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Review Article

Systemic Mastocytosis: Multidisciplinary Approach

Roberta Zanotti[1,2], Ilaria Tanasi[1,2], Lara Crosera[1], Massimiliano Bonifacio[1,2], Donatella Schena[2,3], Giovanni Orsolini[2,4], Francesca Mastropaolo[2,4], Morena Tebaldi[2,5], Elisa Olivieri[2,6] and Patrizia Bonadonna[2,6].

[1] Hematology Unit, Department of Medicine, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy.
[2] Interdisciplinary Study Group for Mastocytosis (GISM), Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy.
[3] Dermatology Unit, Department of Medicine, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy.
[4] Rheumatology Unit, Department of Medicine, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy.
[5] Gastroenterology Unit, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy.
[6] Allergy Unit, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy.

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Abstract. Systemic mastocytosis (SM) is a heterogeneous group of diseases that affect almost exclusively adults and are defined by the proliferation and accumulation of clonal mast cells (MC) in various tissues. Disease subtypes range from indolent to rare aggressive forms. Although SM is classified as a rare disease, it is believed to be likely underdiagnosed. Major signs and symptoms mainly depend on MC activation and less frequent organ infiltration, typical of more aggressive variants. Diagnosis may be challenging, and symptoms can be aspecific and involve several organs. Therefore, it is advisable to refer patients to specialized centers, having sufficient knowledge of the disease, sensitive diagnostic procedures, offering a personalized and multidisciplinary diagnostic approach, including at least hematological, allergological, dermatological, and rheumatological evaluations. A precise and timely diagnosis is required for: a) adequate counseling of patients and their physicians; b) beginning of symptomatic treatment (anti-mediator therapy); c) prevention of severe manifestations of the disease (i.e., recurrent anaphylaxis, osteoporosis, and bone fractures); d) cytoreductive treatment of advanced SM variants.
This review summarizes the disease's main manifestations and describes the ideal diagnostic approach for adult patients with suspected SM, giving physicians the main notions for correct patient diagnosis and management. This review also highlights the importance of a multidisciplinary approach in this very complex disease.

Keywords: Mastocytosis; Osteoporosis; Anaphilaxis; Cytoreductive therapy; Multidisciplinary approach.

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Correspondence to: Roberta Zanotti. Department of Medicine and Interdisciplinary Study Group for Mastocytosis (GISM), Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy. E-mail: roberta.zanotti@univr.it

Introduction. The term mastocytosis comprises a heterogeneous group of clonal diseases characterized by

proliferation and accumulation of mast cells (MC) in different tissues, mainly skin and bone marrow (BM).[1] Cutaneous mastocytosis (CM) is a skin-limited disease, typical of childhood, that may spontaneously regress during puberty.[2] Conversely, more than 90% of adults have a systemic disease (SM) involving one or more extracutaneous organs [BM, gastrointestinal tract (GI), lymph nodes, and spleenm], with or without skin involvement.[1] The great majority of SM shows a "self-activating" somatic point mutation at codon 816 of the c-Kit receptor gene.[3,4]

SM may present with a variety of clinical manifestations due to inappropriate release of MC mediators (i.e., pruritus, urticaria, angioedema, flushing, nausea, vomiting, abdominal pain, diarrhea, episodic anaphylactoid attacks, osteopenia or osteoporosis) and skin diseases (urticaria pigmentosa – UP or maculopapular CM - MPCM); in the rare cases of aggressive disease, clinical features are due to MC tissue infiltration and subsequent organ dysfunction (i.e., hypersplenism, pathological bone fractures, ascites, malabsorption, cytopenia).[1]

Classification. The 2016 World Health Organization (WHO) distinguishes upon major categories and subvariants of mastocytosis. Diagnosis of SM is based on one major and four minor criteria (**Table 1**) and requires the presence of the major histological criterion, together with at least one minor criterion.
In the absence of the major criterion, at least three out of four minor criteria need to be satisfied.[5,6] SM patients can be further sub-classified depending on the presence of B or C findings, defining the MCs' burden and the disease aggressiveness, respectively (**Table 2**).[5,6] Based on histological criteria, clinical parameters, and organ involvement, SM is divided into indolent SM (ISM), smoldering SM (SSM), and advanced SM variants (AdvSM). AdvSM are subclassified into SM with associated hematologic neoplasia (SM-AHN), aggressive SM (ASM), and MC leukemia (MCL) (**Table 2**). ISM is the most common subtype and has a relatively benign prognosis, although a small percentage of patients progress to SSM or AdvSM. Bone marrow mastocytosis (BMM) represents a provisional variant of ISM, without skin involvement, and characterized by low MC burden, low serum tryptase levels, and frequent association with anaphylaxis, mainly after hymenoptera sting.[7] The prognosis of this variant is considered particularly good, but no significant difference in survival compared to typical ISM with skin involvement has been documented until now.[8] Recent data from the European Competence Network on Mastocytosis (ECNM) suggest that patients with BMM and low disease burden (defined as the absence of any B-Finding and a tryptase level <125 ng/ml) have a better prognosis than patients with typical ISM. As a consequence, the authors proposed redefining BMM with these characteristics as a different SM variant.[9]
SSM is characterized by a higher disease burden than ISM, but the actual prognostic relevance of SSM is debated: a first report documented an inferior survival of SSM with respect to ISM,[10] but in a recent large

Table 1. Criteria for diagnosis and definition of major clinical variants in systemic Mastocytosis (SM) (WHO, 2008; updated in 2016).[5]

Major criterion: Multifocal, dense infiltrates of MC (15 or more MC in aggregates) detected in section of BM and/or other extracutaneous organ(s) and confirmed by tryptase immunohistochemistry or other special stains
Minor criteria: a) In biopsy sections of BM or other extracutaneous organs, more than 25% of MC in the infiltrate are spindle-shaped or have atypical morphology or, of all MC in BM aspirate smears, more than 25% are immature or atypical MC. b) Detection of *KIT* point mutation at codon 816 in BM, blood or other extracutaneous organ(s) c) Co-expression of CD25 and/or CD2 on MC in BM, blood or other extracutaneous organ(s) d) Serum total tryptase persistently > 20 ng/ml (if there is an associated myeloid neoplasia this criterion isn't valid)
B findings: 1) > 30% infiltration of cellularity by MC (focal, dense aggregates) in BM biopsy and serum total tryptase >200 ng/ml 2) Myeloproliferation or signs of dysplasia but criteria are not met for definitive diagnosis of an associated haematological neoplasms, no prominent cytopenias; 3) Hepatomegaly and/or splenomegaly on palpation without impairment of organ function and/or lymphadenopathy on palpation/imaging (> 2 cm)
C findings: 1) BM disfunctyons caused by neoplastic MC infiltration manifested by 1 ore more cytopenia: ANC < 1 x 109/L, Hb < 10 g/dL, or platelets < 100 x 109/L without other haematological neoplasms 2) Hepatomegaly on palpation with impairment of liver function, ascites, and/or portal hypertension 3) Skeletal lesions: osteolyses and/or pathologic fractures 4) Palpable splenomegaly with hypersplenism 5) Malabsorption with weight loss from gastrointestinal tract MC infiltrates

Legend: MC: mast cells. BM: bone marrow; ANC: absolute neutrophils count.

