

Mastocytosis and clonal mast cell activation syndrome

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Abstract

Mastocytosis is a group of disorders characterized by the abnormal proliferation and accumulation of atypical mast cells (MC) in one or more organs. In the majority of patients the bone marrow is affected. The clinical presentation of this disease is heterogeneous, ranging from asymptomatic to aggressive with fatal prognosis. Symptoms of mastocytosis result from MC-derived mediators and, less frequently, from destructive infiltration of MCs in tissues. The symptoms of mastocytosis include episodes of MC mediator release and anaphylactic reactions. The diagnosis of mast cell activation disorder (MCAD) has been proposed for subjects without skin lesions (such as urticaria pigmentosa) and unexplained anaphylactic reactions who only meet one or two minor criteria for systemic mastocytosis (SM) (so SM cannot be recognized). The presence of both KIT-mutated and aberrant CD25 expression on bone marrow MCs, defined as clonality, occurs in c-MCAD. Those patients lacking both criteria are considered non-clonal (nc-MCAD). Patients with c-MCAD might correspond to indolent systemic mastocytosis (ISM) at the early phase of the disease. Further follow-up of patients fulfilling only one or two minor criteria for SM is required to determine whether they evolve to SM and to detect disease progression. The diagnosis of MCAD is crucial for the treatment of allergy and anaphylaxis, for example for Hymenoptera venom allergy therapy, which is similar to that applied in patients with SM.

Key words: systemic mastocytosis, mast cell activation disorder, monoclonal mast cell activation syndrome, mast cell mediators, tryptase, anaphylaxis.

Introduction

Mastocytosis is a group of disorders characterized by the abnormal proliferation and accumulation of atypical mast cells (MC) in different organs including bone marrow, which is affected in the majority of patients, but also skin, liver, spleen, lymph nodes and the gastrointestinal tract [1]. The clinical presentation of the disease is heterogeneous, with the course ranging from asymptomatic to aggressive with fatal prognosis. Symptoms of mastocytosis result from MC-derived mediators and, less frequently, from destructive infiltration of MCs in tissues. The most favourable prognosis is assigned to cutaneous mastocytosis (CM), which is frequent in infancy and could resolve spontaneously during the second decade of life [2].

Depending on the age of onset, two main categories of the disease can be distinguished. In patients with typical childhood-onset mastocytosis, the disease is limited to the skin and the first symptoms develop in the first

years of life. In these cases the prognosis is favourable [3]. Possible improvement of the skin lesions or remission of the disease usually occurs in adolescence. In contrast, patients with adult-onset mastocytosis present more often persistent systemic involvement, where not only skin but also other organs are affected – first of all the bone marrow (systemic mastocytosis – SM) [4]. A point mutation in codon D816V of C-KIT is usually present [5].

Diagnosis

The disease cannot be diagnosed only on the basis of clinical symptoms. The most important step in the diagnostic process is the histological examination of the bone marrow biopsy, which is the reference test to diagnose SM in adult patients. Diagnostic work-up also includes examination of bone marrow aspirate: cytology, immunophenotype of mast cells with expression of CD2

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and CD25, activating point mutation of c-kit. Further, serum tryptase level must be determined [6].

The WHO classification of mastocytosis provides criteria of diagnosis of SM based on major and minor criteria. The major diagnostic criterion is the presence of compact multifocal dense infiltrates of MC in bone marrow or another extracutaneous organ (> 15 MC in aggregate). The minor diagnostic criteria are as follows:

- 1) the presence of > 25% spindle-shaped or atypical MCs in bone marrow aspirate,
- 2) activating point mutation in codon D816V of c-kit in any extracutaneous biopsy,
- 3) atypical immunophenotype of MC with CD2 and/or CD25 expression and
- 4) chronically elevated serum tryptase level more than 20 ng/ml.

The diagnosis of SM can be established if the major and at least 1 minor or 3 minor criteria are present [2, 5, 7].

