REVIEW ARTICLE

Mastocytosis

A Disease of the Hematopoietic Stem Cell

Hans-Peter Horny, Karl Sotlar, Peter Valent, Karin Hartmann

SUMMARY

Introduction: Mastocytosis is an unusual clonal disease of the hematopoietic stem cell.

Methods: This article is based on a selective literature search and on the authors' clinical and pathological experience.

Results: The clinical manifestations of mastocytosis range from cutaneous mastocytosis, a common, prognostically favorable presentation, to mast cell leukemia, a rare, life-threatening disease. The mediator-induced symptoms usually respond well to H1 antihistamines. Therapeutic standards for cytorreduction in the progressive, systemic forms of mastocytosis are still lacking.

Discussion: Because some of the manifestations of mastocytosis are nonspecific and can be mimicked by other diseases, there is a risk of two types of diagnostic error: Mastocytosis may remain undiagnosed when it is actually present, or it may be diagnosed even though morphological and molecular findings rule out mastocytosis. Well-defined criteria should be used to differentiate mastocytosis from other diseases with a similar clinical presentation.

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Key words: mastocytosis, diagnosis, differential diagnosis, anaphylactic reaction, urticaria

First described in the 1870s by Paul Ehrlich (1), the tissue mast cell (= mast cell) has seldom attracted as much interest as it is attracting today. Until recently, the mast cell was viewed principally as an effector cell in allergic diseases. In the past decade, however, new findings have shown that mast cells also play a crucial part in defense against pathogens and have an important immunoregulatory role in many processes such as wound healing, tumor control, and transplant tolerance (2, 3). Primary clonal proliferation of mast cells is found in the various forms of mastocytosis.

Soon after the discovery of the mast cell, researchers linked the so-called urticaria pigmentosa to cutaneous proliferation of mastocytes. It was not until the middle of the 20th century, however, that systemic mastocytosis was recognized and, shortly thereafter, the first case of mast cell leukemia was identified.

Patients with mastocytosis present widely varying clinical manifestations. Apart from the characteristic maculopapular skin lesions of urticaria pigmentosa, however, none of the signs initially point clearly to the diagnosis. Besides pruritus, hives, and anaphylactic reactions, there are often nonspecific complaints such as headache, dizziness, or gastrointestinal symptoms, which can be attributed to increased, quasi-excessive release of mast cell mediators (among others: histamine, heparin, tryptase, leukotrienes, prostaglandins, and cytokines such as interleukins and tumor necrosis factor). Therefore, mastocytosis is more and more frequently considered in the differential diagnosis of patients with nonspecific gastrointestinal symptoms. Nevertheless, mastocytosis should always be diagnosed according to the accepted WHO criteria, including the histological, immunohistochemical, and molecular examinations that these criteria require (4, 5). Confirmation of the diagnosis of mastocytosis by means of an anamnestic questionnaire does not fulfill the WHO criteria. "Mast cell activation syndromes" in reactive (nonclonal) proliferation of mastocytes display similar, partially overlapping clinical manifestations but must be clearly differentiated from mastocytosis (6).

Methods

This article is based on the published literature on mastocytosis (selective review of the publications found by searching for "mastocytosis," "systemic mastocytosis," and "human" in PubMed) and on the authors' personal experience of the clinical care of patients with mastocytosis

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Figure 1:

Typical maculopapular skin lesions (urticaria pigmentosa) in adults with cutaneous or systemic mastocytosis

Figure 2:

The maculopapular skin lesions are usually larger in children than in adults; as a rule there is no systemic involvement

or the morphological and histopathological examination of tissue from patients.

Definition

Mastocytosis is a clonal disease of the hematopoietic stem cell with a broad range of clinical symptoms and morphological manifestations (4, 7). In cutaneous mastocytosis, mast cell proliferation is confined to the skin. Systemic mastocytosis involves at least one extracutaneous organ. The bone marrow is then almost always affected; less frequently, the disease is also demonstrated histologically in the lymph nodes, spleen, liver, or other organs. Most patients display an activating point mutation of the Kit gene (Kit^{D816V}). However, neither the expression of Kit on the cell membrane nor the Kit^{D816V} mutation is specific for mastocytosis.

