



THE MASTOCYTOSIS SOCIETY

Mast Cell Disorders

## International Consensus Statements, Position Papers and WHO Criteria Medical References

### Mastocytosis and Mast Cell Activation Syndromes

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**DISCLAIMER:** Patients should consult with their doctors, or, if necessary, mast cell specialists, regarding any questions or concerns related to applicability, accuracy and individual usefulness of information presented in these articles.

Valent P, Horny H-P, Li CY, Longley JB, Metcalfe DD, Parwaresch RM, Bennett JM.

**Mastocytosis.** Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization (WHO) Classification of Tumours. Pathology and Genetics. Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2001.

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Valent P, Horny HP, Escibano L, Longley BJ, Li CY, Schwartz LB, Marone G, Nunez R, Akin C, Sotlar K, Sperr WR, Wolff K, Brunning RD, Parwaresch RM, Austen KF, Lennert K, Metcalfe DD, Vardiman JW, Bennett JM. **Diagnostic criteria and classification of mastocytosis: a consensus proposal.** *Leuk. Res.* Jul 2001;25(7):603-625.

<http://www.ncbi.nlm.nih.gov/pubmed/11377686>

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 (=extracutaneous 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.

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Valent P, Akin C, Escribano L, Fodinger M, Hartmann K, Brockow K, Castells M, Sperr WR, Kluijn-Nelemans HC, Hamdy NA, Lortholary O, Robyn J, van Doormaal J, Sotlar K, Hauswirth AW, Arock M, Hermine O, Hellmann A, Triggiani M, Niedoszytko M, Schwartz LB, Orfao A, Horny HP, Metcalfe DD. **Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria.** *Eur. J. Clin. Invest.* Jun 2007;37(6):435-453.

<http://www.ncbi.nlm.nih.gov/pubmed/17537151>

Although a classification for mastocytosis and diagnostic criteria are available, there remains a need to define standards for the application of diagnostic tests, clinical evaluations, and treatment responses. To address these demands, leading experts discussed current issues and standards in mastocytosis in a Working Conference. The present article provides the resulting outcome with consensus statements, which focus on the appropriate application of clinical and laboratory tests, patient selection for interventional therapy, and the selection of appropriate drugs. In addition, treatment response criteria for the various clinical conditions,

disease-specific symptoms, and specific pathologies are provided. Resulting recommendations and algorithms should greatly facilitate the management of patients with mastocytosis in clinical practice, selection of patients for therapies, and the conduct of clinical trials.

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Horny HP, Akin C, Metcalfe DD, Escribano L, Bennett JM, Valent P, Bain BJ. **Mastocytosis (mast cell disease)** Swerdlow SH, Campo E, Harris NL, et al., editors. World Health Organization (WHO) Classification of Tumours. Pathology and Genetics. Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2008.

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Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, Castells M, Escribano L, Hartmann K, Lieberman P, Nedoszytko B, Orfao A, Schwartz LB, Sotlar K, Sperr WR, Triggiani M, Valenta R, Horny HP, Metcalfe DD. **Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal.** *Int. Arch. Allergy Immunol.* 2012;157(3):215-225.

<http://www.ncbi.nlm.nih.gov/pubmed/22041891>

Activation of tissue mast cells (MCs) and their abnormal growth and accumulation in various organs are typically found in primary MC disorders also referred to as mastocytosis. However, increasing numbers of patients are now being informed that their clinical findings are due to MC activation (MCA) that is neither associated with mastocytosis nor with a defined allergic or inflammatory reaction. In other patients with MCA, MCs appear to be clonal cells, but criteria for diagnosing mastocytosis are not met. A working conference was organized in 2010 with the aim to define criteria for diagnosing MCA and related disorders, and to propose a global unifying classification of all MC disorders and pathologic MC reactions. This classification includes three types of 'MCA syndromes' (MCASs), namely primary MCAS, secondary MCAS and idiopathic MCAS. MCA is now defined by robust and generally applicable criteria, including (1) typical clinical symptoms, (2) a substantial transient increase in serum total tryptase level or an increase in other MC-derived mediators, such as histamine or prostaglandin D(2), or their urinary metabolites, and (3) a response of clinical symptoms to agents that attenuate the production or activities of MC mediators. These criteria should assist in the identification and diagnosis of patients with MCAS, and in avoiding misdiagnoses or overinterpretation of clinical symptoms in daily practice. Moreover, the MCAS concept should stimulate research in order to identify and exploit new molecular mechanisms and therapeutic targets.

