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Diagnostic criteria and classification of mastocytosis: a consensus proposal

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Abstract

The term 'mastocytosis' denotes a heterogeneous group of disorders characterized by abnormal growth and accumulation of mast cells (MC) in one or more organ systems. Over the last 20 years, there has been an evolution in accepted classification systems for this disease. In light of such developments and novel useful markers, it seems appropriate now to re-evaluate and update the classification of mastocytosis. Here, we propose criteria to delineate categories of mastocytosis together with an updated consensus classification system. In this proposal, the diagnosis cutaneous mastocytosis (CM) is based on typical clinical and histological skin lesions and absence of definitive signs (criteria) of systemic involvement. Most patients with CM are children and present with maculopapular cutaneous mastocytosis (= urticaria pigmentosa, UP). Other less frequent forms of CM are diffuse cutaneous mastocytosis (DCM) and mastocytoma of skin. Systemic mastocytosis (SM) is commonly seen in adults and defined by multifocal histological lesions in the bone marrow (affected almost invariably) or other extracutaneous organs (major criteria) together with cytological and biochemical signs (minor criteria) of systemic disease (SM-criteria). SM is further divided into the following categories: indolent systemic mastocytosis (ISM), SM with an associated clonal hematologic non-mast cell lineage disease (AHNMD), aggressive systemic mastocytosis (ASM), and mast cell leukemia (MCL). Patients with ISM usually have maculopapular skin lesions and a good prognosis. In the group with associated hematologic disease, the AHNMD should be classified according to FAB/WHO criteria. ASM is characterized by impaired organ-function due to infiltration of the bone marrow, liver, spleen, GI-tract, or skeletal system, by pathologic MC. MCL is a 'high-grade' leukemic disease defined by increased numbers of MC in bone marrow smears ($\geq 20\%$) and peripheral blood, absence of skin lesions, multiorgan failure, and a short survival. In typical cases, circulating MC amount to $\geq 10\%$ of leukocytes (classical form of MCL). Mast cell sarcoma is a unifocal tumor that consists of atypical MC and shows a destructive growth without (primary) systemic involvement. This high-grade malignant MC disease has to be distinguished from a localized benign mastocytoma in either extracutaneous organs (= extracu-

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taneous mastocytoma) or skin. Depending on the clinical course of mastocytosis and development of an AHNMD, patients can shift from one category of MC disease into another. In all categories, mediator-related symptoms may occur and may represent a serious clinical problem. All categories of mastocytosis should be distinctively separated from reactive MC hyperplasia, MC activation syndromes, and a more or less pronounced increase in MC in myelogenous malignancies other than mastocytosis. Criteria proposed in this article should be helpful in this regard.

1. Introduction

In 1869, Nettleship and Tay described a unique cutaneous disease that showed a symmetrical spread with pigmented maculopapular lesions and an urticaria-like response to rubbing or scratching [1]. The disease was termed urticaria pigmentosa (UP). Soon after the discovery of the mast cell (MC) by Paul Ehrlich in 1879 [2], the lesions were found to contain focal accumulations of MC. For a long time, it was assumed that such pathologic accumulation of MC, called mastocytosis, is restricted to skin. However, in 1949, Ellis described a systemic form of mastocytosis with involvement of visceral organs [3]. During the last few decades, it was found that systemic mastocytosis (SM) can present with or without skin lesions and may show an either indolent or aggressive clinical course [4–7]. It was also found that SM might be complicated by an associated hematologic clonal, non mast cell lineage disease (AHNMD). In most cases, a myeloproliferative syndrome (MPS) or myelodysplastic syndrome (MDS) is diagnosed [4,5,8–10]. In a few cases, acute myeloid leukemia (AML) occurs [8–10]. In other patients, the MC disease itself was found to develop as a leukemia (mast cell leukemia) [4,5,11]. These patients are rare and have a poor prognosis.

Cutaneous mastocytosis (CM) without systemic involvement preferentially develops in childhood and has a favorable prognosis. Spontaneous remissions are often seen during (or shortly after) puberty [12]. The potential of spontaneous regression may have led to the speculation that (pediatric) CM is a non-neoplastic (reactive) disease, and to the use of the suffix — 'osis', traditionally used for reactive pathologies. However, recent data suggest that most variants of mastocytosis (at least SM) represent clonal disorders. This assumption has been based primarily on recurrent somatic (gain of function) mutations of *c-kit* (encoding the SCF receptor) that have been detected in MC in patients with SM [13,14]. Moreover, specific recurrent abnormalities in the cell surface phenotype of MC have been described [15]. The notion that mastocytosis (at least SM) is a clonal disease process raises several questions. One important question is whether mastocytosis (SM) can be discussed in association with other clonal hematologic disorder. In this regard, it is important to note that MC share a common progenitor as well as differentiation antigens with myelomonocytic cells [16–19]. In fact, today, MC can be regarded as myeloid cells. Moreover, in patients with SM, *c-kit* mutations can be detected not only in MC, but also in other myeloid cells, $CD34^+$ progenitors, and sometimes even in B-lymphocytes [20]. In light of these findings and the potential occurrence of an AHNMD, systemic mastocytosis may be regarded as related to hematopoietic stem cell disorders — in fact, based on current knowledge, SM may best be addressed as a myeloproliferative disease.

Based on organ involvement, impairment of organ function, and other aspects, a number of classification systems for mastocytosis have been established and have been used [4,5,21–25]. However, the knowledge about MC and mastocytosis has increased in recent years. In addition, a number of useful novel markers have been developed, and re-evaluation of older and new markers of disease has resulted in the potential to introduce well-defined disease criteria [26]. In light of these developments, it now seems justified to reconsider diagnostic aspects and to propose an updated consensus classification system for mastocytosis. In the present article, we propose such a consensus classification system together with consensus criteria to diagnose mastocytosis and to define each category of disease.

2. Patients, parameters, and analyses

We have retrospectively analyzed patients with established mastocytosis in different centers of Europe and North America. In addition, a larger number of control cases without mastocytosis (myeloid neoplasms) were examined. In all cases, clinical findings, laboratory findings, and histologic and immunohistologic data have been collected. The clinical course was compared to, and correlated with, laboratory and histologic parameters. Data from almost all patients have been published previously. In addition, we reviewed the entire literature whenever possible to compare and discuss our findings. Final discussions and preparative work were made in the 'Year 2000 Working Conference on Mastocytosis'.

2.1. Case history, symptoms, clinical findings, and clinical staging

The time of onset of disease (usually the first time of appearance of skin lesions recognized by patients or parents) defines mastocytosis of childhood (before puberty) and mastocytosis of adulthood (after puberty).

In general, mastocytosis appears to be a sporadic disease. Nevertheless, in a very few cases, the family history may reveal 'familial mastocytosis'. In such patients, the definitive diagnosis of non-sporadic familial mastocytosis should be based on a thorough examination of relatives.

Constitutional symptoms may be present or absent in patients with mastocytosis. If present, they may be quite variable and include weight loss, pain, nausea, headache, malaise, or fatigue [6,7,21–23]. Constitutional symptoms may be due to uncontrolled proliferation of MC, involvement of distinct organs (central nervous system, GI tract, skeleton, bone marrow-anemia), or systemic mediator activity [6,7,27–32]. In fact, MC produce and release a variety of clinically relevant mediators such as histamine, leukotrienes, proteases, or heparin (Table 1). Depending on the type of MC involved, burden of MC, course of disease, and co-existing disorders, these mediators may be released to a variable degree resulting in different clinical patterns [27–32]. In some of the patients, the symptoms are mild and may not require therapy. In other patients, however, symptoms are severe, despite the use of antihistamines or other drugs. Severe and life-threatening, mediator-related symptoms may also be recorded and may represent a major clinical problem [7,27,28,33]. Such severe and recurrent MC mediator-related symptoms (one of the following: syncope, hypotensive shock, diarrhoea, abdominal pain, peptic ulcer, bone pain, headache, or flushing; see Table 2) should be noted and used to help define the final diagnosis using 'SY' as an added subscript (N_{SY}; for example: SM_{SY}). Patients with mastocytosis may also have a co-existing allergy, although the incidence may be the same as that in the general population.

Macroscopic examination of the skin can show typical lesions that may be almost diagnostic (maculopapular, erythrodermic/diffuse, Darier's sign, mastocytoma) [34]. However, in each case, the diagnosis must be confirmed by biopsy and histology [34]. The absence of skin lesions does not rule out the diagnosis 'mastocytosis'. An extensive bleeding tendency (spontaneous petechiae or/and hematomas) may be found in advanced disease as a result of thrombocytopenia or/and a coagulation disorder (consumption, hyperfibrinolysis). Physical examination reveals organomegaly in some SM patients: in fact, palpable lymphadenopathy, hepatomegaly, and/or splenomegaly may be recorded. Organ infiltration by MC may lead not only to organomegaly, but also to impairment or even loss of organ function [35–42]. Typical clinical findings (= C-findings) are malabsorption with weight loss, hepatomegaly with ascites, splenomegaly with hypersplenism, or pathologic (spontaneous) fractures due to osteolysis [35–42] (Table 3). In severe (high grade) disease, bone marrow failure with anemia, thrombocytopenia, and/or recurrent infections (due to neutropenia) may occur (Table 3). In aggressive disease variants (progressive organopathy), but not in indolent SM, the infiltration by MC in the affected organ(s) should be confirmed by a biopsy.

