Mast Cell Activation

Subjects: Oncology
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Mast cell activation (MCA) may occur in different physiologic and pathologic conditions. Clinical symptoms resulting from MCA can be observed not only in the setting of allergic diseases, but even in the context of MC neoplasms. If MCA symptoms are severe and recurrent, the possibility of mast cell activation syndrome (MCAS) should be considered.

Keywords: mast cell ; mastocytosis ; mast cell activation ; bone marrow ; gut

1. Introduction

Mast cells (MCs) are multifunctional cells involved in innate and acquired immunity and attendant inflammatory reactions [1][2][3]. They have high-affinity receptors for IgE (IgERs) and synthesize inflammatory and vasoactive mediators, which are stored in the metachromatic granules of mature MCs [1][2][3]. After activation, MCs determine clinical manifestations through mediator release [1][2][3].

Mastocytosis represents a highly heterogeneous group of neoplastic MC disorders, characterized by abnormal growth and accumulation of MCs in one or more organ system [4]. Its clinical presentation is variable with a course ranging from indolent to aggressive [4].

The basic classification of mastocytosis into pure cutaneous forms (90%) and systemic forms (10%) remains valid. The pure cutaneous forms are mainly pediatric with often spontaneous regression at puberty and a favorable outcome [4]. Multi-organ involvement, with or without a cutaneous disease, is generally seen in adult patients, with the most advanced forms of systemic mastocytosis (SM) usually lacking skin involvement. The diagnosis of SM in absence of skin involvement, may be particularly challenging and needs a high index of suspicion. In SM, the most commonly involved sites are bone marrow (BM), liver, spleen, gastrointestinal tract (GIT), and lymph nodes [4]. Symptoms can result from either release of MC mediators or organ damage due to MC infiltration.

Gastrointestinal (GI) symptoms are present in 60–80% of SM patients, representing one of the major causes of morbidity [5][6][7][8]. GI symptoms are largely caused by release of mediators and in rare advanced forms by MC infiltration of the gut causing malabsorption. Direct gut involvement by neoplastic MCs has been documented only in a limited number of cases and the histopathologic spectrum of GI mastocytosis is still incompletely characterized [5][6][9]. Because of its multifaceted manifestations and progression, mastocytosis is a disease hard to diagnose, with different specialists involved in the patient's clinical work-up. An early and prompt diagnosis is of importance not only to cure disabling symptoms, but also to limit disease progression.

2. Mast Cells and Mast Cell-Related Disorders

2.1. Mast Cell Physiology

MCs develop from pluripotent precursors in BM; they circulate in the blood as MC precursors and differentiate after migration into different tissues, including skin, lungs, and GIT, in response to tissue-specific cytokines [10]. Mature MCs contain granules storing mediators such as histamine, enzymes and neutral proteases. The majority of the granule components is made by neutral proteases, including chymase and tryptase [10].

MCs are activated on binding to an antigen, which cross-links antigen-specific IgE on the MC surface [10]. Non-specific triggers such as the physical stimuli of pressure and stress and some substances (alcohol or drugs) may also cause MCA and subsequent secretion of vasoactive and proinflammatory mediators. GI symptoms have been specifically attributed to mediators including histamine, platelet activating factor (PAF), prostaglandin D2 (PGD2), serotonin, tryptase, leukotrienes, tumor necrosis factor-alfa (TNF-alfa), and interleukin-6 (IL-6) [10][11]. Normally, MCs in the gut account for 2–5% of mononuclear cells in the lamina propria [7][12]. MCs are usually scattered in the gut mucosa of healthy subjects; in irritable

bowel syndrome (IBS) patients, MCs may be increased in number, but are dispersed without forming aggregates, whereas MCs aggregates may be observed in GI mucosa of SM patients [12].

2.2. Mast Cell Activation Syndrome: Consensus Criteria and Classification

MCA may occur in different physiologic and pathologic conditions. In case of severe and recurrent symptoms of MCA, the diagnosis of MCAS need to be considered. To call a condition MCAS, the following consensus criteria defined by Valent et al. [3][13], are required to be fulfilled:

- typical clinical features of severe, acute systemic MCA (especially signs and symptoms of anaphylaxis);
- increase in serum total tryptase level by at least 20% above baseline plus 2 ng/mL during or within four hours after a symptomatic period;
- response of symptoms to MC blocking agents. MCA symptoms may range from mild to severe and sometimes life-threatening, correlating with the extent of mediator release from MCs [13].

Common symptoms of systemic MCA are acute urticaria, flushing, abdominal cramping, diarrhea, tachycardia, hypotension, and syncope [1][2][3][13]. Acute, severe, and recurrent symptoms involving more than one organ or tissue often with severe hypotension and anaphylaxis are generally present in MCAS. It is important to point out that MCA may present with chronic and less severe, nonspecific symptoms; however these symptoms alone are not considered sufficient criteria for MCAS [1][2][3][13]. Of note, MCAS may occur not only in the context of SM.

MCAS is sub-divided in primary or clonal MCAS in which a clonal MC disease is identified, the KIT D816V mutation is detected and MCs aberrantly express CD25 in most cases; secondary MCAS where an IgE-mediated allergy or another hypersensitivity/immunologic reaction that can induce MCA is diagnosed, in absence of neoplastic MCs or KIT D816V mutation. Idiopathic MCAS is diagnosed when the consensus criteria for MCAS are fulfilled, but no neoplastic MCs, no IgE-dependent allergy, no other hypersensitivity reaction or immunologic disease are identified [3][13].