Table 2. Classification of systemic mastocytosis.[1,5]

Diagnosis	Diagnostic criteria
Systemic Mastocytosis (SM):	Satisfied major criterion + one minor criteria or at least 3 minor criteria
• Indolent SM (ISM)	Less than 2 B findings, no C findings
• Bone marrow mastocytosis (provisional entity)	Less than 2 B findings, no C findings, absence of skin lesions
• Smoldering SM (SSM)	More than one B findings, no C finding
• Aggressive SM (ASM)	At least one C finding
• SM associated to other hematological neoplasia (SM-AHN)	SM criteria and WHO criteria for a clonal hematological neoplasm
• Mast cell leukemia (MCL)	BM smear >20% MC; BM biopsy diffuse infiltration of immature MC

retrospective study by the ECNM, the estimated survival of SSM patients was similar to that of ISM.[8]

ASM is characterized by signs of organ damage due to MC infiltration, and patients have a reduced life expectancy and poor prognosis.

SM-AHN represents a very complex SM variant. In 85-90% of cases, SM is associated with a myeloid disease (i.e., myelodysplastic/myeloproliferative neoplasms, myelodysplasia, acute myeloid leukemia, myeloproliferative neoplasms), more rarely with lymphomas or myelomas.[5,6] It is generally considered an advanced variant, multilineage-mutated myeloid neoplasia with a fatal outcome. However, the prognosis of SM-AHN depends on both the SM variant and the associated disease. For example, the prognosis may not be severe when ISM is associated with a relatively indolent disease (such as essential thrombocythemia). It is also often challenging to accurately correlate the B/C findings to the SM or the associated disease, and therefore the correct classification of the SM variant. Therefore, the incidence of SM-AHN is probably underestimated, especially when the MC burden is low.

ASM accounts for approximately 5% of all SM and has a poor prognosis, with an average survival rate of 2-4 years.[11] Skin lesions are frequently absent, while "C" findings such as hepatosplenomegaly associated with signs of organ failure, malabsorption with weight loss, blood count cytopenias or extensive osteolysis may be dominant aspects of the clinical picture.[1]

MCL is the leukemic form of SM, a rare entity characterized by diffuse medullary infiltration of MCs (>20% in the medullary smear), often with an immature or blastic appearance.[1,12] Skin lesions are absent in almost all patients, and the course is fatal, with a reported prognosis of fewer than six months. However, a "chronic" form of MCL was recently defined, characterized by the absence of "C" findings and less aggressive clinical course, with survival even longer than two years.

Epidemiology. Reports on epidemiological aspects of mastocytosis in adults are limited, and it is widely believed that the disease is highly underdiagnosed due to a lack of knowledge about it and the very heterogeneous clinical presentation. A nationwide study based on Danish health registries reported an estimated prevalence of SM in adults of 10 per 100.000 inhabitants,[13] and a similar prevalence of ISM had been reported in the Groningen region adult population (13.0 per 100,000 inhabitants).[14]

We believe that the growing diffusion of sensitive diagnostic methods and the creation of multidisciplinary groups dedicated to mastocytosis will allow us to document a greater number of SM diagnoses. Based on the database of our Interdisciplinary Study Group for Mastocytosis (GISM), the estimated prevalence of SM in the population aged 15≥ years of the Italian province of Verona is 17.2 per 100.000 inhabitants (unpublished data based on ISTAT report of Verona province population at Jan 1, 2021).

No apparent gender predominance has been documented in adult mastocytosis.

Although mastocytosis is considered a non-hereditary somatic disease, familial cases have been reported in pediatric series, with an estimated frequency of 11–13%.[15,16] Recently, a study conducted on a large series of adult patients reported an estimated prevalence of familial cases of 1.5%.[17]

Pathogenesis. MC progenitor cells express the tyrosine kinase receptor KIT, involved in the development of MC by binding its ligand, the stem cell factor (SCF).[18] The majority of adult patients with SM harbor an activating KIT receptor mutation responsible for the autonomous growth and expansion of neoplastic MC.[3] D816V mutation of *KIT* is the most frequently detected, independently of the SM variant and the aggressiveness; moreover, it is documented in about 40% of pediatric

CM.[4,15,19] Although *KIT* D816V mutation is undoubtedly the major driver of SM pathogenesis, it is not considered a fully transforming oncoprotein.

Additional non-*KIT* mutations not specific for SM (i.e., *ASXL1, SRFS2, RUNX1, CBL, EZH2* mutations) are detected mainly in advanced SM and associated with poorer prognosis.[20–22] The role of these mutations in SM pathogenesis is still unclear.

Hematologic Diagnostic Workup. The diagnostic pathway should begin with the search for characteristic skin lesions, that even if isolated constitute an indication to perform a complete BM assessment.[23] Skin biopsy is not strictly necessary if skin lesions are typical.[2]

In the absence of typical skin lesions, the diagnostic pathway varies according to the tryptase value detected. However, it must be taken into account that, during and following an anaphylactic event, tryptase increases, and therefore, it is necessary to re-evaluate it 24 hours after the complete resolution of the symptoms.[23,24] If the basal serum tryptase value is higher than 25 ng/ml, a complete BM evaluation is immediately indicated, while if the value is inferior to 15 ng/ml, it could be monitored over time. For tryptase values ranging from 15 to 25 ng/ml, the indication to proceed with the BM evaluation depends upon additional parameters, such as a REMA score ≥2 (**Table 3**), the detection of the D816V mutation on peripheral blood (PB), or the presence of extra symptoms suggestive of the disease.[25]

BM and PB diagnostic workup is detailed in **Table 5**. They should include:

- *Morphological examination of BM smear*, using the classic staining with May Grunwald-Giemsa.[26] BM smear examination is necessary to evaluate the percentage of MC and their morphology that it was classified in four subtypes: a) spindly shaped with hypo-granulated cytoplasm, b) well-differentiated (round, hyper-granulated), c) immature (promastocytes with a bilobed or indented nucleus), and d) metachromatic blasts.[26] The BM smear should also be reviewed for AHN features. The stain with Toluidine Blue could allow to easily identify atypical MC distinguish them from basophils for the presence of the typical metachromatic granules.[6]
- *Morphological examination of PB smear*. PB smears should be examined for the presence of circulating

