Mastocytosis

A Comprehensive Guide

Cem Akin
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Preface

Mast cells are important components of our immune system, and they are designed to alert us to various external and internal danger signals. They are found in the skin, along mucosal surfaces and around blood vessels, as well as distributed interstitially, and their activation can affect almost every organ system. Mastocytosis is a hematopoietic disorder of the mast cell progenitor resulting in clonal expansion and abnormal activation of mast cells.

Mastocytosis is increasingly recognized and considered in differential diagnosis of a variety of patients presenting with allergic, dermatologic, gastrointestinal, and hematologic symptoms and findings. This is partly due to increased public awareness of the diagnosis, thanks to the efforts of patient support organizations and professional medical societies, as well as recognition of mastocytosis as the underlying diagnosis in some patients with recurrent anaphylaxis and hymenoptera allergy. Furthermore, the increasing use of tryptase test in allergy practice helped to identify more patients with potential mast cell disease. Most importantly, recent availability of new treatment options such as new tyrosine kinase inhibitors or therapies to target activation of mast cells made it even more important to correctly diagnose the disease. Once the diagnosis is made, the patient must be classified into one of the seven categories of disease with different prognostic and treatment guidelines. As with any rare disease, many practicing physicians have questions along the diagnostic and treatment path they embark with their patients. Specialized centers of expertise are limited and not all patients have access to them.

This book is designed mainly to provide guidance to fulfill the educational needs of providers; however, I also hope the patients can also find it useful as an educational tool. The opening chapter provides an excellent overview of mast cells in human biology. There are detailed descriptions and photographs of skin lesions observed in adult and pediatric populations which will be helpful as a visual guide in diagnosis of skin disease. Other chapters guide the reader on commonly encountered questions such as how to interpret elevated tryptase tests and urinary markers, diagnosis and management of gastrointestinal and bone involvement, pediatric disease, and special issues relating to management of disease in pregnancy, in hymenoptera and drug allergies, and in patients with recurrent anaphylaxis. There is

emphasis on molecular pathobiology and treatment of mast cell-targeted therapies taking into account the recent advances in drug development. Two unique chapters describe the current status of patient organizations and peer support internationally and networking of clinical care and research in Europe.

I am thankful to the outstanding group of authors in this book, each of whom is an expert in their field. I am also grateful to Springer who recognized the emerging importance of the field and gave me the opportunity to edit this book. Finally, my heartfelt thanks go to my family, my mentors, and my patients who supported, taught, and guided me on our collective journey to understand and cure mast cell disease.

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Chapter 1
Overview of Mast Cells in Human Biology

Dean D. Metcalfe, Do-Kyun Kim, and Ana Olivera

Abbreviations

5-LO	5-Lipoxygenase
ADGRE2	Adhesion G-protein-coupled receptor type E2 or EGF-like module-containing mucin-like hormone receptor-like 2 (EMR2)
CCL2	CC-motif chemokine ligand 2
CD203c	Ectonucleotide pyrophosphates/phosphodiesterases type 3 (E-NPP3)
CD25	α-Chain of the IL-2 receptor
CD30	Tumor necrosis factor receptor/nerve growth factor receptor superfamily member
CD63	Membrane tetraspanin protein family member
COX	Cyclooxygenase
CTMC	Connective tissue mast cell (rodents)
CysLTs	Cysteinyl leukotrienes
DJ-1	Antioxidant protein DJ-1 or Parkinsonism-associated deglycase (PARK7)
ERK1/2	Extracellular-signal-regulated kinase 1 and 2
FcεRI	High-affinity receptor of IgE
GAB2	GRAB2-associated binding protein 2
GEF	Guanine exchange factor

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GPCR	G-protein-coupled receptor
GPR-35	G-protein-coupled receptor 35
GRB2	Growth factor receptor-bound protein 2
IL-2R	IL-2 receptor
JNK	c-Jun N-terminal kinase
KIT	Receptor for stem cell factor
LAT	Linker of activation of T cells
LTB4	Leukotriene B4
LTC4	Leukotriene C4
MAPK	Mitogen-activated protein kinase
MCT	Mast cell tryptase (humans)
MCTC	Mast cells containing tryptase and chymase (humans)
MMC	Mucosal mast cells (rodents)
MRGX2	Mas-related G-protein-coupled receptor member X2
MyD88	Myeloid differentiation primary response 88
NLR	NOD-like receptors
PAF	Platelet-activating factor
PGD2	Prostaglandin D2
PH domain	Pleckstrin homology domain
PI(3,4,5)P3	Phosphatidylinositol-3,4,5,-triphosphate
PI3K	Phosphatidylinositol-3-kinase
PKC	Protein kinase C
PLCγ	Phospholipase C γ
PTB domain	Phosphotyrosine-binding domain
SCF	Stem cell factor
SFK	Src family kinase
SH2 domain	Src homology 2 domain
SHC	Src Homology 2 domain-containing adaptor protein
SOS	Son of Sevenless
ST2	IL-33 receptor
SYK	Spleen tyrosine kinase
TLR	Toll-like receptors

Introduction

Mast cells are among the first recognizable immune cells in evolution, and recent phylogenetic studies now give insights into how some of the functional capabilities of mast cells have evolved [1]. Metachromatically staining granulated cells with cardinal characteristics of mast cells first appeared more than 500 million years ago in urochordates as granulated hemocytes and "test cells" with properties indicative of a role in innate immunity and tissue repair [2–4]. Cells with the histochemical and biochemical characteristics of mast cells have also been detected in various fish species including primitive jawless fish. Zebrafish mast cells express KIT, the receptor for mast cell growth factor, stem cell factor (SCF),

and Toll-like receptor (TLR) adaptor protein MyD88, which provides the capacity for recognition of a broad range of microbes and parasites [5, 6]. Following transition to vertebrate species and the emergence of the Ig-based recombination-activating gene (RAG) network, mast cells appeared to have successfully acquired adaptive immune functions [1]. Although the γ subunit of FcεRI and a receptor with similar functionality as that of the IgE receptor are detectable in the intestinal mast cells of zebrafish [7], FcεRI is a relatively late acquisition with the appearance of genes encoding both IgE and FcεRI, which is evident only in marsupials and mammals [8].

Mast cells are of hematopoietic lineage and originate principally from the bone marrow. However, unlike other myeloid cells, they enter the circulation as progenitor cells rather than as mature cells. At an early stage, these progenitor cells express both FcεRI and KIT as well as the cell marker CD34, and when cultured in SCF, they develop into mature mast cells (Fig. 1.1). Progenitor cell transit through the circulation is believed to be rapid, and entry into tissues is constitutive and enhanced by infection or inflammation. In tissues, the progenitor cells differentiate into two principal subtypes. In rodents, these two subtypes are referred to as connective tissue mast cells (CTMC) found particularly in skin and connective tissues, and mucosal mast cells (MMC), which are localized in the mucosa of airways and gastrointestinal tract. These two subtypes can be differentiated histologically by the different types of proteoglycans contained in their granules. CTMCs are rich in heparin, which stains metachromatically by toluidine blue, while MMCs contain chondroitin sulfate E, which stains yellow/green by safranin. The major human mast cell subtypes are distinguished by the types of proteases within the granules, with one subtype expressing tryptase and chymase, while the other type expressing tryptase alone. These subtypes are referred to as MCT and MCTC and correspond in many respects to rodent CTMCs and MMCs, respectively. It is likely that the differences among mast cell subtypes reflect some degree of functional specialization, as MRGX2 receptors, for example, are expressed in CTMC but not MMC.

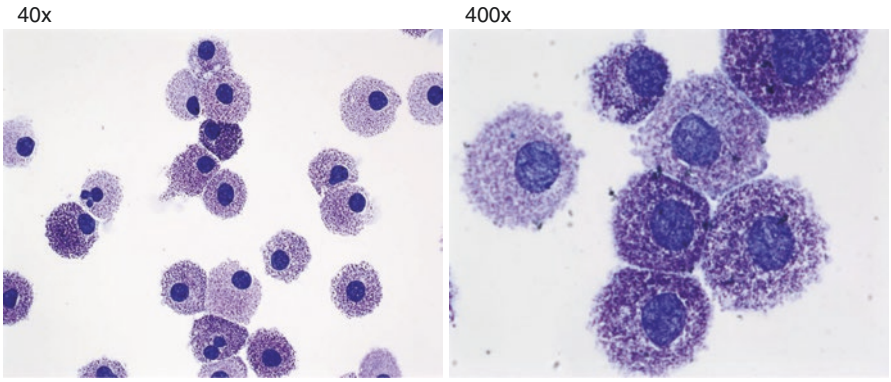

Fig. 1.1 Human mast cell cultures from CD34+ cells in SCF and IL-6 at 7 weeks. Cytopreparation stained with toluidine blue. Right panel: 40×; Left panel: 400×

Within tissues, mature human mast cells express a number of distinct receptors in addition to KIT, FcεRI, and MRGX2 receptors. These include Toll-like receptors (TLRs) and receptors for cytokines (Table 1.1). Activation through these diverse receptors leads to the production and release of a wide variety of biologically active molecules (Table 1.1), which induce local and systemic inflammatory reactions. In mast cell proliferative disorders, manifestations of disease depend on not only the mass effect of clusters of mast cells but also on the variable release of mast cell mediators, with biologic effects ranging from hypotension (Chap. 9) to fibrosis. Some of these mast cell-derived mediators are useful both in the diagnosis of mastocytosis and in following the course of the disease (Chap. 3). Additionally, they serve as targets of symptomatic management. The remainder of this chapter will focus on those receptors and mediators of inflammation that are believed to most influence the phenotype in allergic inflammation and in mastocytosis and its variants or to be upregulated in these disorders.

Table 1.1 Major mediators and cell surface receptors in human mast cells

Mediators	
Major mediators performed and stored in cytoplasmic granules	Histamine, heparin,[a] chondroitin sulfates,[a] chymase,[a] tryptase,[a] cathepsin G,[a] carboxypeptidases, major basic protein, acid hydrolases, peroxidase, phospholipases
Major lipid mediators produced on appropriate activation	Leukotriene B4, prostaglandin D2, leukotriene C4, platelet-activating factor
Cytokines released on appropriate activation	TNF, TGF-β, IFN-α, VEGF-A–D, IL-6, IL-11, IL-13, IL-16, IL-18, GM-CSF, NGF, PDGF
Chemokines	IL-8 (CXCL-8), I-309 (CCL-1), MCP-1 (CCL2), MIP-1α (CCL3), MIP-1β (CCL-4), MCP-3 (CCL-7), RANTES (CCL-5), Eotaxin (CCL-11)
Receptors	
Ig receptors	FcεRI, FcγRI (after IFNγ exposure), and FcγRIIA
Cytokine or growth factor receptors for	SCF (ligand for kit), IFN-γ, IL-4, IL-5, IL-6, IL-9, and IL-33; chemokines (CCR1, −3, −4, −5, −7; CXCR1, −2, −3, −4, −6); thrombopoietin receptor (CD110), GM-CSF, NGF
TLRs	TLR-1, −2, −3, −4, −5, −6, −7, and − 9

Note: Expression of these and other surface structures including chemokine receptors and production of individual cytokines and chemokines vary in different in vitro or in vivo derived mast cell populations

IFN interferon, *Ig* immunoglobulin, *IL* interleukin, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *MCP* monocyte chemotactic protein, *MIP* macrophage inflammatory protein, *NGF* nerve growth factor, *PDGF* platelet-derived growth factor, *RANTES* regulated upon activation, normal T-cell express sequence, *SCF* stem cell factor, *TNF* tumor necrosis factor, *TGF* transforming growth factor, *TLR* Toll-like receptor, *VEGF* vascular endothelial growth factor

[a]Mast cell content of these (and perhaps other) mediators varies, for example, in different subjects and tissues, and/or in association with certain inflammatory diseases

Cell Surface Receptors and Mast Cell-Related Diseases

FcεRI, the High-Affinity Receptor for IgE

FcεRI is the primary receptor in mast cells for mediating allergic reactions and is thought to have evolved as a defense mechanism against parasites and animal venoms [1]. Aggregation of FcεRI through multivalent binding of allergen to IgE bound to FcεRI activates a broad spectrum of responses. These include rapid degranulation with release of preformed mediators such as histamine, sulfated proteoglycans (heparin or chondroitin E), and mast cell-specific proteases that exist exclusively in the granules. This is followed by rapid production of lipid-derived inflammatory mediators, notably prostaglandin D2 (PGD2), leukotriene C4 (LTC4) and platelet-activating factor (PAF), and subsequently by numerous transcriptionally derived cytokines and chemokines that may promote or suppress inflammation and regulate tissue remodeling [9, 10]. The constellation of symptoms upon mast cell activation depends upon the site of challenge [9]. The immediate effects, referred to as immediate hypersensitivity reactions, are due to the rapid release of preformed mediators and synthesis of lipid-derived mediators. If localized to skin, this results in a weal and flare reaction or, in airways, contraction of airway smooth muscle, mucus secretion, and an increase in vascular permeability (Fig. 1.2). If systemic, the result can

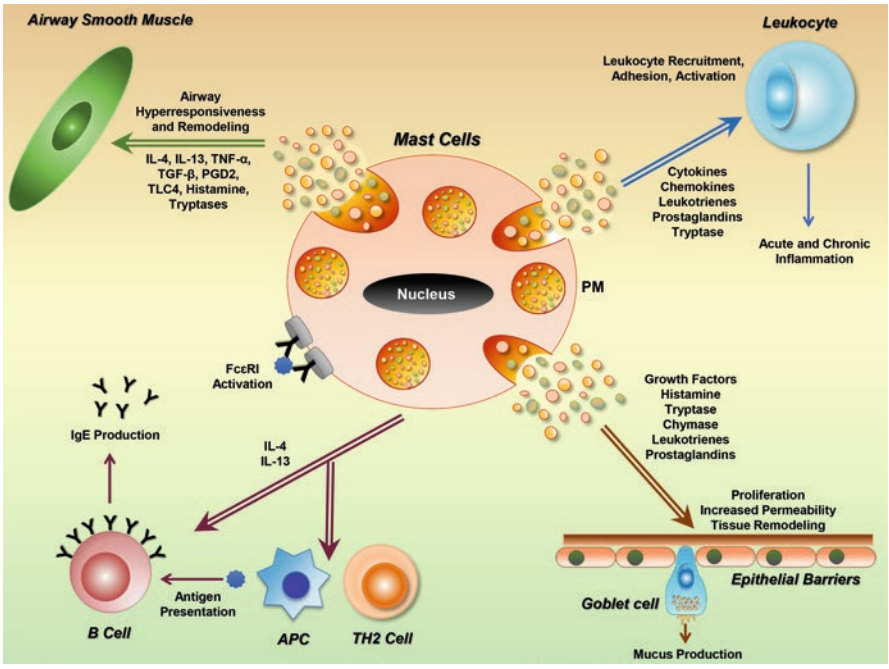

Fig. 1.2 Biologic consequences of activation of mast cells in tissues

be generalized anaphylaxis associated with vascular dilation and vascular leakage among other effects. These early responses within target tissues, which usually resolve within a few hours, may transition into a “late phase reaction” hours later associated with an influx of circulating leukocytes, which may promote further inflammation or bronchoconstriction. This is accomplished by upregulation of adhesion molecules on vascular endothelial cells and by secretion of chemotactic factors such as LTB4, PGD2, IL-8, and CC-chemokine ligand 2 (CCL2).

The ability of an antigen to induce the release of all major categories of inflammatory mediators from mast cells and to promote mast cell chemotaxis requires the coordinated activation of sequential, parallel, and interacting signaling pathways that generate the divergent processes required for these multiple responses (Fig. 1.3) [10]. The more proximal receptor signaling events generally share common signaling elements, whereas the more distal events show significant divergence. It is the divergence in these signaling pathways that may allow chemotaxis or release one category of mediators in the absence of the others. Although the pathways regulating mast cell activation are complex, they can be condensed into the following major signaling sequences and axes [10, 11] (Fig. 1.3): (1) Aggregation of FcεRI α-bound IgE by the antigen allows the Src family kinase (SFK) LYN to transphosphorylate tyrosine residues in the FcεRI β and γ chains that are recognized by the Src homology 2 (SH2) of spleen tyrosine kinase (SYK), resulting in the recruitment of SYK, and consequently its phosphorylation by LYN and activation (2). SYK-mediated activation of the linker of activation of T cells (LAT) leads to the activation of the phospholipase C γ (PLCγ)-calcium/protein kinase C (PKC) axis, critical for all mast cell functions (3). Phosphorylated LAT also leads to mitogen-activated protein kinase (MAPK) pathway activation and transcriptional regulation (4). In addition to LYN, the SFK FYN is also activated after antigen binding and phosphorylates the adaptor protein GAB2 (GRAB-associated binding protein), which recruits and activates phosphoinositide 3-kinase (PI3K) and PI3K-dependent pathways, including the activation of sphingosine kinase (SPHK), necessary for degranulation and cytokine production. Other recent modifications of the signaling cascade include the recognition of DJ-1 (PARK7) as a protein interacting with LYN and facilitating Lyn activation and human mast cell degranulation [12].

Fcγ Receptors

In addition to FcεRI, multiple other receptors for IgG are expressed on mast cells [13]. Such expression is dependent on the cytokine content of the surrounding tissues. Under appropriate conditions, human mast cells may express FcγRI and FcγRIIb and, to a lesser extent, FcγRIII IgG receptors [14]. Both the FcγRI and FcγRIII consist of IgG-binding α subunits and the γ chain homodimer, which is identical to the FcεRI γ subunit. The FcγRIα subunit binds IgG with high affinity, whereas the FcγRIIIα subunit binds IgG with relatively low affinity [13]. FcγRI has the capacity to activate mast cells under appropriate conditions. Under resting

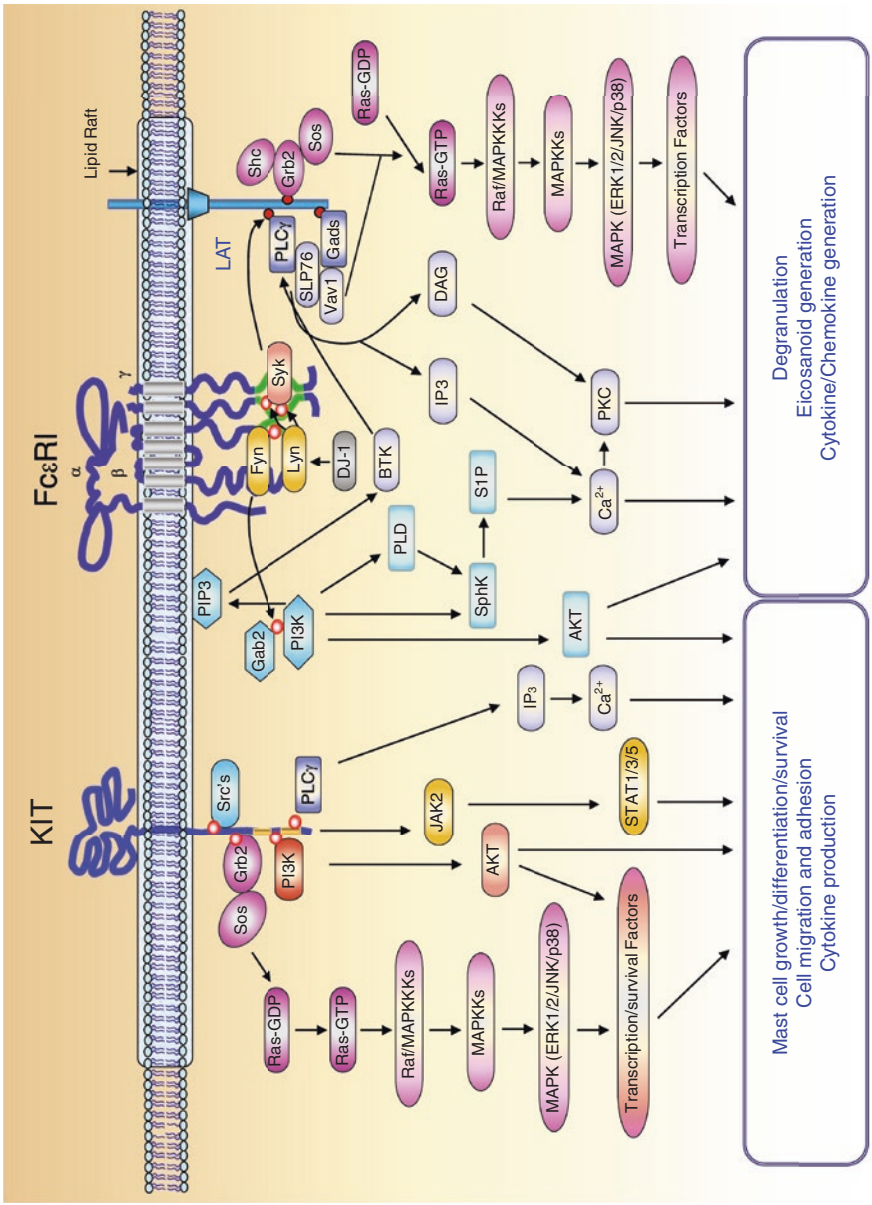

Fig. 1.3 Signal transduction cascades triggered through FcεRI and or KIT

conditions, FcγRI is not generally expressed on human mast cells. However, in CD34+ peripheral blood-derived human mast cells, exposure to IFN-γ results in upregulation FcγRI on the cell surface [13]. Furthermore, FcγRI is present on mast cells in psoriatic skin where IFN-γ levels are elevated [15], implying that mast cell FcγRI expression is associated with specific disease states. The FcγRI expressed on human mast cells has been shown to be functional in that FcγRI aggregation results in degranulation and cytokine production in a similar manner as that observed following FcεRI aggregation [13]. In contrast to the FcγRI and FcγRIII, the FcγRIIβ receptor is a single-chain receptor that is not associated with the common signaling γ chain homodimer. It appears that FcγRIIβ does not possess the capacity to induce mast cell degranulation. However, due to the immunoreceptor tyrosine-based inhibitory motif (ITIM) contained within the cytosolic tail, FcγRIIb, when co-ligated with the FcεRI, downregulates antigen-induced degranulation [16].

KIT

The *KIT* proto-oncogene is the cellular, untruncated counterpart of the gene in the Hardy-Zuckerman feline sarcoma virus genome (v-Kit) responsible for its transforming activity [17]. Gain-of-function mutations in *KIT* promoting tumor formation and progression have been identified in certain human cancers, knowledge that has boosted an interest in targeting the activity of this receptor. *KIT* encodes for a protein, KIT (CD117), belonging to a family of transmembrane growth factor receptors with intrinsic tyrosine kinase activity [18]. Its specific ligand is SCF, also known as KIT ligand, mast cell growth factor, or steel factor [19]. SCF is primarily, but not exclusively, produced by stromal cells such as fibroblasts in two major forms, a soluble form and a membrane-bound form, which are present at varying ratios in different tissues [20]. Both forms activate KIT but may mediate qualitatively and quantitatively different types of responses, although the specific mechanisms remain largely unknown.

KIT is highly expressed in hematopoietic stem cells from the bone marrow and its activity is critical for hematopoiesis and for the proliferation, survival, differentiation, and homing of these cells [21]. Expression of KIT is generally lost during the differentiation process of most hematopoietic cells, except for mast cells, which retain KIT through their lifespan. KIT thus plays a critical role in mast cell proliferation, survival, and function [22]. KIT is also expressed in melanocytes, interstitial cells of Cajal in the gastrointestinal tract [23], and other cell types.

In humans, loss-of-function mutations in *KIT* are associated with piebaldism, a rare, autosomal dominant disorder characterized by congenital white patches in the skin and hair caused by improper migration of melanoblasts in the embryo [24], while acquired gain-of-function mutations in *KIT* result in particular neoplastic diseases.

Human malignancies associated with activating *KIT* mutations include mast cell proliferative disorders, gastrointestinal stromal tumors, and, less commonly,

melanoma and acute myeloid leukemia. Approximately 85–90% of adults with mastocytosis have at least a point missense mutation (D816V), resulting in the substitution of aspartic acid to valine in the catalytic domain of KIT, rendering it constitutively active [25] and/or other mutations in *KIT* (see Chap. 14). The D816V mutation is less frequently found in cases of children with mastocytosis. Transforming mutations in *KIT* appear in approximately 3% of all melanomas [26]. Mutations or internal tandem duplications in *KIT* that contribute to pathogenesis have been observed in approximately 17% of acute myeloid leukemias [27]. These are acquired somatic mutations present in a clonal lineage population, and it is thought that the ultimate phenotype of malignant hemopoietic cells of a specific lineage-expressing mutant KIT is influenced by additional complementing co-oncogenic events or epigenetic modifications that affect their differentiation process, proliferation, and survival [27].

In addition to promoting mast cell proliferation and survival, persistent activation of KIT may reduce the threshold of mast cell activation to other stimuli. Thus, it is not unexpected that patients with mastocytosis may suffer recurrent spontaneous episodes of flushing, shortness of breath, palpitations, nausea, diarrhea, abdominal pain, and hypotension [28] as a consequence of increased mast cell mediator release.

KIT is a type III receptor tyrosine kinase that contains five extracellular immunoglobulin-like domains [29]. The distal D1, D2, and D3 domains constitute the SCF-binding portion of KIT with SCF and KIT forming a 2:2 stoichiometry, supporting suggestions that KIT dimerization is a consequence of bivalent binding to SCF homodimers [30]. The intracellular juxta-membrane domain of KIT in the inactive, monomeric state interacts with the kinase domain, preventing its catalytic function and providing a negative switch regulatory mechanism [31]. In response to SCF, KIT dimerizes, allowing for the transphosphorylation of tyrosine residues in the juxta-membrane, kinase insert (which splits the kinase domain (KD) in two), and cytoplasmic tail domains (Fig. 1.3). Phosphorylated tyrosine residues in these domains act as docking sites for signaling proteins containing either SH2 or phospho-tyrosine binding (PTB) domains [32], resulting in the activation of signaling cascades. One of the early signaling events is the recruitment and activation of SFKs to the juxta-membrane domain of KIT [33], which is critical for SCF-induced proliferation and chemotaxis. SFKs are also critical for anchoring kinases to the plasma membrane and to specialized membrane microdomains (lipid rafts). Lipid rafts may also be important for signal transduction through PI3K [34]. PI3K phosphorylates the plasma membrane-associated phosphatidylinositol-4,5-biphosphate (PI(4,5)P2) to form phosphatidylinositol-3,4,5,-triphosphate (PI(3,4,5)P3), which, in turn, recruits pleckstrin homology (PH) domain-containing signaling proteins to the plasma membrane initiating proliferation and survival signals. In addition, PI3K also appears to play an important role in mast cell chemotaxis [35].

Activation of KIT by SCF also triggers activation of the MAPKs, including extracellular signal-regulated kinase 1 and 2 (ERK1 and ERK2), c-Jun N-terminal kinases (JNK), and p38 [36]. The adaptor protein GRB2 (growth factor receptor-bound protein 2) is recruited via its SH2 domain to activated KIT and then forms a

complex with the guanine exchange factor (GEF) SOS (Son of Sevenless). SOS activates the G protein RAS by promoting the exchange of GDP by GTP (Fig. 1.3). GTP-bound, active RAS initiates a cascade of serine/threonine kinases (RAF, MEK) that lead to the activation of the ERK1/2 [36]. The RAS–RAF–MEK–ERK pathway regulates many cellular processes, particularly survival, proliferation, and cytokine production in mast cells. Pharmacological targeting of KIT catalytic activity has been a major strategy for blocking KIT-mediated responses (see Chaps. 15 and 16).

Mas-Related G Protein-Coupled Receptors

Following the initial identification of mast cells in 1877 by a metachromatic staining technique, Paul Ehrlich noted that mast cells were abundant in chronically inflamed tissues and tumors, which he attributed to the high nutritional requirements of these tissues (hence his coining of the term "mastzellen" or fattening cell) [37, 38]. But the function of mast cells eluded him, as it did for others, for many decades. A major defining event was the discovery that mast cells were the main repository of histamine and heparin [39] and of the potent histamine liberating properties of a polymeric methoxyphenethyl–methylamine product referred to as compound 48/80. This compound caused degranulation of mast cells in rodents and elicited reactions reminiscent of anaphylaxis. Compound 48/80 caused a rise in serum histamine and physiological reactions that correlated with the extent of disruption of mast cells. However, the mechanism of action of compound 48/80 and of a wide range of polybasic neuropeptides remained an enigma until the relatively recent identification of the receptor involved as one of the Mas-related G protein-coupled receptors (MRGX2, in humans). The MRGX receptors (MRGX1–MRGX4) were originally thought to be expressed exclusively in human dorsal root ganglia and associated sensory axons but were subsequently found to be expressed in human cord CD34+ blood cell-derived mast cells [40].

In addition to the prototypic compound 48/80, other cationic mast cell activators include a variety of components of insect venom (e.g., mastoparan and polistes kinin), antimicrobial peptides (e.g., α and β defensins and cathelicidins), secreted eosinophil products (eosinophil peroxidase and major basic protein), and neuropeptides (e.g., substance P, vasoactive intestinal peptide, neuropeptide Y, somatostatin, and cortistatin). These compounds also stimulate the production of prostaglandin D2 and a variety of chemokines and cytokines [41–43]. They act independently of FcεRI in a pertussis toxin-dependent manner, resulting in the activation of phospholipase Cβ, phosphatidylinositol 3′-kinase and calcium mobilization [43]. In humans, MRGX2 is now also reported to be the common receptor for cortistatin, tubocurarine, atracurium, icatibant, ciprofloxacin, and other fluoroquinolone antibiotics [44].

The expression of MRG receptors in mast cells does not appear to be homogeneous among mast cell subtypes. The MCTC subtype was found to express almost 4000 higher copy number of MRGX2 RNA than the MCT subtype, which did not respond to these stimulants, supporting the concept of functional differences

between these two mast cell subtypes. The LAD2 human mast cell line, considered as a MCTC subtype, has been found to express MRGX1 and MRGX2 proteins and degranulate in response to compound 48/80, retrocyclin, and protegrin. In comparable experiments, both LAD2 and human peripheral CD34+ blood-derived mast cells were similarly activated by human antimicrobial peptides, β-defensins, and a C-terminal fragment of cathelicidin [45].

The pathological implications of MRGX2 have yet to be explored in detail. In addition to anaphylactoid reactions to drugs, the presence of MRGX2 in mast cells may contribute to the well-established roles of mast cells in innate and adaptive immunity; allergic disease; and, potentially, neurogenic inflammation, pain, and itch [44–49]. The demonstrated ability of various cationic substances to activate mast cells via MRPX2, whether initiated by venom components such as mastoparan or by release of β-defensins and cathelicidins upon infection and secondarily by subsequent release of cationic neuropeptides from the same sensory neurons, may reinforce sensory nociception and/or antimicrobial efficacy by increasing vascular permeability and recruitment of neutrophils to sites of infection [45, 48]. A cross-talk between eosinophils and mast cells via MRGX2 during inflammation is also possible, as eosinophil-derived peroxidase and major basic proteins activate skin mast cells via MRGX2 and accumulation of eosinophils and mast cells is typically observed in affected tissues in atopic urticaria, asthma, and other allergic disorders, as well as mastocytosis, in which mast cell tumor expansion coincides with an expanded eosinophil population [45–47]. Thus, selective antagonists for MRGX2 receptors may be of therapeutic and investigational interest.

GPR-35

The prototypic mast cell stabilizer cromolyn (disodium cromoglycate) [50], a derivative of the folk medicine khellin, was first described as an inhibitor of experimental asthma and successfully tested for allergic asthma in humans. It is believed to act through GPR-35, an orphan G-protein-coupled receptor (GPCR), although the endogenous ligand for this receptor has not been clearly identified [51, 52]. Early reports indicated that GPR-35 inhibited the release of histamine and slow-reacting substance of anaphylaxis (SRS-A, most likely PGD2) from the human lung passively sensitized with human reaginic serum. It inhibited the passive cutaneous anaphylaxis reaction in rats and compound 48/80-induced histamine release from rat peritoneal mast cells. Studies of the human lung showed that cromolyn was a weak inhibitor of anti-IgE-mediated histamine release from lung fragments [53], but later studies indicated that cromolyn (and nedocromil) were more effective inhibitors of histamine release from lung cells obtained by bronchial lavage than from dispersed lung cells, which was attributed to the different phenotypic characteristics of mucosal and parenchymal mast cells in the human lung [54]. Overall, the precise role of this receptor and the endogenous ligands and the function of cromolyn on mast cells are still ill-defined.

Adhesion G-Protein-Coupled Receptor E2 (ADGRE2)

ADGRE2, also known as EGF-like module-containing mucin-like hormone receptor-like 2 (EMR2) or CD132, belongs to a large family of adhesion GPCRs. Adhesion GPCRs generally contain a seven-transmembrane (7TM) domain (β subunit), whose sequence provides the basis for the classification of adhesion GPCRs into subfamilies, and a large extracellular domain (α subunit), which facilitates interactions with proteins from the extracellular matrix or expressed on the surface of other cells. The ligands for most of these receptors are not known, and even if they are identified, only a few are actual agonists that can evoke an intracellular response mediated by the 7TM domain [55]. ADGRE2 binds dermatan sulfate, the predominant glycosaminoglycan in the skin. However, binding of ADGE2 to dermatan sulfate does not elicit, by itself, a detectable mast cell activation response. As is true for other adhesion GPCRs involved in mechanosensation, a mechanical force is needed in addition to dermatan sulfate binding to trigger mast cell degranulation. The α and β subunits of ADGRE2 are translated into a single polypeptide precursor, but early during the trafficking of the receptor to the plasma membrane, this protein undergoes autocatalytic cleavage within its G-protein proteolytic site motif rendering the two subunits that for the most part remain non-covalently bound [56]. During mechanical vibration of mast cells attached to dermatan sulfate, the α subunit dissociates from the 7TM allowing it to signal. Thus, it appears that mechanical forces activate this receptor by separating the α and β subunits. In patients with severe vibratory urticaria, a p.C492Y mutation destabilizes the inhibitory interaction between the α and β subunits, thereby increasing the susceptibility of these mast cells to vibration-induced degranulation [57]. Although the physiological relevance of the limited mast cell responses to friction in normal individuals is not completely understood, possibilities are that ADGRE2 may subtly alert both resident and immune cells to combat potential injury and wound healing, play a role in pain modulation, and perhaps help to sense a parasite migrating through dermal tissues.

IL-33 Receptor

Ample experimental and clinical evidence has implicated interleukin 33 (IL-33), one of the IL-1/IL-18 family of cytokines, as a major player in type 2 (TH-2) immune responses and the pathogenesis of allergic diseases. Genes encoding for IL-33 and its receptors have been identified as susceptibility loci in asthma [58]. Although IL-33 is produced in epithelial and other stromal cells after cell damage induced by either injury or environmental agents [59], its receptor, ST2, is expressed in a variety of immune cells including mast cells. IL-33 binding to ST2 induces the differentiation, survival, chemotaxis, and cytokine production by mast cells, amplifying the inflammatory effects of IL-33 [60]. Furthermore, IL-33 also potentiates antigen-induced degranulation and cytokine release by mast cells via ST2, and

evidence using animal models suggests an important role for this receptor in food allergy, asthma, and other allergies [61]. Human mast cell progenitor cells also express ST2 during development, even before expression of the IgE receptor and produce TH-2 and pro-inflammatory cytokines in response to IL-33 even more abundantly than mast cells, suggesting progenitors may also play a role initiating IL-33-mediated responses [62, 63].

CD63

CD63 belongs to the family of tetraspanins, which comprise a superfamily of cell surface-associated membrane proteins characterized by four transmembrane domains [64]. At the cell surface, tetraspanins form networks with a number of proteins, including cell surface receptors, kinases, integrins, and other tetraspanins. CD63 at the cell surface is endocytosed via a clathrin-dependent pathway. In late endosomes, CD63 is enriched on the intraluminal vesicles, which are secreted by specialized cells as exosomes through fusion of endosomes with the plasma membrane [64]. CD63 is an activation marker for mast cells [65], as it is rapidly increased in the plasma membrane following allergen challenge, reaching the maximum at 20–30 min. CD63 is upregulated on bone marrow mast cells in mastocytosis.

CD203c

CD203c (E-NPP3) belongs to a family of ectonucleotide pyrophosphates/phosphodiesterases (E-NPPs). E-NPPs catalyze the cleavage of phosphodiester and phosphosulfate bonds of molecules, including deoxynucleotides, NAD, and nucleotide sugars [66]. E-NPP3 is composed of a short N-terminal cytoplasmic domain, a transmembrane region, two somatomedin-like domains, a catalytic domain, and a C-terminal endonuclease-like domain. CD203c is associated with malignancy and tumor invasion [67]. CD203c has been defined as an activation-linked surface antigen on mast cells that is upregulated in response to IgE receptor cross-linking and is overexpressed on neoplastic mast cells in patients with mastocytosis [68].

CD30

CD30 is a member of the tumor necrosis factor/nerve growth factor receptor (TNFR/NGFR) superfamily [69]. Ligation of the CD30 ligand (CD30L or CD153) to CD30 elicits multidirectional signals leading to either cell activation or apoptosis. Under physiological conditions, expression of CD30 is restricted to T and B cells, mainly to activated TH2 cells. CD30 is expressed typically on the surface of Hodgkin's

Reed–Sternberg cells and anaplastic large cell lymphomas. Human mast cells from normal donors do not express CD30. CD30 expression is upregulated aberrantly in most indolent and aggressive forms of systemic mastocytosis [70].

CD25

CD25 is in the α chain of the IL-2 receptor. The high-affinity IL-2 receptor (IL-2R) is a heterotrimer consisting of the IL-2R α chain (IL-2Rα, CD25) and the IL-2R β and γ chains (IL-2Rβ and IL-2Rγ) [71]. CD25 serves as a major growth factor receptor by binding IL-2. The IL-2Rα does not contain an intracellular signaling domain; therefore, binding to IL-2Rα alone does not result in T cell activation. The high-affinity IL-2R heterotrimer is expressed on activated T cells and regulatory T cells. Mast cells in systemic mastocytosis aberrantly display CD25, which is a marker of neoplastic mast cells in systemic mastocytosis variants and in platelet-derived growth factor receptor alpha (PDGFRA)-associated myeloproliferative disorders [72]. It is not known whether the aberrant expression of this receptor has pathological implications.

Mast Cell Mediators

Histamine

Histamine is the main biogenic amine released from human mast cells upon IgE-receptor activation. Histamine can be measured in body fluids and is increased in bronchoalveolar lavage fluid from patients with allergic asthma and plasma from patients with atopic dermatitis or chronic urticaria [73, 74]. Histamine is rapidly metabolized either by methylation into methyl histamine catalyzed by histamine N-methyltransferase or by oxidative deamination into imidazole acetaldehyde catalyzed by diamine oxidase. The metabolite 1-methyl-4-imidazole acetic acid (tele-MIAA) represents 70–80% of metabolized histamine [75] and is excreted in urine. Increased levels of histamine in the serum or histamine metabolites in the urine can be evidence of systemic mastocytosis and/or mast cell activation [76]. There are a number of approaches to measure histamine and histamine metabolites, including ELISA, high-performance liquid chromatography (HPLC), and HPLC coupled to mass spectrometry (HPLC–MS).

Heparin

Heparin is produced by mast cells, and human lung mast cells contain approximately 2.4–7.8 μg of heparin per 106 cells [77]. Human heparin is associated with the collections of mast cells associated with urticaria pigmentosa (maculopapular

cutaneous mastocytosis) [78]. In rare cases of advanced systemic mastocytosis, a heparin-like anticoagulant may be released, which leads to hemorrhagic complications [79]. However, in most cases, the thrombin time and partial thromboplastin time remain normal in patients with mastocytosis. Measurement of mast cell-derived heparin should be considered in mastocytosis when there is clinical evidence of hemorrhagic complications.

Proteases

Proteases are stored in mast cell granules and represent a high fraction of all protein content. Whole-transcriptome analysis has revealed that expression of transcripts for serine proteases constitutes the most significant category of gene products that differentiate tissue-resident mast cells from other immune cells [80]. These proteases, together with other granule contents, are released into the interstitial space upon mast cell activation. Mast cell proteases then cleave a number of functionally diverse protein substrates through recognition of specific peptide sequences. Proteolytic cleavage of these substrates may result in either their activation or their inhibition, and thus, their specific roles in specific physiopathological conditions is complex and depend on the specific environment [81]. For example, mast cell proteases released have been linked to angiogenesis, cancer, bone homeostasis, and inflammation in allergic diseases and other inflammatory conditions including inflammatory bowel disease and arthritis. Venom-induced innate activation of mast cells results in the release of proteases that can degrade certain animal venoms including honey bees, scorpions, and reptile venoms, neutralizing them and thus reducing morbidity and mortality to these venoms [6, 82]. Furthermore, venom-specific IgE antibodies and IgE-mediated mast cell responses after re-exposure to venoms contribute to protection against lethal doses of these toxic venoms. An interpretation of these observations is that anaphylaxis, when appropriately regulated, is beneficial rather than detrimental in the pathology associated with envenomation [6].

Tryptase

The mast cell tryptase loci in humans may encode α or β tryptases (TPSAB1) and only β tryptases (TPSB2). While one locus always expresses a β-tryptase, the other locus can express either α- or β- tryptase, resulting in α:β tryptase gene ratios of 0:4, 1:3, or 2:2 in different individuals. α/β-Protryptases are processed to maturity by cathepsins B and L, while β-protryptase can also be sequentially processed by autocatalysis and cathepsin C. Despite the homology between the two tryptases, mature β-tryptase is proteolytically active as a homotetramer, but mature α-tryptase appears less enzymatically active [83]. Protryptases are constitutively secreted by resting mast cells, whereas mature tryptases, which are stored in secretory granules, are secreted in association with mast cell activation. An increase in the serum

tryptase level by 20% over the individual baseline plus 2 ng/ml total within a 4-hour window after the reaction provide laboratory evidence of such mast cell activation [84]. Baseline serum levels of α/β-tryptases (pro + mature), range from 1 to 11 ng/ml in healthy subjects and serve as a minor diagnostic criterion for systemic mastocytosis when >20 ng/ml. In subjects with systemic anaphylaxis to insect stings, serum basal tryptase levels between 11 and 20 [85] raise suspicion for an underlying clonal mast cell disorder.

While about a fourth of the general population is deficient in α-tryptase without any noticeable manifestations, recent studies suggest that germline duplications and triplications of α-tryptase are linked to subjects with dominantly inherited elevated basal serum tryptase levels and with multisystem disorders in cases where clonal mast cell disease or mast cell activation syndrome is not evident [86]. The symptom complexes in these patients include irritable bowel syndrome, cutaneous flushing, connective tissue abnormalities, and dysautonomia.

Chymase

Human chymase is a chymotrypsin-like serine protease. It is found in a subset of human mast cells, usually in conjunction with human mast cell carboxypeptidase A3. It is released from mast cells in large complexes containing heparin proteoglycan and carboxypeptidase and distinct from complexes containing tryptase [87]. Human chymase is the major non-angiotensin-converting enzyme (ACE) that generates angiotensin II as well as a non-endothelin-converting enzyme (ECE) that generates endothelin-1. As such, chymase is thought to possibly participate in inflammatory responses impacting the vasculature, including blood pressure regulation and plaque instability [88]. Chymase degrades lipoproteins, which promotes macrophage foam cell formation. Chymase can also degrade the extracellular matrix, generate fibronectin and transforming growth factor-β, and activate IL-1β and has been implicated in the pathogenesis of tissue fibrosis and wound healing [89]. In human serum, chymase is subject to inhibition by endogenous circulating inhibitors including α-1 antitrypsin, α-1 antichymotrypsin, α-2 macroglobulin, and locally secreted inhibitors including secretory leukocyte protease inhibitor (SLPI) [90]. An α-2 macroglobulin capture assay using a synthetic substrate, which detects enzymatic activity in chymase-spiked serum with a threshold of approximately 30 pg/ml, revealed detectable chymase activity in the serum of most patients with mastocytosis [91].

Carboxypeptidase A3

Carboxypeptidase was identified in human mast cells in 1989 [92]. Mast cells containing carboxypeptidase A3 (CA3) have been reported in association with allergic disease of both the lower and upper airways [93]. CPA3 is also one of the ten genes overexpressed in the bone marrow mononuclear cells of adult patients with

systemic mastocytosis [94]. Serum CPA3 levels have been reported to be elevated in those with a clinical diagnosis of anaphylaxis but not in the serum of healthy adults or individuals with a diagnosis of asthma. The serum levels of tryptase and of CPA3 after anaphylaxis do not necessarily correlate [95]. CPA3 levels appear to remain elevated longer than the tryptase levels. Further, CPA3 serum levels have also been reported to be detected in individuals with anaphylaxis, where elevations in total serum tryptase levels were not observed.

Prostaglandin D2 and *Cysteinyl Leukotrienes*

Prostaglandin D2 (PGD2) and cysteinyl leukotrienes (Cyst LTs) are the major lipid mediators synthesized after mast cell activation [96]. They are released as part of the immediate mast cell response. Prostaglandins and leukotrienes are synthesized from arachidonic acid (AA), which is released by the action of cytosolic phospholipase A2 on membrane phospholipids. In the PG pathway, AA is first converted to PGG2 by cyclooxygenase (COX)-1 and COX-2 and then reduced to PGH2. The latter serves as the precursor for PGD2 as well as other prostanoids PGE2, PGF2a, PGI2, and thromboxane A2 through terminal PG synthases. PGD2 is also produced by eosinophils and in lesser quantities by other immune cells such as TH-2 cells and dendritic cells. Non-hematopoietic tissues such as brain, heart, lungs, and kidneys also produce PGD2 via lipocalin-type PGD2 synthase. PGD2 exerts its biologic actions by binding to two receptors, named DP1 and DP2. End-organ functions of PGD2 in humans include vasodilation and bronchoconstriction. Pulmonary, nasal, and ocular allergen challenges result in increased levels of PGD2 in relevant biologic fluids. PGD2 and its metabolite, 11b-PGF2a, are found to be increased in the urine of patients with mastocytosis [97]. The diagnostic and therapeutic clinical utility of PGD2 as a marker of mast cell activation is limited by its production by cells other than mast cells.

Historically known as the slow reacting substance of anaphylaxis, LTC4, LTD4, and LTE4 are collectively termed “CysLTs.” 5-Lipoxygenase (5-LO) along with the perinuclear membrane protein called the 5-LO-activating protein converts AA to 5-hydroxyperoxyeicosotetraenoic acid, which then gets dehydrated to the unstable leukotriene precursor LTA4. LTA4 is then conjugated to reduced glutathione by LTC4 synthase, which is secreted out of the cells. LTC4 is converted first to LTD4 then to the most stable form LTE4 extracellularly. CysLTs are generated by mast cells, basophils, eosinophils, macrophages, and myeloid dendritic cells. There are at least three CysLT receptors: CysLT1R, CysLT2R, and CysLT3R (GPR99) [98]. As a mediator associated with allergic inflammation, the importance of LTC4 resides in its capacity to induce smooth muscle contraction at a concentration that is 100–6000 times lower than that for histamine, and this contraction also lasts substantially longer. CysLTs also induce wheal and flare reactions in humans. Urinary LTE4 is elevated in mastocytosis and correlates with 24 h urine N-methylhistamine and serum tryptase levels [99].

Concluding Remarks

Mast cells participate in virtually all inflammatory, allergic, and autoimmune diseases, and they contribute to defense against infectious organisms. The role of these cells in human diseases is beneficial, for example, in combating insect venoms, or detrimental as in allergic inflammation in mast cell proliferative disorders. Thus, an understanding of mechanisms whereby mast cells may be activated and how to assess the degree of activation of these cells in vivo is desirable to monitor mast cell burden and degree of activation and to assess response to therapy. There is good evidence that some mast cell mediators can function as surrogate markers of disease and the state of mast cell activation in vivo. Some of the markers are relatively cell-specific, for example, tryptase for mast cells. Others such as histamine and CysLTs are not cell specific. Surface markers and activation molecules expressed on the membrane of mast cells can, in some cases, be used in the diagnosis of mast cell proliferative disorders. Select biomarkers of mast cell activation are modulated by pharmacologic treatment and therefore, in some instances, may be used to monitor the response of disease to treatment.

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Chapter 2
Mastocytosis: Overview of Diagnosis and Classification

Cem Akin, Sigurd Broesby-Olsen, and Peter Valent

Mastocytosis is a disorder characterized by clonal expansion of mast cells. In most cases, it is caused by gain-of-function mutations in the KIT gene, which encodes a critical growth factor receptor involved in mast cell growth, differentiation, and survival [1]. Clonal mast cells can be found in skin, bone marrow, liver, spleen, and gastrointestinal tract. The symptomatology is due to local expansion and accumulation of mast cells, release of vasoactive mediators as well as cytokines from activated mast cells, and, in some patients, presence of an associated hematologic disorder.

Epidemiology

The estimated prevalence is approximately 1 in 20,000. It can be seen in both children and adults [2, 3]. In children, the disease is limited to skin and diagnosed by typical cutaneous lesions usually noted in the first year of life. Ninety percent of childhood-onset disease resolves by adolescence. In contrast, adult-onset mastocytosis involves the bone marrow and is persistent. It is seen in all ethnic populations, although most diagnosed cases in the Western world are Caucasians.

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Clinical Presentations

The disease has protean clinical manifestations and may present in one of the clinical scenarios described below:

1. Urticaria pigmentosa (maculopapular cutaneous mastocytosis = MPCM): This is the most common presentation in both children and adults. MPCM consists of hyperpigmented, fixed lesions usually less than 2 cm in diameter, involving trunk and extremities, usually sparing sun-exposed areas in adults (Fig. 2.1a, b). Children generally have lesions of varying sizes (polymorphic MPCM) and may have scalp involvement (Fig. 2.2). Blistering of the lesions may be seen earlier in life, mostly in the first 3 years (Fig. 2.3). The lesions are generally not pruritic at baseline but urticate with friction, temperature changes, fever, emotional stress, and exercise. Darier's sign, defined by a wheal and flare reaction of the skin lesions upon mechanical rubbing, is a pathognomonic hallmark of cutaneous disease involvement and confirms the diagnosis of mastocytosis in the skin (Fig. 2.4a, b). MPCM is the most common variant. Less common variants include diffuse cutaneous mastocytosis and mastocytomas in children [4] (Fig. 2.4). A skin biopsy confirms the diagnosis.
2. Anaphylaxis and symptoms of mast cell activation: These patients may or may not have skin lesions but come to clinical attention due to recurrent anaphylaxis or other episodic symptoms of mast cell activation including flushing, abdominal cramps, diarrhea, tachycardia, hypotension, and loss of consciousness. Flushing

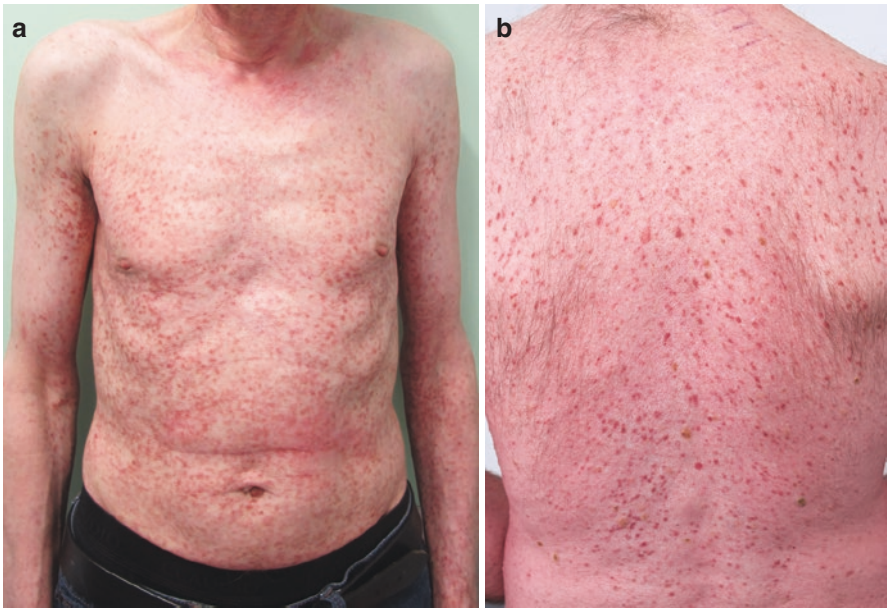

Fig. 2.1 **a**, **b**. Adult-onset maculopapular cutaneous mastocytosis

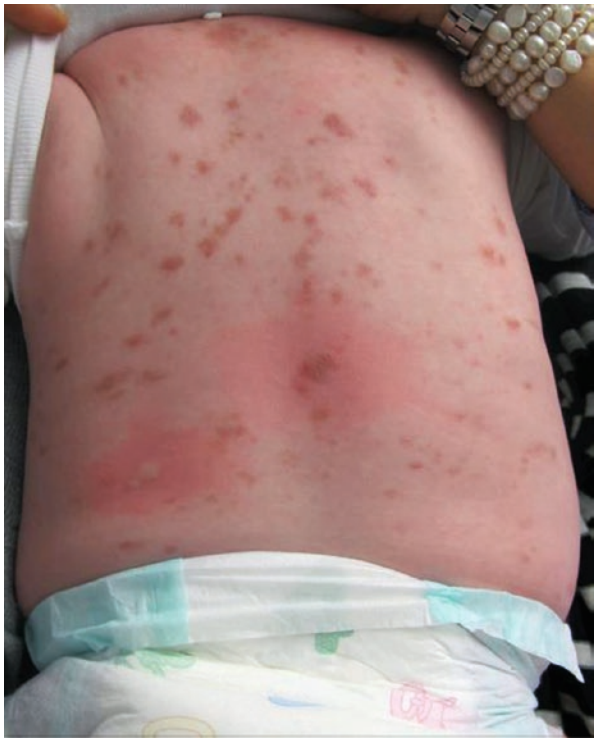

Fig. 2.2 Typical MPCM skin lesions in pediatric cutaneous mastocytosis

episodes typically last for 15–30 minutes. Acute urticaria and angioedema are uncommon [5, 6].

3. Hematologic disorders: Approximately 10–15% of the patients are diagnosed because of abnormalities in their blood counts, prompting a bone marrow biopsy. These patients show evidence of an associated hematologic disorder, usually myeloproliferative or a myelodysplastic syndrome (MDS), in addition to mastocytosis [7].
4. Bone disease: A small number of patients are initially diagnosed due to bone pain; vertebral compression fractures; and osteopenia, osteoporosis, or rarely sclerotic or even osteolytic lesions shown by imaging studies, prompting a bone biopsy [8].

Diagnosis

Cutaneous disease is diagnosed by observing typical skin lesions, by testing for Darier's sign, and by a skin biopsy. Systemic disease is diagnosed by a bone marrow biopsy, aspiration, and demonstration of World Health Organization (WHO) diagnostic criteria for systemic mastocytosis (Table 2.1) [9, 10]. These criteria are discussed in more detail in other chapters of this book.

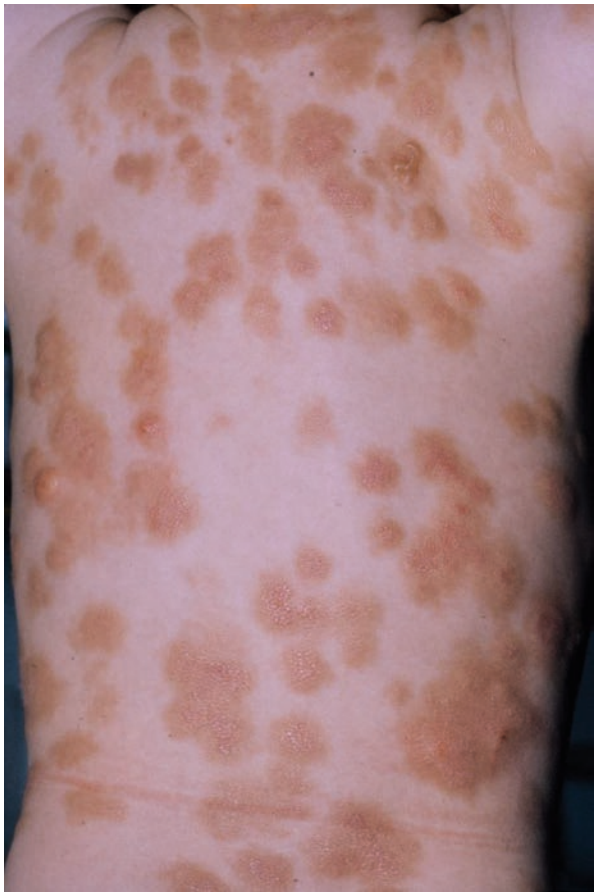

Fig. 2.3 Bullous MPCM in a patient with pediatric cutaneous mastocytosis

Major Criterion

Multifocal mast cell accumulations of >15 cells per collection. Tryptase, CD117, and CD25 staining of the core biopsy is recommended to evaluate for the presence of the major criterion.

Minor Criteria

1. Aberrant Mast Cell Morphology: Normal mast cells have a round shape and are fully granulated with a central nucleus. Mast cells in mastocytosis are spindle shaped and have cytoplasmic projections and an oval off-center nucleus, which, in advanced disease, may be clefted or multilobated. This abnormal morphology can be demonstrated in bone marrow sections or in aspirate smears. Mast cells in aspirate smears are usually found in or around spicules and are degranulated or hypogranulated [11].

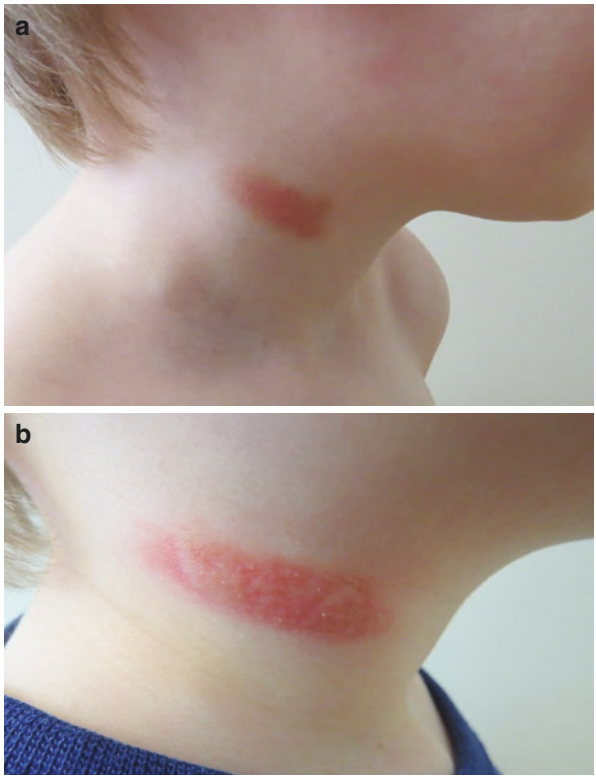

Fig. 2.4 Darier's sign. **a**. Mastocytoma prior to rubbing. **b**. Wheal and flare formation after rubbing of the lesion

Table 2.1 World Health Organization diagnostic criteria for systemic mastocytosis

Major SM criterion
Multifocal dense aggregates of mast cells (≥15 mast cells per aggregate) in bone marrow and/or other extracutaneous organ
Minor SM criteria
a. More than 25% of all mast cells have atypical morphology (e.g., spindle shaped) in bone marrow aspirates
b. Codon 816 KIT point mutation in the bone marrow, blood or another extracutaneous organ
c. CD2 and/or CD25 expression on mast cells in the bone marrow, blood, or other extracutaneous tissues
d. Baseline serum tryptase level > 20 ng/mL

Major + one minor or three minor criteria are required. Tryptase criterion is not valid if there is an associated hematologic (myeloid) neoplasm [9, 10]

2. CD2 and/or CD25 Expression: Normal mast cells do not express CD2 or CD25. Aberrant CD25 expression can be detectable by immunohistochemistry or flow cytometry. In flow cytometry, detection of mast cells requires acquisition of at least 500,000 or more events and appropriate gating strategies, and they may not be detectable by routine leukemia/lymphoma phenotyping. IHC can be performed in archival paraffin blocks. Serial sections should be evaluated for

tryptase and/or CD117-positive mast cells co-expressing CD25. CD2 is also aberrantly expressed, but it may be variably detectable and is especially low or even absent in mast cells in many cases of advanced disease [12].

3. KIT D816V Mutation: KIT encodes for the receptor of stem cell factor, which is the most important growth factor for mast cell growth and development. D816V somatic gain-of-function mutation is found in >90% of adult cases with systemic mastocytosis and approximately 30% of pediatric cutaneous mastocytosis [13]. The most sensitive method to detect this mutation is an allele-specific qPCR in bone marrow aspirate. Peripheral blood may yield wild-type results in patients with low mast cell burden unless very sensitive (not yet widely available) PCR techniques are used [14] and in patients with non-D816V KIT mutations. Therefore, mutation analysis studies should be performed on bone marrow cells when the blood test is negative.
4. Serum Tryptase >20 ng/ml: Tryptase is a relatively specific marker, as this enzyme is primarily synthesized by mast cells. Mature tryptases (mainly beta tryptase) are stored in mast cell granules and are released during mast cell activation [15]. Pro-tryptases (mainly alpha tryptase) are secreted constitutively from mast cells, resulting in a stable baseline serum level that reflects the total body burden of mast cells. Commercially available tryptase assays test for total (pro- and mature tryptases). Normal median serum or plasma baseline tryptase is approximately 5 ng/ml. Values greater than 20 ng/ml are typically found in systemic mastocytosis. Tryptase levels <20 ng/ml can be seen in patients with low mast cell burden, monoclonal mast cell activation syndrome, bone marrow mastocytosis, and cutaneous mastocytosis. An important aspect is that tryptase levels >20 ng/ml can also be seen in conditions other than mastocytosis, including hereditary alpha tryptasemia [16], chronic renal disease [17], and myeloid neoplasms [18]. Therefore, an elevated basal tryptase level is a minor (but not major) criterion of systemic mastocytosis.

Presence of at least the major plus one minor or three minor criteria is required to establish the diagnosis of systemic mastocytosis. In patients with hematologic disease, tryptase criterion is not valid, as it can be elevated due to the hematologic disease itself. Patients presenting mast cell activation symptoms who show CD25 expression in mast cells and/or KIT D816V mutation are termed to have monoclonal mast cell activation syndrome (MCAS) when all MCAS criteria are fulfilled [19–21].

Well-Differentiated Systemic Mastocytosis

A histopathologic variant termed “well-differentiated mastocytosis” was described in 2002, and consists of mast cells with a round, fully mature morphology, absence of CD25 expression, and usually lack of KIT mutations. This variant usually satisfies the diagnostic criteria due to the presence of the major criterion, demonstration of clonality by either Kit mutation or HUMARA assay, and elevated tryptase levels [22, 23]. However, the well-differentiated variant of mastocytosis can be detected in all WHO categories of mastocytosis including indolent mastocytosis and mast cell leukemia.

Classification

WHO recognizes seven categories of the disease [9]:

1. Cutaneous Mastocytosis: This category of disease is almost exclusively seen in children and means that the disease is limited to skin [4]. It should be noted that "mastocytosis in skin" is the preferred term for adult patients with skin lesions in whom systemic involvement cannot be ruled out because no bone marrow studies were performed. Cutaneous mastocytosis can present as MPCM, diffuse cutaneous mastocytosis or mastocytoma of the skin (Please see the Chap. 5 by Hartmann et al. in this book for more information).
2. Systemic Mastocytosis: This is the most common category in adults and means that the disease is detectable in an extracutaneous tissue, most often in bone marrow (see above for systemic mastocytosis diagnostic criteria). It has five subcategories.
   (a) Indolent Systemic Mastocytosis: This category of disease is characterized by the presence of systemic disease in bone marrow but absence of a hematologic disorder, multiple B findings, any C findings, and less than 20% mast cells in bone marrow aspirate smears. The life expectancy is similar to that in the general population**,** but mast cell mediator-related symptoms occur frequently. Rate of progression to a more advanced category is low (less than 5%).
   (b) Systemic Mastocytosis (SM) with Associated Hematologic Neoplasm (AHN): This category is diagnosed by demonstrating SM criteria as well as another coexisting hematologic disease meeting the WHO criteria. The AHN is often a chronic myeloproliferative disease (MPN-U), MDS, or MDS/MPN (CMML), but occasionally, a lymphoproliferative disease can also be diagnosed. In patients with ISM-AHN, the prognosis depends on the AHN. In advanced SM associated with AHN, the prognosis depends on both the SM and the AHN components of the disease.
   (c) Smoldering Systemic Mastocytosis: This category is marked by presence of 2 or 3 so called B-findings indicating large mast cell burden. First B finding is tryptase levels of >200 ng/ml and bone marrow infiltration of >30% mast cells in biopsy sections. As a second B-finding, splenomegaly and/or lymphadenopathy is frequently recorded without liver dysfunction or hypersplenism. Finally, signs of dysplasia or myeloproliferation in non-mast cell lineages may be found without an evidence of an overt hematologic disorder meeting WHO criteria. The smoldering type of SM is considered an intermediate category. Rate of progression to an advanced disease variant may be low but is not precisely known due to the rarity of this category of disease [24].
   (d) Aggressive Systemic Mastocytosis: This rare subtype (less than 5% of all cases) presents with C findings, reflecting organ damage (C-findings) resulting from tissue infiltration by immature mast cells. Involved tissues may include bone marrow (cytopenias: absolute neutrophils counts <1000/microliter, hemoglobin <10 g/dl, platelets <100,000/microliter), liver (hepatomegaly, portal hypertension, ascites, elevated liver function tests),

spleen (splenomegaly with hypersplenism), bone (lytic lesions >2 cm with pathologic fractures), and gastrointestinal (malabsorption with hypoalbuminemia and weight loss). The C-findings must be due to mast cell infiltration [25]. Sometimes, a bone marrow-related C-finding may be difficult to attribute with certainty to mast cell infiltration in patients with AHN.

(e) Mast Cell Leukemia: This is the rarest category with the poorest prognosis. Bone marrow typically shows diffuse dense infiltration with atypical mast cells. It is characterized by presence of >20% abnormal mast cells in bone marrow aspirate smears [26]. In patients with classical MCL, >10% mast cells are found in peripheral blood smears. If this is not the case (<10% mast cells of all circulating blood leukocytes), the diagnosis is aleukemic MCL.

3. Mast Cell Sarcoma: These are rare isolated solid mast cell tumors consisting of immature mast cells with local invasion. In most patients, mast cell sarcoma progresses to MCL within short time and the prognosis remains poor [27].

Prognosis

Prognosis for cutaneous mastocytosis is excellent. In 90% of the children, skin lesions resolve or improve spontaneously. The remaining 10% is persistent and may later be diagnosed with systemic mastocytosis. SM is suspected in children who keep skin lesions after adolescence, those with persistently elevated tryptase levels >20 ng/ml, hematologic abnormalities, or hepatosplenomegaly. These patients should be evaluated for consideration of a bone marrow biopsy and aspiration [28]. Otherwise, patients with typical childhood-onset mastocytosis do not require bone marrow biopsy. Prognosis for indolent systemic mastocytosis is good, and these patients have a life expectancy comparable to that in the general population [3]. Risk of progression to an advanced variety is rare (<5%). SM-AHN, ASM, and MCL are collectively termed as advanced mastocytosis. Prognosis in SM-AHN is poorer and depends on the AHN. ASM carries a poor prognosis with an estimated 50% survival rate of about 3 years. MCL has the poorest prognosis, with most cases being fatal within a year unless treated with intensive therapy or KIT-targeting drugs [29, 30]. A chronic form of MCL with long-term survival (over 5 years) has been described, which meets histopathologic criteria for MCL but without C-findings [31].

Treatment

Treatment of mastocytosis is explained in more detail in other chapters of this book. All categories of mastocytosis should be treated for mast cell mediator-related symptoms [32]. H1 antihistamines are used for itching, flushing, and prophylactic treatment of anaphylactic episodes. H2 antihistamines are recommended for those with gastrointestinal symptoms such as abdominal cramping, peptic ulcers, reflux, bloating, and diarrhea. Anti-leukotriene agents may be added in patients with refractory skin or GI symptoms. Oral cromolyn can be used as a mast cell stabilizer especially

in patients with gastrointestinal symptoms. Oral steroids may be effective in those with advanced disease with liver involvement or recurrent anaphylaxis. Omalizumab has been reported to be effective in preventing anaphylactic episodes [33, 34]. There is a clearly increased risk for anaphylaxis compared to the healthy background population, and the lifetime risk of anaphylaxis is approximately 40% in adult-onset mastocytosis (<10% in children-onset cases) [35]. Anaphylaxis may be associated with IgE-mediated (hymenoptera stings) sensitization or non-IgE-mediated drug reactions (such as NSAIDs, physical factors including exercise) or idiopathic [5]. Risk factors for anaphylaxis include IgE levels of >15, tryptase <40 ng/ml, absence of skin lesions, and male gender [36]. Self-injectable epinephrine should be prescribed for all patients. All patients with anaphylaxis should be evaluated thoroughly for an underlying, relevant IgE-mediated allergy, and relevant prophylactic measures should be taken (e.g. allergen avoidance or immunotherapy in patients with venom allergy) [37]. In this regard, it is worth noting that in patients with mastocytosis, it is sometimes difficult to document IgE involvement by conventional allergy tests. In patients with severe recurrent anaphylaxis (MCAS) without identifiable cause, treatment with omalizumab may be required to control symptoms. Treatment of advanced disease requires cytoreductive therapies such as IFN-alpha, cladribine [38], or tyrosine kinase inhibitor midostaurin [39]. Newer kinase inhibitors such as avapritinib [40] and a monoclonal antibody targeting Siglec 8 [41], a surface receptor with inhibitory signaling, are under clinical trial at the time of writing this text. Stem cell transplantation may also be considered in select cases [20].

Conclusions

Mastocytosis is a hematopoietic disorder of the mast cell progenitor resulting in pathologic accumulation and activation of mast cells. It has been increasingly recognized and diagnosed owing to increased public awareness, especially of low disease burden states presenting with mast cell activation symptoms or anaphylaxis, and refining of diagnostic criteria including availability of sensitive KIT D816V mutation detection techniques. Emerging therapies include cytoreductive avapritinib targeting KIT D816V mutation as well as those targeting mast cell activation such as omalizumab, midostaurin, or anti-Siglec 8. More research is needed in areas of therapeutics, biomarker discovery, and prognostic markers.