Frequency

There are no accurate data on the frequency of mastocytosis. Annual incidence of 5 to 10 new cases per million population has been estimated (3). In dermatological practices and hospital departments of dermatology, 1 of every 1000 to 8000 new patients has mastocytosis (8). The most frequently encountered forms are cutaneous mastocytosis and indolent systemic mastocytosis. The least

common is mast cell leukemia, which is thought to be the rarest human leukemia of all. About two thirds of the patients are children, one third adults.

Pathogenesis

Important studies on the molecular pathogenesis of mastocytosis have been published in the past 15 years (9). In normal mature mast cells, activation of the Kit receptor (CD117) by its ligand stem cell factor (SCF) leads to increased proliferation, prolonged survival, and intensified release of mediators. In mastocytosis, these functions are reinforced by a somatic mutation of the coding Kit gene in terms of autocrine dysregulation. The majority of patients with mastocytosis display a point mutation of the Kit gene in codon 816 (=Kit^{D816V}) (10, 11, e1). Occasionally, additional mutations of the Kit gene occur (10, e1, e2).

Kit, together with platelet-derived growth factor receptor alpha (PDGFRA), is assigned to subgroup III of the transmembrane receptor tyrosine kinases. Activation of PDGFRA by the gene rearrangement Fip1-like 1–PDGFRA (FIP1L1–PDGFRA) is frequently associated with hypereosinophilia syndrome or chronic eosinophilic leukemia (12). Some overlap with systemic mastocytosis has been observed: Most patients with hypereosinophilia syndrome show proliferation of atypical mast cells, and conversely occasional cases of systemic mastocytosis with associated chronic eosinophilic leukemia (SM-CEL) have been seen (7, 13). The two molecular defects—Kit^{D816V} and FIP1L1–PDGFRA—have not yet been demonstrated simultaneously in the same patient (13). In contrast, in other hematological neoplasias associated with mastocytosis, the molecular alteration characteristic for the respective neoplasia has been identified (14). The demonstration of Kit^{D816V} or FIP1L1–PDGFRA has particular therapeutic relevance, in that the tyrosine kinase inhibitor imatinib is active only against FIP1L1–PDGFRA (10, 15).

Clinical findings

The symptoms of mastocytosis vary widely (3, 4). Around 80% of patients develop characteristic brownish-red skin lesions. In adults, these maculopapular lesions are generally less than 0.5 cm in diameter and initially occur particularly on the thighs and trunk (*figure 1*). In children, the efflorescences are usually larger (0.5 to 3 cm) and often affect the entire integument (*figure 2*), typically including the head and the lateral face. Both forms are referred to as maculopapular cutaneous mastocytosis (previously: urticaria pigmentosa). Solitary mastocytoma of the skin is rare (*figure 3*). An unusual cutaneous subtype is diffuse erythrodermic mastocytosis, characterized by uniform yellowish-red coloration of the entire integument (*figure 4*). Mechanical irritation of the mastocytosis foci leads to release of mast cell mediators and thus to reddening, urticarial swelling, and itching (Darier's sign). The small maculopapular skin lesions can occur not only in the purely cutaneous but also in the systemic mastocytoses. Patients with skin lesions frequently suffer from itching and hives, particularly when

exposed to heat or cold. In young children the mastocytosis lesions may be associated with vesicles (bullous cutaneous mastocytosis).

All forms of mastocytosis can be accompanied by gastrointestinal symptoms such as nausea and spasmodic diarrhea, probably brought about by histaminemia (5, 16). Many patients report musculoskeletal symptoms and fatigue, and in rare cases neurological symptoms are described. Particularly important are anaphylactic reactions, especially after insect stings (17, e3). Occasionally, a patient who visits the doctor because of an anaphylactic reaction to a wasp or bee sting is found to have previously unrecognized mastocytosis (17, e3). These individuals generally have isolated bone marrow mastocytosis without skin changes. About 10% to 30% of patients with systemic mastocytoses develop osteopenia or osteoporosis. Pathological fractures may also be the first symptom of mastocytosis (e4).

A subgroup of patients with mastocytosis display significant changes in blood count, e.g., eosinophilia, monocytosis, or blast proliferation. These findings point to systemic mastocytosis with associated hematological non-mast cell lineage disease (SM-AHNMD). This association between mastocytosis and non-mast cell hematological neoplasia is unique in the whole spectrum of hematological neoplasias (5, 7). Almost all myeloid and lymphatic neoplasias have been described as associated hematological disorders, with varying frequency. Members of the group of myeloid neoplasias, particularly myelodysplastic/myeloproliferative syndromes (MDS/MPS), are much more frequent than lymphatic neoplasias, among which multiple myelomas predominate (7). The independent nosological status of SM-AHNMD is confirmed by molecular findings: Microdissection analyses have demonstrated that the activating mutation $\text{Kit}^{\text{D816V}}$ is found not only in mast cells but also in cells of the AHNMD compartment (14).