2.3. 2017 WHO Classification of Mastocytosis

In the current 2017 WHO classification, mastocytosis represents a separate category, not included any more among myeloproliferative neoplasms, and sub-divided into three main groups: a pure cutaneous mastocytosis (CM) with skin-limited disease, more frequent in children and with good prognosis; SM characterized by involvement of one or more extra-cutaneous organs, more common in adults and with less favorable outcome and mast cell sarcoma (MCS), a very rare, localized and high-grade MC tumor [4] (**Table 1**).

Table 1. Classification of mastocytosis.

Cutaneous mastocytosis
• Urticaria pigmentosa/maculopapular cutaneous mastocytosis • Diffuse cutaneous mastocytosis • Solitary mastocytoma of the skin
Systemic mastocytosis (SM)

- Indolent systemic mastocytosis (ISM)

  Meets criteria for SM. No B or C findings. No evidence of AHN

- **Smoldering systemic mastocytosis** (SSM)

  Meets criteria for SM; at least 2 B findings, but no C findings. No evidence of AHN

- **Systemic mastocytosis with an associated hematological neoplasm** (SM-AHN)

  Meets criteria for SM and criteria for an associated hematological neoplasm as a distinct entity according to WHO classification

- **Aggressive systemic mastocytosis** (ASM)

  Meets criteria for SM. One or more C findings

- **Mast cell leukemia** (MCL)

  Meets criteria for SM plus at least 20% of immature MCs in BM aspirate; MCL can be leukemic (at least 10% of MCs in PB) and aleukemic (less than 10% of MCs in PB). MCL is also divided into an acute form, with organ damage (C findings) and a chronic form, without organ damage

Mast cell sarcoma **Unifocal mast cell tumor. No evidence of SM. Destructive growth pattern. High grade cytology**

Legend: AHN: associated hematological neoplasm; ASM: aggressive systemic mastocytosis; BM: bone marrow; ISM: indolent systemic mastocytosis; MCs: mast cells; MCL: mast cell leukemia; PB: peripheral blood; SM: systemic mastocytosis; SM-AHN: systemic mastocytosis with an associated hematological neoplasm; SSM: smoldering systemic mastocytosis; WHO: World Health Organization.

In all patients with clinical suspicion of SM, the BM biopsy represents the first diagnostic step.

2.4. Treatment

Treatments of SM are of two types: medications to control MC mediator-related symptoms and cytoreductive treatments to limit MC burden and increase survival mainly in ASM and MCL. In ISM and SSM, the management is mainly symptomatic plus a correct monitoring to identify signs of progression. Additionally, all SM patients should be aware of potential triggers of MC activation. The triggers of MC degranulation may be different, including emotional stress, physical stimuli, infections, allergies, and drugs such as alcohol, aspirin, non-steroid anti-inflammatory drugs, and opioids.

Treatments of MC mediator GI symptoms rely on anti-mediator therapy such as antihistamines [11]. H_1 and H_2 receptor antagonists are often used in combination. H_1 antagonists can treat skin symptoms [14]. To control GI symptoms, H2 antagonists are generally used as 1st-line therapy and proton pump inhibitors as 2nd-line [15][16]. Cromolyn sodium as a MC stabilizer has been reported to be effective in reducing GI symptoms (especially diarrhea, abdominal pain, and nausea) and it is used as 3rd-line therapy [17]. Leukotriene antagonists and IgE-binding treatment with the monoclonal antibody omalizumab are included among therapies to treat MC activation symptoms [18][19]. The use of systemic steroids is limited to specific situations, for instance in the setting of organ damage; low-dose corticosteroids are reported to reduce malabsorption and ascites [20].

In ASM, treatments interfering with MC proliferation and survival are used. Tyrosine kinase inhibitors (TKIs), chemotherapy, and allogenic stem cell transplantation (allo-SCT) are considered the best therapeutic options for ASM, including MCL [21][22][23]. Imatinib and Nilotinib demonstrate effect against wild-type KIT and a limited activity against KIT D816V; however, there are reports of response to these drugs in patients with atypical KIT mutations [4][24]. Midostaurin, a TKI with activity against KIT D816V, represents the only approved therapy for advanced SM, including MCL [25]. In advanced SM, most responses with Midostaurin are only partial and not sustained. Other medications potentially effective for SM patients are under investigation. Recent and promising results have been obtained with Avapritinib, a KIT and PDGFRA inhibitor [26][27]. Interferon alpha and cladribrine have also been used [28][29]. Allo-SCT needs to be considered in young and otherwise healthy patients with ASM, as this is the only option for a sustained response [30]. Prior to SCT, therapies such as either midostaurin or cladribrine should be used to bring the patients to the best response.

3. Conclusions

In SM, the GIT is frequently affected with rather vague and nonspecific clinical manifestations, making the diagnosis of GI mastocytosis particularly difficult.

In patients presenting with GI symptoms, which cannot be attributed to more common GI diseases, SM needs to be taken in consideration. Because endoscopy is often unremarkable and involvement can be focal, multiple biopsies should be taken by endoscopists. A high index of suspicion of both clinicians and pathologists is essential to correctly recognize GI involvement by mastocytosis.

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