Table 3. The REMA Score (Red Española de Mastocitosis).[64]

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

Table 4. Factors that can lead to mast cells mediators release.[114]

1. Physical agents
   - Heat
   - Cold
   - Pressure or rubbing of skin lesions
2. Emotional factors
   - Fatigue
   - Anxiety
3. Drugs and medications
   - Acetylsalicylic acid
   - Non-Steroidal Anti-Inflammatory Drugs
   - Cough suppressants
   - Alcohol
   - Muscle relaxants used in general anesthesia
   - Inductors used in general anesthesia
   - Local anesthetics
   - Contrasts iodized
   - alpha-adrenergic
   - beta-adrenergic blockers
   - antagonists of cholinergic receptor
   - Interferon alpha
4. Poisons
   - Hymenoptera
   - Snake
5. Others
   - High molecular weight molecules used in case of hypotension o hypovolemia such as dextran.

Table 5. Workup for diagnosis and complete evaluation of systemic mastocytosis; modified from Gotlib et al 2018.

Careful medical history, including allergic reactions, presence of mediator-induced symptoms and related triggers, previous and current drug treatment, previous fractures	Mandatory
Physical examination to evaluate the presence and distribution of typical skin lesions, hepatosplenomegaly and/or lymphadenomegaly	Mandatory
Laboratory tests: Basal serum tryptase level Complete blood count, alkaline phosphatase, lactate dehydrogenase, liver function tests, beta2microglobulin 25-OH-vitamin D, serum CTX (C-terminal telopeptide of type I collagen), parathormon, serum calcium and phosphorus, 24h calciuria and phosphaturia, serum Vitamin B12, folate, iron, albumin, cholesterol	 Mandatory Mandatory Recommended to evaluate bone turnover Recommended to evaluate malabsorption
Histological examination of the BM biopsy with evaluation of the MC infiltrate, BM cellularity, dysmyelopoiesis, reticulin fibrosis and collagen and immunohistochemical examination for the al least the following markers: CD117, CD25, tryptase (optional CD30)	Mandatory
BM smear stained with May-Grünwald Giemsa (MGG) with evaluation of MC count and morphology, blast count, dysmyelopoiesis. Additional stain with Toluidine Blue strongly suggested for MC count and morphology	Mandatory
Detection of KIT mutation in BM with:* - ASO-qPCR, ddPCR - PNA-mediated PCR technique - Next generation sequencing.	Mandatory Strongly recommended If D816V *KIT* negative If D816V *KIT* negative also with PNA mediated PCR
Detection of *KIT* D816V mutation on PB with ASO-qPCR, ddPCR	Useful as screening. The BM study is necessary in any case
Detection of V617F of *JAK2* mutation (or *MPL, CARL* mutations), *FIP1L1-PDGFRalfa* rearrangement.	If suggestion of associated MPN or marked eosinophilia
NGS for other myeloid mutations	Suggested in advanced SM (prognostic value)
Multi-parameter flow cytometry on BM samples using a panel including at least CD45, CD34, CD117, CD25, CD2 (optional CD30)	Strongly recommended, mandatory in cases with normal or slightly raised tryptase levels
PB smears (for evaluation monocytosis, eosinophilia, dysplasia, circulating MC)	Mandatory
BM Cytogenetic study	Mandatory in advanced variants or suspicion of myeloid neoplasia
Radiological investigations: Evaluation of abdomen by US scan or RMN or CT Bone densitometry Study of the whole skeleton or limited to x-ray of the whole column and pelvis Bone scan, PET-CT	 Mandatory Mandatory Mandatory Only in selected cases
Esophagogastroduodenoscopy and colonscopy with immunohistochemistry with CD117, tryptase, CD25	Only in selected cases, if significant and/or unresponsive symptoms to the anti-mediator therapy
Organ-directed biopsy (eg. liver) with immunohistochemistry with CD117, tryptase, CD25	If needed
Allergologic evaluation including delivery and instruction on the use of self-injecting adrenaline (2 autoinjectors/year) Tests for hymenoptera allergy, drugs or food Venom immunotherapy	Mandatory If needed If needed
Osteometabolic evaluation: for diagnosis and treatment of any bone involvement	Mandatory
Dermatological evaluation for presence and extension of skin lesions, skin biopsy if needed, management of skin symptoms	Mandatory

Abbreviation: MC: mast cells, BM: bone marrow; PB: peripheral blood; SM systemic mastocytosis, ASO-qPCR: allele specific oligonucleotide quantitative polymerase chain reaction (PCR); ddPCR: digital droplet PCR; PNA: peptide nucleic acid; MPN: myeloproliferative neoplasia.*[40]

MC and eventually for excluding signs of an associated hematological neoplasm (i.e., dysplasia, monocytosis, eosinophilia).[1]

- *Histological and immunohistochemical examination of the BM biopsy* that must include, in addition to the normal Giemsa and Hematoxylin-eosin stains, the

following immunohistochemical investigations: tryptase, CD117, CD25 (and CD2).[1,27] In fact, neoplastic MC aberrantly express, in addition to CD117 and Tryptase, antigens related to the lymphoid lineage, such as CD2 and CD25, absent in the normal MC.[28,29] In particular, CD25 showed high sensitivity and specificity (close to 100%) for the diagnosis of SM[30] and is therefore considered the best immunohistochemical diagnostic marker.[27] Recently, the abnormal MC expression of CD30 has emerged as a useful feature, especially in advanced forms of SM.[31] Furthermore, recent reports have shown that CD30 is also frequently expressed in CM and all subtypes of SM, being useful in diagnosing CD25 negative well-differentiated SM.[32] The BM evaluation should also include the extent of infiltration, the atypia of MCs, the presence of fibrosis, and signs of other associated hematological neoplasms.[1] An accurate diagnosis of SM can be challenging in some cases, particularly when the major histological criterion is not fulfilled and only isolated atypical MC or small sub-diagnostic aggregates are observed. (**Figure 1**)