Aggressive systemic mastocytosis (ASM) is characterized by diffuse displacing mast cell infiltration leading to impairment of organ function, specifically bone marrow insufficiency (4). As a consequence of this rare excessive proliferation of mast cells the patients have organomegaly, particularly splenomegaly, cytopenia, liver failure, malabsorption, cachexia or osteolyses with pathological fractures.

Mast cell leukemia must be distinguished from ASM and is characterized by more than 20% atypical mast cells in a bone marrow smear. There is also significant mast cell proliferation in the blood (>10% of leucocytes). Aleukemic mast cell leukemias occur. Here, too, the criterion of mast cell proliferation involving more than 20% of the nucleated cells in a bone marrow smear must be fulfilled (differentiation from ASM).

A rare form of mastocytosis is the initially localized, later generalized or leukemic mast cell sarcoma (4).

Prognosis

Patients with cutaneous and indolent systemic mastocytosis have a favorable prognosis, i.e., in over 95% of them life expectancy is not reduced (4, e5). In

Figure 3:

Solitary mastocytoma of the distal lower leg. Mastocytomas are brown or brownish-red, usually well defined and raised. After mechanical irritation with a wooden spatula, the various mastocytic skin lesions show reddening and urticarial swelling (Darier's sign). After the reddening has worn off it may be followed by a white anemic discoloration of a few minutes in duration, as can be seen here to the left of the mastocytoma

Figure 4:

In diffuse cutaneous mastocytosis the skin is uniformly yellowish-red in color and thickened; histological examination shows marked mast cell proliferation in the dermis

more than half of the cases of cutaneous mastocytosis in children, there is spontaneous remission by the time the patient reaches adolescence. In adults the disease is generally chronic; only in a small proportion of patients with indolent systemic mastocytosis does it tend to regress. In patients with SM-AHNMD, the associated hematological neoplasia determines the prognosis. The progressive forms of systemic mastocytosis, specifically ASM and mast cell leukemia, are life-threatening: Without cytoreductive treatment they lead to death within a few months (16).

Classification

The first attempt to classify the mastocytoses was made in 1979 by the pathologists Lennert and Parwaresch of Kiel, Germany (18). After various modifications, in 2000 an international group of experts agreed on the categorization that was then adopted by the WHO in 2001 (4) and remains largely unchanged in the revised 2008 WHO publication on the classification of hematological neoplasias (box). This classification distinguishes seven categories:

- Pure cutaneous mastocytosis (most frequent variant: maculopapular cutaneous mastocytosis or urticaria pigmentosa)

BOX

Classification of the mastocytoses (WHO)

- Cutaneous mastocytosis
- Indolent systemic mastocytosis
- Systemic mastocytosis with associated clonal hematological non-mast cell lineage disease (SM-AHNMD)
- Aggressive systemic mastocytosis
- Mast cell leukemia
- Mast cell sarcoma
- Extracutaneous mastocytosis

Figure 5: Focal infiltration of the bone marrow by systemic mastocytosis. The mast cells are densely packed, mostly spindle-shaped, and hypogranulated. This meets the major criterion (compact mast cell infiltrate) and one of the minor criteria (spindle-shaped mast cells) of the WHO for the diagnosis of systemic mastocytosis

- Indolent systemic mastocytosis with involvement of at least one extracutaneous tissue, principally the bone marrow
- Systemic mastocytosis with associated clonal hematological non-mast cell lineage disease (SM-AHNMD)
- Aggressive systemic mastocytosis
- Mast cell leukemia
- Mast cell sarcoma
- Extracutaneous (benign) mastocytosis.

Historical terms such as "generalized mastocytosis," "malignant mastocytosis," "mast cell reticulosis," and "Rywin disease" (so-called eosinophilic fibrohistiocytic lesion) are obsolete (7).

