither disappear nor progress) and must not reach diagnostic criteria of an MPN, MDS, or MPN/MDS in which case the diagnosis changes to SM-AHN. The presence of a myeloid AHN excludes B-findings and SSM by definition.

[c]Alkaline phosphatase levels are typically elevated in patients with advanced SM and SM-induced liver damage. In some of these patients, only elevated liver enzymes but no (clinically relevant) ascites is found.

AHN = associated hematologic neoplasm; ANC = absolute neutrophil count; BM = bone marrow; CT = computed tomography; GI = gastrointestinal; HαT = hereditary alpha-tryptasemia; Hb = hemoglobin; IHC = immunohistochemistry; LN = lymph node; MC = mast cells; MDS = myelodysplastic syndrome; MPN = myeloproliferative neoplasm; PB = peripheral blood; PLT = platelet count; SM = systemic mastocytosis; SSM = smoldering systemic mastocytosis; ULS = ultrasound; VAF = variant allele frequency.

Criteria for ASM and ASM variants

The diagnosis ASM is based on SM criteria and visible signs of SM-induced organ damage (C-findings) as well as absence of signs/criteria indicative of MCL or AHN.[5–10,97] At least 1 C-finding must be documented to call a condition ASM. MC on BM smears and PB smears must be below 20% (to exclude MCL).[5–10,69,89] Based on established criteria, ASM can be divided into classical ASM (MC in BM smears <5%) and ASM in transformation to MCL (MC in BM smears 5%-19%) (Table 5).[5,97] In addition, patients with ASM can be classified into pure ASM and ASM-AHN (Table 5). Finally, ASM can be split into primary ASM and secondary ASM following CM, BMM, ISM, or SSM (Table 5).[5,97] All patients with ASM should have a close follow-up employing all clinical and laboratory parameters required to document progression and response to therapies. Indeed, despite therapy, patients with ASM may progress to MCL, ASM-AHN, or MCL-AHN.[5–10,53–55,64]

SM-AHN and AHN variants

In accordance with previous proposals, any type of a hematologic neoplasm should qualify as an AHN, including myeloid neoplasms and (rarely) lymphoid neoplasms.[5–10] An exception are lymphoid neoplasms detected in a separate organ system, for example, a stage 1 non-Hodgkin lymphoma (NHL) in a peripheral lymph node in a patient with BMM. In these exceptional cases, the NHL should not count as AHN. All AHN should be diagnosed, staged, and classified according to WHO criteria.[5–10] Pre/subdiagnostic clonal conditions, such as clonal hematopoiesis with indeterminate potential, monoclonal gammopathy of undetermined significance or monoclonal B lymphocytosis, do not count as AHN.

MCL and MCL variants

The principle definition and diagnostic criteria for MCL defined by the WHO remain unchanged.[5–10] The WHO classification also divides MCL into a classical (leukemic) form (MC ≥10% of all leukocytes in PB smears) and a more frequent, aleukemic variant (aleukemic MCL: MC <10% in PB smears).[5–10,97] MCL can further be classified into primary MCL (no previous SM known) and secondary MCL following a previous (lower grade) SM (Table 5).[97] In addition, MCL can be split into acute MCL (C-findings detectable) and chronic MCL where C-findings are not detectable (Table 5).[5,97] Compared with acute MCL, patients with chronic MCL have a better prognosis and may respond to therapy with KIT-targeting drugs. However, many of these patients progress to acute MCL over time. Finally, MCL can be classified into pure MCL and MCL-AHN where the prognosis is particularly poor.[96,97]

An important differential diagnosis to MCL is myelomastocytic leukemia (MML).[5–10,97–99] In these patients, SM criteria are not fulfilled and neoplastic MC (≥10% in BM or blood smears by definition) are derived from neoplastic stem cells of an underlying myeloid neoplasm.[99] In a subset of these patients, *KIT* mutations outside of codon 816 may be found. Based on our updated SM criteria, some of these cases may be reclassified as true MCL over time.

MCS and extracutaneous mastocytoma

The definition and criteria of classical MCS are shown in Supplemental Digital Content, Table S7, http://links.lww.com/HS/A201. As per definition, MCS is a localized tumor consisting of more or less immature MC that expand rapidly and show an aggressive and often invasive (sarcoma-like) growth pattern.[5–10] Any organ system may be affected and the disease can occur at any age.[11–14] As per definition, SM criteria are not fulfilled.[5–10] Apart from the classical MCS variant, a MCS-like progression of SM, including SM-AHN or MCL may be seen. In these patients, the primary diagnosis remains SM. Our faculty discussed whether in these cases, the term "secondary MCS" would be appropriate. However, to avoid confusion, the term "MCS-like progression" was selected as more appropriate. This decision is supported by the observation that MC in true MCS usually lack *KIT* mutations, whereas in most SM patients with "MCS-like progression," *KIT* D816V is detected.[11–14] Despite

Table 5.

