

Short Communication

Mastocytosis and the Updated WHO Classification (2016, 2017): What is Really New?

Hans-Peter H^{1*}, Sotlar K², Metzgeroth G³, Reiter A³ and Valent P⁴

¹Institut für Pathologie, Ludwig-Maximilians-Universität, Germany

²Institut für Pathologie der Universität Salzburg, Austria

³Hämatologie und Onkologie, Universitätsmedizin Mannheim, Medizinische Fakultät der Universität Heidelberg, Germany

⁴Klinik für Innere Medizin I, Abteilung für Hämatologie, Medizinische Universität Wien, Austria

*Corresponding author: Hans-Peter H, Institut für Pathologie, Ludwig-Maximilians-Universität, Germany

Received: February 01, 2018; Accepted: March 05, 2018; Published: April 24, 2018

Short Communication

Mastocytosis is a unique disease amongst hematopoietic neoplasms regarding clinical presentations, molecular findings, cytomorphological characteristics and immunophenotypical features of neoplastic mast cells. Compared to the previous edition of 2008, the following was changed in the updated Blue Book of the World Health Organization (WHO) 2017):

1. Mastocytosis has been removed from the myeloproliferative disorders and thus gained back an own chapter covering all the different clinical and morphological subtypes of the disease.
2. Regarding systemic mastocytosis (SM), the smoldering SM variant which was defined as a provisional SM entity in the previous WHO edition, is now included as a separate category (Table 1 and 2).
3. The abbreviation for SM with an associated hematologic non-mast cell lineage disease (AHNMD) has been shortened to SM-AHN: SM with an associated hematologic (non-mast cell) neoplasm. Both terms, SM-AHNMD and SM-AHN now can be used synonymously.
4. The disorder termed “extracutaneous mastocytoma” has been deleted from the list of mastocytosis categories, because this variant is extremely rare.
5. The presence of > 25% spindle-shaped and/or immature atypical mast cells in the diffuse infiltrate (outside the compact

infiltrate) in bone marrow histology now is defined a minor diagnostic SM criterion.

6. Immunohistochemical prove of aberrant expression of CD25 (and of CD2) by mast cells is now accepted as a minor diagnostic criterion (formerly only flow cytometrical findings were accepted); moreover, the superior diagnostic value of CD25 (specificity: almost 100% in typical SM) over CD2 (only 60% specificity) is highlighted.

7. Well-differentiated SM (WD-SM) is clearly defined as a morphological subvariant of mastocytosis, but not as a separate disease category. In fact, WD-SM features may occur in every subtype of SM, even in mast cell leukemia. WD-SM shows the exclusive presence of round, mature-appearing mast cells containing abundant metachromatic granules but missing both aberrant expression of CD25 (CD2) and the activating point mutation *KIT*-D816V in the vast majority of cases. However, in WD-SM, neoplastic mast cells commonly express CD30. Therefore, CD30 may assume the status of a new minor criterion for SM. Features of a well-differentiated morphology rarely occur in cutaneous mastocytosis (“WD-CM”).

8. The term “mastocytosis in the skin” (MIS) should be used by the pathologist in all patients with proven mast cell infiltration of the dermis and missing possibility to establish the diagnosis of CM or SM, usually because no bone marrow examination was performed and/or clinical information is lacking. It has to be emphasized that presence of skin lesions resembling urticaria pigmentosa in the adult are usually associated with indolent SM rather than pure CM, while in children CM is much more common than indolent SM.

Future Perspectives

The classification system of mastocytosis needs continuous refinements. In the current update, several new definitions have been introduced. For example, sub-variants of mast cell leukemia (MCL) have been recognized and added. Well-known is the separation of “leukemic” MCL (by definition circulating mast cells here comprise >10% of leukocytes, irrespective of the WBC) from “aleukemic” MCL presenting with <10% circulating mast cells. However, a new subvariant of MCL evolving from a pre-existing SM, usually aggressive SM (ASM), was introduced and secondary. Secondary MCL presumably is more frequent than *de novo* MCL which belongs

Table 1: Updated WHO classification of mastocytosis (2017).