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Chapter 3
Clinical Approach to a Patient with Elevated Serum Tryptase: Implications of Acute Versus Basally Elevated Levels

Jonathan J. Lyons and Lawrence B. Schwartz

Abbreviations

AML	Acute myeloid leukemia
BST	Basal serum tryptase
CML	Chronic myeloid leukemia
CsU	Chronic spontaneous urticaria
FIP1L1/PDGFRA	FIP1-like-1/platelet-derived growth factor receptor-α fusion gene
GATA2	GATA binding protein 2
GBA	Glucosylceramidase
HαT	Hereditary alpha tryptasemia
HES	Hypereosinophilic syndrome
JAK2	Janus kinase 2 gene
JMML	Juvenile myelomonocytic leukemia
KIT	KIT proto-oncogene receptor tyrosine kinase
PAF	Platelet-activating factor
PAR	Protease activated receptor
PLCG2	Phospholipase C gamma 2 gene
PRSS22	Serine protease 22 gene
rh-SCF	Recombinant human stem cell factor
TPSAB1	Tryptase alpha/beta 1 gene
TPSB2	Tryptase beta 2 gene

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TPSD1	Tryptase delta 1 gene
TPSG1	Tryptase gamma 1 gene

Overview of Tryptases

Tryptases comprise a family of serine proteases with trypsin-like activity expressed predominantly by two allergic effector cell types: mast cells residing in tissues and, to a much lesser extent, in circulating basophils, where expression levels are up to 500-fold lower than those in mast cells [1–3]. Tryptases are translated as pre-pro-peptides requiring step-wise proteolytic processing to remove the pre- and then pro-peptide domains, and stabilization by heparin proteoglycans, in order to enable mature tetramer formation and enzymatic activity [4]. Upon formation, the stabilized mature tetramer is stored in secretory granules with other mediators of allergic reactions until cellular activation triggers granule release [5].

The five known paralogous genes encoding human tryptases evolved very recently in *Homo sapiens*, ostensibly through several gene duplication events; homologous orthologs are not present in other mammals, even in the most closely related of non-human primates [6]. All currently known human tryptase genes are located within or near the tryptase locus on chromosome 16p13.3 and include *TPSG1*, *TPSB2*, *TPSAB1*, *TPSD1*, and *PRSS22*. Of the identified human tryptases, α-tryptase encoded by *TPSAB1* and β-tryptases encoded by either *TPSAB1* or *TPSB2* are the only isoforms known to be secreted constitutively or released *en masse* during degranulation [7]. While the composition of the α- or β-tryptase isoforms encoded at *TPSAB1* appears to be skewed in different ethnic and racial groups, it is estimated that approximately 30% of individuals in the USA possess only β-tryptase-encoding sequences at both *TPSAB1* and *TPSB2* and thus are α-tryptase deficient [8].

While mature tryptases are retained within intracellular secretory granules, α- and β-pro-tryptases are constitutively secreted by mast cells and diffuse into the systemic circulation [5, 7] (Fig. 3.1). Whereas the serum half-life of mature tryptase has been characterized, the serum half-life of pro-tryptases is unknown [9]. Most individuals have approximately 5 ng/mL of pro-tryptase(s) in serum and do not have detectable mature tryptase in circulation. However, this can increase substantially during systemic immediate hypersensitivity reactions or anaphylaxis, where the rise is caused by release of mast cell granule contents, which includes mature tryptases. During such a reaction, levels of primarily mature tryptase(s) increase as reflected in the increase in total tryptase (pro + mature forms of α- and β-tryptases) as measured by the ThermoFisher ImmunoCAP® Tryptase assay. Using another assay that measures only mature forms of α- and β-tryptases, the ratio of mature to total tryptase is generally <10 in systemic anaphylactic reactions with the greatest elevations in serum tryptase, and this ratio can approach 1 in very severe reactions [10]. The immunoassay that is specific for mature tryptase is available only at Virginia Commonwealth University (LBS), and no assay exists that clearly distinguishes between α- and β-tryptases due to the substantial sequence homology between these two isoforms. Thus, when serum tryptase is measured clinically, the result reflects total tryptase, comprising almost exclusively pro-tryptases at a patient's clinical baseline.

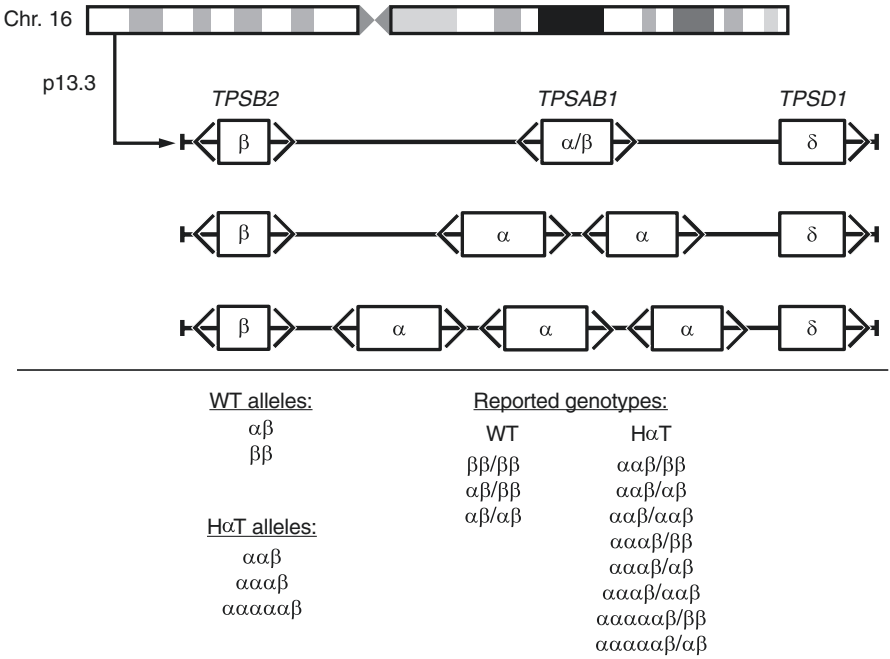

Fig. 3.1 Genetics of human tryptases. A schematic of the human tryptase locus at chromosome 16p13.3 (top) containing wild-type copy number or increased TPSAB1 copy number. Five currently reported alleles (bottom left) – two wild-type (WT) and three with increased copy number associated with hereditary alpha tryptasemia (HαT) – and resulting WT and HαT-associated genotypes (bottom right). (Data sources for models: https://swissmodel.expasy.org/repository/uniprot/P20231, https://www.rcsb.org/structure/1a0l tetramer, https://www.rcsb.org/structure/5f03 monomer)

There is a substantial body of literature examining the putative effects of mature tryptases on cells, tissues, and proteins, as well as on phenotypes in both in vitro and animal models, although demonstrable effects on human disease phenotypes in vivo have been modest. The reported properties of mature tryptase include, but are not limited to, recruitment of eosinophils (Eos) and neutrophils (PMN) [11], degradation of extracellular matrix proteins [12, 13], mitogenic activity on smooth muscle (SM) and fibroblasts [14, 15], promotion of angiogenesis [16], and stimulatory activity on nerves and epithelial cells [17, 18]. Potential proteolytic targets by which tryptase may mediate these effects may include, but are not limited to, fibrinogen [19, 20], kininogens [21–23], prostromelysin [24], complement factors 3 and 5 [25], cytokines [26], and protease-activated receptors (PAR) such as PAR2 [27] (Fig. 3.1).

Mast cells and tryptase proteolytic activity have been studied in a large number of animal models of disease. In an OVA asthma model, tryptases have been reported to contribute to airway hyper-responsiveness [28]. Indeed, an inhaled tryptase inhibitor showed some preliminary promise in reducing acute airway obstruction before stalling during a phase II clinical study [29]. Development of a second tryptase inhibitor was similarly halted for lack of efficacy in patients with ulcerative colitis, where it was hoped that it would limit overall disease activity [30].

In the context of anaphylaxis, it is believed that mature tryptases act as mast cell mediators contributing to symptoms of immediate hypersensitivity including vascular leak [31, 32]. While it is likely that tryptases at least modify many disease states and reactions such as these, the relative contribution of tryptases in the immunopathogenesis of asthma, inflammatory disorders such as colitis, or anaphylaxis in humans remains to be determined.

Heritable Conditions Leading to Elevated Serum Tryptase

Hereditary Alpha Tryptasemia (HαT)

In individuals for whom baseline serum tryptase (BST) levels have been extensively studied, a level above the upper limit of the normal range, 11.4 ng/mL, is present in approximately 5–7% of those populations [33, 34]. The majority of these studies have involved Caucasians, and the cause for this finding in most individuals is a genetic trait called hereditary alpha tryptasemia (HαT) that is caused by increased copies of *TPSAB1* encoding α-tryptase [35]. These gene replications have been seen only for α-tryptase-encoding alleles, with as many as four extra copies of *TPSAB1* being present in seven affected subjects from three generations of one family [36]. Among individuals with HαT, a gene–dosage effect on BST levels has been reported. Duplications yield average BST levels of 15 ± 5 ng/mL, triplications 24 ± 6 ng/mL, and the identified quintuplication 37 ± 14 ng/mL [37].

The penetrance of this genetic trait appears to be complete, as all reported individuals with HαT have had a BST level >8.0 ng/mL. However, a number of variably expressed clinical phenotypes have been reported among individuals with HαT (Table 3.1). Approximately half of reported individuals presented with a multisystem or syndromic presentation that has been called HαT syndrome (HαTS) [35, 36, 38]. These symptoms have also been reported with increased prevalence among individuals in a large Austrian cohort with elevated BST levels of unknown cause [33]. Several of these associated symptoms were validated in an unselected cohort [35] and are also commonly seen in the context of mast cell-associated disorders [39–41]. Between one-third to one-half of individuals report recurrent cutaneous symptoms with flushing and pruritus being predominant. Importantly, many individuals with HαT were reported to have urticaria and angioedema, symptoms frequently not reported in patients with clonal mast cell disorders. Up to one-quarter of individuals report having had moderate to severe systemic immediate hypersensitivity reactions, with reactions to stinging insects being the most common reported trigger affecting 14–22% of individuals studied.

Because of the repetitive nature of the tryptase locus and high sequence homology between paralogous genes, conventional next-generation sequencing, Sanger sequencing, and microarray technologies available clinically cannot accurately identify patients with HαT [7, 37]. However, a droplet-digital PCR-based genotyping assay has been developed and is now available to clinicians [35]. Because of the nature of the locus and the presence of isoform copy number variation among sub-

Table 3.1 Clinical features reported in association with hereditary alpha tryptasemia (HαT)

Manifestation	Reported prevalence[a]	Association supported in an unselected cohort[b]
Basal serum tryptase >8 ng/mL	100%	Yes
Chronic gastroesophageal reflux symptoms	56–77%	No
Arthralgia	44–45%	No
Body pain/headache	33–47%	No
Flushing/pruritus	32–55%	Yes
Irritable bowel syndrome (Rome III)	28–49%	Yes
Sleep disruption	22–39%	No
Systemic immediate hypersensitivity reaction	21–28%	No
Retained primary dentition	20–33%	Yes
Systemic venom reaction	14–22%	Yes
Congenital skeletal abnormality	11–26%	No
Joint hypermobility	0–28%	No
Positive tilt-table test	0–11%	No

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[a]For reported prevalence, ranges are derived from available data in three reports [35, 36, 38]

[b]Finding was identified as significantly associated with increased *TPSAB1* copy number in an unselected volunteer adult population

jects with a normal tryptase genotype, that is, wild-type (WT) genotypes may contain zero to two α-tryptase copies and two to four β-tryptase copy number, there is frequently confusion on the part of patients and clinicians in interpreting this test result. The assay detects β- and α-tryptase sequences from both *TPSB2* and *TPSAB1* within the tryptase locus. Wild-type (WT) tryptase genotypes contain four total gene copies from the two inherited haplotypes, each haplotype having one *TPSB2* and one *TPSAB1*. Since *TPSB2* has been observed to encode only β-tryptase, WT genotypes always contain at least two β-tryptase copies. The remaining two copies are either two β-tryptase, two α-tryptase, or one of each sequence, yielding the associated genotypes: ββ/ββ, αβ/αβ, and ββ/αβ. On HαT-associated alleles, an additional copy of α-tryptase is present on a single allele: ααβ for a duplication, αααβ for a triplication, and αααααβ for a quintuplication. *TPSAB1* quadruplications or other structural variants at these loci have not yet been reported. The three identified haplotypes may rarely be paired with one another, or more commonly with one of the two WT haplotypes, ββ or αβ, to yield a number of potential genotypes (Fig. 3.2). The most common misconception is that an individual with a genotype composed of 3α and 2β tryptase-encoding genes has a triplication, when in fact this individual has a duplication with the following genotype having ααβ and αβ alleles. While it is believed that HαT alleles were created via tandem gene duplication, this has never been observed; to date, all individuals identified with HaT have inherited this trait, and de novo duplications, although theoretically likely, have not yet been identified or described.

What role the increased BST and/or increased *TPSAB1* copy number may play in the multisystem complaints reported among affected individuals is currently unknown. In the relatively small number of individuals in whom bone marrow biopsies were systematically examined, a modest increase in mast cell

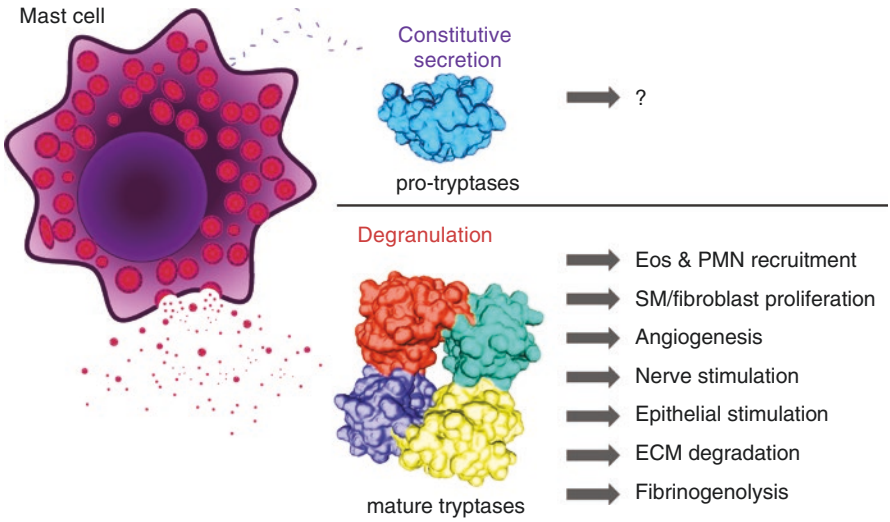

Fig. 3.2 Release of mature and pro-tryptase from mast cells have distinct mechanisms and effects. Monomeric pro-tryptases are secreted constitutively from mast cells and do not have known activity or function (top), whereas mature tetrameric tryptases are stored in secretory granules until mast cell activation and degranulation occurs (bottom). A number of functional activities relating to the serine proteinase activity of mature β-tryptases have been identified

number was reported relative to healthy volunteers [38], but this result has not yet been replicated in unselected populations. Furthermore, clonal mast cell disease has been reported in association with HαT [36]. Thus, confirmation of this genetic trait does not exclude the possibility of another cause for symptoms and/or increased serum tryptase, including clonal mast cell disease. Accordingly, it is imperative to exercise clinical judgment, and in patients with severe or pervasive signs or symptoms including, but not limited to, hematologic dyscrasia, lymphadenopathy, or hepatosplenomegaly (Table 3.2), the diagnosis of HαT as the sole cause for clinical symptoms should be considered as one of exclusion.

Other Heritable Disorders Associated with Elevated Serum Tryptase

While increased *TPSAB1* copy number appears to account for a majority of patients with inherited increases in BST, a few additional single gene disorders have been identified in which affected individuals have increases in BST. Individuals with heterozygous *PLCG2* deletions that cause hyperactivation of mast cells in the cold and associated cold evaporative urticaria have modest increases in BST (unpublished data); it is not known whether this is a mature or a pro-tryptase. Individuals with the protean disorder GATA2 haploinsufficiency also frequently have elevated BST [43]. However,

Table 3.2 Signs and symptoms warranting additional clinical workup for clonal myeloid or mast cell disease

Hepatosplenomegaly
Lymphadenopathy
CBC abnormalities Thrombocytopenia Anemia Pancytopenia Polycythemia Neutrophilia Hypereosinophilia (AEC >1500 cells/μL)
Anaphylaxis Idiopathic Insect venom-triggered Severe reactions with syncope and/or hypotension
Urticaria pigmentosa
Eosinophilic tissue infiltration and/or inflammation
Premature osteopenia/osteoporosis or pathological fracture
BST discordant with *TPSAB1* copy number

it is unclear whether this is related to the genetic lesion directly or whether increases are indicative of clonally expanded myeloid cells that are commonly seen in these patients. Finally, one individual with Gaucher's disease due to heterozygous loss-of-function mutations in *GBA* has been reported to have persistently elevated BST [42]. While this was complicated by an acute increase in serum tryptase due to an immediate hypersensitivity reaction to imiglucerase, the enzyme replacement product the patient had received, BST elevations persisted after he was transitioned to an alternative replacement regimen.

Somatic Diseases Leading to Elevated Serum Tryptase

Mastocytosis and Clonal Mast Cell Diseases

Clonal myeloid disease is frequently associated with elevated basal serum tryptase, with clonal expansion of mast cells as seen in mastocytosis being the archetypal disease in this context [44]. Mastocytosis can be confined to the skin (cutaneous mastocytosis) or present with evidence of more widespread involvement in extracutaneous tissues (systemic mastocytosis); specific consensus criteria have been established for the diagnosis of systemic and cutaneous mastocytosis [45] (Table 3.3). Both cutaneous and systemic mastocytosis have a number of phenotypic subcategories that have implications for prognosis and management that are addressed elsewhere in this textbook.

The majority of individuals with systemic mastocytosis have elevated BST; as such, BST >20 ng/mL is one of four minor criteria used for diagnosis. Based on

Table 3.3 WHO diagnostic criteria for systemic mastocytosis[a]

Major criterion
Multifocal dense aggregates of mast cells (≥15/HPF) in bone marrow or extracutaneous sections
Minor criteria
>25% of the mast cells are spindle-shaped, atypical, or immature in morphology
KIT p.D816V or other *KIT* GOF mutation present.
Aberrant expression of CD2 and/or CD25[b]
Total serum tryptase >20 ng/mL[b]

[a]One major and one minor or three minor criteria must be met for diagnosis
[b]Invalid when another clonal myeloid disorder is present

available data, tryptase genotyping may lower this threshold among individuals with WT genotypes who do not have HαT. However, the consensus recommendations do not take into account tryptase genotyping at this time. Given the rarity of alleles with greater than two copies of *TPSAB1*, in the absence of other disease processes known to affect BST, such as renal failure, BST levels >30 ng/mL are likely to represent clonal myeloid disease, and BST >50 ng/mL is predominantly associated with clonal myeloid and/or mast cell disease.

In some symptomatic individuals, two minor criteria for the diagnosis of systemic mastocytosis indicative of clonal mast cell disease, namely the gain-of-function *KIT* p.D816V missense variant or aberrant expression of CD25, may be present. The majority of these individuals have been reported with elevated BST. However, serum BST and mast cell burden in these patients – which positively correlate with overall mast cell burden in clonal mast cell diseases – are frequently both inadequate to achieve the diagnosis of mastocytosis [46].

Individuals with clonal mast cell disease are at risk for idiopathic and antigen-mediated anaphylaxis, in particular following envenomation by stinging insects [47–49]. The lifetime prevalence of anaphylaxis among individuals with systemic mastocytosis approaches 50%, at least twice the prevalence reported in HαT and at least tenfold more than the prevalence estimates for the general adult population in the USA and England [50, 51].

Hypereosinophilic Syndromes

Individuals with myeloproliferative variant hypereosinophilic syndrome (HES) and the closely related chronic eosinophilic leukemia (CEL) associated with *FIP1L1–PDGFRA* gene fusion have increased numbers of mast cells and elevated BST [52, 53]. Moreover, such bone marrow mast cells also aberrantly express CD25, but do not typically form dense mast cell aggregates as is commonly seen in systemic mastocytosis [54]. Because of similarities with a subset of patients with *KIT* p.D816V missense-associated systemic mastocytosis who present with concomitant

peripheral eosinophilia, these distinct clinical entities can sometimes be conflated. However, it is important to distinguish between these two disorders, as the natural history and severity of disease, the risk of insect venom-triggered anaphylaxis, and the choice of therapy are substantively distinct. Importantly, hypereosinophilia of unknown significance with elevated serum tryptase has also been reported in association with both the *FIP1L1/PDGFRA* and *KIT* p.D816V missense, as well as the recurrent gain-of-function *JAK2* p.V617F missense frequently identified in myeloproliferative diseases [55].

Idiopathic HES – generally defined as persistently having greater than 1500 eosinophils/μL in peripheral blood with evidence of related tissue inflammation and damage, in the absence of an identifiable genetic, infectious, or iatrogenic cause – frequently present with elevated BST [52, 56]. In one of the largest studies examining this association, approximately 20% of individuals with idiopathic HES had elevated BST, while BST was within the normal range for virtually all those identified with lymphocytic variant HES. These and other data suggest that elevated BST identifies a myeloproliferative basis for HES in these patients [57]. Whether these individuals represent a more indolent form of myeloproliferative HES or clonal mast cell disease with hypereosinophilia is currently unknown.

Other Myeloid Dyscrasias

In addition to diseases in which mast cell expansion is associated with elevated BST, a number of other myeloproliferative diseases are associated with high serum tryptase. Approximately 30–40% of patients with acute and chronic myeloid leukemia (AML and CML) have been reported with elevated BST [58, 59], and a number of studies have reported overexpression of *TPSAB1* in malignant clones from patients with AML [57, 59–61], juvenile myelomonocytic leukemia (JMML) [62], and CML [63]. In AML, sustained elevations in BST during treatment are associated with a high risk for relapse – likely indicating persistent disease – and in certain forms of CML, a poorer prognosis [64, 65]. While generally these myeloproliferative neoplasms are often distinguishable from individuals with mastocytosis or myeloid HES on the basis of clinical presentation, it is helpful to keep in mind that serum tryptase may derive from malignant non-mast cell clones of myeloid lineage.

Other Conditions Associated with Increased Serum Tryptase

A positive correlation has been reported between BST and age, body mass, and gender, where greater body mass and age as well as gender have been associated with modest effects – between 0.2 and 1.1 ng/mL – on serum levels [66, 67]. The presence of wild-type α-tryptase containing alleles is also associated with an

approximately 0.5 ng/mL increase in BST per allele [66]. Chronic kidney disease has been reported to cause significant elevations in BST, and confirmation of intact renal function is important in the evaluation of individuals with elevated BST [68, 69].

Up to 10% of individuals with chronic spontaneous urticaria (CsU) have also been reported with BST >11.4 ng/mL, correlating in part with disease severity [70, 71]. Genetic testing for increased *TPSAB1* copy number has not been undertaken systematically in CsU patients, and it is possible that this trait or other heritable or acquired causes for elevated BST may lead to this association. Both in renal failure and CsU, it has been reported that individuals with elevated serum tryptase have more pruritus [68], and in one study of CsU, there are more systemic complaints [70].

Certain infections or responses to therapies have also been reported to cause sustained elevations in BST. Individuals infected with *Onchocerca volvulus* treated with ivermectin have been reported to display an approximately 60% rise in serum tryptase that is sustained during induction of therapy and correlates with mast cell infiltration of the skin and subsequent inflammatory response [72]. Modest elevations in serum tryptase have been reported among individuals infected with *Strongyloides stercoralis* [73]. It is likely that other parasitic infections and/or their treatment(s) may also lead to serum tryptase elevations.

Finally, administration of recombinant human stem cell factor (rh-SCF) or a methionylated form of this cytokine has led to local and systemic reactions that mimic immediate hypersensitivity [74, 75]. Prolonged administration (1–2 weeks) of rh-SCF has been shown to result in elevated BST associated with systemic mast cell expansion in tissues.

Mast Cell Activation

Tryptase Levels in Diagnosis

During systemic immediate hypersensitivity reactions that may occur spontaneously as seen in idiopathic anaphylaxis, or in response to antigen challenge as seen with venom allergy, a number of mediators contained in mast cell secretory granules are released, leading to some of the symptoms commonly attributed to mast cell activation [76]. Among these mediators, tryptase is the most abundant granule protein [77]. Given the relatively slower rise and longer half-life of tryptase in serum – 90–120 min for tryptase compared to the 1–6 min half-life of histamine or 3–13 min half-life of platelet-activating factor (PAF) [78] – total serum tryptase levels measured within two half-lives, or approximately 4 hours after symptom onset, is currently the most precise clinical laboratory test to confirm the diagnosis of systemic mast cell-mediated immediate hypersensitivity reactions (Fig. 3.3). The current consensus recommendation is that an acute serum tryptase level should be greater than $1.2 \times \text{BST} + 2$ ng/mL to be clinically significant and consistent with mast cell

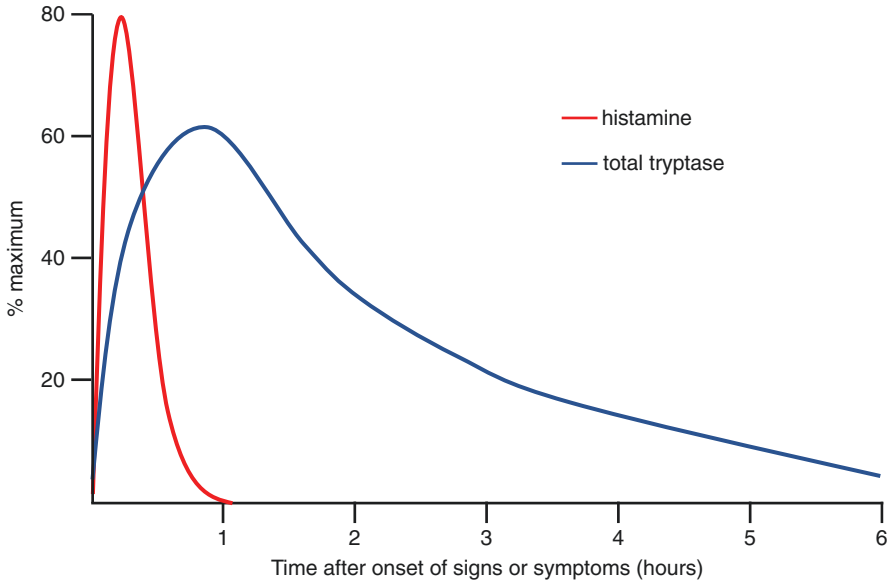

Fig. 3.3 Idealized time-course and magnitude of histamine and tryptase appearance in the serum following activation and degranulation of mast cells in tissues during severe insect sting-triggered systemic anaphylaxis

degranulation [79]. Although this algorithm seems to have a high positive predictive value, the negative predictive value varies with reaction severity, where minimal serum tryptase increases in more severe reactions have a better negative predictive value. If a BST level has not been obtained prior to the acute event, this can be established at least 24 hours after all signs and symptoms have resolved. An alternative assay is the measurement of mature tryptase in peripheral blood within 4 hours of clinical onset, which would be indicative of mast cell and/or basophil degranulation [5]. While this test appears to be less sensitive than the acute versus baseline total tryptase algorithm described above, it might be useful when there is no baseline sample available, for example postmortem cases, or cases in which a patient does not return to have a baseline sample obtained. No consensus recommendation exists with regard to its clinical use.

Several studies have indicated that greater increases in serum tryptase levels are associated with more severe anaphylaxis [80, 81]. However, some individuals who develop systemic anaphylaxis may not have a rise in acute serum tryptase above the 1.2 × BST + 2 ng/mL cut-off. This is more common when systemic anaphylaxis is less severe, particularly in the absence of hypotension, when acute blood is collected outside of the 4-hour window, or when a BST level is collected too soon after a systemic reaction. Also, food-induced allergic reactions seem to be less likely than parenteral antigens, for example, insect venoms, to produce an elevated acute serum tryptase level. Serum tryptase levels have been reported to increase significantly as a percentage of baseline levels in a majority of peanut allergic adults

undergoing food challenge [83]. While the median increase observed among those who experienced anaphylaxis was more than 70% above baseline, this failed to achieve the current consensus threshold for diagnosis in most patients due to low BST levels (median ~4 ng/mL). Small but reproducible increases in serum tryptase during food allergic reactions have also been reported in shrimp-allergic patients, where only 4 of 12 individuals who experienced anaphylaxis following challenge met consensus criteria, despite a median increase of 40% over basal levels [84]. Why systemic rises in serum tryptase are of lesser magnitude among certain individuals or in response to certain antigens such as foods remains speculative but may be a product of dosage, pathway of delivery and location of mast cells being activated, preferential involvement of basophils (which have less tryptase than mast cells) or other effector cells, as well as other host or cell intrinsic factors.

Elevated Tryptase as a Risk Factor

In addition to being a diagnostic tool for the evaluation of patients with mast cell-related disorders and anaphylaxis, the presence of elevated BST has also been identified as a risk factor for certain allergic disorders and reactions, including anaphylaxis [85]. Multiple studies have identified an association between elevated BST and the clinical severity of allergic reactions to stinging insects (e.g., hymenoptera species), commonly called venom allergy, where there is a positive correlation between BST and severity of anaphylaxis [33, 47, 86–88]. For reasons that are incompletely understood, a strong association likewise exists between clonal mast cell disease and venom allergy even in the absence of elevated BST. Many individuals with elevated BST and venom allergy have clonal mast disease as the underlying etiology for this observed association, although individuals with venom allergy have not yet been systematically evaluated for other causes of BST elevation, such as HαT.

Outside of venom allergy and anaphylaxis, there are limited data correlating BST levels in patients with other clinical allergic disorders. One study in children with food allergy, demonstrated a positive correlation between elevated BST and anaphylaxis severity where a BST >14.5 ng/mL identified 90% of children who has a history of moderate to severe anaphylaxis to foods [89].

Two other relatively small studies reported an elevated BST to be present in 12–17% of individuals with idiopathic anaphylaxis in whom clonal mast cell disease could not be identified; this prevalence is at least twice as high as that reported in the general population [90, 91]. There are not yet published studies examining potential causes for elevated BST among individuals with idiopathic anaphylaxis.

In two retrospective clinical studies, a history of anaphylaxis among individuals with elevated BST was reported in 21–36% of individuals [33, 92]. While these individuals were not systematically evaluated for clonal mast cell disease, clonal disease alone is unlikely to fully explain the association. In the larger of the two studies, nearly 200 individuals out of approximately 15,000 (1.3%) were reported from a general clinical allergy practice to have a BST >11.4 ng/mL. Were this to

reflect the underlying clonal disease, the prevalence in this population would be approximately 100 times higher than current estimates for the prevalence of mastocytosis [93]. See Table 3.4 for a summary of inherited and acquired conditions associated with baseline and/or acutely increased serum tryptase levels.

Falsely Elevated Serum Tryptase Measurements

Historically, heterophilic antibodies, namely, human anti-mouse antibodies (HAMA) that can occur following exposure to chimeric antibodies or extensive environmental exposure to mice, could interfere with and lead to falsely elevated serum tryptase measurements [94–97]. A similar phenomenon has been reported in patients who are rheumatoid factor positive [94]. However, ThermoFisher has been adding a heterophilic antibody suppressor to their commercial assay for nearly a decade, making false-positives uncommon, and in the late 2018 altered the detection mAb from being an intact IgG to its $F(ab')_2$ fragment to further reduce the occurrence of false positives.

Table 3.4 Causes for basal or acute elevation in serum tryptase and associated clinical disorders

Heritable causes	Acquired causes	Associated disorders
Hereditary alpha tryptasemia[a]	*Clonal myeloid disease*	Venom allergy[a]
GATA2 haploinsufficiency	Mastocytosis[a]	Idiopathic anaphylaxis[a]
PLCG2 deletions (PLAID)	Cutaneous	Chronic spontaneous urticaria
Gaucher's disease (*GBA* LOF)	Systemic	Mast cell activation syndrome[a]
	Mastocytoma	
	Hypereosinophilic syndromes	
	Myeloproliferative variant	
	Idiopathic	
	Chronic eosinophilic leukemia	
	Myeloid leukemias	
	Mast cell sarcoma	
	Myelodysplastic syndrome Myelofibrosis and refractory anemias	
	Other	
	IgE-mediated immediate hypersensitivity[b]	
	Renal failure	
	Parasitic infection	
	rh-SCF administration	

[a]Mast cell activation in these conditions can also result in an acute rise in serum tryptase
[b]IgE-mediated immediate hypersensitivity reactions in the absence of the other listed conditions are associated only with acute rises in serum tryptase

Inadvertent activation of basophils may potentially occur during blood processing and, in theory, lead to a falsely elevated increase in serum tryptase, although this has never been reported. While tryptase expression in basophils is highly variable between donors [98], the total number of basophils in blood is low (normal range is 0–300 cells/μL), and the mass of tryptase in these cells is modest [2]. Thus, even if all basophils in a blood sample became inadvertently activated during processing, the incremental rise for individuals with a normal concentration of blood basophils would be approximately 10 ng/mL.

Summary Recommendations

When evaluating a patient with an elevated BST, it is critical to exercise clinical judgment in order to stratify patients based on initial clinical presentation and symptomatology. There are a number of clinical and laboratory findings that are suggestive of clonal myeloid disease, which include, but are not limited to, hepatosplenomegaly, lymphadenopathy, urticaria pigmentosa, tissue eosinophilia, osteoporosis, premature bone loss or pathologic fracture, and significant CBC abnormalities such as cytopenias or expansion of myeloid lineages. A clinical history of venom-associated or idiopathic systemic anaphylaxis, particularly if hypotensive syncope has occurred, is more suggestive of an underlying clonal mast cell disease, while the presence of urticaria and/or angioedema makes a diagnosis of clonal disease less likely but does not exclude the possibility.

A concerning history and/or presence of these findings should prompt additional workup independent of the level or degree of BST elevation. Depending on the specific presentation, this would include bone marrow biopsy and genetic testing for the *KIT* p.D186V missense, and if significant eosinophilia (AEC >1500 cells/μL) or polycythemia were present, *FIP1L1–PDGFR* gene fusion or *JAK2* p.V617F missense testing should also be considered, respectively (Fig. 3.4). Tryptase genotyping for HαT should be considered in patients with BST >8 ng/mL and may be of particular use in stratifying symptomatic individuals with tryptases ranging from 10 to 20 ng/mL in whom there are no clinical or laboratory findings of clonal disease, or in individuals with mild to moderate symptoms but a BST >20 ng/mL. Those with a history of venom anaphylaxis or a systemic immediate hypersensitivity reaction resulting in hypotensive syncope still warrant workup for clonal mast cell disease regardless of the genotyping result. Individuals with elevated BST in the absence of an increased *TPSAB1* copy number, even when less than 20 ng/mL, or who present with discordance of BST and tryptase genotype (Table 3.5), where BST is in excess (>50%) of what is described for a given *TPSAB1* genotype, likewise should be evaluated for clonal disease. A clinical workflow utilizing tryptase levels and genotyping in the workup of patients with suspected clonal mast cell disease is provided (Fig. 3.4).

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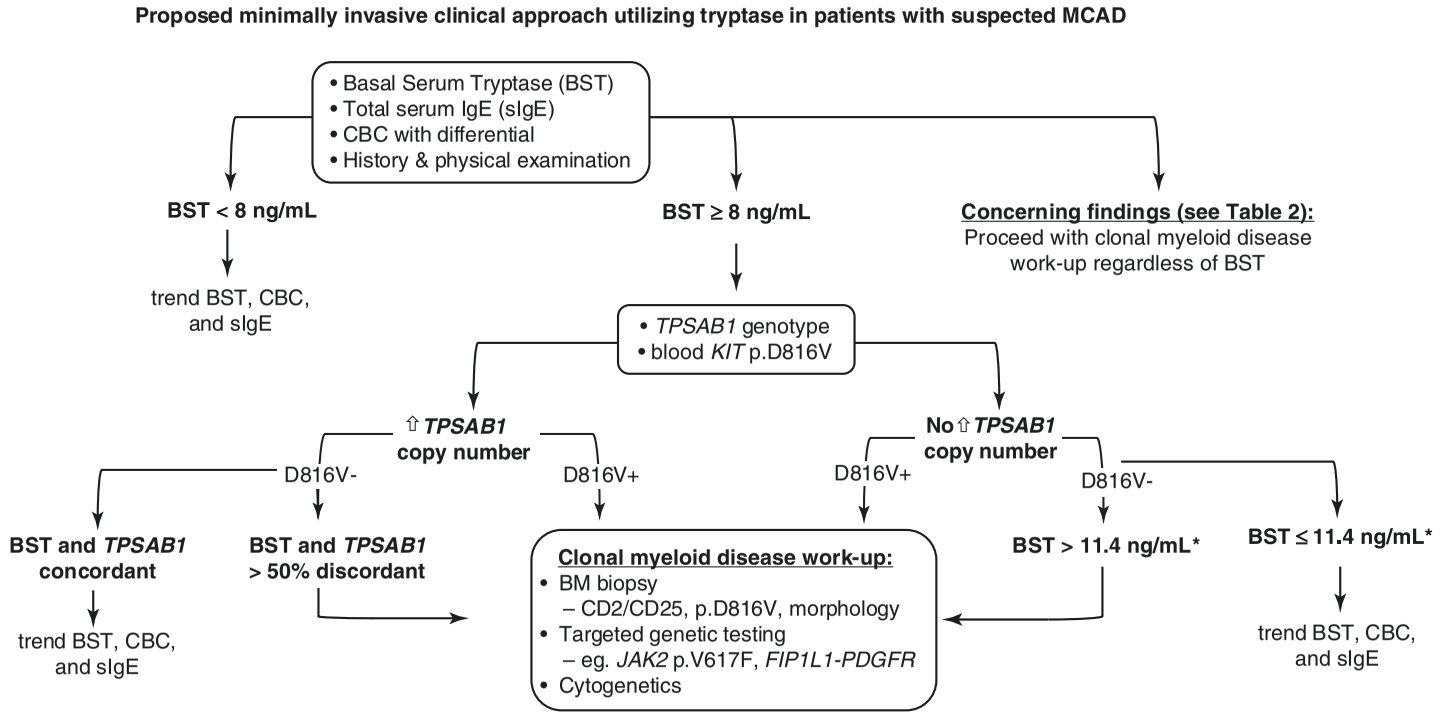

*The upper limit of normal may be lower than 11.5 ng/mL, but has not yet sufficiently been studied in the context of HαT.

Fig. 3.4 Proposed workflow utilizing tryptase levels and genotype for the evaluation of patients with suspected mast cell-associated disorders. (*The upper limit of normal may be lower than 11.5 ng/mL, but has not yet sufficiently been studied in the context of HαT)

Table 3.5 Basal serum tryptase by extra *TPSAB1* copy encoding α-tryptase

Additional copy number	0	1	2	3	4
Tryptase Genotypes (*TPSAB1*, *TPSB2*)	β,β/β,β; α,β/β,β; α,β/α,β;	αα,β/β,β; αα,β/α,β	αα,β/αα,β; ααα,β/β,β; ααα,β/α,β	ααα,β/αα,β	αααα,β/β,β; αααα,β/α,β
BST (ng/mL) Median (range)	4.1 (0–14.4)	14.5 (8–31.5)	21.7 (14–39.5)	27.3 (23.4–40)	37 (25.5–62.7)

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Chapter 4
Urinary Markers of Mast Cell Disease and Their Role in Diagnosis and Management

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Urinary Markers of Mast Cell Disease and Their Role in Diagnosis and Management

Leukotrienes

Measurement of urinary (U) leukotriene (LT)E4 (ULTE4) is a sensitive and noninvasive method that can be used to quantitate whole-body production of cysteinyl leukotrienes (CysLT), and it reliably reflects short-term changes in LTC4 secretion [1, 2]. Moreover, there is no diurnal variation in the levels of ULTE4 [3]. ULTE4 has been measured by enzyme immunoassays [3] and, more recently, by liquid chromatography, followed by tandem mass spectrometry (LC-MS/MS) [4] with levels expressed as picograms LTE4 per milligram of creatinine. This normalization to creatinine controls for urine dilution and allows measurements to be made using small volumes of urine (instead of 24-hour collections) that can more easily be obtained contemporaneously with the occurrence of symptoms.

The cascade of leukotriene (LT) mediator production via the 5-lipoxygenase pathway begins with the derivation of arachidonic acid (AA) from membrane phospholipids and continues with subsequent conversion of AA to 5-hydroperoxyeicosatetraenoic acid and LTA4, an unstable intermediate, by membrane-bound 5-lipoxygenase and 5-lipoxygenase-activating protein. In certain cells, LTC4 is then generated from LTA4 by the action of LTC4 synthase with incorporation of glutathione. The other pathway for LTA4 metabolism occurs primarily in neutrophils and monocyte/macrophages yielding LTB4. LTC4 is then rapidly converted to LTD4 and subsequently to the stable final metabolite LTE4 by the enzymes gamma-glutamyl transpeptidase and a dipeptidase [5, 6]. LTC4 is produced

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at low rates physiologically and is rapidly metabolized to LTD4 and LTE4 in the vasculature [2].

LTs are primarily produced by mast cells (MCs), basophils, and eosinophils, and although not stored in these cells, LTC4 is rapidly generated after stimulation, although transcellular biosynthesis has been reported by other cell types such as platelets and endothelial cells [7]. The levels released by MCs (0.01–0.1 pg/cell) on a molar basis are approximately 1/30th the amount of histamine released following activation with anti-IgE [8]. Purified human lung MCs produce about ten times as much LTC4 as do purified basophils (200 vs. 20 pg/10^6 cells) [8]. LTC4 is also the main 5-lipooxygenase pathway metabolite synthesized by eosinophils [9], with subsequent metabolism to LTD4 and LTE4 [10]. After preincubation with IL-3 or IL-5, eosinophils will also produce LTC4 upon subsequent stimulation with formyl-methionyl-leucyl-phenylalanine (FMLP), C5a, or platelet-activating factor (PAF) but generate at least one order of magnitude more LTC4in response to FMLP than that produced by stimulation with C5a or PAF [11]. Purified populations of basophils (45.6 +/− 22.6 ng/10^6 cells) and eosinophils (46.5 +/− 11.7 ng/10^6 cells) generate approximately the same amount of LTC4 when stimulated with calcium ionophore [12]. The eosinophil's production of substantial amounts of CysLT is clinically important in asthma [13].

Anaphylaxis, Asthma, Mast Cell Activation Syndrome: Non-SM Conditions Associated with Increased Urinary Excretion of LTE4

Increased levels of urinary ULTE4 have been reported in a number of non-mastocytosis conditions notably in anaphylaxis, asthma, and, more recently, mast cell activation syndrome (MCAS). A series of patients having anaphylactic reactions were found to have 5.5- to 52-fold increases in urinary CysLT during the reactions [14], where the known effects from LT (smooth muscle contraction and microvascular leakage) contribute to symptoms [15].

Significantly elevated excretions of both ULTE4 and the urinary PGD2 metabolite 9α, 11βPGF_2 also were found in a series of 32 patients with anaphylactic episodes when compared with asthmatic patients and healthy controls. There was a significant correlation between maximum urinary concentrations of ULTE4 and 9α, 11βPGF_2 in all the patients during the anaphylaxis event ($r = 0.672$, $p = 0.005$). Significantly higher levels of ULTE4 were found in those patients with anaphylactic *shock* when compared to patients without anaphylactic *shock* (863 pg/mg Cr vs. 552 pg/mg Cr, $p = 0.002$). In these same groups, there was no significant difference in concentrations of eosinophil-derived neurotoxin and LTB4 glucuronide, suggesting that eosinophils did not contribute to the rise in ULTE4 [16].

After provocation testing of patients with a history of anaphylaxis with the suspected triggering antigen, a significant increase above baseline of ULTE4 was observed in the first 3 hours after the challenge as well as 3–6 hours after the challenge, whereas for 9α, 11βPGF_2, a significant increase above baseline was found

only in the first 3 hours after the challenge. At these time points, there was no change in the serum tryptase concentrations [16].

In other conditions, parallel changes between reported excretion of ULTE4 and 9α,11β-PGF_2 were found; however, divergences between excreted levels of these mediators have also been reported. For example, in patients with aspirin-exacerbated respiratory disease (AERD), at the time of reactions to a COX-1 inhibitor, *parallel increases* in PGD2 and LTC4 metabolites were found [17, 18]. AERD patients treated with omalizumab, a monoclonal antibody against Il-5, showed significantly *decreased* concentrations of *both* ULTE4 and PGD2-M [19]. A similar pattern is seen in aspirin-intolerant asthmatic patients who have significantly higher levels of both ULTE4 and PGDM (a metabolite of PGD2) during reactions to aspirin [20].

However, no increase in ULTE4 levels was reported during exercise-induced bronchospasm in asthmatic children, whereas urinary excretion of 9α,11β-PGF_2 was increased significantly [21, 22]. In another example of divergent mediator excretion, wine-sensitive asthmatics challenged with high- but not low-sulfite-containing wines showed a significant increase in the urinary 9α, 11βPGF_2 without a significant accompanying change in ULTE4 with either high- or low-sulfite wine [23].

Control of mast cell activation syndrome in a patient with normal tryptase values but elevated urinary 9α,11β-PGF_2 and ULTE4 using a combination of imatinib and aspirin has been associated with parallel reductions of both urinary 9α,11β-PGF_2 and LTE4 concentrations [24].

ULTE4 Measurements in Mastocytosis

The consensus proposal for the diagnosis of mast cell disorders published by an expert panel in 2012 did not include a cutoff value for ULTE4 as a criterion for systemic mastocytosis (SM) or mast cell activation syndrome (MCAS) [25].

The 95th percentile for measurement of urinary excretion of ULTE4 by liquid chromatography, followed by tandem mass spectrometry (LC-MS/MS), among normal volunteers is <104 pg/mg creatinine (Cr) [4]. Because ULTE4 excretion is expressed as pg/mg Cr, levels can now be measured on random urine specimens, removing the need for 24-hour urine collection. This simplification allows a closer contemporaneous measurement of this important mediator during episodic MC mediator release. The result of ULTE4 excretion by LC-MS/MS compares closely to that reported in another group of healthy controls (80+/−7 pg/mg Cr) that utilized a peptidoleukotriene immunoaffinity resin to first purify LTE4, followed by enzyme immunoassay [26]. In the same study, a ULTE4 value of 103.9 pg/mg Cr was reported for healthy children (age 3–12 years).

ULTE4 concentrations were examined using LC-MS/MS in a cohort of over 400 patients referred for allergic disease evaluations. In this population, 66 patients (16.5%) were diagnosed with SM. The median ULTE4 concentration was significantly higher among patients with SM than in the non-SM group (97 vs. 50 pg/mg

Cr; P <0.01). The elevated level was 48% sensitive and 84% specific for SM [4]. The combined measurements of ULTE4, urinary 9α, 11βPGF_2, and N-methyl histamine (N-MH) improved SM diagnostic sensitivity to 97% with little change in specificity [4], a result that was not significantly improved by the addition of measuring serum tryptase [27]. Patients with SM have higher mean ULTE4 levels compared to a cohort of non-mastocytosis patients reporting symptoms that possibly could be ascribed to excessive mast cell mediator release including "spells," abdominal pain, angioedema, hives, pruritus, drug allergy, dermatographia, food intolerance, and exercise-induced asthma [28].

A study of nine SM patients, including patients with high and with low disease activity by symptom score, showed increased cysteinyl LT excretion, including LTB4 and LTC4-D4-E4, in both SM groups compared to a group of 11 healthy controls. In this series, cysteinyl LT values correlated with urinary N-MH excretion as well ($r = 0.536$; $p = 0.005$). Although LTB4 was also increased in both mastocytosis groups, there was no correlation to urinary N-MH [29] nor to disease activity.

Summary

MCs are a source of cysteinyl LT (CysLT), and because of their greatly increased numbers in SM, they are likely the predominant source in this condition. The ULTE4 can be used to quantitate whole-body production of CysLT, and it reliably reflects short-term changes in LTC4 secretion. When measured along with urinary N-MH and 9α,11β-PGF_2, the combination of urinary mediators has high sensitivity and specificity for SM that is not increased by additionally measuring the serum tryptase level. The ability to measure ULTE4 on random urine specimens simplifies sample acquisition and allows measurements contemporaneously to MC mediator release events.

Histamine

Histamine (2-[4-imidazolyl]-ethylamine) is an endogenous amine created by the removal of a carboxylic acid residue from the amino acid L-histidine by the enzyme histidine decarboxylase (HDC). Histamine may be produced by several cell types expressing HDC including mast cells, basophils, gastric enterochromaffin-like cells, histaminergic neurons, platelets, dendritic cells, and lymphocytes. Mast cells and basophils store large quantities of histamine in secretory granules, whereas other cell types such as lymphocytes do not store histamine intracellularly and only secrete histamine after synthesis. Mast cells and basophils release histamine on degranulation in response to immunologic and nonimmunologic stimuli [30, 31]. The classic pathway for histamine release involves immediate-type hypersensitivity responses, whereby antigen exposure generates antigen-specific IgE antibodies that attach to the high-affinity receptors on the surface of mast cells and basophils.

Subsequent antigen exposure binds and crosslinks these receptors, resulting in the release of large amounts of histamine (10^{-5}–10^{-3} mol/L) during the early stages of an allergic response [31, 32].

Once released, histamine is rapidly metabolized (half-life 1 minute) via two enzymatic pathways. Histamine is primarily metabolized by histamine N-methyltransferase (HNMT), which is an S-adenosyl-methionine-dependent enzyme responsible for 70–80% of histamine biotransformation. HNMT acts as a catalyst for the transfer of a methyl group from S-adenosyl-L-methionine to histamine, resulting in the formation of N-methylhistamine. N-methylhistamine (N-MH) is then metabolized further by monoamine oxidase to N-methylimidazole acetic acid, which is then excreted in the urine. HNMT is found in tissues throughout the body [31, 33]. The remaining 20–30% of histamine is metabolized by diamine oxidase (DAO). DAO is a membrane glycoprotein that is mainly found in the kidney and colon. DAO is stored in plasma membrane vesicles and is released upon stimulation to oxidatively deaminate histamine and other substrates. DAO converts histamine to imidazole acetaldehyde, which is then subsequently converted to imidazole acetic acid and conjugated with ribose phosphate [31, 33]. Elevated plasma histamine levels in SM have been reported for decades, but determination of such levels has not proven to be reliable to screen patients for mastocytosis [34]. However, measurement of the urinary histamine metabolites N-methylhistamine (N-MH) N-MH and N-methylimidazole acetic acid, rather than measurement of urinary histamine, has been shown to correlate with serum tryptase levels and bone marrow biopsy findings in multiple studies [35–39].

Oranje et al. found that in 37 patients with elevated levels of urinary N-MH, the optimal predictive value for detecting mast cell aggregates in the bone marrow biopsy was an N-MH level of 297 μmol/mol creatinine at which the specificity was 84% and sensitivity was 67% [36]. In a study by van Toorenenbergen and Oranje, involving 161 different patients, a significant correlation was demonstrated between serum tryptase and urinary N-MH levels. Of these 161 patients, 13 patients had retrievable bone marrow biopsies, and significant differences were found for both serum tryptase and urinary N-MH levels between bone marrow biopsies with increased numbers of mast cell aggregates and those without such increases. It was noted, however, that serum tryptase discriminated better than urinary N-MH between patients with and without increased mast cell aggregates in bone marrow biopsies [37].

A study by van Doormaal et al. involved 142 patients undergoing evaluation for mastocytosis and included 53 patients without urticaria pigmentosa who were diagnosed with indolent SM and 89 patients who ultimately were not diagnosed with mastocytosis. In this study, when the tryptase levels were >10 μg/L, the highest combination of sensitivity and specificity for a diagnosis of SM was 2.0 mmol/mol creatinine for methylimidazole acetic acid (sensitivity 0.85, specificity 0.86) and 176 μmol/mol creatinine for methylhistamine (sensitivity 0.81, specificity 0.93) [38].

One final study by Divekar and Butterfield involving 90 patients found that urinary N-MH levels positively correlated with serum tryptase levels and the

percentage of mast cells on bone marrow biopsy. A significant difference was also found of urinary N-MH levels between subjects found to have atypical mast cells on bone marrow biopsy and those who did not. Furthermore, urinary N-MH levels were statistically different between the patient group positive for *c-kit* mutation versus the group that lacked the mutation. It was also noted that as urinary N-MH levels increased, greater proportions of patients demonstrated the aforementioned associated correlations. In conclusion, this study proposed that a urinary N-MH level that is twice the upper limit of normal (400 μg/g creatinine), which corresponds to 95% mast cell atypia and 85% mast cell aggregates being found on bone marrow biopsy, may be clinically useful to predict bone marrow findings in mastocytosis [39].

In summary, several investigations of urinary histamine metabolites have demonstrated clear utility to aid with the evaluation and diagnosis of SM. Due to these multiple findings, urinary histamine metabolite measurements have been included in diagnostic algorithms proposed by the European Competency Network on Mastocytosis and other groups to select patients for bone marrow examination to establish a diagnosis of SM [38].

Mast Cell Activation Syndrome

Although measuring urine N-MH levels in SM has demonstrated clinical utility in multiple studies [35–39], the same studies did not report any correlations between elevated urine N-MH levels and symptoms of mast cell activation. Only a few studies have investigated a potential role for the measurement of urine N-MH levels in mast cell activation syndrome (MCAS). In one study by Ravi et al., involving 25 patients with MCAS, the presence of MCAS symptoms was reviewed in association with levels of serum tryptase, 24-hour urine N-MH, and 24-hour urine 11β-$PGF_2\alpha$. All 25 patients had two or more organ systems that exhibited chronic or recurrent symptoms of mast cell activation, including urticaria, pruritus, flushing, diarrhea, and abdominal pain, and all patients had acute or chronic elevation in one or more mast cell mediator levels. Patients with SM or cutaneous mastocytosis were excluded. Elevation of 24-hour urine N-MH was defined as >200 μg/g creatinine. In this study cohort, only two patients had elevated 24-hour urine N-MH levels. In contrast, 17 patients had elevated 24-hour urine 11β-$PGF_2\alpha$, and 10 had elevated serum tryptase levels. Thus, in this study, measurement of urine N-MH was less helpful for the diagnosis of MCAS when compared to 24-hour urine 11β-$PGF_2\alpha$ and serum tryptase levels [40].

In a study by Vysniauskaite et al., 24-hour urinary N-MH levels were investigated in 257 MCAS patients. In this study, a broader definition of MCAS was used, in which elevation of a mast cell mediator was not required for diagnosis, whereas symptomatic response to medications inhibiting mast cell activation or mediator production/action alone was considered sufficient for a diagnosis of MCAS. In this context, the sensitivity of urinary N-MH for indicating increased mast cell activation in MCAS patients was low at 22% [41].

Another study by Pardanani et al. involved 22 patients with mast cell activation symptoms without evidence of a clonal mast cell disorder. A large symptom inventory was queried including cutaneous symptoms, respiratory symptoms, neurocognitive issues, gastrointestinal symptoms, and chronic pain. In this cohort, only 18% of patients had an elevated 24-hour urine N-MH level [42]. Lastly, in a study by Butterfield and Weiler, none of the four patients with mast cell activation symptoms demonstrated elevations in 24-hour urine N-MH levels [43].

In summary, several investigations of urinary histamine metabolites have demonstrated clear utility to aid in SM evaluation and diagnosis. However, in a limited number of studies investigating MCAS, measurement of urine N-MH has demonstrated little clinical utility and appears to be inferior when compared to tryptase as a marker of mast cell activation. These findings may be due, in part, to urine not being reliably collected during an acute period of symptoms, and thus, in that scenario, urine N-MH levels would not correlate well with symptomatology. Further studies are needed to evaluate how measurement of urine N-MH levels may be used optimally for the evaluation and management of MCAS.

Prostaglandins

Prostaglandin (PG)D2 is a lipid-derived MC mediator that is rapidly degraded into D-, F-, and J-ring metabolites, which are excreted as more stable urinary metabolites [44]. Mast cells, not basophils, remain the predominant source of PGD2. The predominant clinically measured urinary metabolite is 2,3-dinor-11β-prostaglandin F2α (2,3-BPG) [45].

Systemic Mastocytosis

(SM) patients excrete four times more PG-F-ring compared to PG-D-ring metabolites. During an exacerbation, an SM patient had 80,000-fold increase in the plasma concentration of 9α,11β-PGF_2 [46].

To further evaluate the biomechanics of PGD2 and niacin-induced flushing, ten healthy individuals ingested niacin, inducing endogenous release of PGD2. Blood PGD2 peaked at 2 hours and declined gradually but remained elevated up to 6–8 hours. The initial serum levels of the major urinary PGD2 metabolite 9α,11β-PGF_2 peaked by 30 minutes and returned to baseline by 2 hours [47]. In two healthy controls who received niacin, there was a correlation of elevated 2,3-BPG and flushing [44].

Multiple studies have shown elevated urinary excretion of PGD2 in SM. An early study by Roberts et al. in 1980 first revealed increased PGD2 production in two patients with SM. One of the patients treated with antihistamines and aspirin 975 mg PO QID for 8 months had reduced excretion of the PGD2 D-ring metabolite 9α-hydroxy-11,15-dioxo-2,3,4,5-tetranorprostane-1,20-dioic acid (Tetranor

PGD-M) by 80–85%. This patient also had a reduction of symptoms from several mild attacks of flushing daily and hospitalization every 2 weeks to no attacks of flushing and hypotension, except one mild flushing episode in the setting of strenuous exercise [48].

PGD-M (9α,11β-dihydroxy-15-oxo-2,3,18,19-tetranorprost-5-ene-1,20-dioic acid) is a downstream F-ring metabolite of PGD2. Measurement of urine PGD-M was increased above normal by as much as 300% in SM patients [49]. PGD-M is measured by gas chromatography compared to the measurement of 2,3-BPG, which uses liquid chromatography and tandem mass spectrometry. The 2,3-BPG assay is not often performed in other laboratories, as the mass spectrometry instrument is expensive and large. Mean urinary excretion of PGD-M was significantly higher (p <0.01) in patients with SM than in controls (37.2 vs. 11.5 ng/mg Cr), with 65% of 17 SM patients showing elevated levels [50].

The clinical sensitivity of 11β-$PGF_2\alpha$ (>1000 ng/24 hours) alone for the diagnosis of SM was determined to be 53% [4]. In a Mayo Clinic study of 22 SM patients, elevated urinary excretion levels of 11β-$PGF_2\alpha$ >3494 ng/24 hours correlated with the presence of bone marrow MC aggregates (89%) and atypical MC (100%) but not with c-kit positivity [39].

Mast Cell Activation Syndrome

The diagnosis of idiopathic MCAS requires evidence of validated mast cell mediator elevation during the symptomatic periods when compared to their baseline. In addition to serum tryptase (obtained within 4 hours after the onset of symptoms), 24-hour urine 11β-$PGF_2\alpha$ is a validated mast cell mediator [51]. A clinically significant elevation of tryptase is calculated as baseline serum tryptase (bT) + 20% bT + 2 ng/mL [25]. A similar calculation for urinary prostaglandin has not been established. It is important to note that elevation of urinary prostaglandin alone in the absence of other diagnostic criteria would not be sufficient to make the diagnosis of MCAS.

In a retrospective Mayo Clinic study of 25 MCAS patients, 24-hour urine 11β-$PGF_2\alpha$ was the most frequently elevated product when compared to urinary N-MH and serum tryptase. Flushing and pruritus had the greatest correlation with baseline 24-hour urinary 11β-$PGF_2\alpha$. Eight of nine MCAS patients with elevated 24-hour urine 11β-$PGF_2\alpha$ who underwent aspirin therapy had normalization of this mediator on follow-up urine studies. One of the nine patients did not have a follow-up urine study. Six of these nine MCAS patients had symptomatic improvement with aspirin therapy. Measurement of urinary 11β-$PGF_2\alpha$ can help avoid misdiagnosis and overinterpretation of MCAS symptoms in clinical practice [40].

We recommend measurement of urinary 2,3 BPG in patients with symptoms suggestive of MCAS. Future studies hope to elucidate the elevation from baseline needed to be considered clinically significant, such as that determined with serum tryptase.

Children

In a retrospective Mayo Clinic study of 104 children who underwent evaluation for mast cell disorders, 32 patients had one or more elevated urine MC mediators, based on established adult reference intervals. Of this total, one patient had systemic mastocytosis, four patients had cutaneous mastocytosis, and nine (6%) patients had MCAS. More patients had an elevated 2,3-BPG ($n = 5$) than serum tryptase ($n = 2$). There was an equal or greater percentage of patients who had an elevated 2,3-BPG than an elevated serum tryptase for flushing (80% vs. 50%), diarrhea (100% vs. 100%), and abdominal pain (100% vs. 50%). Urinary 2,3-BPG is the most frequently elevated product in our pediatric MCAS cohort, resembling adult MCAS [52]. We recommend measurement of tryptase and urinary N-MH, 2,3-BPG, and LTE4 in children with MCAS symptoms.

Method of Urine Mast Cell Mediator Collection

With combined testing of urine 2,3 BPG, LTE4, and N-MH, the sensitivity for SM is 97%. The method of collection for urine mast cell mediators is critical in ensuring test accuracy. There are two important times to measure urinary mast cell mediator levels. Baseline assays are performed during assessment at a time when clinical symptoms are stable or absent. Samples can also be "mailed in" using a kit designed by Mayo Medical Laboratories (MML). The latter method allows (1) routine monitoring of mediator levels as well as (2) contemporaneous sampling during episodic mast cell activation. Figure 4.1 illustrates our mail in kit.

One must also consider the stability of the urine mast cell mediators. The frozen stability may be indefinite but has not been further tested in our lab. Please refer to Table 4.1. Urine mast cell mediator stability at room temperature/ambient temperature is only 8 hours.

Thus, urine specimens returned via mail-in kit must be refrigerated or frozen until ready to mail. Mail must be performed via overnight express, with samples enclosed by frozen refrigerant packs. Mayo Clinic mail-in kit comes ready with the mailing label and refrigerant packs.

Either a 24-hour collection or spot (random) collection may be performed. Mayo Clinic data have shown that the random collection is comparable to the 24-hour collection results. Random collection has two advantages: convenience and contemporaneous accrual at times of symptoms (vs. a 24-hour sample). We suggest that at the onset of symptoms, patients empty their bladder and then collect a fresh urine sample. Both baseline and symptom-associated samples are important, and each can yield essential information.

Urine specimens are clean catch specimens. In children who are not toilet-trained, a bagged specimen can be utilized. In male children, a bag can be placed around the penis. In female children, a bag can be placed around the child's waist.

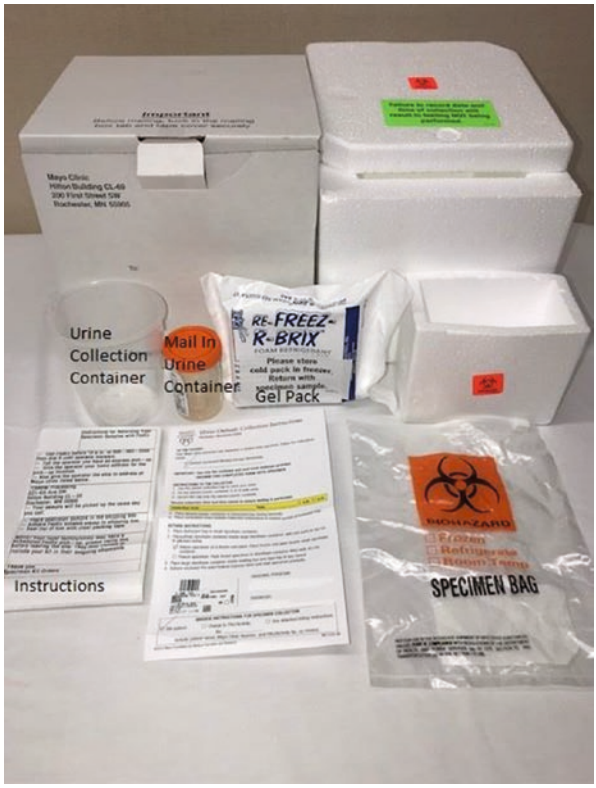

Fig. 4.1 Contents of mail-in kit

Table 4.1 Stability of urine mast cell mediators

	Ambient (room temperature)	Refrigerated	Frozen
NMH	24 hours	8 days	14 days
LTE4	24 hours	7 days	30 days
BPG	8 hours	14 days	30 days

Source: Mayo Medical Laboratories

MML test codes for random testing include 2,3BPG (2,3-dinor-11beta-prostaglandin F2 alpha), LTE4 (leukotriene E4), and NMHIN (N-methylhistamine). Optimal urine collection container is preservative free, but some preservative options are accepted. MML may be contacted for additional information: www.mayomedicallaboratories.com, 1-800-533-1710, 507-266-5700, or mml@mayo.edu.

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Chapter 5
Skin Disease in Mastocytosis

Zita-Rose Manjaly Thomas and Karin Hartmann

Abbreviations

ASM	Aggressive SM
DCM	Diffuse cutaneous mastocytosis
ECNM	European Competence Network on Mastocytosis
ISM	Indolent systemic mastocytosis
MCL	Mast cell leukaemia
MPCM	Maculopapular cutaneous mastocytosis
SM	Systemic Mastocytosis
SM-AHN	Systemic mastocytosis with an associated haematological neoplasm
TKI	Tyrosine kinase inhibitors
TMEP	Telangiectasia macularis eruptive perstans
UV	Ultraviolet
WHO	World Health Organization

Introduction

Mastocytosis is characterised by an abnormal accumulation of tissue mast cells affecting a variety of organs, most commonly the skin and bone marrow [1–3]. An important clinical distinction is made between cutaneous mastocytosis and systemic mastocytosis,

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whereby the latter can also include cutaneous involvement. Skin lesions in mastocytosis are classified into three subforms, namely maculopapular cutaneous mastocytosis (MPCM; syn. urticaria pigmentosa), diffuse cutaneous mastocytosis (DCM) and cutaneous mastocytoma (Table 5.1, Figs. 5.1, 5.2, and 5.3) [4]. A common diagnostic hallmark of all three subforms is the presence of Darier's sign, that is whealing and reddening of the skin lesions in response to mechanical stroking (Fig. 5.4) [4, 5].

The first clinical description of mastocytosis dates back to the nineteenth century. In 1869, Nettleship recognised a case of an 'unusual pattern of urticaria' in a 2-year-old girl and, following Ehrlich's description of mast cells in the skin in 1879, this clinical picture later became known as urticaria pigmentosa on the basis of its characteristic skin lesions [6, 7]. Early attempts at classifying cutaneous lesions in mastocytosis by different categories were made by Sagher and Even-Paz in 1967 [8]. However, it was not until a few decades later that consensus was reached on a classification system that is now widely used in clinical practice [4]. This system combines two of the originally described categories by Sagher and Even-Paz, namely distribution and morphology of the lesions [8].

In the majority of cases, mastocytosis occurs sporadically, where it is usually associated with somatic *KIT* mutations, most frequently the *KIT* D816V mutation in exon 17 [9–12]. In rare cases of familial mastocytosis, germline *KIT* mutations can often be detected that are inherited in an autosomal dominant manner [13–17].

This chapter will provide an overview of cutaneous involvement with an emphasis on the classification, clinical manifestations, differences between the paediatric *versus* the adult population, diagnosis and treatment.

Table 5.1 Classification of cutaneous involvement in mastocytosis (modified from [4])

Subform	Variant	Disease course	Characteristics
Maculopapular cutaneous mastocytosis (syn. urticaria pigmentosa)	Monomorphic	Usually chronic Sometimes progressive Rarely regressive	Usually associated with systemic mastocytosis Usually adult patients Predominantly on thighs and trunk Can be associated with telangiectatic lesions
	Polymorphic	Usually regressive	Usually no systemic involvement Usually paediatric patients Predominantly on trunk and head, typically lateral forehead involved Can be associated with blisters in the first 2–3 years
Diffuse cutaneous mastocytosis		Often regressive Sometimes chronic	Starts in infancy Can be associated with familial mastocytosis Pronounced dermographism Usually associated with blisters, particularly in the first years Can be associated with extracellular *KIT* mutations
Cutaneous mastocytoma		Always regressive	Starts in infancy Can present with one or up to three lesions Can be associated with blisters

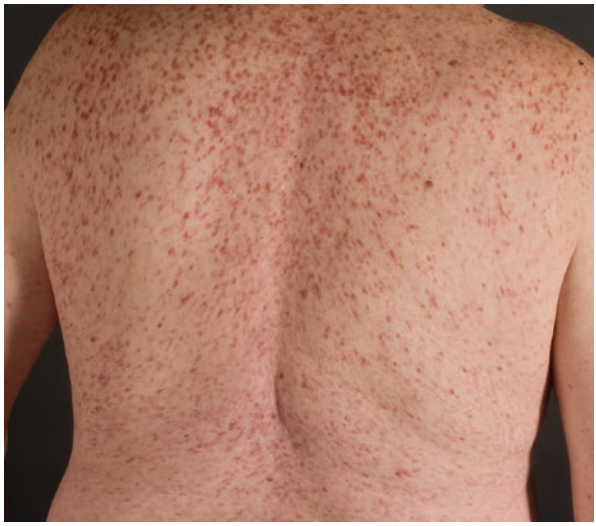

Fig. 5.1 Maculopapular cutaneous mastocytosis, monomorphic variant. Monomorphic maculopapular cutaneous mastocytosis presents with brown or red symmetrically distributed skin lesions. The lesions typically follow Blaschko's lines. Patients with monomorphic cutaneous mastocytosis often have additional systemic involvement

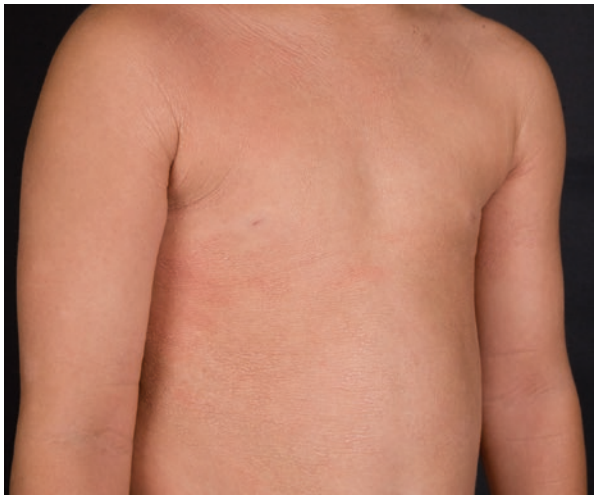

Fig. 5.2 Diffuse cutaneous mastocytosis. Patients with diffuse cutaneous mastocytosis are characterised by oedematous erythroderma with a brown or yellow tint

Classification of Cutaneous Involvement in Mastocytosis

The current classification of cutaneous involvement in mastocytosis is based on the morphology and distribution of the lesions (Table 5.1) [4]. Skin lesions are divided into three main clinical subforms, namely (1) MPCM, (2) DCM and (3) cutaneous mastocytoma (Figs. 5.1, 5.2, and 5.3). The concept of this classification system has been recognised and adapted by the World Health Organization (WHO) [1, 18].

