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Original Article

Guidelines and diagnostic algorithm for patients with suspected systemic mastocytosis: a proposal of the Austrian competence network (AUCNM)

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Abstract: Systemic mastocytosis (SM) is a hematopoietic neoplasm characterized by pathologic expansion of tissue mast cells in one or more extracutaneous organs. In most children and most adult patients, skin involvement is found. Childhood patients frequently suffer from cutaneous mastocytosis without systemic involvement, whereas most adult patients are diagnosed as suffering from SM. In a smaller subset of patients, SM without skin lesions develops which is a diagnostic challenge. In the current article, a diagnostic algorithm for patients with suspected SM is proposed. In adult patients with skin lesions and histologically confirmed mastocytosis in the skin (MIS), a bone marrow biopsy is recommended regardless of the serum tryptase level. In adult patients without skin lesions who are suffering from typical mediator-related symptoms, the basal serum tryptase level is an important diagnostic parameter. In those with slightly elevated tryptase (15-30 ng/ml), additional non-invasive investigations, including a *KIT* mutation analysis of peripheral blood cells and sonographic analysis, is performed. In adult patients in whom i) KIT D816V is detected or/and ii) the basal serum tryptase level is clearly elevated (> 30 ng/ml) or/and iii) other clinical or laboratory features are suggesting the presence of occult mastocytosis, a bone marrow biopsy should be performed. In the absence of *KIT* D816V and other indications of mastocytosis, no bone marrow investigation is required, but the patient's course and the serum tryptase levels are examined in the follow-up.

Keywords: Mastocytosis, tryptase, KIT D816V, diagnostic algorithm, staging

Introduction

Mastocytosis is a term collectively used for a heterogeneous group of myeloid neoplasms characterized by abnormal expansion and accumulation of mast cells (MC) in one or more organ systems [1-9]. Depending on the organ(s) involved, mastocytosis is divided into cutaneous mastocytosis (CM), systemic mastocytosis (SM), and localized MC tumours [1-9]. The classification of the World Health Organization (WHO) includes several distinct categories of CM and SM [10-13]. The clinical course and prognosis vary considerably between such patients [14-17]. While the long-term outcome in CM and indolent SM (ISM) is excellent, the prognosis and life-expectancy in advanced SM, including aggressive SM (ASM) and MC leukemia (MCL), are poor, and the same holds true for most patients with SM accompanied by an associated hematologic non-MC-lineage disease (SM-AHNMD) [1-8, 11-17]. These patients suffer from "hematologic" problems, such as cytopenia, ascites, malabsorption, lymphadenopathy, splenomegaly, hepatopathy or huge osteolyses [1-8, 11-17].

In addition, patients with mastocytosis can suffer from the symptoms caused by diverse mast cell mediators, especially when patients have a co-existing IgE-mediated allergy [18-24]. Mediator-related symptoms may be mild, extensive, or even life-threatening [18-24]. In several of these patients, a MC activation syndrome (MCAS) can be documented [18-24]. Apart from mediator-related symptoms, patients with SM may also suffer from the cosmetic issue or from osteoporosis.

Most adult patients with SM are presenting with urticaria pigmentosa-like skin lesions [1-8]. However, the absence of skin lesions does not exclude the presence of SM. These patients are a diagnostic challenge, especially when the symptoms are non-characteristic, the physician is not aware of the potential etiology and/or the serum tryptase level is relatively low (below 20 ng/ml). These patients may or may not suffer from an IgE-dependent allergic disease or from an atopic disorder [19-24]. During the past few years, more and more of such cases have been referred in specialized centers, and many were found to have a slightly elevated serum tryptase (15-20 ng/ml) without definitive signs or symptoms of mastocytosis. For these patients, a clear diagnostic algorithm is lacking.

The European Competence Network on Mastocytosis (ECNM) has been established in 2002, with the intention to increase awareness and to improve diagnosis and therapy in mastocytosis patients [25, 26]. In 2011, the Austrian Competence Network on Mastocytosis (AUCNM) has been inaugurated as part and partner of the ECNM. Members of the AUCNM are organizing Annual Meetings as well as seminars. In 2012, the 10 year jubilee of the ECNM has been celebrated in Vienna together with members of the AUCNM, who were involved as organizers and/or presenting experts. The aim of the first defined scientific project of the AUCNM was to establish robust diagnostic algorithms for patients with suspected mastocytosis. The resulting proposed algorithms and recommendations are presented in this article.

