

Mastocytosis

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Mastocytosis is defined by a pathological increase in mast cell numbers in tissues. Recent clinical observations on rare manifestations highlight the diversity of this disease. The diagnosis is now aided by new surrogate markers. At the molecular level, recent studies have reinforced the role of activating mutations in KIT in the etiology of mastocytosis. These findings provide a conceptual basis for the development for new therapeutic strategies. *Curr Opin Allergy Clin Immunol* 1:449–454.

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Abbreviations

AHD	associated hematological disorder
CMML	chronic myelomonocytic leukemia
SCF	stem cell factor
TMEP	telangiectasia macularis eruptiva perstans
UP	urticaria pigmentosa

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Introduction

Mastocytosis is defined by an excessive number of mast cells in characteristic distributions in the skin, bone marrow, gastrointestinal tract, lymph nodes, liver and spleen. Mast cell hyperplasia may be restricted to the skin (cutaneous mastocytosis), but may also be found in extracutaneous organs (systemic mastocytosis). Mastocytosis is classified into indolent mastocytosis, mastocytosis with an associated hematological disorder (AHD), aggressive mastocytosis, and mast cell leukemia [1]. The prognosis primarily depends on the degree of bone marrow involvement and the evolution of AHD. Recent reports have focused on unusual disease manifestations, on disease etiology, and on new approaches to diagnosis.

Unusual clinical presentations of mastocytosis

Clinical signs and symptoms of mastocytosis typically involve the skin [urticaria pigmentosa (UP), pruritus, urtication, flushing], the gastrointestinal tract (nausea, diarrhea, abdominal pain), the bone marrow (bone marrow lesions, hematological disease), and the cardiovascular system (anaphylaxis). Recent observations have highlighted that mastocytosis may have clinical presentations that are less typical and are not always easily recognized.

Cutaneous lesions

In a recent retrospective review of 173 children diagnosed with cutaneous mastocytosis, 51% had mastocytomas, 47% had UP, and 2% had diffuse cutaneous mastocytosis [2•]. Mastocytomas typically resolved spontaneously during childhood. The most common clinical cutaneous manifestation in adult patients with mastocytosis is UP.

Telangiectasia macularis eruptiva perstans (TMEP) is a rare manifestation of mastocytosis, primarily seen in adults [3•]. Systemic involvement appears to be less common in patients with TMEP compared with UP, although systemic involvement and associated hematological diseases have been described in individual cases [4]. It is characterized by matted strongly erythematous telangiectatic macules on a tan to brown background. TMEP has to be differentiated from 'less pigmented UP lesions' and from telangiectasias developing in areas long involved with UP. TMEP may also occur in children [5].

Another cutaneous form of mastocytosis is that of the solitary mast cell tumor. In a case report, a solitary fluctuating swelling on the forehead in a 27-year-old

woman was reported, which was successfully removed just below the galea [6•]. The diagnosis of mastocytoma was made on the basis of histological analysis.

Papillomatous verrucous mastocytomas in the inguinopubic area were described in a 29-year-old patient with cutaneous mastocytosis since childhood who had bone marrow involvement [7]. Similar nodular forms of cutaneous mastocytosis have also been described [8]. A nodular cutaneous mastocytosis of the xanthelasmoid type was reported in a 7-month-old infant, with red to yellowish-brown xanthelasmoid papules and nodules covering a large part of the body surface [9•]. Lesions were associated with pruritus and recurrent episodes of blistering.

Cases of congenital symptomatic dermographism as the first symptom of mastocytosis and chronic urticaria developing into mastocytosis were recently reported [10,11]. These represent unusual examples of initial presentations of mastocytosis.

Extracutaneous manifestations

The bone marrow is the most commonly documented site of mast cell accumulation in mastocytosis outside of the dermis. Focal mast cell lesions of the bone marrow have been reported to be present in up to 90% of adults with systemic mastocytosis [12••]. One recent study [13•] investigated the frequency of bone marrow involvement in 13 adults with mastocytosis, but without systemic symptoms, using bone marrow biopsy and aspirate. In 10 out of 12 patients, a mast cell infiltrate was demonstrated in the bone marrow biopsy, and in 10 out of 13 patients mast cell numbers were increased in the bone marrow aspirate. These findings highlight that bone marrow involvement may occur in patients with cutaneous mastocytosis, even in the absence of systemic symptoms.