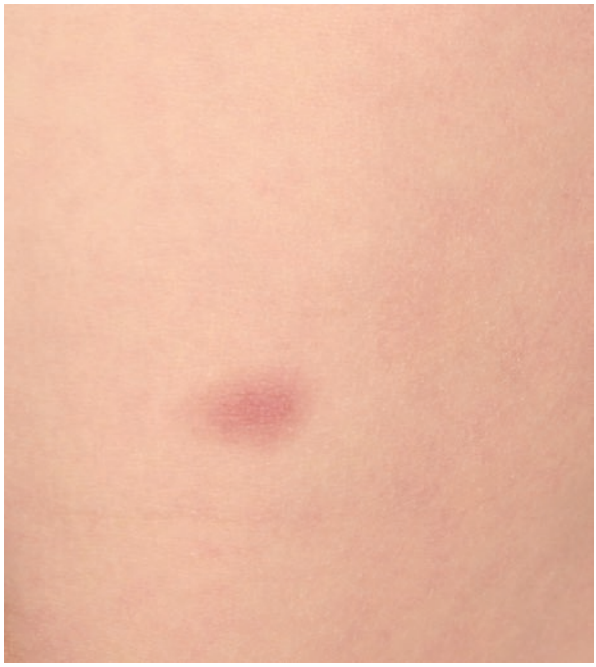

Fig. 5.3 Cutaneous mastocytoma. Typical mastocytoma lesions are brown and nodular

In a consensus report of an international task force involving the European Competence Network on Mastocytosis (ECNM), the American Academy of Allergy, Asthma and Immunology and the European Academy of Allergy and Clinical Immunology, the previous classification, which distinguished (1) MPCM/urticaria pigmentosa, (2) DCM and (3) solitary mastocytoma of the skin, was further refined to include two variants of the MPCM subform, namely the monomorphic and polymorphic MPCM variants [4, 19]. The former (monomorphic variant) refers to the presence of small maculopapular lesions and is seen in the majority of adult patients, but also in a subgroup of children (Fig. 5.5). The latter (polymorphic variant) refers to larger lesions of various sizes and is seen exclusively in children; it can sometimes present with nodules or plaques initially (Fig. 5.6). The monomorphic variant, when present in the paediatric population, often persists into adulthood, whereas the polymorphic variant in children usually resolves spontaneously around the time of puberty [20].

The task force also agreed on two further refinements that differ from previous classification systems: One of these refinements is that the subform of cutaneous mastocytoma can have up to three lesions instead of, as previously defined, just one solitary lesion [4]. If more than three lesions are present, skin lesions would fall under the category of polymorphic MPCM. The other refinement is that telangiectatic lesions can occur in addition to maculopapular lesions in patients with MPCM, but do not represent another variant per se. Thus, the earlier described subform telangiectasia macularis eruptiva perstans (TMEP) should no longer be diagnosed [4, 21].

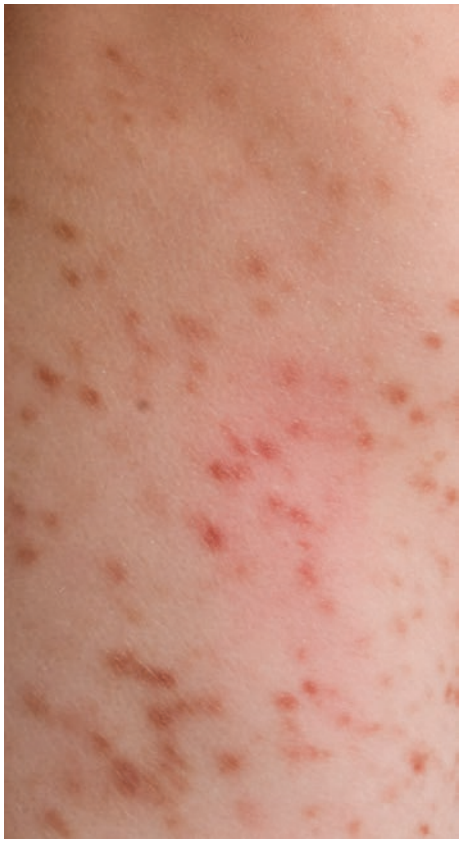

Fig. 5.4 Darier's sign. Upon stroking of mastocytosis lesions with moderate pressure, a wheal and flare reaction ensues around the lesions. A positive Darier's sign is highly specific for mastocytosis

Clinical Manifestations of Cutaneous Involvement in Mastocytosis

Characteristic skin lesions in mastocytosis are brown or red in colour and associated with a positive Darier's sign (Fig. 5.4) [5]. The Darier's sign is a highly specific feature of mastocytosis skin lesions and hence an important clinical diagnostic sign (Table 5.2) [4]. To elicit this pathognomonic sign, a lesion is stroked approximately five times with moderate pressure using a wooden spatula. The wheal and flare reaction that ensues is limited to lesional skin only, which is how it is differentiated from dermographism. The Darier's sign can be reduced in patients on antihistamine therapy.

MPCM is characterised by round, brown or red lesions. In the monomorphic variant, which predominantly manifests in adult patients, lesions are small and usually symmetrically and regularly distributed (Fig. 5.7) [4]. There is a predilection in monomorphic MPCM for initial lesions to appear on the thighs and lower trunk with subsequent involvement of the upper trunk and distal extremities; with relative sparing of the face and head (Fig. 5.8). In the polymorphic variant, typically occurring in children, lesions tend to be larger and can, particularly in the beginning,

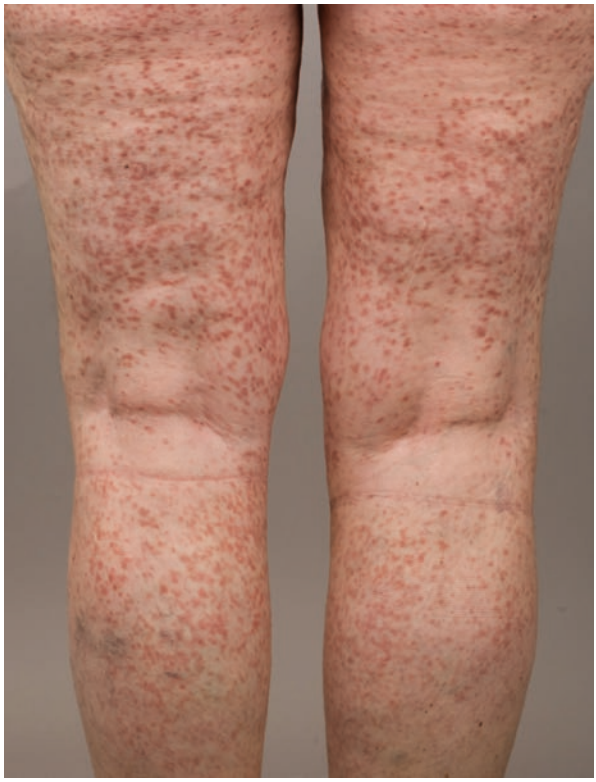

Fig. 5.5 Maculopapular cutaneous mastocytosis, monomorphic variant. Small brown or red lesions usually spread over several years from thighs and trunk to the distal extremities

also present as nodular lesions or plaques (Figs. 5.6 and 5.9) [20]. The polymorphic lesions are usually more randomly and less regularly distributed, and mostly also include the scalp and sometimes the face (Figs. 5.10 and 5.11). Typically, the lateral and upper forehead is also involved (Fig. 5.12). In both MPCM variants, the number of lesions can range from a few solitary lesions to numerous lesions, resulting in confluent areas and even almost entire coverage of the skin (Figs. 5.13 and 5.14). In monomorphic MPCM, but not in polymorphic MPCM, the extent to which the skin is affected also correlates with the degree of systemic involvement and the level of serum tryptase [22].

The recommendation of the international task force has been to replace the former name urticaria pigmentosa by MPCM to better reflect the stable lesions in mastocytosis in contrast to the transient nature of the wheals in true urticaria [4].

Adult patients with maculopapular lesions tend to have concurrent mast cell infiltrates present in the bone marrow, leading to a diagnosis of systemic mastocytosis (SM) with cutaneous involvement, most frequently the indolent type of systemic mastocytosis (ISM). Maculopapular lesions without systemic involvement in adults are rare, but can be observed [23]. Overall, the prevalence of cutaneous involvement in ISM is estimated at 95% [4, 24]. The proportion of patients with advanced SM, that is SM with an associated haematological neoplasm (SM-AHN), aggressive SM

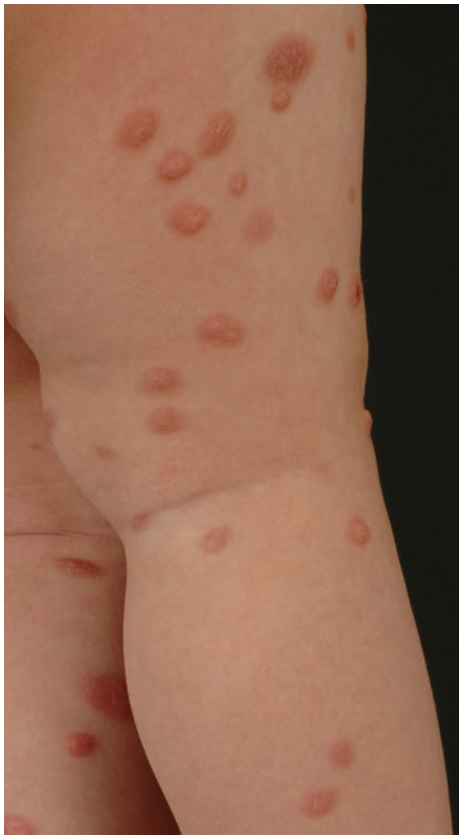

Fig. 5.6 Maculopapular cutaneous mastocytosis, polymorphic variant. Polymorphic maculopapular cutaneous mastocytosis presents with large nodular or plaque-like lesions of different sizes. Usually, there is no systemic involvement. Skin lesions often resolve spontaneously after several years

Table 5.2 Diagnostic criteria of cutaneous involvement in mastocytosis [4]

Major criterion
Typical skin lesions of mastocytosis associated with a positive Darier's sign
Minor criteria
Increased numbers of mast cells in biopsy sections of lesional skin
(Activating) *KIT* mutation in lesional skin tissue

(ASM) and mast cell leukaemia (MCL), who have coexisting cutaneous involvement is lower at around 50%. Skin lesions in ISM are usually more regularly distributed, whereas lesions in advanced SM are often less regularly distributed, and confluent in specific areas such as the thighs and inframammary or abdominal folds (Figs. 5.7 and 5.13).

Regression of cutaneous lesions can correlate with different outcomes depending on the category of mastocytosis: Whilst regression of cutaneous lesions in advanced systemic mastocytosis can indicate progression of the disease, this is not true for ISM. Although the course of ISM is usually chronic, there are a few patients who

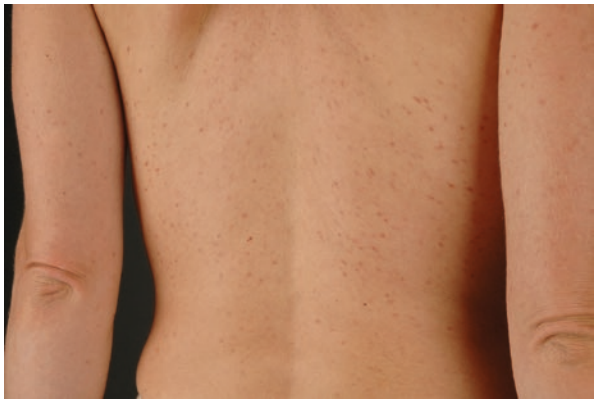

Fig. 5.7 Maculopapular cutaneous mastocytosis, monomorphic variant. A typical feature of monomorphic maculopapular cutaneous mastocytosis is the regular distribution of the small brown lesions

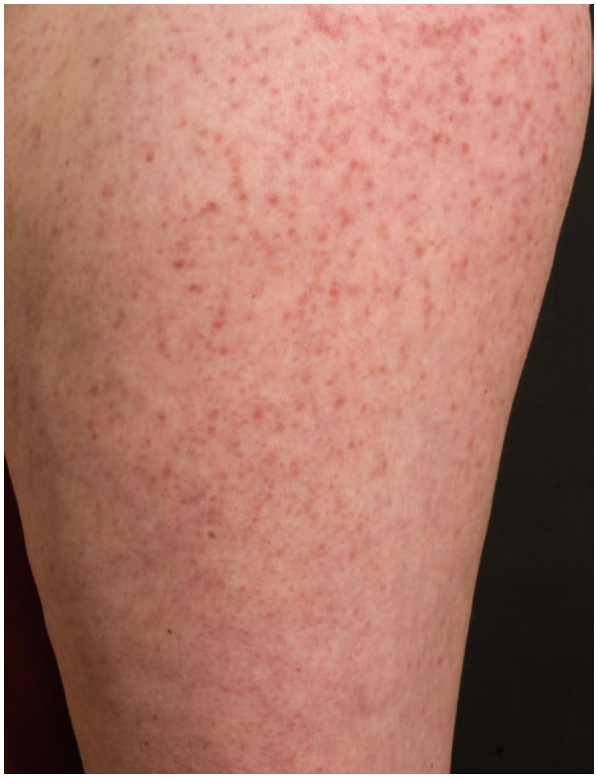

Fig. 5.8 Maculopapular cutaneous mastocytosis, monomorphic variant. Often, monomorphic maculopapular cutaneous mastocytosis starts on the thighs with subsequent involvement of the trunk and extremities

experience spontaneous regression of skin lesions, which then often coincides with a reduction in symptoms and serum tryptase level, although not always with complete remission of bone marrow infiltrates [25]. In contrast to adult patients, regression of lesions in children with polymorphic MPCM typically occurs after several years, usually between 8 and 18 years of age, and correlates with gradual symptom reduction and associated disease remission [20, 26, 27].

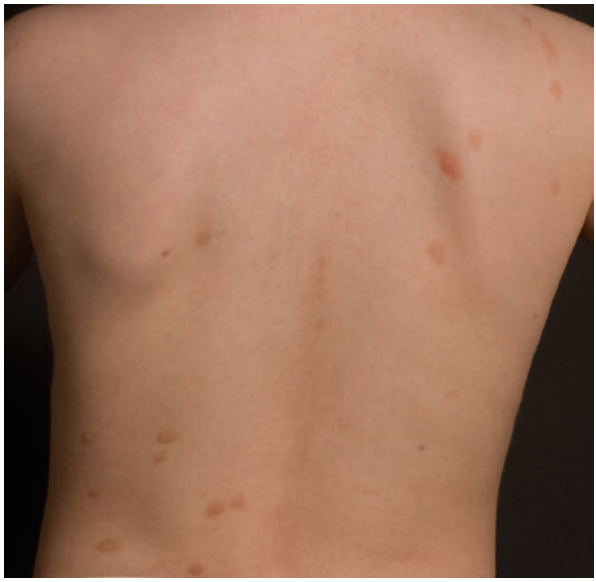

Fig. 5.9 Maculopapular cutaneous mastocytosis, polymorphic variant. In contrast to the monomorphic variant, the polymorphic variant of maculopapular cutaneous mastocytosis presents with large plaque-like or nodular and irregularly distributed lesions

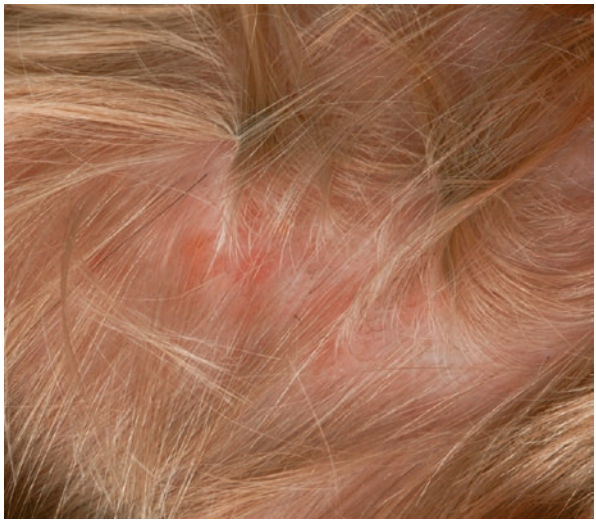

Fig. 5.10 Maculopapular cutaneous mastocytosis, polymorphic variant. The scalp and head are often involved. Scalp lesions typically show pronounced whealing upon stroking

DCM is characterised by oedematous erythroderma with a brown or yellow tint that covers the entire body (Fig. 5.2) [4]. Dermographism is usually very pronounced and persistent in this form (Fig. 5.15). DCM generally starts in early childhood and often resolves by adolescence, but can also persist into adulthood. Most affected individuals develop blisters in the first few years following disease onset (Fig. 5.16). DCM may also occur in patients with familial mastocytosis, where it then usually persists into adulthood [13, 16, 17].

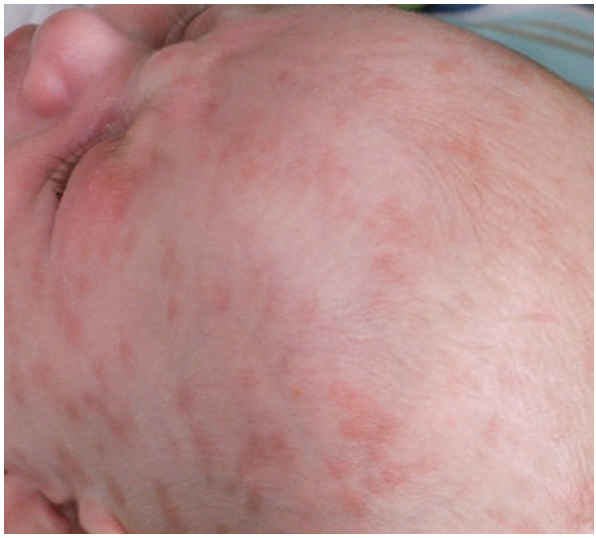

Fig. 5.11 Maculopapular cutaneous mastocytosis, polymorphic variant. The face may also be involved in the polymorphic variant of maculopapular cutaneous mastocytosis

Fig. 5.12 Maculopapular cutaneous mastocytosis, polymorphic variant. Involvement of the lateral and upper forehead is typical in this variant

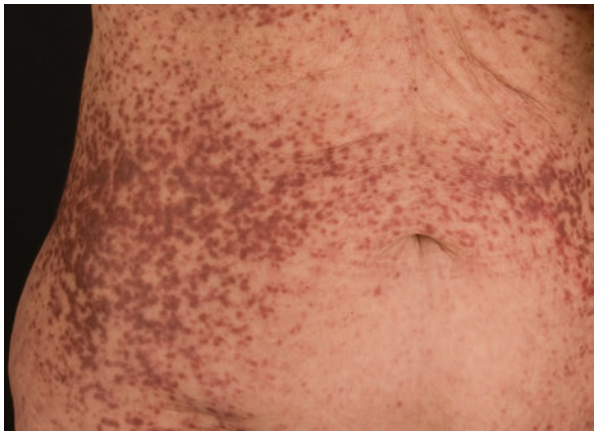

Fig. 5.13 Maculopapular cutaneous mastocytosis, monomorphic variant. Confluent lesions, typically seen in body folds, can be associated with advanced systemic mastocytosis

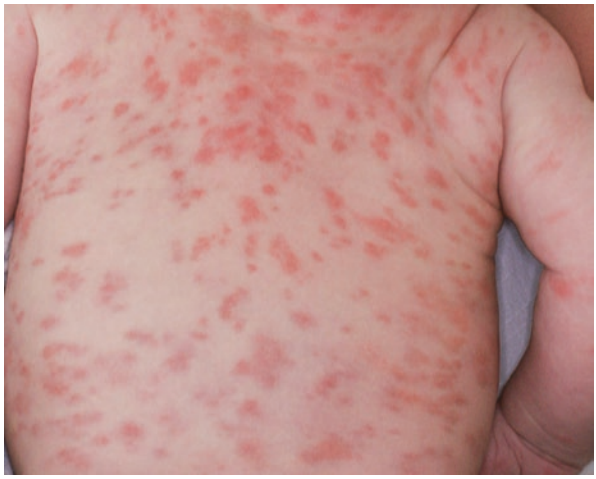

Fig. 5.14 Maculopapular cutaneous mastocytosis, polymorphic variant. Patients can also present with numerous skin lesions. Over time, polymorphic maculopapular cutaneous mastocytosis usually shows spontaneous regression

Cutaneous mastocytoma, the third subform, describes one to three brown nodular lesions that are often initially associated with blisters and commonly manifest in the first 6 months of life (Figs. 5.3 and 5.17) [4, 26, 27]. As mentioned, up to three lesions are still classified as cutaneous mastocytoma, but those with any more than three lesions would be reclassified as MPCM, usually as polymorphic MPCM. Although only limited skin surface is involved in this subform, friction in the form of significant stroking, for instance, can – akin to the other subforms – lead to flushing, sudden reddening of the skin and sweating. Serum tryptase level in this subform is usually normal, and there is no systemic involvement.

Patients with skin lesions, regardless of whether the bone marrow is involved, can all experience symptoms attributable to the release of mast cell mediators

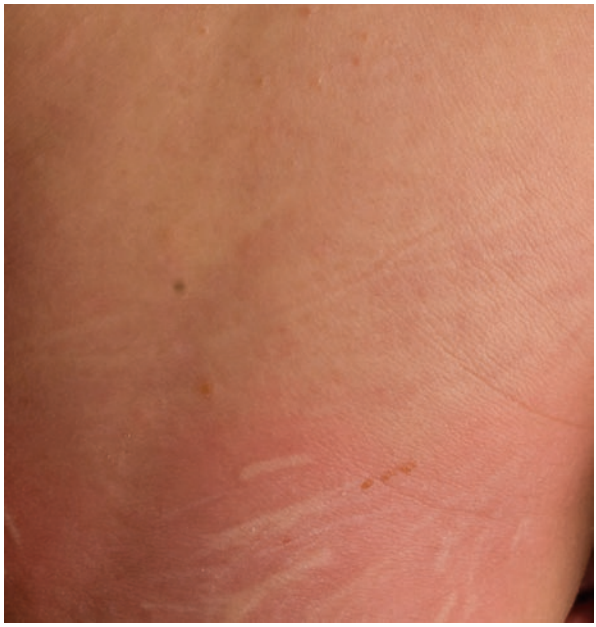

Fig. 5.15 Diffuse cutaneous mastocytosis. Patients with diffuse cutaneous mastocytosis often suffer from pronounced dermographism and pruritus

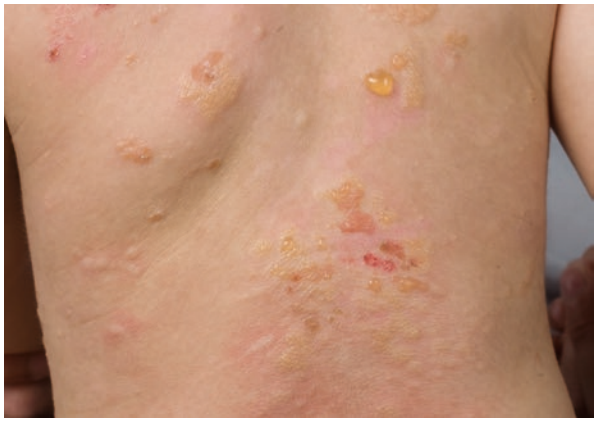

Fig. 5.16 Diffuse cutaneous mastocytosis. In the first years, diffuse cutaneous mastocytosis is usually associated with blisters

(Fig. 5.18). Once triggered, systemic release of mast cell mediators can cause a range of symptoms from flushing to anaphylaxis and circulatory collapse as well as gastrointestinal symptoms such as abdominal pain, diarrhoea, vomiting and peptic ulcer disease. Mastocytosis patients, who have a concomitant IgE-dependent allergy, are prone to experience more severe symptoms in case of anaphylaxis. For instance, insect venom allergies in these patients are often associated with life-threatening anaphylaxis [28–30].

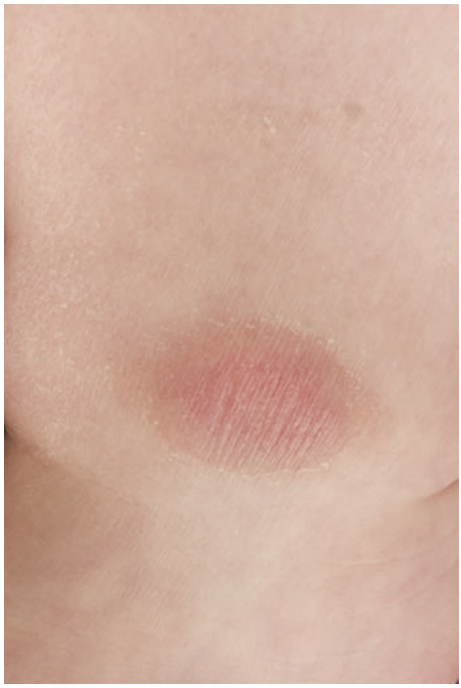

Fig. 5.17 Cutaneous mastocytoma. Blistering can be associated with a cutaneous mastocytoma

Differences in Characteristics of Mastocytosis Between Children and Adults

The age of onset of mastocytosis can vary, but there are important differences between childhood- and adulthood-onset mastocytosis (Table 5.3) [4].

In children, the peak of onset is during the first 6 months of life, and in adults, it is usually before the age of 60 years, although there are patients with a later disease onset. Within the adult population, the majority of patients below the age of 60 years suffer from ISM, whereas those few patients with a late disease onset above the age of 60 years often develop advanced SM [31].

With respect to skin lesions, the prevalence is different in children and adults. M PCM Maculopapular lesions are frequent in both age groups, but represent, by far, the most frequent lesion type in the adult population. As mentioned, children with MPCM often show the polymorphic variant, whereas adults regularly have the monomorphic variant (Figs. 5.6, 5.9, and 5.19). DCM always starts in early childhood and can either spontaneously resolve by adolescence or persist into adulthood. Existing studies indicate that spontaneous remission of DCM is more frequent than persistence into later life. DCM in adults is either associated with germline *KIT* mutations in the case of familial mastocytosis or with somatic *KIT* mutations in exon 8 or 9 in rare sporadic cases [10, 13, 16, 17]. Cutaneous mastocytomas are exclusively found in the paediatric population.

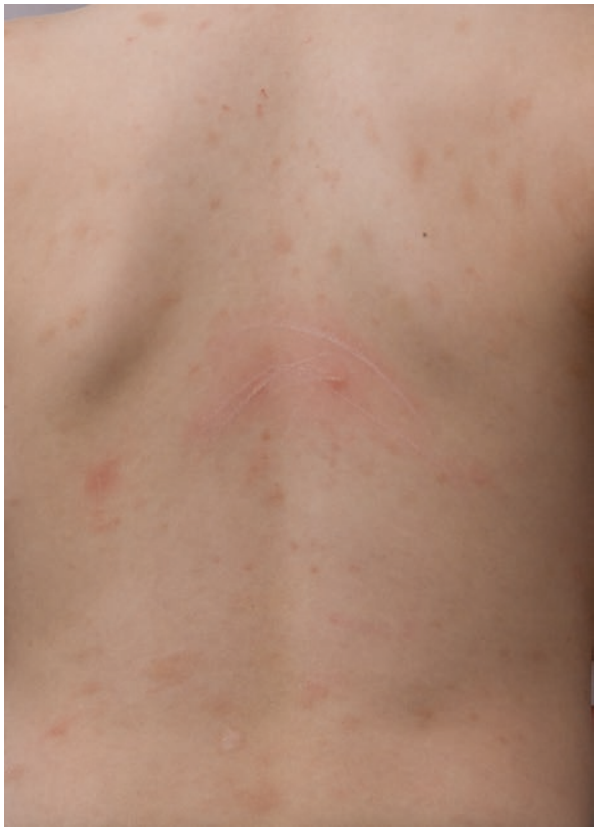

Fig. 5.18 Maculopapular cutaneous mastocytosis, polymorphic variant. Pronounced dermographism may develop upon stroking

Within the MPCM subform, the polymorphic lesions in children are more commonly oval rather than round in shape, larger than the adult lesions and often initially have a nodular or plaque-like character to them (Figs. 5.6 and 5.9). Of note, the morphological character of the polymorphic lesions can transform with time, that is nodules in infancy, turning into plaques at the age of 5 years, and then into macules at the age of 10 years before subsequent regression in puberty [20]. Another difference observed in the paediatric population is the distribution of skin lesions in the polymorphic variant of MPCM, namely, more asymmetrical and generalised, and typically involving head, neck and extremities (Figs. 5.9, 5.10, 5.11, and 5.12). It is worth mentioning that the lesions on the head are more prone to blistering.

Paediatric cases of DCM and to a lesser extent MPCM and mastocytoma, are often characterised by blistering within the first 2–3 years of life, a phenomenon rarely seen in adult patients (Fig. 5.16). Children with mastocytosis can also have a bleeding tendency, probably due to local release of heparin, which is rarely seen in adults.

Patients with childhood-onset mastocytosis usually have cutaneous disease without systemic involvement and accordingly show a normal or only transiently elevated serum tryptase level at the time of disease onset in the context of clinically

Table 5.3 Characteristics of childhood-onset and adulthood-onset mastocytosis (modified from [4])

Characteristics	Childhood-onset mastocytosis	Adulthood-onset mastocytosis
Most frequent tissue involvement	Skin	Bone marrow Skin
Most frequent category of mastocytosis	Cutaneous mastocytosis	Indolent systemic mastocytosis
Most frequent subform of cutaneous involvement	Cutaneous mastocytoma Maculopapular cutaneous mastocytosis, polymorphic variant	Maculopapular cutaneous mastocytosis, monomorphic variant
Preferential body sites involved in maculopapular cutaneous mastocytosis	Trunk Head, scalp, and lateral forehead	Thighs Trunk
Frequency of blisters associated with skin lesions	Frequent in all subforms of cutaneous involvement	Very rare, only in selected patients with severe diffuse cutaneous mastocytosis
Typical tryptase levels	Within the normal range (<11.4 μg/L)	Increased (>20.0 μg/L)
Typical *KIT* mutations	D816V in *KIT* exon 17 Other mutations in *KIT* exon 17 Various mutations in *KIT* exons 8, 9, 10, and 11	D816V in *KIT* exon 17
Typical course of the disease	Transient, with spontaneous regression around puberty	Chronic Rarely progressive
Frequency of anaphylaxis	Not frequent (around 10%)	Frequent (around 50%)

pronounced MPCM or DCM. In contrast, adulthood-onset patients typically suffer from systemic mastocytosis associated with elevated serum tryptase levels.

Another difference between childhood- and adulthood-onset disease, which is insufficiently understood, is the frequency of anaphylaxis. Paediatric patients only rarely develop anaphylaxis, whereas around 50% of adult patients suffer from anaphylaxis [28]. In the adult population, predominantly patients with ISM develop anaphylaxis, whereas patients with advanced SM do not regularly experience anaphylaxis [29].

Diagnostic Workup of Cutaneous Involvement in Mastocytosis

Typical skin lesions of mastocytosis can serve as a diagnostic hallmark of the disease, for instance, in patients with a history of anaphylaxis, other symptoms of mast cell mediator release, osteoporosis, pathological fractures, fatigue, weight loss or cytopenia. For the evaluation of suggestive skin lesions, it is always recommended to elicit Darier's sign (Table 5.2, Fig. 5.4). A positive Darier's sign further strengthens the clinical diagnosis of mastocytosis.

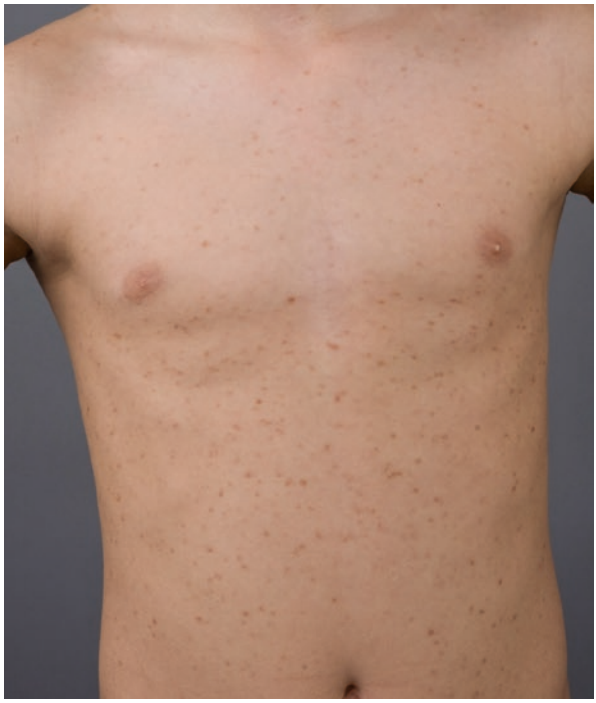

Fig. 5.19 Maculopapular cutaneous mastocytosis, monomorphic variant. Rarely, paediatric patients also present with monomorphic maculopapular cutaneous mastocytosis, which may then indicate a chronic or prolonged disease course

Measurement of the serum tryptase level also assists the diagnostic process and can additionally be utilised as a biomarker [32]. Patients with SM usually have elevated serum tryptase levels above 20 µg/L, whereas patients with sole cutaneous involvement, without systemic disease, tend to have a tryptase level within the normal range below 11.4 µg/L, or at least in the borderline range below 20 µg/L. Children with pronounced cutaneous mastocytosis may initially show increased tryptase levels, which, however, steadily decrease over several years as they go into clinical remission [20, 33].

Measuring the *KIT* allele burden from peripheral blood by allele-specific quantitative real-time PCR or digital PCR is also helpful to diagnose mastocytosis in doubtful cases and to monitor severity of mastocytosis [15, 34–36].

Confirmation of cutaneous involvement in mastocytosis is obtained by skin biopsy, where infiltration of mast cells is demonstrated on histology (Table 5.2, Fig. 5.20). Preferentially, immunohistochemical staining with an antibody against tryptase is used to quantify mast cells. Alternatively, histochemical staining with Giemsa or toluidine blue can be used, although hypogranulated mast cells can be missed with these methods. Mast cell infiltration is primarily seen in the upper dermis with more pronounced accumulation around skin vessels and appendages in adults in contrast to a more diffuse pattern in children. On average, mast cell numbers are increased fourfold to eightfold in lesional skin of mastocytosis patients compared to those in the healthy skin or twofold to threefold compared to those in

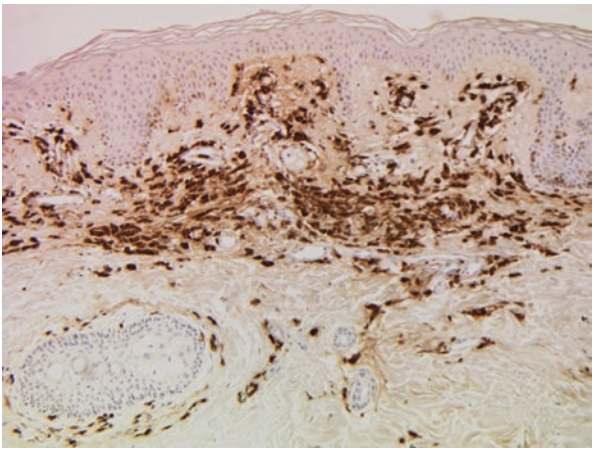

Fig. 5.20 Histology of skin lesions in mastocytosis. Mast cell infiltrates, stained with an antibody against tryptase, are typically seen in the upper dermis and around skin vessels and appendages

the skin of patients with other inflammatory cutaneous diseases. However, the results of a skin biopsy do not always yield a conclusive diagnosis. In addition to false positives in alternative inflammatory diagnoses, false negatives can also occur depending on the site of the biopsy. It should be noted that the extent of mast cell infiltration visualised histologically does not necessarily correlate with disease severity [22, 33].

To screen for advanced SM, a full blood count, blood biochemistry profile and a peripheral blood film should be routinely done in all adult patients. Whereas cutaneous mastocytosis and ISM are typically associated with blood results within the normal range, any derangement may indicate advanced disease. In particular, elevated alkaline phosphatase levels, monocytosis and eosinophilia can point to the beginning of ASM or SM-AHN. Moreover, cytopenia such as anaemia and thrombocytopenia are typically associated with advanced SM.

In all adults with skin lesions of mastocytosis, a bone marrow investigation is pivotal to identify or exclude systemic involvement. As mentioned, most adult patients have the underlying systemic disease, whereas most children have purely cutaneous mastocytosis without systemic involvement [37]. Due to this key difference, a diagnosis of adult-onset pure cutaneous mastocytosis (without SM) is a diagnosis of exclusion and necessitates a negative bone marrow histology. In contrast, a bone marrow biopsy is not routinely performed in paediatric disease.

Since adult patients with ISM often show osteopenia or osteoporosis, osteodensitometry should routinely be performed in all adult patients with SM to exclude skeletal involvement [38, 39].

Further diagnostic testing is guided by symptoms to exclude, for example gastrointestinal, splenic or hepatic involvement.

In suspected cases of familial mastocytosis, genetic profiling such as sequencing of the whole *KIT* gene is recommended to identify the molecular defect, which may then guide the counselling of the family and treatment.

Principles of Treatment of Cutaneous Involvement in Mastocytosis

Primary treatment strategies in patients with cutaneous involvement focus, on the one hand, on the reduction of triggers in order to avoid anaphylaxis and, on the other hand, on the mediator-targeted treatment of symptoms (Table 5.4) [2, 19]. Here, we mainly describe the principles of anaphylaxis prevention as well as skin-targeted treatment. Treatment of advanced SM in the form of disease-modifying or molecular targeted treatment is discussed elsewhere in this book in more detail.

Avoidance or at least reduction of triggers that could precipitate anaphylaxis is critical in all patients with mastocytosis, particularly in patients with cutaneous mastocytosis and ISM [31]. Common triggers of anaphylaxis include hymenoptera venom, certain drugs, sudden temperature changes, infection and mechanical irritation [28, 29]. Specifically, a heightened risk of anaphylaxis upon wasp and bee stings as well as perioperatively is well described in mastocytosis patients. A key approach to the management of these patients is educating them and their caregivers in the recognition of anaphylactoid reactions. Given the high risk of anaphylaxis, all adult mastocytosis patients and children with severe disease should always carry emergency medication in the form of adrenaline and potentially also antihistamines and corticosteroids and be trained in their use.

Alleviation of mast cell mediator symptoms can be achieved by therapy with antihistamines for relief from pruritus and whealing, but also gastrointestinal symptoms such as abdominal pain and diarrhoea. H1 antihistamines should always be considered if pruritus, whealing or bullae are an issue. H2 antihistamines are likely to be beneficial in patients with gastrointestinal symptoms, especially diarrhoea, abdominal cramping and peptic ulcer disease. Sodium cromoglycate has

Table 5.4 Mast cell mediator-targeted therapy in mastocytosis

First-line treatments
Counselling Recognition of anaphylaxis symptoms Avoidance/reduction of trigger factors such as hymenoptera venom, anaesthesia, specific drugs, infections, alcohol, physical exercise
Adrenaline, emergency medications
H1 antihistamines
Sodium cromoglicate
Hymenoptera venom immunotherapy
Second-line treatments
H2 antihistamines
Corticosteroids
Ketotifen
Omalizumab
UV radiation

been shown to also ameliorate gastrointestinal symptoms [40]. Prophylactic H1 and H2 antihistamines are advised in patients with recurrent anaphylaxis [2].

In patients with a past medical history of anaphylaxis following an insect sting, an allergy assessment should be performed. In mastocytosis patients with a confirmed allergy to insect venom, immunotherapy with the respective hymenoptera venom should be initiated and continued lifelong. If induction of immunotherapy is not well tolerated, additional administration of omalizumab can be helpful [41, 42].

Patients with a history of anaphylaxis scheduled for anaesthesia should receive empirical antihistamine and corticosteroid treatment preoperatively to reduce the trigger threshold [43].

Bullae associated with mastocytosis skin lesions are treated like scalds, with the main aim being prevention of infection. Progressive bullae might require high-dose antihistamines and intravenous corticosteroids. Shock-like mastocytosis flares with diffuse bullous eruptions in infants may also require treatment in an intensive care setting with careful fluid management, high-dose H1 and H2 antihistamines and systemic corticosteroids. As a sequalae of blisters, hyperpigmentation can occur in areas of healed bullae, but usually without scar tissue.

Despite the fact that non-steroidal, anti-inflammatory agents can induce mast cell degranulation, they might be cautiously trialled to reduce the prostaglandin-dependent flushing [2]. However, given that these NSAIDs also aggravate the effects of gastric histamine-induced hyperacidity, their therapeutic utility in this context is limited.

Ultraviolet (UV) radiation can reduce the appearance of skin lesions – mainly by aligning the colour of the surrounding skin areas – and also alleviate the sensation of itch, but the effects are usually transient and the symptomatic relief has to be weighed up against the risks of prolonged UV exposure.

Local treatments of mastocytomas in the form of topical immunosuppressants such as corticosteroids and calcineurin antagonists and local UV radiation are considered especially in patients with pronounced symptoms or increase in the size of the mastocytoma [44]. Topical corticosteroid treatment enhanced with occlusive dressings may also be beneficial in mastocytomas, but given the inherent risk of cutaneous atrophy and the potential for suppression of the adrenal axis, this should be used with caution and, if utilised at all, restricted to short-term use. Surgical excision of mastocytoma is an effective invasive approach, especially when these are cosmetically unpleasing. However, given that the typical outcome is spontaneous resolution of the lesion, an invasive approach is rarely necessary in affected infants.

Tyrosine kinase inhibitors (TKI) have been shown to reduce mast cell infiltration in different organs, including skin, in patients with mastocytosis [45]. Moreover, TKI have also been found to reduce the release of mast cell mediators [46, 47]. To date, the TKI midostaurin has only been approved for the treatment of advanced SM, although a first clinical trial also showed beneficial effects in ISM [48]. Imatinib is not effective in patients with *KIT* D816V mutations, but can be used in patients with extracellular *KIT* mutations [13, 49, 50]. Several reports showed that imatinib also improved skin lesions and mediator symptoms in these patients with extracellular mutations in addition to bone marrow infiltrates. Thus, it is likely that

specific TKI targeting the patient's individual *KIT* mutation will soon also be relevant in the treatment of skin involvement in mastocytosis.

Patients with advanced SM should, in addition to the treatment of their possible cutaneous involvement, also receive therapy targeting systemic mast cell infiltrates depending on their disease category. These treatments may include, among others, cladribine, midostaurin, imatinib and bone marrow transplantation. As mentioned, therapy of advanced SM is discussed in detail elsewhere in this book.

Prognosis of Cutaneous Involvement in Mastocytosis

Skin lesions in adults, as part of a diagnosis of either cutaneous mastocytosis or systemic mastocytosis with cutaneous involvement, usually follow a chronic course. Rarely, cutaneous lesions also progress, usually associated with progression of the systemic part, or actually regress, particularly in patients with mild ISM [25]. In terms of overall prognosis and survival, SM is worse than cutaneous mastocytosis without systemic involvement [24, 51]. Amongst patients with a diagnosis of SM, those with ISM have the best outcome, whereas those with advanced SM often show a poor prognosis and shorter survival.

In contrast, for the majority of paediatric patients with mastocytosis, the prognosis is favourable, with spontaneous resolution of cutaneous lesions and mediator symptoms around the time of puberty [27]. Especially with mastocytomas, persistence into adulthood or transition to SM has not been described. In patients with polymorphic MPCM and most patients with DCM, the course is typically self-limiting with spontaneous remission after several years [20, 27, 52]. Only the small subgroup of paediatric patients with monomorphic MPCM (Fig. 5.19) and a few selective patients with DCM show a persistent course lasting to adulthood.

Future Considerations

Much progress has been made in the past few years in terms of reaching consensus on an international classification system and standardising terminology in the field of cutaneous involvement in mastocytosis (Tables 5.1 and 5.2) [4]. This internationally accepted terminology will facilitate future studies on large patient cohorts in the form of registries that aim to better characterise different subforms, predict the clinical course, explore the use of biomarkers and unravel the pathogenesis of mastocytosis [24]. This in turn will aid the development of an optimal approach to diagnosis and treatment of mastocytosis in the future.

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Chapter 6
Pediatric Mastocytosis

Iván Alvarez-Twose and Melody C. Carter

Abbreviations

BM	Bone marrow
CM	Cutaneous mastocytosis
DCM	Diffuse cutaneous mastocytosis
ISM	Indolent systemic mastocytosis
MC	Mast cell
MIS	Mastocytosis in the skin
MPCM	Maculopapular cutaneous mastocytosis
NIH	National Institutes of Health
PB	Peripheral blood
qPCR	quantitative polymerase chain reaction
REMA	Spanish Network on Mastocytosis
SM	Systemic mastocytosis
UP	Urticaria pigmentosa
WHO	World Health Organization

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Spectrum of Disease in Pediatrics

All categories of mastocytosis share clinical features caused by the overproduction of mast cell (MC)-dependent mediators. The skin is often the first visible sign of the disease, but the gastrointestinal tract, lymph nodes, liver, spleen, BM, and skeletal system all express manifestations of MC burden. In children, the skin is the most common organ involved and may be the only manifestation of the disease. Interestingly, patients with mastocytosis do not suffer from recurrent bacterial, fungal, or viral infections, even though MCs release mediators such as histamine that inhibit immune responses in vitro. In 2007, a proposed addition to the nomenclature was introduced to clarify the pre-diagnostic state before a more definite diagnosis is made prior to a BM biopsy known as mastocytosis of the skin (MIS) [1]. The typical exanthema is considered the major criterion, and one of the two minor criteria based on abnormal MCs in clusters (>15) or >20 cells scattered per high power field (HPF) and/or detection of a KIT mutation at codon 816 is needed for the diagnosis. Thus, the term "cutaneous mastocytosis" (CM) is reserved

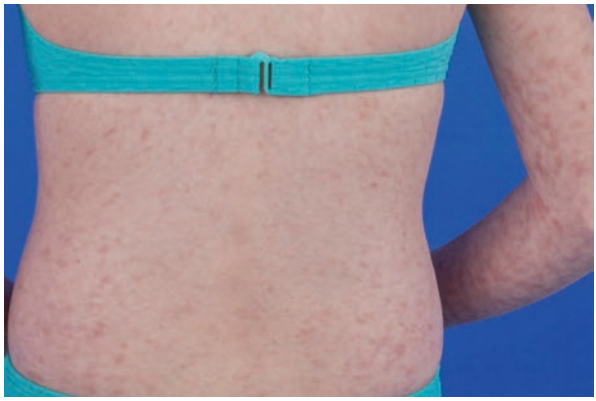

Fig. 6.1 Maculopapular cutaneous mastocytosis (MPCM), monomorphic-characteristic small red-brown, mainly uniform-sized lesions

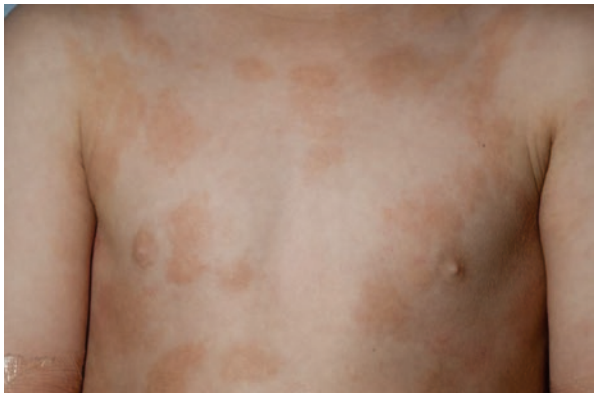

Fig. 6.2 Maculopapular cutaneous mastocytosis (MPCM), polymorphic-larger, varied-sized lesions that are asymmetric with hyperpigmentation

for cutaneous disease only and subdivided into maculopapular CM (MPCM) or urticaria pigmentosa (UP), diffuse cutaneous mastocytosis (DCM), and mastocytoma.

The most common skin manifestation in children (Fig. 6.1 and 6.2) is MPCM or UP, but the size and number are more variable in children with CM and more uniform in adults [2]. UP lesions are seen in almost all children with indolent systemic mastocytosis (ISM). A few studies have documented a regression of the skin lesions with a decrease in serum tryptase and severity of the disease in adults [2, 3]. The typical appearance of UP are yellow-tan to reddish-brown macules or slightly raised papules scattered mainly on the trunk and legs with generally less involvement of the sun-exposed areas. The palms, soles, face, and scalp are generally spared, especially in adults. Dermatologic symptoms include pruritus, flushing, and blistering, with the latter symptom almost uniquely seen in children. Darier's sign is the local whealing of a lesion induced by friction and, when present, can be diagnostic but may not be consistently elicited.

Diffuse cutaneous mastocytosis and mastocytoma have an onset almost exclusively in childhood. Although DCM may persist into adulthood, mastocytomas usually regress spontaneously. DCM is characterized by thickened skin and may exhibit a peau d'orange appearance with a reddish-brown discoloration without characteristic lesions (Fig. 6.3) but may also have scattered nodules similar in appearance to mastocytomas. The skin may be dermatographic, and the formation of hemorrhagic

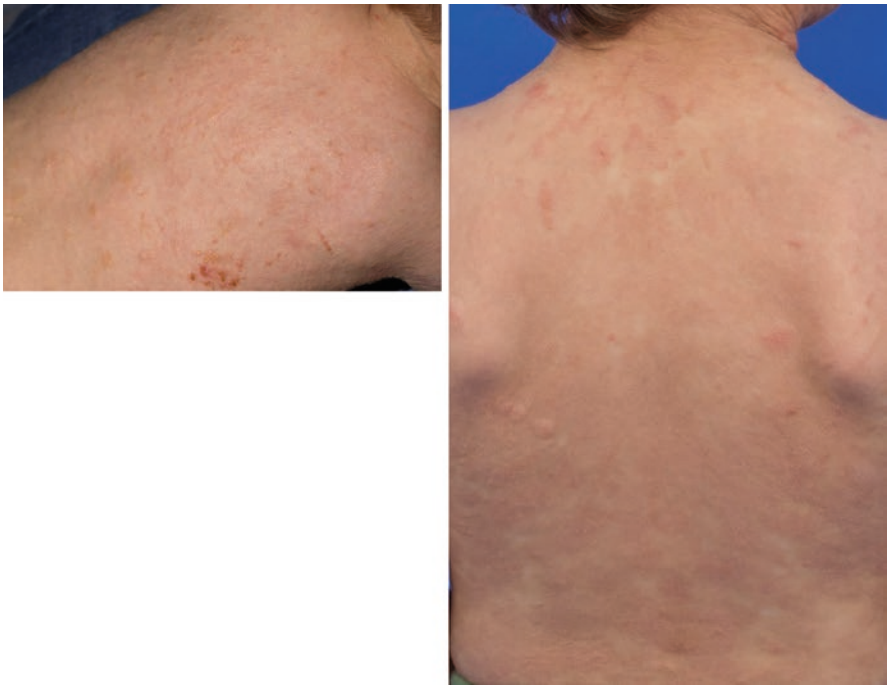

Fig. 6.3 Diffuse cutaneous mastocytosis (DCM) – typical skin manifestations with erythematous thickened skin and "peau d'orange" texture. Dermographism is characteristic

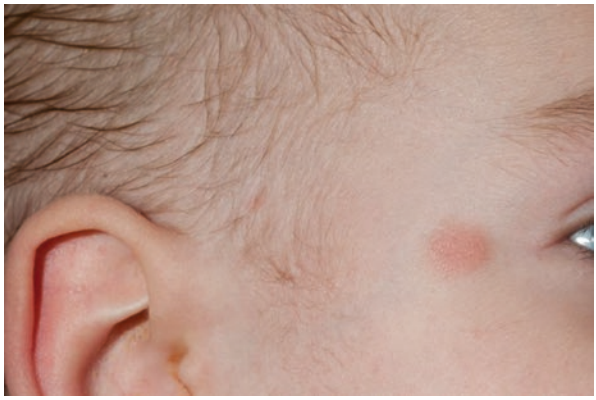

Fig. 6.4 Mastocytoma – the lesion usually presents as a reddish brown or dark pink nodule and is typically seen as a single lesion. The consensus group for mastocytosis notes that a maximum of three lesions can be present with this diagnosis [20]

blisters is common. Solitary mastocytomas are red-brown or yellow-orange nodules, which, when traumatized, may cause systemic symptoms such as flushing and hypotension (Fig. 6.4). The onset is generally before the age of 6 months, and it is unusual to develop subsequent skin lesions more than 2 months after the presentation of the initial lesion [4]. UP and DCM are associated with pruritus of varied intensity, which may be exacerbated by changes in climatic temperature; skin friction; and ingestion of hot beverages, spicy foods, alcohol, or certain drugs. Bullous formation is a characteristic limited to pediatric-onset cutaneous disease and usually is associated with lesional skin. Bullae may erupt spontaneously or in association with infection and immunization. This feature is mostly limited to the first few years of life and may need to be distinguished from other bullous diseases of childhood.

Systemic mastocytosis (SM) can occur in both adults and children and is diagnosed on the basis of BM histopathology outlined by the WHO consensus panel [5]. ISM, the most common variant of systemic disease, is diagnosed when criteria for mastocytosis are met, and there is no evidence of an associated clonal hematologic disorder or severe liver disease, hypersplenism, or significant lymphadenopathy. Isolated BM mastocytosis is a sub-variant of ISM with a low BM burden of MCs, a lower tryptase value, and the absence of skin lesions. The skin lesions in systemic disease may present with the typical monomorphic pattern seen in adults is also seen in pediatrics (Fig. 6.5) or the polymorphic pattern seen in children with cutaneous disease (Fig. 6.6). Several clinical conditions should heighten suspicion of this variant such as idiopathic anaphylaxis, venom anaphylaxis, unexplained osteoporosis, or chronic diarrhea [6–9]. This variant of systemic disease has not been reported in children. There are case reports in the literature of children with mast cell leukemia [10, 11] and other associated hematologic diseases [12–15]; however, these are rare associations. The majority of children with ISM have a good prognosis as shown in a study of long-term follow-up of children with mastocytosis [3, 11, 16].

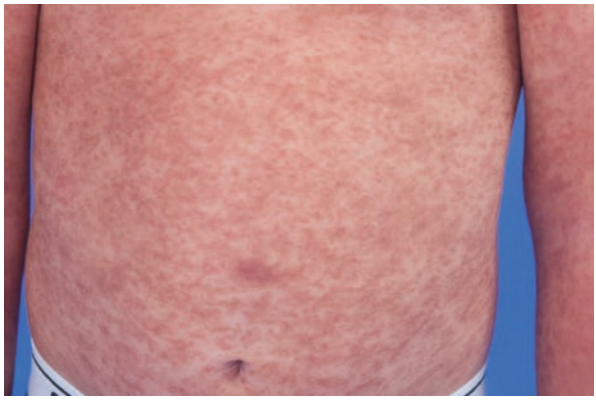

Fig. 6.5 MPCM, monomorphic pattern in a child with indolent systemic mastocytosis. Skin lesions are red-brown in color with mainly small uniform-sized lesions

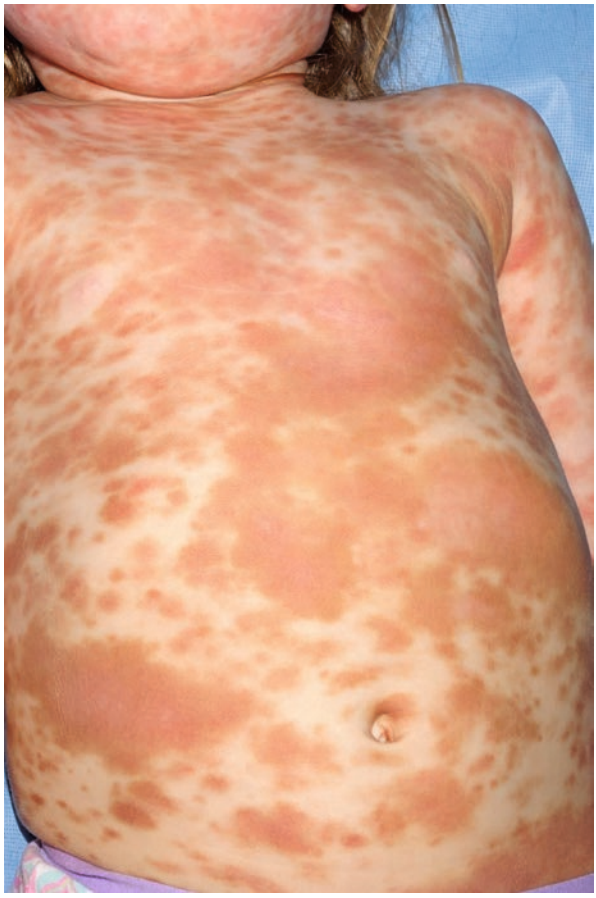

Fig. 6.6 MPCM, polymorphic pattern in a child with indolent systemic mastocytosis. Skin lesions vary in size with a red-brown vascular appearance

Disease Onset

Mastocytosis in children usually presents as a cutaneous rash together with variable type and degree of symptoms secondary to the effect of a wide variety of proinflammatory mediators released from activated MCs [17, 18]; more rarely, anaphylaxis in the absence of skin lesions may be the clinical presentation of the disease in a small subset of pediatric patients. The vast majority of children who show skin lesions of mastocytosis are assumed to have CM [1] even though BM studies to rule out SM are not routinely performed at the pediatric age. In children with signs or symptoms suggesting systemic involvement such as megalies or cytopenias and in those who have persistently increased serum tryptase levels >20 μg/L, SM should be suspected [1, 3].

Although pediatric mastocytosis can arise at any age, the onset usually occurs during the first 6 months of life, and in some patients, the disease is already present at birth [16, 19–21]. Importantly, the age of disease onset has been suggested to show prognostic impact in terms of persistence of the disease into adulthood; thus, children who have a late onset of the disease appear to have lower probability of spontaneous remission of mastocytosis than those with onset at early ages [22–24].

Classically, the WHO has recognized three main subtypes of CM (or MIS): (1) maculo-papular cutaneous mastocytosis (MPCM), formerly known as *urticaria pigmentosa* (UP), (2) diffuse cutaneous mastocytosis (DCM), and (3) mastocytoma of the skin [5, 25]. Despite the unquestionable value of the WHO classification of CM as a tool for the distinction among the most prevalent clinical forms of cutaneous involvement by mastocytosis, this classification shows several pitfalls that mainly include terminological and conceptual issues. Some of these limitations have already been addressed by an international task force involving experts from the European Union (EU) and the United States (USA) [20], while others remain to be solved.

The most recent version of the WHO classification of mastocytosis, which was updated in 2016 [5], still accepts the term “urticaria pigmentosa” as a synonym of MPCM. The classical term “urticaria pigmentosa” was coined in 1878 by the English dermatologist Alfred Sangster and described as “an anomalous mottled rash accompanied by pruritus, factitious urticaria, and pigmentation” [26]; 9 years later, the German dermatologist Paul Gerson Unna documented for the first time the presence of MCs in skin biopsies of UP lesions [27]. Given the fact that skin lesions of mastocytosis fail to show the typical transient course of urticaria and, in many cases, mastocytosis skin lesions do not contain the melanic pigment that would define the term “*pigmentosa*” of UP, the international task force of experts have recently suggested to use the more descriptive term “maculopapular cutaneous mastocytosis” to refer to this subtype of CM [20].

MPCM is characterized by brownish to reddish oval or round macules and papules with variable sizes, distribution, and density, although, in some children, plaques and/or nodules can also be observed or even be the predominant skin lesions; in fact, an early proposal of classification of CM in 2002 already included

nodular and plaque-type presentations of CM as independent entities separated from MPCM [28]. It should be noted that the macroscopic appearance of skin lesions can vary during the course of the disease in children, usually from nodules or plaques at disease onset to macules and papules after several years [20]. The heterogeneity of MPCM has also been emphasized in the recent classification proposed by the EU/US consensus group, where MPCM is divided into two categories: (1) monomorphic MPCM, characterized by the presence of skin lesions that show a similar shape and size, usually round and small, which, although is the clinical presentation typically associated with adult-onset mastocytosis (with cutaneous involvement), can be also found in a subset of pediatric mastocytosis; and (2) polymorphic MPCM, which is almost exclusively seen in children and consists of the coexistence of skin lesions displaying different sizes and shapes where large, nodule, or plaque-mimicking lesions frequently predominate [20].

DCM is a rare subtype of CM mostly seen in newborns and infants, defined by a generalized erythema and thickening of almost the entire skin without identifiable individual skin lesions, which shows a typical appearance of orange's peel ("peau d'orange" in French) or elephant skin ("pachyderma") [20, 25]. As per definition, DCM shows a very extensive cutaneous involvement by mastocytosis (typically >90% of the whole-body surface area). According to the etymology of the term "diffuse" (i.e., spread over a wide area), patients with extensive MPCM can be misdiagnosed as DCM; hence, the 2015 US/European consensus classification of CM tackles this issue accurately and highlights that the lack of hyperpigmented individualized lesions is a condition sine qua non for the diagnosis of DCM [20]. Moreover, some authors prefer the term "erythrodermic mastocytosis" over DCM to prevent misinterpretations of the adjective diffuse of DCM [29, 30].

Mastocytoma usually presents as a brownish to yellowish, large and solitary nodular-like skin lesion; in other patients, mastocytoma lesions are smaller and less elevated, resembling a solitary form of MPCM. Moreover, both the US/European task force as well as the 2016 WHO classification of mastocytosis still recognize under the denomination of mastocytoma the presence of up to three skin lesions, provided that they show the nodular appearance typically associated with mastocytoma [20]; accordingly, it has been also recommended to change the classical term "solitary mastocytoma" to "cutaneous mastocytoma" [20].

Clinical Symptoms

Clinical manifestations of pediatric mastocytosis mostly include a wide variety of symptoms secondary to the effect of different proinflammatory mediators released from MCs upon their activation; exceptionally, signs and symptoms of end-organ damage due to tissue infiltration by MCs can also occur in cases with advanced mastocytosis, although these are rarely seen in children.

Regarding MC mediator release symptoms, itching, redness, and swelling of lesional skin are common features of CM in children. Urtication together with an erythematous halo can be reproduced by firmly rubbing the skin lesions in what is known as the Darier's sign, which is considered as pathognomonic of mastocytosis [31]. Frequently, local MC activation of lesional skin results in the development of blisters, particularly during the first months following the onset of the disease. Severe and extensive spontaneous blistering is associated with extensive cutaneous involvement including MPCM cases with >90% of body surface area affected and patients with DCM, where the disease commonly presents itself with generalized blistering [2, 16, 19, 32]; this translates into the need for making a differential diagnosis in these latter cases with other bullous skin diseases of infancy such as bullous pemphigoid, epidermolysis bullosa, or staphylococcal scalded skin syndrome, among other entities. In a few cases of DCM, the content of blisters becomes hemorrhagic, which can be accompanied by some degree of anemization [20]. Of note, extensive blistering has been regarded by some authors as a predictor of massive MC activation and severe complications in pediatric mastocytosis [2, 32]. In fact, markedly increased levels of both total and mature serum tryptase as well as high tryptase levels in blister fluid have been documented in children with extensive blistering in association with other MC-activation symptoms who required hospitalization and emergency therapy [19]; moreover, the rare fatal outcomes of pediatric mastocytosis reported in the literature are practically restricted to children with DCM who developed severe systemic MC activation symptoms preceded by extensive blistering [11, 33]. Other cutaneous manifestations of pediatric CM are dermographism, urticarial rash, and exaggerated local reactions to insect sting/bite.

Flushing is also a relatively common finding in pediatric mastocytosis, which consists of a sudden warmth and reddening of the face and the upper chest caused by increased cutaneous blood flow as a result of the vasodilatory effect of certain MC mediators (e.g., histamine) on the thin and superficial dermal capillaries of these areas of the skin; thus, despite flushing is still largely considered as a cutaneous manifestation of mastocytosis, it should be actually recognized as an early primary vascular event which might precede the development of more severe symptoms including hypotensive collapse in some cases [32].

Other MC mediator release symptoms that can be observed in children with mastocytosis include gastrointestinal complaints (i.e., abdominal cramping, nausea/vomiting, and diarrhea) and, less frequently, dyspnea, fatigue, headache, or neuropsychiatric symptoms such as irritability and attention deficit/hyperactivity-like syndromes.

Overall, anaphylaxis or anaphylactoid reactions are rarely seen in pediatric mastocytosis. In a study by Brockow et al., 4 out of 46 children with mastocytosis (9%) had suffered from anaphylaxis [34]; similarly, the Spanish Network on Mastocytosis (REMA) has reported an incidence of severe MC mediator release symptoms requiring emergency therapy and hospitalization among children with mastocytosis of 11% (12/111 patients) [19]. Of note, in both studies, the severity of MC mediator-related symptoms was closely related to the extent of cutaneous involvement and also with the levels of serum tryptase.

Common elicitors of symptoms in pediatric mastocytosis include the friction of lesional skin, heat and hot water, fever, irritability, and teething [19]. Vaccines are also a relevant trigger for MC activation in children with mastocytosis, particularly among those with DCM [19, 35, 36]; for this reason, an appropriate premedication of vaccines has been recommended by some authors in such cases. Similarly, although the risk of MC mediator release symptoms during anesthesia is relatively low in children with mastocytosis (i.e., 4% in a series reported by the Spanish group including 42 patients undergoing different anesthetic procedures), such risk is clearly increased compared to that found in the general population; thus, it seems also reasonable to adopt preventative measures in this setting, as well as in other procedures associated with increased risk for MC activation such as the administration of iodinated contrast media [37]. Regarding anaphylaxis, idiopathic cause constitutes the most frequent trigger in pediatric mastocytosis; in turn, in contrast to adult-onset mastocytosis, insect-induced anaphylaxis appears to be exceptional in children [19, 34, 38].

Other Associated Diseases (Allergy)

Although it might be hypothesized that mastocytosis could confer an increased risk for other MC-mediated diseases and conditions, different studies have shown controversial results. Despite an early study by Caplan in 1963 suggesting that the prevalence of atopy could be doubled among patients with mastocytosis as compared to the general population (44% vs. 20%) [4], further studies have failed to demonstrate an association between mastocytosis and atopy. In 1990, a Swiss study showed no significant differences in the overall prevalence of atopic diseases (i.e., allergic rhinitis, bronchial asthma, and atopic dermatitis) between a series of 33 patients with mastocytosis and a control group of 52 blood donors (21% vs. 16%) [39]. More recently, a prospective analysis of 67 patients diagnosed with mastocytosis at the National Institutes of Health (NIH) showed a history of atopic diseases including atopic dermatitis, allergic rhinoconjunctivitis, allergic asthma, and food allergy in 31% of the cases [2]. Moreover, in this study, the density (but not the extent) of skin lesions seemed to inversely correlate with the coexistence of atopy in adults (but not in children) [2]. A further study by Brockow et al. in 74 adults and 46 children with mastocytosis revealed the presence of atopic eczema, allergic rhinoconjunctivitis, or allergic asthma in 28% and 11%, respectively [34]. Similarly, a study carried out by the REMA in 210 patients with mastocytosis including 163 adults and 47 children revealed that the prevalence of allergy as defined by clinical symptoms in association with specific IgE was 23.9% and 17%, respectively [38]. Altogether, these observations support that the prevalence of atopy or allergy in patients with mastocytosis does not significantly differ from that found in the general population and that the rate of allergen sensitization might be lower in children than in adults; nevertheless, there are no prospective studies so far that compare the prevalence of allergic diseases in children with mastocytosis versus non-mastocytosis individuals.

Overview of the Differences from Adult Disease

Mastocytosis constitutes a paradigmatic example of a complex and heterogeneous disease, which shows highly variable presentations in terms of age at onset, clinical manifestations, biological features, and outcomes.

Despite the fact that the vast majority of children with mastocytosis are not routinely studied in depth, principally as regard to BM examination, clear differences between pediatric-onset mastocytosis and cases arising in the adulthood have been largely established. First, the clinical spectrum of cutaneous involvement in children is broader than that in adults; thus, although MPCM is the most common subtype of cutaneous disease at any age, mastocytoma of the skin and, less frequently, DCM can be also found in children, whereas these latter clinical forms are rarely seen in adult patients [20]. In addition, MPCM appears to be more heterogeneous among children, in whom both the monomorphic and polymorphic variants of MPCM can occur; by contrast, adult-onset mastocytosis is typically characterized by skin lesions, consistent with the monomorphic variant of MPCM [20]. On the other hand, mastocytosis without skin involvement is relatively frequent among adults, particularly in patients suffering from anaphylaxis with a cardiovascular profile (e.g., hypotension, dizziness, loss of consciousness) in the absence of cutaneomucosal symptoms [40], but it is extremely uncommon in children.

Second, it is widely accepted that mastocytosis is a clonal systemic disease in nature when it arises in the adulthood but mostly restricted to the skin at the pediatric age. However, the assumption that children with serum tryptase levels below 20 μg/L are more likely to have CM [1] seems arbitrary and is not based on prospective studies. Taking into account the limitations mentioned above about the lack of complete BM studies in most children, the concept of "pure" CM in children is, at least, questionable, provided that dermal MCs derive from a precursor cell originated in the BM [41]. In the largest cohort of children with mastocytosis who underwent a BM study published so far, more than one-third of patients (19 out of 53) were shown to have SM [3]; however, it should be noted that these 53 children had been selected from a total of 105 patients for the BM analysis on the basis of severe MC mediator release symptoms and/or organomegalies. Interestingly, this study revealed that the presence of organomegalies was the most robust predictor of systemic involvement in children with mastocytosis, as all the patients with organomegalies who were studied but none of those without them had systemic disease [3]. Another fact to consider regarding systemic involvement in mastocytosis is a potentially higher prevalence of the so-called "well-differentiated SM" (WDSM) in children than in adults. This biologically unique variant of SM is characterized by a clonal expansion of MCs in the BM that typically displays an apparently normal morphology together with the lack of CD25 (and CD2) immunophenotypic expression in the absence of the D816V KIT mutation [42, 43], which means that three out of the four minor diagnostic criteria for SM according to the WHO are actually missing in a substantial subset of patients with WDSM; furthermore, these characteristics make the diagnosis of WDSM particularly challenging, since, frequently,

only those patients with a significant BM MC infiltration would meet criteria for SM according to the WHO, whereas most of the remaining cases would be misdiagnosed as CM. The skin lesions in WDSM have been noted to present with two patterns. One pattern is more typical of DCM with diffusely thickened skin (Figs. 6.7 and 6.8) and the other with a pattern similar to that of MCPM with distinct red-brown macules and papules (Fig. 6.9). To overcome the diagnostic limitations, specific minor criteria for the diagnosis of WDSM have been recently proposed, which include several biological features together with the onset of mastocytosis skin lesions during childhood [43] (Table 6.1). Because this latter clinical finding accounts for more than 90% of adult patients with WDSM [43], it could be hypothesized at least almost an equal prevalence of such SM variant in children and adults. Moreover, considering the fact that WDSM is typically associated with subtypes of CM rarely seen in adults, such as DCM or polymorphic MPCM [20], it would be expected even a higher frequency of WDSM cases in children vs. adults; in any case, future investigations are warranted in order to establish the true prevalence of WDSM among the pediatric population.