Table 1
Mast cell mediation-related disease features[a]

Disease feature(s)	Mediator(s)
Systemic:	
Vascular instability	Histamine, cysLT, PGD_2, PAF
Increased vasopermeability	Histamine, cysLT, PAF
Fibrosis	Transforming Growth Factor-β
Eosinophilia	IL-5
Lymphocytic infiltration	IL-6, chemokines
Local anticoagulation	Heparin
Fibrinolysis	Tissue type plasminogen activator
Fibrinogenolysis	Beta-tryptase
Mast cell hyperplasia	SCF, IL-3, IL-6
Cachexia	Tumor necrosis factor
Skin:	
Pruritus	Histamine
Urticaria	Histamine
Lungs:	
Bronchoconstriction	Histamine, PGD_2, cysLT, PAF, Endothelin
Secretion of mucus	Histamine, proteases, PGD_2, LTC_4
Pulmonary edema	Histamine, cysLT, PAF
GI-Tract:	
Gastric hypersecretion	Histamine
Cramping, abdominal pain	Histamine, cysLT, PAF
Diarrhea	Histamine
Skeletal system:	
Bone remodeling	Tryptase, chymotryptic proteases
Osteoporosis	Heparin, proteases

[a] LT, leukotriene; PG, prostaglandin; PAF, platelet activating factor; IL, interleukin. cysLT refers to the parent, LTC_4, and its receptor active metabilites, LTD_4 and LTE_4.

2.2. Complementary staging

Depending on the age of the patient, clinical findings, and laboratory parameters, staging of mastocytosis

Table 2
Mediator-related symptoms defined by subscript 'SY' in final diagnosis[a]

Recurrent syncope
Hypotensive shock
Diarrhea with abdominal pain
Peptic ulcer disease
Severe bone pain
Severe headache
Recurrent flushing

[a] The subscript '$_{SY}$' should be added to the diagnosis if one or more of these symptoms have been recorded and have persisted or recurred – and have required the use of anti-mediator drugs.

Table 3
B- and C-findings[a]

B-findings	C-findings (impaired organ function)[b]	Organ failure
(1) High MC burden: Infiltration grade (MC) in bm >30% in histology and serum tryptase >200 ng/ml	–	–
(2) Dysmyelopoiesis: hypercellular marrow with loss of fat cells or discrete signs of Myelodysplasia or Myeloproliferation, normal blood counts or slight persisting deviation without progression	(1) Organopathy (bm) Cytopenia/s: ANC <1000/μl Hb <10 g/dl Plt <100 000/μl. (one or more found)	Severe progressive pancytopenia ANC <500/μl + recurrent Infections Transfusion dependence Plt <20 000/μl, recurrent bleedings
(3) Organomegaly: palpable hepatomegaly without ascites or other signs of organ impairment or/and lymphadenopathy palpable or visceral LN-enlargement found in US or CT (>2 cm) or/and palpable splenomegaly without hypersplenism	(2) Organopathy (liver) Palpable hepatomegaly with ascites, abnormal liver function tests and/or portal hypertension (3) Organopathy (spleen) Palpable splenomegaly with hypersplenism (4) Organopathy (GI tract) Malabsorption with hypalbuminemia and weight loss (5) Organopathy (skeleton) Bone lesions with large osteolyses or/and severe osteoporosis with pathologic fractures	Progressive deterioration of liver function, loss of appropriate protein synthesis, hepatic coma, severe coagulation disorder

[a] bm, bone marrow; Plt, platelets; ANC, absolute neutrophil count; LN, lymph node.
[b] C-findings: Impaired organ function due to infiltration by neoplastic MC.

should include one or more of the following: X-ray of chest, X-ray of skeletal system, ultrasound (US) of abdomen, and endoscopy of the GI tract (with biopsy) [43–45]. Extensive staging may be required in cases of suspected aggressive (high grade) disease or suspected AHNMD. By contrast, the staging should be kept to a minimum whenever the likelihood for non-systemic disease is high, especially in childhood (in most pediatric cases, complementary staging is not required!). In some cases with SM, an MRI analysis of the bone marrow, a bone scan, or a CT may be helpful [45]. The X-ray, US, or CT may reveal hepatomegaly, splenomegaly, or lymphadenopathy (significantly enlarged lymph nodes: >2 cm) [45]. The X-ray of the skeleton may disclose signs of osteoporosis, osteosclerosis, or focal areas of osteolysis [21,41–43]. In most cases, the osteolytic lesions are small in size (<0.5 cm) and not accompanied by clinical symptoms. In a few cases, however, larger osteolyses with pathologic (spontaneous) fractures are found [41,42]. Endoscopy may show diffuse infiltration of the GI tract by MC infiltrates, ulcer(s), or diffuse bleeding [29–31].

2.3. Histology and immunohistochemistry

The histomorphological examination of MC in tissue sections in patients with (suspected) mastocytosis requires the use of appropriate stains. We recommend that Giemsa-stained, Toluidine Blue-stained, and anti-tryptase-stained tissue sections be used in all cases. In addition, MC can be made visible using the chloroacetate esterase (CAE) reaction [4,5,46]. However, CAE is not specific for MC, but is also expressed in neutrophils [46]. The diagnosis 'mastocytosis' is traditionally based on the demonstration of focal accumulations of MC with typical histological and cytomorphological properties [4,5,21,46–68]. However, depending on the organ system analyzed, shape of MC, maturation stage of MC, type of MC-disease, and presence of other (concomitant) disorders, it may be sometimes difficult to diagnose mastocytosis by routine histology [46–68].

In the skin, the multifocal accumulation of MC that accompanies clinically evident UP will directly lead to the diagnosis of cutaneous mastocytosis [34,58]. Similarly, it is straightforward to diagnose mastocytoma of skin by histology. In other cases (diffuse infiltrates,

telangiectatic variant), it may be more difficult to establish the diagnosis of CM by histology.

Systemic mastocytosis (SM) is usually diagnosed by histological examination of the bone marrow, the organ system most frequently affected. In SM, the infiltration pattern varies, however [4,5,46–50,61–63]. The typical lesion is the multifocal dense infiltrate. Sometimes, however, MC are loosely scattered without focal dense infiltration sites. In these cases, the diagnosis of SM may be missed unless clear (diagnostic) morphologic or biochemical signs of (systemic) involvement are also present. If such additional signs are not found, the pathologist may ask for additional biopsy material. The use of antibodies against tryptase is always superior in the screen for diagnostic histological lesions [46,48,62–64,67–69].

The most common type of histological lesion found in the bone marrow in SM is the multifocal dense, sharply demarcated infiltrate of MC (= major criterium) [4,5,46–50]. The diagnostic aspects of these infiltrates relate to cell density (aggregate formation) and appropriate number of MC in aggregates (> 15). Moreover, these infiltrates may show a characteristic apposition to the endosteal surface or to blood vessels. The typical histomorphological aspects of neoplastic MC (spindle-shaped) may be regarded as second (minor) diagnostic criterium. In fact, if a significant percentage of MC in focal dense bone marrow infiltrates are spindle-shaped (> 25%), then the diagnosis is SM (diagnostic criteria fulfilled). However, in some cases, most of the MC are round and almost indistinguishable from normal tissue MC. Then, the diagnosis may be more difficult to be substantiated, especially when infiltrates are small in size and accompanied by a diffuse increase in bone marrow MC, or by an AHNMD. In such cases, the application of additional, disease-related markers/SM-criteria (*c-kit* mutation, expression of CD2 or CD25, serum tryptase levels) may be helpful. In other cases, the predominant type of infiltrate in the bone marrow is of a diffuse and dense (extensive) pattern. Such a pattern is more closely related to the leukemic variant of SM in which the normal marrow is replaced by MC infiltrates [11,21,46,48,63]. Sometimes, these MC are very immature and hypogranulated and therefore difficult to identify unless specific stains (tryptase) are applied [62–68]. An important differential diagnosis in such cases is the diffuse and extensive spread of very immature, often blast-like MC (= metachromatic blasts) seen rarely in patients with MDS, AML or MPS without mastocytosis [70–72]. Also, in MDS, MPS, or AML, non-metachromatic blasts (without metachromatic granules) may express small amounts of tryptase (aberrant expression) [73]. Again, the use of additional disease-related markers (criteria) may be helpful to confirm or exclude SM in such patients. In all cases, tryptase-immunohistochemistry is useful to determine the infiltration grade of MC in the bone marrow [46,48,63]. Thus, in all patients with SM, the grade of bone marrow infiltration by MC should be estimated based on a representative tryptase-stained bone marrow biopsy section. In mixed infiltrates (focal dense plus diffuse), two subtypes of patterns can be distinguished: the mixed type that does not affect the remaining bone marrow — seen in indolent SM, and the mixed type affecting the surrounding bone marrow [48] — this type of mixed infiltrate is seen in aggressive or leukemic variants of disease [46,48]. Another important histological feature in SM is the increase of collagen fibres in MC infiltrates, and — if they are peritrabecular — a thickening of the adjacent bone (sclerosis). Pathologic bone formation independent of SM infiltrates is seen only rarely in SM. Fibrosis and osteosclerosis are frequently seen in indolent SM, but apparently not in mast cell leukemia [74].

In contrast to the bone marrow, the diagnostic criteria discussed above may not be applicable in other organ systems [48,50–58]. Likewise, an increase in MC in the spleen should always lead to the suspicion of mastocytosis (SM) since the number of MC in normal/reactive spleen is very low [48]. In other organs, however, like the GI tract, the physiologic concentration of MC is rather high, so that an additional increase or even the formation of dense MC infiltrates may not automatically lead to the histological diagnosis of mastocytosis. Independent of the organ system, however, a multifocal dense sharply demarcated, infiltrate of spindle-shaped MC is diagnostic for SM [46,48].