	Subtype
Cutaneous Mastocytosis (CM)	<ul style="list-style-type: none"> • Urticariapigmentosa/maculopapulosa cutaneous mastocytosis • Diffuse cutaneous mastocytosis • Mastocytoma of the skin
Systemic Mastocytosis (SM)	<ul style="list-style-type: none"> • Indolent SM (including BMM) • Smoldering SM • Aggressive SM • SM with an associated hematological neoplasm (SM-AHN or SM-AHNMD) • Mast cell leukemia (MCL)
Mast Cell Sarcoma (MCS)	

Table 2: Updated WHO diagnostic criteria for systemic mastocytosis (SM).

	Diagnostic SM criteria according WHO 2017
Major criterion	Multifocal dense mast cell infiltrates (containing ≥ 15 mast cells) in bone marrow or other tissues/organs except the skin
Minor criteria	>25% of mast cells in compact and/or diffuse infiltrates are spindle-shaped and/or immature <i>KIT</i> -D816V or other activating point mutations of <i>KIT</i> Aberrant expression of CD25 (or CD2) by mast cells Serumtryptase >20 $\mu\text{g/L}$
SM	Major and at least 1 minor or ≥ 3 minor criteria are fulfilled

to the rarest forms of human leukemia. Moreover, it could be shown that a very rare variant of MCL exists, namely chronic MCL which has a better prognosis than the more frequently encountered acute and clinically very aggressive MCL. A unique and extremely rare condition is MCL associated with pronounced hemophagocytosis (hemophagocytic MCL) with highly atypical mast cells exhibiting signs of erythrophagocytosis.

It could also be shown that SM-AHN is a very heterogeneous disease including not only almost all defined subtypes of myeloid neoplasms but also lymphatic neoplasms like plasma cell myeloma. Regarding myeloid neoplasms, chronic myelomonocytic leukemia (CMML) is the most frequent subtype encountered but acute myeloid leukemia and chronic eosinophilic leukemia also do occur often causing extreme diagnostic difficulties. In SM-SHN demonstration of a great variety of mutations (i.e., *ASXL1*, *RUNX1*, *SRSF2*, *SF3B1*, *TET2*, *JAK2*, *MPL* etc.) associated with myeloid neoplasms was reported. Myeloid-associated mutations in patients with SM-AHN have a statistically significant negative prognostic impact. In those patients who have advanced SM with more than one mutation, the prognosis is particularly poor. Microdissection analysis showed that such “myeloid” mutations could be also carried by mast cells while *vice versa KIT*-D816V was found not only in the mast cell compartment but also in the “AHN component” of patients with SM-AHN. It seems clear that such findings have also a major impact on therapy of patients with advanced SM.

Therapeutic options and the prognosis of patients with advanced SM which comprises ASM, SM-AHN, and MCL, have improved over the last couple of years. A broadly acting tyrosine kinase inhibitor against *KIT*, midostaurin, which blocks mast cell survival and also mediator release from neoplastic mast cells, was found to significantly increase the survival of patients with advanced SM including MCL. Such patients have been formerly treated with various conventional cytostatic drugs including cladribine and interferon-alpha. In patients with rapidly progressing ASM or even ASM in transformation (ASM-T) and MCL, hematopoietic stem cell transplantation (SCT) is a therapeutic option and should be offered to all eligible patients who are young and fit. However, most of these patients require drug-induced debulking before SCT.