Other differential feature of pediatric versus adult-onset mastocytosis is the higher frequency of mutations involving exons other than 17 of the KIT gene in children. In a study by the French group published in 2010, where the entire KIT sequence was analyzed in skin biopsies from 50 children with mastocytosis, a mutation of codon 816 (exon 17) was found in 42% of cases, whereas mutations outside exon 17 were detected in 44% [44]; these findings contrast with an overall

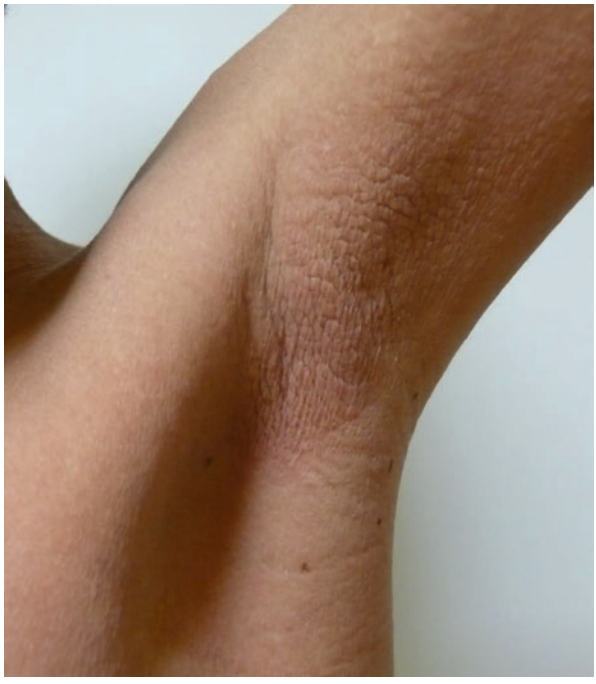

Fig. 6.7 DCM variant of WDSM: The skin is thickened with exaggerated skin folds particularly in the axilla

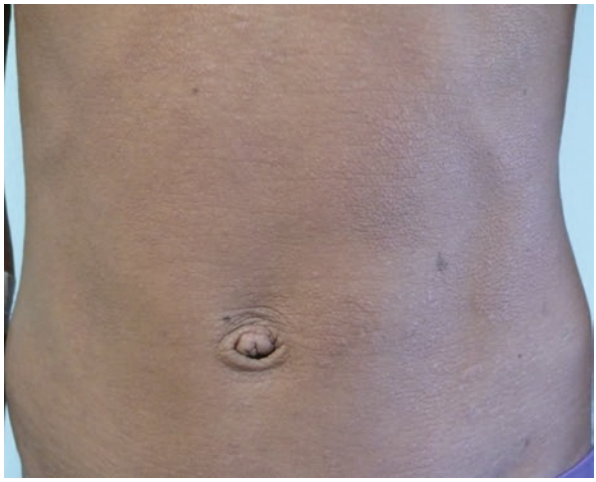

Fig. 6.8 DCM variant of WDSM: The skin is thickened with exaggerated skin folds and a lack of hyperpigmented skin lesions

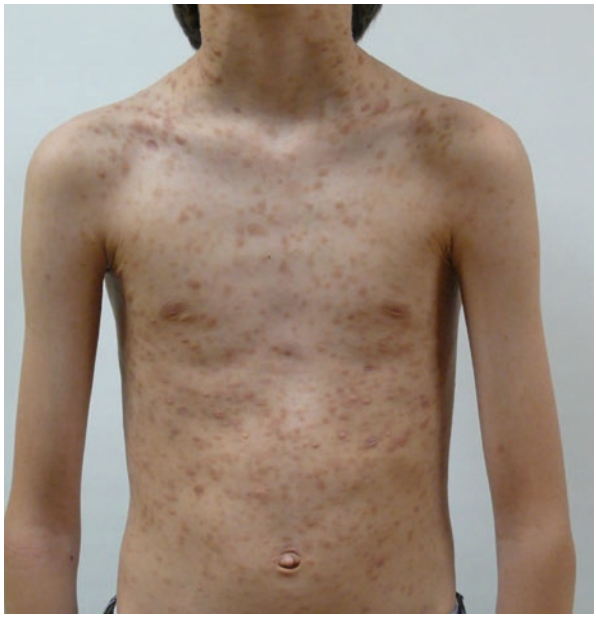

Fig. 6.9 The MPCM variant of WDSM-skin lesions is usually small (<0.5 cm) reddish-brown with both macules and papules. The trunk and neck are the main areas of involvement with relative sparing of the extremities

frequency of detection of the D816V KIT mutation in >90% of adult patients, provided that highly sensitive molecular assays are applied [45, 46]. Moreover, the results in terms of frequency of mutations involving the extracellular membrane and transmembrane domains (exons 8–10) of KIT reported in this study together with the well-known close association of this type of KIT mutations with WDSM [43, 47] also support the fact that pediatric WDSM is probably underestimated.

Table 6.1 Diagnostic criteria[a] of SM and WDSM according to the WHO [16, 17] and the REMA [38], respectively

Type of SM	Major criterion	Minor criteria
Conventional (CD25+) SM	Multifocal compact aggregates of >15 MCs in BM sections	Aberrant CD25 (and/or CD2) expression on BM MCs
		Abnormal MC morphology in >25% of BM MCs
		Mutation at codon 816 of the KIT gene
		Serum tryptase >20 μg/L
WDSM[b]	Multifocal compact aggregates of >15 MCs in BM sections and/or smears	Aberrant expression of CD30 and/or overexpression of cytoplasmic proteases on BM MCs
		Clusters of at least two MCs outside BM particles in BM smears
		Any mutation in the KIT gene or clonal HUMARA test
		In adult females, childhood-onset or familial aggregation

SM systemic mastocytosis, *WDSM* well-differentiated systemic mastocytosis, *WHO* World Health Organization, *REMA* Spanish Network on Mastocytosis, *MC* mast cell, *BM* bone marrow, *HUMARA* human androgen receptor assay

[a]In both cases, diagnosis is established if one major criterion and at least one minor criterion, or three or more minor criteria in the absence of the major criterion are fulfilled

[b]Diagnostic criteria for WDSM should be applied only in those cases in which BM MCs show an apparently normal morphology in the absence of strong expression of CD25 and CD2

Regarding MC mediator release symptoms, there are clinical manifestations typically seen in children that never occur in adults such as blistering and others that are much more common in adults than in children such as anaphylaxis. Also, the different triggers that can potentially activate MCs appear to play different roles depending on the age of the patients. Thus, whereas insect sting/bite is by far the most common elicitor of anaphylaxis in adult patients with SM [40], such trigger has virtually no clinical relevance in pediatric mastocytosis. By contrast, triggering factors such as fever, teething, and vaccines seem to be almost exclusively restricted to children with mastocytosis.

In terms of outcome, adult-onset mastocytosis is widely considered a chronic and incurable disease. Although the life expectancy of the vast majority of adults with indolent SM (ISM) does not differ from that of the general population [48], a small fraction of patients may evolve with time to advanced forms of the disease, including aggressive SM (ASM), SM with an associated hematological neoplasm (SM-AHN), or MC leukemia (MCL). The most important prognostic factors associated with an increased risk of disease progression in adult patients diagnosed with ISM are the presence of high levels of β2-microglobulin at diagnosis and the demonstration of multilineal involvement of hematopoiesis by the D816V KIT mutation [49]. It has been recently suggested that the crucial event that finally determines progression to advanced mastocytosis is the acquisition of genetic mutations in genes commonly involved in the pathogenesis of other hematological neoplasms, such as SRSF2, ASXL1, or RUNX1 [50, 51]. By contrast, the natural history of pediatric mastocytosis is toward spontaneous regression in most cases, generally before puberty, with only a minority of children remaining with persistent disease

in the adulthood, either as conventional SM or as WDSM. Although no definitive factors predicting the persistence of pediatric-onset mastocytosis in adult age have been identified so far, it has been suggested that the aberrant expression of CD25 on cutaneous MCs could be highly predictive of SM in adults [52]. Thus, if such hypothesis was extrapolated to children, then it might be speculated that the expression of this immunophenotypic marker in skin biopsies from children with mastocytosis could be of relevance in the persistence of the disease into the adulthood as a classical CD25+ SM. Regarding WDSM, the only factor that has been suggested to play a role in the persistence of mastocytosis after puberty is the gender, since more than 85% of patients diagnosed with WDSM at adult age who had a previous history of pediatric mastocytosis reported in the literature are women [42, 43, 53–55].

Diagnostic Evaluation

Mastocytosis is diagnosed on the basis of history, clinical manifestations, histopathology, and laboratory evaluation and classified based on the WHO criteria for mastocytosis [5]. A history of daily and episodic symptoms should be obtained along with possible triggers, alleviating and exacerbating factors. A thorough physical exam should include details of the skin lesions, lymph node examination, and careful abdominal exam to assess possible organomegaly.

Maculopapular cutaneous mastocytosis (MPCM) is usually seen in two patterns, namely polymorphic and monomorphic [20], and has been shown to be associated with prognosis. Patients with a polymorphic pattern tend to have an earlier onset of disease and resolution of skin manifestations over time, whereas the monomorphic pattern, similar to adult presentation, is associated with a more prolonged course and systemic disease [3]. MPCM lesions have MCs in increased numbers in the dermal papillae beneath macules and papules, particularly near blood vessels in the upper dermis [56]. A band-like infiltrate of MCs is distributed in the papillary dermis or appears as nodular infiltrates from the papillary dermis to subcutaneous tissues. Typically, there is a 15- to 20-fold increase in MCs beneath those lesions, but in some patients, only a twofold to fourfold increase in MCs is found (Fig. 6.10). Thus, it is important to correlate the gross skin examination with skin MC numbers and to avoid the diagnosis of UP exclusively on the basis of small increases in dermal MCs. MCs may also be found in increased numbers in the normal-appearing skin between lesions of UP [56]. The differences in the histologic pattern in cutaneous disease are generally based on the density of the MC infiltrate. In patients with DCM, the skin is typically thickened and described as “peau d’ orange” and diffuse red-brown color. These lesions are more prone to blistering with hemorrhagic crusts with minor friction. There have been two subtypes described, one with plaque-like lesions interspersed with normal-appearing skin and a diffuse thickening or pachydermic pattern [57]. The former has a better prognosis for complete resolu-

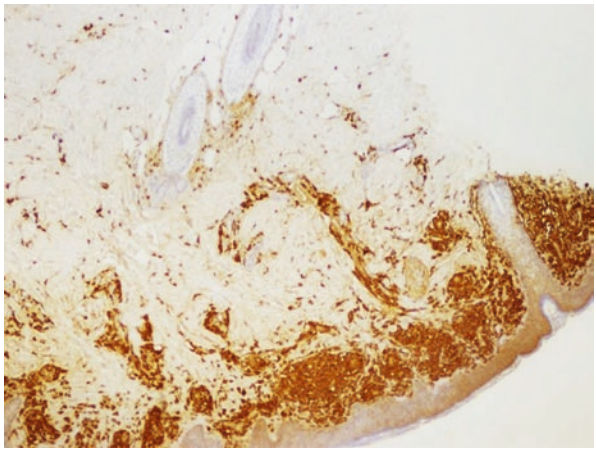

Fig. 6.10 Histopathology of DCM (40×), shown here stained with tryptase antibody demonstrating band-like infiltrates of MCs that extend into the papillary dermis

tion. MCs are observed around blood vessels and throughout the dermis. These band-like infiltrates may be indistinguishable from some lesions of MPCM or from biopsies obtained from mastocytomas. Mastocytomas typically present as a single lesion that is raised with a reddish-brown color, flesh colored, or yellowish color. It is quite sensitive to friction and can be associated with total body flushing. Darier's sign has been used as a diagnostic expression of CM. A wheal and flare response to rubbing or scratching the lesions with a blunt object is characteristic of MC infiltration. Since mastocytomas have an abundance of MCs and can cause a significant release of mediators, this diagnostic test should be avoided in these patients.

Laboratory assays that are helpful in the management are complete blood count and differential, liver function tests, vitamin D level, baseline serum tryptase, and IgE if there is a suspected allergic disease. Most laboratory tests are in the normal range with the exception of eosinophilia, lymphocytosis, and thrombocytosis that have not been shown to be of clinical significance and resolved without intervention. If there is a strong suspicion for systemic disease with organomegaly, elevated serum tryptase (>20 ng/ml), and/or severe mast cell mediator symptoms, a peripheral blood allele-specific assay for the KIT D816V mutation is helpful to guide decision for a BM study. The assay is specific for the D816V and may be negative in patients with other mutations in KIT or those patients with a low allelic burden [58]. An abdominal ultrasound is helpful when organomegaly is suspected.

CM is confirmed by a lesional skin biopsy demonstrating characteristic skin histopathology. Blind skin biopsies are not recommended, since other skin conditions including eczema and recurrent episodes of anaphylaxis may be associated with a twofold to fourfold increase in dermal mast cells [56, 59]. In addition, MCs may also be increased at skin sites involved in scleroderma [60], chronic urticaria [61], and prolonged antigenic contact [62]. CM must also be distinguished from other diseases with similar cutaneous characteristics as those of mastocytosis and are included in Table 6.2.

Table 6.2 Differential diagnosis

Dermatologic presentation	Most likely	Consider	Always rule out
No skin lesions		Idiopathic flushing	Identifiable causes of anaphylaxis
			Idiopathic anaphylaxis
Diffuse or localized hyperpigmented macules	Café au lait spots	Post-inflammatory hyperpigmentation	Scabies
	Neurofibromatosis	Atopic dermatitis	Secondary syphilis
	Albright syndrome	Chronic urticaria	Addison's
			Lentigo
Bullous lesions	*Staphylococcus* infection	Bullous disease of childhood	Incontinentia pigmenti
	Drug eruption of infancy	Linear IgA dermatosis	Bullous impetigo
	Incontinentia pigmenti		
	Bullous pemphigoid		
Solitary or multiple nodules	Congenital nevus		Leukemia
	Juvenile xanthogranuloma		Lymphoma

Currently, the standard for the diagnosis of SM is by performing a BM biopsy and aspirating with demonstration of the major criterion, consisting of multifocal dense MC aggregates, and one minor criterion or if three minor criteria are present (Table 6.1). The most useful stain for MCs is tryptase using a monoclonal antibody. In trephine core BM biopsies, decalcification interferes with subsequent attempts to visualize MC granules with metachromatic stains, thereby making tryptase the stain of choice. In addition, immunohistochemistry and/or flow cytometry to identify CD25+ MCs is useful since this parameter has been shown to correlate with the presence of activating mutations in KIT [63].

Other tissue specimens such as lymph nodes, spleen, liver, and gastrointestinal mucosa delineate the extent of MC involvement but are not typically sampled. Gastrointestinal biopsies are obtained only if a gastrointestinal workup is indicated, and lymph nodes are biopsied only if lymphoma is considered. When biopsies have been obtained of involved tissue such as the GI tract, the histopathologic pattern of MC aggregates or sheets is similar to that seen in the BM and is often CD25 positive [64–66].

In patients suspected of having mastocytosis, the diagnosis of a carcinoid tumor or pheochromocytoma should be ruled out. Importantly, patients with mastocytosis do not excrete increased amounts of 5-HIAA. Patients with carcinoid tumor or pheochromocytoma do not have histologic evidence of significant MC proliferation and should have normal serum tryptase levels [67].

Follow-Up and Management

Patients can typically be followed by their primary care providers if the above assays are obtained on an annual basis or in association with an acute illness or severe mediator symptoms. Patients should receive routine vaccines since the incidence of unexpected adverse reactions is low [68]. Children with mastocytosis, unlike adults, have not been reported to have an increased risk of anaphylaxis in association with venomous insect stings. Annual serum tryptase values along with peripheral blood allele-specific qPCR in children with suspected or confirmed systemic disease is helpful to determine if a more aggressive workup is needed. Patients with organomegaly should have a repeat ultrasound every 1–2 years until resolution or with acute enlargement.

A referral to a specialist, allergist/immunologist or hematologist, familiar with MC diseases is warranted for the following:

- The diagnosis is questionable and needs tissue confirmation.
- Symptoms are not sufficiently controlled with an anti-mediator therapy.
- There is a suspicion for systemic disease.
- A persistently elevated or increasing baseline serum tryptase.
- A peripheral blood assay that is positive for the KIT D816V mutation.
- Other signs and symptoms of a myeloproliferative disease.

Therapy for mastocytosis is based on the amelioration of symptoms and applies to patients with CM and SM. Cytoreductive therapy for MCs is typically reserved for more aggressive variants such as smoldering SM (SSM) or aggressive SM (ASM). These variants are rarely seen in the pediatric population. Therefore, cytoreductive agents are discussed in detail in other chapters. The most prominent complaints are cutaneous and gastrointestinal problems. Cutaneous symptoms such as flushing, blistering, and pruritus are proportional to the skin MC burden, with more frequent and severe symptoms in patients with DCM and mastocytoma than in patients with MPCM. In a previous study, it was noted that these cutaneous symptoms could be present through the adolescent period, although less severe [3]. Gastrointestinal symptoms were also distinguished by variants noting that patients with ISM had more problems such as diarrhea and reflux, but patients in all variants complained of abdominal cramping. Of note, during an acute flushing and/or blistering event, many patients complained of associated abdominal cramping and diarrhea. Headaches were due to non-mastocytosis-related complaints such as migraines and possibly mastocytosis-related events such as vasodilatation. The therapy is based on the underlying etiology. Musculoskeletal complaints were mainly unrelated to the diagnosis of mastocytosis or unknown etiology, and thus, the approach was again based on the etiology. Therapeutic options are summarized in Table 6.3.

Table 6.3 Therapy

	Preventive	Symptomatic-chronic	Acute
Cutaneous			
Flushing	Emollients	H1 antihistamines	Oral H1 antihistamines
Pruritus	Cromolyn-based cream[a]	Surgical excision-mastocytoma	Topical corticosteroids
Bullae	Topical calcineurin inhibitors[b]		
Second infection		Oral and/or topical antibiotics	Oral and/or topical antibiotics
Gastrointestinal			
Cramping	Oral cromolyn	Oral cromolyn	
Diarrhea		Fluids, rarely antidiarrheal	Fluids, rarely antidiarrheal
Constipation	Diet, bulk fiber agents	Bulk fiber agents	
Reflux	H2 antihistamines	Proton pump inhibitors	
Vomiting		Anticholinergics, antiemetics	Anticholinergics, antiemetics
Systemic			
Generalized hives	Avoidance of known triggers	H1 and H2 antihistamines	Epinephrine, IV fluid support,
Generalized bullae		Cromolyn-based cream	Corticosteroids and antihistamines
Anaphylaxis			
Other			
Headache	Avoid triggers such as heat	Etiology-specific targeted therapy	Tylenol or NSAIDs if no prior adverse reactions
Musculoskeletal pain	Appropriate conditioning for sports	Tylenol or NSAIDs if no prior adverse reactions	
Neuropsychiatric	Vitamin D supplements for deficiency	Appropriate referral for DX and TX	Emergent referral
CV-hypotension, reflex tachycardia	Adequate sleep and relaxation techniques	Mild, associated with flushing, supine position, and cool compresses	Treatment based on etiology, if associated with anaphylaxis, see above

[a]Product compounded by pharmacy
[b]No control studies to support usage, only case reports. CV-cardiovascular, DX-diagnosis, TX-therapy

Prognosis and Disease Resolution

Children generally have a favorable prognosis and a measurable resolution, especially when the onset of disease is prior to the age of 2 years. Patients with the onset of disease after the age of 5 years tend to have a more persistent pattern, but there is not much information in the literature regarding the progression to a more severe

variant. Resolution tends to occur in late adolescence [1, 3, 16] without reoccurrence of disease. Patients diagnosed with cutaneous disease in adolescence are more likely to have SM; however, children can be diagnosed with systemic disease as early as infancy. These patients mainly expressed the *KIT* D816V mutation, and the prognosis is dependent on the degree of involvement, but patients are reported to have a normal life expectancy. Further, in a long-term follow-up study of children with systemic disease, the overall clinical outcome reflected an improvement of cutaneous manifestations, organomegaly, and serum tryptase values [3].

In summary, children with CM and SM have a good prognosis. Patients with cutaneous disease only can have complete resolution of the disease, with minimum or no symptoms in most patients . Those with systemic disease will have a chronic pattern with varying degrees of resolution based on the initial presentation. This allows for a conservative approach to management without a need for cytoreductive therapy.

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Chapter 7
Gastrointestinal Manifestations of Systemic Mastocytosis

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Mast cells arise from the bone marrow and complete their maturation in various tissues that interface with the external environment. These may include the skin, airway, and gastrointestinal (GI) tract. Although mast cells reside in many other organs and tissues, symptoms that are attributed to mast cells manifest predominately in these locations [1]. In the clinical series of patients with systemic mastocytosis (SM) that have been published, the GI tract is among the most common sites where patients experience symptoms [2, 3]. In the clinical care of patients with SM, it is therefore important to elicit and characterize GI symptoms to be able to direct therapy.

The GI tract may be divided into the "upper GI tract" that includes the esophagus, stomach, and the first part of the small intestine and the "lower GI tract," which includes the distal part of the small intestine and the colon and rectum. Symptoms may be due to pathology at the mucosal surface, which affect absorption and fluid and electrolyte secretion and may contribute to diarrhea and abdominal cramping, for instance. GI symptoms may also be caused by the interplay between the tissue resident cells of the GI tract and the enteric nervous system that controls GI tract motility and pain hypersensitivity. In this regard, disorders leading to abnormalities in motility may cause dysphagia (esophagus), nausea and vomiting, and early satiety (gastric emptying delay), bloating (small intestine), or constipation (colon). Abnormalities of pain sensitivity can lead to symptoms such as abdominal pain and cramping.

Mast cells are known to play key roles in the GI tract on the mucosal surface through functions that affect the host response to infectious organisms, response to allergens, and homeostasis [4]. Mast cells also play an important role on the serosal side of the intestine by directly interacting with the nervous system to communicate

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important response signals to infection, stress, and dietary antigens, among others [5]. Due to the numerous functions of GI mast cells and the diverse locations throughout the GI tract, mast cells may be implicated in a host of GI symptoms that a patient may experience.

Patients with SM experience GI symptoms for three reasons, all of which need to be teased out to provide optimal therapy.

Symptoms Due to Mast Cell Activation

This is the most common mast cell-specific cause of GI symptoms and may occur with any type of SM. It is the most common cause of mast cell symptoms in patients with indolent SM. During mast cell activation, symptoms arise depending on the mediators that are released and the stimulus and overall activation state of the patient at that time. Patients often experience symptoms in multiple organ systems during this time and may recall a typical trigger. Typical GI symptoms that are thought to be caused by mast cell activation may include heartburn, nausea, abdominal bloating and cramping, and loose stools [3]. As mentioned, these symptoms usually occur with other symptoms in other organ systems such as flushing and hives and usually resolve when the trigger is removed or treatment is given. GI symptoms that respond to as-needed mast cell mediator blockers such as diphenhydramine are more likely to be related to mast cell activation.

Symptoms Due to Mast Cell Infiltration

Patients with indolent SM have elevated numbers of mast cells in the GI tract but oftentimes do not have a significant cellular burden to affect absorption. When the colon mucosal histology of a series of patients with SM was reviewed, there was a large range of mast cells per high-power field (HPF), that is, 20–278 with a median of 109 [6]. The clonal mast cells were seen in isolated aggregates in the mucosal lamina propria in the involved biopsies (most often seen in patients with indolent SM) or sheets and multiple clusters of cells below the surface epithelium (seen in those with aggressive SM). Perhaps, not surprisingly, based on these data, it is the patients with aggressive disease who may manifest with malabsorption. Symptoms include abdominal bloating and cramping and loose often foul-smelling stools, and workup may reveal evidence of a low serum albumin and various nutritional deficiencies including the fat-soluble vitamins A, D, E, and K. A helpful way to distinguish whether or not GI symptoms and signs are due to malabsorption is to assess response to a course of corticosteroids.

Symptoms Unrelated to Mastocytosis

Once the patient has been assessed for all possible mast cell-related symptoms, it is important to evaluate for other diseases or disorders that affect the GI tract and may also be at play, particularly when there has been a suboptimal response to mast cell-directed therapies. Patients with more chronic GI symptoms such as abdominal pain and loose stools should be assessed for celiac disease, eosinophilic inflammatory disorders affecting the GI tract, and inflammatory bowel disease including Crohn's disease, ulcerative colitis, and microscopic colitis. Patients may also have primary motility disorders such as achalasia, gastric emptying delay, and, most commonly, slow transit constipation. To add to the complexity, diseases or disorders that manifest outside of the GI tract may cause GI symptoms. Nausea, for instance, is a symptom that may occur in disorders affecting the central nervous system, endocrine, and gynecologic systems.

Diagnostic Considerations

In patients with SM and prominent GI symptoms, it is recommended to refer to a gastroenterologist for specialty care. Before or while waiting for the consultation, a thorough physical exam will help to assess for the possibility of malabsorption or portal hypertension such as peripheral edema, ascites, and splenomegaly. Certain tests may be ordered that can help differentiate or pinpoint particular symptoms. Laboratory tests should include a complete blood count to assess for anemia and iron studies, folate, and B12 if this is found. Patients with chronic GI symptoms and iron-deficiency anemia typically will require upper endoscopy and colonoscopy plus or minus small bowel evaluation to asses for inflammation, ulcers, and malignancy. Lab tests to assess for inflammation can help differentiate between inflammatory causes of chronic diarrhea and abdominal pains, and these include a C-reactive protein and stool calprotectin test, tissue IgA transglutaminase antibody test to screen for celiac disease, and differential test on the complete blood count to assess for elevations in peripheral eosinophils. Blood tests to screen for malabsorption include serum albumin, pre-albumin, folate, vitamin D, and PT and INR. In patients with prominent diarrhea lasting more than a week, stool infectious studies to rule out *Clostridium difficile* and *Giardia* should be considered. In patients with abdominal pain, liver function tests and lipase should be checked along with electrolytes including calcium and magnesium and thyroid function in those with constipation. There is no specific mast cell test that may be ordered to help guide treatment for the GI manifestations, although the degree of elevation of serum tryptase may make one think that infiltration of mast cells in the GI mucosa plays a role in the symptoms.

If a patient is having GI symptoms as well as systemic signs or symptoms such as fevers or weight loss, a CT of the abdomen and pelvis can be ordered to check for intestinal inflammation, infectious complication such as abscess, or signs of malignancy.

Additional testing will be considered by the consulting gastroenterologist. An upper endoscopy with biopsies can help to assess patients with prominent esophageal symptoms such as dysphagia or new or worsened reflux, evidence or a suspicion of GI bleed, early satiety, weight loss, persistent nausea and vomiting, or chronic diarrhea. In those with lower abdominal pains, cramping or bloating, or change in bowel movements, or blood in the stool, a colonoscopy is performed. The gastroenterologist may order other testing including esophageal, stomach, and colon motility tests. In patients with abdominal cramping and bloating and loose stools, breath tests are ordered to assess for bacterial overgrowth, or intolerances to lactose and fructose. In patients with significant constipation, additional tests may include MR defecography or anal manometry to assess for pelvic floor dysfunction.

Patients with indolent SM without any other primary GI disorder typically have a fairly normal GI diagnostic workup. The upper endoscopy and colonoscopy do not show obvious mucosal abnormalities (see Fig. 7.1a). It is important that the endoscopist knows to biopsy in all segments of the normal-appearing bowel including stomach, duodenum, terminal ileum, right colon, and left colon in order to assess for the findings of mastocytosis seen on histology. A KIT stain should be performed in addition to the standard hematoxylin and eosin stain to highlight the mast cells and to evaluate whether or not they are clustered or in sheets. This finding fulfills a major criterion for the diagnosis of SM. A CD25 stain is used to confirm the clonal mast cells, which is a minor criterion [7]. Intestinal involvement of clonal mast cells in SM is typically minimal with scattered clusters of mast cells dispersed in the upper and/or lower GI tracts (see Fig. 7.1b). In patients with indolent SM without other primary GI issue, the abdominal imaging is also typically normal.

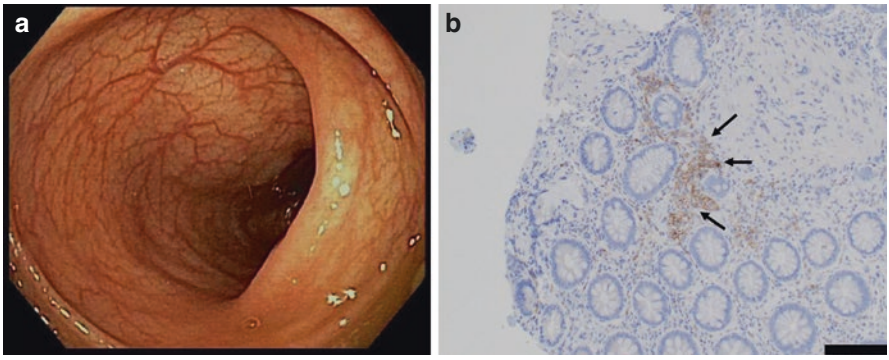

Fig. 7.1 Images showing a normal appearing colon at colonoscopy (**a**) and the corresponding pathology (**b**) from a random biopsy of a patient with indolent systemic mastocytosis. In image **b**, the clonal mast cells stained brown are seen in a cluster in the lamina propria (black arrows, CD25 stain; black bar represents 100 μm)

Patients with smoldering or aggressive SM often have abnormalities seen on upper endoscopy and colonoscopy, such as erythema, edema, and granular appearance (see Fig. 7.2a), with biopsies showing a larger burden of clonal mast cells in the lamina propria and often just beneath the surface epithelium where they may be aggregated in sheets as well as multiple clusters (see Fig. 7.2b). Abdominal imaging may show features of malabsorption such as intestinal wall edema and ascites and/or signs or portal hypertension related to the infiltration of mast cells in the liver and portal system (see liver below). This may include the presence of esophageal and gastric varices, and an enlarged spleen.

Treatment

As mentioned above, when deciding on the optimal treatment strategy, it is important to tease out which symptoms are related to mast cell activation, infiltration of mast cells, or other unrelated causes. The typical GI symptoms of mast cell activation are listed above and often occur in association with mast cell activation symptoms involving other organ systems. These symptoms typically respond well to a "step" approach with medications used to block the release of mast cell mediators and the mediators themselves [8]. H1 and H2 antihistamines are often the first-line treatment for mast cell activation and H2 blockers such as famotidine and ranitidine can be further titrated to treat related peptic symptoms. Oral cromolyn sodium is highly effective in treating GI symptoms including nausea, abdominal bloat and cramping, and loose stools [9]. The standard dosing of 200 mg four times a day taken ideally on an empty stomach is used with further dose titration if GI symptoms attributed to mast cell activation persist. Additional medications may be added if a patient continues to have signs and symptoms of mast cell activation

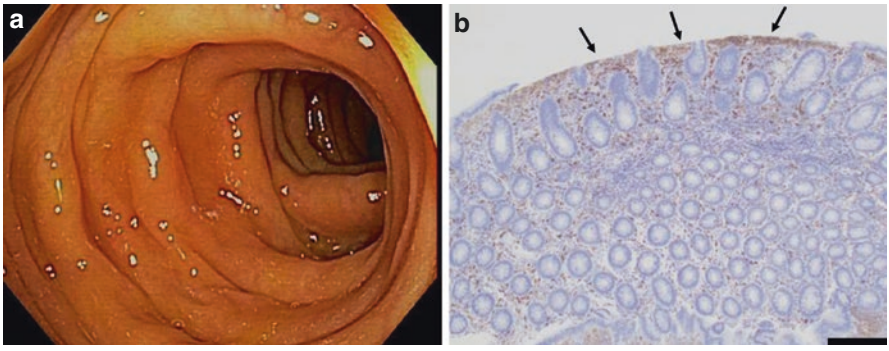

Fig. 7.2 Images showing the edematous-appearing folds of the colon at colonoscopy of a patient with aggressive systemic mastocytosis (**a**) and the corresponding pathology (**b**) from a targeted biopsy. In image **b**, sheets of infiltrated mast cells stained brown are seen beneath the surface epithelium (black arrows, KIT stain; black bar represents 200 μm)

and include leukotriene inhibitors [10] and ketotifen [11]. Aspirin should be used with caution due to the baseline increased risk of peptic ulcer disease in patients with SM.

In patients with smoldering and aggressive SM who are thought to have intestinal symptoms attributed to malabsorption, cytoreductive therapies can reduce the mast cell burden to reverse this manifestation [12]. If these signs and symptoms continue or in patients who do not use cytoreductive agents, a trial of corticosteroids may help to reduce the number of mast cells in the intestine. More recently, oral budesonide given daily at a 6 or 9 mg dose has been used for several months at a time and can provide treatment for the malabsorption with less risk of steroid side effects due to the high level of hepatic first-pass metabolism of budesonide.

In patients with SM, nutrient deficiencies should be addressed with proper diet and supplementation. There is no specific diet that is known to reduce the burden of mast cells or to lessen mast cell activation. Dietary recommendations should include avoidance of known triggers and eating whole foods as possible where all the ingredients are known. Patients can be advised to avoid processed foods and foods with preservatives. In general, a whole food diet with lean proteins, whole grains, cooked vegetables, and some starches is well tolerated. Patients with diarrhea-predominant symptoms are encouraged to avoid roughage, heavy dairy, greasy and fatty foods, and refined sugars. Patients with constipation and constipation mixed with loose stools are recommended to increase the amount of fiber consumed to at least 25 g per day.

In patients with ongoing GI symptoms, despite the above treatments, medications directed at symptoms can be prescribed. As needed, ondansetron and Compazine can be tried for nausea; Imodium for diarrhea; and Colace, senna, linaclotide, and polyethylene glycol 3350 for constipation. If a motility disorder is suspected, metoclopramide can be tried in the short term to test its efficacy. A longer term option is domperidone, which does not cross the blood–brain barrier and has a better side effect profile.

Special Situations

Peptic Ulcer Disease

Mast cell-derived histamine has a direct effect on gastric production by acting on the acid-producing parietal cells. In the original series of patients with SM, there was an increased incidence of peptic ulcer disease and with related complications that include intestinal bleeding and gastric outlet obstruction [1]. The incidence appears to have decreased in areas where proton pump inhibitors are typically used to control peptic-type symptoms. Type 2 antihistamines block

histamine but do not have the same GI mucosal ulcer protection as that of proton pump inhibitors [13].

GI Tract Cancers

There have been studies that suggest an increased incidence of adenoma-type precancerous polyps in patients with mast cell disorders [14]. However, no study has shown an increased incidence of colon adenoma polyps or colon cancer in patients with SM compared with patients without SM, and the typical screening guidelines used for colon cancer are typically applied. There is also no recommendation to screen for upper GI tract, liver, or pancreas tumors in patients with SM. Nevertheless, it is important to have a low threshold to assess for malignancy in patients with SM who have chronic GI symptoms such as GI bleeding and systemic issues such as fever and weight loss.

Liver Involvement

Patients with indolent SM may have involvement of mastocytosis in the parenchyma of the liver, but the presence of clonal mast cells in this setting typically does not affect liver function or cause portal hypertension [6]. In patients with smoldering or aggressive mastocytosis, however, clonal mast cell infiltration may result in portal hypertension. If suspected, these patients should be assessed for gastric and esophageal varices. Upper endoscopy is the best way to screen and potentially treat varices through band ligation procedures. The presence of abdominal ascites needs to be worked up with the appropriate tests to determine the etiology and exclude infection (spontaneous bacterial peritonitis) if new symptoms rise. Patients should also be screened for hepatic encephalopathy. Signs of hepatic synthetic dysfunction are rarely seen in SM and a full workup should be performed by a specialist to evaluate for other possible causes in this scenario.

Conclusion

In summary, it is important to be able to recognize and characterize the various GI symptoms that patients with SM often experience. Through a systematic approach to history taking, physical exam, and diagnostic testing, symptoms can be attributed to mast cell activation, mast cell infiltration, or due to other primary GI disorders or diseases unrelated to the mastocytosis. If this approach is followed, specific treatments can be tried or titrated to reach the desired effect of relief of symptoms and prevention of complications.

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Chapter 8
Systemic Mastocytosis and Bone-Related Events

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Abbreviations

BMD	Bone mineral density
DKK1	Dickkopf-related protein 1
DXA	Dual-energy X-ray absorptiometry
FN	Femoral neck
IL	Interleukin
IL	Interleukins
ISM	Indolent systemic mastocytosis
LS	Lumbar spine
LT	Leukotrienes
OPG	Osteoprotegerin
P1CP	Propeptide of type I C-terminal procollagen
P1NP	Propeptide of type I N-terminal procollagen
PAF	Platelet-activating factor
PGD2	Prostaglandin D2
PTH	Parathyroid hormone
PTH-rP	Parathyroid hormone-related peptide
RANK	Receptor activator of nuclear factor-κB (NF-κB)
RANKL	Receptor activator of nuclear factor-κB (NF-κB) ligand
SCF	Stem cell factor

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SM	Systemic mastocytosis
TGF-β	Transforming growth factor-beta
TH	Total hip
TNF	Tumor necrosis factor
VEGF	Vascular endothelial growth factor

Introduction

Mastocytosis is caused by a neoplastic proliferation of abnormal mast cells (MC), driven by the binding of stem cell factor with the tyrosine kinase receptor KIT(CD117), in the mast cell progenitor, resulting in the activation and proliferation of mast cells. This accumulation and infiltration of mast cells in different tissues and organs lead to a heterogeneous group of diseases, ranging from cutaneous mastocytosis, involving the skin, to systemic mastocytosis (infiltrating deep organs). Cutaneous mastocytosis is usually seen during infancy and childhood and typically associated with a relatively good prognosis and spontaneous remission. Systemic mastocytosis, the most common form in adults, is generally more disturbing and associated with involvement of multiple organs and tissues other than skin, organ failure, and reduced life span. Furthermore, systemic mastocytosis (SM) is itself a heterogeneous group of diseases with variable prognoses. The clinical spectrum of SM varies from pre-diagnostic SM to mast cell leukemia. Other clinical varieties include indolent SM, smoldering SM, aggressive SM, and SM associated with hematologic malignancy or mast cell leukemia. Mast cell sarcoma (MCS) and extracutaneous mastocytoma are two other clinical conditions that have no SM criteria. Pre-diagnostic SM is the term for colonization of abnormal mast cells in bone marrow that does not fulfill the criteria of SM [1–3].

According to World Health Organization (WHO) classification, major criteria for SM are the presence of multifocal, dense infiltration of mast cells (aggregation of ≥15 mast cells) in biopsy of bone marrow or extracutaneous organs. Minor criteria include >25% mast cells with atypical or immature morphology; activating mutation D816V; presence of CD2- or CD25-positive mast cells in bone marrow, blood, or other extracutaneous organs; and tryptase level persistently >20 ng/ml. The presence of the major criterion and one minor criterion or at least three minor criteria support the diagnosis of SM. Serum tryptase level has a positive correlation with mast cell burden [2]. Other helpful tools for diagnosis include immunohistochemical staining against CD117 (KIT) and tryptase in bone marrow and analysis of urine histamine mediators [3].

Indolent SM is the most common type of SM that is usually associated with skin and gastrointestinal manifestations [4]. Disease progression is manifested by the appearance of B and/or C findings, which correlate with poorer prognosis. B findings include >30% infiltration of bone marrow by mast cells, serum total tryptase level >200 ng/mL, dysplasia or myeloproliferation in hematopoietic lineage other than mast cells, hepatomegaly with normal liver function, palpable splenomegaly with no signs of hypersplenism, and lymphadenopathy. C findings include cytope-

nia of one or more hematopoietic cell lineages without evident malignancy, palpable hepatomegaly associated with liver function abnormalities, ascites, portal hypertension, bone involvement manifested with large osteolytic lesions and/or pathological fractures, palpable splenomegaly accompanying with signs of hypersplenism, and malabsorption concomitant with weight loss [2].

The most common mutation (found in 80–90% persons with systemic mastocytosis) is a gain-of-function mutation in the KIT receptor (D816V mutation) that leads to the neoplastic growth of MCs. The oncogene c-kit encodes c-Kit receptor, a class III receptor tyrosine kinase, which has five extracellular domains that are structurally like immunoglobulins, and a transmembrane portion. The gain-of-function mutation can potentiate the interaction of stem cell factor (SCF) with upper extracellular domains of receptor by inducing dimerization in lower extracellular domains. This interaction leads to a signaling transduction that plays a crucial role in facilitating angiogenesis, migration, cell survival, and proliferation of MCs [5, 6].

Pathogenesis and Etiology of Bone Disease in Mastocytosis

Bone is one of the major organ involvements in adult SM [1]. The exact mechanisms of bone involvement, including fragility, bone infiltration, bone loss, and sclerosis, in SM patients are not completely understood.

Osteoporosis and fracture occur more commonly in the lumbar spine than in the hip, demonstrating that the major underlying pathogenic process that leads to greater trabecular bone loss than cortical bone loss, in a similar pattern as most forms of osteoporosis. This preferential loss in the trabecular bone might be explained by the fact that neoplastic proliferation of abnormal mast cells occurs in bone marrow with higher metabolic activity [1, 3].

It is generally believed that neoplastic infiltration of mast cells, mast cell activation with release of different mediators (histamine, tryptase, and heparin), and inflammatory markers (TNF, growth factors, and ILs), all critically contribute to bone loss [3] (Fig. 8.1).

The bone histomorphometric information in SM patients with osteoporosis showed increase [7] or no change [8] in osteoclast number. However, the deterioration of bone health could be due to alteration of bone structure, increased bone turnover, increased osteoid tissue, fibrosis of peritrabecular area, and changes in trabecular structure [1, 3, 7, 9].

In addition, osteoclasts themselves express KIT on their surfaces that can also interact with SCF, but an increase in osteoclast activity due to this interaction is not proven definitively [10]. At the same time, KIT D816V mutation may increase oncostatin M, a mast cell secretion that stimulates proliferation of osteoblasts, endothelial cells, and fibroblasts and serves as a profibrogenic and angiogenic modulator [11]. However, the fraction of cells that acquire the KIT D816V mutation has no correlation with disease severity in ISM patients [12].

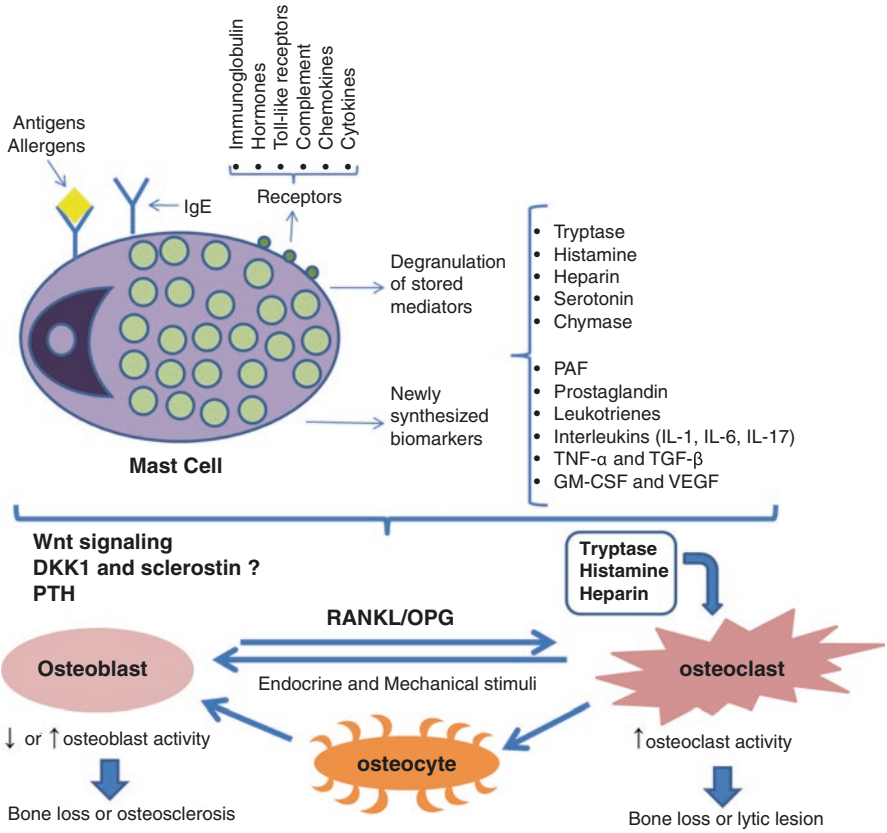

Fig. 8.1 Pathogenesis of SM-related bone events. Local release or newly synthesized mediators of mast cells lead to bone pain, osteopenia, osteoporosis, osteolysis, and/or osteosclerosis

The process of mast cell activation has three steps, namely, degranulation, which occurs in a few seconds; synthesis and release of mediators originating from the lipid bilayer of the cell membrane in several minutes; and finally, within minutes to hours, synthesis of a mass of inflammatory cytokines [1, 3]. Mast cell products include [1] stored mediators in the granules such as tryptase, histamine, serotonin, heparin, and chymase, which can be secreted immediately; [2] newly synthesized biologic markers such as platelet-activating factor (PAF), prostaglandin D2 (PGD2), and leukotrienes (LTB4 and LTD4), produced after stimulation; and [3] different cytokines such as interleukins (IL-1, IL-3, IL-5, IL-8, and IL-10), TNF-α, TGF-β, GM-CSF, and VEGF. Thus, mast cells can secrete different biologic markers and have the ability to express variable receptors such as receptor for immunoglobulin, hormones, or Toll-like receptors, complement, chemokines and cytokines. The interaction between these highly complex structures of cells and biomarkers may augment or downregulate the immune response to allergens or antigens [6] (Fig. 8.1).

The bone remodeling process is a coordinated interaction between osteoblasts, osteoclasts, and osteocytes, which is, in turn, regulated by mechanical stimuli and diverse endocrine, paracrine, and autocrine biologic markers. PTH (parathyroid hormone) and the Wnt signaling pathway play crucial roles in osteoblast development and function. Receptor activator of nuclear factor-κB ligand (RANKL) is encoded by type 11 of tumor necrosis factor superfamily gene (TNFSF11) and leads to osteocyte formation and activation. Wnt activation also increases β-catenin levels, which increase osteoblast secretion of OPG (osteoprotegerin), which competitively blocks RANKL, blocking osteoclast stimulation [13, 14]. Sclerostin, a product of osteocytes stimulated by PTH, and DKK1 (Dickkopf-related protein 1), a soluble protein from osteoblasts, both act as endogenous inhibitors of the Wnt pathway [1].

The underlying processes that have been involved in the impairment of bone health in SM patients are highly complex. Interactions between bone cells including osteoblasts, osteoclasts and osteocytes, immune cells, inflammatory mediators, and endocrine parameters determine the severity and type of bone involvement. Cytokines, including TNF-α, IL-1, and IL-6, can increase osteoclast activity and reduce osteoblast performance [10, 15, 16]. However, increase in the serum levels of bone formation markers such as OPG and bone-specific alkaline phosphatase and bone resorption markers including RANKL, SOST (Sclerostin gene), DKK1, and CTX (C-terminal telopeptide or carboxy-terminal collagen crosslinks) are also reported [17, 18], which perhaps means SM upregulates bone turnover with the dominancy of bone resorption over bone formation. The level and role of the Wnt inhibitors DKK1 and sclerostin are controversial. Rossini reported that serum levels of DKK1, but not sclerostin, were significantly higher in ISM patients and had positive correlation with PTH and bone turnover markers, CTX and bALP, but ISM patients with one or more vertebral fracture had lower serum DKK1 levels [18]. However, Rabenhorst found significant increase in serum levels of sclerostin, but not DKK1, in ISM patients [17]. RANKL is consistently elevated in SM patients in different studies, and to the best of our knowledge, there are no reports of decreased RANKL serum level in ISM patients. Additionally, treating ISM patients with denosumab (anti-RANKL human monoclonal antibody) for 1 year not only improves BMD and reduces bone turnover markers but may also decrease tryptase levels, which correlate with mast cell mass [19] (Fig. 8.1).

It seems that histamine can also modify the function of both osteoblasts and osteoclasts. Histamine serum levels have a positive correlation with osteoporosis in SM patients. Antihistamines (H1 blocker) can block differentiation of mesenchymal stem cells into osteoblasts [20]. However, regulating the gene for histamine synthesis by knocking out the histidine decarboxylase gene is associated with elevated calcitriol, alkaline phosphatase, and RANKL, while this suppresses PTH, which might explain protection from ovariectomy-induced bone loss [21]. Additionally, ketotifen (a mast cell degranulation inhibitor) improved bone pain, increased 1,25-dihydroxyvitamin D3 and osteocalcin levels, and normalized elevated plasma and urine histamine levels in a 59-year-old man with SM [22].

Clinical Bone Manifestations of Systemic Mastocytosis (SM)

Bone involvement can manifest with a varying clinical spectrum from asymptomatic to bone pain, with osteopenia, osteoporotic with fragility fractures, osteolytic lesions, osteosclerosis, and sometimes multiple conditions together in the same individual [1, 3]. Bone pain is often devastating and could be potentially due to bone marrow involvement, osteoporotic/pathologic fracture, osteolytic lesion, and/or anaphylaxis [1, 3, 23].

The incidence of fracture was variable in different studies (6–57%) [24, 25] (Table 8.1 and Fig. 8.2), and it was mainly fragility fracture. The source of the variability of fracture in different population groups could be due to sample size, population age, and other contributing risk factors such as duration of disease, disease progression, and medication history. As in postmenopausal osteoporosis, vertebral fracture occurs more than nonvertebral fracture (Table 8.1). The overall incidence of osteoporosis, which has been mainly reported according to WHO criteria, was between 12% and 60% in different studies (Table 8.2). It is noteworthy to mention that the incidence of fracture was higher than that of osteoporosis in some population

Table 8.1 Fracture incidence rate and risk factors in SM patients in the reverse order of the year of publication

Author/year	Fracture results	Population	Comments
Degboé Y *Bone*. 2017 Dec [26]	Fracture 28% (25/89) 106 fractures (83% vertebral) Multiple vertebral Fx 14.6%	89 SM	Risk factors for fracture: Age, telangiectasia macularis eruptiva perstans, symptoms of mast cell activation, digestive symptoms, increased bone marrow tryptase and low femoral and lumbar spine BMD Higher bone marrow tryptase level was associated with FF
Orsolini G *Calcif Tissue Int*. 2017 [19]	All patients had fracture	Four females with SM	Denosumab reduced the tryptase level and improved BMD
Artuso A *Calcif Tissue Int*. 2017 Jan [27]	Fragility fracture 30% (60/200)	200 ISM	ISM patients with no history of osteoporotic fracture and with normal BMD or osteopenia who were supplemented with vitamin D or calcium (if needed) after 30 ± 6 months did not have fracture or significant reduction in BMD
Alpay Kanıtez N *Turk J Haematol*. 2015 [28]	No fracture on radiograph	17 adult SM patients	Sclerotic lesion was associated with more severe disease
Rossini M *Calcif Tissue Int*. 2015 [18]	Fracture 48% (11/23) and 23 times	26 adult ISM patients	Osteosclerosis was associated with higher tryptase level Lower DKK1 in fracture patients Higher DKK1 and sclerostin in ISM

Van Der Veer E *J Allergy Clin Immunol.* 2014 [25]	Fracture 57% (127/221) and 389 events Fragility fracture 40% (90/221) and 264 events Traumatic fracture 17% (37/221) and 125 events	228 total population 221 ISM patients with fracture data	Risk factors for fracture: Male sex, older age, more frequent anaphylactic reactions, less urticarial pigmentosa, higher methylimidazole acetic acid, higher osteocalcin, higher CTX levels, lower hip BMD, and more frequent alcohol intake
Seitz S *Osteoporos Int*. 2013 [9]	Vertebral fracture 39% (118/300) Fragility fracture 36% (109/300)	300 ISM patients	Osteosclerosis 5.3% (16/300) with no fragility fracture Higher fracture rate in ISM with negative skin lesion compared to positive skin lesion (44% vs. 21%)
Guillaume N *Am J Med.* 2013 [24]	Fracture 6% (3/45)	45 patients	Systemic mastocytosis: 84% [29] ISM 64% [30] ASM 11% [5] SM-AHNMD 9% [4] Cutaneous mastocytosis 7 (16%)
Van Der Veer E *Allergy*. 2012 [31]	Fracture 54% (83/154) and 235 times Fragility fracture 37% (57/154) and 140 times Vertebral fracture (62%) > nonvertebral (36%)	157 ISM patients	Fracture risk factors: absence of urticaria pigmentosa, older age, and male sex
Laroche M *Am J Med*. 2011 [32]	All had atraumatic vertebral fracture No peripheral fracture	10 patients	
Rossini M *Bone*. 2011 [30]	Vertebral fracture 20% (17/82) Nonvertebral fracture 6% (5/82)	82 ISM patients	35 ISM with positive skin lesion The spine bone density was generally lower than the hip
Barete S *Ann Rheum Dis*. 2010 [33]	Bone involvement 49% (37/75) Vertebral fracture 19% (14/75) Peripheral fracture 8% (6/75)	75 SM patients	Osteoporosis and osteosclerosis associated with more aggressive form No correlation between bone involvement and D816 V mutation of KIT Osteoporosis 31% (23/75), axial osteosclerosis 8% (6/75)
Escribano L *J Allergy Clin Immunol*. 2009 [34]	Fragility fracture 10% (4/39)	145 patients	Biological progression in 27% (39/145) Osteoporosis 56% (22/39) Diffuse bone sclerosis 10% (4/39) Patchy bone sclerosis 13% (5/39)
Johansson C *Age and Ageing*. 1996 Jan [35]	Vertebral fracture 31% (5/16)	16 patients	Vertebral fracture in patients with moderately increased cell mass

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groups (Tables 8.1 and 8.2). While low femoral and lumbar spine BMD are associated with an increased risk of fracture [26], it seems that DXA may underestimate the risk of fracture in SM patients (Tables 8.1 and 8.2), so we must consider risk factors other than osteoporosis determination by bone density to be able to predict and determine when to intervene to prevent fracture better.

Available data around risk factors of fracture in SM patients are not consistent. Degboé reports age of disease onset, a skin pattern of telangiectasia macularis eruptiva perstans, symptoms of mast cell activation, digestive symptoms, and increased bone marrow tryptase predict increased fracture risk. Furthermore, higher bone marrow tryptase, low femoral neck bone density, and older age at the onset of disease could independently predict a higher risk of low trauma fracture [26]. Johansson states that moderately increased mast cell mass is associated with lower hip bone density and higher risk of vertebral fracture [35]. Van Der Veer indicates that fragility fracture happens more in older age, male, with a history of more anaphylactic reactions, fewer skin lesions (urticarial pigmentosa), higher bone and mastocytosis markers (higher methylimidazole acetic acid, osteocalcin and CTX levels), lower hip BMD, and history of more alcohol consumption at the time of diagnosis. Additionally, male sex, high CTX, lower hip BMD, absence of skin lesion (urticaria pigmentosa), and alcohol consumption at the time of diagnosis independently predict fracture [25]. Rossini reports that patients with low BMD or vertebral fracture are older and have lower osteocalcin serum levels [30]. To further confuse the biochemical markers, DKK1 was higher in ISM patients, but patients with vertebral fractures had lower DKK1 serum levels [18]. It seems that a comprehensive approach including fracture risk factors, DXA values, patient age, and associated conditions should be taken into account to institute appropriate management policies in preventing SM-related bone events.

Osteosclerosis occurs in 2–17% of SM population, mainly involving the vertebral spine and may be patchy or diffuse sclerosis (Tables 8.1 and 8.2). Paradoxically, osteosclerosis is associated with very high tryptase levels [18], more aggressive disease [33], increased bone turnover markers [30], and abnormal hematologic findings including anemia, thrombocytopenia, and eosinophilia [33]. Also, it seems that risk of fragility fractures is lower in SM patients with osteosclerosis [9].

Few studies report osteolytic lesions in SM patients. Sometimes, osteoporotic bone involvement is associated with concomitant osteosclerosis or osteolytic lesions [38] (Tables 8.1 and 8.2).

Treatment

The overall composite process of bone involvement in SM is bone resorption, which predisposes the patients to fragility fractures. Increased osteoclast activity is probably the main reason for bone resorption and bone loss, which occurs secondary to mast cell activation and proliferation. The concept of increased osteoclast activity and bone resorption might recommend antiresorptive therapies, such as

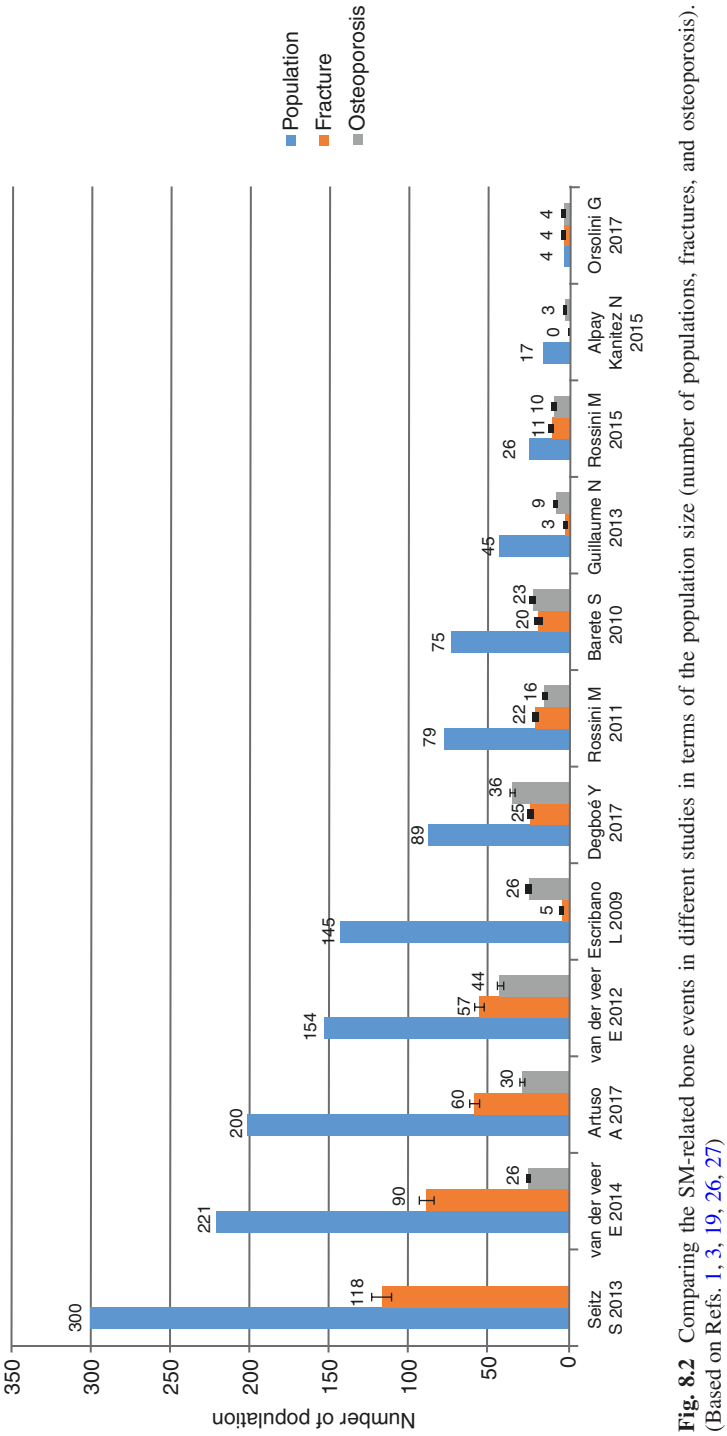

Fig. 8.2 Comparing the SM-related bone events in different studies in terms of the population size (number of populations, fractures, and osteoporosis). (Based on Refs. 1, 3, 19, 26, 27)

Table 8.2 Studies reporting bone density measurement, imaging studies, and biochemical markers of bone turnover in adult patients with mastocytosis in the reverse order of the year of publication

Author/journal and year	Radiological findings	Population	Comments
Degboé Y *Bone*. 2017 Dec [26]	Osteoporosis 40% (36/89) Osteosclerosis 4.4% (4/89)	89 SM	31.5% (28/89) had at least one of the osteoporosis risk factors The few patients had usual risk factors of osteoporosis In fractured patients, 48% (12/25) had LS BMD T score > −2.5 and 88% (22/25) had FN T score > −2.5 SD
Orsolini G *Calcif Tissue Int*. 2017 [19]	Osteoporosis 100% (4/4)	Four females with SM	Denosumab improved BMD and reduced tryptase level and BTM Denosumab was injected every 6 months for 1 year
Artuso A *Calcif Tissue Int*. 2017 Jan [27]	Osteoporosis 30% (60/200)	200 ISM	BMD (Z-score and T-score) LS < hip Improvement in BMD LS > hip Vitamin D/Ca did not change tryptase, PTH, and BTM
Alpay Kanitez N *Turk J Haematol*. 2015 [28]	Osteopenia 52% (9/17) Osteoporosis 17% (3/17)	17 adult patients Ma	Severity of the disease correlated with osteolysis, osteosclerosis, pyridinoline level, and tryptase level Higher BMD correlated with more sever disease
Rossini M *Calcif Tissue Int*. 2015 [18]	Osteopenia 38% (10/26) Osteoporosis 38% (10/26) Osteosclerosis 7% (2/26)	26 adult ISM	Lower DKK1 correlated with vertebral fracture Higher DKK1 correlated with bone involvements
Rossini M *Am J Med*. 2014 [36]	Osteoporosis 100% (25/25) LS BMD < Hip BMD Vertebral deformity 52% (13/25)	25 ISM	Zoledronic acid reduced BTMs but not tryptase
Rabenhorst A *J Allergy Clin Immunol*. 2013 [17]	Osteopenia 60.7% (34/56) Osteosclerosis 10% (6/56) LS BMD < FN BMD	56 ISM	Advanced SM often associated with normal or increased BMD RANKL, SOST, and OPG were higher in patients with ISM but not DKK-1 level
Seitz S *Osteoporosis Int*. 2013 [9]	Osteosclerosis 5.3% (16/300)	300 ISM	

Guillaume N *Am J Med*. 2013 [24]	Osteoporosis 20% (9/45) Osteopenia 33% (15/4) Osteolysis and/or osteosclerosis 28% (13/45)	45 Ma: SM 84% (38/45) CM 16% (7/45)	Tryptase correlated with CTX and OPG Severity of mastocytosis correlated with higher CTX and OPG Osteolysis 2% (1/45), osteosclerosis 17% (8/45) Bone lysis+sclerosis 8.8% (4/45)
Van Der Veer E *Allergy*. 2012 [31]	Osteoporosis 27.3% (43/157) Osteosclerosis 3.8% (6/157)	157 ISM	LS BMD was negatively associated with MH and MIMA Tryptase was positively associated with duration of the disease Predictors of osteoporosis or FF are older age, male sex, and high urinary MH
Laroche M *Am J Med*. 2011 [32]	Osteoporosis 100% (10/10)	10 SM	Bisphosphonate and interferon together reduced CTX, bone alkaline phosphatase, and tryptase levels
Rossini M *Bone*. 2011 [30]	Osteoporosis 19.5% (16/82) LS BMD < hip BMD Osteosclerosis 2% (2/82)	82 ISM	Osteosclerosis was associated with more aggressive disease, higher BTM, and higher tryptase Tryptase levels had no correlation with BMD Low BMD/vertebral fracture was associated with older age and lower serum osteocalcin but no difference in BMI, smoking, and skin involvement
Barete S *Ann Rheum Dis*. 2010 [33]	Bone involvement 49% (37/75) Osteoporosis 31% (23/75) Axial osteosclerosis 8% (6/75) LS BMD < TH BMD	75 SM	Bone involvement: more in male (57% vs. 26%); No association with clinical characteristics and D816V KIT mutation Osteosclerosis was associated with more severe disease and abnormal complete blood count (anemia, thrombocytopenia, and eosinophilia)
Kushnir-Sukhov NM *Int Arch Allergy Immunol*. 2006 [37]	Osteopenia 37% (7/19) Osteoporosis 16% (3/19)	21 SM	Lower serum tryptase in less severe disease Higher BMD in more severe disease Higher BMD associated with higher tryptase level FN Z-score positively correlated with tryptase

(continued)

Table 8.2 (continued)

Johansson C *Age and Ageing*. 1996 Jan [35]	Osteopenia 12% (2/16) Osteosclerosis 12% (2/16)	16 SM	Low hip BMD, osteoporosis, and vertebral fracture in patients with moderately increased mass cell mass Increased histamine metabolite excretion linked with higher hip BMD

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Abbreviations: *ASM* aggressive systemic mastocytosis, *bALP* bone-specific alkaline phosphatase, *BMD* bone mineral density, *BTM* bone turnover marker, *Ca* calcium, *CM* cutaneous mastocytosis, *CTX* C-telopeptide, *DPyD* deoxypyridinoline, *Dx* diagnosis, *DXA* dual-energy X-ray absorptiometry, *Fx* fracture, *FF* fragility fracture, *FN* femoral neck, *HS* hepatosplenomegaly, *INF* interferon, *ISM* indolent systemic mastocytosis, *ISMs* ISM with no evidence of skin lesions, *ISMs+* ISM with skin lesion, *Ma* mastocytosis, *M* men, histamine metabolites, *MH* methyl histamine, *MIMA* methylimidazole acetic acid, *NA* not available, *Obl* osteoblast, *Ocl* osteoclast, *OP* osteoporosis, *OPG* osteoprotegerin, *OC* osteocalcin, *Phos* phosphorus, *PTH* parathyroid hormone, *PyD* pyridinoline, *SC* subcutaneously, *SM* systemic mastocytosis, *SM-AHNMD* systemic mastocytosis with an associated clonal hematologic non-MC-lineage disease, *SSM* smoldering systemic mastocytosis, *TF* high-energy trauma fractures, *TH* total hip, *TBV* trabecular bone volume, *TT* trabecular thickness, *T No.* trabecular number, *UP* urticaria pigmentosa, *W* women

bisphosphonates or denosumab, as the first line of treatment of osteoporosis in SM patients. However, Rossini and Rabenhorst report that elevated bone turnover (documented by both increased bone formation and resorption markers) is an important reason for SM-related bone events [17, 18]. While antiresorptive therapy can alleviate bone loss that is accompanied by increased bone turnover, this is not as effective as governing of underlying disease activity as adding interferon to pamidronate. This combination had better effects on BMD and could reduce tryptase level simultaneously [32, 39]. Therefore, it seems that management of the underlying disease might be the best way to prevent disease-related bone complications in the setting of increased bone turnover, in SM, similar to other bone disease with high turnover such as hyperthyroidism or hyperparathyroidism.

Bisphosphonates were shown to be effective in improving lumbar spine BMD but have lesser beneficial effects or even negative effects on femoral neck BMD [32, 39–41] (Table 8.3). They may also improve bone pain associated with osteopenia in SM patients [42]. While poor compliance is a well-documented problem with oral bisphosphonates, this could be addressed by recommending zolendronic acid yearly infusion to improve spine and hip BMD [36].

RANKL, the product of type 11 of tumor necrosis factor superfamily gene (TNFSF11), has quite an important role in bone biology and the immune system. It is secreted by osteoblasts and leads to osteoclastogenesis [13]. Elevation of serum RANKL levels has been reported in SM patients [17]. Additionally, denosumab, a human monoclonal antibody to RANKL, in SM patients was effective in

Table 8.3 Treatment of SM-related bone events in reverse order of the publication year

Author/year	Treatment result	Number of participants	Comments
Degboé Y *Bone*. 2017 Dec [26]		89 SM	29 patients bisphosphonates 1 patient teriparatide 1 patient denosumab 36 patients calcium and vitamin D
Orsolini G *Calcif Tissue Int*. 2017 [19]	All patients had fracture BMD increased, especially in LS BMD Reduced tryptase level and BTMs (especially CTX)	Four women with SM	Denosumab 60 mg SC every 6 months for 1 year
Artuso A *Calcif Tissue Int*. 2017 Jan [27]	No fracture Increase in LS BMD No change in hip BMD No change in serum tryptase, PTH, or BTM	200 ISM Normal BMD or osteopenia and no fragility fracture	Calcium and vitamin D supplementation for at least 2 years 30% did not take supplementation 20% had low compliance to treatment
Rossini M *Am J Med*. 2014 [36]	No new fractures Increased spine and hip BMD, especially spine Decreased BTMs	25 ISM with osteoporosis	Single zolendronic acid 5 mg IV Follow-up after 1 year
Laroche M *Am J Med*. 2011 [32]	Three patients had vertebral fracture on alendronate Group 1 (INF-α + pamidronate) No fracture Increase in spine and hip BMD Decrease in tryptase level and BTMs Group 2 (pamidronate alone) No fracture Increase in spine and hip BMD but < group 1 Decrease in BTMs	Ten Ma	Three patients received alendronate before Dx Eight patients pamidronate + INF Two patients pamidronate INF (1.5 million U three times/week) Pamidronate 1 mg/kg/month for 2 years then every 3 months
Barete S *Ann Rheum Dis*. 2010 [33]	No vertebral fracture Increase in LS BMD but stable hip BMD (nine patients) Decrease in hip BMD in three patients	75 SM	−23 patients with OP treated with bisphosphonate, calcium, and vitamin Mean follow-up 65 (26–84) months

(continued)

Table 8.3 (continued)

Author/year	Treatment result	Number of participants	Comments
Laroche M *Clin Rheumatol*. 2007 [39]	No new vertebral or nonvertebral fracture Increase in LS and hip BMD on INF + pam Decrease or increase in BMD with pamidronate alone Reduced BTMs with IFN + pam Increase in BTMs with pam alone	Four SM (three M, one W)	Three patients IFN + pamidronate, 2 years One patient IFN + pamidronate, 1 year All on pamidronate for 2 years IFN (three million units three times/week) Pamidronate (90 mg/month)
A Y N Lim *Ann Rheum Dis*. 2005 [40]	No further fractures Improvement in pain Increase in LS BMD of all patients (two patients excluded due to fractures) Increase in hip BMD of three patients	Six SM	Five patients pamidronate (IV annual), then alendronate One patient alendronate only
Marshall A *Br J Rheumatol*. 1997 [41]	One patient had two new fractures Increase in LS BMD in all Decrease in FN BMD in all	Three SM	Annual pamidronate for 2–5 years

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improving lumbar spine and femoral neck BMD (increase in LS BMD > FN BMD) and also could reduce bone markers (CTX and bALP) and tryptase levels (Table 8.3) [19]. It seems that blocking RANKL could be fairly effective, not only in improving bone condition, but also in alleviating mast cell burden. However, denosumab is a monoclonal antibody, and some patients with SM are at higher risk of anaphylactic reaction to foreign antigens. But, it is important to mention that denosumab belongs to immunoglobulin of the IgG2 subclass [29], and it is generally agreed that infusion of IgG may cause mild reaction while chance of developing anaphylactic reaction is extremely rare [43]. The Freedom trial with denosumab in postmenopausal women with osteoporosis did not show a significantly higher risk of anaphylactic or even skin reaction to denosumab versus placebo (eczema 3.0% vs. 1.7%) [44]. Furthermore, a subcutaneous desensitization protocol in an eight-step escalating titration process is reported to be successful to make denosumab tolerable even in the patient with a history of anaphylaxis to denosumab [45]. However, there are only anecdotal reports of the use of denosumab in patients with mastocytosis, and these reports do not include patients with a history of anaphylaxis.