Patients with mastocytosis in the skin (MIS)

In children with MIS, a bone marrow biopsy is usually not required, unless the tryptase level is very high, organomegaly (splenomegaly, lymphadenopathy) is found, an abnormal blood count has been documented, or other signs and symptoms would argue for the presence of a systemic hematologic disease [18, 23]. Even if a *KIT* mutation is detectable in the skin or blood, no bone marrow biopsy is performed in these cases. However, these patients are followed until adulthood. In adult patients with MIS, a bone marrow biopsy is recommended independent of the clinical course, symptoms, and serum tryptase level [18, 23]. Even if no *KIT* mutation in the skin and/or peripheral blood is detectable in these patients and even if the serum tryptase level is normal, a bone marrow biopsy is usually recommended [18]. In those in whom SM is diagnosed, a complete staging is performed [18]. In patients who are not agreeable to undergo a bone marrow investigation, the provisional diagnosis of MIS is established and no detailed staging is performed unless clinical signs and symptoms would argue for organ damage [18]. Many of these patients agree to undergo a bone marrow test after some time in the follow up.

Approach to patients with slightly elevated serum tryptase but no evidence of MIS

A more difficult challenge are patients without MIS who otherwise have symptoms or laboratory parameters suggesting the presence of mast cell activation or a clonal mast cell disease [23]. Allergy tests may be positive or negative in these cases. In some of these patients, the case history may reveal typical signs of histamine effects or typical clinical patterns suggesting the presence of SM [18, 23] (**Table 1**). One example is severe anaphylaxis after hymenoptera venom exposure combined with advanced osteopenia or osteoporosis. In such patients, a bone marrow biopsy is recommended independent of the serum tryptase level and other test results. In those with unclear symptoms (and otherwise normal laboratory values), we recommend to perform a *KIT* mutation analysis using peripheral blood cells and a highly sensitive test such as the DNA clamp PCR [27]. If in such a patient, *KIT* D816V is detectable, a bone marrow biopsy should be recommended, whereas in those without a mutation at codon 816 of *KIT*, a wait-and-watch strategy is appropriate, unless other signs and symptoms would argue for the presence of a mast cell proliferative neoplasm or another bone marrow disease.

Table 1. Typical clinical features and symptoms suggesting the presence of systemic mastocytosis (SM)* or a mast cell activation syndrome

Feature/symptom	Typical laboratory findings
Anaphylaxis with hypotension	Allergy tests (specific IgE) negative
Severe anaphylactic shock after hymenoptera venom exposure**	Allergy tests positive or negative and: tryptase elevated during the event**
Headache plus diarrhea responsive to histamine receptor antagonists	increased histamine levels (plasma, urine), tryptase may or may not increase
Unexplained pruritus (+/- urticaria or flushing) responsive to histamine receptor antagonists	no skin disease, allergy, or internal disorder explaining symptoms are found, tryptase may or may not increase
Other allergy-like symptoms that are responsive to histamine receptor antagonists or mast cell-targeting drugs (like cromolyn)	no allergy and no other disease explaining the symptoms are found, tryptase may or may not increase
Bone pain due to osteopenia or osteoporosis***	T score below -2 (below -2.5) as assessed by age-adjusted osteodensitometry

*if two or more of these features/symptoms are recorded in the same patient, the likelihood increases that the patient is suffering from SM. **meeting the criteria of mast cell activation syndrome (MCAS). ***counts especially in man, and when other causes of osteoporosis have been excluded.

The follow up may also reveal a constantly increasing serum tryptase level. In these patients, a bone marrow examination is also recommended in order to exclude (or reveal) the development of SM or another myeloid neoplasm. An algorithm for adult patients with slightly elevated tryptase without MIS is shown in **Figure 1**.

Patients with a clearly elevated serum tryptase but no evidence of MIS

In adult patients with clearly elevated basal serum tryptase levels, a bone marrow examination should be performed regardless of laboratory findings or symptoms [18, 23]. This recommendation is based on the fact that clearly elevated tryptase levels are primarily and rather specifically found in patients with mastocytosis or other myeloid neoplasms, such as a myeloproliferative neoplasm (MPN), myelodysplastic syndrome (MDS) or myeloid leukemia. A list of differential diagnoses in patients with slightly elevated serum tryptase levels (relevant in those without MIS) is shown in **Table 2**.

An important aspect is that tryptase levels also increase during and shortly after an anaphylactic episode [23, 28-30]. Therefore, in such patients, the serum tryptase level has to be re-evaluated at least 2 days after complete resolution of all symptoms [23, 28-30]. Another important question is: what is “clearly elevated”? The diagnostic cut off level in SM remains 20 ng/ml. However, more and more apparently healthy individuals appear to have a slightly elevated tryptase, ranging between 15 ng/mL and 30 ng/mL. Therefore, we recommend that a tryptase level exceeding 30 ng/mL should be considered as clearly elevated in adult patients. In such patients, a bone marrow investigation is justified even if the serum tryptase level remains at a constant range in the follow up and no signs or symptoms indicative of SM or another myeloid neoplasm are found.