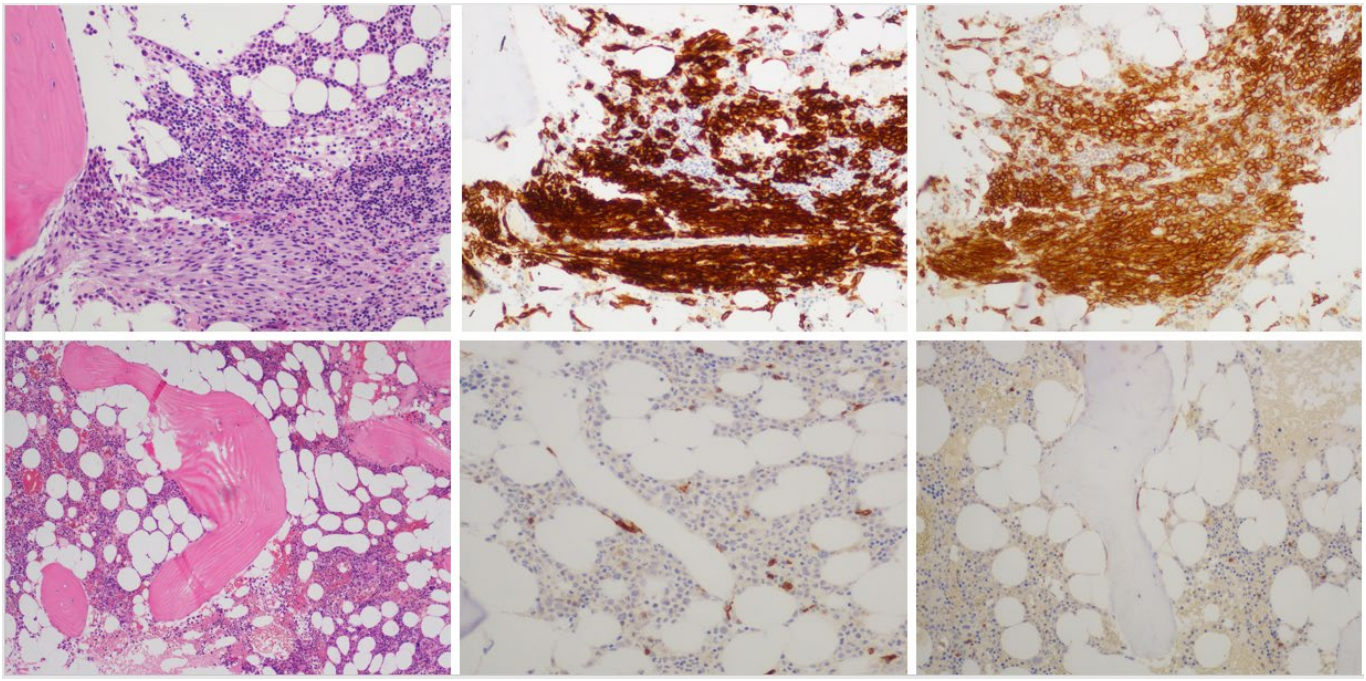

Figure 1. Bone marrow histology of two patients with D816V *KIT*-mutated ISM. Case 1 (upper panel) shows an aggregate of more than 15 mast cells, i.e. the major diagnostic criterion (A: H&E; B: CD117 staining, C: CD25 staining). Case 2 (lower panel) shows isolated spindle-shaped paratrabecular atypical mast cells (A: H&E; B: tryptase staining, C: CD25 staining). (courtesy of dr Alice Parisi).

- *Multi-parameter flow cytometry on BM samples* requires a panel including at least monoclonal antibodies anti-CD45, CD34, CD117, CD25, CD2 (and optionally CD30).[27,32,33] In case of minimal MC infiltration, a high number of events should be acquired (up to 3-6 million events).[33,34]
- *Detection of KIT D16V mutation in BM with highly sensitive KIT mutation assay* to minimize the risk of false-negative results. For instance, in ISM the allelic burden can be very low and often less than 0.01%.[25,35] Currently, the allele-specific oligonucleotide quantitative polymerase chain reaction (ASO-qPCR) is considered the most sensitive technique (0.01%). Droplet Digital PCR (ddPCR) is a promising method for quantifying *KIT* D816V mutation with similar sensitivity to ASO-qPCR (0.01%) and without the need for standardization.[36] Both these techniques detect the D816V *KIT* mutation only. At this moment, Next Generation Sequencing (NGS) is not routinely recommended for the search of the D816V *KIT* mutation, as it has been proved to be less sensitive than RT-qPCR (sensitivity 1-5%).[37] Approximately 5-10% of SM are negative for the D816V *KIT* mutation,[4] generally because of a) false-negative results due to low MC burden or sub-optimal sample or the use of a less sensitive method; b) Wild-type *KIT*; c) presence of another rare *KIT* mutation at codon 816 (F/ H/ I/Y) or in other codons. In the case of D816V negativity and strong suspicion of SM, other *KIT* mutations at position 816 (i.e., D816Y, D816H, etc.) should be ruled out with PNA-mediated PCR technique on BM samples or sorted MC with a sensitivity of 0.1%.[4,19,38–40] Moreover, mutations in other regions of a *KIT* gene may be assessed by NGS.[40] Molecular testing in PB with an ASO-qPCR-based method or ddPCR may be used as a screening method in patients with suspicion of SM.[36,41] However, it must be taken into account that about

30% of BMM and 10% of ISM patients result negative for the mutation assessed in PB, also with sensitive techniques.[39]

- *BM conventional cytogenetics analysis* is indicated in patients with suspected or confirmed advanced SM, especially in SM-AHN cases.[27]
- *NGS study for other myeloid gene mutations* is recommended to search for mutations of other myeloid genes in advanced forms, mainly for prognostic purposes.[27,42,43]

Prognosis. Several clinical, serological, cytomorphological, immunological have been reported to be prognostic in SM. Some of these variables have been included in the WHO classification, such as cytopenia and organomegaly.[1,5] Other variables associated with poorer prognosis are age >60 years, low albumin serum level, increased serum β2-microglobulin and alkaline phosphatase levels.[44–46]

Some biological parameters have been proposed and tested in SM to improve WHO-based risk stratification: poorer prognosis is associated with a multilineage *KIT* mutation involvement, high *KIT* D816V allele burden, and presence and number of mutations in genes other than *KIT* (e.g., *SRSF2*, *ASXL1*, *RUNX1*).[20,46,47] Several integrated prognostic models, as IPSM, MAPS, MARS, GPSM score have been still proposed, all demonstrated on large retrospective patient cohorts and also confirmed in external series.[48–51] Some models include only clinical information and are particularly useful in routine practice, while other scores include both mutational and clinical data. Further longitudinal studies in a large series of SM patients with long follow-up may help select better scores for adequate patient stratification, treatment decisions, and clinical management of SM patients.

Multidisciplinary Evaluation and Treatment

General considerations. Mastocytosis is a complex disease presenting with several clinical manifestations and with a variable clinical course. In non-advanced variants, patients mainly refer to skin symptoms (i.e., pruritus, flushing) or other mediators-release symptoms (i.e., anaphylaxis, osteoarticular pain, GI symptoms), and management often relies upon symptoms control and elimination of additional risk factors and comorbidities. In advanced forms of SM, organ damage prevails, and cytoreductive treatment is needed. Thus, a multidisciplinary diagnostic approach is needed for all these reasons, and a treatment strategy should be tailored to a single patient. Additionally, these patients may need psychological or psychiatric support.

