Mastocytosis

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Diagnostic recommendation

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Definition and characteristics

Mastocytosis is characterized by an accumulation of neoplastic mast cells in one or more organs. It is a heterogeneous disease ranging from skin lesions to aggressive hematological neoplasms.

Classification of Mastocytosis

According to WHO 2017, mastocytosis can be classified into three major categories: Cutaneous mastocytosis, systemic mastocytosis and the rare mast cell sarcoma. Cutaneous and systemic mastocytosis can each be divided into further subgroups. While in cutaneous mastocytosis the mast cells accumulate in the skin, the systemic variant involves at least one extracutaneous organ, with the bone marrow almost always being infiltrated. A mast cell sarcoma is a solid tumor consisting of atypical, malignant mast cells.

WHO classification 2017 of mastocytosis (Swerdlov et al. 2017)

Cutaneous mastocytosis
- Urticaria pigmentosa/maculo-papular cutaneous mastocytosis
- Diffuse cutaneous mastocytosis
- Solitary mastocytoma of the skin

Systemic mastocytosis
- Indolent systemic mastocytosis (SM)
- Smouldering systemic mastocytosis (SSM)
- Systemic mastocytosis with an associated hematological neoplasm (SM-AHN)*
- Aggressive systemic mastocytosis (ASM)
- Mast cell leukemia (MCL)

Mast cell sarcoma
*Systemic mastocytosis associated with hematologic neoplasm can cause all known lymphoid and myeloid neoplasms. However, myeloid neoplasms, especially CMML, represent the majority.

Diagnostic criteria according to WHO 2017:

Cutaneous Mastocytosis
Skin lesions demonstrating the typical findings of urticaria pigmentosa/maculo-papular cutaneous mastocytosis, diffuse cutaneous mastocytosis or solitary mastocytoma, and typical histological infiltrates of mast cells in a multifocal or diffuse pattern in an adequate skin biopsy. In addition, features/criteria sufficient to establish the diagnosis of systemic mastocytosis must be absent.

Systemic mastocytosis
The diagnosis of systemic mastocytosis can be made when the major criterion and at least 1 minor criterion are present, or when >3 minor criteria are present.

Major criterion:
Multifocal dense infiltrates of mast cells (>15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s)

Minor criteria:
1. In biopsy sections of bone marrow or other extracutaneous organs,
   >25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology or
   >25% of all mast cells in bone marrow aspirate smears are immature or atypical.
2. Detection of an activating point mutation at codon 816 of KIT in bone marrow, blood or another extracutaneous organ
3. Mast cells in bone marrow, blood or other extracutaneous organ express CD25, with or without CD25 in addition to normal mast cell markers
4. Serum total tryptase is persistently >20 ng/mL, unless there is an associated myeloid neoplasm, in which case this parameter is not valid.

Diagnostics of Mastocytosis

Cytomorphology

The cytomorphology can detect an increase of atypical mast cells in the bone marrow or very rarely a leaking into the peripheral blood. Furthermore, it is particularly relevant in SM-AHN, as it contributes to the classification of associated hematological neoplasm. The major and minor criteria are better understood in histology and immunohistochemistry.

Immunophenotyping

Neoplastic mast cells express CD25 with or without CD25 compared to normal/reactive mast cells.

Chromosome analysis

Although cytogenetic examination is recommended for patients with systemic mastocytosis, cytogenetic aberrations can usually only be detected in SM-AHN. No specific aberrations occur and in most cases they correspond to those described for other myeloid neoplasms. Deletions (de(5q), de(11q), de(20q)) are most frequently detected, followed by trisomy (+8), monosomy (-7) and complex karyotypes. In addition, cytogenetics can help to assess the prognosis (see Prognosis) (Naumann et al. 2018, Oktapedia Guideline systemic mastocytosis 2020).

FISH
In the diagnosis of mastocytosis, FISH analysis is usually seen as a complementary method to classical chromosome analysis and is used specifically to answer specific questions.

**Molecular genetics**

A gain-of-function mutation in codon 816 of the receptor tyrosine kinase KIT can be detected in ≥90% of patients with systemic mastocytosis. In more than 95% of the patients with KIT mutation aspartate is substituted by valine (KIT D816V). Alternative KIT mutations have also been described, but are rare. These include D816Y, D816H, D816T, D815K, F822C, V560G and D820G (<5%). Depending on the subgroup of mastocytosis, the mutation load in peripheral blood and bone marrow may vary, so a quantitative analysis of both materials is recommended. The quantitative determination of the mutation load is also important as a progression parameter under therapy.

In more than 80% of patients with advanced systemic mastocytosis (including ASM, SM-AHN and MZL) additional mutations are described in addition to the KIT mutation. Affected genes include TET2, SRSF2, ASXL1, RUNX1, JAK2, CBL, N/KRAS, EZH2, IDH1/2 and SF3B1. Especially a mutation in at least one of the genes SRSF2, ASXL1, RUNX1 (so-called SARA gene panel) has a significant influence on prognosis and therapy response (see Prognosis). Therefore, in case of a suspected advanced systemic mastocytosis, an extended molecular biological diagnosis is recommended in addition to the detection of the KIT mutation (Jawhar et al. 2016, Schwaab et al. 2013, Onkopaedia Guideline Systemic Mastocytosis 2020).

**Prognosis of Mastocytosis**

Cutaneous mastocytosis usually proceeds favourably. It occurs more frequently in childhood. In most cases, the skin lesions regress on their own by adulthood (Vaient et al. 2017).

Systemic mastocytosis develops almost exclusively in adulthood. The prognosis depends on the subgroup of patients. ISM is generally favourable and patients in most cases have a normal life expectancy. However, 5-10% of ISM show a progress to advanced systemic mastocytosis and a less favourable prognosis. There are data suggesting that in ISM, in addition to the KIT mutation, additional mutations in the ASXL1, RUNX1 and/or DNMT3A (V667E >30%) genes are associated with shorter progression-free and overall survival (Muñoz-González et al. 2019).

The ASM, the MZL and the mast cell sarcoma each have an unfavourable prognosis (Lim et al. 2009, Monnier et al. 2016). In the case of SM-AHN, the associated haematological neoplasm and the associated cytogenetic and/or molecular genetic changes should also be taken into account for the assessment of the prognosis (Naumann et al. 2018, Wang et al. 2019). Classification into risk groups is possible for cytogenetic changes depending on the associated haematological neoplasm. A study by Naumann et al. shows that an unfavourable karyotype is an independent factor with regard to overall survival. In patients with associated MDS a complex karyotype (≥3 aberrations) or monosomy 7 is assigned to the unfavourable risk group. However, the favorable risk group includes patients with a normal karyotype, del(5q), trisomy 8, del(1q) or del(12p). In associated AML, patients with a complex karyotype, monosomy 7 or del(5q) are included in the unfavorable risk group (Naumann et al. 2018).

≥90% of patients with systemic mastocytosis have a KIT D816V mutation. Additional mutations are found especially in ASM, SM-AHN and MZL. The most frequently additionally mutated genes are TET2, SRSF2, ASXL1, RUNX1 and CBL, whereby an unfavorable prognosis has been described especially for mutations in the genes SRSF2, ASXL1 and RUNX1 (Jawhar et al. 2016, Schwaab et al. 2013, Naumann et al. 2018). Recently the scoring system MARS (Mutation-Adjusted Risk Score for Advanced Systemic Mastocytosis) was published (Jawhar et al. 2019).

**References**