As mast cell degranulation and proliferation may directly promote SM-related bone complications, it is suggested to use adding medication to block mast cell degranulation or their mediators potentially to improve bone health in SM patients. Graves et al. (1990) reported that ketotifen, an inhibitor of mast cell degranulation,

administered for 3 months could reduce bone pain and histamine level; they also found no further bone loss in BMD after 6 and 14 months of therapy [22]. However, cromolyn, antihistamines, and sodium fluoride were effective. Moreover, even chemotherapeutic agents such as chlorambucil and mithramycin are recommended for refractory disease, but they were not superior to bisphosphonate (oral clodronate) regarding the SM-related bone circumstances [1, 46]. However, cytoreductive medications (interferon, 2-chlorodeoxyadenosine, or cladribine/2-CdA), which are currently recommended in advanced or aggressive forms of SM, may be used in treating osteoporosis secondary to ISM or SM [2, 3].

As PTH may stimulate mast cell proliferation and elicit histamine release from mast cells [47], teriparatide may increase symptomatology. Given the concerning data about osteosarcoma risk in rats and the understanding that mastocytosis may be a premalignant condition, we would recommend caution and further study, before consideration of teriparatide therapy for bone disease in this population.

Future Direction

Sclerostin, encoded by the SOST gene, is a glycoprotein secreted by osteocytes that downregulates bone formation. Romosozumab, a human monoclonal antibody against sclerostin, reduces fracture risk in postmenopausal women but is associated with increased adjudicated serious cardiovascular events [48]. However, the role of sclerostin in bone complications of SM is controversial (Tables 8.2 and 8.3) [17, 18]. Additionally, blocking sclerostin can lead to the activation of the Wnt pathway and increase in the β-catenin level, which might lead to malignant transformation or progression [49]. We could not find a study or abstract that reported effects of romosozumab on SM-induced osteoporosis.

Cathepsin K is a protease secreted by mature osteoclasts that destroys collagen and other matrix proteins. Cathepsin K inhibitor (odanactib) improves lumbar spine BMD and reduces clinical vertebral fractures (72%) and hip fractures (47%) versus placebo in postmenopausal women. However, it was associated with some complications such as skin lesions, atypical femoral fractures, and stroke [50]. Immunoreactivity to cathepsin-G in human mast cells with cutaneous mastocytosis has been reported [51]. Given systemic mastocytosis is associated with the increased osteoclastic activity and higher risk of vertebral fracture (Tables 8.2 and 8.3), the cathepsin K inhibitor (odanactib) might decrease SM-related bone loss. However, adverse vascular events associated with this drug present an important barrier to its usage.

Avapritinib (BLU-285), in phase I trials for the treatment of advanced systemic mastocytosis, targets D816V mutant KIT and probably affects the activity of the disease and may improve bone damage also. Trials show a relatively good response rate (72%) without serious complications. However, the comparative cost and benefit of this medication should be investigated before being recommended. [52].

Summary

Bone consequences of systemic mastocytosis are heterogeneous, ranging from bone edema with or without pain, osteoporosis, lytic lesions, to osteosclerosis. Some patients may have one or more of these complications. In theory, controlling proliferation and activation of mast cells might also even prevent or delay bone disease in systemic mastocytosis. Additionally, applying antiresorptive therapy may help to improve bone density and reduce the risk of fracture. However, it is not known if anabolic agents for bone promote mast cell proliferation; this concern should be addressed with appropriate preclinical studies.

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Chapter 9
Anaphylaxis in Mastocytosis

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Abbreviations

CM	Cutaneous mastocytosis
ISM	Indolent systemic mastocytosis
MC	Mast cell
MIS	Mastocytosis in the skin
MMAS	Monoclonal mast cell activation syndrome
NSAIDs	Nonsteroidal anti-inflammatory drugs
REMA	Spanish Network on Mastocytosis
sBT	Serum baseline tryptase
SM	Systemic mastocytosis
VIA	Venom-induced anaphylaxis
VIT	Venom immunotherapy
WHO	World Health Organization

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Introduction

Mast Cells

Mast cells (MCs) are stationary cells present in many organs including the skin, bone marrow, liver, spleen, and cardiovascular and gastrointestinal tracts. Their physiological role is unclear; however, results from animal models suggest that MCs have a critical role in host defense and acute inflammatory responses [1]. The multifunctional capacity of MCs originates from their ability to detect triggers of internal or external stress or danger, such as microbial peptides, which leads to the release of a spectrum of different mediators, often, but not exclusively, through the cross-linking of IgE molecules bound to their surface by FcεRI receptors [2]. Upon activation, MCs release preformed and newly synthesized mediators including histamine, proteases, proteoglycans, eicosanoids, and cytokines such as TNF-α [1, 2]. Nevertheless, inappropriate release of these MC mediators is the source of so-called "mast cells mediator-release symptoms," which can occur either spontaneously or in response to stimuli. Both the number of MCs and their activation in the tissue increase in inflammation, but it remains elusive how the MC reactivity is regulated.

Mast cells are widely known as effector cells of hypersensitivity disorders such as asthma, rhinoconjunctivitis, and anaphylaxis. They are involved in many other diseases including chronic skin inflammation, autoimmune diseases, and cardiovascular disease; however, MCs play a crucial role in the pathogenesis of mast cell disorders, including spontaneous urticaria/angioedema and mastocytosis. Although the underlying mechanisms that activate the MCs differ significantly in allergy/hypersensitivity disorders and in mastocytosis, patients present with a similar symptomatology. This is not surprising since local or remote effects of excessive mediator release from MCs cause the clinical symptoms in both conditions.

Anaphylaxis

Anaphylaxis is one of the most alarming emergency conditions that presents with a broad array of symptoms and signs, many of which can mislead to other acute conditions including asthma attack, laryngeal edema, generalized urticaria, myocardial infarction, panic attack, and vocal cord dysfunction. Anaphylaxis is almost always unexpected, and if not promptly treated, it may lead to death by airway obstruction or cardiovascular collapse or both.

The available epidemiological data about the exact prevalence and incidence of anaphylaxis are limited and often inconsistent. This is mainly due to different definitions of anaphylaxis, and lack of reporting or misdiagnosing [3, 4]. In addition, most of the published data are based on hospital and emergency

admissions; however, the International Classification Codes (ICD) recording anaphylaxis are insufficient and do not properly reflect the epidemiological needs. With these limitations, it is, however, widely accepted that anaphylaxis is a relatively rare condition. The lifetime prevalence of anaphylaxis has been estimated to be approximately 0.3% [5]. Although rare, deaths may also occur and suggested to be at a rate of 1 per three million population per year [6]. Data from the USA on the epidemiology of anaphylaxis suggest an incidence of up to 40–50 people per 100,000 person-years [7], whereas the results of ten European studies suggest a lower incidence of 1.5–7.9 per 100,000 person-years [5], with studies from the UK showing an increase in admissions with anaphylaxis over the last two decades [8].

Until recently, there has been no globally recognized definition of anaphylaxis because anaphylaxis comprises a constellation of features. That has not only caused failure to diagnose and delayed treatment in patients but also hampered research facilities. Subsequently, multinational, multidisciplinary symposia were convened to achieve a true international consensus on the definition of anaphylaxis and its clinical criteria for the diagnosis [9]. Today, anaphylaxis can be defined as an acute, severe, potentially life-threatening systemic hypersensitivity reaction [9].

Anaphylaxis represents a constellation of varied symptoms that generally are related to the cutaneous, gastrointestinal, respiratory, and cardiovascular systems. In accordance with NIH clinical criteria, anaphylactic reactions can be diagnosed, when either reduced blood pressure or associated symptoms such as syncope/pre-syncope and/or respiratory compromise or laryngeal edema are present accompanied by the involvement of the skin–mucosal tissue or gastrointestinal symptoms [9]. Distribution of different signs and symptoms were reported in a series of 601 patients as follows: involvement of skin in 90%, respiratory symptoms in 59%, whereas 33% of patients experienced syncope or lightheadedness and 29% abdominal cramps or diarrhea [10]. Respiratory symptoms are more common in children, whereas cardiovascular symptoms appear to dominate in adults [11].

Foods, insect venoms, and drugs are the most common triggers of anaphylaxis, although prevalence of these elicitors varies among studies. In emergency department studies, food is the most common cause in children corresponding to 80–92% of the anaphylaxis [11, 12]. Regarding adults, venom- or drug-induced anaphylaxis is more common, followed by idiopathic (no apparent cause) anaphylaxis [10, 13].

Interestingly, a large Central European non-population-based case collection cohort study of 1985 patients involving 2012 anaphylactic episodes was recently published [14]. In this study, the age of patients ranged from 2 months to 87 years (median, 42.5 years), and insect sting was the most common elicitor (50%), followed by food (24%) and drugs (17%). The range of elicitors varies depending on the geographical area. A high percentage of venom-induced anaphylaxis in this cohort was striking, as the corresponding numbers differed widely from the studies performed in the USA (19%) and Australia (30%) [7, 15]. When data from the

European cohort analyzed children (<18 years) separately, the most common trigger was food (58%), followed by insects (24%) and drugs (8%) [16]. Sometimes simultaneous occurrence of certain cofactors is needed in order to trigger anaphylaxis. This so-called "summation or augmentation anaphylaxis" may account for certain cases of unexplained anaphylaxis and can also explain why some patients experience only intermittent anaphylaxis [17]. Such cofactors include viral infections, stress, physical exercise, some drugs (β-blockers, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs [NSAIDs]), alcohol, or spicy food intake [18].

Mastocytosis

Mastocytosis refers to a heterogeneous group of disorders characterized by excessive accumulation, proliferation, and activation of abnormal mast cells in several organs, including the skin, bone marrow, liver, spleen, lymph nodes, and gastrointestinal tract [19, 20]. The true incidence and prevalence of mastocytosis are unknown, but existing evidence suggests that it is a rare condition. In recent studies, the prevalence of ISM is estimated to be 9.6–13 in 100,000 people and an incidence for all subtypes of SM of 0.89 per 100,000 per year [21, 22]. The World Health Organization (WHO) introduced a classification of mastocytosis into two main groups: cutaneous mastocytosis and systemic mastocytosis (SM) involving at least one additional organ than the skin. Moreover, SM has been classified into several subgroups, with about 90% having indolent SM (ISM) with good prognosis. Rarely, more aggressive variants of the disease with poor prognosis occur. There are established WHO diagnostic criteria for SM [23], and the diagnosis requires the existence of a major and a minor criterion or that there are three minor criteria on biopsy materials. Refer to relevant chapter in this book for a more extensive review of mastocytosis.

The clinical picture of systemic mastocytosis is extremely heterogeneous, ranging from asymptomatic disease to a highly aggressive course with multisystem involvement. In patients with indolent disease, symptoms result from the local or remote effects of excess mediator release from mast cells, such as histamine, proteases, leukotrienes, and prostaglandins. These so-called "mast cell mediator-release symptoms," which can occur acute or chronic, include flushing, pruritus, palpitations, dizziness, hypotension, syncope, breathing difficulties, abdominal pain, nausea, vomiting, diarrhea, headache, sweating, lethargy, fatigue, lack of concentration, irritability, anxiety, depression, arthralgia, and myalgia [24]. Furthermore, symptoms may either present isolated, or in some patients, a constellation of symptoms may resemble an anaphylactic reaction [24].

Recently, novel variants of mast cell disorder have been introduced, so-called "monoclonal mast cell activation syndrome" (MMAS) [25, 26]. These patients are also mainly characterized by recurring episodes of anaphylaxis with hypotension and syncope and carry clonal MCs expressing the D816V mutation and/or CD25+

aberrant markers. However, they do not fulfill the WHO criteria for SM diagnosis and lack typical skin changes.

Anaphylaxis in Mastocytosis

Anaphylaxis is an extreme example of inappropriate, systemic MC activation and can be potentially fatal. Therefore, it can be described as a "unique" condition, and it represents a linkage between allergic disorders and mastocytosis. This is because the underlying mechanisms that cause mast cell activation in anaphylaxis might be driven either by exogenous stimuli or, as in mastocytosis, by uncontrolled aberrant MCs without detection of relevant allergies or both.

Existing evidence suggests a strong association between anaphylaxis and mastocytosis. Several reports in literature indicate a higher prevalence of anaphylaxis varying from 23% to 56% in adult patients with various forms of mastocytosis [24, 27, 28], thereby representing a 100- to 1000-fold increased risk than that in the general population [29]. These large discrepancies in the prevalence of anaphylaxis may result from a number of reasons, such as heterogeneity of the patients in investigated cohorts and lack of a uniform definition of diagnostic criteria for anaphylaxis. Moreover, varying recruitment strategies in different centers may cause a selection bias; this is mainly due to the fact that anaphylaxis is the presenting symptom of mastocytosis, particularly, in patients without skin involvement. In addition, SM investigation routines are unfortunately not standardized in different centers, for instance, allergy workup is not routinely performed in all mastocytosis centers.

The mechanisms of anaphylaxis in mastocytosis vary and may be related to an IgE-mediated elicitor, may be caused by direct mast cell activation, or may have no apparent trigger at all. Among IgE-mediated triggers, hymenoptera venom appears to be the most common elicitor [24, 30]. In a study analyzing 226 patients presenting with anaphylaxis to an emergency care setting, systemic mastocytosis was diagnosed in 7.7% of adults; flying insects were the etiologic factors in half of these patients [31]. Additionally, another study reported a 28% overall prevalence of venom-induced anaphylaxis among 122 SM patients, which is clearly increased compared to that in the general population [32].

In some patients, venom-induced anaphylaxis may be the presenting symptom that may lead to the diagnosis of mastocytosis. There seems to be a clear correlation between elevated serum baseline tryptase (sBT) levels and the severity of systemic reactions to hymenoptera stings [33]. One large study reported that approximately 10% of 379 subjects with systemic reactions to hymenoptera sting had elevated sBT levels ($\geq$11.4 ng/mL), and most of these subjects had mastocytosis or MMAS diagnosed by bone marrow biopsies [34]. Most of these patients have evidence of venom-specific IgE on blood, although specific IgE levels may be lower compared with the non-mastocytosis venom-allergic population. This is possibly due to the adsorption of IgE onto the increased numbers of MCs, making it less available to be

detected in the serum. Remarkably, skin test reactions to venom extract may also be diminished in size or even absent [35].

Among other IgE-mediated anaphylaxis in mastocytosis patients, drug- or food-induced reactions can be mentioned. Although these elicitors were reported in the context [27, 28], reactions often remain patient-reported and unconfirmed. Therefore, interpretations of these data should be cautious due to the lack of reliable in vitro tests and the lack of provocation tests. There are occasional case reports of patients with allergy to foods or preservatives [36]. Additionally, in one report, two cases of IgE-mediated fish- and crustacean-induced anaphylaxis were investigated, where further assessment showed an underlying ISM [37]. Another case report presented a patient with more than 10 anaphylactic episodes after eating meat, where a provocation test with pork resulted in delayed occurring severe anaphylaxis with only low levels of specific IgE to meats and galactose-alpha-1,3-galactose [38]. Further diagnostic workup confirmed and underlying ISM. Overall, cumulative clinical experience suggests that the incidence of IgE-mediated food allergy is not, or not fundamentally, increased in mastocytosis patients compared with that in the general population [39]. Some patients with mastocytosis complain about flushing and gastrointestinal symptoms triggered by spicy foods and alcohol; however, these symptoms rarely progress to anaphylaxis.

Likewise, it is not known whether the incidence of IgE-mediated drug allergy is increased in mastocytosis. It is often believed that the prevalence of drug-induced anaphylactic reactions is increased in patients with mastocytosis; however, most literature relates to case reports [40, 41]. Remarkably, most of these cases are related to general anesthesia and radiocontrast media exposure [42, 43]. Experience suggests some patients with mastocytosis may be at risk for severe non IgE-mediated reactions, such as those experienced with perioperative muscle relaxants. Such risk is probably lower in patients who have tolerated previous general anesthesia and/or who have no history of anaphylaxis during anesthesia. Presently, available data in the literature is scanty on this topic, and it is not possible to provide clear recommendations, although some experts suggest performing premedication with antihistamines and corticosteroids before anesthesia and recommend perioperative drugs with lower intrinsic mast cell activation properties. This topic is extensively reviewed in another chapter of this book.

Additionally, there are scarce data evaluating the frequency of underlying mastocytosis in patients with drug-induced anaphylaxis. In that context, a study investigating patients with nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity and potential underlying mastocytosis failed to show elevated sBT levels [44]. By contrast, reactions without a clear identified trigger, that is, idiopathic anaphylaxis, appear to be increased among patients with SM [24, 27]. Another remarkable point to note regarding elicitors is the observation that individual patients seem to maintain their elicitor profiles in subsequent reactions, as no elicitor switches among different episodes were noticed [24].

Table 9.1 Comparison of major studies regarding clinical and demographical characteristics of adult patients with mastocytosis in relation to anaphylaxis

		Gonzales de Olano et al. 2007 [27]	Brockow et al. 2008 [28]	Gülen et al. 2014 [24]
Number of adult patients with mastocytosis		155	74	84
Patients with anaphylaxis		36 (23%)	36 (49%)	36 (43%)
Number of anaphylaxis patients with indolent SM		32 (89%)	34 (94%)	35 (97%)
Gender, male % in general (% of those with anaphylaxis)		46% (72.2%)	35% (54%)	50% (61%)
Reaction pattern, syncope %		n/a	43%	72%
Mastocytosis in the skin %		n/a	88%	71%
Triggers	Insect venom	25%	27%	53%
	Idiopathic	42%	20%	39%
	Food + drug	28% (3 + 25)	42% (24 + 18)	9% (3 + 6)

Table 9.1 shows a comparative overview of clinical and demographical characteristics and presents somewhat differing elicitor patterns in three comprehensive studies in the context of anaphylaxis and mastocytosis.

Clinical Manifestations of Patients with Anaphylaxis

A distinct feature of anaphylaxis in patients with SM is the clinical course of reactions. These patients often present with severe cardiovascular signs and symptoms including hypotensive syncope [24, 28], whereas urticaria and angioedema appear to be rare [30]. These observations led to the development of a predictive model of the Spanish Network on Mastocytosis (REMA) to discriminate patients presenting with anaphylaxis and underlying clonal mast cell disorders, that is, SM and MMAS, in which male gender, elevated baseline tryptase levels (≥25 ng/mL), and syncopal episodes in the absence of urticaria/angioedema during the anaphylactic event(s) were considered to be risk factors [30]. Because the diagnosis of mastocytosis requires a tissue biopsy, it may be challenging for clinicians to decide whether to pursue with further evaluation. In this regard, the REMA score showed a sensitivity of 92% and specificity of 81%, regardless of the trigger; therefore, it is recommended to apply this screening tool in patients presenting with severe anaphylactic episodes but lack typical signs of mastocytosis in the skin (MIS) [45]. When available, the REMA score should be used together with peripheral blood D816V mutation analysis. The presence of this mutation in peripheral blood is a strong indicator of the underlying systemic mastocytosis [46]. Additionally, measuring urinary histamine metabolites methylimidazole acetic acid (MIMA) and N-methylhistamine might be helpful as another complementary tool. Elevated levels of these metabolites were shown to be a good predictor of mastocytosis when combined with a sBT level greater than 10 ng/mL [47].

Risk Factors for Anaphylaxis in Mastocytosis

While the risk of having underlying mastocytosis in patients presenting with anaphylaxis has been studied (REMA score); until recently, the risk of developing *de novo* anaphylactic reactions in SM patients without previous anaphylaxis episodes was not studied well. Although anaphylaxis is a prominent feature in almost 50% of the patients with SM, the remaining patients with SM never experience anaphylaxis. This, in turn, creates a challenge for the clinician to make an adequate anaphylaxis risk assessment for the patient who has already been diagnosed with SM. Our clinical experience supports this notion as well, since only a few patients without a previous history of anaphylaxis develop anaphylactic reactions. Therefore, the majority of patients who already experienced anaphylactic episodes before the diagnosis of SM have apparently a higher risk of developing new episodes. There is no clear explanation for this phenomenon; nonetheless, this notion generated the idea of a specific SM anaphylaxis phenotype and hyperreactive MCs. However, by now, there has not been convincing evidence that MCs of patients with SM are inherently hyperreactive. Additionally, responsiveness to local activation of skin MCs by morphine and airway MCs by mannitol was shown to be similar in patients with SM and healthy controls and among SM patients with and without anaphylaxis [35]. Similarly, the allele burden of the D816V mutation in KIT does not differ between adults with or without anaphylaxis [48].

Previous observational studies on patients with anaphylaxis and SM suggest that anaphylaxis occurs more often in patients with SM lacking mastocytosis in the skin [24, 28] and in those with atopic predisposition [24, 32]. A male predominance has also been observed in patients with SM with anaphylaxis [27]. In contrast, sBT levels have been controversial to predict the risk of anaphylaxis in these patients, since both higher [28] and lower [24] tryptase levels have been reported in patients with SM with anaphylaxis than those without anaphylaxis. Moreover, the risk for anaphylaxis also appears to be significantly higher in patients with ISM as compared with the more advanced form of mastocytosis [24, 27]. However, anaphylaxis still may occur in the latter patient group [49].

Recently, a systematic study was undertaken to determine predictive markers of developing *de novo* anaphylactic reactions in SM patients without previous anaphylaxis [32]. After analyzing 122 patients with SM, an anaphylaxis risk scoring tool to discriminate SM patients who have high risk versus low risk of developing anaphylaxis with an 86% of sensitivity was proposed. Accordingly, SM patients with anaphylaxis displayed unique clinical and laboratory features, where male sex, absence of mastocytosis in the skin, presence of atopy, IgE levels of $\geq$15 kU/L, and sBT levels of less than 40 ng/mL turned out to be risk factors for having higher risk [32]. Remarkably, the correlation between higher sBT levels and the prevalence of anaphylaxis in patients with SM does not appear to be linear but shows rather a bell-shaped association where the risk is indeed lower with very high levels of sBT. This finding is consistent with that of a study by van Anrooij et al. on venom-induced anaphylaxis in patients with SM [50]. Thus, these observations may support the existence of a distinct SM anaphylaxis phenotype. Additionally, the proposed risk

Table 9.2 Risk factors showing relation between anaphylaxis and mastocytosis

Risk factors	Predicting underlying mastocytosis in patients presenting with anaphylaxis		Predicting risk of developing *de novo* anaphylaxis in patients with mastocytosis	
	Yes	No	Yes	No
Presence of syncope	3	0	n/a	n/a
Absence of Urt/Ang	1	−2	n/a	n/a
sBT <15 ng/mL	−1	n/a	n/a	n/a
sBT 15–25 ng/mL	0	n/a	n/a	n/a
sBT >25 ng/mL	2	n/a	n/a	n/a
Gender, male	1	−1	1	0
sBT <40 ng/mL	n/a	n/a	2	0
Absence of MIS	n/a	n/a	3	0
Presence of Atopy	n/a	n/a	1	0
Total IgE ≥15 kU/L	n/a	n/a	3	0
Cumulative score	≥2 points	<2 points	≥3 points	<3 points
Outcome	High risk	Low risk	High risk	Low risk

Modified from Refs. [30, 32]
Urt urticaria, *Ang* angioedema, *MIS* mastocytosis in the skin, *sBT* serum baseline tryptase; *n/a* nonapplicable

scoring tool may improve the care of patients with SM by enabling the physicians to make more adequate risk assessment and determine individual patient's need, for instance, to prescribe lifesaving self-injectable epinephrine for appropriate patients.

Table 9.2 illustrates risk factors and risk-predicting tools both predicting underlying mastocytosis in patients with anaphylaxis and predicting the risk of developing anaphylaxis in anaphylaxis-naïve mastocytosis patients.

Anaphylaxis in Pediatric Mastocytosis

In patients with pediatric mastocytosis, the prevalence of anaphylaxis has been reported to range from 6% [27] to 9% [28], which is lower than that in adult mastocytosis patients, but still higher compared to the general population. Accordingly, a clear elicitor has not been identified in the majority of episodes, that is, reactions were idiopathic in 67% [27] and 60% [28]; this is followed by

anaphylaxis evoked after food ingestion. In contrast to adult patients, hymenoptera stings are not a common elicitor of anaphylaxis in children with mastocytosis.

A larger study comprising 111 children with CM investigated the risk factors for anaphylaxis and found that severe MC mediator-related symptoms requiring hospitalization had extensive skin involvement (>90% of the body surface area) and elevated sBT levels (median 45.5, range 24–213 μg/L) [51]. Another analysis reported that blistering episodes was an additional risk factor [52]. The most frequent triggers in these studies were skin friction, heat, stress, vaccines, and fever [51, 52].

Treatment of Anaphylaxis in Mastocytosis

Acute Management

Anaphylaxis is a medical emergency and requires prompt recognition and treatment. Most recommendations regarding mastocytosis patients with anaphylaxis are extrapolated from the literature. Roberts et al. [53] stressed the unique role of epinephrine in the treatment of anaphylactic shock in a patient with SM who was refractory to vasopressor therapy with dopamine, yet it was quickly responsive to epinephrine. Therefore, not every catecholamine may be equally effective in this disease, and epinephrine could act differently on a different set of adrenergic, or other receptors [53, 54].

Anaphylaxis in patients with mastocytosis should be treated in the same manner as that in patients without mastocytosis. Therefore, intramuscular epinephrine is the drug of choice for immediate episodes of anaphylaxis, as this drug reverses the inappropriate effects of the mast cell mediators produced during anaphylaxis [55, 56]. Unfortunately, the usage of adrenaline is still underutilized, whereas steroids are widely used as first-line therapy despite the lack of evidence [57]. In refractory cases of severe hypotension not responding to repeated doses of intramuscular epinephrine or cardiac arrest, intravenous epinephrine should be given under continuous monitoring of cardiac response, blood pressure, and oxygen saturation. Supplemental high-flow oxygen and intravenous fluid replacement should be administered. Additionally, it is important to place the patient on the spine, Trendelenburg position. With severe, unresponsive bronchospasm, inhaled beta-agonist (e.g., salbutamol) can be given additionally. When patients' cardiovascular and respiratory functions are stabilized, second-line medications such as H1 and H2 antihistamines, as well as corticosteroids, are usually recommended [56]. However, particularly, the value of steroids in the acute management of anaphylaxis is unclear. Their effect seems to be on the prevention of protracted or biphasic reactions, although there is no substantial evidence to support this action.

Maintenance Therapy

Prevention is the most important aspect of the anaphylaxis management. Therefore, all SM patients who have a history of anaphylaxis should be prescribed self-injectable epinephrine after giving adequate information and training on the appropriate use. Information and education should also be extended to the patient's relatives and care providers, and an action plan for the management of acute episodes should be implemented.

Avoidance is the mainstay of the prevention and may prevent systemic mediator release. Nevertheless, there is a wide individual variation between patients. Therefore, the general advice to avoid all of the literature-reported potential triggers for mast cell degranulation is not recommended; instead, a tailored management strategy is necessary [58]. Patients should therefore undergo a thorough allergological evaluation including allergy tests for a number of known/potential triggers in order to assess the culprit agent, if possible. In addition, an allergy workup can be used as guidance to map out patients' individual trigger profile to avoid relevant food, medication, and inhalational triggers of mast cell activation. For instance, eliminations of histamine-rich diets or avoidance of certain drugs including NSAIDs is not routinely recommended. In contrast, hymenoptera stings appear to be the most frequent cause of anaphylaxis in adult mastocytosis patients. Therefore, those with sting anaphylaxis who are sensitized to hymenoptera venom should be recommended life-long venom immunotherapy, which has been shown to reduce recurrent anaphylaxis risk with re-stung [59]. This issue is extensively reviewed in another chapter of this book.

Currently, there is no consensus among experts whether to prescribe epinephrine to all patients diagnosed with mastocytosis or to prescribe it only to those patients with a history of anaphylaxis or who are at increased risk for anaphylaxis. This issue has been discussed in a recent study, where a risk assessment tool to predict occurrence of anaphylaxis in patients with mastocytosis was developed [32]. This tool facilitates the determination of "right" mastocytosis patients who need epinephrine auto-injectors. Nevertheless, this approach needs validation.

The prophylactic therapy aims to decrease the severity and/or frequency of the acute anaphylactic episodes. Nonetheless, there are currently no randomized studies to show what treatment(s) are superior in these patients. Therefore, a stepwise approach should be considered in all patients. The first step includes H1-histamine receptor antagonists [58]. Doses can be adjusted individually and can be used up to four times higher doses of recommended doses similar to those in patients with chronic urticaria. In the same manner, H2 blockers, antileukotrienes, oral cromolyn, and steroids can be additionally given in unresponsive patients. If the combination therapies are ineffective, omalizumab, which is a humanized monoclonal antibody that specifically binds to free human immunoglobulin E (IgE), can be used. It has been shown to diminish the frequency of anaphylactic episodes in anecdotal reports and case series with varying success [60–63]. Nevertheless, there are presently no randomized, placebo-controlled studies to recommend omalizumab in routine use.

Another factor to remember is that omalizumab, as all the others, is not a curative therapy.

In rare, refractory cases, cytoreductive or immunomodulatory therapy including interferon alpha 2b [64] and cladribine (2-CDA) [49] might be beneficial in controlling symptoms. Another potential therapy is tyrosine kinase inhibitors targeting the MC growth receptor KIT. A recent open-label study provided initial evidence that midostaurin showed efficacy in patients with advanced SM to reverse organ damage and decreased splenomegaly and bone marrow MC burden; additionally, midostaurin was found to improve mediator-related symptoms and quality of life, suggesting that the drug may also be useful in patients with indolent SM suffering from mediator-related symptoms resistant to conventional therapies [65, 66]. However, existing data are not sufficient to recommend this drug in anaphylaxis treatment yet.

Concluding Remarks

Clinically severe anaphylaxis is an important feature of patients with systemic mastocytosis. Hence, mastocytosis should be considered as a differential diagnosis in patients with recurrent unexplained (idiopathic) and hymenoptera venom-induced anaphylaxis. Presence of severe hypotensive, syncopal anaphylaxis episodes should be further evaluated for underlying systemic mastocytosis, especially if the sBT level is elevated ($\geq$11.4 ng/mL).

Appropriate treatment with epinephrine is not administered in a majority of cases, thereby increasing the risk of poor outcomes. Expanding knowledge regarding the presentation, causes, and triggers for anaphylaxis in mastocytosis among patients, their relatives, and health care providers will improve its recognition and management and increase patient safety. This could consequently decrease risk of mortality as well.

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Chapter 10
Venom Allergy and Management in Mastocytosis

Patrizia Bonadonna and Roberta Zanotti

Introduction

The prevalence of anaphylaxis in mastocytosis patients (20–30%) is much higher than the estimated frequency of anaphylaxis in the general population (0.05–2%) [1, 2].

The triggers that can induce massive degranulation of mast cells (MC) and cause anaphylaxis in adult subjects with mastocytosis are numerous, but hymenoptera stings are the most frequent (19–60% of cases of anaphylaxis), followed by foods (3–16% of cases) and drugs (5–9%) [3–6].

The literature confirmed that there is a preferential association between HVA and mastocytosis [7] and that the prevalence of mastocytosis in patients with HVA is significantly higher than that in the general population. Allergic/anaphylactic symptoms after hymenoptera sting are mostly present in patients with an indolent variant of systemic mastocytosis (SM) without skin lesions where the allergic reactions represented the initial clinical manifestation and the reason for bone marrow (BM) biopsy in the majority of cases [8]. Therefore, patients with both diseases represent a population requiring specific management.

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Hymenoptera Venom Allergy

HVA is a typical IgE-mediated disease, whose clinical manifestations are the result the mast cell (MC) degranulation, which is triggered by the binding of the venom allergens to specific IgE (sIgE). Severity can vary from large local reactions (LLR) to systemic anaphylaxis.

Prevalence rates of systemic reaction to hymenoptera sting are estimated to reach up to 7.5% in the adult European population and up to 3.3% in the United States [8].

LLRs in most cases involve itching, erythema, and edema of limited extension; they are transient and are normal consequences of the vasoactive and inflammatory action of some venom components.

Various classifications of the degree of the severity of systemic reactions have been proposed. The most frequently used are those by Mueller (Table 10.1) [9] and by Ring and Messmer [10] (Table 10.2). Both classifications have limitations: Mueller's does not take into account the possible absence of cutaneous symptoms and that an isolated cardiovascular shock might be the only allergic sting-induced manifestation, while Ring's is almost entirely focused on cardiovascular collapse, which is considered more severe than respiratory impairment The European Academy of Allergy and Clinical Immunology (EAACI) has recently proposed a simplification of the diagnostic criteria of acute allergic reactions, dividing them into local (grade 1) and systemic (grades 2 and 3) [11].

The insects responsible for allergic reactions are hymenoptera belonging to the suborder Aculeate, which includes the Apidae, Vespidae, and Formicidae families. The Apidae family includes Apis mellifera (Fig. 10.1) and Bombus (Fig. 10.2). The Vespidae family takes in the Vespinae subfamilies: *Vespula* species (yellow jacket; Fig. 10.3) and *Vespa crabro* (hornet; Fig. 10.4) and Polistinae subfamilies (Polistes species), among which *Polistes dominula* is widespread, especially in the Mediterranean area [12] (Fig. 10.5).

Table 10.1 Classification of systemic reactions: Mueller

Grade I	Generalized urticaria, itching, malaise, and anxiety
Grade II	Any of the above plus two or more of the following: Angioedema, chest constriction, nausea, vomiting, diarrhea, abdominal pain, dizziness
Grade III	Any of the above plus two or more of the following: Dyspnea, wheezing, stridor, dysarthria, hoarseness, weakness, confusion, feeling of impending disaster
Grade IV	Any of the above plus two or more of the following: Fall in blood pressure, collapse, loss of consciousness, incontinence, cyanosis

Table 10.2 Classification of systemic reactions modified according to Ring and Messmer

Grade I	Generalized skin symptoms (e.g., flush, generalized urticaria, angioedema)
Grade II	Mild to moderate pulmonary, cardiovascular, and/or gastrointestinal symptoms
Grade III	Anaphylactic shock, loss of consciousness
Grade IV	Cardiac arrest, apnea

Fig. 10.1 Apis mellifera (bee)

Fig. 10.2 Bombus

Fig. 10.3 Vespula species (yellow jacket)

Fig. 10.4 Vespa crabro (hornet)

Fig. 10.5 Polistes dominula

The bees and the vespids of the genus *Vespula* are widely spread also in the far northern regions of Europe, while in the south of Europe, a frequent cause of allergic reactions is also represented by the hornets (genus *Vespa*), including the most widespread species *Vespa crabro* and some species of Polistes, such as *Polistes dominula* [12]. The genus *Dolichovespula* has a more limited diffusion and can be considered similar to *Vespula* from an allergological point of view.

In 2005, *Vespa velutina nigrithorax* from South East Asia, belonging to the genus *Vespa*, was detected in the south of France. The *Vespa velutina* is a predator of bees and is rapidly spreading from France to neighboring countries. Some anaphylactic reactions have been described after *Vespa velutina* stings with a variable degree of cross-reactivity with other vespids [13]. For this kind of wasp, diagnostic extracts are not available, even if some laboratories in Europe are going to prepare them because, in the future, this insect will probably give clinical problems in terms of anaphylaxis.

Table 10.3 Prevalence of CMD in patients with systemic reactions to hymenoptera venom, screened on the basis of elevated tryptase

	Patients	Raised tryptase (%)	CMD	%
Haeberli et al. (2003)[a] [17]	259	19 (7.3)	3 CM	1
Dubois (2004)[b] [23]	2375	32 (1.3)	22 SM	1
Rueff et al. (2006)[c] [18]	1102	106 (9.6)	21 CM + 8 SM	2.6
Bonadonna et al. (2009) [25]	379	44 (11.6)	21 ISM + 9 MMAS	7.9
Potier et al. (2009)[c] [19]	138	22 (15.9)	1 CM + 5 SM	4.4
Guenova et al. (2010)[cd] [20]	274	30 (10.9)	1 CM + 3 ISM	1.5

Serum basal tryptase level (SBT) > 11.4 ng/mL
[a]BM evaluation not performed
[b]Screening with urinary histamine metabolite
[c]Evaluation of CD25/CD2 MC coexpression and Kit mutation not performed or reported
[d]BM performed if SBT > 15 ng/mL

HVA and Mastocytosis

During the last few years, it has increasingly been seen that there is a preferential association between HVA and mastocytosis for several reasons:

- The prevalence of HVA in SM patients (20–30%) is higher than that in the general population (0.3%–8.9% in the European adult population) [14–16].
- The Hymenoptera venom sting represents the most common trigger of anaphylaxis in adult mastocytosis patients (22–60% of cases) (3–6, on the contrary, in children with mastocytosis, hymenoptera stings play no role in eliciting anaphylaxis [3, 4].
- The association between HVA and mastocytosis is also confirmed by the higher prevalence of CMD in patients with systemic HVA (1–7.9%) (Table 10.3) than that in the general population (1–1.3 cases per 10,000) [17–22]. The lower prevalence rate of CMD in patients with HVA reported in some study could be explained by the low sensitivity of the screening test used [23], by the lack of a BM evaluation [17], or by some sensitive BM diagnostic tests [18–20].

Clinical Features of Patients with HVA and Clonal Mast Cell Disorders

- In the past, diagnostic workups for SM in patients with HVA have usually been limited to evaluating the presence of maculo-papular cutaneous mastocytosis (MPCM) or urticaria pigmentosa. Instead, in later years, it has been shown that HVA is more frequently reported in SM patients without skin involvement [7]. This is a very crucial point because if we focus attention on skin lesions only, there is a risk of not diagnosing a high percentage of SM.

- The CMDs associated with HVA are represented by not only SM but also monoclonal MC activation syndromes (MMAS), characterized by the absence of skin lesions and the demonstration of BM MC clonality by detection of KIT D816V Kit mutation and/or abnormal expression of Cd25 and/or CD2 on MC, but lacking sufficient criteria for SM [24, 25].
- An increased serum basal tryptase (SBT) appears to be a useful criterion for selecting patients with HVA eligible for BM evaluation when SM is suspected [25, 26]; nevertheless, a CMD cannot be excluded in subjects with systemic severe HVA but with normal SBT [27]. The REMA Score, proposed by the Spanish group, identified four clinical elements (male sex, presyncopal and/or syncopal episodes, absence of urticarial/angioedema, and serum tryptase >25 ng/mL) as independent predictive factors of CMD in patients suffering from severe mediator symptoms without mastocytosis in the skin [28]. The application of this score, which shows high sensitivity (91%) and specificity (75%), provides a good tool for screening patients with suspected mastocytosis with HVA but without typical skin lesions [29, 30] (Table 10.4).
- More frequently, patients with HVA and indolent systemic mastcytosis are without skin involvement [ISMs(−)], and they are the prevalence of male sex, a significantly lower MC burden, lower levels of serum tryptase and lower frequency of dense compact MC aggregates in BM sections than in indolent systemic mastocytosis patients with skin involvement [ISMs(+)]. They also frequently show coexisting populations of phenotypically normal and aberrant MC in BM and a lower frequency of multilineage KIT mutation [28, 30].
- The anaphylactic reactions of patients with CMD and HVA are characterized in most of cases by the absence of angioedema and erythema and the predominance of cardiovascular symptoms, such as hypotension leading to loss of consciousness [27, 29].
- The majority of patients do not report MC activation symptoms between acute episodes; therefore, most of these patients may have HVA severe reactions as the unique clinical manifestations of mastocytosis [5, 28, 31].

Table 10.4 The REMA score (Red Española de Mastocitosis): Proposed as a screening method for the presence of clonal mast cells in patients presenting with anaphylaxis in the absence of cutaneous mastocytosis before a bone marrow study

Variable		Score
Gender	Male	+1
	Female	−1
Clinical symptoms	Absence of urticaria and angioedema	+1
	Urticaria and/or angioedema	−2
	Presyncope and/or syncope	+3
Basal tryptase	<15 ng/mL	−1
	>25 ng/mL	+2

- Progression to aggressive mastocytosis has not been yet reported in SM patients with HVA [32] and, on the contrary, HVA seems to be very rare in patients with the aggressive subtypes of SM, who harbor the highest mast cell load [33, 34].
- In order to minimize the risk of failure in identifying a CMD in patients with normal or very slightly increased SBT and very low MC burden, the technical approach used is very important. In these cases, very sensitive techniques for BM MC immunophenotyping and detection of the KIT-D816V mutation (as RT-qPCR) are needed [27].

Management of Patients with CMD and HVA

Diagnosis

Diagnosis of HVA is based on the combination of a history of reactions to stings and positive IgE antibodies, which can be revealed by intradermal testing with venom or by measurement of sIgE in serum [14].

Current guidelines indicate that the diagnostic tests should be performed only on patients who have suffered from an anaphylactic reaction [14, 35]. In fact, asymptomatic sensitization (AS) to bee and wasp venom occurs frequently in vitro tests, and 27.1%–40.7% of the general population are reported to have detectable sIgE to hymenoptera venom [36, 37]. One of the main causes of AS is the presence of sIgE to cross-reactive carbohydrate determinants (CCDs) in the serum [38, 39]: these carbohydrate structures are present in plants and invertebrates, and IgE antibodies against CCDs are found in patients allergic to pollen or insect venom. Nevertheless, a large portion of subjects sensitized to nonglycosylated venom allergens tolerate hymenoptera stings well.

It has recently been seen that in subjects who tolerated hymenoptera sting and with detectable sIgE, only 5.3% of sensitized patients had severe systemic reactions (SSRs) after the sting challenge. These subjects presented a 9.5-fold higher risk than that in the general population for LLRs but not for SSRs. Therefore, the frequency of reactors seems to be comparable with the risk in the general population and far less than the risk for a re-sting reaction in allergic patients, which was reported to be between 25% and 52% after deliberate sting challenges [40].

History

Difficult as it may be, identifying the stinging insect remains crucial in the management of the allergic reactions since it is an integral part of the diagnostics flow in the choice of specific immunotherapy; thus, information of behavior and morphological

characteristic of the culprit insects and the description of the nests (photos) allows the clinician to figure out the correct clinical history and the diagnosis. It may be useful to show the patient an entomological notice board to facilitate the identification of the stinging insect.

Apis mellifera has a characteristic serrated sting that remains stuck into the tissues of the victim together with the venom sack. The bee dies by self-evisceration when flying away from the victim. The vespids and other Apids (bumblebees), instead, have smooth stings, which can be extracted from their victims allowing them to sting several times consecutively.

Allergy to *Bombus*, due to its low aggressiveness, concerns a limited number of subjects, in particular professionally exposed individuals [41], and it should therefore be investigated on the basis of a specific anamnestic suspicion, provided that a suitable extract is commercially available for diagnosis.

If it is sometimes easier to distinguish between wasps and bees, it can be more difficult to distinguish between the different kinds of *Vespula* and therefore, in such cases, in order to identify the insect, a description of the nests can also be useful; in fact, *Polistes dominula* usually builds its nest under roofs (Fig. 10.6), in little spaces or inside hedges. On the other hand, *Vespula* (yellow jackets) make their nests underground, and nests of *Vespa crabro* are very recognizable due to their large size (Fig. 10.7).

Fig. 10.6 Nest of Polistes dominula

Fig. 10.7 Nest of Vespa Crabro

Tests

Skin tests, such as in vitro tests, should be carried out at least 2 weeks after the last sting, to exclude a false-negative response during the refractory period [14, 42]; if negative, the test can be easily repeated because, in some cases, it may become positive a few weeks later [42, 43]. On the other hand, if the time period between the sting and the test is longer, the result may be falsely negative.

In Vivo Tests

Skin prick tests are performed with a standard concentration of insect venom ranging from 1 to 100 μg/ml. If skin prick tests are negative, intradermal tests are then performed with concentrations of 0.001–1 μg/ml. Higher concentrations may lead to false-positive results [44].

In Europe, standardized venoms for *Apis mellifera*, *Vespula* spp., *Polistes* spp., and *Vespa crabro* are currently available; the venoms of *Vespula* and *Polistes* consist of a mix of clinically relevant species (*Vespula* spp.: *Vespula vulgaris, Vespula flavopilosa, Vespula germanica, Vespula maculifrons, Vespula pennsylvania, Vespula squamosa* – *Polistes* spp. [American]: *Polistes annularis, Polistes exclamans, Polistes fuscatus, Polistes metricus*). Because of low cross-reactivity between European and American *Polistes* venoms [45], extracts of *Polistes dominula* are now available for both diagnosis and VIT.

In fact, it is very important for a correct diagnosis and subsequent prescription of immunotherapy, to include *Polistes dominula*, which is largely diffused in Europe [12], especially in the Mediterranean areas (Italy, Greece, Spain, France, and North Africa).

Skin tests with venoms are generally safe, even in patients with mastocytosis [7, 44, 46]. A study has highlighted their safety even when the tests are carried out simultaneously at different concentrations, but a preliminary step has been

recommended where the same concentration of more venoms is simultaneously used for skin testing. Only after reading the reactions to this first set, a higher concentration should be used. This caution is to be maintained specially in patients with severe anaphylactic reaction or suffering from mast cell disorders [47].

In Vitro Test

The first-level test is the detection of sIgE against major natural allergens of venom (CAP assay). Thanks to modern molecular biology technology and the increasing knowledge about venom composition on a molecular level, in the last decade it has become possible to develop an advanced molecular or component-resolved diagnostics (CRD) approach to hymenoptera venom allergy, and this has largely contributed to solving many diagnostic challenges [48]. The detection of these recombinants led a more precise diagnosis with the identification of the causative venom in patients with apparent double sensitization to *Vespula* and *Polistes dominula* venom or to apis and vespula venom [49]. The Hymenoptera venom allergens currently available on various diagnostic platforms are for honey bees (Apis): Api m1, Api m2, APi m3, Api m4, Api m5, and Api m10, for yellow jacket (*Vespula vulgaris*): Ves v1, Ves v5 for European paper wasp (*Polistes dominula*): Pol d 1 e Pol d 5.

Regarding the test, it is very important to know that in mastocytosis patients, a diagnostic sensitivity is reached using the recombinant allergens and the cut-off of 0.1 kUA/L, instead of the cut-off of 0.35 kUA/L [46]. Therefore, more recently, it has been confirmed that with lower cut-off, the diagnostic sensitivity improved and therefore a lower cut-off level of 0.17 kUA/L is preferable, which gives a sensitivity and specificity of 83.6% and 85.0%, respectively [50].

Basophil Activation Test (BAT)

The basophil activation test has been proposed as a useful adjunct in the diagnosis of allergic disease, especially in patients with negative or contradictory conventional tests [51]. In the BAT, basophils are used as an in vitro model for mast cells because both contain granules of preformed molecules that can cause an anaphylactic reaction after degranulation. By using the BAT, both IgE-mediated and IgE-independent type 1 hypersensitivity can be measured in vitro [52]. In hymenoptera venom allergy patients, the BAT was proposed as a third-level test for selected cases, and it can be useful in polisensitization patients [53–55]. Regarding mastocytosis patients, the role and usefulness of the BAT remain a topic of discussion in the current literature, with earlier studies reporting conflicting evidence [44, 54, 56, 57].

Based on these data from the literature, we would therefore postulate that the in vivo BAT does not add useful information to the conventional diagnostic tests for HVA.

In clinical practice where there is doubt with a patient who has had a severe reaction after hymenoptera sting, sIgE and in vivo test are not of help in the diagnosis

required to start the immunotherapy; it is possible to try and perform the BAT and in case of positivity start the immunotherapy for the test-positive venom.

In general, it would be of great value to identify those patients who are sensitized to Hymenoptera venom before they experience anaphylaxis, and maybe even preemptively treat them with immunotherapy. Conventional tests including intradermal tests and measurement of specific immunoglobulin E (sIgE) in serum are feasible to confirm sensitization after a patient has experienced an anaphylactic reaction, but they are not currently deemed useful for screening purposes. In particular, the presence of sIgE does not always predict hymenoptera venom-related allergy (HVA) and also the BAT is not a useful test to screen random SM patients for their risk of HVA [57].

Immunotherapy

There is no preventive pharmacological treatment available for HVA. Venom immunotherapy (VIT) represents a safe and effective treatment, which decreases the risk of subsequent systemic reactions and reduces morbidity and mortality [8].

The only curative treatment that is effective in reducing the risk of subsequent systemic reactions and improving patients' quality of life is VIT. VIT in the general population is reported to be effective in 77–84% of patients treated with honeybee venom and in 91–96% of patients receiving vespid venom [8].

After some debate, which were mainly due to safety concerns, it is now generally accepted that VIT is clinically justified in those patients with severe HVA and documented mastocytosis [7]. In fact, it is now generally accepted that VIT should be given always. Based on the data of literature available up to now, VIT conferred a full protection in the majority (86%) of re-stung mastocytosis patients, although this percentage is slightly smaller than that reported in patients without SM [58].

According to the published case series, conventional, cluster, and rush protocols (Table 10.5) are well tolerated and effective in patients with SM associated with anaphylaxis to hymenoptera venom-induced anaphylaxis [59, 60].

In patients with HVA and SM not fully protected at field re-stings, an increase of the maintenance dose to 200 mcg venom can be recommended. Before increasing the dose, it is mandatory to ensure that the diagnosis is correct and to exclude a new sensitization [31].

Furthermore, in mastocytosis patients, a pretreatment with an H1 antihistamine can be used in order to reduce the number and severity of LLRs and mild SRs to VIT, such as urticaria and angioedema [35, 61]. More recently, several case reports have shown that pretreatment with anti-IgE monoclonal antibodies may permit more rapid and higher doses of allergen immunotherapy: ISM patients who experienced SRs to VIT were able to tolerate immunotherapy following pretreatment with omalizumab [32, 62–65]. In the normal HVA population, the literature confirmed that a minimum of a 5-year treatment is better for long-term effectiveness [8] and life-long therapy should be considered in patients with severe initial SSR, systemic

Table 10.5 Examples of VIT protocols

Day	Hour	Conventional[a]	Cluster[a]	Rush[a]	Ultrarush[a]
1	0 0.5 1 1.5 2.5	0.01 0.1	0.001 0.01 0.1	0.01 0.1 1 2	0.1 1 10 20 30 40
2	0 1			4 8 10 20	
3	0 1 2			40 60 80	
4	0			100	
8	0 1	1 2	1 5 10	100	
15	0 1	4 8	20 30	100	50 50
22	0 1	10 20	50 50		100
29		40	100	100	
36		60	100		
43		80		100	100
50		100			
57		100			
64			100		
71		100		100	100
85		100			
92			100		
99				100	100
106			100		

[a]Dose in μg of venom

adverse events during VIT, and honeybee venom allergic patients with high risk of future honeybee stings. Patients with mastocytosis and HVA, who were protected during VIT, may have very severe reactions after VIT discontinuation [66, 67].

Moreover, the probability of having mastocytosis (in any form) is quite high when VIT protection is lost after treatment. This would suggest that patients with HVA-induced anaphylaxis who lose protection after a proper course of VIT should be investigated for mastocytosis. When a diagnosis of mastocytosis is established, these patients should continue life-long VIT [68]; therefore, from a practical point of view, regardless of the tryptase value, it has been suggested that an accurate hematological workup be performed before stopping immunotherapy in those patients with very severe reactions with hypotension and without urticaria and angioedema in order to exclude CMD. In general, in order to improve the compliance of patients in the HVA population who have to continue life-long injections, a

3- to 4-month extended interval can be proposed, and this schedule, adopted after 5 years of immunotherapy, seems to be safe and effective [69]. We can hypothesize that mastocytosis patients can also adopt this schedule even if up to now there have been no studies about the efficacy and protection in case of re-sting.

All VIT-treated mastocytosis patients, even in the maintenance phase, should carry epinephrine self-injectors with them because of the persistent risk of SSR and the possibility that SSR may also occur after a sting of an insect whose venom was not used for VIT [70].

Self-Emergency Treatment of the Patient with Anaphylaxis

Patients with CMD should carry an emergency kit with them irrespective of test result.

Adrenaline It is the treatment of choice for anaphylaxis [2, 71]. It slows the progression of symptoms and can prevent the development of fatal or biphasic reactions. If a correct dosage is administered, it can be used, without absolute contraindications, in pediatric and geriatric populations and in cardiopathic patients [2, 71, 72], except for some cardiac pathologies such as long-QT syndrome (in this case, the administration should be performed with extreme caution, in case of real need and in the presence of the cardiologist).

Adrenaline remains the drug of choice for the treatment of anaphylaxis also for pregnant women [73–75]; in fact, ephedrine may have a lower risk of uterine contractions but, if inefficacious, it may lead to an escalation of the anaphylactic reaction with the consequent risks.

Adrenaline should be administered intramuscularly in the lateral thigh (vastus lateralis muscle), at a dose of 0.01 mg/kg of a 1/1000 solution, with a maximum dose of 0.3 mg in children and 0.5 mg in adults .The dose may be repeated after 5–15 minutes if necessary [76, 77].

Moreover, patients with mastocytosis who have experienced severe systemic reactions should carry two or more epinephrine self-injectors. In the recent European's Academy position paper, this is also advised for all mastocytosis patients treated with VIT, even if they had reached the maintenance dose [78].

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Chapter 11
Drug Allergy and Perioperative Management of Mastocytosis

Mariana Castells

Introduction

Mastocytosis are rare clonal disorders characterized by the proliferation and accumulation of mast cells (MC) in different tissues, with a preferential localization in skin and bone marrow (BM) [1]. The increased MC burden as well as increased releasability of clonal MC leads to provoked and unprovoked acute episodes of mast cell activation and anaphylaxis. It is estimated that over 50% of adults with mastocytosis experience anaphylaxis [2]. Triggers for anaphylaxis include drugs, which can activate mast cells through IgE- and non-IgE-mediated mechanisms [3]. Fatal anaphylaxis has been described following hymenoptera stings, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and antibiotics in the perioperative setting in patients with mastocytosis [4, 5]. Data on the frequency of drug hypersensitivity in mastocytosis is limited, and it is not currently possible to predict which patients are at risk for anaphylaxis during anesthesia, radiocontrast media administration, or other procedures [6]. Since there is no increase in IgE-mediated drug reactions in patients with mastocytosis [3], it is possible that KIT mutations including D816V may lower the threshold for activation during NSAID exposures and COX-1 blockade [7] and/or opioid exposure. New mast cell surface receptors including G-protein-coupled receptors such as MRGPRX2,which are the target for the general anesthetics atracurium and rocuronium and the quinolones ciprofloxacin and levofloxacin [8] with THIQ motifs, have been recently described, with capacity for inducing anaphylactic reactions [9, 10], and their expression in mastocytosis patients and clonal mast cells is not known. Fear of inducing mast cell activation and anaphylaxis has limited surgical procedures and drug administration in mastocytosis patients [11]. We review here up-to-date information of drug

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allergy and anaphylaxis and focus on the perioperative and obstetric management of mastocytosis patients. The aim of this study is to provide clinicians with tools for safe and effective management of patients at critical times of need and to improve the quality of life of mastocytosis patients, who should not be deprived of first-line therapies.

General Concepts and Epidemiology

Current clinical practice indicates that an excess of mast cells and/or increased mast cell reactivity due to KIT mutations are risk factors for drug-induced reactions and anaphylaxis in mastocytosis patients [6]. In children, it is estimated that 9% of patients with cutaneous mastocytosis can present with environmental, food, or drug-induced anaphylaxis, and in adults with systemic mastocytosis, the frequency increases to 22% [3], and when hymenoptera is considered, up to 49% of patients with mastocytosis and hymenoptera allergy present with anaphylaxis [5, 12]. Drug-induced anaphylaxis can be the presenting symptom of mastocytosis, and cases have been described of fatal contrast dye-induced anaphylaxis and near-fatal antibiotic-induced anaphylaxis during delivery in women with previously unrecognized systemic mastocytosis [13].

According to the ENDA/EAACI position paper [5] based on an extensive review of all published literature on drug-induced reactions and anaphylaxis in mastocytosis up to 2015, there is no definitive incidence or prevalence, but anecdotal evidence has linked NSAIDs, opioids, radiocontrast media, and drugs used in the perioperative period with anaphylaxis and fatalities. There is an association between baseline elevated tryptase above the normal range of 11.4 ng/ml and reactions to drugs, and hymenoptera, although the data is scarce [14]. Regional anesthesia for delivery was well tolerated by women with mastocytosis based on 45 deliveries [15]. Local anesthetics including lidocaine and bupivacaine have been associated with anaphylactic reactions in mastocytosis patients, but the frequency is low and similar to that in the general population, and there is no evidence for contraindicating these drugs in patients with mastocytosis [16]. There are also reported cases of anaphylaxis during general anesthesia, but there is no evidence of increased frequency in patients with mastocytosis, although reactions may be more severe and massive mast cell activation has led to fatal cases. The risk for anaphylaxis during anesthesia has been linked to patients with systemic mastocytosis and elevated tryptase with a lower risk in children [17]. No control study has addressed the need for pre-medication for mastocytosis patients undergoing surgery, and there are no biomarkers to address at-risk patients [6]. All mastocytosis patients should be evaluated prior to general anesthesia for previous reactions, and in patients with prior reactions, the severity of the reaction should dictate risk stratification. Patients with prior anaphylactic reactions should have investigation of potential drug culprits with skin testing and drug challenges. Avoidance is recommended once a culprit drug is identified and an individualized plan should be provided to each patient. Radiocontrast media have been

found as triggers for anaphylaxis in anecdotal cases, but the majority of adult mastocytosis patients tolerated them well and radiological studies with contrast are not contraindicated. Pre-medications are recommended for all patients with previous reactions, patients with elevated tryptase, and patients with systemic mastocytosis [18, 19].

In a Spanish population of 210 adults and pediatric patients, the prevalence of allergy and anaphylactic symptoms was found to be 23.9%, similar to that in the general population with anaphylaxis present at a higher rate of 22% (36 patients) and more prevalent in males [3]. The causes of anaphylaxis included nine drug reactions: COX-1 inhibitors in four cases, antibiotics in three cases, general anesthesia in one case and phenylephrine in one case. In a retrospective study of German patients with drug-induced anaphylaxis, only a minority were associated with mast cell diseases and mostly due to general anesthesia [6, 20]. The authors concluded that general anesthesia appears to be a procedure associated with increased risk of mast cell degranulation in mastocytosis patients, and special precautions should be considered [6].

Aspirin and NSAIDs

An important class of drugs for consideration for mastocytosis patients is the family of NSAIDs and aspirin, and most information found through the Internet indicates that these medications are contraindicated, but these recommendations have not been validated by large outcome studies or mechanistic data on the effects of COX-1 inhibition on clonal mast cells [7]. Personalized recommendations for patients without prior reactions to aspirin and/or NSAIDS require standardized challenges to assess tolerance. In a recent study [21] of aspirin tolerance in mastocytosis, 50 patients underwent an ASA challenge and none developed anaphylaxis, only one developed urticaria. Seventy percent of patients had indolent systemic mastocytosis, 18% had cutaneous mastocytosis, and 12% had advanced mastocytosis. An additional retrospective chart review revealed that eight of 191 mastocytosis patients had a history of NSAID-related hypersensitivity reaction and three reported severe systemic reactions. All eight patients had prior NSAID-related hypersensitivity reactions before the diagnosis of mastocytosis, and the authors concluded that the frequency of ASA hypersensitivity was 2% in the prospective challenge study and 4.1% in a retrospective chart review, lower than the reported incidence of about 25–30%. Because aspirin irreversibly binds to COX-1, it is the best blocker of prostaglandin generation and a useful medication for patients with elevated prostaglandins in urine, which has been associated to flushing and mixed organic brain symptoms [22, 23]. All patients without prior reactions to ASA or NSAIDs should undergo an aspirin challenge at the time of mastocytosis diagnosis [24] to assess ASA and NSAIDs tolerance, and if the challenge is negative, these medications should not be avoided when needed for fever, pain, inflammation, arthritis, and other diseases or symptoms.

Chemotherapy

Mastocytosis can be associated with solid malignancies [25–27] and treatment of these malignancies can be associated with mast cell activation events and anaphylaxis. A recent report of four patients diagnosed with mastocytosis and solid malignancies who presented with reactions during chemotherapy illustrates the potential for reactions and its treatment with drug desensitizations. The patients received intravenous paclitaxel, cisplatin, and oxaliplatin and experienced hypersensitivity reactions during standard administration of chemotherapy, three during their first administration [28]. Two patients were diagnosed with mastocytosis after they presented a hypersensitivity reaction with elevated tryptase and were investigated for systemic mastocytosis. All four patients were treated with drug desensitization and were able to receive their first-line therapy without or with mild breakthrough reactions, indicating that drug desensitizations are not contraindicated in mastocytosis patients.

Perioperative Hypersensitivity and Anaphylaxis

Many factors can influence mast cell activation during the perioperative period such as anxiety and emotional factors including psychological stress, changes in temperature and extremes of temperatures (hypothermia and hyperthermia), physical factors such as trauma, rubbing, pressure and resections, needle biopsies in particular of the gastrointestinal tract, positioning, manipulation, and pain [29].

Common drugs used in the perioperative period are listed in Table 11.1, with the available evidence for mast cell activation. Histamine-releasing benzylisoquinolines (e.g., atracurium and mivacurium) and nefopam, which are non-sedative benzoxazocine analgesics, are not recommended in mastocytosis. Rapid intravenous administration of histamine-releasing medications should be avoided whenever possible. Perioperative hypersensitivity (including one fatality) was found to be linked to atracurium in two cases [30]. Because pain by itself may induce mast cell degranulation, the use of analgesics, specifically opioids, is indicated for intraoperative and postoperative analgesia and should be titrated to patient tolerance and, in some cases, administered with pre-medications such as Anti-histamine H1 and H2 receptors antagonists blockers [31].

The management of perioperative reactions must be specific and adapted to the severity of the clinical features and cardiovascular disturbances. The culprit drug should be discontinued; in cases of severe reactions, anesthetic agents likely to cause vasodilation and negative inotropic effects should be discontinued. In addition, epinephrine and 100% oxygen should be administered. Fluid therapy should be immediately initiated with either crystalloids or colloids and titrated to hemodynamic effects. Corticosteroids and/or H_1- and H_2-receptor antagonists should be administered next (Fig. 11.1).

Table 11.1 Local and general anesthetics and other drugs recommended for perioperative administration in mastocytosis patients

Family of drugs	Accepted	Not recommended
Intravenous, inhalation, and local anesthetics		
Benzodiazepine	Midazolam	
Hypnotics	Etomidate Ketamine Propofol Thiopental	
Halogenated gases and nitrous oxide	Desflurane Isoflurane Sevoflurane Nitrous oxide	
Local anesthetics	Amide type Ester type	
Neuromuscular blocking agents		
Depolarizing NMBA	Succinylcholine	
Nondepolarizing steroidal NMBAs	Pancuronium Rocuronlum Vecuronium	
Nondepolarizing benzylisoquinolin	*Cis*-atracurium	Atracurium
NMBAs		Mivacurium
Reversal of neuromuscular blockade		
Anticholinesterase agent	Neostigmine	
Cyclodextrin	Sugammadex	
Intravenous analgesics		
Opioids	Alfentanil Fentanyl Remifentanil Sufentanil	
Morphine	Requires titration	
Analgesic	Paracetamol (acetaminophen)	Nefopam
Other agents		
Antiseptics	Chlorhexidine Povidone iodine	
Plasma substitutes	Albumin Gelatin Hydroxyethylstarch	
Miscellaneous agents	Aprotinin (topical glue) Atropine Ondansetron Oxytocin Protamine	

Adapted from [29]

Tryptases are neutral serine proteases predominantly stored in mast cells. Two major forms can be measured in vivo: *pro-α tryptase*, which reflects the mast cell burden and is increased in mastocytosis, and mature *β-tryptase*, which is preferentially stored in mast cell granules and released during mast cell activation such as IgE-

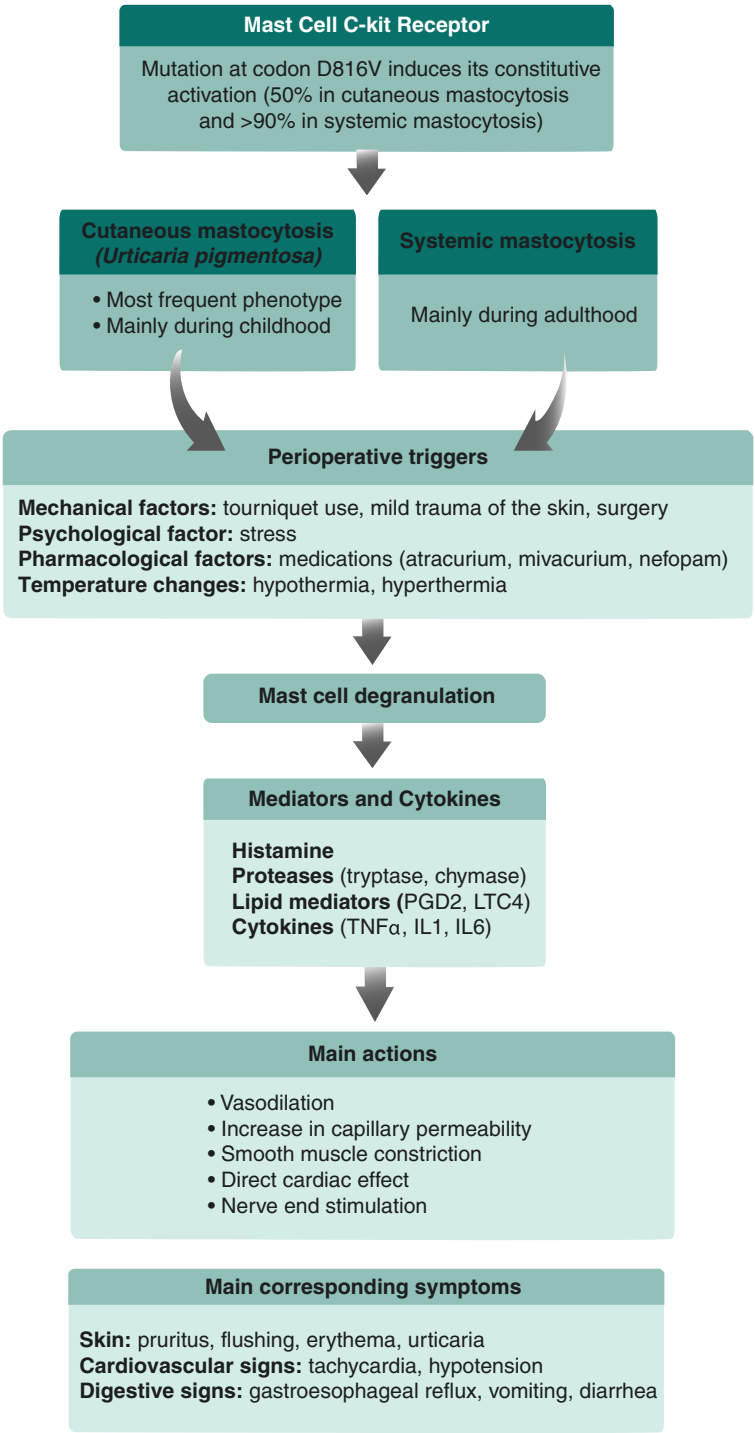

Fig. 11.1 Effect of Perioperative triggers on cutaneous and systemic mastocytosis [29])

mediated anaphylaxis [32–34]. The total tryptase level measured in serum by fluoroimmunoassay measures *pro-α tryptase* and mature *β-tryptase*. Serum total tryptase concentrations reach a peak between 30 and 60 min after the onset of immediate hypersensitivity, decline under first-order kinetics with a half-life of approximately 2 h, and correlate with the clinical severity of the reaction, and sampling is recommended within 30–120 min of the initial symptoms of a reaction followed by a baseline level [34]. Tryptase can be increased for up to 24–48 h after the initial event in mastocytosis, depending on the severity and the extent of mast cell degranulation [35].

Skin tests are indicated in patients with mastocytosis to evaluate potential culprit drugs and all drugs used before, during, and after anesthesia and surgery should be evaluated as well as latex [14]. A positive skin test to one of the suspected agents confirms the diagnosis of IgE-mediated allergy, and avoidance is recommended for all subsequent surgeries. As found in the general population, antibiotics and general anesthetics are the most common drugs inducing IgE-mediated reactions [36–38].

Obstetric Anesthesia

There is no data to suspect a decreased rate of pregnancies in patients with mastocytosis. Mastocytosis has a diverse clinical presentation during pregnancy, and symptoms may worsen, improve, or stay the same in equal proportion (see Chap. 12). Patients with mastocytosis are considered high risk for delivery due to the potential for anaphylaxis due to mast cell activation induced by the physical strain, pain, and medications administered during labor and delivery. About 50 cases have been published reporting anesthetic management of pregnant women with either CM ($n = 13$) or SM ($n = 33$) giving birth to 65 children [15, 39, 40]. Prophylactic therapy with different combinations of antihistamines and corticosteroids has been used during pregnancy and for delivery. Typically, vaginal delivery is seen in the majority of cases and 20% may need a cesarean delivery. Oxytocin has been used for induction of labor and/or after delivery without complications. The most common symptoms observed during labor include pruritus, generalized erythema, and flushing. These symptoms respond to H_1-antihistamines. The risk of preterm labor is present in a minority. Hypotension and difficulty breathing requiring intravenous epinephrine were reported 10 min after delivery in one patient with SM. The peripartum period is often accompanied with stress, anxiety, pain, and cutaneous compression, which are conditions that may precipitate mast cell degranulation. Early epidural administration is likely to minimize stress and provides an adequate analgesic level, which decreases the possibility of mast cell degranulation.

A series of 30 women with mastocytosis who had 45 pregnancies were followed through delivery for outcomes [15]. The patients completed a specific questionnaire about symptoms and medications received during pregnancy and labor and newborn complication. Worsening of MC-related symptoms during pregnancy was observed in ten cases (22%) and one woman with indolent disease developed skin lesions within the third trimester of pregnancy. In contrast, 15 cases (33%) experienced clinical improvement during pregnancy, with a complete resolution of pregestational symp-

toms in seven cases. MC mediator release symptoms intrapartum were observed in five cases (11%) without any fatal outcome. Newborn medical complications such as prematurity, low birth weight, and respiratory distress were detected in seven infants (16%) who were all successfully managed with conservative measures. One infant developed cutaneous mastocytosis several years after birth. The authors concluded that the profile of MC-related symptoms remained unchanged in half of the cases, while in the other half, pregnant women experienced either an improvement or an exacerbation of the symptoms, with the manifestation of ISM during pregnancy in one case. They recommend adequate prophylactic antimediator therapy intrapartum and indicate that patients with nonaggressive mastocytosis should not be advised against pregnancy [15]. They recommend a baseline serum tryptase level before delivery and during perioperative hypersensitivity reactions. There is no need to perform skin tests in patients with mastocytosis prior to the administration of anesthetic drugs. However, all patients with prior perioperative immediate hypersensitivity should undergo skin tests with the potential culprits including antibiotics, general anesthetics, and latex.