The approach to the patient with SM must include adequate counseling addressed to patients and relatives and physicians involved in the treatment. In addition, information should be given on the natural history of disease and related problems, the drugs to be avoided, and the management of patients requiring anesthesia or surgical treatment. Furthermore, patients should be instructed to avoid triggers for acute mediator release (**Table 4**) and the emergency use of steroids associated with fast-acting antihistamines and self-injectable adrenaline, mainly if they present a high risk of anaphylaxis (i.e., patients allergic to Hymenoptera venom).

Complete workup of patients with SM at diagnosis is detailed in **Table 5**.

History, physical exam, assessment of symptoms burden, laboratory evaluations (annually for patients with ISM and every six months for SSM), and DEXA scan every 1-3 years are recommended for ISM and SSM patients. In addition, patients with ISM and SSM should also be monitored for the development of signs of disease progression to advanced SM (e.g., development of B or C findings).[27] The frequency of monitoring patients with advanced variants of SM should be individualized on the patient conditions and cytoreductive treatment.

Skin manifestations. The classification of CM includes the following variants[2]

- Maculopapular Cutaneous Mastocytosis (MPCM) or Urticaria Pigmentosa, subclassified into monomorphic and polymorphic variants.
- Diffuse Cutaneous Mastocytosis.
- Isolated Mastocytoma.

The presence of telangiectasia, along with MPCM-like skin lesions, has traditionally been termed Telangiectasia Macularis Eruptiva Perstans (TMEP), though the term TMEP should no longer be used.[2] Adult patients with CM who have not undergone BM assessment are more correctly and provisionally referred to as having mastocytosis in the skin (MIS).[1]

The most common presenting symptom in adult mastocytosis is the gradual onset of pigmented, reddish-brown, monomorphic, small-sized (up to 5 mm in diameter) skin lesions (MPCM) (**Figure 2**).[2] Some cases result from the persistence in adulthood of pediatric CM. The frequency of these cases remains to be determined; in clinical practice, monomorphic MCPM generally persists in adulthood, while polymorphic MPCM tends to resolve in puberty, as well as the cutaneous mastocytoma.[2,52] Skin lesions typically show a wheal-and-flare reaction upon rubbing or stroking, the so-called Darier's sign.[2]

Skin symptoms include pruritus, flushing, and wheeling, often triggered by physical stimuli, such as heat, cold, sunlight, and friction.[1] Skin symptoms due to MC mediators release can usually be controlled by H1-antihistamines alone or in association with H2-inhibitors.

Cosmetic complaints could be a significant issue in many patients, especially younger adults, and should not be minimized. Moreover, symptoms could not respond to anti-mediator therapy. At present, ultraviolet A

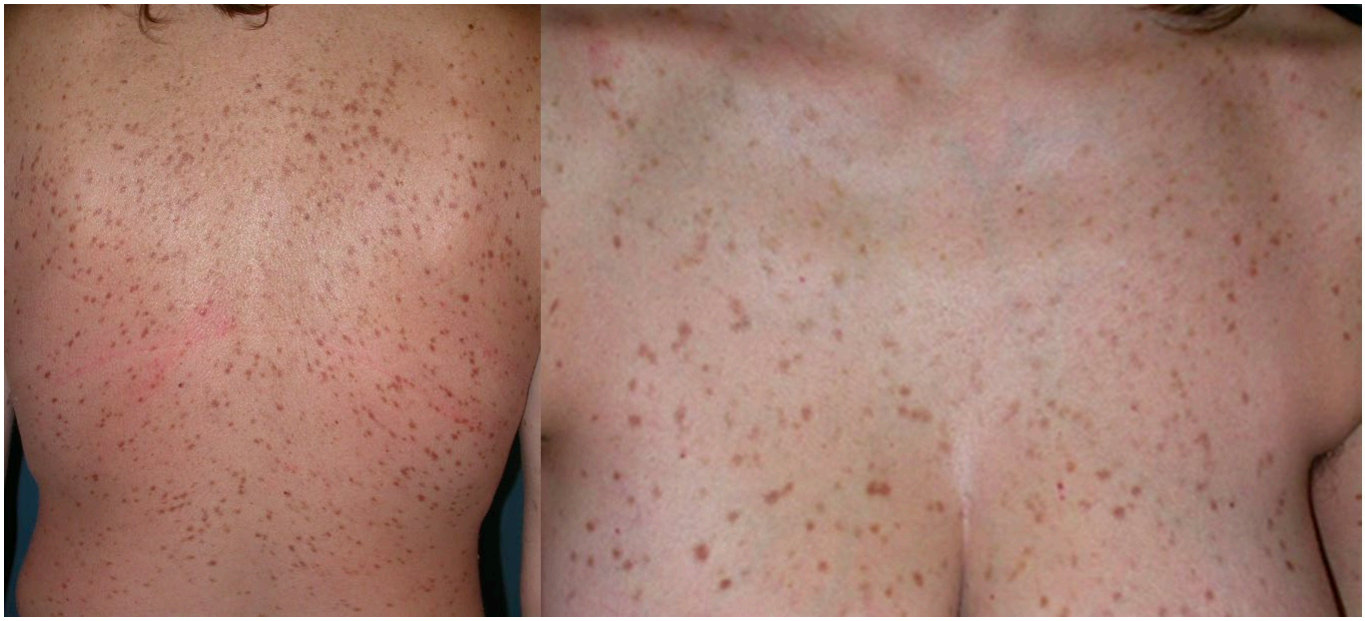

Figure 1. Maculopapular cutaneous mastocytosis (or Urticaria Pigmentosa) (courtesy of dr Donatella Schena).

therapy or Psoralen plus ultraviolet A (PUVA) photochemotherapy can be employed,[1,43,53,54] to reduce MC mediator skin symptoms and visibility of skin lesions, although the effect is temporary. This treatment should be used with caution due to its potential cutaneous side effects.

