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Systemic Mastocytosis: An Intriguing Disorder

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1. Introduction

Systemic Mastocytosis (SM) is a mast cell (MC) neoplasm of the haematopoietic tissue. It is a rare disorder, but perhaps its prevalence is underestimated, as MC infiltrates may often be undetected. The aim of this chapter is to emphasize the importance of an active and careful work-up through multimodality approaches in order to achieve the diagnosis of SM. This might increase the incidence of SM. Moreover, it must be considered that SM is frequently associated with a second and, in rare cases, a third clonal blood disorder that isn't mast cell derived. Similar cases may be important for the correct initial evaluation and classification, as well as for a better risk stratification and management of patients with haematopoietic malignancies. Therapy could also improve, being personalized and tailored for each single SM patient.

2. Disease overview

Mastocytosis is a disorder characterised by clonal mast cells (MC) proliferation and accumulation. It has been described for the first time in 1869 by Nettleship and Tay as a form of urticaria resulting in a "brownish discoloration". Some years later Ehrlich used "mastzellen" to designate MC (Ehrlich, 1877). The term is derived from the German mästung, that means "to overfeed". In fact, the MCs have metachromatic properties that have been originally attributed to an excessive intake of aniline dye. In 1949 Ellis reported the first observation of MCs infiltrating visceral organs. Hence, several reports allowed standardizing the definition and classification of Mastocytosis.

According to the latest WHO classification Mastocytosis is a myeloproliferative neoplasm (MPN) (Vardiman, 2009). Clonal MCs proliferate, infiltrate and accumulate in skin and/or other organ systems. In Cutaneous Mastocytosis (CM) only skin is involved. In Systemic Mastocytosis (SM) at least one extracutaneous organ is infiltrated. This leads to a heterogeneous clinical presentation.

2.1 Epidemiology

Mastocytosis is a rare disorder. Several studies reported an incidence of 5-10 cases/10^6 people/year. However, there's a risk of underestimation due to the difficulty in getting a diagnosis. Recently Nowak et al. have published results of a monocentric retrospective study, reporting that in most patients mastocytosis was correctly diagnosed over a period of 2 years (up to 11 years in some cases), and often required consultation of three or more clinicians (Nowak, 2011). This was consistent with experiences reported by other authors. There are several possible explanations for such diagnostic delays. First, initial symptoms and signs are usually unspecific and overlap with many other diseases. For instance, at presentation some patients show neurological, psychological and psychiatric symptoms, leading to a misdiagnosis of somatoform disorder instead of mast cell syndrome (Amon, 2010). Second, morphological detection of pathological MCs is not obvious, mainly if they exhibit atypical features, such as hypogranulation or abnormal nuclear morphology (Pardanani, 2011). Moreover, as the second most frequent MC disorder is SM associated with haematological non mast cell disorder (SM-AHNMD), extensive bone marrow involvement by a second haematological neoplasm may obscure or distort MC aggregates (Horny, 2004), delaying or obviating at all the correct diagnosis. Taken together, these observations suggest that clinicians should become more confident with MC syndrome and MC disorders, as clinical suspicion should stimulate further appropriate immunochemical and molecular analysis. According to this, Horny proposed a novel routine approach, using antibodies against neoplastic MC markers in all bone marrow trephines presenting Myelodisplastic Syndrome, Acute Myeloid Leukemia and Chronic Myelomonocytic Leukemia (Horny, 2004).

Mastocytosis is more frequent in children, as CM. Adults represent one third of all cases and they are almost all affected by SM. There are no gender differences in incidence rate and clinical presentation. It can onset at any age, with an incidence peak in the first 2 years of life (Pardanani, 2011). Familiar cases have been occasionally observed. Survival is shorter in SM compared to the general population. However, patients classified according to the WHO 2008 system classification show great differences in demographical and clinical features, prognosis and survival (Lim, 2009). Nevertheless, quality of life is generally poor irrespective to subgroups.