Children and Adolescents

Cutaneous mastocytosis is the most common phenotype during childhood, whereas systemic mastocytosis is extremely rare [44, 45]. Although anesthesia experience in pediatric patients with mastocytosis is limited, perioperative outcomes remained mostly uncomplicated in two different series. One report included 22 pediatric CM and SM cases receiving 29 general anesthetics, whereas the other one consisted of six CM cases receiving seven general anesthetics [17, 29]. A retrospective analysis was done of 15 children with cutaneous mastocytosis, urticaria pigmentosa ($N = 12$), and solitary mastocytoma ($N = 3$), who received general anesthesia for 29 procedures. Two patients had pre-medications with H1 antihistamines and the rest had no pre-medications and most anesthetics procedures were uncomplicated, although two children had cutaneous eruptions after administration of codeine. In a recent report [17], 22 patients encompassing multiple variants of pediatric mastocytosis who required anesthesia for invasive procedures were included. Patients were evaluated at the NIH from 1993 to 2006. A multidisciplinary team was involved in the care of these patients, and 22 patients with pediatric mastocytosis were anesthetized for 29 diagnostic and surgical procedures (median age at time of first anesthetic = 3.2 years (Table 11.2)). Among the cohort of patients (15 males and seven females), 14 had cutaneous mastocytosis (CM): six had urticaria pigmentosa (UP), two had maculopapular CM (MPCM), five had diffuse cutaneous mastocytosis (DCM), and one had a mastocytoma (MAST). Eight patients had indolent systemic mastocytosis (ISM), of which all had UP (Table 11.2). The onset of disease ranged from birth to 12 months. Routine prophylactic H1 and H2 blockers and steroids were not administered prior to anesthetics; however, if patients were on chronic therapy ($N = 13$), their medications were continued as scheduled. Fifteen patients (68%) were pre-medicated with midazolam (0.1–0.5 mg/kg) and one (5%) with

Table 11.2 Preoperative symptoms and operative outcomes in 22 children with mastocytosis [17]

Signs and symptoms	Number of patients (%)	Intra-Op or post-Op adverse reaction (%)
Cutaneous		
Flushing	19 (86) [1]	2(9)
Pruritus	17(77)	0
Blistering	4(18)	0
Gastrointestinal		
N/V/ Diarrhea	10(45)	4 [1] (18)
Abdominal pain	9(41)	0
Hepatosplenomegaly	5(23)	–
GERD	5(23)	0
PUD	2(9)	0
Neurological		
Headache	5(23)	0
Cardiovascular		
Hypotension	0(0)	0
Syncope	3(14)	0
Anaphylaxis	1(5)	0

From Carter et al. (2011)
Total number of patients = 22

fentanyl (1.0 mcg/kg). All perioperative courses were uncomplicated. One patient with DCM (patient 13) developed induration on his left heel after a 6-hour procedure. Two patients developed flushing without hemodynamic lability during or after the procedures. Four patients experienced nausea and vomiting shortly after the procedure. Hypotension or bronchospasm associated with mast cell mediator release was not observed during any anesthetic. Intravenous opioids (fentanyl, morphine, or meperidine) were used during and after the procedures followed by oral acetaminophen or ibuprofen as needed for pain. The data suggests that anesthesia is well tolerated by pediatric patients and that pre-medications should be provided to all children with previous reactions, extensive skin disease, elevated tryptase, and systemic mastocytosis.

Recommendations for Premedications

The use of premedications before anesthesia, radiocontrast media, and surgery with H_1- and H_2-receptor antagonists, leukotriene blocker, and low-dose corticosteroids is usually recommended in patients with mastocytosis but has never been evaluated in placebo-controlled trials [41]. In addition to pre-medications, avoidance of known triggers, whether specific such as antibiotics or general or local anesthetics or nonspecific such as psychological, mechanical factors, and temperature changes, is recommended [31]. Medications used for mast cell stabilization and mediator blockers should be continued until surgery and used immediately after surgery [42].

Ambulatory surgery and dental procedures are not contraindicated for patients with mastocytosis unless they have presented reactions in prior surgeries and anesthesia procedures. Patients on Xolair should be provided with a dose up to 7 days prior to surgery to maximize the potential protective effect [43].

Conclusions

The true incidence of drug allergy and anaphylaxis in mastocytosis patients is not known, and patients are reported to react with a higher frequency to certain groups of medications that can trigger mast cells through non-IgE-mediated mechanisms including vancomycin, general anesthetics, radiocontrast dyes, aspirin, and NSAID inhibitors, and morphine derivatives. True IgE-mediated drug allergy is not more frequent than that in the general population, as for environmental and food allergens. The recent discovery of mast cell receptors such as MRGPRX2 which are the target of drugs and substances with THIQ motifs such as general anesthetics, quinolones, and Hymenoptera mastoparan raises the potential for over-expression in clonal mast cells, which could account for increased hypersensitivity reactions and anaphylaxis upon exposure. Patients presenting anaphylaxis during the perioperative period including delivery should be investigated for mastocytosis with tryptase at the time of the reaction and at baseline in addition to skin testing to identify the relevant culprit medications. Personalized medicine should be applied to mastocytosis patients through skin testing and drug challenges to uncover true allergies and intolerances, in particular for NSAIDs to avoid over-diagnosis and avoidance of otherwise important medications for pain and inflammation. Premedications for patients undergoing surgery, radiocontrast dyes, and invasive procedures are recommended until there is better understanding of targeted populations. Protocols should be tailored to the patient's prior history of drug reactions and the medications needed for the procedures. In particular, children with extensive skin disease are targeted for anti-histamines H1, H2, leukotriene blockers, and low-dose steroids. Multi-centered studies are needed to uncover the true incidence of drug allergy and anaphylaxis in mastocytosis patients, and more importantly, basic research is needed to better understand the mechanisms of non-IgE-mediated activation of clonal mast cells.

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Chapter 12
Mastocytosis in Pregnancy

Dawn Lei and Anna Kovalszki

Introduction

Mastocytosis is a rare disorder characterized by increased mast cell proliferation and accumulation in organs. There is, unfortunately, limited information in the literature about the effect of mastocytosis on pregnancy and vice versa.

Mast cells possess both estrogen and progesterone receptors and are present in the myometrium and placenta [1–4]. They have been shown to have a beneficial effect in pregnancy by playing a role in implantation, placentation, and fetal growth [4, 5]. Mast cells further affect pregnancy through nonimmunological avenues by contributing to angiogenesis, remodeling, and spiral artery modifications [5]. Histamine, a mediator produced and released by mast cells, is thought to contribute to placental development; blastocyst implantation; and trophoblast invasion, growth, and adhesion molecule expression [5]. In vitro studies have shown that elevated levels of histamine can increase pregnant myometrial contractions [2, 4–7] and that it may be associated with in vivo increases in preterm labor [2, 4, 5]. Mast cells themselves have been shown to increase in number in the myometrium during pregnancy and are believed to impact uterine contractility and the second stage of labor [2–4, 8].

Evidence suggests that mastocytosis is not a contraindication to pregnancy, provided the disease is appropriately managed [4, 9]. Undiagnosed or poorly controlled mastocytosis can potentially lead to severe maternal and fetal complications [4]. Pregnancy, which is a time of great stress and hormonal change, raises the potential for mastocytosis activation, even in previously well-controlled or quiescent disease.

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Disease Course in Pregnancy

In pregnant women with mastocytosis, approximately 20–33% may experience worsening of mastocytosis-related symptoms [3, 5, 9, 10]. These symptoms most often increased during the first or third trimester, when Th1-mediated pro-inflammatory conditions dominate [4, 5]. Matito et al. noted that 33% of patients had improvement in mast cell mediator related symptoms during the first trimester, which sustained throughout their pregnancy, while 45% experienced no change in symptoms [9].

Mast cell related symptoms increased in frequency as well as with the development of new symptoms that had previously been absent prior to pregnancy [9]. New symptoms often appeared in the first or third trimester, while increase in prior symptoms was seen in the first trimester [9]. The clinical symptoms that most often worsened during pregnancy were cutaneous lesions, pruritus, flushing, or gastrointestinal symptoms [2, 3, 9, 11]. Interestingly, Matitio et al. found in 9 of 45 cases (20%) that mast cell mediator release associated symptoms were worse after delivery when compared to pre-gestation symptom profiles. Fifty percent of patients (five cases) who experienced symptomatic worsening during pregnancy continued to have increased symptoms after delivery. The remaining four cases of increased symptoms occurred in patients who experienced either no clinical change or improvement in symptoms during pregnancy [9].

Many women with mastocytosis need to continue treatment during pregnancy, although the dosages of medications are often reduced for fetal safety, which may contribute to the worsening of mastocytosis symptoms [3–5, 9].

Approach to Management in Pregnancy

Treatment of mastocytosis in pregnancy is directed toward alleviating symptoms while weighing the risks of medications to the fetus. Conservative management typically involves avoidance of triggers, prophylactic antihistamine therapy, corticosteroids, and epinephrine as needed [1–3, 9]. Often, medication doses are reduced for fetal protection. This raises the difficult question of how best to balance maternal symptom management against minimization of fetal harm and whether medication effect or mast cell release might have the greater negative impact on fetal health. There are minimal recommendations in the literature regarding medication use in the management of mastocytosis in pregnancy. The general accepted treatment method, however, favors titration of medications to symptomatic control with the thought that mast cell mediator release has the greater potential for fetal harm than a potential medication effect, while trying to avoid pregnancy category C and higher medications.

Early multidisciplinary team involvement is critical to the management of mastocytosis in pregnancy. The team should include an allergist, obstetrician, anesthesiologist, and the patient. Considerations to be discussed early as a team include risk and benefits of medications used to control mastocytosis related symptoms and whether they can be safely continued during pregnancy; approach to pain and pos-

sible mast cell mediator release symptom management during labor and delivery; plan for perioperative management in the event of a cesarean delivery and indications for preprocedure prophylactic medications; and postpartum medications and adjustments if breastfeeding is desired.

Antimediator Therapy in Pregnancy

Antihistamines

The management of mastocytosis centers on symptom control, with antihistamines forming the cornerstone of pharmacologic treatments [12, 13]. Antihistamines are used in the management of a wide spectrum of mastocytosis symptoms. H1 antihistamines are often used preferentially in the treatment of flushing, pruritus, and urticaria, while H2 antihistamines are used for gastrointestinal-related symptoms [12, 13] Even in the general population, there is significant use of antihistamines during pregnancy with a prevalence of about 10–15% [14, 15]. The literature suggests that antihistamine use in pregnancy is generally safe [9, 14]. Antihistamines carry a US Food and Drug Administration pregnancy risk category rating of B or C (see Table 12.1).

First-generation H1 antihistamines are notably able to cross the blood-brain barrier and are frequently more sedating than second-generation H1 antihistamines [14], which is why second-generation H1 blockers are often preferred. H1 antihistamines have not been associated with increased risk of birth defects [15]. There are

Table 12.1 Mastocytosis treatments and pregnancy risk

Group	Medication	Risk category	Crosses placenta	Pregnancy implications	Excreted in breast milk	Lactation
First-generation H1 antihistamines						
	Chlorpheniramine	C		No increased risk of birth defects	Yes	Excreted in breast milk; use with caution
	Dimenhydrinate	B	Yes	No increased risk of fetal abnormalities	Yes	Excreted in breast milk; use with caution
	Diphenhydramine	B	Yes	Historic association with cleft palate	Yes	Excreted in breast milk; breast feeding contraindicated
	Doxylamine	A		Historical association with neural tube defects, oral clefts, hypoplastic left heart	Yes	Breast feeding not recommended

(continued)

Table 12.1 (continued)

Group	Medication	Risk category	Crosses placenta	Pregnancy implications	Excreted in breast milk	Lactation
	Hydroxyzine	Not assigned	Yes	No increased risk of birth defects but contraindicated in early pregnancy	Unknown	Breast feeding not recommended
	Meclizine	B		Adverse events in animal studies; no increased risk of birth defects in epidemiologic studies	Unknown	Unknown if excreted into breast milk; use with caution
Second-generation H1 antihistamines						
	Cetirizine	B		No increased risk of birth defects	Yes	Second-generation antihistamines preferred; monitor infants for drowsiness, irritability
	Levocetirizine	B		No increased risk of birth defects	Unknown	Breast feeding not recommended
	Loratadine	B		No increased risk of birth defects, prior historical association with hypospadias	Yes	Loratadine and active metabolite, desloratadine, present in breast milk
	Fexofenadine	C		Limited information available	Yes	Limited information available
	Desloratadine	C		Adverse events in animal studies	Yes	Limited information available
H2 antihistamines						
	Cimetidine	B	Yes	Crosses placenta; no increased risk of birth defects	Yes	Breast feeding not recommended
	Famotidine	B	Yes	Crosses placenta; no increased risk of birth defects	Yes	Use with caution; preferred H2 blocker due to lower concentration in breast milk

	Ranitidine	B	Yes	Crosses placenta; no increased risk of birth defects	Yes	Use with caution
Mast cell stabilizer						
	Cromolyn	B		No adverse events in animal studies	Unknown	Use with caution; WHO 2002 – compatible with breastfeeding
	Ketotifen	C		Adverse events in animal studies	Unknown	Breast feeding not recommended
Anti-IgE antibody						
	Omalizumab	B	Unknown	IgG molecules cross placenta; no increased risk of birth defects	Unknown	IgG excreted into breast milk; use with caution
Glucocorticoids						
	Hydrocortisone	C		Increased risk of oral clefts with use in first trimester	Yes	To decrease potential exposure, wait 4 hours after dose before breast feeding
	Prednisone	C/D	Yes	Increased risk of oral clefts with use in first trimester	Yes	To decrease potential exposure, wait 4 hours after dose before breast feeding
	Betamethasone	C	Yes	Increased risk of oral clefts with use in first trimester; non-fluorinated corticosteroid preferred	Yes	Use with caution
	Dexamethasone	C	Yes	Increased risk of oral clefts with use in first trimester; non-fluorinated corticosteroid preferred	Yes	Use with caution

(continued)

Table 12.1 (continued)

Group	Medication	Risk category	Crosses placenta	Pregnancy implications	Excreted in breast milk	Lactation
Leukotriene receptor antagonist						
	Montelukast	B		No adverse events in animal studies; no increased risk of teratogenic effects	Yes	Use with caution
Cytoreductive therapies						
	Cladribine	D		Teratogenic effects and fetal mortality observed		Not recommended
	Imatinib	D	Yes	Pregnancy not recommended (in mother or father) within 2 weeks of last imatinib dose	Yes	Not recommended during and for 1 month after last dose of imatinib
	Midostaurin	Not assigned		Pregnancy not recommended (in mother or father) during or within 4 months of last dose	Unknown	Not recommended during and for 4 months after last dose of midostaurin
	Interferon alpha 2b	C	No	Abortifacient effects in animal studies; contraindicated in combination therapy with ribavirin	Yes	Interferon alpha is endogenous to breast milk; levels not changed significantly

Modified from Table 12.2 in Lei et al. [1]

a few case reports and case series that report associations between diphenhydramine (pregnancy risk category class B, with no reported teratogenic effects in animals) and cleft palate, although this has not been confirmed in the current literature [14, 15]. Doxylamine, an active ingredient in the antinausea agent Benedectin, was voluntarily removed from the market after hundreds of lawsuits contended teratogenicity in the form of neural tube defects, oral clefts, congenital heart defects, amongst others, although several subsequent studies did demonstrate this association [14–16]. Hydroxyzine, which does not carry an FDA risk category designation, has not shown increased risk of birth defects [14]. Of note, the use of most first-generation H1 antihistamines is not recommended during breastfeeding.

Second-generation H1 antihistamines are likewise not associated with significant birth defects [14]. Loratadine has previously been linked to hypospadias,

although multiple recent studies did not demonstrate an association [14, 15]. Newer H1 blockers, such as fexofenadine, lack significant data in pregnancy, thus earning a pregnancy category C designation. Many physicians consider loratadine and cetirizine, both pregnancy class B, to be the preferred H1 antihistamines in pregnancy [17].

H2 antihistamines, such as ranitidine and famotidine, are pregnancy risk category B medications and have not been shown to increase the risk of birth defects [14]. The use of high-dose antihistamines, as often seen in the management of mastocytosis, has not been well studied [17].

Glucocorticoids

Oral glucocorticoids are often used in the management of mastocytosis, particularly for prevention of anaphylaxis, refractory abdominal pain, malabsorption, and widespread cutaneous disease [12, 13]. The ability of glucocorticoids to cross into the placenta raises concern about its use in pregnancy, although the current literature suggests that systemic glucocorticoid use is largely safe [18–20]. The placental enzyme 11B- hydroxysteroid dehydrogenase is able to reduce the percentage of active drug to around 10% through conversion of cortisol/ corticosterone to the inactive 11-keto form [18, 19]. Of note, fluorinated glucocorticoids such as betamethasone and dexamethasone are less readily metabolized by the placenta and should be used sparingly [18]

Risks associated with glucocorticoid use remain controversial and include, in some studies, an approximately threefold risk of oral clefts with use during the first trimester [18–22] as well as an association with reduced fetal size [18, 19]. Dexamethasone in animal studies has been shown to have several hundred-fold "cleft palate activity" than hydrocortisone [23]. There are rare reports of neonatal cataracts [18] and fetal adrenal suppression [18, 19]. The use of moderate doses of glucocorticoids while breastfeeding has been found to be safe, with only trace amounts of steroid excreted into human breast milk [18]. At doses greater than 40 mg, it is recommended to wait at least 4 hours prior to breastfeeding [18].

Omalizumab

Omalizumab, also known as xolair, is a recombinant monoclonal anti-IgE antibody used in the treatment of moderate-to-severe asthma and chronic urticaria [17, 24]. It has shown potential use in the treatment of mastocytosis related symptoms, particularly those with recurrent anaphylaxis [13]. It is classified as a pregnancy category B medication and has not shown significant maternal toxicity, teratogenicity, or adverse fetal effects [24]. Animal reproduction studies similarly have not shown evidence of fetal harm despite doses up to approximately ten times the maximum

recommended human dose [25]. The Xolair Pregnancy Registry (EXPECT) has thus far demonstrated that rates of major congenital defects, risk of preterm birth, or small-for-gestational-age infants are similar to the rates seen in the general asthma population [24]. Given the black box warning for risk of anaphylaxis, some allergists do not recommend initiation of omalizumab during pregnancy [17]. The use of omalizumab in breastfeeding mothers should be approached with caution given the limited data available [25]. It is not yet known whether omalizumab is excreted in breast milk, although it is a reasonable assumption because IgG is excreted into breast milk.

Cromolyn Sodium

Cromolyn, a mast cell stabilizer, is a frequently used medication in mastocytosis for the reduction of gastrointestinal symptoms such as abdominal pain and diarrhea, pruritus, and flushing [12, 13, 26, 27]. It has been designated a pregnancy category B medication and has not demonstrated any increased risk of major congenital malformation [21].

Leukotriene Receptor Antagonists

Leukotriene receptor antagonists, such as montelukast, are used in mastocytosis for recalcitrant symptoms of flushing, musculoskeletal pain [13]. It is classified as a pregnancy category B medication, and studies have not demonstrated teratogenicity [17, 20, 21, 28, 29]. No teratogenicity was noted in animal studies with montelukast at doses 100–110 times the maximum recommended human dose, although montelukast was found to cross the placenta [30]. Rare structural limb defects were reported, although a relationship with montelukast was not established [28]. Two prospective studies using leukotriene receptor antagonists did not show an increase in the rate of major malformation with leukotriene receptor antagonist use. Both studies did report a statistically significant decrease in mean birth weight, which was attributed to maternal asthma severity [28, 29].

Ketotifen

Ketotifen, a medication with mast cell stabilizing and antihistamine properties, has been shown to be useful in treating mastocytosis symptoms such as abdominal pain, flushing, and pruritus [13]. It is a pregnancy category C medication, with animal studies demonstrating adverse events [31].

Cytoreductive Therapies in Pregnancy

Interferon Alpha 2B

Interferon alpha has an unclear mechanism of action but has demonstrated reduction in mast cell mediator release, mast cell infiltration, and symptomatic improvement in mastocytosis [12, 13, 26]. It is assumed to act through restriction of the proliferative potential of hematopoietic cells [12]. Previous use in the literature has been limited to the management of acute hepatitis C, essential thrombocytopenia, and malignancy. In these small case series, interferon alpha 2b use was not clearly associated with maternal or fetal complications or malformations [32, 33]. An increased incidence of intrauterine growth restriction was seen in infants exposed to interferon alpha 2b relative to the general population, but causality could not be established because of the limited data available [33]. In a case report of interferon use in mastocytosis during pregnancy, no significant fetal malformations were seen, although the pregnancy was complicated by fetal bradycardia prompting emergency C-section at 37 weeks [1]. It is a category C medication in pregnancy when used alone, but a category X medication when used in conjunction with ribavirin [34]. Animal studies of interferon alpha 2b in rhesus monkeys have shown abortifacient effects [34].

Tyrosine Kinase Inhibitors

Imatinib mesylate and midostaurin are tyrosine kinase inhibitors approved by the FDA for use in advanced systemic mastocytosis. Use of imatinib is limited to patients without locus 816 KIT mutation, as the conformational change from the point mutation reduces drug binding [12, 13], rendering it useful in only about 10% of patients [35]. A 33% response rate, with reduction of mast cell burden, has been shown in the small portion of patients with systemic mastocytosis without the D816V KIT mutation [13]. Patients on imatinib, and partners of patients on imatinib, are advised not to become pregnant while on the medication. Although there are case reports of successful pregnancies without complications, the current literature suggests increased risk of spontaneous abortion, skeletal abnormalities, and other congenital abnormalities such as, but not limited to, pyloric stenosis and hypospadias [36–39].

Midostaurin inhibits multiple kinases, including mutant and nonmutant KIT D816V, and is able to be used in those with KIT D816V mutation [35]. Phase 2 data suggests midostaurin is able to provide symptomatic improvement, reverse organ damage, decrease splenomegaly, and reduce bone marrow mast cell burden [35]. There have been no studies evaluating use of midostaurin in pregnancy, although animal models demonstrated fetal toxicity and embryo-fetal death at doses lower than the recommended human dose, raising concern for fetal harm in humans [40].

Cladribine

2-Chlorodeoxyadenosine or cladribine is a nucleoside analog that has shown transient improvement in mastocytosis [12, 13, 26]. It is a pregnancy category D medication, with animal studies demonstrating teratogenic effects and fetal mortality. It is not recommended that patients become pregnant while on this medication [41].

Labor and Delivery Management in Mastocytosis

Introduction

Information on management of labor and delivery is limited and much of what follows is extrapolated from literature on peri−/intra-operative management in mastocytosis. A plan of action should be developed with collaboration from a multidisciplinary team comprising a specialist in mastocytosis, obstetrician, and anesthesiologist.

Early preparation should include a detailed survey of the patient's prior history including phenotype of mastocytosis and its activity [42], previous anaphylaxis, and known drug allergies [10]. The focus of planning should be on preventing mast cell degranulation, while also creating a strategy to treat and manage it if degranulation should occur [43]. It is important that all members of the treatment team are aware that physical stimuli, exposure to sensitized antigen, histamine release–stimulating medications, and stress can cause mast cell degranulation [10, 43, 44]. It is critical that medications such as antihistamines, glucocorticoids, and epinephrine are available during the phases of labor and in the early postpartum period [3, 4, 43]. The treatment team should consider management plans for both vaginal delivery as well as, should the need arise, cesarean section. Considerations should include choice of pain regimen, anesthetics, and need for pre-medication. Medications for the induction of labor appear to be safe for use in patients with mastocytosis [9]. Cesarean section should be reserved for obstetric indications [11].

Preoperative Drug Testing

The literature does not recommend routine skin testing patients with mastocytosis prior to receiving anesthesia [42, 44]. Similarly, pregnant patients with mastocytosis do not need skin testing as part of a predelivery/preoperative plan unless previous reactions are known. A detailed history of anaphylaxis and drug allergies is critical to preventing iatrogenic anaphylaxis [44]. A complete workup for specific drug allergies is recommended in the surgical literature only in mastocytosis patients who have previously experienced drug-induced anaphylaxis [44]. Such a workup

may be considered in mastocytosis patients considering pregnancy, but should, unless benefits outweigh risk, be deferred in pregnant patients. If drug sensitization testing is not available, drugs that caused prior adverse reactions should be avoided [44].

Premedication

There are few clear recommendations on the value and use of premedication prior to anesthesia or invasive procedures in mastocytosis. The European Network on Drug Allergy (ENDA) and European Academy of Allergy and Clinical Immunology (EAACI) position paper in 2015 noted the absence of evidence for or against premedication prior to anesthesia in mastocytosis, although most specialist centers continue to recommend pretreatment [45]. Some advocate categorizing procedures as low or high risk and using premedication prior to high-risk procedures [44]. High-risk procedure characteristics include general anesthesia, major surgery, GI, or cardiac surgery [44].

Labor and delivery, while a time of great stress, does not necessarily qualify as a high-risk procedure. Premedication prior to an uncomplicated delivery is not absolutely necessary, but should be considered in patients with a history of anaphylaxis [44]. Patients undergoing general anesthesia for delivery should be premedicated [44]. Prior studies of mastocytosis in pregnancy have varied in their approach to premedication. Ciach et al. recommended premedication prior to delivery in all patients and did not demonstrate any side effects from the premedication. None of the patients in this study showed signs of anaphylaxis, before pregnancy, during pregnancy, or puerperium [4]. Matito et al. utilized prophylactic antimediator therapy prior to labor in 38% (17 of 45 pregnancies). Their team noted that in the 32 cases where epidural anesthesia was used, only three demonstrated signs of mast cell related symptoms intrapartum, of which two had not received pretreatment [9]. Matito et al., in their evaluation of anesthesia management in mastocytosis, demonstrated that the frequency of perioperative mast cell mediator release symptoms was higher in patients who did not receive prophylactic antimediator therapy (55%) compared to 13% who did [46].

There have not been any published studies evaluating the efficacy of one premedication regimen over another, although most recommend inclusion of H1 antagonists [10, 44, 45], benzodiazepines [10, 44, 45], and corticosteroids [44, 45] prior to invasive procedures. The use of H2 antagonists, with the potential synergistic effect on H1 antagonist pharmacokinetics, is sometimes recommended [44, 47]. Corticosteroids are widely used in prophylaxis protocols. In vitro studies have demonstrated that corticosteroids have an acute effect on mast cell activation and degranulation, so it is thought that administration of corticosteroids prior to a procedure may attenuate mast cell degranulation and have a greater effect than administering corticosteroids after anaphylaxis, when extensive degranulation has already occurred [44].

Pain Management

Adequate analgesic and pain control is an integral portion of peri-partum management, particularly in mastocytosis, although it must be balanced against the risk of such medications causing mast cell mediator release.

The use of narcotics should be undertaken with caution. Studies of codeine, meperidine, and morphine demonstrate substantially more histamine release in vivo studies than newer semisynthetic opioids such as fentanyl, sufentanil, and remifentanil [48]. Codeine, in particular, is well known to cause mast cell degranulation [44, 45, 49, 50]. Interestingly, codeine alone has shown both in vitro and in vivo to cause mast cell degranulation, while other opiates have not shown such effects in vitro [44]. Thus, use of codeine should be avoided wherever possible. Morphine has a concentration-dependent release of histamine from skin mast cells, while fentanyl does not induce histamine release [49]. Fentanyl is frequently used for analgesia across surgical and obstetric literature on mastocytosis. Fentanyl, along with new semi-synthetics like sufentanil and remifentanil, is considered safe [10].

Early epidural administration is believed to reduce stress and provide sufficient analgesia, which may decrease the possibility of mast cell degranulation [10]. Amide local anesthetics are preferred over ester-linked ones [10, 49]. As postulated by Ulbrich et al., ester local anesthetics metabolism results in the production of para-aminobenzoic acid, which may be a trigger for possible anaphylaxis [10]. Anesthetic procedures such as epidural analgesics have been well tolerated in mastocytosis [3, 9, 45], but monitoring for signs of anaphylaxis should still be undertaken.

Anesthesia

When choosing an anesthetic, it is recommended that the drug(s) with the lowest risk of mast cell degranulation are used, such as amide-derivative local anesthetics and rigid neuromuscular blockers [46]. (see Table 12.2 for list of medications).

Of the neuromuscular blocking agents, succinylcholine and cisatracurium appear to be the safest with the lowest potency of mast cell activation [44, 49]. Aminosteroids such as vecuronium, rocuronium, pancuronium, and rapcuronium have intermediate potency for mast cell activation, while atracurium and mivacurium are the most potent activators [49].

For general anesthesia, volatile anesthetics do not cause histamine release [10, 47–49] and are often a good choice for anesthesia. Ketamine, propofol, and thiopental do induce histamine release, although mast cell response differed in different tissues [49]. Propofol, despite being shown to cause in vivo histamine release, is felt to be a safe choice in patients with mastocytosis [10, 48, 51, 52]. Ketamine is similarly felt to be safe for use, although the literature suggests avoiding use of thiopental [10]. Etomidate is another safe agent for use [10, 42, 44]. Indeed, etomidate has been described by Hepner et al. as “perhaps one of the most immunologically safe

Table 12.2 Drugs and mastocytosis

Class	Recommended	Unclear	Avoid use
Analgesics			
	Fentanyl	Morphine	Codeine
	Sufentanil	NSAID	Nefopam
	Remifentanil		
	Alfentanil		
	Acetaminophen		
	Tramadol		
Anesthetics			
Benzodiazepines	Midazolam		
	Flunitrazepam		
Hypnotics			
	Etomidate		Thiopental
	Propofol		
	Ketamine		
Halogenated gases	Desflurane		
	Isoflurane		
	Sevoflurane		
	Nitrous oxide		
Local anesthetics			
	Amide type		Ester type
Antiseptics			
	Chlorhexidine		
	Povidone iodine		
Neuromuscular blocking agents			
	Pancuronium	Rocuonium	Atracurium
	Vecuronium	Rapacuroniium	Mivacurium
	Succinylcholine		
	Cis-atracurium		
Misc			
	Atropine	Metylergonovine	
	Ondansetron	Prostaglandins	
	Oxytocin		
Amide	Bupivacaine		
	Lidocaine		
	Mepivacaine		
	Prilocaine		
	Ropivacaine		
	Levobupivacaine		
Ester	Benzocaine		
	Chloroprocaine		
	Procaine (novocaine)		
	Tetracaine		

anesthetics,‘ [53] although it is worth nothing their article did not specifically consider medications in the setting of mastocytosis. Of note, in the surgical literature, Matito et al. found that adult cases that underwent major surgery and general anesthesia had a higher frequency of perioperative mast cell mediator release symptoms and more frequent anaphylaxis [46]. However, data seems to suggest that anesthetics appear to be tolerated at standard doses during general anesthetic procedures in women with mastocytosis, although close monitoring for signs of anaphylaxis must be instituted [3]. As with all patients, consideration of potential harms of general anesthesia should be weighed against benefits.

Anaphylaxis in Pregnancy

Anaphylaxis is a life-threatening emergency that can have a catastrophic effect on both the mother and the fetus. It is the result of massive mast cell activation and degranulation [53, 54]. The risk of anaphylaxis during delivery in the general population is approximately 2.7 per 100,000 deliveries [44, 54, 55]. Mastocytosis, characterized by a pathologic accumulation of mast cells in different tissues, is associated with increased risk of IgE- and non IgE-mediated anaphylaxis [48]. In patients with systemic mastocytosis, a lifetime prevalence of anaphylaxis is estimated to be anywhere from 22% to up to 50% of adult patients [44, 46].

Signs and symptoms of anaphylaxis in pregnancy may include lower back pain, uterine cramps, preterm labor, fetal distress, and vulvar or vaginal itching [54, 56]. Anaphylaxis may result in maternal hypotension and hypoxemia, which can lead to intrapartum asphyxia and decreased uterine blood flow. Fetal injury can result, including severe central nervous system damage, hypoxic-ischemic encephalopathy, or death [56]. The risk of cesarean delivery in anaphylaxis in pregnant patients is significantly elevated, as high as 74% [54, 56].

Significant fetal and maternal morbidity and mortality is seen with anaphylaxis during labor and delivery. Hepner et al. [55] found that in the general population that anaphylaxis during labor resulted in neonatal death or neonatal neurologic abnormalities in 46% of cases, although no maternal morbidity or mortality was seen. This was attributed to delayed cesarean delivery and inappropriate or delayed epinephrine usage. Conversely, Hepner et al. showed that anaphylaxis during cesarean delivery resulted in maternal morbidity in 20% of cases and one case of maternal death, while no neonatal morbidity or mortality was seen. This was attributed to delayed recognition and inappropriate management of maternal anaphylaxis, while concurrent fetal extraction likely improved neonatal outcomes.

The principles of management of anaphylaxis in pregnancy are similar to those of management of anaphylaxis in the general population. The inciting trigger should, if possible, be removed. Maternal airway, breathing, and circulation should be assessed. Supplemental oxygen should be provided, and instruments for endotracheal intubation made available should the patient’s airway become compromised. Epinephrine at a dose of 0.01 mg/kg of 1:1000 solution should be injected intramuscularly and repeated

as needed [54, 56]. Isotonic saline bolus for hypotension should be rapidly administered with a goal of maternal systolic blood pressure of 90 mm Hg to maintain adequate placental perfusion [54]. Fluid therapy is critical to compensate for peripheral vasodilation and interstitial capillary leakages [55]. Continuous monitoring of maternal blood pressure, heart rate, oxygenation, and electronic fetal monitoring should be initiated. The utility of other medications commonly used in the management of mastocytosis, such as H1 and H2 antihistamines or glucocorticoids, in immediate management of anaphylaxis is less clear and should be considered as second-line therapy. They can be administered as long as they do not delay life-saving therapies such as epinephrine.

A concern about the use of epinephrine in pregnancy is the potential reduction in uterine blood flow and its effect on the fetus [54, 55, 57, 58]. However, this concern is diminished in comparison to the more definitive risk of hypoperfusion and uterine contractions associated with anaphylaxis. Additionally, it is thought that an appropriate dose of epinephrine will increase systemic vascular resistance, cardiac output, and uteroplacental perfusion [55]. Ephedrine, which is believed to spare uterine blood perfusion, was previously recommended for hypotension in pregnancy [54, 58]. However, recent literature suggests that intravenous phenylephrine is more effective at maintaining maternal blood pressure than ephedrine, and closely titrated epinephrine remains the vasopressor of choice for anaphylaxis [54].

Notably, a pregnant patient should be placed on her left side to prevent the gravid uterus from reducing venous return from the inferior vena cava [54]. In addition, the patient should not sit or stand abruptly due to the risk of empty IVC/empty ventricle syndrome and potential for resultant cardiac arrest [54]. Any evidence of fetal distress should be managed with aggressive maternal treatment of hypotension and/or hypoxemia.

The decision for emergent cesarean should be weighed against the risks of maternal and neonatal morbidity/mortality, particularly in pregnancies less than 32 weeks of gestation. Stable maternal hemodynamic status does not guarantee fetal oxygenation and placental perfusion [55], so early fetal heart rate monitoring is important in determining fetal status [57]. Early emergency C-section should be considered if there is persistent hemodynamic instability despite resuscitation [55]. If cardiac arrest occurs from anaphylaxis, emergent C-section delivery within 4 minutes of the arrest is recommended if resuscitation has not been successful [55]. It has been shown that 90% of neonates delivered within 5 minutes of an arrest are neurologically intact, while <60% of neonates delivered within 15 minutes are neurologically intact [54]. Furthermore, emptying the uterus removes aortocaval compression, which can increase cardiac output by 60–80%, increasing the likelihood of maternal survival [55].

Obstetrical Complications

It is unclear whether mastocytosis significantly changes the rates of adverse maternal or fetal outcomes. Matito et al. [9] stated that the frequency of spontaneous pregnancy loss in the first trimester, cesarean delivery, prematurity, and low birth

weight was not significantly different than the rates described for the general Spanish population. A concern for increased risk of preterm labor in mastocytosis has been raised in the literature [2, 4, 9], particularly given the associations of elevated levels of histamine and uterine contractions [2, 4–7], but this has not been clearly shown in the limited case series available. A review of 45 cases of pregnancy in mastocytosis, one of the largest case series to date, had three cases (6.6%) of preterm birth [9], which is comparable to the European rate of about 5% [59].

An estimated 25–30% of pregnant women with mastocytosis experience spontaneous miscarriages [4], which may be slightly higher than that of the general population. Agenor et al. [60] described that the "universally quoted figure for sporadic miscarriage" in the general population is one in five, with similar studies reporting a miscarriage rate of 11% for a clinical pregnancy and 26.9% for biochemical pregnancy. Larsen et al. [61] estimated a rate of 15% with significant variation (10–51%) depending on maternal age.

Infertility

While the data in the literature is sparse, mastocytosis does not seem to impact a woman's ability to conceive and carry a child, with rates of infertility issues similar to those of the general population [3]. Matito et al. [9] reported only one case out of 45 pregnancies requiring in vitro fertilization. Ciach et al. [4] did not report any patients requiring active treatment for infertility, and Worobec et al. [3] described one patient (12.5%) who required clomiphene treatment.

Conclusion

Patients with mastocytosis require careful and early interdisciplinary team management to minimize risk to the patient during preconception, pregnancy, and peripartum periods. This patient population is diverse, and each patient should be approached as an individual while managing mastocytosis during pregnancy.

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Chapter 13
KIT and Other Mutations in Mastocytosis

Siham Bibi and Michel Arock

Abbreviations

AHN	Associated hematologic neoplasm
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ASM	Aggressive systemic mastocytosis
ASO	Allele-specific oligonucleotide
BM	Bone marrow
CEL	Chronic eosinophilic leukemia
CFU-GM	Colony-forming unit granulocyte-monocyte
CM	Cutaneous mastocytosis
cMCL	Chronic mast cell leukemia
CMML	Chronic myelomonocytic leukemia
DCM	Diffuse cutaneous mastocytosis
Del	Deletion
DNA	Deoxyribonucleic acid
Dup	Duplication
EAB	Expressed allele burden
ECD	Extracellular domain
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumor
HSC	Hematopoietic stem cells
ISM	Indolent systemic mastocytosis
ITD	Internal tandem duplication

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JMD	Juxtamembrane domain
KID	Kinase insert domain
MCL	Mast cell leukemia
MCS	Mast cell sarcoma
MCs	Mast cells
MC_T	Mast cell tryptase$^+$
MC_{TC}	Mast cell tryptase$^+$ chymase$^+$
MDS	Myelodysplastic syndrome
MPCM	Maculopapular cutaneous mastocytosis
MPNs	Myeloproliferative neoplasms
OS	Overall survival
PB	Peripheral blood
PCR	Polymerase chain reaction
PFS	Progression-free survival
PTD	Phosphotransferase domain
RNA	Ribonucleic acid
RT	Reverse transcription
SCF	Stem cell factor
SM	Systemic mastocytosis
SM-AHN	Systemic mastocytosis with an associated Hematologic neoplasm
SSM	Smoldering systemic mastocytosis
TK	Tyrosine kinase
TKIs	Tyrosine kinase inhibitors
TMD	Transmembrane domain
UP	Urticaria pigmentosa
WDSM	Well-differentiated systemic mastocytosis
WHO	World Health Organization
WT	Wild-type

Introduction

Mast cells (MCs) are multifunctional immune cells derived from hematopoietic stem cells (HSC) in the bone marrow (BM). In humans, agranular committed BM MC progenitors (cMCP), identified as $CD34^+/KIT^+/CD13^+/Fc\varepsilon RI^-$ cells [1], are released into the bloodstream from where they migrate to the peripheral tissues, where they differentiate under the influence of the local microenvironment [2]. Two major subtypes of MCs have been described in humans: MCs expressing only tryptase (MC_T) and MC expressing tryptase and chymase (MC_{TC}), which differ by their tissue location and by their mediator content [3]. The major growth and differentiation factor for the MC lineage is stem cell factor (SCF), the ligand of KIT (CD117), a transmembrane receptor with intrinsic tyrosine kinase (TK) activity [4].

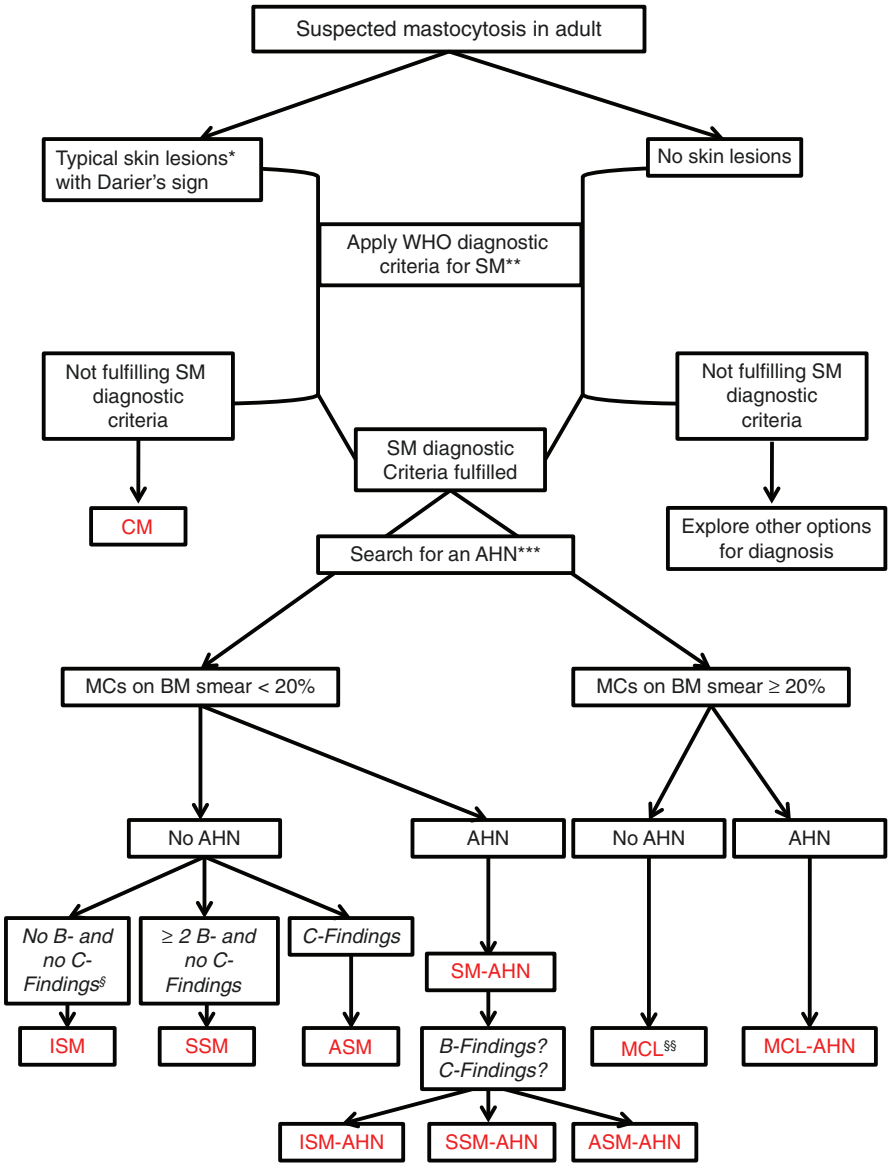
Mastocytosis is a heterogeneous group of rare diseases characterized by an abnormal accumulation of more or less atypical MCs in one or more organs [5]. The

diseases are schematically divided into cutaneous mastocytosis (CM) and systemic mastocytosis (SM) [6], whereas localized MC tumors (i.e., MC sarcoma) are very rare [7]. Pure CM is usually diagnosed in childhood [8], while in most adult patients, the disease is systemic (SM) and involves primarily the BM, although the skin is often also affected [9]. Of note, if mastocytosis can affect either children or adults, the behavior of the disease diverges not only between children (disease usually restricted to the skin and attenuating at puberty), and adults (disease constantly systemic, chronic, and noncurable) but also between SM patients [10]. Indeed, according to the 2016 World Health Organization (WHO) classification of mastocytosis, SM patients may suffer from the indolent form of the disease (ISM) with a good prognosis, or may exhibit slowly progressive SM (smoldering SM; SSM), aggressive (ASM) or even leukemic (mast cell leukemia; MCL) variants, which have respectively intermediate, poor, or very poor prognosis [6]. In addition, in a subset of SM patients, an associated hematologic neoplasm is found (SM-AHN) [11]. In these latter patients, the prognosis depends both on the aggressiveness of the SM component and on that of the AHN [10]. Aggressive SM, MCL, and SM-AHN are collectively termed advanced variants of SM (advanced SM) [12].

The diagnosis of SM is based on stringent criteria defined by the WHO (Fig. 13.1) [13]. If at least one major and one minor criterion or at least three minor criteria are present, the final diagnosis is SM (Fig. 13.1). Once the diagnostic of SM is made, the disease is further categorized into ISM, SSM, ASM, or MCL according to the absence or presence of B-(Borderline benign) findings (reflecting a high MC burden), of C-(Consider cytoreduction) findings, in relation with organ(s) failure because of massive infiltration by neoplastic MCs, and on the percentage of MCs in BM smears (Fig. 13.1) [5, 6, 14]. A proposal of simplified algorithm for the diagnosis and classification of the disease in adult patients with suspected mastocytosis is presented in Fig. 13.1.

Clinically, ISM patients mainly suffer from MC mediator-related symptoms, such as flushing, pruritus, hypotension, syncope, palpitations, and tachycardia [15]. Gastrointestinal (GI) tract symptoms are also frequently recorded in such patients [16]. The mediator-related symptoms are usually well controlled by antimediator therapies [17]. In addition, severe osteoporosis (with or without pathologic fractures) is often seen in SM, particularly in advanced variants [18]. Contrasting to ISM, C-findings are recorded in advanced SM (Fig. 13.1), and targeted and nontargeted cytoreductive treatments or even allogeneic stem cell transplantation are applied in such cases [12].

In most mastocytosis patients, *KIT*-activating mutations are found [19]. While in children, *KIT* mutations frequently affect the extracellular domain (ECD) of the KIT receptor [20], in adult patients, the *KIT* D816V mutation, affecting the phosphotransferase domain (PTD) of the receptor, is recurrently found in neoplastic MCs (in virtually 100% of ISM patients and in >80% of advanced SM patients) [21]. The recurrence of such mutation in SM patients, despite the variable severity of the disease, raised the hypothesis that if in ISM the *KIT* D816V mutation is possibly the main driver of the disease, the same might not be said for advanced SM patients. In order to confirm this hypothesis, several teams have analyzed, in


Suspected mastocytosis in adult
Typical skin lesions* with Darier's sign
No skin lesions
Apply WHO diagnostic criteria for SM**
Not fulfilling SM diagnostic criteria
Not fulfilling SM diagnostic criteria
SM diagnostic Criteria fulfilled
CM
Explore other options for diagnosis
Search for an AHN***
MCs on BM smear < 20%
MCs on BM smear ≥ 20%
No AHN
AHN
No AHN
AHN
No B- and no C-Findings§
≥ 2 B- and no C-Findings
C-Findings
SM-AHN
ISM
SSM
ASM
B-Findings? C-Findings?
MCL§§
MCL-AHN
ISM-AHN
SSM-AHN
ASM-AHN

advanced SM patients, the structure of a number of non-*KIT* genes already found mutated in other (hematologic) neoplasms. In fact, several non-*KIT*-related additional pro-oncogenic lesions affecting, for instance, *RAS*, *TET2*, *SRSF2*, *ASXL1*, *CBL,* and/or *RUNX1,* have been evidenced in such patients [22–28]. Of note, these patients may present with multi-mutated neoplastic cells, and the number and nature of the genetic defects found seem to negatively impact their prognosis [23–28].

In the first part of this chapter, the authors describe the different *KIT* mutants found in the various categories of mastocytosis (their variable sensitivity to KIT-targeted tyrosine kinase inhibitors (KIT-TKIs) as well as the use of such targeted drugs in the management of mastocytosis will be described in Chap. 16 of this book). Afterwards, the authors describe the non-*KIT* additional genetic defects found in advanced SM patients and their impact(s) in terms of aggressiveness and prognosis of the disease.

Fig. 13.1 Simplified algorithm for the diagnosis and classification of the disease in adult patients with suspected mastocytosis. ∗The classification of cutaneous mastocytosis (CM) is based on macroscopic features of skin lesions and their distribution. A generally accepted approach is to classify CM into (1) maculopapular cutaneous mastocytosis (MPCM), also known as urticaria pigmentosa (UP), which is the most frequent type of CM in adults; (2) diffuse cutaneous mastocytosis (DCM); and (3) mastocytoma of the skin. Of note, isolated CM without BM involvement is usually rarely seen in adult patients. ∗∗According to the World Health Organization (WHO), systemic mastocytosis (SM) diagnosis requires the presence of both the major criterion and one minor criterion or at least three minor criteria. The major criterion consists in the presence of multifocal, dense infiltrates of aggregated MCs (>15 MCs) detected in bone marrow and/or other extracutaneous organs. Minor criteria are the following: (i) atypical morphology in >25% of MCs in infiltrates; (ii) presence of an activating *KIT* point mutation at codon 816 in bone marrow, blood, or an extracutaneous organ; (iii) aberrant expression of CD2 and/or CD25 by neoplastic MCs; and (iv) elevated serum tryptase level > 20 ng/ml (does not apply in patients who have an associated AHN). ∗∗∗ SM-AHN (5–20% of all SM cases) is a special subvariant of the disease. In most SM-AHN patients, an associated myeloid neoplasm is diagnosed, such as chronic myelomonocytic leukemia, myeloproliferative neoplasm, myelodysplastic syndrome, chronic eosinophilic leukemia, acute myeloid leukemia. In contrast, lymphoid variants of AHN (multiple myeloma, B-cell lymphoma, chronic lymphocytic leukemia) are rarely found. §B- and C-Findings reflect respectively a high mast cell burden without organ dysfunction, and destructive organ infiltration by neoplastic mast cells. B-Findings are the following: (i) BM biopsy showing >30% infiltration by MCs (focal, dense aggregates) and serum total tryptase level > 200 ng/mL, (ii) myeloproliferation or signs of dysplasia in non–MC lineage(s), no prominent cytopenias; criteria for AHN not met, and (iii) hepatomegaly and/or splenomegaly on palpation without impairment of organ function and/or lymphadenopathy on palpation/imaging (> 2 cm). C-Findings are defined by (i) Cytopenia(s): ANC < 1×10^9/L, Hb < 10 g/dL, or platelets < 100×10^9/L, (ii) hepatomegaly on palpation with impairment of liver function, ascites, and/or portal hypertension, (iii) skeletal lesions: osteolyses and/or pathologic fractures, (iv) palpable splenomegaly with hypersplenism, and (v) malabsorption with weight loss from gastrointestinal tract MC infiltrates. §§ In mast cell leukemia (MCL), circulating neoplastic MCs can be detected or not in the bloodstream. When circulating MCs represent less than 10% of total white blood cells, the subvariant is termed "aleukemic MCL". In addition, MCL can be separated into acute and chronic subvariants based on the morphology of neoplastic MCs and on the presence or absence of C-Findings. ANC absolute neutrophil count, ASM aggressive SM, BM bone marrow, MCs mast cells, SM-AHN, SM with an associated hematologic neoplasm

KIT Mutations Found in the Different Categories of Mastocytosis

KIT mutations are recurrent genetic alterations found in the vast majority of mastocytosis patients (CM in children and SM in adults). However, the *KIT* mutants found, which have all been reported as activating defects, that is, constitutively phosphorylated in the absence of the KIT ligand, SCF, may differ in their nature and position, depending on the disease variants (Fig. 13.2 depicts the difference in repartition of *KIT* defects between children and adults, while Fig. 13.3 provides an updated overview of *KIT* mutations described in patients with mastocytosis). Therefore, the following part will emphasize similarities and differences in the nature of the *KIT* defects found in different categories of mastocytosis.

Pediatric Cutaneous Mastocytosis (CM)

The frequency and the role of *KIT* mutations in childhood-onset mastocytosis and whether CM in children is a clonal or a reactive disease have long been a matter of debate. Indeed, an early study published by Buttner et al. has reported that on 11 pediatric patients, none had codon 816 mutation [29]. Later, Longley et al. found that six pediatric mastocytosis patients lacked mutations in codon 816 but that three had a dominant inactivating mutation, K839E [30]. More recently, Verzijl et al. found that on eight children with urticaria pigmentosa (UP), two had the D816V mutation [31]. However, in a more recent study conducted on a large cohort of 50 pediatric patients, the entire *KIT* sequence from cutaneous biopsies of lesional skin has been examined [20]. The authors found 18 children (36%) with the D816V point mutation and 3 additional patients with other 816 mutations: D816Y ($n = 2$) and D816I ($n = 1$) [20]. Of note, new *KIT* mutations were identified in nearly 40% of the children tested [20]. All these mutations, mainly located in exons 8 and 9 (Del417–418, D419Y, C443Y, S476I, internal tandem duplication (ITD) 502–503, K509I) and in exon 11 (D572A), were mutually exclusive of mutations in codon 816 and caused constitutive activation of KIT, but with different functional and signaling properties as compared to KIT D816V [32]. An additional study carried out on 60 other pediatric cases confirmed the results published (Fig. 13.2, Dubreuil et al., unpublished data). Thus, in total, 76% of the children tested have alterations in *KIT*, confirming that pediatric mastocytosis is a clonal disease similar to SM in adults but with a larger spectrum of *KIT* mutations. Later, Ma et al confirmed in part these data by studying nine cases of pediatric solitary mastocytoma [33]. Indeed, they identified a *KIT* mutation in six of nine children (three *KIT* D816V mutations

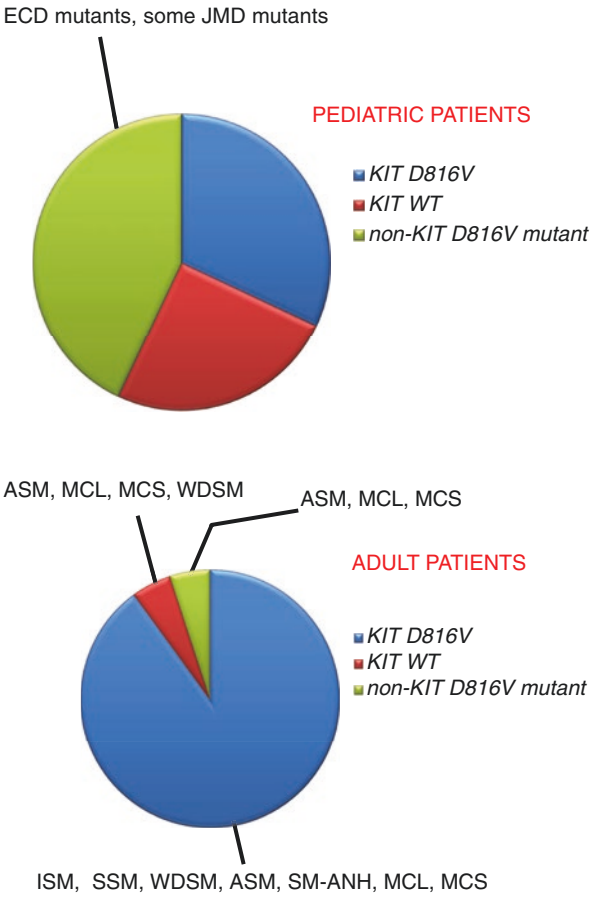


Fig. 13.2 Differential repartition of *KIT* mutations between pediatric and adult patients and, in adults, between SM variants. In pediatric patients (upper panel), analysis of the KIT structure in lesional skin biopsies has revealed that the *KIT* D816V mutant can be found in 32% of the cases, while 43% of the patients harbor non-*KIT* D816V mutants, principally located in the ECD of KIT. Finally, 25% of the pediatric patients are *KIT* WT. By contrast, in adults (lower panel), most if not all ISM, SSM, ASM, and SM-AHN patients harbor the *KIT* D816V mutation, as found in BM and/or PB. By contrast, MCL and MCS patients are less frequently positive for this mutation and may harbor other non-*KIT* D816V mutants, or no mutation in *KIT* (*KIT* WT). Besides, in WDSM, only a minority of patients present with the *KIT* D816V mutation or with other non-*KIT* D816V mutants, while the majority of the patients are *KIT* WT. ASM aggressive SM, BM bone marrow, ECD extracellular domain, MCL mast cell leukemia, MCS mast cell sarcoma, ISM indolent SM, PB peripheral blood, SM systemic mastocytosis, SM-AHN SM with an associated hematologic neoplasm, WDSM well-differentiated SM, WT wild-type, SSM smoldering SM

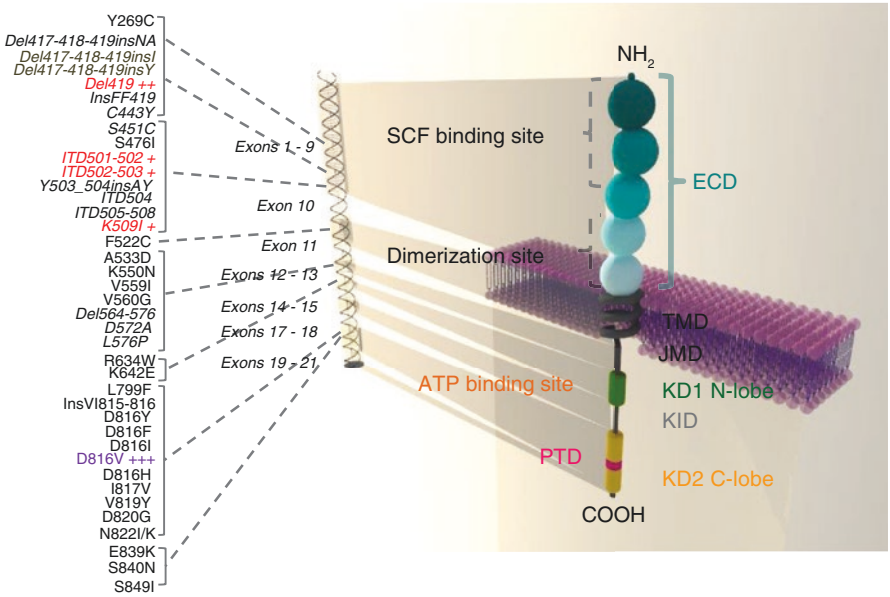


Fig. 13.3 Representation of the structure of KIT, illustrating the known function of its domains and the localization of the more frequently observed mutations in the *KIT* sequence in pediatric or adult patients with mastocytosis. The KIT receptor is presented under its transmembrane monomeric form, whereas its wild-type counterpart dimerizes upon ligation with SCF before being activated in normal cells. Mutations described primarily in pediatric cases with cutaneous mastocytosis (CM) are depicted in italics and those found preferentially in adults with systemic mastocytosis (SM) in straight letters. The most frequently detected *KIT* mutations are marked (CM, red color; SM, violet color). In addition, the frequency of mutations is defined by the following score: no symbol: mutations found in less than 1% of the pediatric or adult patients; +: mutations found in 1%–5% of pediatric patients; ++: mutations found in 5%–20% of pediatric patients; +++ (*KIT* D816V): mutation found in around 30% of pediatric patients and in >80% of all adult patients. Del deletion, ECD extracellular domain, ITD internal tandem duplication, JMD juxtamembrane domain, KD kinase domain, KID kinase insert domain, PTD phosphotransferase domain, SCF stem cell factor, TMD transmembrane domain

and three *KIT* ITD p.A502_Y503). More recently, Meni et al. have performed a literature review of all pediatric cases published between 1950 and April 2014 [34]. Over the 1747 cases reported, 215 patients were tested for *KIT* mutations and the *KIT* D816V mutation was found in 34% of these later patients [34], confirming the relatively low frequency of this mutation in pediatric mastocytosis. However, to date, there is no evidence suggesting a correlation between the nature of the *KIT* mutations in childhood and patient outcomes in adulthood. Indeed, Sotlar et al. failed to correlate the presence of the *KIT* D816V mutation with clinical outcomes in 20 patients with childhood-onset mastocytosis after a mean follow-up of 11.2 years [35]. In another study, Lanternier et al. did not find any link between the presence of the *KIT* D816V mutation and pediatric-onset ISM, whereas this combination was statistically significant in the group with adult-onset mastocytosis [36].

Finally, very recently, Meni et al. found no significant association between evolution and *KIT* mutation or between evolution and type of CM in a cohort of 53 pediatric cases with a mean disease duration of 12.1 years [37]. However, in the same study, a late onset of the disease (after 2 years) was found to be associated with worst evolution [37]. Therefore, the reasons why pediatric mastocytosis, which is characterized by recurrent mutations in *KIT*, is usually restricted to the skin and can spontaneously resolve at adolescence in a majority of the patients are still not clearly understood.

Indolent Systemic Mastocytosis (ISM)

ISM is the most common subtype of SM and is usually a chronic but stable disease [10]. Several studies have reported that the *KIT* D816V mutant is the most frequent *KIT* abnormality, detected in virtually 100% of the ISM cases, when using a sensitive technique on purified BM MCs [21, 38]. In a part of ISM cases, the mutation is found primarily in the neoplastic MC compartment [39]. However, in a number of ISM patients, the mutation may be detected in other mature BM and PB cells such as basophils, eosinophils, neutrophils, as well as B- and T-lymphocytes, depending on the patient [21, 40–44]. Furthermore, precursors of erythroid and myeloid cells as well as $CD34^+$ progenitors may carry the *KIT* D816V mutation, suggesting the involvement of a pluripotent stem cell in such cases [21, 40, 45, 46]. Of note, in one study, multilineage *KIT* D816V involvement was found to be the most important prognostic criterion for the progression of ISM to more advanced SM subtypes [39].

In some ISM patients with minimal MC burden, mutation levels may be very low, thus requiring highly sensitive technique(s) for mutation analysis. Interestingly, *KIT* D816V mutation analysis may be performed on genomic DNA (gDNA) or on the expressed messenger RNA (mRNA). In a first study performed on 25 patients using a sensitive allele-specific quantitative PCR (ASO-qPCR), the *KIT* D816V mutation was detected in both BM and peripheral blood (PB) cells in all cases, meaning that circulating *KIT* $D816V^+$ non-MCs in PB can be considered characteristic of ISM [47]. However, the technique used in this study quantified gDNA and the same authors have more recently observed discrepant results depending on the material tested. Indeed, when comparing gDNA-based and mRNA-based *KIT* D816V mutation analysis of PB and BM aspirate from 82 SM patients (76 ISM, 4 SSM, and 6 SM-AHN), they found that mRNA-based *KIT* D816V mutation analysis was positive in 29% of the patients in PB and in 98% of the patients in BM, whereas gDNA-based *KIT* D816V mutation analysis was positive in 94% and 100% of the patients in PB and BM, respectively [48]. These data point to the lower sensitivity of mRNA-based *KIT* D816V mutation analysis as compared to gDNA-based *KIT* D816V mutation analysis, particularly in PB samples, confirming similar results reported in other studies [45, 49]. Of note, gDNA-based *KIT* D816V mutation analysis, besides being a very sensitive technique, allows the measurement of *KIT* D816V expressed allele burden (EAB), whose level correlates with disease

severity and risk of progression, and is used to monitor treatment efficacy [50]. In addition, gDNA-based *KIT* D816V mutation analysis can be performed on unfractionated whole blood (without leukocyte isolation), with the same sensitivity and specificity, thus being less time-consuming and less expensive [51]. Very recently, a study that used digital PCR (dPCR) performed in PB and BM samples has been conducted on 156 SM patients, allowing to further confirm the value of the measurement of *KIT* D816V EAB to predict disease severity and prognosis [52]. Indeed, in this study, advanced SM patients showed a significantly higher *KIT* D816V EAB (median: 2.43%) than patients with ISM (median: 0.14%) [52]. Moreover, dPCR confirmed the prognostic significance of a high *KIT* D816V EAB regarding survival [52]. Therefore, the present consensus in the medical community is that *KIT* D816V mutation analysis has to be performed, in SM-suspected patients, preferably by the use of ASO-qPCR, which is highly sensitive and allows appreciation of disease severity and risk of progression as well as to monitor treatment [19]. Finally, it has to be underlined that if the *KIT* D816V mutant is found in nearly all ISM patients, a recent study has reported that some *KIT* D816V$^+$ patients may present with concurrent activating *KIT* mutations in their neoplastic MCs, such as Y269C, Y503_F504insAY, V560G, or K642E [53]. Interestingly, in such cases, the concurrent mutation may or may not be expressed by the same neoplastic MC sub-clone that harbors the D816V mutant, and the sub-clone presenting the concurrent mutation alone may be predominant over the *KIT* D816V$^+$ sub-clone [53]. This latter finding might have therapeutic implication since these concurrent mutations may respond to imatinib, while the *KIT* D816V mutant receptor does not. Of note, such multiple *KIT* defects have been also described very recently in a study conducted on the skin biopsies of nine pediatric patients (aged from 1 month to 9 years) with UP ($n = 6$), diffuse cutaneous mastocytosis (DCM; $n = 2$) or mastocytoma ($n = 1$) [54]. Interestingly, of the nine patients, six presented with multiple *KIT* defects in their skin MCs (one with *KIT* E414D, Del419, and L862 L; one with *KIT* 501_502insAF, M541 L, and L862 L; one with *KIT* M541 L, I798I, and L862 L; one with *KIT* D816V, E885D, and W557R; one with *KIT* D816Y, and Q515H; and the last one with KIT 502_503dupAY, 541 L, and L862 L) [54]. Nevertheless, in such patients, the number of activating KIT mutations did not predict disease extent [54]. However, it appears from the two later studies that concurrent *KIT* mutations, apart from D816V, may occur in neoplastic MCs, in the same sub-clone or in different sub-clones, underlining the complexity of the molecular pathology of mastocytosis in some patients, even at the single level of *KIT* mutations.

Well-differentiated SM (WDSM) is a subset of ISM characterized by the presence of compact multifocal infiltrates of round mature, CD2- and CD25-negative MCs in BM, and by constant skin involvement [55]. In a recent study performed on 33 WDSM patients, *KIT* mutations were detected in only 10 (30%) of 33 patients, including *KIT* D816V ($n = 5$), *KIT* I817V ($n = 1$), *KIT* N819Y ($n = 1$), and *KIT* K509I ($n = 3$) [56]. This low incidence of the *KIT* D816V mutant in WDSM might have therapeutic consequences since in patients with non-D816V mutations, or with *KIT* wild-type (*KIT* WT), imatinib treatment may be effective [57].

Smoldering Systemic Mastocytosis (SSM)

SSM is a distinct category of SM characterized by slow progression without signs of aggressive disease or an AHN and is defined by the presence of at least two B-findings (Fig. 13.1), indicative of a high neoplastic MC burden [14, 58]. Of note, patients with SSM may remain stable for years or may progress into a more advanced variant of SM [39]. However, if the prognosis of SSM regarding progression-free survival (PFS) and overall survival (OS) is better than that in ASM or MCL, it is poorer than that in typical ISM [39]. In SSM cases already published, the *KIT* D816V mutant was found not only in neoplastic MCs but also in other myeloid lineages [39, 58], correlating thus with the highest *KIT* D816V EAB as compared to that in ISM patients [59]. Finally, while in the past, SSM was considered as a rare variant of SM [58], a recent study tends to demonstrate that SSM is more frequent than previously believed [10].

Aggressive Systemic Mastocytosis (ASM)

ASM is a subtype of SM with a progressive evolution and a poor prognosis (median survival of 41 months), characterized by the presence of at least one C-finding (Fig. 13.1) [60, 61]. Of note, ASM may progress to MCL [62]. Most ASM patients harbor the *KIT* D816V mutation, but other *KIT* mutations (D820G or V559I) can be found more rarely [63, 64]. Finally, in ASM, neoplastic MCs typically show an immature phenotype with clonal involvement of all myeloid lineages by the *KIT* D816V mutation [65]. As expected, the *KIT* D816V EAB has been repeatedly found high in such patients, with a mean EAB in BM of 9.346% [50, 59]. In addition, disease progression in ASM, together with treatment response, can be monitored by serial measurement of *KIT* D816V EAB [66].

Systemic Mastocytosis with an Associated Hematologic Neoplasm (SM-AHN)

SM-AHN is a complex variant of advanced SM at the biological and clinical levels. The SM compartment can be ISM, SSM, ASM, or MCL (the latter being more rarely associated with AHN) [10, 62], while the AHN is of myeloid origin in most cases (Fig. 13.1) [10]. However, AHNs cover all major subtypes of hematologic malignancies including, in rare cases, lymphomas, myeloma, or chronic lymphocytic leukemia [10, 67, 68]. These various AHNs may present with their own recurrent genetic defects, such as t(8;21) in acute myeloid leukemias (AML) or *JAK2* V617F mutation in *BCR-ABL1*-negative myeloproliferative neoplasms (MPNs) [69]. While the

existence of a clonal relationship between the two disease components in SM-AHN has long remained unexplored, Sotlar et al. have investigated the presence of the *KIT* D816V mutant in the SM and AHN components in 48 patients with SM-AHN [70]. In this study, the *KIT* D816V mutant was found in the SM compartment of almost all the patients, apart from those with a SM-chronic eosinophilic leukemia (SM-CEL) [70], and in AHN cells of most patients with SM-chronic myelomonocytic leukemia (SM-CMML), suggesting that the *KIT* D816V mutation occurs in a common MC/monocytic precursor, unlike SM-AML (30%) or SM-MPN (20%) patients, where the *KIT* D816V mutant was far less frequently detectable in the non-MC neoplastic cells [70]. By contrast, none of the patients with lymphoid AHNs displayed the *KIT* D816V mutation in the AHN compartment [70]. Interestingly, in a more recent study, Jawhar et al. have analyzed the mutation status of granulocyte–macrophage colony-forming progenitor cells (CFU-GM) in patients with different categories of *KIT* D816V$^+$ SM (ISM, $n = 4$; SSM, $n = 2$; ASM, $n = 1$; SM-AHN, $n = 5$ and ASM-AHN, $n = 7$) [46]. Concerning (A)SM-AHN patients, all were found to carry at least one (median = 3) additional mutation in 11 genes tested, most frequently mutations in *TET2*, *SRSF2*, *ASXL1*, *CBL,* and *EZH2*. In these latter patients, *KIT* D816V$^+$ single-cell-derived CFU-GM colonies were identified in 8 of 12 cases, whereas additional mutations were identified in CFU-GM colonies in all patients, suggesting that mutations in *TET2*, *SRSF2,* and *ASXL1* preceded the appearance of the *KIT* D816V mutant during hematopoietic differentiation [46]. These data indicate that (A) SM-AHN is a multi-mutated neoplasm, where mutations in *TET2*, *SRSF2,* or *ASXL1* may precede *KIT* D816V. In this case, *KIT* D816V is thus a late event modifying the phenotype of a preexisting hematopoietic neoplasm toward SM [46].