References

- Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016; 127: 2391-2405.
- Gotlib J, Kluijn-Nelemans HC, George TI, Akin C, Sotlar K, Hermine O, et al. Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis. *N Engl J Med*. 2016; 374: 2530-2541.
- Horny HP, Akin C, Metcalfe DD, Escribano L, Bennett JM, Valent P, Bain BJ. Mastocytosis. In: WHO classification of tumours of haematopoietic and lymphoid tissues (eds.: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW). 2008; IARC Press, Lyon, Frankreich.
- Horny H-P, Akin C, Arber DA, Peterson LC, Tefferi A, Metcalfe DD, Bennett JM, Bain BJ, Escribano L, Valent P. Mastocytosis. In: WHO classification of tumours of haematopoietic and lymphoid tissues (eds.: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Arber DA, Hasserjian RP, LeBeau MM, Orazi A, Siebert R). IARC Press, Lyon, Frankreich. 2017.
- Jawhar M, Schwaab J, Schnittger S, Meggendorfer M, Pfirrmann M, Sotlar K, et al. Additional mutations in *SRSF2*, *ASXL1* and/or *RUNX1* identify a high-risk group of patients with *KIT* D816V(+) advanced systemic mastocytosis. *Leukemia*. 2016; 30: 136-143.
- Jawhar M, Schwaab J, Hausmann D, Clemens J, Naumann N, Henzler T, et al. Splenomegaly, elevated alkaline phosphatase and mutations in the *SRSF2/ASXL1/RUNX1* gene panel are strong adverse prognostic markers in patients with systemic mastocytosis. *Leukemia*. 2016; 30: 2342-2350.
- Jawhar M, Schwaab J, Naumann N, Horny HP, Sotlar K, Haferlach T, et al. Response and progression on midostaurin in advanced systemic mastocytosis: *KIT* D816V and other molecular markers. *Blood*. 2017; 130: 137-145.
- Jawhar M, Schwaab J, Meggendorfer M, Naumann N, Horny HP, Sotlar K, et al. The clinical and molecular diversity of mast cell leukemia with or without associated hematologic neoplasm. *Haematologica*. 2017; 102: 1035-1043.
- Pardanani A, Lasho T, Elala Y, Wassie E, Finke C, Reichard KK, et al. Next-generation sequencing in systemic mastocytosis: Derivation of a mutation-augmented clinical prognostic model for survival. *Am J Hematol*. 2016; 91: 888-893.
- Schwaab J, Schnittger S, Sotlar K, Walz C, Fabarius A, Pfirrmann M, et al. Comprehensive mutational profiling in advanced systemic mastocytosis. *Blood*. 2013; 122: 2460-2466.
- Ustun C, Reiter A, Scott BL, Nakamura R, Damaj G, Kreil S, et al. Hematopoietic stem-cell transplantation for advanced systemic mastocytosis. *J Clin Oncol*. 2014; 32: 3264-3274.
- Ustun C, Arock M, Kluijn-Nelemans HC, Reiter A, Sperr WR, George T, et al. Advanced systemic mastocytosis: from molecular and genetic progress to clinical practice. *Haematologica*. 2016; 101: 1133-1143.
- Valent P, Horny H-P, Escribano L, Longley JB, Li CY, Schwartz LB, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res*. 2001; 25: 603-625.
- Valent P, Akin C, Sperr WR, Arock M, Escribano L, Horny HP, et al. Standards and standardization in mastocytosis. consensus statements on diagnostics, treatment recommendations, and response criteria. *Eur J Clin Invest*. 2007; 37: 435-453.
- Valent P, Escribano L, Broesby-Olsen S, Hartmann K, Grattan C, Brockow K, et al. European Competence Network on Mastocytosis. Proposed diagnostic algorithm for patients with suspected mastocytosis: a proposal of the European Competence Network on Mastocytosis. *Allergy*. 2014; 69: 1267-1274.
- Valent P, Akin C, Hartmann K, Nilsson G, Reiter A, Hermine O, et al. Metcalfe DD. Advances in the Classification and Treatment of Mastocytosis: Current Status and Outlook toward the Future. *Cancer Res*. 2017; 77: 1261-1270.