Anaphylaxis. The prevalence of anaphylaxis in adult patients with mastocytosis ranges from 20% to 49%,[55–57] much higher than the 0.05–2% estimated frequency in the general population.[58,59] Discrepancies between different studies might be a result of the heterogeneity of the patient cohorts, the definition of anaphylaxis, varying recruitment strategies but also be due to the sensitivity of the diagnostic techniques. Allergic/anaphylactic symptoms are mostly present in patients with BMM, often representing the initial clinical manifestation and the indication for BM evaluation in most cases.[60]

The triggers that can induce a massive degranulation of MC and subsequent anaphylaxis in adult SM patients are numerous, Hymenoptera stings being the more frequent (19-60% of cases of anaphylaxis), followed by foods (3-16% of cases) and drugs (5-9%).[55–57,60] Alcohol, exercise and temperature changes are other possible triggering factors of anaphylaxis in mastocytosis, acting mainly as co-factors.[56]

Idiopathic anaphylaxis is not infrequent in SM, reported in up to 29-39% of cases.[57,60]

The higher prevalence of HVA confirms a significant association between HVA and SM in SM patients (up to 20-30%) compared to the general population (00.5-3.3% of adults in the US and 0.3-7.5% of adults in Europe).[61–63] Patients with SM and severe HVA are typically affected by indolent SM lacking skin lesions in the majority of cases (i.e., BMM), are mainly of the male gender, have not very high basal tryptase levels, and allergic reaction is characterized by hypotension with the absence of urticaria and angioedema.[64,65] Early diagnosis of SM in patients with severe HVA represents a substantial advantage because they are at high risk of severe osteoporosis, and early therapy can be immediately started to prevent vertebral fracture. Furthermore, proper advice and prescription of adrenaline (two autoinjectors) can be assessed. Finally, venom immunotherapy should be continued lifelong to prevent fatal events.[66]

Gastrointestinal symptoms. Patients with SM frequently complain of GI symptoms, including abdominal pain, cramping, diarrhea and gastritis.[1,67] Symptoms may be mild or severe, and differential diagnosis with other GI diseases could be difficult. The pathogenesis of GI symptoms in SM is, in most cases, related to MC mediator release, but especially in advanced forms, it could also involve the accumulation of clonal MC in the GI tract. Various stimuli may trigger GI symptoms, i.e., foods, alcohol, stress, but they also can occur spontaneously.

In patients with SM, endoscopic abnormalities are frequently nonspecific. Histological features may include the presence of MC in aggregates or sheets in the lamina propria and the detection of aberrant CD25-expressing MC.[68] However, the involvement can be focal and subtle, making the diagnosis challenging. Moreover, clinical symptoms do not always correlate with histological findings.

Treatment options include H2 blockers, proton-pump inhibitors, and oral sodium cromolyn, alone or in combination. Complete patient history is helpful to identify the triggers of symptoms. In the rare, aggressive subtypes of SM, severe MC infiltration in the GI tract may lead to malabsorption and weight loss. In these cases,

cytoreductive therapy is indicated.[1]

Bone involvement: diagnosis and treatment of related symptoms. According to the cohort of Hermans et al.,[69] osteoporosis and bone lesions are among the most frequent manifestations of SM. On the other hand, a recent study on over 8000 osteoporotic patients recognized SM as its cause in 0.5% of the population.[70] Osteoporosis' prevalence settles down to 8-40% in patients affected by SM while fractures to 3-41%.[71–76] Useful imaging modalities in this context are dual-energy X-ray absorptiometry, radiography (skeleton in toto or at least axial), computed tomography, and magnetic resonance imaging and advanced techniques such as PET could be reserved for special cases.[77] Alongside imaging, it is therefore very important to evaluate laboratory tests (such as the serum dosage of 25-OH-vitamin D, s-CTX, Parathormone, alkaline phosphatase, calcemia, phosphoremia, 24-hour calciuria, and phosphaturia, see **Table 3**).

SM-related fragility involves most prominently the spine, provoking frequently vertebral fragility fractures.[77] Given this, SM diagnosis should be considered when approaching a patient with unexplained fragility fractures, osteoporosis, or inappropriate low bone mineral density (BMD), as a possible underlying etiology.[78] The presence of osteoporosis in male patients or young premenopausal women should induce the suspect of SM.[70] Osteoporosis secondary to SM frequently causes a lower BMD at the lumbar spine than the hip, indicating a greater loss of trabecular with respect to cortical bone. This could be due to either a higher sensitivity of trabecular bone to local factors synthesized by MC or MC's development from BM, which is predominantly localized in the trabecular bone.[70] Furthermore, both the Z-score and the T-score should be considered in these patients since the latter could be misleading due to the low sensitivity and specificity to detect secondary bone disease, especially in men and premenopausal women.[79] When facing a low BMD with a Z-score < -2, secondary causes of osteoporosis should be excluded with further diagnostic examinations. Likewise, fragility fractures occurring in the context of normal or almost normal BMD values should be investigated to rule out possible secondary causes.[78] Bone involvement in patients affected by mastocytosis comprises both a qualitative and a quantitative problem, as shown by the occurrence of fractures in osteopenic patients or those with normal values of BMD. Patients affected by osteoporosis secondary to SM often display a high bone turnover. Interestingly, many studies evidenced a correlation of C-telopeptide and osteoprotegerin to tryptase levels, highlighting a possible correlation to the number of MC.[70,80,81] Of note, serum tryptase elevation (>25 ng/mL) is considered a useful screening tool to predict SM and select patients who should undergo BM biopsy. In cases of mild increase of serum tryptase levels (15-25 ng/mL), BM biopsy should also be considered based on the concomitant clinical elements of suspicion. However, it is not completely reliable as with any biomarker due to possible false positive and negative results. Data from Carosi et al. described serum tryptase elevation in a large cohort of patients with osteoporosis, but only a small percentage (19%) of those who underwent BM biopsy was confirmed to have SM.[81] Therefore, as serum tryptase values lack the high reliability needed in this group of patients when a high clinical suspicion is present, BM biopsy should be considered regardless of serum tryptase value. The picture is even more complicated because, according to recent data, the absence of skin involvement represents a significant risk factor for fractures in SM. This is probably due to a higher diagnostic delay and misdiagnosis in patients not presenting typical skin lesions.[74,79] It must be remembered that osteoporosis and fragility fractures are not the only bone manifestations of SM. A minority of patients present with a diffuse osteosclerotic pattern, characterized by high BMD, high bone turnover, and diffuse bone scintigraphy uptake ("super scan").[78,82] In most cases, these patients also display a very high level of serum tryptase and have a higher chance to be affected by advanced forms of SM.[83] It may also happen that in the context of a sclerotic bone, small lytic lesions may appear, not having the classical appearance of "C-criteria" lytic lesions. A small percentage of patients may also have single or multiple focal sclerotic or lytic lesions.[77,78,82] Antiresorptive drugs are the mainstay of treatment in osteoporosis induced by mastocytosis. In particular, zoledronate 5 mg IV per year seems to be an effective therapeutic option to reduce bone turnover markers and prevent bone loss,[84] but in aggressive forms with lytic involvement and recurrent fracture a monthly protocol for myeloma could be applied. The most frequent side effect, which occurs more frequently than in the general population, is the acute phase reaction to the first administration of zoledronate. However, this reaction is transient, manageable with symptoms and with adequate patient information before administration. Given the pivotal role that the RANK-RANKL system seems to play in the pathogenesis of osteoporosis caused by SM, denosumab might be a further therapeutic option.[77,85]

In patients with severe osteoporosis or refractory to bisphosphonates, therapy with alpha-interferon is suggested based on some studies which reported a good efficacy of the combined use of bisphosphonates and interferon, also if with tolerance problems.[86] In the future, the role of alpha-interferon could be replaced by more innovative drugs.