3. Mast cells

Typical MCs are round or oval cells. Their size is small to medium, with a low nucleus/cytoplasm ratio. The nucleus is round or oval, in a central position, with condensed chromatin. The cytoplasm is large with plenty of metachromatic granules. However granules may also be few or lack at all, resulting in hypo-/de-granulated mast cells. Atypical MCs may present an oval nucleus and a hypogranulated cytoplasm. Generally they are spindle-shaped or with prominent projections on membrane surface and their nucleus is eccentric, sometimes with two or more lobes. Cells may appear more immature, with a large size, a high nucleus/cytoplasm ratio and a dispersed chromatin with nucleoli. The grade of immatureness may allow to the diagnosis of mast lineage blasts, characterized by the virtual absence of cytoplasm, with or without metachromatic granules, and fine chromatin with nucleoli.

3.1 Mast cell physiology

Mastocyte is a cell of the immune system. It derives from the haematopoietic stem cell. It is preferentially localized in the skin, respiratory and gastrointestinal mucosa.

MC growth, differentiation, proliferation, survival and activation are mediated by several factors The most important is SCF, that interacts with the tyrosine kinase receptor KIT (CD117 antigen). KIT is a key protein, either in normal or in clonal MCs, and its detection is essential in order to identify MCs and achieve the diagnosis of mastocytosis. Therefore, a multimodality approach should be routinely performed, including flow cytometry, immunochemistry and PCR (see below).

MCs play a main role in type I hypersensitivity reactions. Antigen-IgE complexes bind to the $Fc_{\varepsilon}RI$ on MC membrane and induce MC degranulation. Secretory granules contain histamine, tryptase, proteoglycans, TNF-α and other proteases. Tryptase is the most important mediator: it is virtually present in all MCs, therefore its expression on membrane surface identifies MCs, and serum levels may represent a useful marker of disease (see below).

After MC activation and degranulation, new phospholipid derived mediators are generated (e.g. leukotrienes, prostaglandins and PAF). The clinical manifestations are therefore heterogeneous and depend on the site of reaction. Atopic responses may vary in severeness between transient urticarial eruption and life-threatening anaphylactic shock. Several dermal inflammatory diseases are MC mediated, e.g. atopic dermatitis, bullous pemphigoid and psoriasis. However, MCs have also important physiological fuctions, as they are involved in antimicrobial defense, wound healing, angiogenesis, tumor surveillance and graft tollerance.

4. Pathogenesis

In more than 90% of affected adults a recurrent somatic mutation of *kit* can be detected (Garcia-Montero et al, 2006), suggesting that KIT plays a central role in autonomous proliferation of MC clone as well as in normal mastocytes (Orfao et al., 2007). Usually mutation occurs on exon 17 and results in a substitution of aspartic acid at codon 816 with valine. This mutation affects the tyrosine kinase TK2 domain and activates the receptor independently on ligand binding and dimerisation. According to its high occurrence, WHO diagnostic criteria for SM include *kit*D816V screening. Thus, it should be always investigated in bone marrow or blood or other organs when mastocytosis is suspected. Moreover, *kit*D816V represents an important prognostic factor and should be considered for planning and personalizing the therapeutic strategy.

The same mutation is less frequent in children, with an incidence of 42%. However, also most of the affected children share somatic *kit* point mutations that often involve exon 8 or 9, resulting in changes of the extracellular part of receptor (Bodemer, 2009).

Other mutations have been reported: they usually cluster at exon 11 or 17 affecting the juxtamembrane regulatory domain or TK2 enzymatic domain. Sometimes they've been reported at exons 2, 8, 9, 13 or 14 involving extracellular or TK1 domains. Interestingly, it has been observed a significant correlation between mutation type and disorder class. In fact, these specific genetic alterations have not been detected in different *kit* related

neoplasms (e.g. GIST) and seem to be strictly associated with MC disorders (Orfao et al., 2007).

As *kit* is mutated in most patients without subgroup differences, the heterogeneous behaviour of each variant suggests that perhaps several different pathways may be involved in the pathogenesis and progression of the disease. Some authors have demonstrated that NF-κB and cyclin D3 may play a role. (Tanaka A, 2005). In addition, since a second haematological neoplasm is often associated with SM, the pathogenic mechanisms can be more difficult to understand.