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Gotlib J, Pardanani A, Akin C, Reiter A, George T, Hermine O, Kluijn-Nelemans H, Hartmann K, Sperr WR, Brockow K, Schwartz LB, Orfao A, Deangelo DJ, Arock M, Sotlar K, Horny HP, Metcalfe DD, Escribano L, Verstovsek S, Tefferi A, Valent P. **International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis.** *Blood.* Mar 28 2013;121(13):2393-2401.

<http://www.ncbi.nlm.nih.gov/pubmed/23325841>

Systemic mastocytosis (SM) is characterized by accumulation of neoplastic mast cells and is classified into indolent and aggressive forms. The latter include aggressive SM (ASM), mast cell leukemia (MCL), and SM associated with a myeloid neoplasm wherein 1 or both disease compartments exhibit advanced features. These variants, henceforth collectively referred to as advanced SM for the purposes of this report, are typically characterized by organ damage and shortened survival duration. In contrast to indolent SM, in which symptoms are usually managed by noncytotoxic antimedator therapy, cytoreduction is usually necessary for disease control in advanced SM. Unfortunately, current drug treatment of these patients rarely results in complete clinical and histopathologic remissions or improved survival time. Previously defined response criteria were adapted to the heterogeneous presentations of advanced SM and the limited effects of available drugs. However, recent advances in understanding the molecular pathogenesis of SM and the corresponding prospect in targeted therapy make it a priority to modify these criteria. Our current study is the product of an international group of experts and summarizes the challenges in accomplishing this task and forwards a new proposal for response criteria, which builds on prior proposals and should facilitate response evaluation in clinical trials.

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Valent P, Escribano L, Broesby-Olsen S, Hartmann K, Grattan C, Brockow K, Niedoszytko M, Nedoszytko B, Oude Elberink JN, Kristensen T, Butterfield JH, Triggiani M, Alvarez-Twose I, Reiter A, Sperr WR, Sotlar K, Yavuz S, Kluijn-Nelemans HC, Hermine O, Radia D, van Doormaal JJ, Gotlib J, Orfao A, Siebenhaar F, Schwartz LB, Castells M, Maurer M, Horny HP, Akin C, Metcalfe DD, Arock M. **Proposed diagnostic algorithm for patients with suspected mastocytosis: a proposal of the European Competence Network on Mastocytosis.** *Allergy*. Oct 2014;69(10):1267-1274.

<http://www.ncbi.nlm.nih.gov/pubmed/24836395>

Mastocytosis is an emerging differential diagnosis in patients with more or less specific mediator-related symptoms. In some of these patients, typical skin lesions are found and the diagnosis of mastocytosis can be established. In other cases, however, skin lesions are absent, which represents a diagnostic challenge. In the light of this unmet need, we developed a diagnostic algorithm for patients with suspected mastocytosis. In adult patients with typical lesions of mastocytosis in the skin, a bone marrow (BM) biopsy should be considered, regardless of the basal serum tryptase concentration. In adults without skin lesions who suffer from mediator-related or other typical symptoms, the basal tryptase level is an important parameter. In those with a slightly increased tryptase level, additional investigations, including a sensitive KIT mutation analysis of blood leucocytes or measurement of urinary histamine metabolites, may be helpful. In adult patients in whom (i) KIT D816V is detected and/or (ii) the basal serum tryptase level is clearly increased (>25-30 ng/ml) and/or (iii) other clinical or laboratory features suggest the presence of 'occult' mastocytosis or another haematologic neoplasm, a BM investigation is recommended. In the absence of KIT D816V and other signs or symptoms of mastocytosis or another haematopoietic disease, no BM investigation is required, but the clinical course and tryptase levels are monitored in the follow-up. In

paediatric patients, a BM investigation is usually not required, even if the tryptase level is increased. Although validation is required, it can be expected that the algorithm proposed herein will facilitate the management of patients with suspected mastocytosis and help avoid unnecessary referrals and investigations.

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Valent P, Sotlar K, Sperr WR, Escribano L, Yavuz S, Reiter A, George TI, Kluijn-Nelemans HC, Hermine O, Butterfield JH, Hagglund H, Ustun C, Hornick JL, Triggiani M, Radia D, Akin C, Hartmann K, Gotlib J, Schwartz LB, Verstovsek S, Orfao A, Metcalfe DD, Arock M, Horny HP. **Refined diagnostic criteria and classification of mast cell leukemia (MCL) and myelomastocytic leukemia (MML): a consensus proposal.** *Ann. Oncol.* Sep 2014;25(9):1691-1700.