Diagnostic criteria

Mastocytosis can be diagnosed only by histological examination of a tissue sample. The crucial biopsy sites

are the skin for cutaneous mastocytosis and the bone marrow for the systemic forms of the disease (4, 16). The WHO classification's criterion for cutaneous mastocytosis, besides the histological demonstration of intradermal mast cell infiltrates, is the presence of the typical skin lesions in their various forms. Since normal and reactive mast cells only very seldom—after administration of hematopoietic growth factors—form compact, cohesive infiltrates in bone marrow, the demonstration of compact mast cell infiltrates is used as the sole, decisive major criterion for the diagnosis of systemic mastocytosis. Two of the four minor diagnostic criteria for systemic mastocytosis (accumulation of spindle-shaped mast cells and aberrant expression of CD25 and/or CD2 on mast cells) can also be readily demonstrated or excluded in the tissue sample. Besides immunohistochemistry, CD25 expression can also be efficiently depicted and quantified by flow cytometry of bone marrow (e5). Further diagnostic criteria are the demonstration of an activating Kit mutation, usually Kit^{D816V}, and a chronic increase in serum tryptase concentration (>20 µg/mL). The diagnosis of systemic mastocytosis demands fulfillment of either the major criterion and at least one minor criterion or, in the absence of the major criterion, three of the four minor criteria. As a rule, therefore, the pathologist can diagnose systemic mastocytosis from examination of the tissue sample alone (figures 5 to 7). The tissue examined is usually bone marrow, more rarely gastrointestinal mucosa. For both tissues, the demonstration of compact infiltrates containing at least 25% spindle-shaped and/or CD25-positive mast cells is required (4).

Procedure on suspicion of mastocytosis

1. Determination of serum tryptase
2. Dermatological examination to confirm or exclude cutaneous mastocytosis
3. Histological/immunohistochemical investigation of the bone marrow (iliac crest trephination) or another tissue (e.g., gastrointestinal mucosa)
4. Molecular investigation of the tissue to confirm or exclude an activating Kit mutation in exon 17 (possibly also investigation of microdissected pooled mast cells and, in the case of SM-AHNMD, cells from the associated neoplasia).

Treatment

Explanation and counseling with regard to the increased tendency towards anaphylactic reactions is especially important for all patients with mastocytosis. Such a reaction can be triggered by, for example, insect stings, medications, anesthetics, or foodstuffs (17, e3). We therefore recommend all patients with a history of anaphylaxis, bullous skin lesions or diffuse cutaneous mastocytosis to carry an emergency kit with them at all times.

To date there are only a few nonrandomized controlled studies on the pharmacotherapy of mastocytosis (19, 20), with small numbers of cases, and the level of evidence for the following recommendations is thus low (levels 4a and 4b). Clinical experience shows that many

cutaneous and also systemic symptoms caused by increased release of mast cell mediators can be relieved by H₁ antihistamines (20, e6). With regard to the antihistamine treatment of urticaria, which is also associated with mediator release, it is recommended to give non-sedating or only slightly sedating antihistamines, because they have a similar mediator-inhibiting effect to the older antihistamines but a more favorable side-effect profile (21). In some mastocytosis patients treatment with UV light temporarily lessens the coloration of the skin lesions and partially relieves the urge to scratch (22, e7). Cromoglycic acid (disodium cromoglycate) can be given for gastrointestinal symptoms (3). Corticosteroids are sometimes effective for prophylaxis in patients with frequent anaphylactic reactions or severe forms of mastocytosis with malabsorption, diarrhea, and ascites (19). Cyto-reductive substances should be reserved for aggressive and leukemic systemic mastocytoses or cases of SM-AHNMD (10, 16, 23). In small groups of patients, cladribine (2CdA) and interferon alpha, sometimes combined with low-dose corticosteroids, have been found to inhibit mast cell growth in about 20% to 50% of patients (24). In cases of SM-AHNMD, the AHNMD is generally the clinically crucial component of the illness and must be managed according to established oncological treatment protocols. Specific treatment with the tyrosine kinase inhibitor imatinib is not possible in patients with the Kit^{D816V} mutation, because this mutation is linked with imatinib resistance (15). The newer Kit tyrosine kinase inhibitors (PKC412/midostaurin, dasatinib, and others) exert a marked antiproliferative action on mast cells with the Kit^{D816V} mutation in vitro, but their clinical value remains unclear (10, 23).