2.4. Bone marrow aspirates — cytology

The cytomorphological examination of the bone marrow is an important diagnostic approach and integral part of staging in mastocytosis. We recommend the use of both Giemsa-stained and Toluidine Blue-stained bone marrow smears for cytomorphologic assessments in SM. Cytological aspects of MC may be examined in the vicinity of bone marrow particles. However, the actual percentage of MC (given as a percentage of all nucleated bone marrow cells counted) has to be determined a fair distance from any marrow particles. Otherwise, the general guidelines for counting and cytological classification of bone marrow cells should be applied. In many patients with SM, the percentage of MC in bone marrow smears (among all nucleated cells) is less than 5% or even less than 1%, even if the histology records a high infiltration grade [75]. This information by itself may be diagnostic (exclusion of MCL). A percentage of bone marrow MC $\geq 20\%$ in the smear is almost diagnostic for mast cell leukemia [11,73,75]. The MC in mastocytosis may show distinct morphological characteristics [75]. In most cases of SM,

bone marrow MC show the following cell atypias (deviations from normal tissue MC) (Table 4): (i) cytoplasmic extensions (special shapes: spindles or fusiform shapes), (ii) oval nuclei with excentric (decentralized) position, and (iii) hypogranulated cytoplasm with focal accumulations of granules with or without granule fusions. If two or three of these criteria are fulfilled, the cells are referred to as 'atypical mast cells characteristically found in SM' (proposed term: 'atypical mast cell type I') [75]. In a smaller group of patients, however, the bone marrow MC resemble mature round (normal) tissue MC without prominent or only minor cytological deviations. In more aggressive cases and in MCL, the cellular atypias are more prominent and often extensive (high-grade cytology): in a subset of these patients, many atypical bone marrow MC exhibit bi- or multilobed nuclei (proposed term: 'atypical mast cells type II') or a 'blast-like' morphology ('metachromatically granulated blasts' or 'metachromatic blasts') (Table 4) [75]. A percentage of such high-grade (immature) MC lineage cells ('atypical mast cells type II' + 'metachromatic blasts') of greater than 20% (of all counted MC in marrow smears) is almost invariably associated with high-grade (malignant) SM [75]. In case of established MC disease, the metachromatic blasts should be recorded as MC lineage cells. However, if the diagnosis is unclear, the morphologic examination of these cells will not allow discrimination between MC- and basophil-lineage cells. Therefore, in such cases, additional phenotypic or electron microscopic analyses are required to determine their identity [71,72]. Apart from MC, all other cell lineages of the bone marrow should be examined carefully in mastocytosis. In fact, a thorough examination of other myeloid cells may disclose signs of myelodysplasia or myeloproliferation. If so, the question arises whether such findings would meet a diagnostic level to establish the diagnosis of an AHNMD. To clarify this, additional studies (blood counts, cytochemistry, immunophenotyping, chromosome analysis) may be necessary, and well-established criteria for disease delineation should be applied. We recommend use of the guidelines provided by the FAB cooperative study group and WHO work proposals [24,76–80] in this regard. The peripheral blood counts may also show specific abnormalities in patients with SM. Apart from cytopenias, leukocytosis, eosinophilia, monocytosis, or thrombocytosis, the blood smear may contain detectable numbers of MC [4,5,9,11]. Especially in cases of suspected MCL ($\geq 20\%$ MC in bone marrow smears), a thorough investigation of Giemsa-stained and Toluidine Blue-stained blood smears for the presence of MC-lineage cells is required. In a group of patients, the percentage of MC is $\geq 10\%$ (= classical variant of MCL), whereas in other cases, the percentage of MC is less than 10% (aleukemic subvariant, previously termed malignant mastocytosis with circulating MC).

2.5. Mast cell tryptase and other laboratory parameters

A well-established and important marker of disease is the level of tryptase. In fact, serum levels of total mast cell-tryptase (all forms of alpha- and beta-tryptases; referred to as tryptase in this article) reflect the total burden of MC and average about 5 ng/ml in healthy controls (range: <1 to 15 ng/ml) [81–84]. In patients with CM (no systemic involvement), serum tryptase levels are also normal or slightly elevated [82,85,86].

Table 4
Morphologically distinct subsets of mast cell lineage cells to be recorded in the bm of patients with mast cell disease[a]

Cell type — proposed nomenclature	Cytological features — cytological criteria
Blast, non-metachromatic	No signs of maturation, minor cytoplasmic compartment, fine nuclear chromatin, prominent nucleoli
Metachromatic blast	Blast-like morphology; nuclear pattern as in blasts, nucleoli, several metachromatic granules (it is impossible to distinguish between mast cells and basophils at this maturation stage)
Mast (cell lineage) cells:	
Typical tissue mast cell	Round or oval cell, small to medium sized, round or oval nucleus with central position, condensed chromatin, low N/C ratio, cytoplasm typically well granulated, may be hypo-/de-granulated
Atypical mast cell type I	Two or three of the following: (1) Prominent surface projections (special form: spindle shaped cell); (2) Oval nucleus with or without excentric position, (3) hypogranulated cytoplasm with focal accumulations of granules with or without granule fusions, but no signs of degranulation. These cells may exhibit a more mature or immature morphology
Atypical mast cell type II	Variable form of cell, nuclei bi- or poly-lobed, N/C ratio high (immature) or low (mature) nuclear chromatin fine (immature) or condensed (mature), nucleoli may be present, the cytoplasm is often hypogranulated (without signs of degranulation)

[a] According to morphologically defined subtypes of MC and comparison with clinical course [75], a cytopathological grading is proposed: High Grade: In bm smears, 'metachromatic blasts' plus atypical MC with bi- or polylobed nuclei (type II) comprise more than 20% of all recorded MC. Low Grade: In bm smears, 'metachromatic blasts' plus atypical MC with bi- or polylobed nuclei (type II) comprise less than 10% of all recorded MC. The remaining cells can be typical tissue MC or atypical MC characteristically found in SM (type I). Intermediate Grade: neither low- nor high-grade criteria fulfilled.

The same may hold true for an entity referred to as 'isolated bone marrow mastocytosis' [21,84]. Higher tryptase values increase the likelihood of SM with multiorgan involvement [85,86]. Thus, in most patients with SM, serum tryptase levels exceed 20 ng/ml [82,86]. Moreover, tryptase levels in SM seem to correlate with the burden of (neoplastic) MC [86]. The major biological basis of this correlation is the constant release of (pro-alpha) tryptase from MC in various organs and the lack of 'mast cell'-tryptases in most other hemopoietic and non-hemopoietic cells in physiologic tissues or blood [81,82,87]. In line with this notion, serum tryptase levels exceed whole blood tryptase levels in SM. All in all, the serum levels of 'mast cell'-tryptase appear to be an important marker of SM [81,82]. However, elevated tryptase levels have been detected not only in SM, but also in other myeloid neoplasms, especially acute and chronic myeloid leukemias and MDS without mastocytosis [75,86]. Moreover, serum beta-tryptase levels can increase transiently (also reflected as an elevation of total tryptase levels) during an allergic reaction [81,86]. Thus, 'mast cell'-tryptase levels cannot be regarded as a disease-specific marker for SM. Based on these limitations, we propose to use a clearly and persistently elevated tryptase level as a criterion of SM, provided that an AHNMD has been excluded. Apart from tryptase, routine laboratory parameters, including blood counts, chemistry, and routine coagulation parameters, should be recorded in patients with mastocytosis. In low-grade disease without AHNMD, these tests should disclose normal results. In aggressive or high-grade disease or an AHNMD, however, significant abnormalities may be found such as cytopenia(s), leukocytosis, eosinophilia, basophilia, monocytosis, circulating MC, elevated LDH, elevated liver enzymes, hypalbuminemia, or abnormal coagulation parameters [10,11,35–40,62].

2.6. Recurrent somatic c-kit mutations

Growth and differentiation of MC are regulated by stem cell factor (SCF), a cytokine that signals through the Kit tyrosine kinase receptor [88–91]. SCF receptors are expressed on hemopoietic progenitors and neoplastic MC as well as on normal (mature) MC [92,93]. Deactivation of Kit is associated with a MC-deficient phenotype in the mouse [94], whereas certain 'gain-of-function' mutations are associated with autonomous kinase activity and ligand-independent growth of MC. The HMC-1 cell line, derived from a patient with MCL, exhibits such an activating *c-kit* mutation at codon 816 (Asp-816 → Val) [95]. Interestingly, this *c-kit* mutation is also detectable in the majority of patients with (adult onset) SM [13,14,25,96–103]. Other *c-kit* mutations have also been reported to occur in SM, but appear to be confined to a minority of patients with MC disease [25,104]. In most cases with typical childhood CM/UP (no extensive or persistent disease, no systemic involvement), the mutation Asp-816 → Val is not detectable [25,99,102]. However, the *c-kit* mutation Asp-816 → Val is detectable in some atypical pediatric cases. Recently, the *c-kit* mutation Gly-839 → Lys was reported in a patient with pediatric CM [99]. Although the incidence of Gly-839 → Lys is not known, these observations suggest that typical childhood CM (MPCM) and persisting SM (or SM detected in adulthood) represent separate disease entities [25,99,102].

Interestingly, in patients with SM, the *c-kit* mutations are not only detectable in MC, but may also be detected in 'non-MC lineage' cells including blood monocytes or even B cells [20]. In cases with associated myeloproliferation (smouldering state), the mutation may even be detected in unfractionated mononuclear cells of the peripheral blood [105]. In SM with an AHNMD, *c-kit* mutations are sometimes, but not always, detectable in both neoplasms [13,100,105,106]. However, not all patients with SM exhibit *c-kit* mutations. In some cases, *c-kit* mutation(s) may be missed because the abnormality is restricted to MC, which are outnumbered by other cells in the test samples [100].