<http://www.ncbi.nlm.nih.gov/pubmed/24675021>

Mast cell leukemia (MCL), the leukemic manifestation of systemic mastocytosis (SM), is characterized by leukemic expansion of immature mast cells (MCs) in the bone marrow (BM) and other internal organs; and a poor prognosis. In a subset of patients, circulating MCs are detectable. A major differential diagnosis to MCL is myelomastocytic leukemia (MML). Although criteria for both MCL and MML have been published, several questions remain concerning terminologies and subvariants. To discuss open issues, the EU/US-consensus group and the European Competence Network on Mastocytosis (ECNM) launched a series of meetings and workshops in 2011-2013. Resulting discussions and outcomes are provided in this article. The group recommends that MML be recognized as a distinct condition defined by mastocytic differentiation in advanced myeloid neoplasms without evidence of SM. The group also proposes that MCL be divided into acute MCL and chronic MCL, based on the presence or absence of C-Findings. In addition, a primary (de novo) form of MCL should be separated from secondary MCL that typically develops in the presence of a known antecedent MC neoplasm, usually aggressive SM (ASM) or MC sarcoma. For MCL, an imminent prephase is also proposed. This prephase represents ASM with rapid progression and 5%-19% MCs in BM smears, which is generally accepted to be of prognostic significance. We recommend that this condition be termed ASM in transformation to MCL (ASM-t). The refined classification of MCL fits within and extends the current WHO classification; and should improve prognostication and patient selection in practice as well as in clinical trials.

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Bonadonna P, Pagani M, Aberer W, Bilo MB, Brockow K, Oude Elberink H, Garvey L, Mosbech H, Romano A, Zanotti R, Torres MJ. **Drug hypersensitivity in clonal mast cell disorders: ENDA/EAACI position paper.** *Allergy.* Jul 2015;70(7):755-763.

<http://www.ncbi.nlm.nih.gov/pubmed/25824492>

Mastocytosis is a clonal disorder characterized by the proliferation and accumulation of mast cells (MC) in different tissues, with a preferential localization in skin and bone marrow (BM). The excess of MC in mastocytosis as well as the increased releasability of MC may lead to a higher frequency and severity of immediate hypersensitivity reactions. Mastocytosis in adults

is associated with a history of anaphylaxis in 22-49%. Fatal anaphylaxis has been described particularly following hymenoptera stings, but also occasionally after the intake of drugs such as nonsteroidal anti-inflammatory drugs, opioids and drugs in the perioperative setting. However, data on the frequency of drug hypersensitivity in mastocytosis and vice versa are scarce and evidence for an association appears to be limited. Nevertheless, clonal MC disorders should be ruled out in cases of severe anaphylaxis: basal serum tryptase determination, physical examination for cutaneous mastocytosis lesions, and clinical characteristics of anaphylactic reaction might be useful for differential diagnosis. In this position paper, the ENDA group performed a literature search on immediate drug hypersensitivity reactions in clonal MC disorders using MEDLINE, EMBASE, and Cochrane Library, reviewed and evaluated the literature in five languages using the GRADE system for quality of evidence and strength of recommendation.

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Arock M, Sotlar K, Akin C, Broesby-Olsen S, Hoermann G, Escibano L, Kristensen TK, Kluijn-Nelemans HC, Hermine O, Dubreuil P, Sperr WR, Hartmann K, Gotlib J, Cross NC, Haferlach T, Garcia-Montero A, Orfao A, Schwaab J, Triggiani M, Horny HP, Metcalfe DD, Reiter A, Valent P. **KIT mutation analysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis.** *Leukemia*. Jun 2015;29(6):1223-1232.  
<http://www.ncbi.nlm.nih.gov/pubmed/25650093>

Although acquired mutations in KIT are commonly detected in various categories of mastocytosis, the methodologies applied to detect and quantify the mutant type and allele burden in various cells and tissues are poorly defined. We here propose a consensus on methodologies used to detect KIT mutations in patients with mastocytosis at diagnosis and during follow-up with sufficient precision and sensitivity in daily practice. In addition, we provide recommendations for sampling and storage of diagnostic material as well as a robust diagnostic algorithm. Using highly sensitive assays, KIT D816V can be detected in peripheral blood leukocytes from most patients with systemic mastocytosis (SM) that is a major step forward in screening and SM diagnosis. In addition, the KIT D816V allele burden can be followed quantitatively during the natural course or during therapy. Our recommendations should greatly facilitate diagnostic and follow-up investigations in SM in daily practice as well as in clinical trials. In addition, the new tools and algorithms proposed should lead to a more effective screen, early diagnosis of SM and help to avoid unnecessary referrals.