Initial diagnosis of SM based on gastrointestinal tract or spleen biopsy is exceptional. Furthermore, MC infiltrates may occur in chronic inflammatory diseases of the gastrointestinal tract with no connection with SM.

The WHO classification defines 7 variants of mastocytosis:

- cutaneous mastocytosis (CM),
- indolent systemic mastocytosis (ISM),
- systemic mastocytosis with clonal haematological non-MC-lineage disease (SM-AHNMD),
- aggressive systemic mastocytosis (ASM),
- MC leukaemia (MCL),
- MC sarcoma (MCS),
- extracutaneous mastocytoma [1].

In order to differentiate the subtypes of SM it is necessary to assess the presence of clinical symptoms caused by tissue or organ infiltration of MC, especially so-called B-findings (borderline benign), referring to organomegaly, and C-findings, indicating organ failure and eligibility for cytoreductive therapy [1]. B-findings carry the message “be careful, wait and watch if progression of this disease occurs” and include the following: signs of multilineage involvement (hypercellular marrow, dysplasia), huge MC marrow infiltration (a massive MC burden), significantly elevated serum tryptase level (> 200 ng/ml) and organomegaly (hepatomegaly, splenomegaly, lymphadenopathy) [8, 9]. If at least 2 B-findings are documented, the diagnosis of smouldering systemic mastocytosis (SSM) should be established. Smouldering systemic mastocytosis is a type of SM associated with a higher risk of developing myelodysplastic, myeloproliferative or even leukaemic transformation syndrome [1]. C-findings mean “consider cytoreduction with chemotherapy or with targeted drugs”, and include: cytopenia, pathological fractures, hepatosplenomegaly with liver and/or spleen dysfunction, ascites, malabsorption syndrome, weight loss, lymphadenopathy and eosinophilia. These symptoms occur in ASM, MCL and MC lymphoma.

Thus, C-findings result from clinically relevant impairment or loss of organ function due to MC infiltration and are eligible for intensive or targeted treatment [7].

The severity of skin lesions often shows an inverse correlation with bone marrow involvement. Absence of urticaria pigmentosa is often seen in ASM or MCL. The lack of skin lesions is also found in isolated bone marrow mastocytosis (BMM), a subtype of SM without skin involvement and low serum baseline tryptase (sBT) in contrast to SSM [6, 10]. Additionally, significantly increased serum sBT is considered as a potential indicator of aggressiveness of the disease in SM patients without skin lesions [10].

Mast cell activation syndrome

Mast cell activation disorder (MCAD) is a mast cell disease characterized by abnormal MC activation leading to enhanced release of mediators without clear triggers.

For subjects without skin lesions who experienced anaphylactic reactions but who only meet 1 or 2 minor criteria for SM (excluding raised sBT), the diagnosis of monoclonal mast cell activation syndrome (MMAS) has been proposed [11]. The presence of both KIT-mutated and aberrant CD25 expression in bone marrow MCs, defined as clonality, occurs in clonal mast cell activation disorder (c-MCAD). Those patients lacking both criteria are considered to have non-clonal mast cell activation disorder (nc-MCAD) [12]. Álvarez-Twose *et al.* [12] presented clinical, biological and molecular characteristics of adult patients with c-MCAD and nc-MCAD. Overall, the most common triggers for acute MC activation and mediator release were as follows: (1) Hymenoptera stings, horsefly and unidentified insects, (2) hypersensitivity to drugs: antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), codeine, mepivacaine, rocuronium, (3) food: fish, egg, sunflower oil, alcohol, and (4) intestinal manipulation during abdominal surgery. Insect venom allergy was the most common causative factor of anaphylaxis in patients with ISMs– (indolent systemic mastocytosis without involvement of the skin), and drugs in patients with nc-MCAD. Eighty percent of patients had severe life-threatening respiratory and/or cardiovascular symptoms. Regarding the clinical presentation of the most severe anaphylaxis, significantly higher frequencies of skin and respiratory symptoms were found among nc-MCAD, and cardiovascular symptoms among ISMs. Frequency and intensity of anaphylactic episodes were similar in both ISMs– and ISMs+ groups. Interestingly, 14% of patients with ISMs+ with anaphylaxis in medical history had MC mediator release symptoms from 12 to 32 months before the occurrence of skin lesions and recognition of SM. These data suggest the need for long-term follow-up of patients with c-MCAD to rule out the diagnosis of SM.