If the diet is low in calcium, the prescription of vitamin D supplements and even calcium supplements

remains pivotal in all conditions ranging from mild osteopenia to severe osteoporosis.

Special Aspects

Anesthesia. Currently, there are no reliable data on the safety of anesthetic drugs in patients with mastocytosis, and it is impossible to provide general recommendations on the safety of drugs, or drug families, used in the perioperative period.

The risk appears to be greater in adult patients with mastocytosis than in children, regardless of skin involvement, particularly in those with a history of previous adverse drug reactions.[87,88] From a practical point of view, a detailed allergological history is necessary. In patients who have undergone previous surgery under general anesthesia, it may be advisable to consult the medical record and learn about the drugs used during surgery and in the postoperative period.[88] However, routine preoperative skin testing with drugs to be used is not recommended.[88] Prudentially, a reasonable approach is to choose those drugs with low capacity to elicit MC degranulation in each pharmacologic group and to use drugs with known tolerance by individual patients. The following drugs, employed for general anesthesia, are considered safe: propofol, a sedative-hypnotic anesthetic; sevoflurane and isoflurane, inhaled anesthetic agents; fentanyl, sufentanil, remifentanil and alfentanil, opioid anesthetics; local anesthetics such as lidocaine and bupivacaine; skin antiseptics such as povidone-iodine. Finally, curares drugs such as Vecuronium, pancuronium, and cisatracurium have been less frequently associated with the risk of adverse reactions.[88,89]

In SM patients, it is also recommended to avoid potential physical triggers, such as sudden temperature changes, cold fluid infusions, extensive tissue trauma, vigorous skin rubbing, and other mechanical factors.[88] In addition, anxiety can trigger MC degranulation so that patients could be premedicated with sedatives (benzodiazepines) before the surgical procedure.[89]

There is no consensus about the routine administration of premedication before anesthesia or its efficacy to prevent or reduce the severity of reactions. Premedication is recommended in patients with previous perioperative anaphylaxis and in general, depending on the individual patient's risk.[87,88]

Venom Immunotherapy. Venom immunotherapy (VIT) is recognized as a life-saving treatment for HVA patients. After some debate, mainly due to safety concerns, it is now generally accepted that VIT should be given anyway.[90] SM patients who had experienced systemic reactions after Hymenoptera sting should undergo allergological workup. The tests can be performed following the standard protocols (in vivo and in vitro), currently used for patients without mastocytosis. Although skin tests are generally safe, considering the increased risk of patients with SM, they should be performed in a hospital setting.[66] It is also helpful to perform the dosage of specific IgE towards the whole extracts of the poisons of the main Hymenoptera, as well as the dosage of the specific IgE towards the single species-specific molecular markers available (Api m1-2-3-5-10 for the bee, Ves v1, and Ves v 5 for Vespula spp and Pol d 5 for Polistes Dominulus), and the cross-reactive carbohydrate determinants (CCD).[91]

This helps define the individual sensitization profile and discriminate among the poison molecules involved in the allergic reaction and the cross-reactive ones. As SM patients may have very low specific IgE levels, a cut-off level of specific IgE for recombinant molecules lower than 0.10 kUA/L is preferable to ensure better sensitivity and specificity.[92]

Venom immunotherapy (VIT) is universally considered the only life-saving and effective treatment in patients with Hymenoptera venom allergy, even in SM patients, protecting them from severe allergic reactions to subsequent punctures.[90]

Given many reports on fatal Hymenoptera sting reactions after discontinuation of treatment, it is advisable to continue the VIT life-long in patients with SM.[66]

To reduce the number and severity of extensive local reactions or mild systemic reactions to VIT, premedication with an H1 antihistamine can be used in patients with Mastocytosis, while Omalizumab can be used in case of more severe systemic reactions (i.e., urticaria or angioedema) occurring during immunotherapy.[93,94]

Pregnancy. Diagnosis of SM does not appear to affect fertility.[95] There is little evidence regarding the impact of mastocytosis on pregnancy compared to the general population.[95] Based on limited reports, patients with mastocytosis seem not to show a significant increase of maternal-fetal adverse events during pregnancy and delivery (i.e., miscarriage, preterm birth, complications of labor and delivery) compared to the general population.[95,96] Patients with nonaggressive categories of mastocytosis should not be advised against pregnancy,[95] but they must be evaluated before conception, during pregnancy, and postpartum by a multidisciplinary team (which also includes a midwife and an anesthetist).[95]

The management of symptoms of women with SM during pregnancy and early postpartum should combine drugs with no or very limited teratogenic potential to relieve symptoms of MC activation, avoid known triggers, and eventually use prophylactic anti-mediator drugs (steroids, antihistamines), as needed.[27] Interferon-alpha cytoreductive therapy may be considered for pregnant women with severe symptoms and refractory to conventional treatments. The use of cladribine or

tyrosine kinase inhibitors (TKI) is not recommended.[27]

Vaccination. Patients with mastocytosis generally have an increased incidence of adverse reactions to exogenous agents. Although there are no data on the prevalence of adverse reactions to vaccines in adult patients with mastocytosis (i.e., influenza, hepatitis B, or travel-related vaccinations), experts have a consensus that mastocytosis does not represent a contraindication to vaccinations in adults.[97]

In a few cases, reactions were observed, particularly in children. Although patients with Mastocytosis can be vaccinated according to the standard schedule, precautions to prevent MC activation and degranulation have been formulated by experts, under observation with medications available to treat anaphylaxis, particularly in cases of diffuse skin manifestations. Protocols for premedication with steroids, antihistamines, and leukotriene receptor antagonists or cromolyn therapy have been applied to prevent complications, but official guidelines have not to be released.[98]

Although the reported frequency of severe side effects is low, there is an emerging discussion about the safety of COVID-19 vaccination in patients with severe allergies and Mastocytosis. However, severe adverse reactions are rare even in these patients, and the general use of COVID-19 vaccination in patients with Mastocytosis is recommended globally. The only well-established exception is a known or suspected allergy against a constituent of the vaccine. Safety measures, including premedication with anti-H1 and post-vaccination observation, should be considered in all patients with Mastocytosis, depending on the individual risk.[99]

