CORRESPONDENCE

Mastocytosis

A Disease of the Hematopoietic Stem Cell

by Prof. Dr. med. Hans-Peter Horny, Prof. Dr. med. Karl Sotlar, Prof. Dr. med. Peter Valent, PD Dr. med. Karin Hartmann in volume 40/2008

Problematic Criteria

In their review article on systemic mastocytoses, Horny et al. consider the 2001 diagnostic criteria of the World Health Organization (WHO) as the gold standard for diagnosing systemic mastocytosis. In view of today's insights into mast cell pathology, this significance is no longer justified. The occurrence of the phenomena listed as the primary criterion and two secondary criteria seems to be linked to the simultaneous presence of a point mutation in codon 816 of the amino acid sequence of the tyrosine kinase Kit. Consequently, these criteria are not suitable for determining systemic mastocytosis as a result of other mutations in Kit and in other kinases. Additionally, bone marrow examination may yield negative results even in patients whose disease matches the remaining WHO criteria (1). Besides, the speckled distribution of mast cells in bone marrow can influence the results of the investigation in such a crucial manner that bilateral sampling of several specimens may be necessary to be able to draw a definite conclusion (2), which may raise problems in terms of clinical practice and professional ethics.

From an internist's perspective, a diagnostic approach seems more appropriate in which the pathologically altered mast cell with its pathologically increased mediator release is the main criterion for a diagnosis of systemic mastocytosis. The symptoms of the mast cell mediator syndrome can be reliably detected in a standardized manner with an internationally validated questionnaire (for example, those from the Association Française pour les Initiatives de Recherche sur le Mastocyte et les Mastocytoses) (3).

When the presence of disorders is excluded in which normal mast cells may be activated, the occurrence of pathological excess production and release of mast cell mediators can only be a manifestation of pathological, uncontrolled, hyperactive mast cells. For this reason, the disorder is appropriately termed as the systemic mast cell hyperactivity syndrome and, in terms of terminology, is a systemic mastocytosis. If the pathologically increased mast cell activity is regarded as main diagnostic criterion, systematic mastocytoses are by no means rare disorders but very likely to be underdiagnosed. DOI: 10.3238/arztebl.2009.0173

REFERENCES

1. Johnson MR, Verstovsek S, Jorgensen JL et al.: Utility of the World Health Organization classification criteria for the diagnosis of systemic mastocytosis in bone marrow. Mod Pathol; 2008: DOI: 10.1038.modpathol.2008.141.
2. Butterfield JH, Li CY: Bone marrow biopsies for the diagnosis of systemic mastocytosis—is one biopsy sufficient? Am J Clin Pathol 2004; 121: 264–7.
3. Molderings GJ, Kolck U, Scheurlen C et al.: Die systemische Mastzellerkrankung mit gastrointestinal betonter Symptomatik – eine Checkliste als Diagnoseinstrument. Dtsch Med Wochenschr 2006; 131: 2095–100.
4. Horny H-P, Sotlar K, Valent P, Hartmann K: Mastocytosis—a disease of the hematopoietic stem cell. Dtsch Arztebl Int 2008; 105(40): 686–92.

On behalf of the the research group for systemic mast cell disorders, Bonn

Prof. Dr. med. Jürgen Homann
Evangelische Kliniken Bonn
Betriebsstätte Waldkrankenhaus
CA der Inneren Medizin
Waldstr. 73
53177 Bonn, Germany
Juergen.Homann@ek-bonn.de

Ulrich Kolck
Evangelische Kliniken Bonn
Betriebsstätte Waldkrankenhaus
OA der Kardiologie
Waldstr. 73
53177 Bonn, Germany
Ulrich.Kolck@ek-bonn.de

Prof. Dr. med. Gerhard J. Molderings
Institut für Humangenetik
Universitätsklinikum Bonn
Wilhelmstr. 31
53111 Bonn, Germany
molderings@uni-bonn.de

In Reply:

The desire to diagnose mastocytosis with clinical certainty is understandable, but it is not possible in practice because of the overlapping symptoms with the so-called ‘mast cell activation syndrome’ (MAS) mentioned by Molderings et al.

The diagnosis of mastocytosis is based on the generally recognized and precise criteria defined by the WHO, in particular on a finding of a compact mast cell infiltrate by the histopathologist ("major diagnostic criterion"), as well as additional findings that relate to specific morphological phenotypical and molecular changes ("minor diagnostic criteria") of the mast cells in mastocytosis. If these criteria are met then "reactive" mast cell hyperplasia can be excluded, as can disorders "in which healthy mast cells may be highly active".

The concept of diagnosing mastocytoses by combining clinical, morphological, and molecular findings has become the standard approach internationally. It is confirmed not least by the fact that the 2001 WHO classification of mastocytoses has now been included without major modifications in the WHO book on the classification of hematological neoplasias and will thus continue to be applied in all leading centers (1).

The mast cell activation syndrome to date is not a clearly defined diagnosis but always fails to meet the diagnostic criteria of mastocytosis. Initiating unnecessary diagnostic or therapeutic measures under the heading of "mast cell activation" should be avoided. On the other

hand, missing staging investigations, especially histological evaluation of the bone marrow in adults and faulty application of the mastocytosis criteria defined in the WHO classification may not only result in misinterpretation of findings in patients with mastocytosis but also runs the risk that other possibly life-threatening hematological disorders are overlooked (2).

We agree that mastocytosis is an underdiagnosed disorder. We should, therefore, all aim to improve this situation by providing information and training, not by extending the definition of the disease as suggested by Molderings et al..

DOI: 10.3238/arztebl.2009.0174

REFERENCES

1. Horny H-P, Akin C, Metcalfe DD: Mastocytosis. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (eds): WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC Press 2008.
2. Horny H-P, Sotlar K, Valent P, Hartmann K: Mastocytosis—a disease of the hematopoietic stem cell. Dtsch Arztebl Int 2008; 105(40): 686–92.

Prof. Dr. med. Hans-Peter Horny
Institut für Pathologie
(Referenzzentrum für Hämatopathologie
im Rahmen des ECNM)
Escherichstr. 6
91522 Ansbach, Germany

Prof. Dr. med. Karl Sotlar
Institut für Pathologie
Ludwig-Maximilians-Universität München
80337 München, Germany

Prof. Dr. med. Peter Valent
Innere Medizin I (Hämatologie)
Universität Wien
1090 Wien, Austria

PD Dr. med. Karin Hartmann
Klinik und Poliklinik
der Abteilung für Dermatologie und Venerologie
Universität Köln, 50937 Köln, Germany

Conflict of interest statement
The authors of the letter and of the reply declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.