Among patients with elevated sBT > 20 ng/ml, ISMs– was diagnosed more frequently, while in patients with

sBT < 20 ng/ml, nc-MCAD was diagnosed more frequently. The average level of sBT in c-MCAD patients was 14.3 µg/l. In this study the authors also found an increase in male predominance in ISMs- patients, which is consistent with reports of male predominance among patients with ISM and IgE-mediated anaphylactic reactions versus patients without SM. Moreover, these data suggest a relationship between male gender and severity of reactions associated with the release of MC mediators in mastocytosis, especially in ISMs.

The results show a high sensitivity and specificity of sBT > 25 µg/l or sBT < 15 µg/l for the diagnosis of MC clonality. Furthermore, there was no specific relationship between the sBT levels and the severity of clinical symptoms in ISMs-, c-MCAD and nc-MCAD. The presence of KIT-mutated MC in bone marrow was detected mostly in ISMs- patients.

Based on clinical and laboratory findings, a screening model is proposed to predict MC clonality in patients presenting with anaphylaxis without skin lesions (Tab. 1) [12].

The authors of this study demonstrated that a significant proportion of patients with c-MCAD correspond to an early stage of ISM [12]. Thus further follow-up of patients who meet only 1 or 2 criteria of SM is reasonable since there is a risk of progression to systemic disease. The presence of KIT mutations in MC should always prompt performance of diagnostics to find an early phase of progression [12].

Compared to patients with idiopathic anaphylaxis, patients with MCAD have more episodes of hypotension. The reason for this clinical distinction is unclear. Thus the exclusion of bone marrow involvement by the pathological process is important because it enables one to recognize MCAD as a cause of anaphylaxis [4].

The detection of activating point mutations in KIT tyrosine kinase of identifying mast cells is essential for the development of clinically symptomatic mast cell disease – monoclonal mast cell activation syndrome (MMAS). Molderings *et al.* [13] showed that MMAS is a disease with clonal proliferation of mast cells which is usually associated with the presence of different mutations in the tyrosine kinase kit. In mast cells of 13 out of 20 patients with MMAS multiple new point mutations or complex changes in the mRNA sequences encoding the tyrosine kinase kit were detected. Interestingly, in all but one healthy subjects in the control group (in 19/20 persons) functionally irrelevant changes were not detected, which confirms earlier reports [14]. It is likely that the patient with multiple changes in c-kit transcripts suffered from the disease without clinical symptoms. In addition to the D816V point mutation in KIT, which occurs in more than 90% of patients with SM, there were evaluated functional consequences of mutations D419H and M541L [15]. However, more studies are needed in larger patient groups.

Patients with mastocytosis often have symptoms resulting from the activation and release of mediators

Tab. 1. Scoring model to predict MC clonality in patients presenting with anaphylaxis without skin lesions (before bone marrow study) [11]

Variable	Score	
Gender	Male	+1
	Female	-1
Clinical symptoms	Absence of urticaria and angioedema	+1
	Urticaria and/or angioedema	-2
	Fainting and/or syncope	+3
Tryptase sBT	< 15 ng/ml	-1
	> 25 ng/ml	+2

Score < 2 – low probability of c-MCAD, score > 2 – high probability of c-MCAD, sensitivity 0.92, specificity 0.81

from mast cells, such as generalized itching, redness, headache, abdominal cramps, diarrhoea, bone pain or arthritis, hypotension and shock [16]. Anaphylactic reactions occur in 30% of all patients with mastocytosis, and in 50% of patients with systemic mastocytosis [4, 17, 18]. The activation of mast cells might result from an immune response (e.g., allergy to food, insect venoms, drugs, latex), or non-allergic mechanisms of hypersensitivity after activation of non-specific stimuli such as heat, exercise, and also stress. Although the incidence of IgE-mediated allergic diseases is not higher than in the general population, it is believed that mast cells in mastocytosis patients may have an internal defect lowering the threshold for activation and/or increasing its sensitivity to activation [4].