Refined Classification and Criteria for Advanced SM, Including SM-AHN, ASM, and MCL.

Category	Subvariant	Defining Key Features (Criteria)
SM-AHN	According to SM variant:	
	BMM-AHN	WHO criteria (consensus criteria) for SM variants
	ISM-AHN	
	SSM-AHN[a]	
	ASM-AHN	
	MCL-AHN	
	According to the AHN:	
	SM with myeloid AHN (SM-CMML, SM-AML, …)	WHO criteria for myeloid AHN type
	SM with lymphoid AHN (SM-ALL, SM-MM, …)	WHO criteria for lymphoid AHN type
ASM	According to a previous MC neoplasm:	
	Primary ASM	No previous SM known
	Secondary ASM	Previous BMM, ISM, SSM, …
	According to an AHN	
	ASM without AHN	
	ASM-AHN	WHO criteria for AHN
	According to signs of progression:	
	ASM	<5% MC in BM smears
	ASM in transformation (=ASM-T)	5%–19% MC in BM smears
MCL	According to a previous MC neoplasm	
	Primary MCL	No previous MC disease known
	Secondary MCL	Previous BMM, ISM, SSM, MCS, …
	According to an AHN	
	MCL without AHN	
	MCL-AHN	WHO criteria for AHN
	According to organ damage	
	Chronic MCL	No C-finding(s)
	Acute MCL	One or more C-finding(s)
	According to blood involvement	
	Aleukemic MCL	MC <10% of blood leukocytes
	Leukemic MCL	MC ≥10% of blood leukocytes

[a]SSM-AHN is an extremely rare condition as signs of myeloproliferation and/or dysplasia will be regarded as sign of the (myeloid) AHN in almost all cases. However, SSM may still be diagnosed in a patient with AHN, for example, when the AHN is a lymphoid neoplasm (eg, SSM-CLL).
AHN = associated hematologic neoplasm; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; ASM = aggressive SM; BMM = bone marrow mastocytosis; CMML = chronic myelomonocytic leukemia; ISM = indolent SM; MCL = mast cell leukemia; MCS = mast cell sarcoma; MM = multiple myeloma; SM = systemic mastocytosis; SSM = smoldering SM; WHO = World Health Organization.

local and systemic therapy, the prognosis in MCS is unfavorable. Most patients progress to ASM or secondary MCL within short time.[11–14] The only curative approach appears to be SCT.[100]

Extracutaneous mastocytoma is an extremely rare localized benign tumor consisting of mature MC without histopathological evidence of invasive growth or major cell atypia. So far, less than 10 well-documented cases have been described, most of them in the lung.[101–103] Because of its rarity, extracutaneous mastocytoma was eliminated from the WHO classification in 2017. Since then, only 2 well-documented cases have been reported. Therefore, our faculty concluded that this very rare MC disease should not be reincorporated.

Impact of WD MC morphology

In some of the patients with SM, MC exhibit a rather mature morphology. In these cases, MC appear as round cells containing a round centralized nucleus and a well-granulated cytoplasm. These patients are often referred to as "well-differentiated SM."[104–107] However, a WD MC morphology can be detected (rarely) in almost all forms of SM and even in CM.[104–107] Therefore, our faculty concluded that the WD morphology should be added as appendix to the diagnosis and WHO variant of mastocytosis. Indeed, the clinical course and prognosis of patients with WD mastocytosis depends on the WHO type of the disease. For example, patients with ISM with a WD morphology of MC would be classified as ISM-WDSM (ISM_{WDSM}).

An important aspect is to recognize that in most patients with WDSM, *KIT* codon 816 mutations are not detected and neoplastic MC usually lack CD25 and CD2.[105] However, other *KIT* mutations (like K509I or F522C) may be detected, and neoplastic MC often display CD30. Therefore, the diagnosis of WDSM should be based on SM criteria, including expression of CD30 and KIT-activating *KIT* mutations. An important aspect is that several KIT mutant forms detected in WDSM are sensitive to imatinib therapy.[18,104,106,107]

Diagnostic criteria and classification for MCAS and related disorders

Diagnostic criteria and a classification for MCAS have been proposed by the EU/USA consensus group.[24,27–29] In addition, a diagnostic algorithm for patients with MCAS has been published.[29,108] Our group is of the consensus opinion that these diagnostic criteria and standards should be followed in the evaluation and classification of cases with suspected MCAS. Diagnostic criteria for MCAS are shown in Supplemental Digital Content, Table S8, http://links.lww.com/HS/A201, and the consensus classification of MCAS is shown in Supplemental Digital Content, Table S9, http://links.lww.com/HS/A201. Based on the underlying condition, MCAS can be divided into primary (monoclonal) MCAS (=MMAS) where clonal MC (and usually SM or CM) are found, secondary MCAS, where an allergic disease or another reactive condition is present, and idiopathic MCAS, where neither clonal MC nor another underlying condition (allergy and other) are detected (Supplemental Digital Content, Table S9, http://links.lww.com/HS/A201).[24,27–29,108] An important aspect is that MCAS can present as a mixed (clonal plus secondary) form where both SM and an underlying IgE-dependent allergy have been diagnosed.[29] These patients are at high risk to develop fatal episodes of MCAS.