Several studies suggests that mastocytosis is a haematopoietic stem cell disease (Horny, 2008). It can be hypothesized that *kit* mutation occurs at the level of leukaemia stem cell, the original clone that is responsible of leukaemia relapse. The occurrence of *kit* mutation confers either proliferative or mast cell lineage differentiative potential. Additional aberrations can then occur in the leukaemia stem cell, leading to the development of the associated myeloid neoplasm. Another possibility is the acquisition of *kit* mutation and transformation of a more mature leukaemia progenitor, resulting in the development of a synchronous mast cell malignancy (Pullarkat, 2003). Even less mature progenitors may be involved as also intra- and peri-lesional B and T cells have been demonstrated to carry the *kit*D816V point mutation. However, in SM patients without any associated clonal lymphoid disease most of the lymphocytes are reactive oligoclonal cells.

5. Clinical findings

Clinical features and course are variable, depending on the site and degree of infiltration and WHO subvariant.

Skin is often involved. Pruritus, erithema and orticarioid lesions usually occurs after mechanic irritation (Darier's sign). Hypercromic and infiltrated lesions affect body trunk, upper and lower limbs in 80% of adults, and head in all children. A frequent symptom is hypotension, often with headache and flushing, sometimes of high grade, resulting in syncope and shock. Diarrhoea is very common, with abdominal pain. Sometimes malabsorption cause a severe worseness of general conditions and must be considered clinically equivalent to organ damage. Bone is always involved: usually patients complain of bone pain, with signs of osteopenia, osteoporosis or atypical atraumatic fracture. Bone marrow infiltration may result in pancytopenia. Organomegaly, in particular enlargement of the lymph nodes, spleen and liver, may be present and causes organ damage (hepatic failure, low levels of albumin, etc.). Neuropsychiatric symptoms could be prevalent at diagnosis and they can be related to disfigurement in appearance: depression, suicide ideation, social and professional inefficiency have been reported (Amon, 2010). Risk of anaphylaxis is increased compared with health population, especially after a trigger exposition (physical exercise, psychic stress, alcohol, NSAID, infections and pregnancy) wich can result in MC activation. Based on this, it is recommended to perform a complete work-up after a first case of a severe anaphylactic reaction, especially in the absence of an evident trigger. Finally, there is a high risk of peptic ulcer. Patients must be closed monitored for all these symptoms in order to prevent complications and improve quality of life with anti-mediator drugs. Moreover, recording symptoms is a key part of staging, as established by WHO, and should drive the correct treatment choice and timing (WHO 2008).

Practically, two groups of clinical findings have been defined, the B and the C group. (Table 1). B stands for "burden of disease" and refers to symptoms that reflect the extension of disease. C stands for "cytoreduction requiring" and refers to signs of organ impairment indicating the need of therapy with cytostatic drugs.

C-findings are due to extensive MC infiltration, with direct organ damage and tissue destruction. The presence of at least one C-finding denotes a high grade disorder, referred as advanced systemic mastocytosis. After excluding any other causes of organ failure, cytoreduction must be considered. Symptoms due to MC infiltrates may be difficult to distinguish from indirect symptoms due to massive mediator release. When relationship between MC infiltration and organ impairment is not clear, patients must be closed monitored with serial dosages of serum tryptase level. An increase trend confirms the progression of the disease and the need of cytoreduction. CD30 expression may also be of help, since a strong positivity in most MCs denotes more likely ASM and MCL, while a weak positivity suggests a diagnosis of ISM. According to this, CD30 may perhaps become a useful tool in grading SM (Valent, 2010).

B-findings related to MC mediators	**C-findings** due to direct MC infiltration	**Organ failure**
1. **High MC burden**	**Organopathy**	
Marrow MCs > 30%		
Serum tryptase >200ng/ml		
2. **Dysmyelopoiesis**		
Hypercellular marrow with signs of myelodisplasia or myeloproliferation	Dysmyelopoiesis, with one or more peripheral cytopenias	Severe progressive pancytopenia
3. **Palpable Organomegaly**		
Hepatomegaly	Hepatomegaly with - ascites - abnormal liver function tests - portal hypertension	Progression to liver failure
Splenomegaly	Splenomegaly, with hypersplenism	
Lymph node enlargement	Bone lesions, with - osteolysis - osteoporosis and pathologic fractures	
	Malabsorption, with - hypoalbuminemia - weight loss.	