A key factor in activating mast cells is insect stings. It is estimated that 30% of patients with mastocytosis have insect sting anaphylactic reactions [19], which are more severe than the general population of people with allergies to insect venom (1-3% of the general population) [20]. The treatment of choice in patients with insect venom allergy (IVA) is a specific venom immunotherapy (VIT) with the relevant insect venom. Meta-analysis of research on the effectiveness, safety and efficacy of treatment showed an overwhelming benefit of the treatment of patients and reduction of the risk of life-threatening anaphylaxis. Moreover, in contrast to patients without diagnosed mastocytosis, they have not diminished with time [21, 22]. The mechanism of increased risk of IVA in SM, as compared to the general population, is not completely understood. The introduction of the basophil activation test and histamine release assay from basophils to diagnostic procedures enables the detection of specific IgE in most cases of insect venom allergic patients with SM [23]. Non-IgE mediated IVA are rather rare [24], although specific IgE and skin tests are more often negative than in the general population with the IVA. The suggested explanation for this phenomenon is the adsorption of circulating IgE in numerous mast cells clustered in the tissues [23].

The anaphylaxis may also result from the activation of mast cells by activation of a cascade of intracellular tyrosine kinases: Kit, Lyn, Syk and Fyn. The presence of KIT gene mutations, notably D816V, detectable in more than 90% of patients with SM and resulting in increased activation of mast cells, did not correlate with the severity or the prevalence of anaphylaxis [25]. However, the severity of anaphylaxis correlates with the levels of mast cell tryptase (sBT), which is the determinant of the number and activity of mast cells. The higher sBT serum level indicates an indirect link between SM and IVA. Insect venom allergy is present in 30% of SM patients, compared with a prevalence of 1% to 2.6% in the general population [16, 26]. Approximately 10% to 15% of patients with IVA have high sBT, and up to 5.5% suffer from mastocytosis [4, 16, 21]. Mueller [27] recommends measuring the sBT level in all patients with insect venom anaphylaxis in their history and diagnosing the possible SM in patients with elevated sBT above 20 ng/ml. Because of the reported fatalities of patients with mastocytosis after finishing VIT, in these patients it is recommended to continue VIT for life [27, 28]. The evaluation of sBT should be used routinely in all patients with VIT. The finding of elevated tryptase level significantly modifies the further treatment of the patient (prolonged period of treatment, the use of additional measures to prevent side effects). The diagnostic procedure to establish the diagnosis of SM is typically performed in patients with IVA accompanied by urticaria pigmentosa, although there are reports indicating the absence of skin lesions in 76% of cases with coexistent IVA and SM [29]. Patients with a history of insect sting anaphylaxis and negative results of skin tests and sIgE to insect venom may suffer from mastocytosis [30]. Thus there is an indication to establish a diagnosis of mastocytosis apart from the sBT level and dermatological examination for UP. Bonadonna *et al.* [16] reported that in all patients with non-IgE-mediated venom anaphylaxis sBT was elevated and MCAD was finally diagnosed. The study confirms the association between mastocytosis and systemic reactions triggered by insect stings in patients, despite negative results of tests for insect venom allergy. The criterion for the diagnosis of SM was accepted only if a higher level of sBT (> 11.4 ng/ml) was detected. The study by Potier *et al.* compared the results of diagnostic tests to establish mastocytosis in patients with elevated sBT and IVA [31]. An elevated sBT level was found in 23/140 patients (16.4%) whose skin was less involved and more often with flushing during an anaphylactic reaction. Compared to those patients with normal sBT level the course of the systemic reaction was more severe. Mastocytosis was diagnosed in 7 patients. Among them 5 subjects had been suspected of SM in the past without a definitive diagnosis. These results show a specific clinical insect venom anaphylactic reaction in people with an elevated sBT level, characterized by greater severity, more frequent episodes of redness and rare skin lesions. In this