Treatment of Advanced Systemic Mastocytosis. Cytoreductive therapy is indicated in patients with advanced mastocytosis and includes chemotherapeutics, such as cladribine, alpha-interferon, and tyrosine kinase (TK) inhibitors, such as imatinib, and the multitarget oral TK inhibitor midostaurin.[43]

Interferon-alpha (IFN-α) appears to be of limited efficacy and has its indication in treating slow-progressing forms or, in non-advanced forms, severe osteoporosis refractory to bisphosphonate therapy.[43,86,100,101] The frequency of major response (i.e., complete resolution of one or more baseline "C" findings) ranges from 20% to 30%. The optimal dose and duration of IFN-α therapy for SM is still unknown (typically 1 to 5 MU subcutaneously, three times/week), although concurrent administration of corticosteroids (i.e., prednisone) may improve its efficacy (up to 40% of major response rate) and tolerability.[43,100,101] The pegylated form of alpha-interferon may be better tolerated and is likely to be preferred.[43,102]

Cladribine administered at a dosage of 0.14 mg/kg/day for five days, as a 2-hours infusion or by subcutaneous administration, and for up to 9 cycles, led to clinical improvement by lowering the secretion of mediators and reducing MC infiltration and serum tryptase levels.[43] The most common side effects include myelosuppression and lymphopenia. Reported overall response rates are 43% in ASM, 53% in SM-AHN, and 0% in MCL; the median response duration was 2.47 years.[103]

Imatinib is indicated only in *KIT* wild-type SM variants or harboring rare *KIT* mutations sensitive to this drug and in the rare well-differentiated forms of SM (WDSM).[43,104]

Although the second-generation multi-kinase inhibitor, dasatinib, demonstrated in vitro efficacy against various *KIT* mutants, including *KIT* D816V,[105] two clinical trials reported modest efficacy and significant side effects.[106–108]

Midostaurin is a potent pan-inhibitor of TK, approved in 2017 in monotherapy for treating adult patients with advanced forms of SM, at the recommended starting dose of 100 mg twice/day orally, regardless of the *KIT* mutational status. The registration study demonstrated a high efficacy leading to an overall response rate (including major or partial responses) in 60% of patients, improved symptoms burden and quality of life, and good tolerability.[109] In addition to myelo toxicity, the most common side effects are nausea and vomiting, generally well controlled with prophylactic antiemetics, and taking the drug with food. After a median follow-up of 26 months, the median overall survival in the pivotal study was 28.7 months, with improvement over historical survival data, including a median OS not reached in ASM, of 20.7 months in SM-AHN and 9.4 months in MCL.[109]

Ongoing trials, also led in Italy, aim to evaluate the efficacy of other TK inhibitors such as avapritinib, a potent inhibitor of D816V mutated *KIT*, recently registered in the United States to treat diseases determined by activating *KIT* mutations, including mastocytosis and gastrointestinal stromal tumors (GIST). This drug led to a rapid and deeper response in advanced SM, with an overall response rate greater than 70%, of whom 24% of complete response or complete hematological response.[110] The starting treatment dose was established at 200 mg once daily. The most frequently reported side effects are edema, thrombocytopenia, anemia, diarrhea, nausea, and fatigue. One patient in the pivotal study, who had pre-treatment severe thrombocytopenia (platelets $<50\times10^9$/L), experienced Grade 4 subdural hematoma; consequently, pre-treatment severe thrombocytopenia was defined as an exclusion criterion, and dose interruption for severe thrombocytopenia is recommended.

More than 50% of AdvSM express CD30 on the surface of clonal MC. Nonetheless, a recent phase 2 trial

of Brentuximab Vedotin (BV), a CD30-directed antibody-drug conjugate, on ten patients of CD30-positive advanced SM, failed to demonstrate the single-agent activity of BV in this setting.[111]

The treatment of SM-AHN is very complex, and the strategy relies upon both the clinical variant of SM (advanced or indolent) and the type of associated neoplasm. Usually, treatment is tailored against the more aggressive form or consists of a combined treatment,[54] but responses with midostaurin and avapritinib could be obtained regardless of the presence of concomitant AHN.[42,109,110]

Allogeneic stem cell transplantation in advanced SM can be an option if the associated hematological neoplasm itself has an indication or MCL responsive to TK inhibitors, considering the very severe prognosis. In other advanced forms of SM, the decision is tricky, as few studies demonstrated the superiority of transplant over KIT inhibitor maintenance therapy.[42]

In patients with ISM presenting with severe mediator symptoms and refractory to standard therapy, more aggressive therapy may be indicated; the use of KIT inhibitors in patients with non-advanced forms of Mastocytosis will be assessed in ongoing studies.[43] Masitinib, a TKI inhibitor of Lyn, Fyn, PDGFR-α/β, and wild-type KIT, was recently evaluated in phase III, randomized, double-blind trial, in non-advanced SM unresponsive to optimal symptomatic treatments. Masitinib allowed a 75% of sustained improvement in one symptom as pruritus, flushing, depression, or fatigue, in 18.7% of patients compared to 7.4% of patients taking a placebo without severe toxicity. However, an excess incidence of diarrhea and rush of 9% and 4% respectively was reported in the masitinib group.[112] Recent data from a study enrolling ISM patients with moderate or severe mediators related symptoms, refractory to best supportive care drugs, showed that low doses of avapritinib were well tolerated and produced significantly greater symptoms reduction than placebo.[113]

Conclusions. Mastocytosis presents with a plethora of signs and symptoms, mostly related to the secretion of mediators from clonal MC. In many cases, mediator-release symptoms significantly impact patients' quality of life and could be controlled through the instauration of adequate anti-mediator therapy. Consequently, an early and accurate diagnosis is beneficial for most patients. Patients with a positive history of an anaphylactic reaction to Hymenoptera venom should receive immunotherapy continuously to avoid other systemic reactions. Patients with osteoporosis secondary to SM may benefit from antiresorptive therapy.

Furthermore, patients requiring surgical procedures, both in local or general anesthesia, should be adequately managed to prevent massive degranulation of clonal MC and subsequent severe adverse events. Concerning more advanced forms of SM, treating physicians should be able to handle cytoreductive therapies, considering allogeneic stem cell transplant or enrolment in clinical trials in selected cases. Given the complexity of this rare and often misdiagnosed disease, it is of great importance to address the patient to well experienced and specialized center, possibly performing a multidisciplinary diagnostic evaluation. Additionally, the availability of sensitive molecular techniques is essential for a precise diagnosis.

This review provides a compendium of the current knowledge on the disease, aiming to help physicians easily recognize patients with a high probability of SM, which should be addressed to reference centers.

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