By contrast, in children, the situation is different. Here, the likelihood of a systemic disease (mastocytosis or other myeloid neoplasm) is low even if the serum tryptase level is slightly elevated. Therefore, in childhood patients with MIS, no bone marrow biopsy is performed even if a moderately elevated tryptase is detected [18, 23]. These patients are diagnosed as suffering from CM, unless clear clinical, radiologic or laboratory signs of a systemic disease are present [18]. In cases with a constantly increasing serum tryptase level or massively evelated tryptase (> 100 ng/mL) or other clinical or laboratory signs of a systemic neoplastic process (e.g. organomegaly), a bone marrow biopsy is required, even in children. Detailed diagnostic algorithms for children and adults have been reported previously [18].

Follow up strategies in suspected mastocytosis

The follow up strategy depends on the symptoms and laboratory parameters. In all these

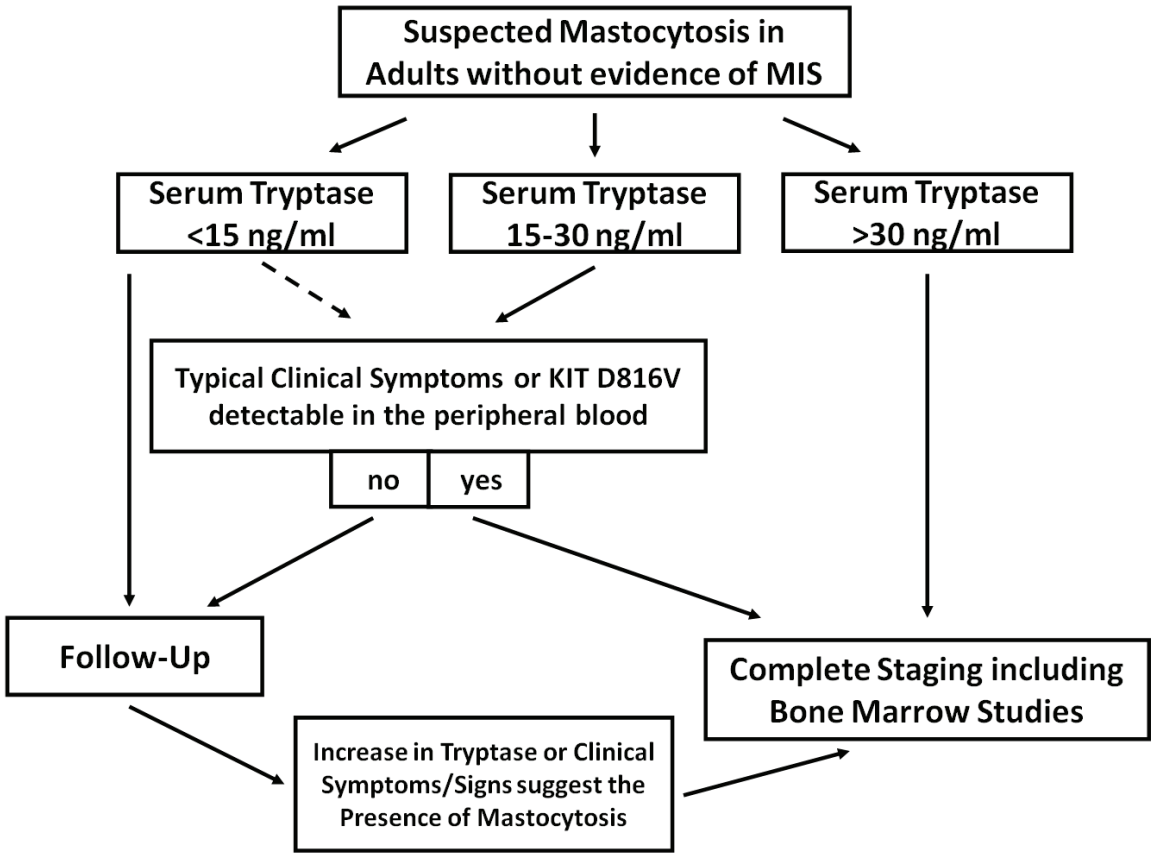

Figure 1. In adult patients without evidence of mastocytosis in the skin (MIS) but suspected systemic mastocytosis (SM), the basal serum tryptase level is an important initial screen parameter. In patients who have a clearly elevated basal tryptase, a bone marrow biopsy has to be considered. In patients with normal or slightly elevated tryptase, peripheral blood cells should be examined for the presence of *KIT* D816V using a highly sensitive test. In patients in whom typical signs and symptoms (osteoporosis, histamine-symptoms, anaphylaxis with negative allergy-test) or *KIT* D816V are detected, a bone marrow biopsy should be performed. If the KIT mutant is not detectable and symptoms are non-specific or can be explained by another disorder involving mast cells (e.g. allergy), the patient will be examined in the follow up, including repeated examinations of blood counts and serum tryptase levels.