Table 1. Clinical findings (adapted from Valent *et al*., 2001).

6. Diagnosis

Mastocytosis must be suspected.

WHO updated diagnostic criteria in 2008. The demonstration of neoplastic MC infiltrates in skin or extracutaneous organ is the *condition sine qua non*. The presence of typical MCs in dermal multifocal aggregates or diffusely infiltrating the skin allows the diagnosis of CM. The involvement of at least one visceral organ denotes SM. However, other criteria must be satisfied, i.e. clinical or biochemical, morphologic, immunophenotypic, molecular (Table 2). This is important to distinguish between any reactive MC proliferation and true clonal MC proliferation, that means Mast Cell Activation Syndrome (MCAS) from Mastocytosis.

Cutaneous mastocytosis (CM) usually presents as maculopapular infiltrates or diffuse erythrodermic rash, with thick skin or multiple nodules. Skin lesions must be biopsied to demonstrate the co-existence of pathological MCs.

The suspicion of mast cell syndrome without any cutaneous signs exclude the diagnosis of CM and requires bone marrow analysis to investigate the possible diagnosis of systemic mastocytosis (SM). Bone marrow biopsy and aspiration should always be performed in such cases as SM involves bone marrow in almost all affected patients. Other specimens may be obtained from other involved organs.

Pathological MCs infiltrates result as aggregates of at least 15 tryptase positive MCs. This is the first major criterion. The following diagnostic steps are BM smear evaluation, flow cytometry characterization and KIT mutational analysis. Finally serum tryptase levels must be dosed.

Cutaneous Mastocytosis	**Typical skin lesions**
• Clinical signs	- Maculopapular cutaneous mastocytosis - Diffuse cutaneous mastocytosis - Mastocytoma
• Microscopic findings	Multifocal or diffuse MC infiltrates
Systemic Mastocytosis	**SM criteria = 1 major + 1 minor or 3 minor criteria**
• Major criterion	Infiltrates of >15 aggregated MCs identified through tryptase immune-histochemistry or other stains in sections obtained from bone marrow or other extracutaneous organs
• Minor criteria	More than 25% spindle shaped MCs in histological sections or more than 25% atypical MCs in BM smear
	Detection of *kit* 816 mutation in BM or blood or any extracutaneous organ
	MC coexpression of CD25 and/or CD2 with CD117
	Serum tryptase levels > 20 ng/ml

Table 2. Proposed criteria to diagnose Mastocytosis (adapted from Valent *et al*., 2001).

6.1 Histology

The typical histological mast cell lesion consists in focal typical and atypical MC aggregates infiltrating tissues. Giemsa or toluidine blue stains can reveal metachromatic granules, allowing discriminating between spindle mastocytes and fibroblasts.

Skin lesions are characterized by perivascular and periadnexal MC accumulation in upper dermis (Amon, 2010). In bone marrow compact infiltrates are perivascular, sharply demarcated from normal tissue, sometimes intermingled with macrophages and eosinophils. Spindle shaped MCs are often more than 25% of the total MCs. Rarely, infiltration is diffuse, with scattered cells that are difficult to recognize. In particular, in SM-AHNMD it is not unusual for the SM component to be unrecognized due to the extensive infiltration of bone marrow by the AHNMD component. This is commonly seen, for example, in SM-acute leukemia and SM with intense eosinophilic infiltration. Monotonous sheets of blasts may help to detect isolated clonal MCs (Horny, 2004). On the contrary, infiltration due to either reactive benign-looking lymphocytes or low grade lymphomatous cells is usually well defined and spindle mast cells cluster in different nodular lesions (Du, 2010). In some cases reactive well-differentiated lymphocytes have been reported to surround central aggregates of clonal mast cells or to be enclosed within malignant mast cells lesions (Kim, 2010). It must be clearly realized that MCs largely infiltrating malignant cells in haematopoietic disorders are clonal in most synchronous myeloid neoplasia, while they are reactive in all described lymphoid associated disorders so far reported. However, our group observed a case that may perhaps represent the first reported exception to this rule (see below).