2.7. Abnormal expression of CD2 and CD25 on mast cells

The cell surface membrane phenotype of MC is different from that of basophils and other myeloid cells. In contrast to other leukocytes, normal tissue MC express substantial amounts of Kit (CD117) on their surface [18]. However, the SCF receptor (Kit) is also expressed on immature multilineage hematopoietic progenitors [92,93]. Recently, Kit has been introduced as a useful marker for the detection and enumeration of MC in patients with SM [15,64,107–112]. Moreover, using antibodies to Kit (CD117) and multiparameter flow cytometry, the phenotype of bone marrow MC can be analyzed in normal subjects and those with SM [15,107–111]. By utilizing this technique, clear immunophenotypical differences are found between MC of normal (or reactive) bone marrow and MC in patients with SM. The most intriguing finding is that MC in most patients with adult onset SM express CD2 and/or CD25 [15,107–111]. CD2 is of particular interest since this antigen (LFA-2) is otherwise restricted to T and NK cells, and not expressed on normal MC or MC in other hematologic neoplasms (Table 5) [111]. Circulating MC in patients with MCL also express CD2 [107,112,113]. Moreover, a subclone of the mast cell leukemia line HMC-1 is CD2-positive [114]. In most patients with SM, expression of CD2 and CD25 on MC is demonstrable by multicolor flow cytometry [15,107–111]. In exceptional cases, flow cytometry may not be applicable (dry tap). Here, CD2 expression may

Table 5
Expression of leukocyte antigens in human mast cells

Antigen	Normal MC	SM bm MC	HMC-1	MDS or MPS[a] bm MC
CD34	−	−	−	−
CD117/Kit	+	+	+	+
Histamine	+	+	+	+
Tryptase	+	+	+	+
Chymase	+/−	+/−	−	+/−
CD2	−	+	+/−	−
CD14	−	−	−	−
CD15	−	−	−	−
CD25	−	+	−/+	−
CD68	+	+	+	+
CAE	+	+/−	−/+	+/−

[a] Without co-existing SM; bm, bone marrow. CAE, chloroacetate esterase.

be detected in bone marrow sections employing immunohistochemical staining techniques [115]. In a small subgroup of patients (a subset of) MC may be CD2-negative. In other patients, expression of CD2 is restricted to a subpopulation of neoplastic bone marrow MC [111]. Nevertheless, flow cytometric detection of CD2 and/or CD25 on CD117 + /CD34- bone marrow MC appears to be a very specific and also a sensitive (probably the most sensitive) method for detection of neoplastic MC in patients with SM, and therefore has been introduced as a disease criterion.

2.8. AHNMD

A significant number of patients with SM (from less than 5% up to 20% in some series) develop an associated hematologic clonal non-MC lineage disease (AHNMD). Any type of clonal hematologic malignancy may occur [4,5,8–10,73,116–128]. However, myeloid neoplasms (MPS, MDS, or AML) develop with a much higher frequency than lymphoid neoplasms [8–10,73]. In fact, concurrent lymphoid neoplasms in SM are very rare [116,127,128]. The diagnosis of AHNMD should be based on criteria established by the FAB cooperative study group and the WHO proposal [24,76–80]. In some cases, the diagnosis of an AHNMD cannot be established (by FAB or WHO criteria), although bone marrow and blood examinations indicate abnormal (sometimes clonal) myelopoiesis (leukocytosis, left shift, hypercellular marrow). This may be a diagnostic problem. In fact, these cases may represent a prephase of a myeloproliferative or myelodysplastic disorder or aggressive mast cell disease or a smouldering state [105,106,129]. Interestingly, patients without skin lesions were found to be at high risk to transform to AHNMD or aggressive SM/MCL, whereas those with typical skin lesions were found to stay in a smouldering state over many years (or even decades) without transformation [4,5,21,105,106,129]. Therefore, such cases should probably be subdivided into those with and those without cutaneous lesions. The pathophysiologic basis of simultaneous occurrence of SM and other myeloid neoplasms is not known [100,116,130]. The currently available data would argue for a monoclonal process in many, but not all, cases [100,116,130]. Notably, concurrent neoplasms may or may not display the respective *c-kit* mutation that was found in the neoplastic MC.

3. Evolution and formulation of criteria

Based on clinical, histological/immunohistochemical, cytological, and laboratory findings, major and minor criteria of disease have been formulated in order to diagnose SM, and to discriminate SM from cutaneous mastocytosis, solitary mastocytoma, mast cell sarcoma, reactive MC hyperplasia, and increase in MC in myelogenous neoplasms without mastocytosis. A number of retrospective and prospective studies published in the same issue of the journal or in the previous literature (see references) constitute the data basis of this formulation that was discussed and approved in the 'Year 2000 Working Conference on Mastocytosis' (Vienna, August 31–September 3, 2000).

4. Proposed criteria and classification of mastocytosis

The proposed classification of mastocytosis is based on formulated criteria. In this concept, the diagnosis cutaneous mastocytosis (CM) is based on clinical and histological findings in the skin together with absence of criteria that would allow the diagnosis SM. SM criteria are divided in major criteria and minor criteria. Major criteria relate to major histological and immunohistochemical (tryptase staining of tissue sections) findings. The most important aspect here is the dense focal infiltrate of MC that consists of a considerable number of MC (> 15) and is detectable in more than one site in the tissue(s) (multifocal pattern). Minor criteria relate to typical cytomorphological aspects of MC (in tissue sections and/or bone marrow smears) as well as to novel biochemical markers that show some degree of specificity for SM. It is proposed that if one major and one minor or three minor criteria for SM are fulfilled, the diagnosis is 'systemic mastocytosis' (Table 6). Likewise, if dense multifocal infiltrates in the bone marrow are composed of > 15 MC that appear to be spindle-shaped ($> 25\%$ MC are spindle-shaped), the diagnosis SM can be made on histology without further investigation (and irrespective of the stain applied). If MC are round, one should ask for additional criteria of SM (morphology of MC in bone marrow smears; CD2/

Table 6
Proposed criteria to diagnose mastocytosis

Cutaneous mastocytosis:	Typical skin lesions = typical clinical signs (UP/MPCM, DCM, mastocytoma) and positive histology with typical infiltrates of MC (diagnostic infiltrate-pattern: multi/focal or diffuse)
Systemic mast cell disease:	'SM criteria'
Major	Multifocal dense infiltrates of MC (>15 MC aggregating) detected in sections of bm and/or of other extracutaneous organ(s) by tryptase-immunohistochemistry or other stains
Minor	a. In MC infiltrates detected in sections of bm or other extracutaneous organs, >25% of MC are spindle-shaped or: in bm smears, atypical MC (type I plus type II)[a] comprise >25% of all MC b. Detection of a *c-kit* point mutation at codon 816 in bone marrow or blood or other extracutaneous organ(s) c. Kit^+ mast cells in bone marrow or blood or other extracutaneous organ(s) co-express CD2 or/and CD25 d. Serum total tryptase concentration persistently >20 ng/ml (in case of an AHNMD, d. is not valid)[b]
If	one major and one minor or three minor criteria are fulfilled →then the diagnosis is systemic mastocytosis (SM)

[a] See Table 4 for morphologic criteria and suggested terms.
[b] In AML or MDS or MPS, elevated serum tryptase levels have been detected without increase in mast cell numbers or signs of mastocytosis.

CD25-expression on MC; serum tryptase, *c-kit* mutation) to establish the diagnosis SM, because focal accumulations of round MC have also been detected in reactive MC hyperplasia (like seen in parasite infections, various neoplastic disorders, aplastic anemia, immunocytoma, or some chronic inflammatory diseases), SCF-treated patients, and myeloid leukemias without mastocytosis. The potential differential diagnoses that have to be considered in patients with suspected SM are listed in Table 7.

Four major variants of SM have been defined by the working group: indolent systemic mastocytosis (ISM), systemic mastocytosis with an AHNMD (SM-AHNMD), aggressive systemic mastocytosis (ASM), and mast cell leukemia (MCL). ISM is characterized by the absence of (i) C-findings, (ii) AHNMD (FAB/WHO-criteria), and (iii) MCL (no circulating MC, low numbers of immature MC in bone marrow smears). A provisional subentity of ISM is smouldering systemic mastocytosis characterized by B-findings (two or more; see Table 3). AHNMD have to be diagnosed by FAB/WHO-criteria. Aggressive systemic mastocytosis is defined by organ impairment due to MC infiltrates = C-findings (one or more; see Table 3). In MCL, significant numbers of (immature) MC are detectable in bone marrow ($\geq 20\%$) and peripheral blood smears. MCL may (first) present as an aleukemic subvariant ($< 10\%$ MC in blood smears) or show a leukemic pattern at diagnosis (MC $\geq 10\%$ in blood smears). Mast cell sarcoma (MCS) is characterized by destructive growth of a local tumor consisting of highly atypical (poorly differentiated) MC without systemic involvement (criteria to diagnose SM not fulfilled). This entity has to be distinguished from extracutaneous mastocytoma, a benign (low-grade) tumor without destructive growth. A summary of entities (classification) is given in Table 8. Fig. 1 shows a practical guide (recommendation) for the diagnostic work up. Distinct entities (variants) of mastocytosis are discussed separately below and listed together with respective criteria in Table 9.

5. Variants of disease

5.1. Cutaneous mastocytosis (CM)

This disease group is defined by the triad of (i) typical clinical aspects of skin lesions, (ii) histological demonstration of typical focal infiltrates of MC in the dermis, and (iii) the absence of SM criteria that would allow the establishment of the diagnosis SM.