study, the authors present the need to determine groups of patients with elevated sBT, who are at risk of mastocytosis. Carrying out sBT measurement is indicated in all patients with insect venom anaphylactic reaction in their history, and the diagnosis of mastocytosis should be made in patients with severe anaphylactic reaction, with redness, without urticaria pigmentosa.

In systemic mastocytosis patients the course of Hymenoptera venom anaphylaxis is usually severe and includes the involvement of the cardiovascular system. Negative prognostic factors of the anaphylactic reaction include cardiovascular disease and β -blocker therapy. Mast cells are present in the heart and coronary arteries, and their number and/or density increases in coronary heart disease [32]. Some MC-derived mediators have cardiotoxic effects including vasoconstriction, negative inotropy and arrhythmia. In patients with anaphylaxis, co-existing cardiovascular disorders, mastocytosis and elevated sBT are risk factors for severe, even fatal anaphylactic reactions or consequences of myocardial infarction or stroke. Treatment with β -blockers or angiotensin-converting enzyme inhibitors (ACEI) may worsen the anaphylactic reaction and cause difficulties in the treatment of anaphylactic shock. However, because of their value in the treatment of cardiovascular diseases, which occur much more frequently than anaphylaxis, their withdrawal should be preceded by a thorough assessment of the relative risk of the consequences of each disease [27].

Idiopathic anaphylaxis is a difficult clinical problem. The triggering factor cannot be diagnosed even in two thirds of patients with a history of anaphylaxis, and preventive therapy is usually ineffective. Since idiopathic hypotension is typical for SM, Akin *et al.* [33] proposed evaluation of clonal proliferation of mast cells in patients with recurrent anaphylactic reactions and patients suspected of mastocytosis. Thus, in this group of patients the presence of clonal proliferation markers of mast cells was determined. The subgroup of patients who could benefit from c-kit targeted inhibitor therapy was indicated. Among patients enrolled in the study, the diagnosis of cutaneous or systemic mastocytosis was confirmed (36/72 persons), although these patients had no episodes of hypotension in the past. The evaluation of KIT gene point mutation D816V was made in two thirds of these patients, confirming its presence in 82% of individuals. There were 12 patients described with idiopathic anaphylaxis who did not have skin lesions typical for urticaria pigmentosa or multifocal infiltration of mast cells in bone marrow biopsy. In 5 of them at least one minor criterion for mastocytosis was confirmed. D816V KIT gene mutation was found in 3 patients with confirmed CD25+ immunophenotype in the bone marrow. These results confirm the presence of atypical mast cell populations and markers of clonality in the subgroup of patients with unexplained episodes of anaphylaxis. Such patients may benefit from C-KIT targeted inhibitor therapy [33].

Although the incidence of anaphylactic reactions (IgE-dependent and IgE-independent) in patients with mastocytosis is significantly higher than in the general population, the frequency of atopy is similar in both populations [34]. De Olano *et al.* [35] showed that 23.9% of patients with CM or SM also suffer from allergic diseases (based on history, skin tests and specific IgE). In 36 patients there were signs of anaphylactic reactions in the medical history, including 9 patients with the IgE-dependent mechanism of anaphylaxis confirmed. In addition, the results of this study confirm the hypothesis that the total concentration of IgE in mastocytosis is generally reduced – probably because of the binding to the surface of an increased number of mast cells [36]. The diagnosis is easier in the presence of urticaria pigmentosa or CM. Increasingly, mastocytosis is diagnosed in the case of recurrent anaphylactic reactions in patients without skin lesions with minimal changes in the bone marrow, but with three minor criteria for mastocytosis fulfilled [37]. In some patients the disease is not diagnosed for a long time because its symptoms are similar to those occurring in allergic diseases, pseudoallergic reactions, gastrointestinal disorders, vasculitis, endocrine diseases and idiopathic anaphylaxis [38]. In all patients suspected of mastocytosis the serum concentrations of sBT should be determined [39]. Recent studies showed that the upper limit of normal sBT is 11.4 ng/ml, and sBT higher than 20 ng/ml is a minor criterion of SM [40].