Immunochemistry is important to recognize clonal MCs and get the right diagnosis. Spindle-shaped instead of round mast cells are more likely pathological and immunochemical reactions demonstrating co-expression of KIT, tryptase and CD25 enhance the probability of the clonal nature of the MCs (Pardanani et al., 2011).

6.2 Immunophenotyping

Flow cytometry represents the gold standard to identify, enumerate and characterise human MCs. The co-expression of CD2 and/or CD25 with CD117 is a minor WHO criterion to diagnose SM (Valent et al, 2010).

6.3 Molecular studies

Routine diagnostics should include the screening for *kit*D816V. Highly sensitive techniques (e.g. PCR) are recommended as the detection of this specific somatic mutation has been recognized as a valid minor diagnostic criterion by WHO system. *kit*D816V may be found also in myeloid and, less frequently, in lymphoid cells associated within the focal MC lesions, particularly in ASM and MCL. On the contrary, the same finding is rare in SM-AHNMD and depends on the concomitant disorder. In fact, the occurrence of *kit*D816V decreases through CMML, MPN, AML and lymphoproliferative disorders respectively.

Identification of different genetic abnormalities is not requested, since it does not have clinical relevance either for diagnosis or for therapy. However, in case of blood eosinophilia clinicians must consider screening for FIP1L1-PDGFRA fusion protein, since it predicts a great response to imatinib. Other rearrangements involving PDGFRB may be appropriately investigated through conventional cytogenetic analysis, allowing to the diagnosis of the entity defined by WHO as myeloid or lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1 (WHO 2008).

6.4 Biochemistry

Serum tryptase dosage and levels monitoring are a useful tools for diagnosis (WHO 2008) and follow-up, as they correlate with MC load and activation and disease progression (Pardanani, 2011). Elevated levels of serum tryptase (>20ng/ml) are consistent with the diagnosis, representing the fourth validated minor criterion to be evaluated according WHO system. Very high levels (>200ng/ml) correlate with more aggressive subvariants, severe course and poor prognosis. Anyway, serum tryptase levels are not clinically significant in case of a concomitant myeloid disorder as a proportion of patients affected by AML, CML and MDS usually show high levels of tryptase without any detectable MC disorder.

Serial dosages are recommended after anaphylactic or anaphylactoid episodes to distinguish between a transient elevation and an abnormal persistent increase. In addition, stable levels during follow up are consistent with stable disease (Quintas-Cardama et al., Cancer 2006).

6.5 Further considerations

SM diagnosis requires the presence of the major criterion together with one minor criterion or three isolated minor criteria (Table 2). Subvariants may be classified depending on the percentage of MCs in BM and PB smears and the clinical presentation. More than 20% MCs in BM smear denotes MCL, in the leukemic or aleukemic (more or less than 10% MC in PB smear) subvariants. Less than 20% MCs in BM smear connotes ISM in asymptomatic patients, SSM or ASM in patients suffering from B- or C-findings respectively.

A cytomorphological grading system has been also proposed (Valent et al., 2001). At BM smear analysis MCs may be typical or atypical. Atypical MCs are classified either type I or type II according to the nuclear feature, oval or bi-/polylobed respectively. The proportion of atypical MCs together with metachromatic blasts define the grade of the disorder: high grade > 20%, low grade < 10%, intermediate grade 10-20% MCs (Valent et al., 2001).

There are some peculiar conditions to be considered. First, sometimes a focal MC infiltrate is found without any MC related symptom or sign and coexists with normal skin and bone marrow, denoting a finding of MC tumour. If the growth pattern is destructive and the cytopathologycal grade is high, the diagnosis is of MC sarcoma. Otherwise, a low grade morphology and a respected tissue architecture denotes benign mastocytomas.

Second, MC aggregates may be scattered. This finding is often consistent with reactive MC hyperplasia and occasionally may be observed during the diagnostic approach for non MC haematologic diseases. A WHO entity is SM-AHNMD, where a myelo-/lymphoproliferative disorder coexists with a clonal MC growth. Myeloid neoplasms usually share the peculiar pattern of diffuse cells proliferation admixed with malignant mast cells, on the contrary lymphoid clones are clearly distinct, with a well-cut separation between the two clonal components, and generally the demonstration of SM in the bone marrow is an occasional histological finding in patients with a previous diagnosis of LNH in a lymph node (Schipper et al, 2011). Thus, a diffuse MC infiltration in the fields of LNH always suggests a reactive MC hyperplasia (Valent, 2001).