5.1.1. Urticaria pigmentosa (UP) = maculopapular cutaneous mastocytosis (MPCM)

UP/MPCM appears to be the most frequent form of CM. Most patients are children. The skin shows a maculopapular rash with a positive Darier's sign. Mediator-related symptoms may be present. Apart from classical UP, a number of (rare) subvariants of UP/MPCM have been proposed based on distinct clinical aspects. In fact, a plaque form, a nodular form, and a telangiectatic subvariant (also referred to as telangiectasia macularis eruptiva perstans, TMEP) have been described [34,58,131,132]. In some cases with a nodular type of UP/MPCM, only a few lesions, similar to mastocytoma, are present — these cases may also be regarded as multiple mastocytoma of skin [34]. The prognosis of UP/MPCM is good. Most cases developing in early childhood resolve at the end of (or shortly after) puberty. The occurrence of an AHNMD is unusual. The diagnosis of UP/MPCM has to be established by histological examination of lesional skin [34]. In cutaneous lesions, MC exhibit a rather mature morphology. Their phenotype corresponds with the phen-

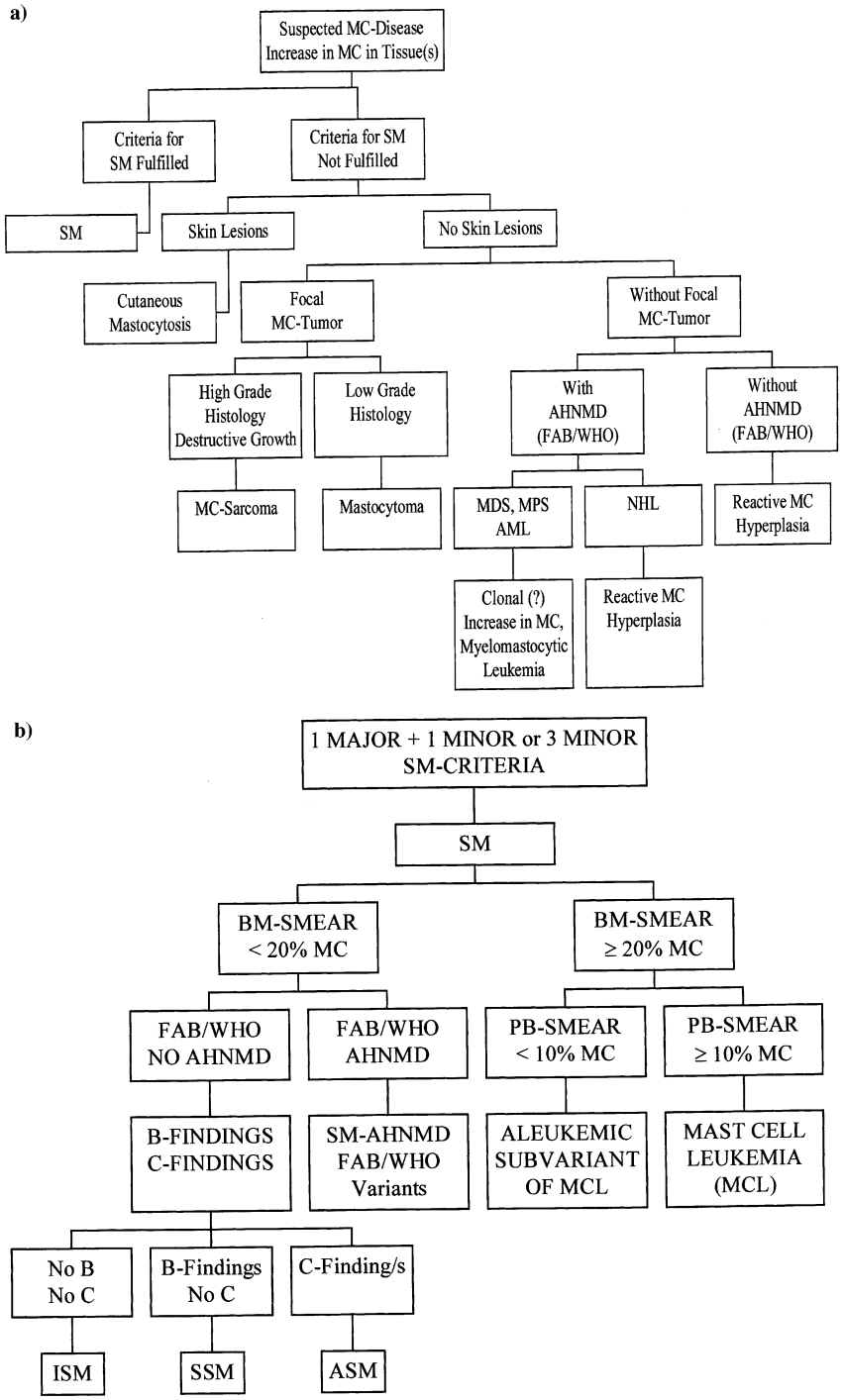

Fig. 1. Suspected mastocytosis — diagnostic work-up. (a) A suspected diagnosis of mastocytosis is usually based on typical skin lesions or an increase in mast cells (MC) in histologies. If SM criteria are not fulfilled, the definitive diagnosis of cutaneous mastocytosis (CM) can be made by a histology of the skin lesion(s). In case of an unifocal extracutaneous mast cell tumor (no SM criteria, no skin lesions), the growth pattern (destructive versus benign) and histomorphological aspects of MC are diagnostic and define mast cell sarcoma (high grade) and extracutaneous mastocytoma (low grade). If no skin lesions, no SM criteria, and no focal MC tumor are found, the increase in MC may be due to a clonal hematologic disease (AHNMD) without mastocytosis (myelomastocytic disease) or/and a reactive increase in tissue MC (mast cell hyperplasia). (b) If SM criteria apply, the diagnosis is systemic mastocytosis (SM) with subvariants to be defined. Mast cell leukemia (MCL) is defined by a percentage of $\geq 20\%$ MC in bone marrow smears and $\geq 10\%$ MC in peripheral blood smears. The aleukemic subvariant of MCL, previously termed malignant mastocytosis with circulating MC, shows $< 10\%$ MC on peripheral blood smears. Subvariants of SM include indolent systemic mastocytosis — ISM (no AHNMD, no C-findings), SM with an associated clonal hematologic non-mast cell lineage disease (SM-AHNMD), and aggressive systemic mastocytosis — ASM (no AHNMD, but C-findings). Smouldering systemic mastocytosis (SSM) is a provisional subentity of (I)SM and defined by B-findings (no AHNMD, no C-findings). AHNMD should be diagnosed and classified according to the proposals of the FAB study group and/or WHO.

Table 7
Mastocytosis — differential diagnosis

Proposed nomenclature	Alternatives, synonyma	Pathobiology	Criteria
Mast cell hyperplasia	Reactive mastocytosis	Cytokine effects? SCF-induced growth of non-neoplastic MC, principally reversible	Local or systemic increase in MC, no typical (CM-like) skin lesions, criteria for diagnosis SM not fulfilled, underlying process (tumor, inflammation)
Mastocytosis	Mast cell proliferative disorder(s) Primary mast cell disease(s) Primary mastocytosis	Neoplastic mast cells SCF-independent growth *c-kit* point mutations	Typical skin lesions (CM) and/or criteria for diagnosis SM fulfilled or local mast cell disease diagnosed
Mastocytic differentiation in myelogenous neoplasm other than mastocytosis	Myelodysplastic mast cell syndrome Myelomastocytic leukemia	Underlying MDS or MPS myeloid progenitors have a certain capacity to differentiate into mast cells	Increase in very immature MC (blast-like) in bm and pb, no typical skin lesions, criteria for diagnosis SM not fulfilled, underlying MDS, MPS, or AML (FAB)
Acute myeloid leukemia with expression of tryptase or/and *c-kit* mutation at codon 816	Tryptase$^+$ AML[a] AML with 816-*c-kit* mutation[a]	Maturation arrest prevents differentiation of immature progenitors into mast cells	AML, no typical (CM-like) skin lesions, criteria for diagnosis SM not fulfilled, but 1–2 minor SM criteria found

[a] AML showing tryptase expression and/or 816-*c-kit* mutations frequently express CD2 and are M4eo, may also be M3 or M2.

toype of normal cutaneous MC: they stain metachromatic and are CAE$^+$, tryptase$^+$, chymase$^+$, and Kit$^+$ [133–135]. Usually, the serum tryptase levels are normal [81–84]. Rarely (as in early infancy), they are slightly elevated. Routine laboratory parameters are also normal. Most pediatric cases do not need to undergo additional diagnostic tests such as bone marrow biopsy. In a majority of pediatric CM patients, *c-kit* mutations are not detectable [99,102]. However, in a few cases, the mutation Asp-816 → Val or Gly-839 → Lys may occur [99]. A bone marrow biopsy should be considered in all patients with (i) adult onset disease, (ii) unexplained organomegaly or -pathy, or (iii) suspected AHNMD or aggressive SM. Tryptase-stained bone marrow biopsy sections may show a discrete increase in MC (morphometry), but no focal dense infiltrates (no major SM criteria) [59,63]. In patients with UP/MPCM, one or two of the following may be found (minor SM criteria): a serum tryptase level > 20 ng/ml, a *c-kit* mutation at codon 816 in bone marrow or peripheral blood, expression of CD2 and/or CD25 on bone marrow MC, or an 'abnormal' morphology of MC (like in SM) in bone marrow smears. Such findings (minor SM criteria) would indicate the possibility of systemic disease and may require re-analysis of the bone marrow. In addition, if three of these findings (minor criteria) have been documented, the diagnosis changes from CM to SM, even in the absence of dense diagnostic MC infiltrates in tryptase-stained bone marrow biopsy sections.

5.1.2. Diffuse cutaneous mastocytosis (DCM)

DCM is less frequently diagnosed than UP. Most patients are children. The clinical aspect of the cutaneous lesions is different from UP in that typical maculopapular infiltrates are not seen [34]. Rather, a more diffuse erythrodermic rash is found [34,136–140]. Some patients with DCM may have extensive MC infiltrates leading to diffusely thikened skin or (additional) nodular lesions (high burden of MC) [136]. Histologically, DCM may show a picture similar to UP/MPCM or solitary mastocytoma of skin [34]. The criteria and recommendations described above for UP/MPCM also apply to patients with DCM. Similarily, the prognosis is good, and AHNMDs usually do not occur.