In infants and children with mastocytosis, mast cell lesions in the bone marrow are less common [8,12••]. In rare cases, hematological abnormalities may also develop in this age group, as highlighted by a case report of an infant with UP and acute lymphoblastic leukemia [14•]. In another case, a 12-year-old child presented with progressive anemia and reticulocytopenia. After a bone marrow biopsy, a myelodysplastic syndrome with trilineage dysplasia and abnormal cytogenetic analysis was diagnosed. However, one year later, this child developed systemic mastocytosis, involving the skin, spleen, liver and bone marrow; and the Asp816Val mutation, which is associated with mastocytosis [15], was detected in the peripheral blood mononuclear cells of the patient.

Localized mast cell sarcomas are rare. They may occur as the only manifestation of mastocytosis in the absence of

other systemic involvement. An 8-year-old girl with an intracranial mast cell sarcoma has been described [16•]. Symptoms included nausea, vomiting, and severe headache. No further evidence of cutaneous or systemic involvement was found.

Another site for pathological mast cell hyperplasia is the lung. A case of a patient with dyspnea and UP for 10 years has been reported [17•]. Chest radiographs and computerized tomography revealed a reticular pattern on both lung fields, faint nodular lesions in the middle and upper regions, and multiple enlarged mediastinal lymph nodes. Transbronchial biopsy was said to confirm the diagnosis of mastocytosis.

Patients with systemic mastocytosis may also be at risk of developing myelogenous malignancies [12••]. Leukemias occurring in patients with indolent or aggressive mastocytosis include acute myeloid leukemia, chronic myeloid leukemia or myelomonocytic leukemia [18••]. Mast cell leukemia is a rare entity, and can be distinguished from non-mast cell lineage leukemias by tryptase-positive, KIT-positive and myeloperoxidase-negative cell infiltrates [18••].

Anaphylaxis

It is well recognized that mastocytosis may be associated with episodes of anaphylaxis. Isolated anaphylaxis as a presentation of mastocytosis is possible [19]. In occasional patients, such reactions can be elicited by hymenoptera stings, certain drugs, alcohol, exercise, or infection. Recently, the prevalence of mastocytosis was said to be greater than expected within a group of patients with a history of severe anaphylaxis to hymenoptera stings [20].