Also AHNMD is recommended to be investigated for biomolecular markers, in order to get a complete characterization and evaluate the event of therapeutic targets.

With regard to MCL, histology must refer to bone marrow areas away from spicules and the proportion of blasts must be cytomorphologically evaluated on the bone marrow smear. Thus histological detection of even more than 20% of blasts is not enough to make a diagnosis of MCL (Valent, 2010).

7. Classification and prognosis

MC disorders are classified in two groups: cutaneous and systemic. The former seems to have a good prognosis (Koga et al., 2011), the latter shows a poor prognosis. More precisely, in case of systemic involvement the observed survival is shorter than general population. The median overall survival is about 5 years (Pardanani et al., 2009), with excess deaths occurring between the third and the fifth year after diagnosis (Pardanani et al., 2011). However, prognosis is heterogeneous among SM subgroups and correlates with the WHO system. In fact, stratifying by the WHO classes, the Kaplan-Meier analysis allows distinguishing between an indolent and a rapidly progressive course. In the first case there is not a significant difference between affected patients and matched controls. By contrast, in the so-called aggressive forms median survival ranges between 2 and 41 months, depending on the variant (Pardanani et al. 2009).

7.1 CM

Cutaneous mastocytosis (CM) is a disorder characterized by accumulation of clonal mast cells isolated in the skin. Dermatologists are used to differentiate some clinical variants based on macroscopic presentation. Maculopapular Cutaneous Mastocytosis denotes the most frequent form, often described as urticaria pigmentosa (UP). It is the typical manifestation of CM, with disseminated small plaques. Sometimes lesions limits appear undefined and skin may be extensively involved, leading to the clinical condition referred as Diffuse Cutaneous Mastocytosis. Children rather than adults may carry a single blistering lesion known as solitary Mastocytoma, that generally goes to spontaneous regression with time. Other rare variants occur almost exclusively during childhood, with aspects of infiltration (bullae, plaques or nodules) or hyperpigmentation (Telangiectasia Macularis Eruptiva Perstans or TMEP) with or without erythema (Amon et al., 2010).

7.2 SM

Systemic mastocytosis (SM) is a disorder classified among Myeloproliferative Neoplasms by WHO in 2008. Unlike CM, clinical SM variants have been universally accepted and included in the international classification system since 2001. In addition, in 2010 Pardanani et al. published results of an observational study on 342 patients, leading to a formal validation of the WHO classification. Thus, SM subgroups are clinical evidence-based entities, with clear definition, characteristic features, definite prognosis and tailored management indications, beyond the clinical usage.

7.2.1 ISM

Indolent systemic mastocytosis (ISM) is the most frequent variant in adults (46%). Patients are young (median age 49) and usually show urticarioid skin lesions, gastrointestinal

symptoms and MC mediator related syndrome. Almost all affected patients show bone marrow involvement, but no B- nor C- findings. Prognosis is very good, life expectancy is similar to general population, but quality of life is definitely poor. No progression risk has been observed, thus no cytoreduction has to be considered and only management of symptoms is needed (Valent et al., 2010).

7.2.2 SSM

Smoldering systemic mastocytosis is a recent subvariant of ISM. B-findings are always present, C-findings never. It is defined by high burden of MC (tryptase levels more than 200 ng/mL), enlarged spleen and/or lymph nodes, multilineage myelodysplasia or myeloid proliferation in the absence of diagnostic criteria for MDS, MPD, LMMC or AML. c-kit D816V should be detected in at least one non MC lineage. 14% of the patients with ISM are SSM affected individuals. They are older than typical ISM variant. Constitutional symptoms are almost constant. 23% patients are affected by a subvariant defined by isolated bone marrow involvement (BMM, Bone Marrow Mastocytosis), often associated with severe MC mediators related syndrome, including anaphylaxis. Prognosis is good, expected survival is even more than ten years, so symptomatic treatment may be enough. However, it must be stated that median survival is significantly inferior in SSM than in ISM (120 *versus* 301 months respectively). Moreover, there is an up to 18% risk of progression to aggressive subvariants as ASM, MCL and SM-AHNMD. Thus, patients must be strictly monitored, in order to switch to a cytoreductive therapeutic program if required. Cytoreduction is indicated even in absence of aggressive SM variants, if tryptase reach levels greater than 1000 ng/mL or symptoms show a worsening trend. Also, recurrent anaphylaxis unresponsive to immunotherapy or without specific IgE suggests that splenectomy or cytoreduction are needed for a better control of MC burden. This is in order to prevent a severe adverse event, as well as in myeloproliferative disorders hydroxyurea is administered to prevent deep venous thrombosis/pulmonary embolism (Valent et al., 2010).