5.1.3. Mastocytoma of skin

Solitary mastocytomas in humans are almost exclusively found in the skin (other organ sites are very rare) [34,141]. Most patients are young infants. Usually, the nodular lesion does not exceed 1 cm in diameter and shows a yellow or reddish color. Histologically, the lesion consists of densely packed, mature-appearing MC without cellular atypia [141]. The phenotype of MC is similar compared to MC in UP. As in UP, the MC are Kit$^+$ and co-express tryptase and chymase (MC_{TC}). No systemic involvement is found (criteria to diagnose SM not fulfilled). In many patients, the disease resolves spontaneously. The remaining cases (large tumor lesions; unclear histology; no regression seen) are cured by excision. Mast cell sarcoma of skin has not been described so far.

5.2. Indolent systemic mastocytosis (ISM)

The criteria to diagnose SM are fulfilled. Bone marrow and blood examinations exclude MCL and an AHNMD. C-findings are not detectable, i.e. organ-function impairment (or -failure) due to MC infiltration is absent, although MC infiltrates may be detected in various organ systems including the liver, spleen, or GI-tract [49–56]. Typical ISM is characterized by a modestly elevated burden of MC, an indolent clinical course, and a good prognosis. Typical cases present with maculopapular/UP-like skin lesions. Mediator-related symptoms are often recorded.

The bone marrow is affected in nearly 100% and contains multifocal dense infiltrates of MC [4,5,21,46–50]. In typical ISM, the infiltration grade in the bone marrow is rather low ($<30\%$). Usually, many of the MC are mature and contain multiple metachromatic granules that are detectable after formalin fixation [142,143]. The typical phenotype of bone marrow MC is: TB^+, CAE^+, Kit^+, $tryptase^+$, $chymase^{+/-}$, $CD25^+$, $CD2^+$. Apart from dense infiltrates, bone marrow MC may show an additional diffuse spread (mixed infiltrate). However, these diffusely scattered MC do not alter the normal bone marrow architecture, and an excessive diffuse spread of MC (like in MCL) is not seen [48]. Also, the remaining bone marrow does not show myelodysplasia or signs of myeloproliferation. A diffuse MC infiltration without focal dense accumulations is a rare finding. A characteristic finding in ISM is

Table 8
Classification of mastocytosis — overview[a]

Disease entities	Investigation(s)[b]	Typical finding(s)
Cutaneous mastocytosis[b] (CM)	SM criteria[b]	Not fulfilled
	Skin lesions	Present, MC infiltrates
	bm histology[b]	Negative, no MC infiltrates
	pb counts	Normal[b]
	Serum tryptase	<20 ng/ml[b]
Indolent systemic mastocytosis (ISM)	SM criteria	Fulfilled
	Skin lesions	Present (vast majority)
	bm histology	Multifocal MC infiltrates
	bm cytology (smears)	bm MC <20%, low grade[c]
	CD2/CD25 on bm MC	Found
	pb counts	Normal or slightly abnormal
	Serum tryptase	>20 ng/ml
	Liver/spleen/LN	Organomegaly may be found
Systemic mastocytosis with an AHNMD (SM-AHNMD)	SM criteria	Fulfilled
	WHO/FAB criteria	AHNMD
Aggressive systemic mastocytosis (ASM)	SM criteria	Fulfilled
	Skin lesions	Often absent
	bm histology	Multifocal MC infiltrates
	bm cytology	MC <20%, low- or high-grade bm may be dys/hyperplastic, but no AHNMD (FAB/WHO)
	pb counts	Abnormal (C-findings)
	Liver/spleen/LN	Organomegaly
	Organ function	Impaired (C-findings)
Mast cell leukemia (MCL)	SM criteria	Fulfilled
	Skin lesions	Absent
Aleukemic subvariant	bm histology	'Positive' (diffuse and dense)
(in pb: MC <10%)	bm cytology	≥20% MC, often high grade
	pb counts	<10% or ≥10% MC
	Organ function	Impaired (liver, bm, others)
Mast cell sarcoma	SM criteria	Not fulfilled
	Macroscopic	Unifocal, destructive growth
	histology	High-grade focal MC tumor
Extracutaneous mastocytoma	SM criteria	Not fulfilled
	Macroscopic	Unifocal, benign tumor
	histology	Low-grade focal MC tumor

[a] bm, bone marrow; pb, peripheral blood; LN, lymph nodes.

[b] Most pediatric cases are diagnosed as CM by skin biopsy and blood examination only — they do not need to have marrow examinations or other tests.

[c] With regard to cytomorphological grading in SM and proposed terms-see Table 4 and reference [75].

Table 9
Classification of mastocytosis — proposed variants and criteria

Variant	Criteria	MC burden	Grade	Pathobiology/typical findings
Cutaneous mastocytosis (CM)	Typical skin lesion(s) with positive histology[a] and: criteria for diagnosis SM Not fulfilled	Low	Low	Abnormal growth of MC in skin; skin MC — progenitors involved? *c-kit* mutations not detectable in most cases (most are pediatric). Codon 816 *c-kit* mutations are found in atypical pediatric cases and a group of adults
Variants:				
Urticaria Pigmentosa (UP)/ maculopapular cutaneous Mastocytosis (MPCM)	maculopapular lesions			
Subvariants:				
Typical UP	Maculopapular	Low	Low	Vast majority of cases
Plaque-form	Plaques	Low	Low	Often found in infants
Nodular	Mastocytoma-like lesions (≥ 2)	Low, rarely high	Low	Rare
Telangiectasia macularis eruptiva perstans (TEMP)	Telangiectasias, macules	Low	Low	Rare
Diffuse Cutaneous Mastocytosis (DCM)	Erythrodermic rash	Low or high	Low	More diffuse pattern
Mastocytoma of skin	Unifocal (local) tumor Single lesion	Low	Low (so far, no mast cell sarcoma of skin described)	
Indolent systemic mastocytosis (ISM)	Criteria for diagnosis SM fulfilled (no B-findings) No C-finding(s) No AHNMD bm smears: $<20\%$ MC pb smears: no MC	Low	Low	816-*c-kit* mutations found in most cases, mast cells usually express CD2 and CD25, in almost all patients maculopapular skin lesions are found — exception: bone marrow mastocytosis
Provisional subvariant:				
(isolated) bone marrow mastocytosis (BMM)	No skin lesions	Low	Low	Only bm affected Serum tryptase usually <30 ng/ml MC progenitor of bm affected? early phase of ISM?
Provisional subvariant: smouldering systemic mastocytosis (SSM)	B-findings (≥ 2) No C-finding(s) No AHNMD bm smears: $<20\%$ MC pb smears: no MC	High	Low or intermediate	Long-lasting (unrecognized) SM or prephase of aggressive mastocytosis or prephase of an AHNMD; typical skin lesions present or absent, *c-kit* mutation at codon 816 found in the cases recorded so far
	B-FINDINGS (borderline 'benign'): Infiltration grade in bm (focal dense MC-infiltrates) $>30\%$ and: serum tryptase level >200 ng/ml Signs of dysplasia or myeloproliferation in non-mast cell lineage compartments of the bm, but no AHNMD, blood counts normal or slightly abnormal Hepatomegaly without impairment of liver function (no ascites) or/and splenomegaly or/and lymphadenopathy (palpable; >2 cm in US/CT)			
Systemic mastocytosis with AHNMD (SM-AHNMD)	Criteria for diagnosis SM fulfilled Criteria for SM to be applied as if no AHNMD would be present subtype of SM should be recorded AHNMD: FAB/WHO criteria	High or low	High or low	Uncertain, monoclonal process? With subclones, biclonal, genetic instability 816-*c-kit* mutations are found in a subset of cases; skin lesions often absent

Table 9 (Continued)

Variant	Criteria	MC burden	Grade	Pathobiology/typical findings
Subvariants:				
SM-MDS	FAB/WHO			
SM-MPS	FAB/WHO			
SM-AML	FAB/WHO			
SM-NHL	REAL/WHO			
Aggressive systemic mastocytosis (ASM)	Criteria for diagnosis SM Fulfilled C-finding(s) No AHNMD bm smears: <20% MC pb smears: no MC	High or low	Intermediate or high rarely low	Significant MC proliferation causing impairment of organ function. Skin lesions are often absent *c-kit* mutations at codon 816 are found in a subset of patients
Subvariant: Lymphadenopathic mastocytosis with eosinophilia	C-FINDINGS (C, critical — consider cytoreductive therapy): Abnormal myelopoiesis with abnormal blood counts[b], but no frank AHNMD Hepatomegaly with impairment of liver function (ascites)[c] Splenomegaly with hypersplenism Malabsorption + weight loss due to GI-tract MC infiltrates[c] Skeletal involvement with large osteolyses[c] and/or pathologic fractures Other organ systems affected by MC-infiltrates with associated impairment of organ function			
Mast cell leukemia (MCL)	Criteria for diagnosis SM Fulfilled bm smears: ≥20% MC pb smear: MC detectable No AHNMD	High	High	Leukemic growth of MC-committed progenitor cell(s) Skin lesions absent High-grade morphology in most cases 816-*c-kit* mutations found in subset of patients. C-findings with rapid loss of organ function in most cases Short survival in most cases
Subvariants:				
Classical MCL	pb smears: ≥10% MC			
Aleukemic variant of MCL	pb smears: <10% MC			
Mast cell sarcoma (MCS)	Unifocal MC tumor No skin lesions Criteria for diagnosis SM Not fulfilled Destructive growth High-grade histology High-grade cytology	Low	High	Unifocal tumor, highly atypical MC, uncertain pathobiology No *c-kit* mutations described so far
Extracutaneous mastocytoma	Unifocal MC tumor No skin lesions Criteria for diagnosis SM Not fulfilled Non-destructive growth Low-grade histology Low-grade cytology	Low	Low	Unifocal tumor, rather mature MC

[a] A positive histology is defined by clearly visible (multi)focal dense accumulation(s) of MC in the dermis.