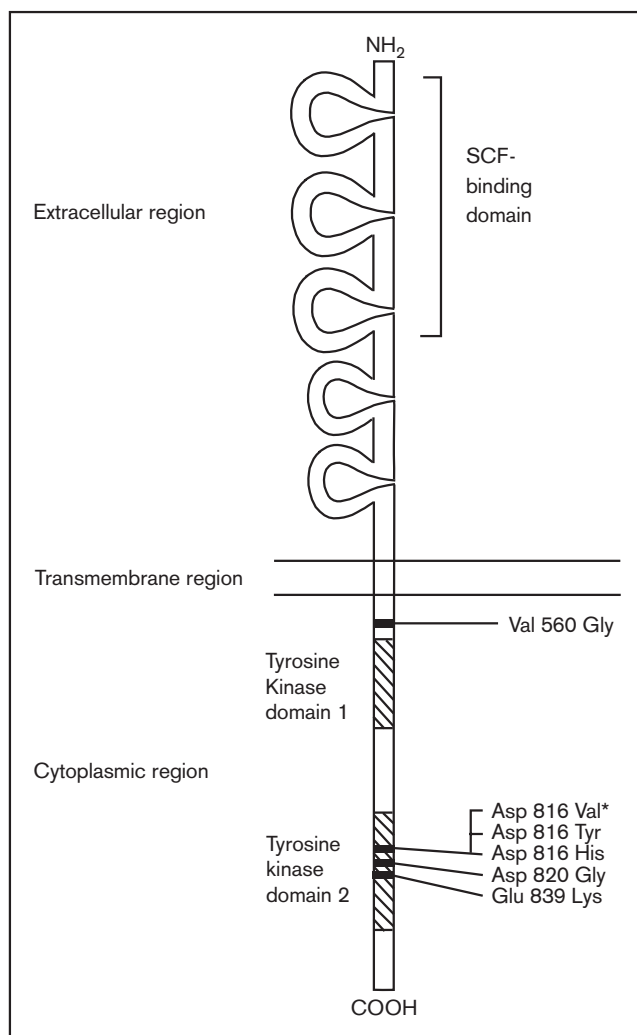
Molecular mechanisms of disease

Our understanding of the pathogenesis of mastocytosis has increased over the past year. Research has focused on activating mutations in KIT, the receptor for stem cell factor (SCF), as well as conditions influencing proliferation and differentiation of mast cells.

Mutations in KIT

The occurrence of mastocytosis is usually sporadic; only a few cases of familial mastocytosis have been described [21]. The regulation of mast cell numbers is controlled by the interaction of specific growth factors with their receptors. The initial event leading to mastocytosis is now believed, at least in adults, to be related to activating mutations in KIT, the receptor for SCF [15]. These somatic mutations lead to SCF-independent autophosphorylation and constitutive activation of KIT (Fig. 1), thus resulting in increased proliferation of mast cells and their progenitors.

Figure 1. Structure of KIT and mutations in the KIT gene in human mastocytosis



The asterisk denotes the mutation present in all adult patients with mastocytosis. SCF, Stem cell factor.

The most common activating point mutation of KIT is a substitution of valine for aspartic acid at codon 816 (Asp816Val) [15,22]. The Asp816Val mutation has been detected in peripheral blood mononuclear cells of patients with mastocytosis [23], and appears to be present in lesional skin of all adult patients with mastocytosis [22]. In a recent study of microdissected bone marrow cells from a patient with systemic mastocytosis and an associated chronic myelomonocytic leukemia (CMML) [24••], the presence of the Asp816Val mutation was demonstrated not only in the mast cell infiltrate, but also in the CMML infiltrate. These data support a monoclonal evolution of systemic mastocytosis and CMML, at least in this patient. Furthermore, in another study [25•], the presence of the Asp816Val mutation was examined in CD3⁺ T

lymphocytes, CD14⁺ monocytes, CD15⁺ myeloid cells, and CD19⁺ B lymphocytes in peripheral blood, and in the bone marrow aspirate of patients with mastocytosis. The Asp816Val mutation was demonstrated in all hematopoietic lineages. These data are consistent with the conclusion that mastocytosis is a hematopoietic stem cell disease. In another report, a 12-year-old girl presented initially with myelodysplastic syndrome without evidence of a mast cell disorder, but later developed systemic mastocytosis [26•]. The Asp 816Val mutation was demonstrated in the bone marrow cells at the initial presentation as well as at the time of overt mastocytosis.

Other mutations of KIT have been detected in adults or children with mastocytosis, such as the recently described Asp 816 His mutation, although the relevance is less clear [27]. The presence of KIT mutations has been related to clinical patterns of mastocytosis, and a suggested classification of mastocytosis incorporating molecular genetics has been published [28].

Regulation of mast cell growth and development

The dependence of mast cells on growth factors produced in the microenvironment is well recognized. SCF, IL-3, IL-4, IL-9, and IL-10 are known to influence mast cell growth and proliferation. The effect of dexamethasone on the expression of SCF and mast cell proliferation was examined in co-cultures of mast cells with fibroblasts or activated hepatic stellate cells [29]. Whereas dexamethasone inhibited mast cell spreading on both stroma cells, it downregulated SCF and abrogated mast cell proliferation only on fibroblasts, but not on stellate cells. In another report [30], the development of pulmonary mast cell hyperplasia was shown to be impaired in IL-9-deficient mice in a model system of pulmonary granuloma formation. Whereas IL-4 and IL-10 induced apoptosis in IL-3-dependent murine mast cells, IL-3-independent mastocytomas and mast cell lines were resistant to IL-4 and IL-10-induced apoptosis [31••]. In human interstitial mature mast cells, IL-4 was reported to enhance mast cell proliferation in synergy with SCF [32].