7.2.3 ASM

Aggressive systemic mastocytosis is less frequent (12%) and occurs generally in adults. It is defined by the presence of at least one C-finding, associated with constitutional symptoms and visceromegaly, particularly of liver, spleen and lymph nodes. Prognosis is poor, with an overall median survival of 41 months. Leukemic transformation occurs in 5% of the patients. Affected patients must be always treated. Treatment depends on clinical course. According to time to progression, patients should be stratified in slowly and rapidly progressing. In the first case the natural history is similar to SSM. In the second case the disease is difficult to control and its behavior is similar to MCL: early blasts may increase, satisfying diagnostic criteria for leukemia. In addition, in some *kit*D816V patients the same mutation may become undetectable with progression. This is somewhat similar to disease progression in acute myeloid leukemia. In slowly progressing ASM milder therapeutic options may be considered, while rapidly progressing ASM always requires heavy chemotherapeutic approaches, according to the rapid multiorgan failure occurring in such patients. Tryptase levels usually increase every day, reflecting the poor clinical course (Valent et al., 2010).

7.2.4 MCL

Mast cell leukemia is the most rare variant, virtually limited to adulthood. In Pardanani's analysis it occurred in 1% of the patients. Median survival is 2 months. Usually MC blasts infiltrate extensively BM, with a range of 60-90%. High intensity chemiotherapy has to be administered, but patients generally result refractory (Valent et al., 2010).

7.2.5 SM-AHNMD

Systemic mastocytosis with an associated non-mast cell lineage disease (SM-AHNMD) is an heterogeneous and intriguing group of haematological malignancies, in which clonal proliferation of mast cells is associated with a second and, in rare cases, a third (Kim, 2010) clonal blood disorder that is not mast cell derived (Horny, 2008; Pardanani, 2010).

SM-AHNMD accounts for 40% of all cases of SM. About 89% of the patients show concomitant myeloid neoplasms: MPN (45%), CMML (29%) and MDS (23%). Among MPN, there is a high prevalence FIP1L1-PDGFRA related HES. In the remaining cases (21%) SM is associated with lymphoma, myeloma, CLL or amyloidosis. Prognosis is poor, with a median overall survival of 31 months in patients with MPN compared to 15, 13 and 11 months in patients with CMML, MDS and AML respectively. Transformation in MC leukemia occurs more frequently in SM-MDS (29%) (Pardanani, 2010).

WHO diagnostic criteria for SM remain valid, except for elevated serum tryptase levels, as they could be very high also in patients affected by AML, MDS and MPS without MC disorders.

The pathogenesis is not clear: in SM associated with myeloid malignancies mast cells and myeloid cells seem to originate from the same clone (Pardanani, 2009; Garcia-Montero 2006); according to this, in SM-LMMC *kit*D816V has been shown in both components. However, in SM-AML the leukemic counterpart generally lacks of *kit* mutation, suggesting a different origin for the two clones. At the opposite, in SM associated with lymphoid proliferative disease a distinct clonal origin has been demonstrated at least in some cases (Kim, 2007). Moreover, it has been hypothesized that malignant mast cells may support and promote the growth of the associated lymphoid disorder (Merluzzi, 2010).