[b] Abnormal peripheral blood counts: Significant and persistent change from normal blood counts (see Table 3) that has to be judged as being directly associated with MC infiltration of bone marrow. Likewise, GI-bleeding with consecutive anemia would not be judged as a C-FINDING. FAB/WHO criteria for diagnosis of AHNMD are not fulfilled!

[c] In suspected ASM, the MC disease-associated organomegaly + organopathy should be confirmed by histology.

osteosclerosis and bone marrow fibrosis [74]. Such abnormalities are also detectable in other non-leukemic variants of SM, but not in MCL. The cytology of bone marrow MC in ISM is variable. In most cases, MC show characteristic cell atypias including cytoplasmic surface projections, excentric oval nuclei, hypogranulated cytoplasm, focal granule accumulations, and granule fusions (= atypical mast cells type I) [75]. In fewer cases, most MC are round and not distinguishable from normal MC. Blood counts and differential counts are normal in most cases. In a majority of patients, serum tryptase concentrations are >20 ng/ml, but usually do not exceed 500 ng/ml [81–84]. By the restriction enzyme digestion technique, the *c-kit* mutation Asp-816→Val is detectable in bone marrow cells in the vast majority of the cases.

(Isolated) bone marrow mastocytosis is a rare entity characterized by a lack of skin lesions (may also be overlooked) and absence of visible signs of multiorgan involvement. In many cases, the bone marrow may indeed be the only affected organ (=isolated bone marrow mastocytosis) [4,5,21]. However, this assumption is difficult to be documented during lifetime and usually is not (and should not be) confirmed by a pathological staging — rather, these patients should be diagnosed as an ISM-subvariant based on bone marrow examination and serum tryptase measurements. Thus, the serum tryptase level is usually below 30 ng/ml in these patients [84,128]. It is important to differentiate (isolated) bone marrow mastocytosis from aggressive systemic mastocytosis or MCL, in which skin lesions are also absent. As mentioned, however, an extensive pathological staging is not required in cases with apparently indolent (isolated) bone marrow mastocytosis.

Smouldering systemic mastocytosis is a provisional subentity of ISM. Criteria to diagnose SM are fulfilled. Bone marrow and blood examinations exclude MCL and an AHNMD. In contrast to typical ISM, B-findings are detectable (but C-findings are absent). In particular, patients show at least two out of the following: (1) a bone marrow infiltration grade of >30% (dense infiltrates detected in tryptase immunostains) and serum tryptase >200 ng/ml, (2) discrete signs of myelodysplasia or myeloproliferation (without major alterations in blood counts or criteria for AHNMD), and (3) palpable organomegaly (hepato-, spleno-, or peripheral lymphadenopathy) or visceral lymphadenopathy (>2 cm) detected by US or CT. These B-findings (Table 3) are due to the MC disease process (MC infiltration or fibrosis). However, impairment of organ function due to MC infiltration (C-findings) is not seen. The clinical course is variable and due to the low number of cases recorded so far, the prognosis is unknown. In some cases, a long-lasting clinically silent course has been recorded over many years [105,129]. These patients presented with (UP-like) skin lesions. An AHNMD or aggressive MC disease (ASM) may develop more frequently in patients who do not show UP-like skin lesions [106]. The bone marrow contains mixed (dense focal and diffuse) infiltrates of MC. The infiltration grade is high (>30%). Bone marrow MC may be mature or immature and contain variable amounts of metachromatic granules. The phenotype of bone marrow MC is: $TB^{+/-}$, $CAE^{+/-}$, Kit^{+}, $tryptase^{+}$, $chymase^{-/+}$, $CD25^{+}$, $CD2^{+}$. Apart from MC infiltrates, the remaining bone marrow appears to be affected as well. In particular, the bone marrow can be hypercellular with a loss of fat cells. Discrete signs of myeloproliferation or dysplasia may be recorded. In bone marrow smears, MC represent less than 20% of nucleated cells. The cytology of bone marrow MC is variable. In some cases, MC may show characteristic cell atypias similar to ISM. In other cases, some of the MC display major cell atypias including bi- or multilobed nuclei or even a blast-like morphology ('metachromatic blasts'). However, such major cell atypias are usually restricted to a minority of MC (<20%). The blood counts and differential counts are normal or slightly abnormal. However, major [clinically significant, progressive, or diagnostic (AHNMD)] abnormalities do not occur. If they occur, progression to ASM or SM-AHNMD is diagnosed. Circulating MC are not detectable. Other routine laboratory parameters are also normal. The serum tryptase concentration is elevated and usually exceeds 200 ng/ml. All in all, the burden of neoplastic MC in smouldering mastocytosis is high. As in typical ISM, the *c-kit* mutation Asp-816→Val is detectable in bone marrow cells in the majority of the cases. In contrast to other variants of SM, the mutation can also be detected in unfractionated peripheral blood mononuclear cells indicating monoclonal hematopoiesis with multilineage involvement [105].

5.3. Systemic mastocytosis with an AHNMD (SM-AHNMD)

The criteria to diagnose SM are fulfilled. In addition, established criteria to diagnose an AHNMD (FAB/WHO criteria) [24,76–80] are fulfilled. The nature and biology of a pre-existing mastocytosis (SM) may be identical to SM without AHNMD (see other entities). According to the type of AHNMD, the SM-AHNMD group of patients should be subdivided further. In fact, myeloid and (rarely) lymphoid neoplasms can develop [4,5,8–10,73,116–128]. Thus, AHNMD are categorized as MDS, MPS, AML, and Non-Hodgkin's lymphomas (NHL). After successful therapy (like chemotherapy for AML), patients may shift back again from SM-AHNMD to another category of SM [73,100]. Concurrent evolution of ASM (or MCL) and AHNMD may also be seen. It is therefore of importance to determine the

accurate type of SM in patients with SM-AHNMD. In all patients, separate treatment plans for SM and the AHNMD should be established.

5.4. Aggressive systemic mastocytosis (ASM)

The criteria to diagnose SM are fulfilled. Bone marrow and blood examinations have excluded MCL and AHNMD. In contrast to ISM and smouldering SM, C-findings (Table 3) are detectable as a sign of organ-function impairment due to infiltration by neoplastic MC. In particular, patients show one of the following: (1) abnormal myelopoiesis with significant blood count abnormalities (Table 3), (2) hepatomegaly with impairment of liver function due to MC infiltration (often with ascites), (3) large osteolyses (sometimes with pathologic fractures), (4) malabsorption with weight loss due to GI-tract infiltration, (5) splenomegaly with hypersplenism, or (6) life-threatening impairment of organ function in other organ systems. The most commonly affected organ systems are liver, bone marrow, spleen, and the GI tract. In many patients, organomegaly may be a prominent clinical feature. A distinct subvariant of ASM is lymphadenopathic mastocytosis with eosinophilia [22,144]. Usually, the burden of MC is high. CM-like skin lesions may be present, but more frequently are absent. The natural clinical course is variable. In a subgroup of patients, a slow progression is seen. In other cases, the disease shows a rapid course with or without occurrence of an AHNMD (then the category changes). In this regard, it is noteworthy that the (biochemical) relationship between ASM, SM-AHNMD, and smouldering SM is not totally clear, and the factors that are responsible for clinical disease heterogeneity still remain to be identified [130]. The histology of the bone marrow in ASM shows a variable degree of infiltration. The MC infiltrates may be mixed (dense focal + diffuse) with alteration of the remaining marrow. Additional signs of dysplasia and myeloproliferation may be found, but the criteria for an AHNMD are not fulfilled [48]. The MC are tryptase$^+$ and Kit$^+$. They are usually hypogranulated and may be CAE$^+$ or CAE$^-$. The bone marrow cytologies (smears) may disclose major MC atypias [75]. In some patients, a significant amount of MC ($>20\%$) may exhibit bi- or multilobed nuclei (high-grade morphology). Metachromatic blasts may also be detectable. However, MC usually comprise less than 20% of nucleated cells in bone marrow smears. Significant abnormalities in (differential) blood counts may be found such as cytopenia(s), leukocytosis, eosinophilia, monocytosis, basophilia, or thrombocytosis. However, FAB/WHO criteria for the diagnosis of AHNMD are not fulfilled, and no circulating MC are detectable. Liver enzymes and liver function parameters may be quite abnormal. The serum calcium and alkaline phosphatase levels may be elevated (osteolysis). An elevated LDH may also be found. The serum tryptase levels are invariably elevated and, in some cases, may be very high reflecting a significant burden of MC. In a majority of patients, bone marrow MC express CD2 and CD25. Mutations in the *c-kit* kinase domain may also be detectable. In some patients, these mutations may differ from those found in ISM [104]. In other cases, the typical *c-kit* mutation Asp-816 → Val is found.