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Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. **The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia.** *Blood*. May 19 2016;127(20):2391-2405.  
<http://www.ncbi.nlm.nih.gov/pubmed/27069254>

The World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues was last updated in 2008. Since then, there have been numerous advances in the identification of unique biomarkers associated with some myeloid neoplasms and acute

leukemias, largely derived from gene expression analysis and next-generation sequencing that can significantly improve the diagnostic criteria as well as the prognostic relevance of entities currently included in the WHO classification and that also suggest new entities that should be added. Therefore, there is a clear need for a revision to the current classification. The revisions to the categories of myeloid neoplasms and acute leukemia will be published in a monograph in 2016 and reflect a consensus of opinion of hematopathologists, hematologists, oncologists, and geneticists. The 2016 edition represents a revision of the prior classification rather than an entirely new classification and attempts to incorporate new clinical, prognostic, morphologic, immunophenotypic, and genetic data that have emerged since the last edition. The major changes in the classification and their rationale are presented here.

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Hartmann K, Escribano L, Grattan C, Brockow K, Carter MC, Alvarez-Twose I, Matito A, Broesby-Olsen S, Siebenhaar F, Lange M, Niedoszytko M, Castells M, Oude Elberink JN, Bonadonna P, Zanotti R, Hornick JL, Torrelo A, Grabbe J, Rabenhorst A, Nedoszytko B, Butterfield JH, Gotlib J, Reiter A, Radia D, Hermine O, Sotlar K, George TI, Kristensen TK, Kluijn-Nelemans HC, Yavuz S, Hagglund H, Sperr WR, Schwartz LB, Triggiani M, Maurer M, Nilsson G, Horny HP, Arock M, Orfao A, Metcalfe DD, Akin C, Valent P. **Cutaneous manifestations in patients with mastocytosis: Consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology.** *J. Allergy Clin. Immunol.* Jan 2016;137(1):35-45.

<http://www.ncbi.nlm.nih.gov/pubmed/26476479>

Cutaneous lesions in patients with mastocytosis are highly heterogeneous and encompass localized and disseminated forms. Although a classification and criteria for cutaneous mastocytosis (CM) have been proposed, there remains a need to better define subforms of cutaneous manifestations in patients with mastocytosis. To address this unmet need, an international task force involving experts from different organizations (including the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology) met several times between 2010 and 2014 to discuss the classification and criteria for diagnosis of cutaneous manifestations in patients with mastocytosis. This article provides the major outcomes of these meetings and a proposal for a revised definition and criteria. In particular, we recommend that the typical maculopapular cutaneous lesions (urticaria pigmentosa) should be subdivided into 2 variants, namely a monomorphic variant with small maculopapular lesions, which is typically seen in adult patients, and a polymorphic variant with larger lesions of variable size and shape, which is typically seen in pediatric patients. Clinical observations suggest that the monomorphic variant, if it develops in children, often persists into adulthood, whereas the polymorphic variant may resolve around puberty. This delineation might have important prognostic implications, and its implementation in diagnostic algorithms and future mastocytosis classifications is recommended. Refinements are also suggested for the diagnostic criteria of CM, removal of telangiectasia macularis

eruptiva perstans from the current classification of CM, and removal of the adjunct solitary from the term solitary mastocytoma.

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Ustun C, Gotlib J, Popat U, Artz A, Litzow M, Reiter A, Nakamura R, Kluin-Nelemans HC, Verstovsek S, Gajewski J, Perales MA, George T, Shore T, Sperr W, Saber W, Kota V, Yavuz AS, Pullarkat V, Rogosheske J, Hogan W, Van Besien K, Hagglund H, Damaj G, Arock M, Horny HP, Metcalfe DD, Deeg HJ, Devine S, Weisdorf D, Akin C, Valent P. **Consensus Opinion on Allogeneic Hematopoietic Cell Transplantation in Advanced Systemic Mastocytosis.** *Biol. Blood Marrow Transplant.* Aug 2016;22(8):1348-1356.  
<http://www.ncbi.nlm.nih.gov/pubmed/27131865>