Mast Cell Leukemia (MCL)

MCL is a rare and very aggressive subtype of SM that can appear *de novo* or can evolve from a previous mastocytosis [62]. Patients with MCL have a particularly poor prognosis with short OS [62]. In acute MCL, at least 20% of neoplastic MCs are found on BM smears and the patients present with C-findings [71]. A leukemic variant of MCL is diagnosed when there are ≥10% circulating MCs; when this criterion is not met, MCL is categorized as an aleukemic variant [71]. In MCL, the frequency of *KIT* mutations is still a matter of debate. Indeed, in a review compiling all the published cases from 1951 to 2012 ($n = 51$), *KIT* D816V mutation was detected only in 13 of 28 MCL patients analyzed (46%) [62]. In two patients without *KIT* D816V, *KIT* was wild-type (WT), whereas in six other cases, mutations were found in exon 9 ($n = 3$), exon 10 ($n = 1$), exon 11 ($n = 1$), or exon 13 ($n = 1$) [62]. In a more recent study, the incidence of *KIT* mutations was analyzed in eight MCL patients [72]. In this study, five patients were found mutated for *KIT* (three with D816V, one each with S451C and

D816Y), confirming the relatively low incidence of mutant at position 816 (4/8; 50.0%) [72]. However, such low incidence was not confirmed in another recent study by Jawhar et al. on a cohort of 28 MCL patients [73]. Indeed, in this later study, the presence of mutations in *KIT* (D816V, $n = 19$; D816H/Y, $n = 5$; F522C, $n = 1$) was reported in 25/28 (89%) patients, with the incidence of mutations at position 816 being found higher than that in previous studies (24/28; 85.7%) [73]. This discrepancy might be perhaps related to the lowest sensitivity of the techniques used to detect 816 mutants in the historical cases published in the compiling review [62], as compared to the highly sensitive ASO-qRT-PCR used by Jawhar et al. [73], or to the low number of cases ($n = 8$) analyzed in the second report [72], as compared to the higher number of cases analyzed in the later study ($n = 28$) [73].

Of note, a subvariant of MCL has been recently identified in a few patients presenting with >20% of neoplastic MCs on BM smears but with a more mature phenotype of the cells and without C-findings, at least within a short time. A recently proposed classification suggests that these cases are referred to as chronic MCL (cMCL) [71]. In some of these patients, MCs express *KIT D816V*, while in other patients, rare *KIT* mutations are detected [74]. In one single case of cMCL [75], a somatic *KIT* S476I mutation has been described which, intriguingly, is also found in some patients with pediatric (indolent) mastocytosis [32].

Mast Cell Sarcoma (MCS)

MCS is an extremely rare and aggressive neoplasm made by very atypical malignant MCs [7]. In the largest cohort reported to date ($n = 23$), *KIT* mutational status has been investigated in 14 patients, which showed the absence of mutations in 50% of the cases, *KIT* D816V mutation in 21% of the patients, and non 816 locations, such as *KIT* Del419, *KIT* V560G, *KIT* L799F, or *KIT* N822K in the remaining cases [7]. More recently, a single case of MCS of the sternum has been reported where a previously undescribed *KIT* Del579 mutation was found in the tumor [76].

Familial Forms of Mastocytosis

Only a few cases of familial mastocytosis have been reported so far [77]. The majority of the cases reported were pediatric CM without *KIT* mutations or with uncommon mutations (i.e., S451C, K509I, A533D, L576P, R634W, N822I, M835K, S849I or deletion of amino-acids 419 or 559–560) [78–83]. All these *KIT* defects have been found activating and some were found sensitive to imatinib, at least in vitro. In most cases, the *KIT* mutation found was of a germline nature, and the intra-familial

cases harboring the same mutant may be affected by mastocytosis, as well as by other *KIT*-dependent neoplasms such as gastrointestinal stromal tumor (GIST) [84]. However, one report has mentioned a family (mother and son) with adult-onset SM associated with a somatic *KIT* D816V mutation [85].

Additional Genetic Defects Found in Advanced Systemic Mastocytosis: Nature and Impact on Disease Aggressiveness and Prognosis

The aggressiveness of the different SM variants is extremely variable. Indeed, patients with ISM have a normal or nearly normal life expectancy, while patients with ASM or SM-AHN have a poor prognosis and may even progress to MCL [14]. However, in most SM patients (> 80% of all SM patients), independently of the variant, the same activating *KIT* mutation, namely the *KIT* D816V mutant, is found [19]. The reason for this discrepant outcome of patients bearing the same *KIT* defect has long been a matter of debate. One early hypothesis was that, depending on the level of hematopoietic development where the *KIT* mutation occurs, only one lineage (MCs) may be targeted, leading to an ISM with low *KIT* D816V EAB, whereas mutilineage hematopoietic involvement might give rise to more aggressive disease phenotype with high *KIT* D816V EAB. Such hypothesis has been partly confirmed by studies reporting that mutilineage *KIT* D816V involvement is one important prognostic criterion for progression of ISM to more advanced SM subtypes [39, 86] or demonstrating that high levels of *KIT* D816V EAB were related to disease aggressiveness and progression [50]. However, this hypothesis failed to fully explain the different behavior of patients where the *KIT* D816V mutation is found in multiple hematopoietic lineages or who have similar *KIT* D816V EAB. Thus, another hypothesis has been more recently proposed, which linked the presence of other (concurrent) genetic aberrations, besides *KIT* mutation, to the aggressiveness of the disease. In line with this hypothesis, several studies have recently demonstrated that the aggressiveness and prognosis of SM is influenced by the presence of additional somatic mutations in genes encoding for epigenetic regulators (*TET2, ASXL1, DNMT3A,* and *EZH2*), signaling molecules (*CBL, JAK2, KRAS,* and *NRAS*), transcription factors (*RUNX1*), or mutations in the spliceosome machinery (*SRSF2, U2AF1,* and *SF3B1*), as summarized in Table 13.1 [22, 23, 25–27, 87].

The presence and the number of additional mutations are adversely associated with advanced disease and poor survival in *KIT* D816V$^+$ SM, whereas these mutations are rare in ISM/SSM patients, which may explain their better prognosis [25, 28, 46, 73, 88]. Several studies have revealed that in advanced SM, the most frequently affected genes are *TET2, SRSF2, ASXL1, RUNX1, JAK2, N/KRAS, CBL,* and *EZH2* (Table 13.1) [23, 26, 27, 46, 88–90]. These studies have highlighted the fact that the molecular pathogenesis of advanced variants of SM is complex and that aggressiveness of the disease is linked to its multi-mutated status, as well as

to the nature of the additional genetic lesions found. In addition, all these mutations may be co-expressed with *KIT* D816V in the same cells or may be expressed in other myeloid cells but not in MCs, especially in (A)SM-AHN with *TET2*, *SRSF2,* and *ASXL1* mutants, where acquisition of *KIT* D816V is often a late event conferring a mastocytosis phenotype on a pre-existing clonal condition [46].

TET2 is among the most frequently mutated gene in *KIT* D816V$^+$ advanced SM patients [22, 23, 25, 46]. Patients carrying *TET2* mutations may express concomitantly other non-*KIT* mutations [46, 90]. However, the impact of *TET2* mutations on the prognosis of advanced SM patients remains controversial. Indeed, if two studies have reported that the presence of *TET2* mutants in *KIT* D816V$^+$ SM patients has no impact on the prognosis of the disease [22, 26], other studies have demonstrated that *TET2* mutants cooperate with the *KIT* D816V mutation by worsening the prognosis [23, 24].

ASXL1 mutations are found at a frequency ranging between 12% and 20% in SM patients, preferably in advanced variants of the disease, and in most cases in SM-AHN [23, 26, 28]. Defects in *ASXL1* were first identified in mastocytosis by Traina et al., in 2012 [23]. After having sequenced the *ASXL1* gene in 26 SM patients (15 ISM, 8 SM-AHN, two ASM, and one MC sarcoma), the authors found *ASXL1* mutations in 1 out of 15 ISM patients and 2 out of 8 SM-AHN patients [23]. Interestingly, the *ASXL1* defect was the only genetic alteration (apart from a *KIT* D816V mutation) found in one patient with ISM, whereas the two SM-AHN patients found positive for *ASXL1* mutation were also positive for *TET2* defects [23]. Moreover, in a study carried out by Schwaab et al., the authors found *ASXL1* defects in eight patients over 39 [25]. All these eight patients were found having a SM-AHN, with the SM compartment being either indolent, aggressive, or even leukemic, whereas the AHN was frequently a CMML [25]. Of these eight patients, four presented with an associated *TET2* mutation and seven presented with one or several additional defects [25]. Besides, Damaj et al. have found *ASXL1* defects in 14% of 62 patients with SM-AHN (AHN being mostly myeloid, and comprising MDS, CMML, or MPN) [26]. In this study, the presence of *ASXL1* mutation was reported to affect significantly and negatively the OS of the patients [25, 26]. More recently, *ASXL1* has been reported to be one of the three genes, together with *SRSF2* and *RUNX1*, whose defects have the worst impact on prognosis and OS of advanced SM patients (Table 13.1) [28].

Interestingly, mutations in genes encoding for splicing factors are also found at various frequencies in advanced SM (Table 13.1). Splicing factors found mutated in SM patients include Splicing Factor 3 Subunit b1 (*SF3B1*), the U2 Small Nuclear RNA Auxillary Factor 1 (*U2AF1*), and the Serine Arginine-Rich Splicing Factor 2 (*SRSF2*). However, mutations in *SF3B1* and *U2AF1* are rarely found in SM as compared to *SRSF2* mutations. Indeed, in a study performed by Schwaab et al., among 39 SM patients tested, none of them were positive for *SF3B1* and only two patients had *U2AF1* mutations [25]. One of the two patients had an ISM and presented only with the *U2AF1* mutation, whereas the other patient had a SM-MDS/MPN and presented several additional genetic defects [25]. More recently, Hanssens et al. have confirmed the low incidence of *SF3B1* or *U2AF1* defects in a cohort of 72 patients,

Table 13.1 Overview of additional molecular defects found associated with the *KIT* D816V mutation in the different variants of systemic mastocytosis (SM)

Gene affected	Occurrence before *KIT* D816V mutation in hematopoietic lineages	Frequency[a]	Impact on prognosis
TET2	Yes	Advanced SM[b]: +++	Controversial
SRSF2 (mainly *SRSF2*-P95 hotspot mutation)	Yes	Advanced SM: +++	S/A/R = > poor prognosis and short OS
ASXL1	Yes	Advanced SM: ++ ISM/SSM: ±	
RUNX1	u.k.	Advanced SM: +	
SF3B1	u.k.	Advanced SM: ±	Shortened OS, particularly in multimutated advanced SM patients
U2AF1	u.k.	Advanced SM: ±	
CBL	u.k.	Advanced SM: + ISM/SSM: ±	
N/KRAS	Yes	Advanced SM: ++	
DNMT3A	u.k.	Advanced SM: ± ISM: ±	
ETV6	u.k.	Advanced SM: ±	
EZH2	u.k.	Advanced SM: ±	
SETBP1	u.k.	ISM/SSM: ±	
JAK2	u.k.	Advanced SM: ±	
IDH2	u.k.	Advanced SM: ±	

Summarized from [22–28, 46, 73, 87, 90, 91]
Abbreviations: *ISM* indolent SM, *OS* overall survival, *SSM* smoldering SM, *u.k.* unknown
[a]±: <5% of the patients tested; +: 5–10%: of the patients tested; ++: 10–20% of the patients tested; +++: >20% of the patients tested
[b]Advanced SM: Aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), mast cell leukemia (MCL). Note that additional genetic defects are more frequently found in SM-AHN than in ASM or MCL

where mutations of *U2AF1* were found only in two patients, while only four patients were affected by *SF3B1* mutations [27].

Of note, Schwaab et al. also have analyzed the occurrence of *SRSF2* mutations in a cohort of 39 patients. Interestingly, they found 14 patients (35%) presenting a mutation in the hotspot region of *SRSF2* [25]. In parallel, Hanssens et al. found that after *KIT* mutations (81%), the *SRSF2*-P95 hotspot mutation was the most frequent

mutation found in their patients: 17/72 patients (23.6%), whereas *TET2* mutants were found in 21% of the patients [27]. It has to be underlined that the *SRSF2*-P95 hotspot mutation was found exclusively in SM-AHN patients (17 patients over 17 positive had an AHN). Nevertheless, the *SRSF2*-P95 mutant was found in MCs as well as in monocytes, supporting a role for *SRSF2*-P95 mutation in MC transformation. Besides, *TET2* and *SRSF2-P95* mutations were both found to be correlated with advanced disease phenotypes, and statistically highly associated, suggesting a mechanistic link between these two factors [27].

More recently, and to study in depth the prognostic impact of each mutation, Jawhar et al. have compared the genotype and clinical characteristics of 70 multi-mutated *KIT* D816V^{+} advanced SM patients [28]. In this cohort, the mutant genes most frequently identified were *TET2* (33/70 patients), *SRSF2* (30/70 patients), *ASXL1* (20/70 patients), *RUNX1* (16/70 patients), and *JAK2* (11/70 patients) [28]. Nevertheless, OS was adversely influenced only by the presence and number of mutated genes within the *SRSF2, ASXL1,* and *RUNX1* (S/A/R) panel but was not influenced by mutations in *TET2* or *JAK2* [28]. These observations have been further confirmed by Pardanani et al. on a larger cohort of SM patients [90]. Indeed, using next-generation sequencing, the authors sequenced 27 genes in 150 SM patients in order to identify mutations that could be integrated into a clinical-molecular prognostic model for survival [90]. Mutations in *TET2*, *ASXL1,* and *CBL* were found at higher frequency in advanced SM patients, while *ASXL1* and *RUNX1* mutations were associated with inferior survival [90]. In line with these findings, Jawhar et al. have recently evaluated the clinical and molecular characteristics of 28 MCL patients during treatment [73]. *De novo* MCL was diagnosed in 16 out of 28 patients and secondary MCL evolving from other advanced SM subtypes in 12 out of 28 patients, of which 7 patients progressed while being on cytoreductive treatment. Mutations in *KIT* were detected in 25 out of 28 patients (89%) and prognostically relevant additional mutations in the so-called S/A/R panel were found in 13 out of 25 patients (52%). In addition, S/A/R mutations impacted negatively the response to treatment and were associated with progression to secondary MCL ($n = 6$) or AML ($n = 3$) while the patients where on treatment [73]. Moreover, S/A/R mutations remained the only independent variable to predict poor prognostic and short OS [73].

To sum up, the clinical and morphological diversity of SM is associated not only with the mutational status of *KIT* but also with the presence and the number of mutations in other genes that play a pivotal role in the pathogenesis, aggressiveness, and poor prognosis of advanced SM. For this reason, the current consensus is that the molecular signature should be determined in all patients with SM because of its significant clinical and prognostic relevance.

Conclusions – Perspectives

In SM, the *KIT* D816V mutation is found in a vast majority of the patients. However, despite the fact that TKIs targeting the KIT D816V mutant harbor excellent activity toward its enzymatic activity *in vitro*, these compounds have

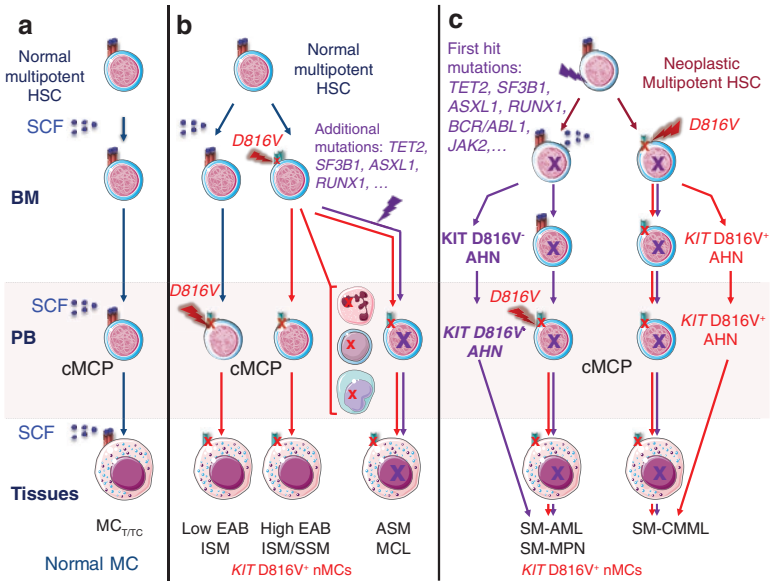


Fig. 13.4 Proposed model of normal and pathologic mast cell differentiation from hematopoietic progenitors in humans. (**a**) (left panel): normal mast cell (MC) differentiation from the normal multipotent hematopoietic stem cell (HSC). Blue arrows mean normal differentiation. Under the influence of stem cell factor (SCF), $KIT^+/CD34^+$ HSCs differentiate into committed mast cell progenitors (cMCP) in the bone marrow (BM). These agranular cMCP, which are $CD34^+/KIT^+/CD13^+/Fc\varepsilon RI^-$ cells, are released into the peripheral blood (PB), then migrate to the peripheral tissues, where they differentiate into granulated MCs expressing only tryptase (MC_T) or into MCs expressing tryptase, chymase, and carboxypeptidase A (MC_{TC}), depending on the influence of various cytokines released in the local microenvironment. Both subtypes of normal MCs express KIT and the high-affinity receptor for IgE (FcεRI). (**b**) (center panel) and **c**) (right panel): pathologic MC differentiation from multipotent HSCs resulting in indolent systemic mastocytosis (ISM), in smoldering SM (SSM) (**b** *left and middle*) or in advanced (**b** right**, c**) SM. (**b**) left: late acquisition of the *KIT* D816V mutant in a cMCP leads to an ISM with a low level of *KIT* mutant-expressed allele burden (EAB). (**b**) middle: early acquisition of the *KIT* D816V mutant in a multipotent HSC leads to an ISM or to a smoldering SM (SSM) with a high *KIT* mutant EAB. In this case, since the mutation occurs at the multipotent HSC level, other hematopoietic non-MC lineages may express the *KIT* mutant at the DNA level (red cross in the nucleus of circulating polymorphonuclear, lymphocytes, and monocytes). (**b**) right: early acquisition of the *KIT* D816V mutant during the differentiation of a multipotent HSC, together with acquisition of additional mutations in other genes than *KIT* leading to multi-mutated aggressive SM (ASM) or even mast cell leukemia (MCL). (**c**) Pathologic MC differentiation in SM with an associated hematologic neoplasm (SM-AHN). (**c**) left: in SM with an associated acute myeloid leukemia (SM-AML) and SM with an associated myeloproliferative neoplasm (SM-MPN), the *KIT* D816V mutant is rarely found in the AHN compartment, which presents its own (recurrent) genetic defect(s). In such case, it is believed that the *KIT* mutation occurs in a late stage, in a cMCP, and the AHN is *KIT* D816V-negative (*KIT* $D816V^+$ SM-*KIT* $D816V^-$ AHN). (**c**) right: in SM-chronic myelomonocytic leukemia (SM-CMML), the *KIT* D816V mutant is constantly found in the non-MC neoplastic myeloid compartment as well as in neoplastic MCs (nMCs). In such case, it is believed that the *KIT* mutant occurs together with other additional defects in an early myeloid progenitor, giving rise to a *KIT* $D816V^+$ SM-*KIT* $D816V^+$ CMML. Red arrows symbolize the presence of the *KIT* D816V mutant. Violet arrows symbolize the presence of additional genetic defects other than mutations in *KIT*. Blue dots represent molecules of stem cell factor. The KIT wild-type receptor is presented in brown, dimerized by stem cell factor, whereas the mutant KIT D816V receptor is presented in green with a red cross, under a monomeric form

only modest and transient activity *in vivo* in the more advanced SM variants. One possible explanation for this discrepancy could rely on a complex molecular pathogenesis of SM, particularly in advanced SM, where the number and nature of genetic defects other than *KIT* may influence the severity and progression of the disease. This hypothesis might explain the relatively poor response to TKIs targeting KIT defects in advanced SM patients. Of note, data summarized here confirm the value of this hypothesis by shedding light on the genetic complexity existing in advanced SM. Indeed, in advanced SM (but not in ISM), there is increasing evidence that most patients present with one or several additional genetic defects, which might explain the aggressiveness of the disease. Interestingly, while some of these additional defects seem to be rare events, encountered in only a small percentage of patients with advanced SM, others appear to be more common. This is particularly the case for *TET2* mutants, which are found in up to 30% of such patients [22, 23, 25, 46]. However, the impact of *TET2* mutants on the aggressiveness of the disease remains a matter of debate, with contradictory results published [22–24, 26].

Besides, mutations in *SRSF2* and in *ASXL1* and *RUNX1* are also present in a significant percentage of patients with advanced SM and are related to a more aggressive disease [28]. In addition, a significant part of the patients may present up to more than five additional mutations, as reported in studies in which *KIT* D816V^{+} patients were found simultaneously positive for *TET2*, *SRSF2*, *ASXL1*, *CBL* and *RUNX1* defects [25, 90].

Thus, present knowledge suggests that stable ISM with good prognosis might be mainly a disease related to the sole presence of the *KIT* D816V mutant, occurring relatively lately in the process of MC differentiation from HSCs, whereas in evolving ISM or SSM, a multilineage involvement of hematopoietic cells by the *KIT* mutant is found, which might explain the disease progression into more aggressive phenotype. By contrast, in advanced variants of the disease, additional genetic defects (pre-existing or acquired during disease evolution) might be responsible for progression and poor prognosis. However, in SM-AHN, these additional genetic defects might reflect the coexistence of two different diseases or, as recently demonstrated, could be related to the late acquisition of the *KIT* D816V mutation conferring a mastocytosis phenotype to a pre-existing clonal condition where *TET2*, *SRSF2* and *ASXL1* mutants are already found [46].

In order to illustrate the complex pathophysiology of SM, and particularly of the advanced variants of the disease, we present in Fig. 13.4 a comparative scheme of normal MC differentiation in human together with that of abnormal differentiation in different types of SM.

In conclusion, the additional genetic defects frequently found in advanced SM variants, and particularly the *SRSF2*, *ASXL1,* and *RUNX1* (S/A/R) mutations, negatively impact the disease prognosis and, overall, are probably responsible for the poor response of advanced SM patients to KIT-targeted TKIs. Thus, targets other than KIT as well as drug combinations might be considered to develop more effective therapies in multi-mutated advanced SM in the future.

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Chapter 14
Management of Hematologic Disease in Mastocytosis

Hyun Don Yun and Celalettin Ustun

Definition of Systemic Mastocytosis with an Associated Hematologic Neoplasm (SM-AHN)

SM-AHN [previously known as "systemic mastocytosis with associated clonal hematological non-mast-cell lineage disease" (SM-AHNMD)] [1] is a distinct category in SM defined by the WHO [2]. In SM-AHN, each component (i.e., SM and AHN) must fulfill WHO criteria for diagnosis.

Epidemiology of SM-AHN

SM-AHN is the most common subtype of advSM (40–64% of advanced SM) [3–6] and the second most common subtype of SM following ISM [7] (AdvSM). The precise incidence of SM-AHN is not known. In a registry study in Denmark, 24 cases of SM-AHN between 1997 and 2010 were reported, which was 4% of total SM cases. The cumulative incidence of SM-AHN was estimated as 0.55 per 100,000, while its prevalence was 0.31 per 100,000 [8]. In 19,500 bone marrow biopsies done for any reason, 20 patients were found to have SM-AHN [7]. However, it is important to note that the results of these two studies represent a referral center experience, not a general population study. In a Surveillance, Epidemiology and End Results (SEER) registry study, 421 adult patients with SM were identified between 2000 and 2014 [9]. This study also showed that patients with SM have a higher chance of developing AHN than healthy age-matched population: 21 patients developed an AHN in a median follow-up of 18 months after diagnosis of SM, while 1.28

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patients were expected to have a hematologic malignancy. In addition, SM can be missed or obscured by more extensive AHN involvement of bone marrow (e.g., myeloblasts infiltration of bone marrow), in particular before induction therapy for AHN at diagnosis. This condition is defined as occult mastocytosis and may underestimate the accurate incidence of SM-AHN [10–13].

SM can be concurrent with, precede, or follow the diagnosis of AHN. Jawhar et al. reported that SM was the first diagnosis in 30 (68%) patients, whereas it was concomitant diagnosis in 14/44 (32%) of patients with SM-AML. Most of SM-AHN occur in male (70%) and older (median age of 65 years) [3].

Epidemiology of AHN in SM-AHN

Myeloid malignancies constitute the majority of AHN SM-AHN [4, 5, 7, 14, 15]. Chronic myelomonocytic leukemia (CMML), myeloproliferative neoplasm (MPN), and myelodysplastic syndrome (MDS) represent the most common types of AHN [4–7, 15, 16]. These AHNs were not therapy-related or secondary malignancies in most patients [15]. In another study, most of these AML patients (80%) progressed from a preleukemic myeloid malignancy (e.g., MDS, MPN) [17]. Patients with SM-MPN may have a better prognosis due to less leukemic transformation than those with SM-MDS or SM-CMML [5].

Origin of SM-AHN

It is known that mast cells stem from a CD34+ bone marrow progenitor. However, knowledge on whether SM and AHN originate from the same clone or SM and AHN are two coexisting neoplasms from different clones is conflicting. A study using microdissection in five patients with SM associated with primary myelofibrosis reported that *JAK2* mutation was present in both mast cells and CD15+ myeloid cells in four patients. *KIT* D816V mutation was detected in mast cells in all five patients but in CD15+ myeloid cells in only two of five patients [18]. Another study using microdissection found *KIT* D816V mutation in CD34+ leukemic blasts in only two of four SM-AML patients, while the mutation was present in mast cells of all four patients [19]. In another study using FISH in five AML patients with t(8;21) and increased mast cells (not fulfilling SM diagnosis), *RUNX1-RUNX1T1* was shown in mast cells in all five patients [20]. With microdissection and molecular analysis, Pullarkat and colleagues reported that t(8;21) (q22;q22) were present in both myeloblasts and mast cells in a patient with SM-AML [21]. *BCR/ABL1* fusion signals were identified in both myeloid cells and mast cells in a case of chronic myeloid leukemia (CML) [22]. In another case report, both CD34+ myeloblasts and CD34- mast cells had *KIT* D816V mutation [23]. Neoplastic mast cells were thought to be derived from CD34 + CD117+ immature leukemic cells, and both myeloblasts

and mast cells expressed both *AML1/ETO* and *KIT* mutation. [24] In another study, *TET2* and *KIT* D816V mutations were detected in CD15+ cells and mast cells in all three patients with SM-AHN, but in CD3+ cells, in only one of these three patients [25]. Next-generation sequencing of DNA derived from CD34+ myeloid blasts of 6 *KIT* D816V-positive patients revealed the presence of *KIT* D816V-positive blasts in only one of six (17%) patients with SM-AML [17]. Using combined morphological and FISH analysis, Wang et al. demonstrated a clonal cytogenetic relationship between mast cells and myeloid cells in two patients with SM-CMML and one patient with SM-MDS but not in a patient with SM with chronic lymphocytic leukemia (CLL). In addition, the patient with CLL had 11q/ATM deletion in CLL cells but not in mast cells [15]. The authors concluded that SM-AHN is heterogeneous, including clonally related and unrelated forms of AHN. Likewise, *KIT* mutation was only found in mast cells but not in neoplastic lymphocytes in a patient with SM-B-cell NHL [26].

Overall, it is clear that these results are not consistent perhaps due to multiple reasons including the method used, the efficiency of cell sorting, and whether mast cells are neoplastic (i.e., SM) or reactive. Nevertheless, these may support that the notion clonal relationship is stronger if AHN is a myeloid malignancy than a lymphoid malignancy and that *KIT* mutations occur later in oncogenesis and thus responsible for evolving the mastocytosis phenotype in most cases.

A recent Mayo Clinic study evaluated if hematologic malignancy without SM is different than when it is associated with SM [27]. In this regard, 50 patients with SM-CMML were compared with 501 patients with CMML. *KIT* and *CBL* mutations were more frequent in SM-CMML. Despite more patients having more advanced CMML (e.g., CMML1 and 2) in the CMML group, the median OS seemed shorter in the SM-CMML group (18 months vs. 24 months).

The Incidence and Clinical Importance of Additional Cytogenetic Abnormalities and Mutations

Chromosomal Abnormalities

Chromosomal aberrations are more common in SM-AHN than in other SM subtypes. In SM-AML, 71% of patients had chromosomal aberrations [17]. In an MD Anderson Cancer Center (MDACC) study, 32% of 28 patients with SM-AHN and 0% of 40 SM (ISM, ASM, and MCL) had chromosomal abnormalities, respectively [15]. These chromosomal abnormalities included trisomy 8 (n = 2, both CMML), del(20q)(q11q13) (n = 2, one CMML and one MDS) , del (7)(q21q36) and del [13](q12q22) (n = 1, MDS), del (13)(q12q14), and –Y (n = 1, CMML), -Y(n = 2, both CMML), and del (11)(q14) with del (13)(q12q14) (n = 1, CLL) [15]. Likewise, another study including patients with advSM and ISM found that an aberrant karyotype was only identified in patients with SM-AHN (16/73, 22%) [28]. In addition, the poor risk karyotype (e.g., −7 or complex karyotype) significantly decreased

survival in advSM patients (4 vs. 39 months, $p < 0\,0.0001$), which was independent from mutational status.

Additional Mutations

Additional mutations (*ASXL1, TET2, SRSF2, RUNX1, CBL, KRAS, and NRAS)* are frequently detected in SM-AHN [17, 29]. This can be an expected finding given that these are commonly present in myeloid malignancies. [30–32] None of these mutations is specific for SM-AHN. Supporting this, the German group showed that 11 out of 12 patients with SM-AHN had additional mutations, whereas none of these mutations was identified in SM patients without AHN [25]. *KIT* D816V mutation was acquired after *TET2* and *ASXL1* mutations, suggesting that *KIT* D816V is a phenotype modifier toward SM. The French group has shown that molecular abnormalities are more common if AHN is myeloid than lymphoid malignancies [33].

TET2 Mutation

TET2 mutation (a loss-of-function mutation involving high self-renewal of hematopoietic stem cells) is the most frequent mutation (20–40%) in advSM [34]. Characteristics of SM patients with *TET2* mutation include older age, monocytosis, and thrombocytopenia [35]. The impact of *TET2* on the outcomes of patients with SM-AHN is conflicting [33, 35, 36].

SRSF2, ASXL1, RUNX1 (S/A/R), and Others

SRSF2, a spliceosome machinery removing introns of pre-mRNA, [37] and *ASXL1,* involved in chromatin remodeling by encoding a protein of the polycomb group and trithorax complex family, [38] are commonly detected in patients with SM-AHN [36, 39, 40]. Both mutations are strongly associated with poor overall survival (OS) in patients with advSM [33, 39]. *RUNX1* (as known as CBFA2), a transcription factor regulating hematopoietic stem cell differentiation, is also frequently detected in advSM [29].

Jawhar et al. described that amongst 70 patients with SM-AHN with *KIT* D816V, all patients had at least one additional mutation [41]. The most frequent mutation was *TET2* (47%), followed by *SRSF2* (43%), *ASXL1* (29%), and *RUNX1* (23%). Harboring one or more mutation(s) in *SRSF2, ASXL1, and RUNX1* (S/A/R^{pos}) was found to be a powerful prognostic indicator with a strong inverse correlation between the number of these mutations and overall survival. Moreover, the impact of S/A/R^{pos} hindered response to midostaurin [41]. A recent study compared molecular mutations between patients with CMML and those with SM-CMML [27]. The S/A/R mutations were found in similar frequency in each group. Moreover, the pres-

ence of *ASXL1* mutation (HR 1.3 [95% CI: 1.2–2.1]), *DNMT3A (*HR 3.0 [95% CI: 1.5–5.3]), and *Tp53* mutation (HR 3 [95% CI: 1.2–6.6]) and the absence of *TET2* mutation was a risk factor of OS for each CMML patient and CMML with SM patients. *RUNX1* mutation was 14% and 8% in CMML patients and CMML with SM patients, respectively.

RUNX1 mutations in normal karyotype AML portend a poor prognosis [42], whereas *RUNX1-RUNX* [t(8;21) (q22;q22)] in core-binding factor (CBF) AML is associated with a relatively good prognosis [43, 44]. Therefore, the incidence of *KIT* mutation and the presence of SM (or increased mast cells) in AML, especially in CBF-AML, have been investigated in a few studies. Pullakart et al. reported that five patients had *KIT* mutation in 31 AML patients; however, none of these patients had increased mast cells [20]. There were another group of five patients who had increased mast cells that were positive for *RUNX1-RUNX1T1*. The Valent group found that 7% of 101 AML patients (no CBF-AML) had *KIT* D816V mutation [19]. All of these seven patients also had SM. Jawhar et al. reported that *RUNX1* mutation was 36%, and only one patient had CBF AML in 44 SM-AML patients [17]. The median OS was 11 months. Cytogenetic risk score but not *RUNX1* mutation was associated with prognosis.

Current Approach for Treatment of SM-AHN

SM-AHN is regarded as a constellation of two distinct diseases, that is, SM and AHN. Hence, it has been traditionally proposed to treat the component that threatens life more acutely first. For example, in ISM-AML, AML requires more urgent clinical attention and treatment. Recently, there have been significant advances in treatment options in SM and AHN along with understanding pathobiology of each disease. In this section, we will discuss currently available or potential treatment options for SM-AHN in light of these progresses.

Tyrosine Kinase Inhibitors (TKIs)

KIT is a type III tyrosine kinase receptor and is activated by its ligand, stem cell factor (SCF) [45]. *KIT* D816V is present in exon 17 and is the most common mutation identified (>80% of adult patients with SM [46, 47] including SM-AHN) [33, 48]. *KIT* D816V results in constitutive tyrosine kinase activation without SCF, [49] inducing downstream signal transduction, activating transcription factors such as STAT3 and STAT5 with subsequent uncontrolled cell proliferation [50, 51]. *KIT* mutations are also present in AML [44], and less frequently in MDS and CMML [52]. Moreover, *KIT* mutation-positive AML patients can also have SM as we mentioned in the sections above [19]. TKIs have been investigated in clinical trials for patients with SM, including SM-AHN (see Chap. 15).

Midostaurin

Midostaurin (PKC 412; *N*-benzoyl-staurosporine) is an oral PKC inhibitor targeting multi-kinases including FLT3, PDGFR, and KIT [53–55] and active in targeting mast cells with *KIT* D816V in in vitro studies [56, 57]. A phase II clinical trial demonstrated an impressive clinical effect of midostaurin (100 mg twice daily PO) on all subtypes of AdvSM (ASM, MCL and SM-AHN) in 89 patients. SM-AHN patients constituted the majority (64%) of these patients. Eighty-seven percent had *KIT* D816V. Overall response rate (ORR) in SM-AHN was 58% with major response (MR) of 40%, which was comparable to ORR of 60% (MR of 45%) in the total cohort. However, median duration of response (DOR) in SM-AHN was shorter than that in other advSM subtypes (12.7 months vs. it was not reached in either ASM or MCL). Likewise, progression-free survival (PFS) at 3 years was inferior in SM-AHN (22 months) compared with ASM (46 months) and MCL (29 months). Regarding responses in AHN, midostaurin significantly reduced eosinophil and monocyte counts within a month. Nonresponders in the entire cohort had a median OS of approximately 1 year. Another prospective phase II study with a long-term (10 years) follow-up included 17 patients (65%) with SM-AHN (CMML 47% of the total cohort, MDS/MPN 12%, and MDS 8%). ORR was 76% with a major response (MR) of 65%, and two patients achieved CR in the SM component [58]. The median OS was 4 years. The duration of response probability was 50.2% at 37.8 months for the entire group (SM-AHN was not specifically given). Two of seven patients experienced disease progression in AHN: one patient progressed from CMML-1 to CMML-2 and another patient progressed from CMML1 to AML 11 years after midostaurin therapy. Response in anemia and thrombocytopenia occurred in eight of 15 patients (53%) and in five of ten patients (50%), respectively. Midostaurin elicited rapid and complete normalization of eosinophilia in all seven patients and significant decrease in monocytosis in 14 patients (the best median reduction was 70% from baseline). Nonresponders in the entire cohort had a median OS of <1 year. One can conclude from these two phase II studies that midostaurin possesses marked efficacy in patients with SM-AHN, and perhaps it is effective in both components, in particular if there is eosinophilia or monocytosis. It is important to note that, however, these studies did not include high-risk AHN and that patients who did not respond to midostaurin had a short OS. Interestingly, a retrospective study at a single institution demonstrated that all advSM patients ($n = 4$) who were treated with midostaurin in combination with cladribine had no disease progression [59]. Furthermore, palbociclib, a CDK 4/6 inhibitor, was found to have synergistic effects with midostaurin in growth inhibition against HMC-1 cell line in vitro [60]. Combinatorial approach of midostaurin therapy with either conventional chemotherapy or targeted therapy may hold promise in the future.

A study investigated factors affecting responses of midostaurin in patients with advSM, including SM-AHN [41]. Additional mutations (S/A/R) impaired the responses of midostaurin. In addition, elevated serum tryptase level, alkaline phosphatase, and expressed allele burden (EAB) of *KIT* D816V mutation at 6 months after midostaurin treatment were associated with a lower OS [41]. The most impor-

tant and independent predictor for OS was the EAB of *KIT* D816V mutation. In a recent correlative study, a comprehensive cytokine profiling revealed that baseline levels of interleukin-7, epidermal growth factor, platelet-derived growth factor (PDGF) BB before midostaurin treatment were positively correlated with increased survival in advSM patients, whereas intercellular adhesion molecule-1 and IL12p40 were inversely correlated with survival [61]. This study highlights the importance of immune underpinnings in outcomes of midostaurin treatment, which deserve further investigation in the future.

Regarding the effect of midostaurin hematologic malignancies, midostaurin was mostly used in FLT3+ AML. Midostaurin alone had limited efficacy (with no CR) in relapsed/refractory patients with FLT3+ AML [62]. When it was added to standard chemotherapy, as shown in a randomized, placebo-controlled phase III clinical trial, midostaurin improved OS in patients with FLT3+ AML [63]. Midostaurin is the first FDA-approved TKI for the treatment of FLT3+ AML.

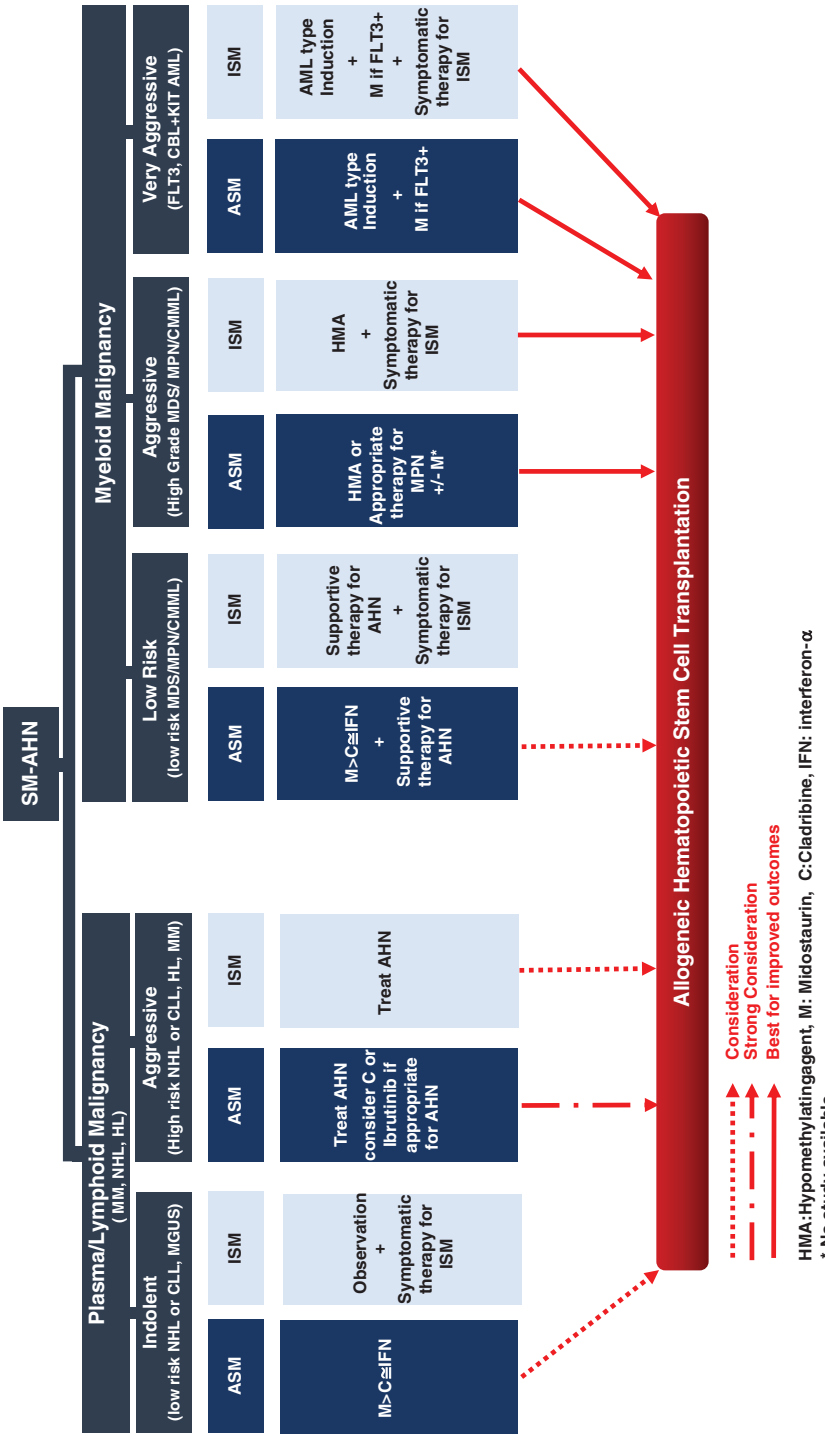
As a subset of myeloid neoplasms (e.g., CMML, CEL, and MPN) are characterized by PDGFRA/B rearrangement and associated with eosinophilia and monocytosis, [64] the WHO 2016 update on classification of myeloid neoplasms and acute leukemia recognized this as a new category of myeloid/lymphoid neoplasms with PDGFR/A rearrangement [2]. PDGFR rearrangement is rarely identified in SM; however, this entity can be associated with eosinophilia [49, 65]. Furthermore, midostaurin exerted an excellent activity against PDGFR (IC 0.08 μM) in an in vitro study [66]. Although *FIP1L1-PDGFRA* T674I mutant is resistant to imatinib therapy, it is responsive to midostaurin treatment in mice [67]. AdvSM patients with monocytosis and eosinophilia responded well to midostaurin therapy in a large phase II clinical trial, although *PDGFR* mutation status was not reported in the study [4].

Most common side effects of midostaurin were gastrointestinal system-related (nausea/vomiting, and diarrhea) and hematologic (cytopenias) in clinical trials, especially in patients with SM.

In conclusion, midostaurin should be considered as the drug of choice in patients with SM-AHN where ASM is aggressive and AHN is not high risk or AHN is FLT3+ AML (with standard AML chemotherapy) (Fig. 14.1). Patients who are not responsive to midostaurin should be treated with other available drugs without delay given that the survival of these patients is short. However, midostaurin is unlikely to cure SM or AHN, and its efficacy may be impaired with frequent dose adjustments due to toxicities; therefore, if cure is a reasonable goal for a young person with advSM, alloHCT should be considered. In SM patients with eosinophilia, PDGFR rearrangement should be tested. If positive, imatinib or midostaurin should be used depending on *KIT* mutation positivity.

Imatinib

Imatinib is the first TKI developed to specifically target Abl tyrosine kinase in chronic CML [68]. Imatinib is also a very effective drug for hypereosinophilia with *FIP1L1-PDGFRA* fusion [69–72].


SM-AHN
Plasma/Lymphoid Malignancy
(MM, NHL, HL)
Indolent
(low risk NHL or CLL, MGUS)
Aggressive
(High risk NHL or CLL, HL, MM)
Myeloid Malignancy
Low Risk
(low risk MDS/MPN/CMML)
Aggressive
(High Grade MDS/ MPN/CMML)
Very Aggressive
(FLT3, CBL-KIT AML)
ASM
ISM
ASM
ISM
ASM
ISM
ASM
ISM
M>C≅IFN
Observation
+
Symptomatic
therapy for
ISM
Treat AHN
consider C or
Ibrutinib if
appropriate
for AHN
Treat AHN
M>C≅IFN
+
Supportive
therapy for
AHN
Supportive
therapy for
AHN
+
Symptomatic
therapy for
ISM
HMA or
Appropriate
therapy for
MPN
+/- M*
HMA
+
Symptomatic
therapy for
ISM
AML type
Induction
+
M if FLT3+
AML type
Induction
+
M if FLT3+
+
Symptomatic
therapy for
ISM
Allogeneic Hematopoietic Stem Cell Transplantation
Consideration
Strong Consideration
Best for improved outcomes
HMA:Hypomethylatingagent, M: Midostaurin, C:Cladribine, IFN: interferon-α
* No study available

Imatinib was investigated in various *KIT* mutations found in SM. Whereas imatinib inhibits survival of normal human mast cells and neoplastic mast cells harboring *KIT* V560G, it is not active against mast cells with *KIT* D816V mutation even at higher doses [73–76]. Consistent with results of preclinical studies, several clinical studies demonstrated poor clinical efficacy of imatinib against SM with MCs harboring *KIT* V816D [5, 77, 78].

Specifically for SM-AHN, imatinib was not effective for *KIT* V816D SM-AHN regardless of the presence of eosinophilia or *FIB1L1-PDGFR* mutation [5, 77]. Imatinib was active against SM with *FIB1L1-PDGFRA* fusion only in the absence of *KIT* D816V mutation [65]. Imatinib can be a particularly effective treatment for a subset of SM-AHN patients with eosinophilia associated with *FIB1L1-PDGFRA* mutation without *KIT* D816V, including chronic eosinophilic leukemia (CEL), CML, MDS/MPN, AML, and lymphoblastic T-cell lymphoma [79–82].

In conclusion, imatinib should be used in patients with SM-AHN with eosinophilia or monocytosis associated with *PDFGR* rearrangements when *KIT* D816V mutation is absent.

Dasatinib

Although dasatinib showed promising efficacy against neoplastic mast cells with *KIT* D816V mutation in vitro study, [83, 84] most of the in-human studies showed disappointing results in patients with SM with *KIT* D816V mutation [85, 86]. Rare successful cases were reported including a patient with SM-AML with *KIT* D816, who had achieved CR after 7 + 3, continued to have CR, and achieved molecular remission after dasatinib was added to consolidation [23]. Patient relapsed 1 year after dasatinib maintenance was discontinued (personal communication). In a phase II MDACC study of dasatinib in SM, only two patients with SM-AHN (one with PMF, and one with CEL) without *KIT* D816V mutation achieved complete response (CR) [86]. In conclusion, the role of dasatinib in the treatment of SM-AHN is limited.

Cladribine

Cladribine [2-chlorodeoxyadenosine (2-CdA)], a purine analogue, has been well known for its lymphotoxicity due to the intracellular accumulation of lymphotoxic metabolites, 2-chlorodeoxyadenosine triphosphate [87]. Therefore, 2-CDA has

Fig. 14.1 Management of systemic mastocytosis with an associated hematological malignancy (SM-AHN). The majority of AHNs are myeloid neoplasms in SM-AHN. Treating the more aggressive component first amongst SM and AHN is appropriate. Drugs targeting the both components need to be considered when appropriate. (E.g., cladribine for SM-hairy cell leukmiea, midostaurin for SM-FLT3 AML) Ultimately, allogeneic hematopoietic stem cell transplantation should be considered if any of SM or ANH is aggressive

been used for indolent NHL [88–94], CLL/SLL [95, 96], and hairy cell leukemia (HCL) [97, 98]. 2-CDA was also found to exhibit a potent cytolytic effect against myeloid cells, including monocytes [99], and has been used to treat Langerhans cell histiocytosis, a monocyte-lineage neoplasm, [100] and CMML [101]. Moreover, cladribine in combination with other leukemia drugs resulted in CR in some patients with AML [102–105].

Tefferi et al. first reported the remarkable clinical efficacy of cladribine in SM treatment in 2001 [106]. Kluin-Nelemans et al. treated ten SM patients with cladribine [107]. Three patients with SM-AHN (one MDS and two atypical CML-aCML) responded well to therapy (e.g., decreased tryptase levels and mast cell burdens in bone marrow exams). A Mayo Clinic study showed ORR of 55% in 13 SM-AHN patients receiving 2-CDA [5]. Presence of circulating immature myeloid cells was independently associated with inferior OS in the cladribine-treated group in the study. Another large long-term follow-up (>10 years) retrospective study of 68 SM patients (17 patients with SM-AHN: MDS (n = 6)/MPN (n = 4), CMML (n = 4), NHL (n = 3), and HCL (n = 1) demonstrated an excellent ORR of 72% to cladribine [6]. However, ORR was higher in indolent mastocytosis than in SM-AHN (>80% in ISM/SSM vs. 45% in ASM-AHN) and responses were deeper (MR >80% in ISM/SSM vs. 27% in ASM-AHN). The median relapse-free survival (RFS) and OS in SM-AHN were 4.7 years and > 6 years, respectively. Seven of 17 patients with SM-AHN died (five deaths due to progression in SM and two deaths from AHN–one MDS and one MPN progressed to AML). Of note, no death occurred in patients with lymphoid AHN including NHL and HCL. Most common severe side effects (grade 3/4 toxicities) of 2-CDA were lymphopenia (82%), neutropenia (47%), and opportunistic infections (13%) [6, 108].

In conclusion, 2-CDA is an effective drug for the treatment of SM-AHN. It should be considered for ASM-AHN patients after midostaurin failure and serve as a drug of choice if 2-CDA is a good option for high-risk AHN (especially for those with lymphoid neoplasms). 2-CDA can also be considered to provide prompt and temporary control of both SM and AHN before alloHCT.

Interferon-a (IFNα)

IFNα has been used for the treatment of MPN as well as of SM; therefore, it is logical to use IFNα in SM-AHN patients. In a case series of five AdvSM, two patients had SM-CMML and IFN$\alpha 2b$ (15–21 million units/week with steroids) showed major, durable responses (e.g., resolution/improvement of ascites, thrombocytopenia, anemia, monocytosis, weight gain, and decreased level of alkaline phosphatase and tryptase) [109]. In a larger series of 22 patients with SM-AHN (3.5–30 million units/week +/− steroids), overall response rate (ORR) to IFN$\alpha 2b$ was 45% [5]. Responses were major (included improvement in C findings) and persisted for a median of 12 months. Interestingly, systemic mediator-related symptoms predicted response to IFNα treatment, [5] indicating IFNα-mediated proinflammatory

responses might have contributed to eradicating neoplastic clones. Steroid use had no significant impact in clinical outcomes. In studies in patients with SM, the major side effects of IFNα include fever, flu-like symptoms, depression, and cytopenias [5, 109, 110].

Later, pegylated IFNα (pegIFNα) emerged in clinical practice with better tolerance and convenience. PegIFNα is an effective treatment for polycythemia vera, [111–116] essential thrombocytosis, [112, 113, 115, 117] and primary myelofibrosis [118, 119]. The molecular response with decreased allele burden of mutant *JAK2* [115, 116, 120] and *CALR* [117] was reported in patients with MPN after treatment with pegIFNα [121]. Some of these results can be related to the effects of IFNα on NK cells (e.g., expansion of circulating $CD56^{bright}$ NK cells and increased IFNγ+ CD56dim NK cells after IL-12 and IL-15 stimulation) [122]. *TET2* mutation may impair the effect of IFNα in MPN.

In conclusion, (peg) IFNα can be considered when SM is not aggressive and AHN is most likely to respond (e.g., MPN), SM is aggressive and not responsive to midostaurin or 2-CDA or in pregnant patients (given its relative pharmacologic safety profile compared with TKIs or purine analogs when used in other hematologic malignancies).

Allogeneic Hematopoietic Stem Cell Transplantation (alloHCT)

AlloHCT is the only potentially curative therapeutic option. A large multicenter retrospective analysis (57 patients) evaluated the outcomes of alloHCT for advSM including SM-AHN [123]. In this study, most patients who underwent alloHCT had SM-AHN (84%). AML comprised the most common AHN (53%). The most frequent cytogenetic abnormality was t(8:21)(q22:q22) identified in five patients (13.2% of SM-AHN, 25% of SM-AML), and all of these patients survived after alloHCT. Amongst SM-AHN, ORR in the SM component (SM ORR) after alloHCT was 50% with 21% CR. AHN other than AML (e.g., MDS, MPN, MDS/MPN, MM, and ALL), achieved SM ORR of 67% with 22% CR. MDS (including MDS/MPN) was the most common non-AML AHN (67%). SM ORR of MDS was the best at 75% with CR 25%. SM-AHN patients had superior OS and PFS compared with patients with ASM and MCL (OS at 3 years: 74% for SM-AHN, 43% for ASM, 17% for MCL; PFS at 1 year: 70% for SM-AHN, 43% for ASM). Although there was no statistical significance, patients treated with myeloablative conditioning had better clinical outcomes than those treated with reduced intensity regimen. Of note, some patients with ASM and MCL also had long-term durable responses after alloHCT. Whether SM patients undergoing alloHCT have different toxicity profile or are more prone to develop certain specific complications to SM after alloHCT remains to be addressed. However, in the retrospective analysis, no allergic type of reactions (e.g., anaphylaxis) or excessive graft failure (due to increased myelofibrosis) was reported. Veno-occlusive disease (VOD) of liver after alloHCT was reported in a patient with ASM who had portal- and periportal-fibrosis, mast

cell infiltration in the liver who had completely normal liver function tests before alloHCT [124].

CBF-AML with t(8:21) AML is often regarded as a favorable prognostic factor [125]. Therefore, alloHCT is not standard therapy for these patients at CR1. However, *KIT* mutation seems to increase relapse in patients with t(8:21) CBF-AML [126]. Therefore, SM-CBF AML patients with *KIT* mutation may be considered for alloHCT at CR1. In the large alloHCT study, 1-year OS and PFS for non-MCL advSM patients with *KIT* mutation (79.2% of SM-AHN patients had a KIT mutation) who underwent alloHCT was 82% and 74%, respectively.

In conclusion, alloHCT is the choice of therapy for patients with life-threatening AHN (e.g., AML, high-risk MDS, CMML, and PMF) regardless of the aggressiveness of SM. In addition, alloHCT can also be considered for SM-AHN in patients with low-risk AHN when SM is aggressive and has already failed to or showing evidence of progression on midostaurin and/or 2-CDA treatment [127]. In younger patients, if cure is the goal of therapy, the pros and cons of alloHCT should be discussed even in patients responding to midostaurin.

Hypomethylating Agents (+/− Midostaurin)

Hypomethylating agents (HMAs) including azacitidine and decitabine have been the standard therapy for patients with high-risk MDS and CMML. Interestingly, HMAs are proapototic for neoplastic mast cells regardless of the presence of *KIT* D816V mutation by inducing "re-expression" of FAS in vitro [128]. Moreover, combination of HMA and midostaurin resulted in an additive effect against neoplastic mast cells in vitro. However, clinical outcomes from patients with SM-AHN who received an HMA are limited. Jawhar et al. reported the clinical outcome of 44 SM-AML patients [17]. Those who received chemotherapy/HMA had a very poor clinical outcome with a median OS of 4 months (range 0–12 months) compared with patients who underwent alloHCT (a median OS of 74 months; range 0–149 months). A case report described an 80-year-old female with high-risk CMML-2 with complex cytogenetics who eventually developed MCL on azacitidine treatment [129]. A SM-CMML patient died 4 months after diagnosis on treatment with azacitidine [130]. A ISM-CMML-2 patient with simultaneous mutations of *KIT* D816V and *JAK2* V617F was treated with azacitidine, whose mediator-related symptoms were well controlled with cetirizine (but clinical outcomes otherwise were not well described) [131]. Ten patients with SM-CMML received azacitidine as a standard therapy for CMML. All patients either died or had progressive disease [132]. Based on the limited published data, the HMA therapy alone does not seem to provide a substantial clinical benefit for patients with SM-AHN.

HMAs are used with some success in AML patients who cannot tolerate conventional induction chemotherapy [133]. An in vitro study demonstrated that a sequential treatment of decitabine followed by midostaurin induced a synergistic apoptotic effect against FLT3+ AML cells [134]. A phase I/II clinical trial using a combination of azacitidine and midostaurin demonstrated that this combination is safe with some

efficacy for patients with high-risk AML and MDS, especially in patients with *FLT3* mutation [135].

In conclusion, HMA should be the drug of choice for patients with ISM-AHN when HMA is the preferred drug for AHN (high-risk MDS, CMML, and AML who cannot tolerate standard chemotherapy). Addition of midostaurin to HMA can be considered if *FLT3* is mutated; however, this can be done in a clinical trial setting. Otherwise, extreme caution should be exercised because this would be an off-label use of midostaurin. There has been no strong clinical evidence to support the efficacy of HMAs in SM.

Future Direction

Several targeted therapeutic options against advSM have been in preclinical and clinical trials.

New Generation of Tyrosine Kinase Inhibitors

Avapritinib (BLU-285)

BLU-285 is a selective inhibitor for KIT exon 17 mutation. A preclinical study showed a potent antiproliferative activity of BLU-285 in HMC-1.2, an SM cell line with *KIT* D816V [136]. When compared to midostaurin, avapritinib has been found to have much more potent activities against KIT^{D816V} mutants: IC50 of avapritinib was 0.27 nM, whereas IC50 of midostaurin was 2.9 nM [137]. Furthermore, BLU-285 inhibited the growth of Kasumi-1 cells, an AML cell line with t(8:21) and *KIT* exon 17 mutation. In a phase I clinical trial, BLU-285 was well tolerated and exerted a robust clinical activity for advSM patients, even for those who are refractory to midostaurin treatment [138] with ORR for advSM ($n = 32$) 72% and ORR specific for SM-AHN ($n = 8$) 63% [139]. The most common adverse event (AE) was periorbital edema (59%), fatigue (41%), peripheral edema (34%), and nausea (28%). Hematological toxicity included anemia (28%) and thrombocytopenia (28%). Notably, complete response in BM MC, nnormalization of tryptase level, and more than 50% reduction of KIT^{D816V} mutant allele fraction (MAF) was observed in 58% of patients (15/26), 60% (15/25), 73% (19/26), respectively. In another phase I study of avapritinib where one SM-CMML patient was recruited, treatment with avapritinib resulted in marked symptom improvement resulting in decreased corticosteroid use [140]. Recently, a phase II study reported avapritinib resulting in marked clinical improvement [141]. In this study, a total of 67 SM patients were enrolled with 60 patients with advSM (90%) and 30 with SM-AHN (45%). ORR (CR and CR with incomplete CBC recovery) was 83%. With 14-month follow-up, DOR was not reached and 12-month duration of response was 76%. The overall AE profile was similar to the one of the phase I study described earlier. The most

common AE was periorbital edema (67%), and the most common hematological AE was anemia (52%). Only 4% of patients discontinued avapritinib due to severe AE, whereas 66% of patients needed dose reduction due to grade 3–4 AE. Overall symptom reduction from the baseline total symptom score (TSS) was 40% based on advSM symptom assessment form (advSM-SAF), with 60% symptom reduction in GI or skin domain. Furthermore, 41% of patients were able to discontinue their steroid use for symptom control during the study period and 80% decreased the steroid doses. Notably, the symptom improvement correlated with the duration of avapritinib treatment and reduction of *KIT*^{D816V} MAF. Avapritinib is one of the most promising future agents for advSM treatment.

Crenolanib

Crenolanib is a selective *FLT3*, *PDGFRA/B* inhibitor. Recently, a preclinical study demonstrated a potent inhibition of cell proliferation driven by *KIT* D816 mutation in both SM and CBF AML models [142]. Crenolanib following 2-CDA treatment also was found to have an additive proapoptotic effect against neoplastic mast cells. Hence, crenolanib may be another effective treatment option for SM-AHN for FLT3+ or *KIT*-mutated AML with or without cladribine.

DCC-2618

An in vitro study demonstrated that DCC-2618, a pan KIT and PDGFRA inhibitor, has impressive antiproliferative, proapoptotic effects on various mast cell lines including HMC-1, MCPV-1, ROSA, and primary neoplastic mast cells obtained from advSM patients [143]. Furthermore, synergistic inhibitory effects of DCC-2618 with midostaurin and cladribine were observed. More importantly, DCC-2618 was found to inhibit proliferation of various AML cell lines, especially MOLM-13, MV4–11 (FLT3- mutated cell lines), primary leukemia cells of CMML, AML patients, and neoplastic eosinophils from EOL-1 cell line and patients with SM, hypereosinophilic syndrome indicating a great therapeutic potential for patients with SM-AHN.

Monoclonal Antibodies

Brentuximab Vedotin

Brentuximab vedotin, a monoclonal antibody against CD30 conjugated with the cytotoxic drug (monomethyl auristatin E), is widely used for the treatment of Hodgkin lymphoma, as CD30 is a common surface antigen of Reed-Sternberg cells [144]. Brentuximab vedotin was described as a great therapeutic option in a preclinical study [145] and a small case series [146], but failed to demonstrate a desirable clinical efficacy for advSM in a phase II clinical trial [147].

Gemtuzumab Ozogamicin (GO)

GO is an immunoconjugate drug targeting CD33+ myeloid neoplasms. Either GO alone with no curative intent or GO in combination with daunorubicin and cytarabine was recently approved for AML treatment [148]. An in vitro study demonstrated the antiproliferative effect of GO against HMC1 cell line [149]. Furthermore, a case report demonstrated the clinical efficacy of GO in a refractory MCL patient [150]. Hence, GO may be considered for SM-AML with CD33 expression. It has significant side effects including VOD and myelosuppression.

Anti-CD123 Monoclonal Antibody

CD123 is α subunit of IL-3 and expressed in various hematological malignancies including Hodgkin lymphoma, AML, ALL, CML, hairy cell leukemia, and plasmacytoid dendritic cell neoplasm [151]. CD123 was also identified in neoplastic mast cells but not in normal mast cells [152]. Neoplastic mast cells expressed CD123 in 64% of 58 patients with SM: the expression of CD123 was 100% in ASM patients, 61% in ISM, 57% in SM-AHN, and 0% in MCL. Interestingly, the presence of CD123+ mast cells was associated with poor OS in SM-AHN; the median OS of patients with CD123+ SM-CMML was 11 months, whereas that with CD123- SM-CMML was 44 months. CSL362, anti-CD123 monoclonal antibody, was tested in a phase I study for patients with high-risk AML in CR ineligible for alloHCT, where 50% of patients maintained CR with a median duration of 34 weeks [153]. Anti-CD123 antibody can be tested as a therapeutic option in the future for SM-AHN (i.e., SM-AML SM-CMML) in clinical trials.

NK Cell-Based Immunotherapeutics (161,533 TriKE)

Our group successfully constructed CD16xIL15xCD33 Trispecific Killer engager (161,533 TriKE) by splicing anti-CD16 single-chain variable fragment (scFv), anti-CD33 scFv, IL15 inserted as a linker. 161,533 potently induced NK cell activation and killing against CD33+ myeloid neoplasms [154].

Neoplastic mast cells were found to be resistant, while myeloblasts were responsive to haploidentical NK cells in two patients with SM-AML [155]. In vitro experiments demonstrated that both HMC 1–1 and ROSA$^{KIT\ D816V}$ were resistant to NK cell killing even with rhIL-15 treatment. Since neoplastic mast cells highly express CD33, *Yun* et al. demonstrated the ability of 161,533 TriKE to activate NK cells against CD33+ ROSA$^{KIT\ D816V}$ and primary bone marrow samples of SM patients by antibody-dependent cell-mediated cytotoxicity (ADCC). [156] The first in-human trial of 161,533 TriKE on CD33+ myeloid malignancies including SM-AHN is planned to open in 2018.

Conclusion

Treatment of SM-AHN is challenging because of its heterogeneity. SM-AHN is not a simple combination of two diseases but, in fact, two groups of diseases in which AHN can be a myeloid or lymphoid malignancy with an aggressive or indolent clinical course. Likewise, SM component can be aggressive or indolent. These two components can have multiple shared or non-shared molecular aberrations, cell surface markers. In addition, many obstacles (e.g., very few FDA-approved treatments available for SM, rarity of SM-AHN, focusing on AHN alone in SM-AHN) have led to paucity of systematic evidence for established treatment. This led to clinicians often relying mostly on retrospective, small studies or case series/reports when treating SM-AHN patients. In the current era, treatment recommendations for SM-AHN pose marked difficulties. However, in this chapter, we summarized the available data as follows (as in Fig. 14.1). As of now, there has been no drug that can effectively treat both components, especially if each component involves an aggressive subtype. Treatment should focus on the disease component (AHN or SM) that most likely would affect the life-expectancy of a patient.

Future prospective studies combining effective agents (e.g., a TKI such as midostaurin combined with a hypomethylating agent, a *JAK-2* inhibitor, or interferon) or novel targeted agents will most likely improve treatment and understanding of the biology of SM-AHN.

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Chapter 15
Tyrosine Kinase Inhibitors in Systemic Mastocytosis

Mohamad Jawhar, Jason Gotlib, and Andreas Reiter

Imatinib

The primary issue related to the use of imatinib in SM is the fact that the *KIT* D816V mutation, which is present in >90% of patients with advanced SM (advSM: aggressive SM, ASM; SM with an associated hematologic neoplasm, SM-AHN; mast cell leukemia, MCL), is imatinib-resistant and should not be used in such individuals. Wild-type *KIT* and some *KIT* mutations (usually in the juxtamembrane or transmembrane regions of KIT) may be imatinib-sensitive [1] (<1–2% of all advSM cases; e.g., V560G, F522C, deletion of codon 419 in exon 8 or p.A502_Y503dup in exon 9). In patients with *FIP1L1-PDGFRA*-positive myeloid neoplasms with eosinophilia, the marrow may exhibit increased numbers of loosely scattered mast cells and a correspondingly elevated serum tryptase level. These patients are recognized as a major clinicopathologic entity separate from SM, and the *FIP1L1-PDGFRA* fusion tyrosine kinase is very sensitive to imatinib (see below) [2].

The first clinical series on the activity of imatinib at the regular dose of 400 mg/day included 14 patients (*KIT* D816V positive, $n = 11$; *FIPL1-PDGFRA* positive, $n = 1$). A decrease in the serum tryptase level > 20% and the number of mast cells in the bone marrow was observed in ten of 14 and eight of 13 patients, respectively, while hepatosplenomegaly improved in three of six patients. Skin symptoms and general symptoms decreased in five of nine patients and eight of 13 patients, respectively [3].

In all other studies, imatinib did not result in appreciable clinical activity in *KIT* D816V positive patients. In a phase II trial, imatinib was evaluated in 20 patients [4]. Median time on therapy was 9 months (range, 0.5–≥44). A complete remission (CR)

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was observed in a single patient with *KIT* D816V negative SM with associated chronic eosinophilic leukemia (SM-CEL) lasting ≥44 months. Six patients showed symptomatic improvement, including two *KIT* D816V positive patients, and 13 patients were without benefit. Further retrospective analyses reported responses in five of 24 (CR, $n = 1$; four partial remission (PR) cases, $n = 4$) [5] and in five of ten patients [6], with all responders being *KIT* D816V negative. The same group reported [7] an overall response rate (ORR) of 19% (five of 27; two major remissions (MR) and two PR) including indolent SM (ISM) and advSM, with three patients being *KIT* D816V positive. Median duration of response was 19.6 months.

There are several case reports of successful treatment of SM in association with mutations besides *KIT* D816V such as V560G or F522C, which are very rarely identified in single patients with *KIT* D816V negative SM. Notably, several small case series reported the activity of imatinib in patients predominantly with a clinicopathologic presentation of CEL, not otherwise specified with the *KIT* M541L variant [8]; however, this is considered a polymorphism by some experts [9].

The Spanish Network on Mastocytosis (REMA) reported on the efficacy and safety of imatinib (300 mg/day or 400 mg/day) in ten adult SM patients lacking mutations in *KIT* exon 17 (where the D816V mutation is located). Nine patients fulfilled criteria for a well-differentiated SM (WDSM) with the subtypes cutaneous mastocytosis (CM, $n = 3$), indolent SM (ISM, $n = 3$), and MCL ($n = 3$). CR was defined as resolution of bone marrow mast cell infiltration, organomegaly, skin lesions, mast cell mediator release-associated symptoms, and normalization of the serum tryptase level. Criteria for PR included ≥50% reduction in bone marrow mast cell infiltration and improvement of organomegaly and/or skin lesions. The ORR was 50%, including early and sustained CR in four patients, three of whom had extracellular mutations of *KIT*, and PR in one case. This later patient and all nonresponders ($n = 5$) showed wild-type *KIT* [1].

The vast majority of patients with eosinophilia-associated myeloid neoplasms and the *FIP1L1-PDGFRA* fusion gene, but also related *PDGFRA*/*B* fusion genes, present with an increased number of loosely scattered, CD25+ mast cells and an elevated serum trytpase level, usually ranging between 15 and 100 µg/l (normal value <11.4 µg/l). This entity is seen by some authors as SM, although the morphological picture of loosely scattered mast cells does not fulfill the major diagnostic criterion of SM with clusters of spindle-shaped mast cells. This entity is exquisitely sensitive to imatinib. No primary resistance has yet been reported, and >90% of patients achieve complete hematologic and complete molecular remissions on low doses, usually 100 mg/day or 3 × 100 mg/week [10, 11].

In conclusion, the *KIT* mutational status is predictive for selecting SM patients as potential candidates for imatinib. Despite some conflicting data, *KIT* D816V positive SM is regarded as imatinib-resistant. In so-called responders, response may be caused by nonspecific myelosuppression or inhibition of unknown targets; there is little evidence of durable remissions including response of objective measures such as reversion of SM-related organ damage nor reduction in measures of mast cell burden such as bone marrow involvement or changes in the serum tryptase level. SM with specific mutations in the intra- or extracellular domains of *KIT* other than

D816V and SM with wild-type *KIT* may be sensitive to imatinib, particularly if SM presents as WDSM. Consequently, imatinib is approved by the Food and Drug Administration (FDA) for the treatment of adult patients with aggressive systemic mastocytosis without the *KIT* D816V mutation or with an unknown *KIT* mutational status. Patients with eosinophilia, increased numbers of loosely scattered mast cells, and/or an elevated serum tryptase level may be positive for the imatinib-sensitive *FIP1L1-PDGFRA* fusion gene (by RT-PCR or FISH), related imatinib-sensitive (*X-PDGFRA*, *X-PDGFRB*, *ETV6-ABL1*) or imatinib-resistant (*X-FGFR1*, *X-JAK2*, X-*FLT3*) TK-fusion genes (diagnosis by cytogenetic analysis and specific FISH/RT-PCR). It should, however, be pointed out that the TK-fusion gene-driven myeloid neoplasms are not considered as SM according to the WHO classification.