5.5. Mast cell leukemia (MCL)

This group of high-grade (malignant) mast cell disease is characterized by a significant number of leukemic MC in peripheral blood and/or bone marrow smears. MCL is defined by the triad of (i) criteria to diagnose SM fulfilled, (ii) circulating MC found and percentage of MC $\geq 20\%$ of all nucleated cells in bone marrow smears, and (iii) multiorgan failure (progressive C-findings). In classical MCL, the percentage of circulating MC is $\geq 10\%$ [11,21,145–148]. In other cases, circulating MC may be less than 10% (aleukemic subvariant, previously called malignant mastocytosis with circulating MC) [67,149]. During the course of disease, patients may shift from the aleukemic to the leukemic subvariant. However, in most cases, a primary form of leukemic disease is diagnosed, and if at all recognized, the prephase of mastocytosis without circulating MC is short. On the other hand, it should be noted that in the few cases of mast cell sarcoma, patients can also present with a picture indistinguishable from MCL in their terminal phase. Therefore, MCL may also be subdivided into cases with known prephase of non-leukemic mastocytosis (= secondary MCL) and those without a known pre-phase (= primary mast cell leukemia). Most patients suffering from MCL are adults. Clinical signs are often non-characteristic and puzzling. Typically, cutaneous lesions are absent [5,11,67,145–149]. Patients may initially complain about episodes of mediator-related symptoms (flushing, hypotension, diarrhoea, others). Later, weight loss, bone pain, and organomegaly occur. In most cases, multiorgan failure including bone marrow failure develops over a short time (weeks to months) [67,145–149]. A longer course is rarely seen. A severe coagulation disorder (signs of consumption, loss of reproduced clotting factors and platelets or hyperfibrinolysis) develops in many cases and often leads to severe bleeding in the GI tract or other organ systems. A curative therapy is not known. The survival time is short. Only a few patients survive more than 1 year [5,11].

The bone marrow is always affected and shows a diffuse and dense infiltration of MC replacing the normal bone marrow (high infiltration grade; major criterion) [5,11,48,67,145–149]. Sometimes, the bone marrow contains mixed (dense diffuse + focal)

infiltrates of MC, but in all cases, the normal bone marrow architecture is replaced by the pathological lesions. Interestingly, bone marrow fibrosis and osteosclerosis (both found in other forms of SM) are usually absent. The bone marrow in MCL may disclose histologic signs of myeloproliferation and dysplasia, but the criteria for an additional hematologic disease (AHNMD) are not fulfilled. Invariably, MC are tryptase$^+$ and express Kit. The MC may be CAE$^+$ or (more often) CAE$^-$ and are hypogranulated. Apart from the bone marrow, other visceral organs are also affected and show diffuse infiltrates of tryptase$^+$ MC. Bone marrow smears contain $\geq 20\%$ MC. In most cases, MC are quite immature or even resemble blast-like cells (metachromatic blasts). In other cases, the majority of MC exhibits bi- or polylobed nuclei. In rare cases, MC may reach a certain degree of maturity. The remaining bone marrow cells in MCL may show cytologic signs of dysplasia or myeloproliferation, but the criteria for an AHNMD are not fulfilled. In most patients, MC exhibit marked cell atypias different from those found in 'low grade' SM. In fact, a significant proportion of MC are immature and hypogranulated. These MC often show a blast-like morphology (metachromatic blasts) with a high nucleus:cytoplasm ratio, fine nuclear chromatin, and prominent nucleoli. Other MC may exhibit bi- or multi-lobed nuclei. In most cases, the percentage of such highly atypical immature MC (metachromatic blasts + 'atypical mast cells type II') accounts for more than 20% of all MC in bone marrow smears (high-grade cytology). Serum tryptase levels are significantly elevated in patients with MCL, indicating a high burden of MC. Other laboratory parameters may also be abnormal. The blood counts may show progressive pancytopenia as a sign of bone marrow failure. In other cases, leukocyte counts may be elevated due to an increase in MC (typical MCL). Multiorgan failure may result in elevated liver enzymes, decreased albumin concentration, elevated LDH and alkaline phosphatase, and decreased fibrinogen. So far, little is known about phenotypic abnormalities of MC in MCL. In those cases recorded, MC were found to express Kit (CD117), CD2, and CD25 similar to other forms of systemic MC disease. The *c-kit* mutation *Asp-816→Val* is detectable in a group of patients. However, not all patients with MCL may have *c-kit* mutations at codon 816.

5.6. Mast cell sarcoma

Mast cell sarcoma is an extremely rare entity. So far, only 3 well-documented cases have been reported. The disease is defined by a local destructive (sarcoma-like) growth of a tumor consisting of highly atypical MC without systemic involvement (criteria for SM not fulfilled). The organ sites described so far were different from bone marrow or skin (larynx, colon ascendens, intracranial site) [150–153]. However, secondary generalization with involvement of visceral organs and hemopoietic tissues has been reported [150–153]. In fact, the terminal phase may be indistinguishable from aggressive mast cell disease or mast cell leukemia (secondary MCL). Furthermore, the cell atypias may be quite similar compared to mast cell leukemia (high-grade cytology). In fact, the cells are rather immature (often blast like) with a high nucleus:cytoplasm ratio, nucleoli, and a hypogranulated cytoplasm. The cells may also exhibit bi- or polylobed nuclei. Pathologic MC were found to be tryptase$^+$ and Kit$^+$. Otherwise, little is known about the phenotype and biology of pathologic MC in patients with mast cell sarcoma. The prognosis is grave, although patients receiving chemotherapy and radiation may survive a few years.

5.7. Extracutaneous mastocytoma

Mastocytoma is a localized benign tumor with unifocal growth of tissue MC without systemic involvement (SM criteria not fulfilled). In contrast to mastocytoma of skin, mastocytomas in extracutaneous organs are very rare. So far, extracutaneous mastocytomas have been detected primarily in the lungs [154–157]. In contrast to mast cell sarcoma, mastocytomas do not show an aggressive (destructive) growth pattern. Also, unlike in mast cell sarcoma, MC in mastocytomas show a low-grade cytology [154–157]. The prognosis for patients with mastocytoma is good — no progression to aggressive disease or mast cell leukemia occurs. Therefore, it is of great importance to differentiate between mastocytoma and mast cell sarcoma at first presentation.

6. Treatment and follow-up

A number of proposals for the treatment of human mastocytosis have been presented. However, in light of the variable clinical picture and almost unpredictable clinical course, these recommendations are difficult to apply to individual patients. A general consensus exists concerning the use of anti-mediator drugs such as antihistamines, cromolyn sodium, acetyl salicylic acid (aspirin), or ketotifen [158–164]. These drugs are usually applied in a step-wise fashion selecting individual drugs on the basis of the organ(s) and/or mediators involved [158–164]. Aspirin is used for flushing, tachycardia, and syncope with recognition that the starting dose may itself cause vascular collapse in an idiosyncratic response [33]. Ketotifen has been recommended for patients with bone pain and/or flushing, whereas gastric ulcerative disease requires the use of H2 antihistamines or a proton pump inhibitor [158–164]. In many

patients, a combination of H_1 and H_2 -receptor antagonists is administered. Malabsorption and ascites may be relieved by the use of low dose corticosteroids [158]. With regard to cytoreductive drugs, all substances are experimental in nature. Cutaneous lesions may show a good (transient) response to Psoralen-Photo-Chemotherapy (= PUVA) [165,166] or local corticosteroids. In ASM or smouldering mastocytosis, 'immunomodulating' anti-neoplastic drugs such as interferon-alpha or corticosteroids, have been employed [167–172]. Unfortunately, however, not all patients with ASM show a response, and long-lasting effects are rare. In cases of MCL, the situation is even more complicated. Again, no curative form of therapy exists for these patients. In typical cases (rapid disease progression, high MC burden), we recommend consideration of experimental poly-chemotherapy or bone marrow transplantation. However, it has to be noted that almost no experience exists concerning the response of MCL to such experimental (high risk) therapies. In patients with SM-AHNMD, the AHNMD should be treated in exactly the same way as if no SM is present [173,174]. Thus, in these patients, treatment plans for both the SM and the AHNMD have to be established. In patients with significant splenomegaly and hypersplenism, splenectomy may be considered [175]. In patients with mast cell sarcoma, surgical excision and consecutive radiation and/or high-dose chemotherapy may be considered. However, again, no standard therapy exists for these patients, and no long-term cure has been described.

When considering the follow-up of patients with mastocytosis, two important questions should be answered: has the patient developed any signs of disease progression (MC disease) or developed an AHNMD? In fact, patients with SM have an increased risk of acquiring an AHNMD compared to the normal population. Therefore, we recommend to examine SM patients in great detail at first presentation and to perform a thorough hematologic follow-up. At first presentation, a bone marrow biopsy and aspiration should be considered in all adult patients with suspected SM. In children, bone marrow examination should only be performed if definitive signs for SM or an AHNMD have been detected in other (non-invasive) tests. The bone marrow biopsy material is subjected to histological analysis including immunohistochemistry. The aspirated material should be used for cytology, determination of colony forming progenitors, cell surface marker studies (CD-typing), chromosomal analysis, and determination of *c-kit* mutations (Asp-816 → Val). The minimal staging program for adult mastocytosis includes physical examination, bone marrow histology and aspirates, complete blood count, routine chemistry (including lactic dehydrogenase and alkaline phosphatase) as well as serum tryptase measurement. In addition, patients may undergo an X-ray of the chest, US of abdomen, endoscopy, and radiography of bones. Depending on the subtype of mastocytosis and test results, the parameters are checked in certain time intervals. In cases of CM or ISM, the time interval should be 1–2 years, and the investigations should be minimized to physical examination, blood picture, LDH, and tryptase unless signs of progression or development of an AHNMD occur. In case of smouldering mastocytosis, the time interval should be 6 months or less, depending on the (known previous) clinical course, and the investigations should include a thorough follow-up of parameters required to monitor the course of disease. In ASM, the patients should be closely monitored, and the response to treatment should be recorded. In cases of MCL or mast cell sarcoma, the patients should be admitted for therapy. It is recommended that cytoreductive or immunomodulating drugs including interferon-alpha be started in hospitalized patients because severe reactions have been noted. In all patients with mastocytosis, the follow-up and treatment plans have to be adjusted to the individual situation of the patient.

7. Future perspectives

During the past few years, substantial new information concerning the biology, phenotype and function of normal and neoplastic human MC has been accumulated. Based on these advances, we have formulated criteria and established a consensus classification for mastocytosis. The applicability and value of this concept should now be tested in prospective studies and clinical trials. In this regard, we hope that the proposal will contribute to a better understanding, management, and treatment of the disease.

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