Other cytokines have also been reported to induce mast cell proliferation. IL-1 α was demonstrated to stimulate growth in mouse bone marrow-derived mast cells in a fibroblast/mast cell co-culture system [33]. Leukemia inhibitory factor is another proinflammatory cytokine, which has recently been reported in association with mast cell hyperplasia around chemically induced skin tumors [34].

Chromosome abnormalities in mastocytosis

Cytogenetic abnormalities are widespread in malignant hematological disorders and have been found in patients with mastocytosis. In a recent case report [35], the

presence of trisomy 4 in CD34⁺ mononuclear cells of a patient with acute myeloid leukemia and mast cell involvement has been associated with an Asp 816 to Tyr mutation of KIT, and mutated KIT was found in both alleles in this patient. However, mastocytosis appears to be related to non-specific rather than to specific chromosomal abnormalities. A recent study in 34 patients with mastocytosis [36], confirmed earlier results of an increased number of non-specific chromosome abnormalities in patients with mastocytosis, which were similar in type and frequency to those found in some malignant hematological disorders [37•]. The comparison of the cytogenetic results at two different time-points showed a change of chromosome pattern in the majority of patients, consistent with a genetic instability of the hematopoietic cells in mastocytosis.

Mediators and markers in the diagnosis of mastocytosis

Most patients with indolent mastocytosis have UP, which is diagnosed on clinical grounds and is confirmed by skin biopsy. The biochemical demonstration of elevated levels of mast cell mediators may support the diagnosis. A bone marrow examination is useful in the diagnostic work-up in patients having mastocytosis without skin lesions, and for staging the disease by excluding associated hematological abnormalities. The bone marrow biopsy is generally considered to be more informative than the bone marrow aspirate, although recent studies [38] indicated that flow cytometric immunophenotyping of bone marrow aspirate cells for surface markers such as CD2 and CD25 may be more sensitive for the detection of early stages of bone marrow involvement in patients with systemic mastocytosis.

Immunohistochemical markers for mastocytosis

The most useful stains for mast cells have been metachromatic stains, such as toluidine blue and Giemsa, or enzymatic stains such as chloroacetate esterase and aminocaproate esterase. However, in patients with an AHD, the discrimination of mast cells from other hematopoietic cells in the bone marrow may be difficult, if mast cells are dysplastic. Recently, it has become accepted that immunohistochemistry with antibodies to mast cell tryptase aids in the diagnosis of mast cell disorders. In a recent publication [39•], this was highlighted by the evaluation of 10 cutaneous and 18 extracutaneous biopsy specimens of patients with mastocytosis in comparison with 94 other hematopoietic neoplasms. Immunohistochemical stains with a series of antibodies revealed that mast cells in all 28 specimens from patients with mastocytosis were positive for tryptase and CD68, and were also positive for KIT and CD43 in more than 90% of cases. In contrast, only one

out of 94 other neoplasms, including 80 B-cell lymphomas, nine T cell lymphomas and five extramedullary myeloid tumors, expressed tryptase. Calretinin, found to be of value in an earlier report, was considered not to add significant information in most cases in this, and in another recent study [40].

Histamine

Levels of histamine are increased in the serum and plasma of patients with mastocytosis. Recently, intradermal histamine levels were reported in seven adult patients with UP by means of cutaneous microdialysis, and were compared with plasma histamine, plasma tryptase, urinary *N*-methyl-imidazole acetic acid and mast cell density [41•]. Histamine concentrations were two- to sevenfold higher in skin eruptions compared with uninvolved skin. However, no correlation of intradermal histamine levels to the density of mast cells in the skin, to plasma histamine, plasma tryptase, or *N*-methyl-imidazole acetic acid, was found.