Discussion and differential diagnosis

Because of the frequently nonspecific symptoms, the differential diagnosis of mastocytosis embraces an unusually broad spectrum of clinical syndromes, e.g., immunological processes such as autoimmune diseases, inflammatory bowel diseases, and carcinoid flush (4, 7). Many patients have morphologically mild tissue infiltration (as a rule those with indolent systemic mastocytosis) yet suffer greatly from their mediator symptoms, e.g., diarrhea. It is therefore remarkable that—in contrast to many other clonal diseases—the degree of infiltration is usually low in mastocytoses, especially in the common forms of the disease (cutaneous and indolent systemic mastocytosis). Thus, in the majority of cases the proportion of mast cells in the bone marrow is below 0.01% of all nucleated cells (e5).

The basis for the diagnosis of systemic mastocytosis is the morphological demonstration of a compact tissue infiltrate of mast cells with an atypical phenotype and co-expression of CD25, usually associated with an activating Kit mutation in codon 816 (4). Any tendencies to arrive at a diagnosis purely by means of serological or other biochemical tests (e.g., urinalysis) and a questionnaire should be firmly resisted. An elevated serum tryptase concentration is observed in proliferation of mast cells but does not alone justify the diagnosis of systemic

Figure 6: Mild diffuse proliferation of partially spindle-shaped, often hypogranulated tissue mast cells without the formation of compact (diagnostic) infiltrates. This pattern is typical for adult patients with the skin lesions of cutaneous mastocytosis (urticaria pigmentosa) in whom the bone marrow is investigated for staging purposes. Clarification by means of special immunohistochemical stains (particularly CD25) and molecular-genetic investigation for confirmation/exclusion of a Kit mutation in exon 17 is necessary in such cases. If an atypical phenotype with mast cell expression of CD25 is demonstrated and a mutation is found, then together with the spindle-shaped cells three minor diagnostic criteria are fulfilled and the diagnosis of indolent systemic mastocytosis with involvement of skin and bone marrow is established

mastocytosis, because reactive mast cell proliferation (mast cell hyperplasia) presents a very similar clinical picture. Mastocytosis is a clonal disorder of the mast cell or of its CD34-positive hematopoietic progenitor cell (precursor cell) and as such must be distinguished from all reactive-hyperplastic mast cell proliferations (6). An elevated serum tryptase concentration, particularly in the presence of blood count anomalies and/or organomegaly, should always prompt one to consider histological examination of the bone marrow.

The morphological differential diagnosis of mastocytosis includes very rare hematological neoplasias such as chronic basophilic leukemia, myelomastocytic leukemia, and tryptase-positive acute myeloid leukemia (7). The differential diagnosis of the variants with unfavorable prognosis, such as ASM and mast cell leukemia, includes malignant lymphomas as well as myelodysplastic and myeloproliferative diseases. Mastocytosis often presents a special diagnostic challenge for the experienced clinician and the hematopathologist.

The authors are active members of the German Competence Network on Mastocytosis and the European Competence Network on Mastocytosis (ECNM). National and international reference centers are listed on the two networks' web-sites (www.mastozytose.net, www.ecnm.net).

Conflict of interest statement

The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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Figure 7: Markedly hypercellular bone marrow with diffuse compact infiltrates of a lymphocytic lymphoma; predominance of small lymphatic cells and subtotal depletion of fat cells and normal blood cell precursors. Note the diffuse proliferation of medium-sized, round, always loosely scattered tissue mast cells with numerous metachromatic granules. Typical appearance of reactive mast cell proliferation (mast cell hyperplasia), clearly distinct in this example from the findings in systemic mastocytosis

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Key messages

- Mastocytosis is a clonal disease of the bone marrow, usually associated with an activating point mutation of the Kit gene, Kit^{D816V}.
- Mastocytosis is very heterogeneous, both clinically and morphologically.
- The prognosis of the most common forms of mastocytosis, cutaneous and indolent systemic mastocytosis, is favorable; nevertheless, many patients suffer from itching, hives, anaphylactic reactions or gastrointestinal symptoms.
- The diagnosis of mastocytosis should be based on the criteria recommended by the WHO. The major criterion is histological demonstration of compact mast cell infiltrates in the tissue.
- Mastocytosis must be distinguished from a "mast cell activation syndrome" subsequent to reactive (non-clonal) mast cell proliferation.
- Cutaneous mastocytosis with itching and hives should be treated with an H₁ antihistamine, while interferon alpha and cladribine are recommended for aggressive systemic mastocytosis. Imatinib is ineffective in Kit^{D816V}-positive mastocytoses.

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