Another important consideration is that in some patients, local mono-organ or chronic MC activation may be found.[29,108] However, it should be pointed out that it is often difficult or impossible to demonstrate the impact of MC in such conditions, and in many instances, other cell types (not MC) may be causative elicitors of clinical symptoms. The reality in these cases is that the terms "MC activation" or "MC involvement" are not justified from a scientific point of view.[108]

Global classification of MC disorders

In 2012, our consensus group proposed a global classification for all MC disorders.[24] In the current project and conference, we discussed novel markers and concepts as well as predisposing conditions and pathologies that may contribute to the manifestation or progression of MC disorders. Table 6 shows an updated version of a proposed global classification of MC pathologies and disorders. Finally, our group discussed the relationship between this classification and the International Statistical Classification of Diseases and Related Health Problems (ICD-10) code. Supplemental Digital Content, Table S10, http://links.lww.com/HS/A201, shows an overview of all MC disorders, pathologies, and predisposing conditions and related ICD-10 codes, and Supplemental Digital Content, Table S11, http://links.lww.com/HS/A201, provides features of ICD-10–defined MC activation disorders.

Standard approaches and diagnostic algorithms in daily practice

During the past 20 years, diagnostic markers, assays, and related diagnostic algorithms for the evaluation of patients with suspected MC disorders have been proposed.[5–10,18,24,27–29,73,97,108] These standards remain valid and their updated versions should be applied in daily practice. An overview of updated standards and refined diagnostic algorithms proposed by our consensus group is provided in the Supplemental Digital Content, http://links.lww.com/HS/A201. The same holds true for prognostic markers and recently established prognostic scoring systems, including the international prognostic scoring system, the molecular-adjusted revised prognostic score, the Red Española de Mastocitosis score, and the global prognostic score.[52–56] In addition, the Supplemental Digital Content, http://links.lww.com/HS/A201, provides a short overview of response criteria recommended in daily practice in MC disorders.

Unmet needs and recommendations provided by patients

Within the frame of the current project, our faculty asked patients and patient groups from 12 countries/regions (global effort) to express their concerns, wishes, and recommendations to the scientific community. Among top issues were better education and knowledge of physicians, increased awareness, better/easier access to specialized centers, and development of improved criteria and better treatments (Supplemental Digital Content, Tables S12, http://links.lww.com/HS/A201, and S13, http://links.lww.com/HS/A201).

Concluding remarks and future perspectives

Based on new markers, tools and recent developments in the field, we propose refined diagnostic criteria for mastocytosis and its variants. Whereas the fundamental classification of the WHO remains unchanged, the updated diagnostic criteria address new disease-related genetic and immunological markers and parameters of MC activation. We also propose an updated global classification of MC disorders, including MCAS. Our refined criteria and classification should support clinicians in daily practice and the conduct of clinical trials.

Table 6.

Proposed Global Classification of Mast Cell Pathologies and Related Conditions.

Disorder/Condition	Diagnostic Criteria/Defining Features
Mast cell hyperplasia	Reactive increase in normal mast cells No evidence for clonal mast cells Criteria for CM/SM/MCS not fulfilled
Mastocytosis	WHO criteria for CM, SM, or MCS fulfilled
MCAS[a]	MCAS criteria fulfilled ± Criteria for CM/SM/MCS fulfilled
Other MCAD[a]	Evidence for a clinically relevant, local or systemic mast cell activation but the criteria for MCAS are not fulfilled[a] ± Criteria for CM/SM/MCS fulfilled
MML	Advanced myeloid neoplasm diagnosed based on WHO criteria (eg, AML) Increase in neoplastic mast cells ≥10% Criteria for CM/SM/MCS not fulfilled

[a]MCAD can be divided into MCAS and other MCAD. The criteria to be used for concluding that there is evidence of clinically relevant, local, or systemic mast cell activation (disorder) in the absence of criteria that fulfill MCAS are discussed in the Supplemental Digital Content, Table S11, http://links.lww.com/HS/A201.

AML, acute myeloid leukemia; CM = cutaneous mastocytosis; MCAD = mast cell activation disorders; MCAS = mast cell activation syndromes; MCS = mast cell sarcoma; MML = myelomastocytic leukemia; SM = systemic mastocytosis; WHO = World Health Organization.

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Author Contributions

All authors contributed equally by actively participating in the Year 2020 Working Conference on Mast Cell Disorders (Vienna, August 30 to September 1, 2020) and by actively participating in preconference discussions (April 2020 until August 2020) and postconference discussions (September 2020 to March 2021). All authors contributed substantially by discussing and establishing refinements in the criteria and the classification of mast cell disorders.

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