Tryptase

Two forms of human tryptase, α and β , have been recognized. A third form, γ -tryptase has recently been described, although its function is not yet clear [42]. β -tryptase levels in biological fluids reflect active histamine release and are elevated in the serum of patients with systemic anaphylaxis. In patients with systemic mastocytosis diagnosed by bone marrow biopsy, 35 out of 42 patients had levels of total tryptase greater than 20 ng/ml, and ratios of total tryptase to β -tryptase greater than 20 [43]. Total tryptase levels were lower than 14 ng/ml in normal subjects and in patients with only cutaneous mastocytosis. However, total tryptase levels did not predict the severity of disease.

Soluble KIT and soluble CD25

In search of surrogate markers for the extent and the severity of systemic mastocytosis, levels of soluble KIT (sKIT) and soluble IL-2 receptor α -chain (sCD25) have been studied in the plasma of eight patients with UP without systemic involvement, 30 patients with systemic indolent mastocytosis, seven patients with systemic mastocytosis with an AHD, three patients with aggressive mastocytosis, and in 60 normal controls [44••]. Plasma sKIT and sCD25 levels were significantly increased in patients with mastocytosis when compared with controls; and levels correlated with disease severity based on clinical categorization, as well as with the severity of the bone marrow pathology and with the detectability of the Asp816Val mutation in blood. Whereas total tryptase appeared to be a more sensitive indicator of mast cell burden and of early forms of the disease, sKIT and sCD25 appeared to be predictors of the severity of bone marrow pathology.

Therapy of aggressive mastocytosis and mastocytosis with an associated hematological disorder

There is no cure for mastocytosis. Treatment is symptomatic. In indolent mastocytosis, aggressive forms of therapy are not indicated [45••]. In patients with aggressive mastocytosis, IFN- α_{2b} has been applied with varying results [46]. Patients with mastocytosis and an AHD are treated appropriately for the AHD. Different chemotherapeutic regimens have been used to treat aggressive mastocytosis and mastocytosis with an AHD, as recently reviewed elsewhere [45••].

A recent case report of an 8-year-old girl with an isolated cerebral mast cell tumor is an example of a typical partial response to chemotherapy [16•]. In this patient the tumor was excised incompletely and treated with post-operative radiotherapy, IFN- α_{2b} and prednisolone, without an objective response. Combination poly-chemotherapy led to a nearly complete remission after 5 months. However, symptoms reoccurred 5 weeks after the completion of chemotherapy and the patient died 6 weeks thereafter.

Recently, encouraging results of chemotherapy with the purine nucleoside analogue, cladribine, (2-chlorodeoxyadenosine) in a 53-year-old patient with systemic mastocytosis not responding to IFN- α_{2b} were published [47•]. A total of six cycles of intravenous cladribine led to a complete resolution of UP and symptoms of disease, and led to a marked reduction of the mast cell infiltration in the bone marrow. Follow-up was limited to one year after the last cycle had been administered.

In the future, alternative approaches may arise from an expanded understanding of disease etiology. Inhibitors of KIT phosphorylation have been studied, and inhibit mast cell proliferation *in vitro* [48•,49]. However, before such a therapy can be employed in clinical trials, preclinical studies must be performed to identify an agent that inhibits mutated mast cells without substantial effects on other KIT-bearing cells. Another future therapeutic option for patients with mastocytosis and AHD may be allogenic bone marrow transplantation, although experience is lacking [45••].

Conclusion

Our understanding of mastocytosis continues to increase. Autophosphorylation of the receptor tyrosine kinase KIT appears to be the critical event in many patients, leading to mastocytosis. Targeting cells expressing mutated KIT may offer new therapeutic options. Advances have been made in the diagnosis of mastocytosis incorporating specific stains, the detection of surrogate markers, immunophenotyping of membrane markers, and molecular analysis for the mutation. A

consensus conference has proposed an updated classification of mastocytosis, incorporating the advances made in the diagnosis of mastocytosis, which will be published this year.

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