An elevated level of sBT can also be detected in myeloproliferative disorders, in chronic eosinophilic leukaemia associated with the occurrence of mutations FIP1L1/PDGFRA, as well as in end-stage renal failure, amniotic fluid congestion, and orthostatic tachycardia [40]. Moreover, an increased number of atypical mast cells in tissues is also found in reactive hyperplasia present in many inflammatory and neoplastic diseases [38].

Akin *et al.* [41] have proposed criteria for diagnosis of mast cell activation syndrome (MCAS) including other diseases in which mast cells are involved. The authors proposed a classification of diseases associated with proliferation and/or activation of mast cells (Tab. 2) [41].

The presence of separate MCAS, with the exclusion of MMAS, has not met with general acceptance. Despite the lack of guidelines MCAS is recognized among patients with unexplained clinical symptoms. The diagnosis of MCAS can be considered after the exclusion of primary, secondary, and idiopathic diseases associated with activation of mast cells and when at least three additional criteria from the following were fulfilled (Tab. 3) [41].

Applying these criteria, MCAS should be considered if the patient has recurrent symptoms from at least two organ systems resulting from the activation of mast cells and these episodes do not meet the clinical criteria for idiopathic anaphylaxis or other well-defined diseases men-

Tab. 2. Classification of diseases associated with mast cell activation

1. Primary
Hypotension with an associated clonal proliferative mast cell disorder (mastocytosis)
MMAS
2. Secondary
Allergic disorder
Mast cell activation associated with chronic inflammatory or neoplastic disorder
Physical urticaria
Chronic autoimmune urticaria
3. Idiopathic
Anaphylaxis
Angioedema
Urticaria
MCAS

Tab. 3. Criteria for the diagnosis of MCAS

1. Episodic symptoms consistent with MC mediator release affecting ≥ 2 organ systems as follows:
skin: urticaria, angioedema, flushing
gastrointestinal: nausea, vomiting, diarrhoea, abdominal cramps
cardiovascular: hypotensive syncope, tachycardia
respiratory: wheezing
naso-ocular: conjunctival injection, pruritus, nasal congestion
2. Effectiveness of antihistamine therapy (H1 and H2 blockers), antileukotriene medications, mast cell stabilizers
3. Evidence of increased MC mediators while clinical symptoms occurred
4. Exclusion of primary, secondary and idiopathic causes of mast cell activation

tioned above. These criteria could be a starting point to classify and diagnose MCAS [41].

Conclusions

Mastocytosis is a proliferative disease, with clonal proliferation of mast cells and their progenitor cells. The symptoms of mastocytosis include episodes of MC mediator release and anaphylactic reactions. In the absence of skin lesions of urticaria pigmentosa type, the clinical presentation may suggest allergic disease. However, patients with severe anaphylaxis, particularly when the cardiovascular and/or respiratory system is involved, should be

diagnosed with SM (regardless of the causative factor). It is believed that during the routine diagnosis of anaphylaxis the evaluation of the sBT level and of the KIT gene mutation D816V should be applied. Patients with an elevated level of sBT and with the presence of Kit mutations should be further referred to specialist centres [3]. Perhaps the development of knowledge concerning the mechanisms of mast cell proliferation will result, in the near future, in new tests to diagnose mastocytosis, even in patients without typical urticaria pigmentosa.

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