patients, the serum tryptase level should be determined in regular time intervals. This holds also true for patients suffering from mastocytosis, independent of the disease variant [18, 23]. In addition, blood counts and serum chemistry parameters should be recorded in the follow up. In those in whom the diagnosis of mastocytosis is likely, a repeated examination of the peripheral blood for the presence of *KIT* D816V should be performed. A re-biopsy of the bone marrow should be considered in patients in whom the serum tryptase levels increase or *KIT* D816V becomes detectable in the follow up. A special situation is suspected SM with or without MIS in children. In these patients, serum tryptase levels and other laboratory parameters should also be recorded in the follow up. An open question is whether these parameters need to be recorded even when skin lesions disappear in the follow up. In those patients in whom serum tryptase levels remain normal, no further follow up may be required. In all patients in whom skin lesions persist into adulthood, a bone marrow biopsy should be performed regardless of the serum tryptase level and other parameters [18, 23]. Whereas childhood patients are usually managed by dermatologists, adult patients should be managed in a multidisciplinary approach involving a hematology center, a bone marrow pathologist, and an experienced dermatologist who excludes or documents the presence of MIS by inspection and biopsy.

Table 2. Differential diagnoses in patients with slightly elevated serum tryptase levels* but no evidence of mastocyosis in the skin

Diagnosis	Major cellular source of tryptase
Hematologic	
Systemic Mastocytosis (SM)	Neoplastic mast cells
Chronic myeloid leukemia (CML)	Neoplastic (immature) basophils
Chronic eosinophilic leukemia (CEL)	Neoplastic mast cells or basophils
Chronic basophilic leukemia (CBL)	Neoplastic (immature) basophils
Acute myeloid leukemia (AML)	Myeloblasts
Myelodysplastic syndrome (MDS)	Blast cells, basophils or mast cells
Myeloproliferative neoplasm (MPN)	Blast cells, basophils or mast cells
MDS/MPN overlap neoplasm	Blast cells, basophils or mast cells
Myelomastocytic leukemia (MML)	Blast cells and neoplastic mast cells
Non-Hematologic Reactive	
Allergic reaction (transient increase)	Mast cells
Mast cell activation syndrome (MCAS)	Mast cells
Atopic disorders	Mast cells
Chronic inflammatory disease (CID)	Mast cells
Chronic helminth infection	Mast cells
Others/Pitfalls/Varia	
Chronic severe renal failure	Mast cells
Normal healthy individual	Mast cells
False positive test result**	-

*Total serum tryptase 15-30 ng/mL as assessed by the flouroenzyme-immunoassay (FIA). **False positive results have previously been produced in a few patients, sometimes on the basis of heterophilic antibodies. However, the new generation of the FIA developed more recently, should avoid this problem.

Summary and future perspectives

The approach to adult patients with suspected mastocytosis is a diagnostic challenge in daily practice, especially when the physician is unaware of the biology and etiology of the disease, no skin lesions are present, blood counts are normal and the serum tryptase level is slightly elevated or within normal range. The *KIT* mutation analysis (*KIT* D816V) in the peripheral blood is an essential pre-invasive test in these patients. A positive test result is suggestive of the presence of SM, with all clinical consequences, including a bone marrow biopsy. Resulting algorithms and recommendations of the AUCNM may greatly assist in reducing unnecessary referrals and investigations, and help avoid unjustified misinformation and disconcertment of patients. In the foreseeable future, additional disease-related markers and genetic testing [31] will also be available and may further improve preinvasive diagnostics and algorithms.

Abbreviations

AHNMD, associated hematologic non-mast cell lineage disease; ASM, aggressive systemic mastocytosis; AUCNM, Austrian Competence Network on Mastocytosis; CM, cuntaneous mastocytosis; ECNM, European Competence Network on Mastocytosis; ISM, indolent systemic mastocytosis; MC, mast cell(s); MCAS, mast cell activation syndrome; MCL, mast cell leukemia; MDS, myelodysplastic syndrome(s); MIS, mastocytosis in the skin; MPN, myeloproliferative neoplasm(s); SM, systemic mastocytosis; SSM, smoldering systemic mastocytosis; TKI, tyrosine kinase inhibitor(s); WHO, World Health Organization.

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