Midostaurin

Midostaurin (PKC412) is an orally active multikinase/KIT inhibitor, including non-mutant and mutant *KIT* D816V, *FLT3*, *PDGFRA*, *PDGFRB*, and *VEGFR2*. Early preclinical studies showed inhibition of proliferation of Ba/F3 cells and human mast cell lines ROSA engineered to express either wild-type *KIT* or *KIT* D816V and demonstrated significant potency (IC_{50} 30–40 nM) compared to imatinib (IC_{50} > 1 μM). In addition, midostaurin almost blocks immunoglobulin E (IgE) receptor-mediated activation and mediator release in human mast cells and basophils [12–14].

The encouraging *in vitro* data, the achievement of a partial response in a patient with MCL treated on a compassionate use program [15], and preliminary results from a multicenter investigator-initiated trial [16] led to a global multicenter, open-label, phase II (single-arm) trial for patients with advSM [17]. A total of 116 patients with advSM (ASM, SM-AHN, MCL) were treated with midostaurin administered continuously at a dose of 100 mg BID. Eighty-nine patients were eligible (based on the presence of one or more signs of SM-related organ damage [C-finding]) for assessment of safety and efficacy. The ORR was 60%, of which 45% were MR by modified Valent criteria for SM (disappearance of at least one C-finding), but no CRs were reported. The response rate was the highest ever reported in this group of poor-risk patients [17]. In a separate post-hoc analysis by the FDA, the ORR was 17% (CR, 2%; PR, 15%) according to the IWG-MRT-ECNM consensus criteria, and 28% when the category of clinical improvement (CI) was considered in the overall IWG-MRT-ECNM response rate per the European Medicines Agency (EMA) post-hoc analysis of the trial data. Symptoms and quality of life were significantly improved on midostaurin. The drug was generally well tolerated with a manageable toxicity profile consisting mostly of gastrointestinal side effects including nausea and vomiting, primarily grades 1–2, but co-medication with ondansetron or other anti-emetics is frequently needed. The median overall survival (OS) was 29 months. The primary cause of death was progression to secondary MCL or secondary acute myeloid leukemia (AML). Based on these results, midostaurin was

approved in 2017 by FDA and EMA as front-line therapy for advSM patients, regardless of *KIT* D816V mutation status.

Midostaurin showed significant disease-modifying activity by a substantial decrease in the bone marrow mast cell burden, serum tryptase level, and *KIT* D816V allele burden [16–18]. Lack of reduction of the *KIT* D816V allele burden ≥25% at month 6 was identified as the strongest adverse prognostic marker on-treatment [18]. In a pooled retrospective analysis of the two midostaurin trial cohorts, midostaurin-treated advSM patients demonstrated a relatively favorable OS of 43 months compared to 24 months for conventionally treated historical controls [19].

Although midostaurin is a breakthrough as the first drug approved for advSM, some patients show primary resistance and/or early progression into leukemic phase (secondary MCL/SM-AML). Additional molecular mutations in myeloid genes (e.g., *TET2*, *SRSF2*, *ASXL1*, *RUNX1*, *JAK2,* and *K/NRAS*) are frequent in advSM patients [20–23]. Since *KIT* D816V is a late event [21] in the disease evolution, such additional mutations are detectable in both *KIT*-mutated and *KIT*-unmutated sub-clones. Recent data revealed the negative impact on response and survival of carrying at least one mutation in the *SRSF2*, *ASXL1,* and/or *RUXN1* genes (S/A/R^{pos}) in midostaurin-treated patients, suggesting resistance and/or outgrowth of a multi-mutated and clinically aggressive *KIT* D816V positive sub-clone [18, 24]. It could also be demonstrated that midostaurin had no effect on the multi-mutated *KIT* D816V negative sub-clone compartment, which may lead to secondary *KIT* D816V negative AML [15, 18, 24, 25].

KIT D816 mutated AML with or without CBF fusion genes is associated with a very poor prognosis [25]. If an underlying SM can be suspected by a high tryptase level or a high *KIT* D816V allele burden and is consequently proven by bone marrow histology, the diagnosis of SM-AML may provide an opportunity to consider midostaurin on an off-label basis in AML treatment protocols similar to *FLT3*-positive AML.

Avapritinib

Avapritinib (BLU-285; Blueprint Medicines) is a highly potent and selective oral type I TK inhibitor, developed specifically to target the active conformation of KIT, including *KIT* D816V (IC_{50} 0.27 nM). Based on its significant activity in several preclinical models including HMC1.2 cell lines and mice xenograft models, a multicenter phase I trial of avapritinib in advSM patients was initiated (NCT02561988). Avapritinib demonstrated an ORR of 77% per modified IWG-MRT-ECNM consensus criteria in 39 evaluable patients [26]. The duration of treatment was up to 31 months as of the data cut-off date, with a median follow-up time of 14 months in evaluable patients. Responses were observed regardless of advSM subtypes, prior therapy (including midostaurin), or additional mutations. Avapritinib showed highly significant disease-modifying activity with reduction of bone marrow mast cell infiltration, serum tryptase level, and *KIT* D816V allele burden. In addition, statistically significant improvements in patient-reported disease symptoms were observed.

Avapritinib was generally well tolerated. In the safety population (n=67), the most common (>25%) treatment-emergent adverse events (AE; all grades; grade ≥3) included periorbital edema (67%; 4%), anemia (52%; 26%), fatigue (37%; 7%), nausea (36%; 4%), diarrhea (34%; 1%), peripheral edema (34%; 0%), thrombocytopenia (31%; 17%), vomiting (28%; 2%), and cognitive effects (28%; 1%). Hematological AEs were the most common reason for dose reduction. The majority of AEs were grades 1/2 and there were no grade 5 treatment-related AEs [26]. The efficacy and safety of avapritinib in advSM patients are currently being evaluated in an open-label, single-arm phase II study (NCT03580655). The recommended phase II dose is 200 mg once daily administered as continuous cycles. A trial evaluating lower doses of avapritinib has commenced in patients with indolent and smoldering SM (NCT03731260).

Ripretinib

Ripretinib (DCC-2618; Deciphera Pharmaceuticals) is a broad-spectrum KIT and PDGFRA kinase switch control inhibitor. Ripretinib inhibits the proliferation and survival of various human mast cell lines (HMC-1, ROSA, and MCPV-1) as well as primary neoplastic mast cells obtained from patients with advSM (IC_{50} < 1 μM) [27]. It is currently being evaluated in patients with gastrointestinal stromal tumors and advSM (NCT02571036).

Masitinib

Masitinib (AB1010) is a potent and selective oral inhibitor of stem cell factor-induced proliferation and KIT tyrosine phosphorylation in Ba/F3 (IC50 of 150 ± 80 nM) cells expressing human or mouse wild-type *KIT*. It blocked tumor growth in mice with subcutaneous grafts of Ba/F3 cells expressing a juxtamembrane KIT mutant [28]. In a phase-II-study [29], masitinib (initial dose levels of 3 or 6 mg/kg/day over 12 weeks) was administered to 25 non-advSM patients (CM or SM and related handicap, e.g., disabilities associated with flushes, depression, pruritus, and quality of life). Response was based on change of clinical symptoms associated with patient handicap at week 12 relative to baseline, regardless of disease subtype. Significant improvement was observed in all primary endpoints at week 12 including reduction of flushes, Hamilton rating, and pruritus by 64%, 43%, and 36%, respectively. An overall clinical response was observed in 14/25 patients (56%), with sustainable improvement observed throughout an extension phase (>60 weeks). Common adverse events were edema (44%), nausea (44%), muscle spasms (28%), and rash (28%), the majority of which were of mild or moderate severity with a significant decline in frequency observed after 12 weeks of treatment. One patient experienced a serious adverse event of reversible agranulocytosis.

A randomized, double-blind, placebo-controlled, phase 3 study assessed the safety and efficacy of masitinib (6 mg/kg per day over 24 weeks with possible extension) in 135 severely symptomatic ISM and smoldering SM (SSM) patients who were unresponsive to optimal symptomatic treatments [30]. The primary endpoint was cumulative response (≥75% improvement from baseline within weeks 8–24) in at least one severe baseline symptom from the following: pruritus score of 9 or more, eight or more flushes per week, Hamilton Rating Scale for Depression of 19 or more, or Fatigue Impact Scale of 75 or more. By 24 weeks, masitinib was associated with a cumulative response in the primary endpoint of 18.7% compared with 7.4% for placebo. Frequent severe adverse events included diarrhea, rash, and asthenia. The most frequent serious adverse events were diarrhea and urticaria while no life-threatening toxicities occurred.

Masitinib is currently neither approved by FDA nor by EMA for treatment of any SM subtype. Additional clinical trials are currently ongoing to obtain a better understanding of its clinical activity.

Nilotinib and Dasatinib

In a phase II, open-label, single-arm study, nilotinib 400 mg twice daily was evaluated in 61 patients with ISM and advSM [31]. Response was evaluated using improvements in laboratory findings (for all patients) and response criteria for patients with advSM. C-findings were collected retrospectively to assess response using criteria proposed after trial initiation. The median nilotinib exposure was 232 days (range 3–1274 days) with a median follow-up of 34.7 months. In patients with advSM ($n = 37$), the ORR was 21.6%. In the eight responders (all *KIT* D816V positive), mast cell infiltration and tryptase levels decreased by 70% and 29.8%, respectively. At the time of reporting, ten of 11 patients with advSM (ASM, $n = 9$, or MCL, $n = 2$) had died due to progressive disease.

In a phase II, open-label study, the efficacy of dasatinib (140 mg/d) was investigated in 33 patients with SM (*KIT* D816V positive, $n = 28$) [32]. The ORR was 33%. Two *KIT*-D816V negative patients (SM-myelofibrosis, SM-CEL) achieved a CR lasting for 5 and 16 months, respectively. Both patients had low tryptase levels, abnormal WBC counts, and anemia. Additional nine SM patients had a symptomatic response only, lasting 3 to ≥18 months. Due to the low ORR, nilotinib and dasatinib are no longer being pursued in advSM.

Practical Guide

The use of KIT inhibitors has a central role in the treatment of advSM. Midostaurin is currently the only FDA- and EMA-approved TKI for treatment of patients with advSM (ASM, SM-AHN and MCL), independent of the *KIT* mutation status.

Responses vary widely between patients, ranging between primary resistance/early progression within weeks and durable responses for many years. Moreover, responses may also be very heterogeneous within the same patient, for example, better response of SM vs. AHN, better response of gastrointestinal vs. hematological C-findings, and vice versa, respectively. Some patients without improvement of C-findings may significantly benefit from improvement of B-findings, for example, bone marrow mast cell infiltration or organomegaly, and/or clinical symptoms, for example, urticaria, flushing, diarrhea, or fatigue. In high-molecular risk patients (median OS of <2 years), or patients with rapidly proliferative disease, combination strategies such as including KIT-inhibition plus chemotherapy (e.g., cladribine) or AML-like high-dose chemotherapy should be further explored. Eligible patients with good disease control (after disease debulking, e.g., with TKI ± chemotherapy) may be good candidates for an allogeneic stem cell transplantation (SCT), particularly in SM-AHN (see Chap. 14). The addition of AHN-directed therapy to KIT inhibitors also requires evaluation since progression of the AHN component remains a major reason for death in these patients. Future studies are needed to understand whether KIT inhibition as a post-transplant maintenance strategy can mitigate the risk of relapse. While second-generation, D816-selective KIT inhibitors are showing promise in early phase clinical trials, the incorporation of myeloid mutation profiling will help identify mechanisms of clonal escape (both KIT-dependent and -independent) and should help inform the design of future clinical trials (Table 15.1).

Table 15.1 Response rates and most frequent adverse effects of tyrosine kinase inhibitors

Tyrosine kinase inhibitor	Overall response rate	Adverse effects
Imatinib (approved)	50% (only in *KIT* D816V negative patients) [1]	Edema (swelling of the face, feet, and hands), muscle cramps, bone pain, nausea, vomiting, diarrhea, cytopenia(s)
Midostaurin (approved)	60% overall response rate according to modified Valent criteria, 17–28% according to IWG-MRT-ECNM criteria (independent of KIT mutation status) [16, 17]	Nausea, vomiting, diarrhea, cytopenia(s)
Avapritinib	83% overall response rare according to IWG-MRT-ECNM criteria [26]	Periorbital and peripheral edema, cytopenia(s), fatigue, diarrhea
Nilotinib	22% (mast cell infiltration and tryptase levels) [31]	Cytopenia(s), rash, headache
Dasatinib	33% (mainly symptomatic response) [33]	Pleural effusion, cytopenia(s), diarrhea, headache, muscle cramps, bone pain, fatigue, fluid retention
Masitinib	Response of symptoms in 19% of ISM and SSM [30]	Diarrhea, rash, asthenia

A direct comparison of efficacy between the various TKIs is not feasible because different response criteria were used

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Chapter 16
International Support and Advocacy for Mast Cell Disease Patients and Caregivers

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Introduction

Mast cell disease (MCD), forms of which are generally considered rare, affects all ages from birth to adult and includes cutaneous mastocytosis; systemic mastocytosis (SM), with indolent or benign variants and more advanced and malignant variants; mast cell sarcoma; and mast cell activation syndrome (MCAS) [1–4]. Elevated basal serum tryptase is frequently, but not always, seen in MCD. Hereditary α-tryptasemia is a fairly common genetic trait that also causes increased basal serum tryptase and has been associated with MCD [5]. The process of mast cell (MC) activation, where MCs release mediators in response to a trigger through both IgE- and non-IgE-mediated reactions, may be seen in MCDs. In addition, comorbidities such as forms of dysautonomia, including postural orthostatic tachycardia syndrome (POTS), and connective tissue abnormalities, including hypermobility,

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are increasingly being identified in patients with MCD. Global collaboration between groups focused on these conditions is essential to provide optimal support and advocacy for patients, including those with multiple diagnoses or who are seeking a correct diagnosis.

Symptoms of MCD, many resulting from the release of MC mediators, vary from patient to patient and may be chronically disabling. The unpredictability of the onset of symptoms is a key concern for patients and caregivers and often makes patients' lives difficult to manage [6, 7]. Skin rashes; itching; flushing of the face and neck; chest pain; gastrointestinal problems including reflux, abdominal pain and bloating, nausea, vomiting, and diarrhea; bone and muscle pain; and cognitive dysfunction, including "brain fog" (difficulty with concentration and memory), anxiety, and depression, are examples of possible symptoms patients may experience. Life-threatening anaphylaxis, which can occur in response to a known or unknown, seemingly innocuous trigger, is a constant risk for many patients. Triggers, which differ for each patient, may include, but are not limited to, heat, cold, medications, stress (physical, emotional, and environmental), fatigue, exercise, insect or other bites or stings/venom, infections, certain foods/beverages, alcohol, odors/perfumes/chemical exposure, and friction or vibration [6]. Symptoms resulting from MC mediator release may be controlled with mediator-blocking therapies, MC stabilizers, and discriminate use of corticosteroids [1]. In specific cases, immunotherapy and IgE-depletion therapy may be helpful [1]. Patients can be dependent on numerous medications to control symptoms, and new treatment options are limited.

Signs of advanced disease can include enlargement of the liver and/or spleen, with or without organ dysfunction, changes in blood counts, enlarged lymph nodes, bone infiltration, and fluid in the abdomen (ascites). For patients with advanced variants or malignant forms of disease, the limited treatment options are geared toward cytoreduction. Older chemotherapeutic agents such as cladribine and newer therapies targeting *KIT* mutations commonly found in mastocytosis, especially *KIT* D816V, such as midostaurin (Rydapt®) and avapritinib, have been used successfully to treat patients with advanced variants; other promising drugs and treatments are also currently in various stages of clinical trials [1]. The need for new therapies is critical.

Patients with MCD can endure years of difficult and frustrating challenges before an accurate diagnosis is identified [7]. Many patients are unable to find a healthcare provider (HCP) who can willingly and capably evaluate and treat them, due to low numbers of such practitioners [7, 8]. In developing countries, this problem can seem nearly insurmountable, as economic, political, geographic, and cultural challenges inhibit progress on multiple fronts.

Medical literature on support and advocacy for patients, caregivers, and others affected by an MCD is limited. However, in many countries, a patient support and/or advocacy group (PSAG) focused on MCDs may be available to provide essential and/or supplemental support, disease education, and advocacy. These groups are often dedicated to those affected by a broad range of MCDs, due to the overlap in presenting symptoms, uncertain diagnoses, and evolving understanding of MCD processes. Due to the rarity and lack of recognition of MCDs, HCPs, patients/

caregivers, industry, and government representatives may not be aware of the existence of these PSAGs, or of the opportunities available for mutual support and advocacy. This chapter represents one of several collaborative efforts of the international MCD PSAG community to help improve the lives of those affected by these diseases and is intended to perform the following:

- Identify some of the many ways HCPs can support and advocate for MCD patients and their patients' caregivers to help improve patient/caregiver quality of life
- Encourage patients to advocate for themselves, and caregivers to advocate for patients in their care, and to identify sources and mechanisms by which support can be obtained
- Encourage collaboration between PSAGs, HCPs, industry, and governments to work toward common goals
- Assist in identification of MCD PSAGs around the world and highlight key achievements
- Inspire establishment of new MCD PSAGs
- Identify unmet needs of the MCD community related to support and advocacy

Guidance for Healthcare Providers: Improving Patient Care and Outcomes

Heterogeneity of MCD patients' clinical profile, trigger reactivity, symptoms, care needs, access to specialists, financial circumstances, and ability to comprehend and manage their disease requires that HCPs individualize their approach to patient care. Support can ideally be provided to patients and caregivers by their HCPs to improve patient outcomes (Box 16.1). Additionally, HCPs should recognize that some patients have been inappropriately labeled hypochondriacs due to of their diverse symptoms. Awareness of MCD patient experiences, frustrations, and perceptions can provide HCPs with an enlightened perspective on challenges faced by those affected by MCD [6–8]. The HCP who compassionately understands the interplay of these factors can help give patients/caregivers the tools necessary to improve quality of life and manage an MCD successfully. Advocacy through sharing of information from this chapter with colleagues and those affected by MCD can assist in arming anyone looking for additional sources of support with the means to identify a community with shared experiences and mutual goals.

Those who treat patients with MCD are uniquely positioned to provide myriad tools for symptom management at home. A review of a patient's symptoms, and medication used to treat each one, is an essential first step, as patients can easily be confused about this issue. HCPs can help patients identify their triggers and develop an avoidance plan. Identifying specific, appropriate steps to take when a symptom flare arises is beneficial, including how to increase doses of antimediator therapy and when to contact their HCP for advice. A personalized, written, and signed emer-

Box 16.1. Helpful Support from Healthcare Providers for Patients and Caregivers

Critical Points for Patients and Caregivers:

- Trigger identification methods and avoidance
- Home management of symptoms and flares
- Recognition of when medical help is needed
- Use of a specific dialogue for seeking emergency or other medical treatment
- Necessity and use of self-injectable epinephrine (in countries where this is available) [9, 14] and other rescue medications
- Education about their condition and prognosis so patients can self-advocate

Resources, Documentation, and Additional Support:

- Emergency action plan or protocol, customized and signed by the physician
- Attention to concerns related to secondary effects of MCD and mental health
- Coordination of care with other HCPs
- Support and documentation when applying for disability payments or accommodations at work/school
- Contact information for country-specific MCD PSAGs
- Additional sources for patient- and caregiver-focused disease information

gency protocol should be provided, helping patients recognize when to seek emergency medical care and how to summon it. In addition, HCPs should carefully instruct patients on the importance of using self-administered epinephrine, as well as *how and when to inject it* [9], remembering that patients will likely be self-administering it when very compromised. The use of other rescue medications, including inhalers and antihistamines, should also be reviewed, especially in countries where self-administered epinephrine is not readily available.

An additional component of the treatment plan involves managing MCD secondary effects, e.g., related to bone health. Discussions should include concerns of mental health, as some neurocognitive and neuropsychiatric illnesses may be related to MCD pathophysiology [10], the stress of a chronic and unpredictable illness may be ever-present, and stress itself can trigger MC reactions. Mental health support for patients with MCD is rarely provided in a clinical setting, but will hopefully soon become part of holistic, comprehensive care.

Some HCPs have limited knowledge of MCD, which can create added difficulties and stress for patients/caregivers seeking emergency care, or care from new providers. Those who treat MCD patients can help such patients to self-advocate by educating them about their condition, empowering them with appropriate dialogue for interacting with other HCPs, identifying which anesthetics and opiates are less likely to provoke MC activation, and providing a signed protocol to be used before

surgery and radiologic procedures with and without contrast (Castells chapter of this book) [11, 12]. Since patients with MCD often see several specialist physicians in addition to their primary care provider, communication and coordination is essential [7, 8]. This is critical when patients need assistance in applying for disability, prescription medication overrides or prior authorizations, or accommodations at work or school. There may also be instances when PSAGs are able to provide supplemental support in areas where HCP help is limited due to time constraints.

Finally, there are important areas outside the clinic where HCPs can support patients/caregivers, PSAGs, other HCPs, MCD-focused industry and the MCD community in general. Participation in educational and support group sessions organized by PSAGs can help to strengthen interactions and relationships between HCPs and these groups. HCPs can work together, with the support of PSAGs, to organize into collaborative networks in their countries and with a goal to partner globally with other such groups. The European Competence Network on Mastocytosis (ECNM) is an excellent example and model for physician and investigator MCD network development, successfully accomplishing a series of important initiatives since its inception in 2002 [13]. In the USA, an initiative has been established to create a network of MCD centers similar to those in Europe. The intention is to eventually expand to include all of North, Central, and South America, hence the name American Initiative in Mast Cell Diseases (AIM; aimcd.net). An inaugural meeting of AIM was held in May 2019 in partnership with a patient/caregiver conference hosted by The Mastocytosis Society, Inc. (TMS; tmsforacure.org). Brazilian MCD physicians have organized a Latin American specialist network with the intent to be an integral part of AIM. Similar coalition development is also underway in the Australasian region. These networks, especially when partnered with PSAGs, have the potential to significantly improve patients' lives.

Support and Advocacy for *All* Patients and Caregivers

Obtaining Access to Appropriate Medical Care

Accessing proper medical care with a multidisciplinary team who can handle diagnosis and treatment is a significant challenge faced by MCD patients across the globe. Large university medical centers are often a good place to seek such care. If a given medical center does not treat MCD, physicians there may be able to refer the patient to colleagues at a different medical center. Medical care of MCD patients is often complex and requires HCPs who remain updated in their specialty area; such physicians may tend to gravitate to university settings.

Established MCD treatment and research programs with excellent patient care tend to exist in major medical centers; however, these are few and far between in the USA, with restricted criteria for admitting patients due to a limited number of appointments per practitioner. In Europe, through the ECNM, more MCD centers have been established, increasing options for patients to access competent care, although access can be limited by referral processes. It is hoped that the establishment of AIM will,

over time, result in the creation of many additional MCD centers across the Americas. Some established centers focused toward treating MCD exist in other parts of North America (Canada), Latin America (Brazil), and Australasia, but numbers are insufficient for the populations of these regions, as they are throughout the world. Care worldwide is therefore, unfortunately, accessible primarily to those who have the means to obtain it. Although related discussion is beyond the scope of this chapter, it is clear that significant changes to medical systems, healthcare policy, insurance access with appropriate benefits, and safety-net systems, in addition to activities directed at increasing MCD HCP numbers, are warranted to address the urgent needs of patients.

In an ideal situation, an MCD patient would have access to a multidisciplinary team, possibly comprising an allergist/immunologist, hematologist, gastroenterologist, dermatologist, endocrinologist, cardiologist, and/or other specialist physicians, as needed, trained in MCD. Some patients are well served by such a team, usually in an established MCD treatment center, with potentially improved care and quality of life [15]. More typically, however, a patient's MCD is managed by an allergist/immunologist, hematologist, or dermatologist, with yearly or biannual appointments, while the patient's local physician manages the disease in between. A successful model has been that MCD specialists in high-demand coordinate care with a local physician who agrees to be the primary care provider. In other cases, physician specialists may play a more dominant role in the total management of patients with MCD. Coordination of care, with excellent communication, is critical for good patient outcomes.

To identify HCPs knowledgeable in MCD, many patients/caregivers turn to professional medical associations or PSAGs, as these groups often maintain lists of specialists. In some countries, an MCD PSAG may be able to provide help and support to obtain care at a specialized center, for example, in those where a national health system is regionally based and a patient resides in a location lacking such care, or in developing countries where inter-specialty communication may be less common.

Healthcare Advocacy for Yourself or Someone in Your Care

Self-advocating, or advocating for an MCD patient for whom you give care, is a key skill when interacting with HCPs. Arriving on time at a medical appointment with a well-prepared, prioritized list of concerns and questions, phrased concisely, can be helpful, as most HCPs have limited time to spend with each patient. This can be a difficult task as many MCD patients are faced with diverse and unpredictable symptoms, unidentified triggers, and uncertainty about diagnoses and future health. Patients/caregivers can consider which issues are most important to discuss with their provider and may want to use the list in Box 16.1 for ideas on types of information or support that would be most helpful to obtain. Bringing another adult to the visit who can provide support and help with documentation of important details may be helpful.

Advice for improving communication with HCPs and emergency room personnel can be found on some PSAG websites. Wearing medical alert jewelry can help inform care when a patient is unable to communicate for themselves. At the emergency room, if a patient is in anaphylaxis, it is important to make this known, in addition to advising emergency personnel if injectable epinephrine has been administered.

Disease Education Resources for Patients and Caregivers

Self-advocacy for MCD patients, or advocacy for someone in your care, can be enhanced and empowered through accurate knowledge about the diagnosed condition and about the critical considerations specific to the patient. Given the rarity of many MCDs, possible HCP unfamiliarity with these diseases, and the diversity of symptoms and triggers, patient and caregiver education is especially warranted. In an emergency situation, a caregiver may be the first person who interacts with HCPs. Sources for accessing patient- and caregiver-focused MCD-related educational materials, and/or for obtaining resources to help a patient or caregiver advocate to meet their needs, vary greatly worldwide. Specialty HCPs, discipline-specific medical associations, such as the American Academy of Allergy, Asthma and Immunology (AAAAI; AAAAI.org), and MCD centers, such as the Center of Excellence in Spain (mastocitosis.org) and other centers associated with the ECNM (ecnm.net), are important resources for disease education. In the USA, the National Organization for Rare Disorders (NORD; rarediseases.org) provides valuable resources, including educational, and many other opportunities for all rare disorder stakeholders. Many MCD PSAGs also provide helpful disease information and educational resources developed in collaboration with specialists.

Workplace Accommodations

It is reasonable to expect that workplace accommodations will be made, allowing MCD patients to continue working; such accommodations are available in many countries and can serve as a model for those where they are not commonly applied. Researching laws for Special Needs and Disabled Persons in the patient's country may yield information about possible accommodations. Simple adjustments, such as reducing room temperature (additional air-conditioning or fans) and moving the patient away from direct heat or sunlight, can be helpful. If a patient is sensitive to odors, perfumes, or chemical smells, reducing the use of these agents in the patient's immediate environment is warranted, and the patient can be encouraged to wear a mask for self-protection. However, the patient should also recognize that there are limitations to the extent to which accommodations can be made, e.g., if the patient works at a location where the patient develops a reaction to a specific trigger that is an integral part of

their everyday work environment, then modifications might not be possible. Additional adjustments to help improve patient outcomes at work might include better/more frequent access to a bathroom, incorporation of rest periods to combat fatigue, shorter workdays, telecommuting, a quieter work environment if noise is a stressor, and any other change directed at reducing trigger exposure. Eliciting cooperation from coworkers to help keep a patient's MCs stable may help coworkers feel that they are an integral part of the solution, yielding a more positive outcome for the patient in the work environment. This may be accomplished by a presentation to coworkers and management by an HCP or patient advocate involved in the patient's care.

Financial Concerns

It is not uncommon for a patient with an MCD to find that, even when workplace accommodations are made, maintaining employment is not possible, resulting in significant financial pressure and stress [7]. Many patients find it necessary to apply for disability payments. In the USA, patients may apply for social security disability or other forms of long-term disability, and similar benefits may also be found in many other countries, dependent on country-specific disability laws; specialized legal assistance in this area may be helpful. However, such benefits are often not enough to live on and few sources are available for patients to access additional financial help. The NORD website lists links to possible financial assistance options. Patients with advanced variants of SM, such as aggressive SM or MC leukemia, can review options identified by the American Cancer Society (cancer.org) and the Leukemia & Lymphoma Society (lls.org). Some pharmaceutical companies have programs to assist with medication costs, and a pharmacist can help identify producers of the drugs taken by the patient so the patient can contact the company regarding assistance.

General Support Considerations

The level of support MCD patients and caregivers require varies significantly. For some patients, standard activities of daily living are exceptionally challenging, requiring supplemental physical and emotional support, while others may require only limited or no additional support [7]. Some patients who have been traumatized by multiple episodes of MC activation and anaphylaxis can become very fearful and unable to function. Patients in this situation may need the support of not only MCD specialists but also a mental health professional. For patients who do need additional help with physical activities, family, friends, a home health aide or visiting nurse can be an excellent support. Utilizing a prescription for physical and occupational therapy in the home can help a patient become strong enough to be able to manage self-care. Visiting nurses can help manage medications and monitor vital signs and

are covered by most private insurance plans and some publicly financed healthcare systems.

There may be additional mental health concerns. The chronic nature of MCDs can present a tremendous burden for patients and caregivers. Anxiety and depression frequently exist in the household, affecting everyone. Recognizing symptoms of depression and/or anxiety, such as excessive fatigue, lack of interest in daily activities, change in appetite or sleep patterns, morbid or suicidal thoughts, crying, and somatic symptoms, such as headache and/or abdominal pain, is an important part of self-advocacy. Anyone affected by these symptoms should contact their HCP immediately, so that effective treatment can be initiated.

Family can play a vital role in patient support, disease management, and self-care. Taking a family member or caregiver to a medical appointment or support group session may help them understand the complex, disabling, and chronic nature of MCDs. Efforts to garner support from others can often be aided by the use of relevant educational materials from reputable sources.

PSAGs can be an excellent resource for group and one-on-one support for both patients and caregivers. For many, the best type of sustaining support can be found in a face-to-face support group, where patients and caregivers interact with others sharing similar challenges and experiences. Support group sessions can help both patients and caregivers deal with isolation and loneliness, in addition to providing information about disease management. Also, difficult subjects can be discussed openly in the secure environment of these gatherings. Ongoing support by phone, text, email, and social media, through the connections made during support group meetings, often becomes a lifeline for patients and caregivers.

Awareness and consideration of caregiver concerns is critical for the patient, caregiver, and extended family, as caregivers of patients with chronic diseases may experience negative effects on both their mental and physical health. Those caring for MCD patients report terrific amounts of strain, frustration, and isolation to PSAGs and often note that finding personal time is an ongoing struggle. MCD-specific caregiver difficulties reported during caregiver support group sessions include watching loved ones suffer with symptoms often presenting unpredictably and frustration at being unable to relieve their misery. Caregivers also report that witnessing anaphylaxis and having to administer injectable epinephrine can be a terrifying experience, and that managing a loved one's complex care, perhaps in addition to their own, can become a tremendous burden. Support and recognition from HCPs and support groups are said to be much appreciated by caregivers. Parents of affected children are especially vulnerable to caregiver burnout due to the normal demands of child rearing, compounded by the increased load of caring for a child with complex medical needs. The same can be said for caregivers of geriatric patients, who often require 24-hour care for complex medical needs.

Accusations of Munchausen's syndrome by proxy have occurred with pediatric and adult patients dependent on caregivers, which is a fear that caregivers of MCD patients with unusual constellations of symptoms may have when presenting at the emergency department. Some PSAGs urge MCD patients to carry an emergency plan, signed by their physician, including documentation of their presenting signs and

symptoms of MC activation/anaphylaxis, and contact numbers for the emergency department to call their primary care physician or specialist, if needed. In addition to care guidance, this may help to validate both the patient and the caregiver.

Lay Organization Resources for Education, Support, and Advocacy

MCD PSAGs and other lay organizations targeting related disease communities can be excellent sources for obtaining relevant education, multi-level support, and self-advocacy skills and for building community strength through collective advocacy initiatives. In the USA, groups such as TMS, Mastokids (mastokids.org), Allergy & Asthma Network (AAN; AllergyAsthmaNetwork.org), Food Allergy & Asthma Connection Team (FAACT; FoodAllergyAwareness.org), Food Allergy Research & Education (FARE; foodallergy.org), and Asthma and Allergy Foundation of America (AAFA; aafa.org) are all dedicated to educating, supporting, and advocating for patients, caregivers, and families affected by MCD, anaphylaxis, and/or allergies. In other parts of the Americas, the Mastocytosis Society Canada (MSC; mastocytosis.ca) and the Associação Brasileira de Mastocitose (ABraMASTO; Brazilian Mastocytosis Association; abramasto.org.br) have been established, with groups in Mexico and Argentina in early development. Active MCD PSAGs exist across Europe, including The UK Mastocytosis Support Group (ukmasto.org) and the Asociación Española de Mastocitosis y Enfermedades Relacionadas (AEDM; Spanish Association for Mastocytosis and Related Diseases; mastocitosis.com). A large geographical area is covered by The Australasian Mastocytosis Society (TAMS; mastocytosis.org.au), which also includes support in Southern Africa and Southeast Asia. Contact and descriptive information of these MCD PSAGs and resources for accessing the many additional MCD PSAGs around the globe can be found later in this chapter. Mastocytosis or MCD specialty centers may also provide country-specific MCD PSAG contact information.

Social Media and Other Online Support Options

For those with Internet access, disease-specific social media discussion groups, such as those found on Facebook and other sites, can be a wonderful communication tool where patients and caregivers can find 24-hour peer-to-peer support from any location. These groups can help raise awareness about the challenges and daily struggles of patients/caregivers and families affected by MCD. However, participants in online discussion groups must be cognizant of the risks that may be generally associated with social media, such as the possible impact on personal privacy and security and exposure to misinformation, biased influences, and negative behaviors.

Many MCD PSAGs encourage community through closed Facebook groups or more anonymous web forums, allowing patients and caregivers a supportive platform to discuss their concerns, fears, experiences, and triumphs and to exchange

ideas and opinions. As member privacy can be a critical concern for health-related discussions, TMS has partnered with Inspire, a secure and moderated online support community for patients and caregivers affected by rare diseases. Inspire is the platform for TMS-trained, registered nurse volunteers to provide education and support to the MCD community, as well as to foster a sense of community (TMS.Inspire.com). The UK Mastocytosis Support Group also has a private web forum.

The education, support, and advocacy missions of some MCD PSAGs are also carried online on websites and public Facebook pages. These online sources commonly contain event information, guidance, advice, and additional resources. MCD PSAG websites, visited by over 200,000 users (TMS and AEDM) per year, provide visibility to the actions, projects, and initiatives promoted by these groups. Social media and other electronic communications have facilitated interchange among MCD PSAGs, allowing for the development of global MCD community initiatives. For example, AEDM and ABraMASTO have created bridges of support and information between those impacted by MCD, including HCPs, in Spanish- and Portuguese-speaking countries. Such communications may help establish MCD PSAGs in other countries who can partner with their countries' HCPs to form MCD clinical networks.

Support and Advocacy for Minors and Their Caregivers

Healthcare and Other Advocacy for Minors

Minors affected by MCD require a community dedicated to advocacy and support for them during their critical years of growth and development. Their parents/guardians perform a critical function in these areas. Parents/guardians can educate themselves about their child's disease, learning about the underlying pathology, symptoms, and treatments, and helping them to be both more confident in managing their child's illness and a better advocate for their child. Parents/guardians can be strong advocates for their children in the emergency room setting, protecting them from trigger exposure and assuring appropriate treatment. At appointments with HCPs, it is important that parents/guardians discuss any new symptom so that it can be thoroughly evaluated within the context of the MCD. One topic parents/guardians may be reluctant to discuss relates to the future health of a child with an MCD. HCPs may offer helpful guidance on this subject [16].

Educating Children About Their Disease

Even at an early age, children can begin to learn about their disease, especially what their triggers are and how to recognize and avoid them, which should be reviewed periodically. Children should also understand the importance of reporting the onset of prodromal symptoms at the very first sign, so treatment can

be initiated early. Children who can actively participate in recognizing their own symptoms will be more confident in managing their disease. Preadolescents and adolescents should be given the opportunity to keep a log of hormonal influences and how they affect the onset of symptoms so that treatment can be adjusted accordingly. The emotional burden of living with an MCD, while challenging, may be lessened somewhat if the disease is discussed openly and calmly on a regular basis.

Once children are accustomed to managing their disease in collaboration with their parent/guardian, they can self-advocate with adult support within their school, other care settings, and their community. Children can educate teachers, coaches, and other adults they interact with about their disease and needs, if given the appropriate tools, such as written literature, online resources, or a personalized presentation. Ultimately, this can help build children's confidence and help reduce their concern about being involved in community activities without a parent.

School and Childcare

In a school/childcare setting, children with MCD need the cooperation of all adults caring for them. Adults should be taught about the pathology of the disease, the child's triggers, presenting symptoms, treatment, and when to seek emergency care. Emergency medication should be immediately available at all times, and all adults in contact with the child should know how to use it. In the USA, an individual education plan (IEP) and a 504 plan can be utilized to meet the specific needs of the child while in school; in different countries, there may be other options. PSAGs may be able to help clarify, and families can explore, what rights to accommodations the child may have.

The school/childcare setting offers many opportunities for accommodations to be made for a child with an MCD, while allowing the child to participate in as many normal activities as possible. This includes sitting the child away from direct sunlight, monitoring room temperature, being aware of a child's specific triggers to avoid exposure, watching for indications that the child needs to go to the nurse or to the bathroom, and watching for presenting symptoms. Children may be too embarrassed/shy about going to the teacher with symptoms in front of peers and may require a pass to be kept at their desk for emergencies, bathroom breaks, or visits to the nurse. Other potential triggers to be aware of may include stress (which may require exam accommodations), excess noise/confusion, friction/vibration, foods/beverages, fatigue, triggers presenting outdoors at recess, and infections/colds. An alert teacher/care worker can be an important ally for a successful school/childcare experience. With a parent/guardian and HCP, children can be involved in creating a presentation for peers about their MCD, with auxiliary material for peers' families. Other children can be very accepting of a medical condition if they are made part of the team that supports the child during the day.

Social Interactions

While all children may face challenges within the school setting, including dealing with bullies, peer acceptance, issues of self-esteem, building self-confidence, and as they grow older, dating, these issues take on a different dimension for patients with MCD. Children whose MCs activate when under stress are further hampered in their response to such stressors. Bullies have more than adequate material to target children with skin lesions who need frequent bathroom breaks and cannot always participate in activities. Education is a key component when working with bullies and developing peer acceptance at school and in the community. Parents/guardians of children with MCD should communicate with teachers and community leaders to prevent issues from escalating and to protect the child's self-esteem. Ongoing education about the type of MCD the child has can help peers feel like part of the child's circle of care. Some PSAGs provide targeted educational tools, such as a story and related film developed by AEDM, aimed at helping children and teens with MCD feel more confident, and at promoting acceptance and respect for diversity. Involving children and teens in fundraising to benefit MCD PSAGs and research can also help minors feel engaged and promote advocacy and community involvement.

Parents need to coach teens to avoid triggers, especially concerning experimentation with alcohol and drugs. Teens may be more likely to be risk-taking than people of other ages [17] and may need encouragement to always carry an epinephrine autoinjector. Discussions about the challenges of dating should start early in the preteen years in order to improve confidence and a strong sense of self. The more support from adults and peers that children with MCD have from the early years, the better prepared they will be to handle complex future challenges. Self-confidence, self-awareness, and self-acceptance are strong building blocks to develop from the child's earliest years.

Support Considerations Related to Minors and Their Caregivers

Support for pediatric patients affected by MCD and their caregivers can be provided by targeted written literature, online materials, chat groups, and online blogs. Preteens and teens, in particular, welcome the opportunity to connect with others in their age group in a neutral setting. Social media sites are therefore very appealing to them as a great communication tool where children and teens can interact and provide mutual support, although parents must be vigilant about online safety. Children of all ages may enjoy meeting peers at in-person support meetings. Parent-to-parent support can be a wonderful resource, whether in person through local support groups, online, or by other means, and the mutual support, ideas, and information shared can provide comfort and a sense of community.

Education, Support, and Advocacy Resources for Minors and Their Caregivers

Multiple MCD PSAGs have or are in the process of developing programs and materials to support minors, caregivers, and families affected by these diseases. AEDM has successfully organized family weekends where children and their families can come together in a relaxed and enjoyable manner to learn about MCD and share their experiences. Many other national organizations also provide helpful resources for families. For example, in the USA, NORD, AAN, FAACT, FARE, and AAFA provide a variety of excellent resources and programs, including educational and school support materials, information on bullying, camps for children, teen retreats, and advocacy toolkits. The American Academy of Pediatrics (AAP; aap.org) provides an *Allergy and Anaphylaxis Emergency Plan* [18] and supports an extensive collection of national and international programs. Supported by the APP, healthychildren.org is an excellent resource and provides information, including this emergency plan, in both English and Spanish.

International Patient Support and Advocacy Groups

Support group meetings, educational sessions, and workshops organized by MCD PSAGs around the world, where patients/caregivers, HCPs, investigators, and others come together to build relationships in a mutually beneficial, interactive environment, are vital components of the initiatives of many of these groups. Globally, MCD PSAGs, all currently volunteer-led, work with HCPs and others to ensure patient voices are shared with the broader biomedical community and government entities, to organize MCD educational programs for HCPs, and to develop and disseminate educational materials. These organizations work with government regulators, industry and distribution networks to help ensure access to necessary medications, distribute research announcements, collaborate with pharmaceutical companies to help advance drug development, and dedicate themselves to the success of diverse initiatives that aim to support and advocate for those affected by MCD, as well as MCD HCPs and investigators.

As their collective reach expands and global initiatives progress, it is hoped that the many successes of existing MCD PSAGs will inspire others to form. An important collaboration between TMS and MCD specialists was the MC Disorder Patient Survey [2, 6, 8], which helped pave the way for multiple additional joint efforts [7], such as the development of the first medical codes for MCAS and comprehensive revised codes for mastocytosis, implemented in 2016 and 2017, respectively, in the USA. In a health system where billing and insurance review and payment are dependent on such codes, ensuring updates are incorporated is a vital aspect of MCD patient support and advocacy. The UK Mastocytosis Support Group collaborated with the Royal College of Anaesthetists to develop an anesthesia protocol and with the Royal College of Paediatrics and Child Health on a “care pathway” for mastocytosis. Such care pathways establish standards and give patients a reputable source of information to which

they can direct HCPs, and allow PSAGs, HCPs, and the UK government to review equity issues regarding access to care. Collaboration between AEDM and HCPs from the Instituto de Estudios de Mastocitosis de Castilla La Mancha (CLMast), a center with exceptional mastocytosis expertise in Spain, resulted in official recognition of CLMast as a Spanish reference center for mastocytosis in 2017, allowing MCD patients in that country access to informed, high-quality care. Collaborative efforts by MCD PSAGs and HCPs to establish clinical networks in multiple countries, along with mutually beneficial support activities, are cardinal and ongoing initiatives for PSAGs. Below are descriptions of some key MCD PSAGs from around the world.

The Mastocytosis Society, Inc. (TMS; tmsforacure.org)

TMS is a 501(c)3 nonprofit organization dedicated to supporting patients, caregivers, and families affected by MCD and HCPs through research, education, and advocacy. Founded in 1995, this US-based but globally active member of NORD, backed by an international medical advisory board, hosts local and national support and education meetings; supplies resources and knowledge essential for self-advocacy; provides educational materials for HCPs; maintains a self-enrolled, online-accessible physician database; advocates and collaborates internationally; and supports an over 8600-member strong online community [6–8]. TMS has funded over $500,000 in MCD-related research in the last decade and offers worldwide free membership to those affected by MCD.

Mastokids (mastokids.org)

Mastokids is an international, nonprofit, charitable organization founded in 2002. Mastokids is dedicated to raising awareness of pediatric mastocytosis among caregivers, patients, educators, medical professionals, and the general public around the world. The organization encourages research through research grants. Children associated with the organization are provided with unconditional acceptance and an environment for self-validation through opportunities for contact with other children with mastocytosis. Parents and caregivers are provided with the tools and information to advocate for their children in schools and while interacting with HCPs and the general public. Family support is found through their email forum and private Facebook group.

Mastocytosis Society Canada (MSC; mastocytosis.ca)

MSC is a registered charity that provides support and guidance to patients affected by MCD, their caregivers, and HCPs. Information about triggers and symptoms, diagnostic testing, medications, treatments, nutrition and other effective ways to

manage symptoms is provided by the organization. Through their Canadian physician list, MSC helps patients find HCPs from their province who have knowledge and experience diagnosing and treating MCD. Ultimately, the goal of this group is to provide awareness, education, and support to patients and HCPs in order to reduce the time to diagnosis and improve quality of life for patients.

The UK Mastocytosis Support Group (ukmasto.org)

The UK Mastocytosis Support Group is a registered charity that supports people with MCD, advocates for patients' needs in the UK's healthcare systems, educates HCPs about these conditions, and promotes research in the field. Founded in 2004, the group hosts patient education and support conferences, shares educational materials at professional medical conferences, interacts with national and EU-wide authorities regarding pharmaceutical development and access, works to ensure that all patients have access to experienced HCPs and needed medications, supports online communities of 800 patients and families, and provides small research grants.

The Australasian Mastocytosis Society (TAMS; mastocytosis.org.au)

TAMS is an advocacy, education, and support body for those throughout Australasia who suffer from or care for those with mastocytosis or MCAS. Established due to the overwhelming need for sufferers and their supporters to find a local voice and active support network, TAMS is an independent, nonprofit, incorporated organization with a dedicated and functional volunteer committee of individuals from throughout Australasia – all of whom are sufferers or caregivers. This organization has a medical advisory board of world-renowned clinicians. Since 2012, TAMS has hosted annual conferences, with support group meetings held on a more frequent basis, and active Facebook support groups for both patients and caregivers.

Asociación Española de Mastocitosis y Enfermedades Relacionadas (AEDM; mastocitosis.com)

AEDM is a nonprofit organization in Spain, created in 2002, whose purpose is to provide support to those affected by MCD. Advised by specialists of CLMast and the Spanish Mastocytosis Network, AEDM contributes to the spread of knowledge about MCD: training of patients and caregivers, for improved symptom management; of HCPs, to decrease the time to diagnosis and improve treatment; of society in

general, for better inclusion. Annual support and educational meetings and an active online community, including roughly 4000 Facebook members, promote contact between those affected by MCD. AEDM also contributes funds to support MCD-related research projects.

Associação Brasileira de Mastocitose (ABraMASTO; abramasto.org.br)

ABraMASTO, supported by an international medical advisory board, is a registered nonprofit organization, founded in 2013. With over 800 members, ABraMASTO works with and refers patients to the Center for Excellence and Reference in Mastocytosis (CEREMA) and a multidisciplinary specialist network consisting of doctors from Brazil and various Latin American countries, the Aliança Latino-Americana em Mastocitose (ALMA; Latin American Alliance in Mastocytosis). Patient support, education, advocacy, disease awareness, and self-advocacy skill development are highlighted through active social media groups and national and regional patient education events. HCP support is a vital activity, providing current literature, education, MCD awareness and connection to ALMA. ABraMASTO is now assisting an international study looking at the connection of MCDs with cognitive dysfunctions.

International Mast Cell Disease Collaborative Efforts

MCD PSAGs around the world have been collaborating on global advocacy and support projects. An *International Mastocytosis and Mast Cell Diseases Awareness Day*, October 20, has been established through collective efforts of nearly 20 MCD PSAGs, led by AEDM, and development has begun on an international website (mastocytosis-mcas.org), led by TAMS, for easy identification of and connection with local MCD groups throughout the globe. This new site will expand the efforts of a long-established European mastocytosis website that has directed visitors to national MCD PSAGs throughout Europe for many years.

Future Considerations

Specialists in multiple countries have increasingly placed value on the collective voice and strength of MCD patients [6–8], inviting input from patients and PSAG representatives on important initiatives and projects. In this spirit, it is worthwhile to exam the status of the field from the viewpoint of MCD PSAGs. While selected

unmet needs of the MCD community have been reported and there have been many accomplishments, in the arena of patient support and advocacy, many needs remain unmet (Box 16.2) [7, 19]. It is imperative that all stakeholders in the MCD community, with the common goal to improve the lives of those affected by MCD, come together to examine such needs and identify means to address them. Starting points to explore include: [1] pursuit of government and other funding earmarked for MCD, aimed at HCP training and recruitment, research, drug development and patient/caregiver support and [2] global establishment of collaborative MCD clinical and investigative networks and PSAGs.

Box 16.2. Unmet Support and Advocacy Needs

For Patients/Caregivers and the General MCD Community

- Establishment of MCD clinical and investigative networks worldwide
- Pan-specialist HCP education in MCDs
- Improved communication among specialists
- Encouragement and payment for additional physicians to specialize in MCDs
- Readily available access to knowledgeable regular and emergency care
- Improved follow-up care and continuity of care
- Development of country- and/or language-specific, readily accessible standard and emergency care protocols/instructions
- Access to appropriate and affordable medications
- Accommodations at work or in school to make the environment safe for the patient
- Access to benefits and help to obtain them if a patient or caregiver is unable to work
- Additional targeted research into different forms of MCD and research funding

For MCD PSAGs

- Free or low cost access to research reports and publications
- Strong, working relationships with HCPs and MCD clinical networks
- Continued and enhanced worldwide collaboration between MCD PSAGs
- Financial resources to allow for paid staff and program support
- Additional dedicated volunteers worldwide for MCD PSAG establishment and assistance
- Assistance and resources to navigate country-specific healthcare systems

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Chapter 17
History and Current Status of Mastocytosis Research in the European Competence Network on Mastocytosis

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Introduction

Mastocytosis is a term used for a group of rare hematopoietic neoplasms characterized by abnormal expansion and accumulation of clonal mast cells (MC) in one or multiple organ systems [1–10]. Depending on the number and types of organs involved, mastocytosis can be divided into cutaneous mastocytosis (CM), systemic mastocytosis (SM), and localized MC tumors [1–10]. The classification of the World Health Organization (WHO) recognizes several variants of CM and SM [11–14]. The clinical symptoms, course, and prognosis vary among patients depending on the WHO subset of disease, presence and nature of an associated hematologic (non-MC) neoplasm (AHN) [15–19], and the presence and severity of comorbidities such as vitamin D deficiency or IgE-dependent allergy [5, 20–25].

Independent of the disease variant, patients may suffer from mediator-induced symptoms that can be mild, severe, or even life-threatening [5, 21–23]. In some of these patients, an MC activation syndrome (MCAS) is diagnosed [24–27]. Apart from mediator-related symptoms, patients may also suffer from osteopenia or osteoporosis, gastrointestinal symptoms, neurological or psychiatric symptoms, and/or skin-related symptoms including flushing and/or pruritus [24, 28, 29]. In advanced forms of mastocytosis, including aggressive SM (ASM) and MC leukemia (MCL), additional pathologic features are often recorded, such as cytopenias, ascites, hypoalbuminemia, malabsorption, lymphadenopathy, splenomegaly, or larger osteolytic bone lesions, sometimes with pathologic fractures [14–19, 30–32]. While the prognosis in patients with CM and indolent SM (ISM) is excellent, the life expectancy and prognosis in ASM and MCL are poor [1–8, 14–19].

Cutaneous lesions of mastocytosis were first described as an unusual form of persistent pigment-exanthema by Nettleship and Tay in 1869 (Table 17.1) [33]. Several years later, after the term urticaria pigmentosa (UP) was coined and tissue MC had been described by Paul Ehrlich in 1879 [34], Paul Gerson Unna was the first to describe that the UP lesions contain increased numbers of MC in 1887 [35] (Table 17.1). At that time, mastocytosis was believed to be a skin disease affecting local MC, although some of these patients complained about systemic mediator-induced symptoms.

First Proposals to Classify Mastocytosis

The classification of mastocytosis stems back to 1949, when a first case of SM was described in an autopsy [36]. This observation formally established that mastocytosis can develop in extra-cutaneous organs and probably independent of skin involvement (no skin lesions were detected in this case). Later, this concept was confirmed by demonstrating that systemic involvement with mastocytosis occurs in many adult patients and that SM may or may not be accompanied by skin lesions. Between 1950 and 1990, a number of different disease variants, including a leukemic variant, termed MCL, were described as clinical entities with unique features [37–39]. A

Table 17.1 Overview of the history of mastocytosis research

Milestone in mastocytosis research	Scientist	Year of publication
Rare form of pigment-exanthema described	Edward Nettleship & Warren Tay	1869
Term urticaria pigmentosa (UP) proposed	Alfred Sangster	1878
Mast cells (MC) discovered and described	Paul Ehrlich	1879
MC increased in lesional skin in UP	Paul Gerson Unna	1887
Darier's sign discovered and described	Ferdinand-Jean Darier	1890
Systemic mastocytosis (SM) reported	John M. Ellis	1949
MC derive from hematopoietic stem cells	Yukihiko Kitamura	1977
Kiel classification includes mastocytosis	Karl Lennert	1979
Serum tryptase as marker of MC activation	Lawrence B. Schwartz	1987
First human MC line established: HMC-1	Joseph H. Butterfield	1988
First consensus classification	Dean D. Metcalfe	1991
HMC-1 cells contain *KIT* D816V	Takuma Furitsu	1993
KIT D816V detected in SM patients	Hiroshi Nagata	1995
Serum tryptase levels reflect the burden of neoplastic MC in mastocytosis	Lawrence B. Schwartz	1995
Tryptase is a robust immunohistochemical marker of MC in BM sections	Hans-Peter Horny	1998
Aberrant diagnostic expression of CD2 and CD25 on neoplastic MC in SM	Luis Escribano	1998
Year 2000 working conference on mastocytosis: consensus criteria & classification proposed	EU/US Consensus Expert Group	2000
WHO classification of mastocytosis established based on year 2000 working conference proposal	WHO Group	2001
European Competence Network (ECNM) initiated	Peter Valent	2002
Standardization and response criteria for mastocytosis established and updated	EU/US Consensus Expert Group	2003–2007
Updated WHO classification	WHO Group	2008
Definition and criteria for MC activation syndrome (MCAS) proposed	Cem Akin	2010
CD30 expression in neoplastic MC in SM	Karl Sotlar	2011
Global consensus classification of MC disorders including MCAS	EU/US Consensus Expert Group	2012
ECNM Registry established	Wolfgang R. Sperr	2012
Updated WHO classification	WHO Group	2016
First successful trial using a KIT-targeting drug (midostaurin[a]) in advanced SM	Jason Gotlib	2016

MC mast cells, *WHO* World Health Organization, *SM* systemic mastocytosis, *EU/US* European plus United States based collaboration

[a]In 2017, midostaurin received approval for treatment of patients with advanced SM by EMA and FDA

first comprehensive classification system was introduced by the Kiel working group with Karl Lennert in 1979 [1]. In 1990 a similar classification was proposed by William Travis, and in 1991 a first consensus proposal was presented by Dean Metcalfe [2].

Between 1979 and 1994, the origin of MC from hematopoietic stem and progenitor cells was established. The origin of mouse MC from transplantable hematopoietic stem cells was demonstrated in a series of elegant transfer experiments conducted by Yukihiko Kitamura and his colleagues [40–42]. Later, the origin of human MC from (transplantable) hematopoietic stem cells was confirmed in a patient with systemic MC disease who underwent hematopoietic stem cell transplantation [43].

These data formally established that MC are hematopoietic cells and originate from hematopoietic stem cells. Nevertheless, for several decades, it remained unclear whether MC are directly derived from stem cells or from mature leukocytes, such as monocytic cells or basophils. Although a phenotypic relationship between MC and basophils and MC and macrophages was noted [44–46], every attempt to culture MC from highly purified blood monocytes or basophils failed [47]. Rather, MC apparently derive directly from $CD34^+$ hematopoietic stem and progenitor cells [47, 48], a concept that was supported by studies on the clonal involvement of basophils and other leukocytes in SM [49]. Consecutive phenotypic and molecular studies also confirmed that MC form a distinct myeloid cell lineage [44, 45, 50].

Based on all these findings, mastocytosis can be regarded as a distinct group within the myeloid neoplasms. Whereas ISM behaves as a nonaggressive chronic disease, advanced SM behaves as an aggressive myeloid (multilineage) stem cell disease [15–19, 30]. The assumption that neoplastic MC derive from myeloid-committed stem cells is also supported by the observation that advanced SM is often accompanied by another myeloid (non-MC lineage) disease, also known as associated hematologic neoplasm (AHN) [1, 12–16, 51, 52]. The most prevalent AHN variants in patients with SM-AHN are chronic myelomonocytic leukemia (CMML) and acute myeloid leukemia (AML) [12–19]. The origin of advanced SM from neoplastic stem cells is also consistent with the observation that allogeneic hematopoietic stem cell transplantation remains the only curative approach for these patients [53].

Consensus Group and the Year 2000 Working Conference on Mastocytosis

Between 1990 and 2000, a number of more or less specific, disease-related morphologic, biochemical, and molecular markers of CM and SM were described and were in part validated [54–61]. These parameters were discussed extensively by a EU/US consensus group and formed the basis to define diagnostic criteria specific for CM and SM [11, 61]. A profound final discussion on these criteria was organized in the Year 2000 working conference on mastocytosis [11]. The resulting consensus proposal to classify CM and SM variants and related diagnostic criteria were adopted by the WHO and formed the basis for the official WHO classification of mastocytosis in 2001 [11–14]. Between 2001 and 2010, the EU/US consensus group, assembled in 2000, continued to work on markers, criteria, and standards, with the aim to improve diagnosis, management, and prognostication in CM and SM and to initiate and support observational and clinical trials [24, 26, 30]. In addition, the EU/US consensus group formulated treatment response criteria and diagnostic algorithms [24, 26, 30].

The European Competence Network on Mastocytosis (ECNM)

In 2002, a group of European experts decided that based on the success of the EU/US consensus group and the unmet need to distribute knowledge and standards into various regions, countries, and centers in Europe, it was time to establish a Competence Network for Mastocytosis in Europe. This network was termed the "European Competence Network on Mastocytosis" (ECNM) and was inaugurated in 2002 [62–64]. The mission, structure, and achievements of the ECNM are described below.

Mission and Aims of the ECNM

The ECNM was established as a non-profit cooperative initiative of experts (clinicians and scientists) in Europe who cooperated with each other and merged their efforts to improve recognition, diagnosis, and therapy of patients with mastocytosis [62–64]. Members of the ECNM are not required to adhere to specific regulations or rules or to conduct observational or interventional studies in the ECNM. Rather, all studies and activities provided in the ECNM by participants are voluntary [62–64]. Every interested colleague, physician, or researcher in Europe can become a member of the ECNM without restrictions or obligations. However, the participating centers (and local groups) have to fulfill certain requirements to qualify as a "center of excellence" or as a "reference center" of the ECNM [62–64] (Table 17.2). Detailed information concerning the ECNM is provided in the ECNM homepage (www.ecnm.net) [63]. Apart from collaborations within the ECNM, ECNM members also have established a number of active and productive collaborations with interested experts and centers in the USA. Furthermore, the ECNM has attracted a number of well-recognized US authorities in the field to join as scientific advisors of the ECNM [63].

The major strategic goal of the ECNM is to increase awareness and networking activities on mastocytosis in Europe and in the USA. Specific operational aims of the ECNM are to improve diagnosis, management, and therapy for patients with mastocytosis in Europe, in the USA, and worldwide [62–64]. To reach these goals, the ECNM has conducted a number of scientific collaborative projects and runs a mastocytosis registry. In addition, the ECNM supports the referral of patients; provides comprehensive information about mastocytosis to patients, caregivers, and medical personnel; and supports the development of diagnostic standards, assays, guidelines, prognostic markers, and new treatment approaches. Moreover, the ECNM facilitates access to diagnostic evaluations and specific treatment modalities for patients in Europe and the enrollment of patients in observational studies and clinical trials. In order to achieve these goals, members and centers of the ECNM merge their activities, share their experiences, and organize pro-active networking, all of which are critical given mastocytosis is a rare disease. For example, the ECNM has organized a series of workshops and annual meetings as well as major working conferences and education meetings over the past 15 years and will continue such activities going forward [11, 24, 26, 62, 64].

Structure of the ECNM and Distribution of Competence

The structure of the ECNM is primarily based on national networks focused on mastocytosis that have been established in most European countries [62–64]. These national networks represent strong interdisciplinary academic platforms in which individual centers and sites are embedded and interactive communications, referrals, and exchanges of ideas and technologies take place. The distribution of competence is mainly based on (i) these national networks, (ii) defined ECNM centers, and (iii) additional collaborating centers and scientists. Two specific types of centers have been defined in the ECNM, a "center of excellence" and a "reference center" [62–64].

Centers of excellence are major referral centers that offer a large panel of technologies and facilities sufficient to guarantee optimal diagnosis, management, and treatment of patients with mastocytosis, including all subtypes and variants of the disease. Centers of excellence are typically localized in (or connected with) major university centers and/or university hospitals. The academic basis of such center type is a local network of interacting (collaborating) expert-physicians and scientists who are focusing their research and clinical work on mastocytosis in an interdisciplinary approach [62–64]. All facilities and logistics relevant to the diagnosis and treatment of patients with mastocytosis must be available in a center of excellence, including dermatology, hematology, and pathology units; routine laboratory support; and the possibility to hospitalize patients and to enroll in clinical trials (Table 17.2). A major responsibility of a center of excellence is to develop local guidelines for the diagnosis, prognostication, and therapy of patients with mastocytosis. Other undertakings of a center of excellence include joining the ECNM registry, including patients into this registry, and conducting one or more ECNM registry projects. Centers of excellence may also establish and manage a local reference center. Finally, centers of excellence can (optionally) organize local meetings and are invited to organize annual meetings of the ECNM.

Reference centers are highly specialized centers that focus on a certain aspect and a distinct discipline relevant to diagnosis, management or treatment of patients with mastocytosis [62–64] (Table 17.2). Typically, a major leading authority in the field is running and chairing a reference center of the ECNM. Typical examples for such a reference site are the ECNM reference center for hematopathology in Munich, Germany (chair: Hans-Peter Horny) and the ECNM reference center for diagnostic multi-color flow cytometry in Salamanca, Spain (chair: Alberto Orfao) [62–64]. Reference centers are highly specialized major active referral sites and are able to provide information and assistance in the diagnosis, management and therapy of patients with mastocytosis, including difficult (confounding) cases. These reference centers may or may not be incorporated in a center of excellence. The most important tasks for a reference center are to develop generally accepted standards and guidelines for diagnostic tests, to offer clinical evaluations and therapies for patients with mastocytosis and to distribute the respective information in the ECNM and through publications [62–64]. Depending on resources and availability

Table 17.2 Center of excellence and reference center of the ECNM: major features

A: Center of excellence
Major local/regional referral site for patients with mastocytosis
Major referral site for patients with suspected mastocytosis
Optimal diagnosis, management and treatment of patients
Is able to manage patients with all variants of CM and SM
Local interdisciplinary network of physicians and scientists
All facilities and logistics relevant to diagnosis and treatment of patients with mastocytosis (all variants) are available
Core basis of center: dermatology, hematology, pathology, and laboratory units, including molecular medicine facilities.
Facilities sufficient for hospitalization and for the application of intensive therapies & access to a stem cell transplant center
Develops local guidelines for the diagnosis, prognostication and therapy of patients with mastocytosis.
Collects data on patients in a core data set and includes data on patients in the ECNM registry
Participates in observational or clinical trials, conducts observational or clinical trials and participates in or conducts ECNM registry studies
B: Reference center
Strong focus on a certain topic or discipline relevant to mastocytosis
Major referral site for difficult (tricky) cases and highest authority
Should develop local (national) standards and approaches in the diagnosis, prognostication, management and therapy in mastocytosis
Should assist in the development of consensus criteria, consensus recommendations, and consensus methodologies
Should assist in the development of generally accepted (global) standards in the diagnosis, prognostication, management, and therapy
Should publish local (national/regional/center-based) guidelines for the diagnosis, prognostication, management, and therapy

of experts, reference centers may also offer specialized training courses and seminars. Standardization is a major issue and should be developed by reference sites within the framework of the ECNM. A major important aspect is the "referral of unusual cases". Experts of a reference center should be able to help in difficult situations concerning test results, diagnosis, classification and therapy. The reference centers should also be able to prepare, initiate and coordinate multi-center studies, observational studies, and clinical trials (clinical reference center). All these activities should provide the basis for the establishment of generally accepted standards, guidelines and diagnostic and therapeutic algorithms.

Apart from centers of excellence and reference centers, *additional collaborating centers and active participants* have been and are being invited to join the ECNM and to participate in ECNM projects. It is a major aim of the ECNM to invite and attract as many experts and physicians as possible. These partners may serve as "collaborating clinical centers," "collaborating experts," and "collaborating research centers."

The ECNM Homepage (www.ecnm.net] contains relevant information concerning the structure, centers, and participants of the ECNM. The visitors (patients, physicians, and scientists) can derive critical information concerning the regional (nearest available) center of excellence and physician and experts working in this center [62–64]. The ECNM homepage is regularly updated and contains announcements concerning annual meetings, other major events, and available literature. Furthermore, the ECNM homepage contains a comprehensive overview on the topics of mast cells and mastocytosis, useful for both patients and doctors. The ECNM homepage is accessed regularly by an increasing number of European and non-European visitors.

Strategic Development of the ECNM in Europe

Important strategic aims of the ECNM are listed in Table 17.3. One major strategic aim is to establish a network of centers of excellence and reference centers in all regions and countries in Europe, so that all patients with mastocytosis in Europe have the chance to receive optimal management and therapy. To cover the total region (Europe), the strategic aim is to establish (i) one national competence network per country, (ii) at least one center of excellence in smaller countries and at least two centers of excellence in bigger countries, and (iii) at least two reference centers per "competence issue." Whereas in many countries these aims have been reached, other countries still have unmet need, and the ECNM is seeking contact with interested sites. Another strategic aim is to interconnect the ECNM centers through collaborative studies, educational meetings, and exchange of ideas and

Table 17.3 Major strategic aims of the ECNM

Establish the network of centers of excellence and reference centers in all regions and countries in Europe
Establish one national competence network per country
Establish at least one center of excellence in smaller countries and at least two centers of excellence in bigger countries
Establish at least 2 reference centers per competence in Europe
Interconnecting centers through scientific networking and collaborations and through collaborative studies in the ECNM registry
Promote education of students, physicians and scientists
Long-term vision: all sites and centers acquire sufficient knowledge and experience in the diagnosis and management of mastocytosis patients
Promote basic science research and to establish a basic science platform in the ECNM where new translational concepts are developed
Establish a robust large-scale biobank-system that can be connected with the ECNM registry data set and with clinical studies
Establish a Clinical Trial Platform (Study Group) in the ECNM

ECNM European Competence Network on Mastocytosis

visiting scientists, with the long-term vision that all interested sites and centers acquire sufficient knowledge and experience in the diagnosis and management of patients with mastocytosis [62–64]. Further strategic aims of the ECNM are to foster basic research on normal and neoplastic MC, to establish a robust large-scale biobank system, to establish a robust registry network in the ECNM, to connect this registry with other available registry data sets, and to support the preparation and conduct of observational and interventional clinical trials (Table 17.3).

Other Network Activities in Europe and in the USA: Network Partners

The ECNM is interconnected with a number of external partners, other scientific networks, and medical societies in Europe and in the USA. In addition, the ECNM has established a series of collaborations with major experts and initiatives in the field of mast cell and mastocytosis research in the USA, including the Mastocytosis Society (TMS) and a forthcoming competence network on mastocytosis in the USA, the American Initiative on Mastocytosis (AIM). These network activities support the development of generally accepted criteria and standards and generally accepted diagnostic and treatment algorithms. Specifically, these networking activities assist in the development of consensus criteria, standard guidelines, and recommendations in the field of mastocytosis. For example, the ECNM collaborates with US colleagues and WHO experts and assists in the development and refinement of criteria and the classification of mastocytosis. The ECNM is also networking by organizing a series of regular (annual) ECNM meetings and conferences as well as by preparing and publishing position papers and guideline documents [62–64]. These meetings and documents as well as educational workshops organized by the ECNM are dedicated to the education of young scientists and physicians. Finally, the ECNM is actively collaborating with patient self-support groups and their representatives, and it promotes the organization of patient-information meetings.

The ECNM Registry

The ECNM registry was established in 2012 based on the need to collect information from a sufficient number of patients suffering from this rare disease [64]. This database is being employed to learn more about the frequency, course, and prognosis of mastocytosis. Through 2019, the ECNM registry has collected data from 25 centers in 12 countries and has enrolled over 3500 patients with mastocytosis. The ECNM registry was started in Europe, but has been extended more recently to the USA. The final aim of the ECNM registry is to collect data from about 10,000 patients with mastocytosis and to evaluate diagnostic and prognostic variables,

clinical courses, and responses to various therapies in patients with different types of mastocytosis using this data set. The hope for the future is that based on information and studies collected in the ECNM registry and ECNM registry projects, the diagnosis, prognostication, and selection of patients with mastocytosis for various therapies will improve substantially in the foreseeable future.

Concluding Remarks and Outlook into the Future

Mast cell and mastocytosis research has been profoundly strengthened in Europe and in the USA in the past 30 years. Major drivers of research activities, of interdisciplinary networking, and of developing diagnostic concepts were the EU-US consensus group and the ECNM. Whereas the consensus group established diagnostic criteria, a WHO-accepted classification and therapeutic concepts, the ECNM provided a platform where these concepts have been (and are currently being) translated into clinical practice. Indeed, together with their US colleagues, members of the ECNM were able to introduce diagnostic and therapeutic concepts and to employ the resulting knowledge to start observational trials, registry studies, and clinical trials. In many instances, the resulting markers, targets, and therapeutic approaches were successfully translated into clinical practice. The ECNM and its centers (and experts) will continue to provide a platform for networking activities in the future and will continue to merge their efforts with US centers, US networks, and the WHO, with the ultimate aim to improve diagnostics, prognostication, therapy, and clinical outcomes (and thus prognosis) for patients with mastocytosis.

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