Lymphoid proliferation as AHNMD component has been rarely observed. More precisely, B cell lymphomas associated with SM usually are low grade. To the best of our knowledge, the occurrence of SM and synchronous high grade lymphoma has been reported so far only by Schipper *et al.*, which described a case of SM associated with diffuse large B cell lymphoma (SM-DLBCL) (Schipper, 2011). Interestingly, we observed another patient, which is unlike to represent an accidental case. In our patient the diagnosis of mast cell disease was made concurrently with that of lymphoma, but we cannot state whether both the malignancies were synchronous or occurred at different time. In addition, the morphological evaluation of the bone marrow revealed a peculiar pattern of diffuse large B-cells proliferation admixed with malignant mast cells (fig. 1). Compared to what we observed, in Schipper *et al.* reported a sharp separation between the two clonal components, with the histological demonstration of SM in the bone marrow and DLBCL in a lymph node at different time. According to typical morphological findings, mastocytes appeared either solitary or clustered in a separate contest from malignant B cell. By contrast, our case of SM

with concurrent large cell lymphoma seems to be unusual because of the great overlap between the two clonal populations of large B lymphocytes and mastocytes. Indeed, in our case, the lymphoid component resulted histologically atypical and new, as diffusely infiltrating within the malignant proliferating mast cells.

As expected, our case was positive for the D816V mutation in exon 17 like the vast majority of SM. Unfortunately, we do not know whether this mutation occurred also in clonal B cells, since they were not sorted from bone marrow specimen for DNA extraction. Therefore it is not possible to rule out any hypothesis about the pathogenesis of such an association.

On the therapeutical side, in SM-AHNMD it is recommended to treat SM as pure SM and AHNMD as pure AHNMD (Valent, 2003; Valent 2010). Accordingly, it is important a complete molecular characterization of both the disorders (Valent et al., 2010).

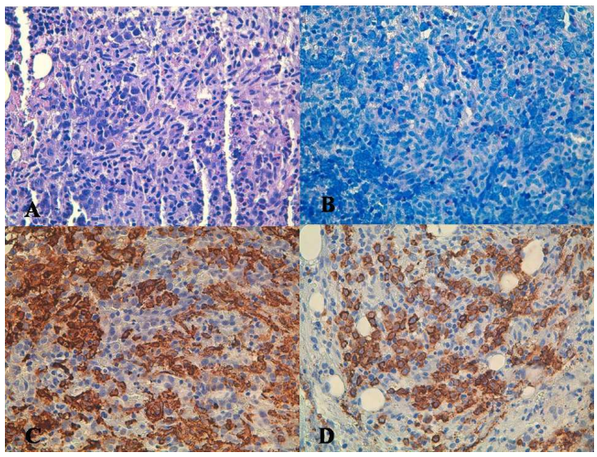

Fig. 1. **A-B** Bone marrow sections stained with haematoxylin and eosin (A) and Giemsa (B), 40x. **C-D** Immunohistochemistry on bone marrow sections with antibodies against tryptase to detect mast cells (C) and antibodies against CD79a to detect B lymphocytes (D), 40x. A great overlap between lymphocytes and mast cells lesions is observed, resulting in a diffuse proliferation of B-cells admixed with mast cells.

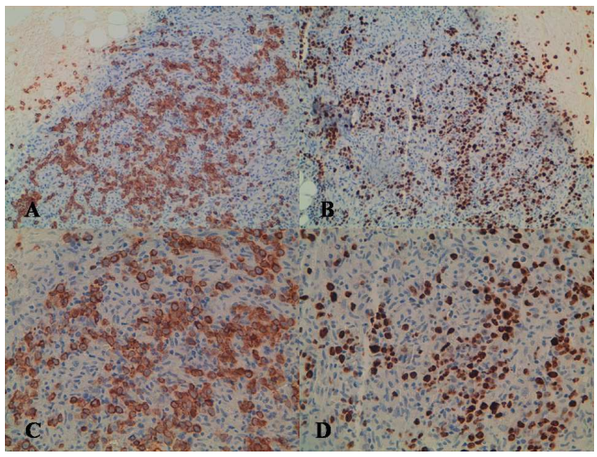

Fig. 2. Immunoperoxidase staining detecting large B lymphocytes, positive for CD79a (A, 20x; C, 40x) and exhibiting nuclear Ki-67 reactivity (B, 20x; D, 40x).

8. Treatment

To date Mastocytosis is incurable, thus clinicians should personalize treatment for each patients in order to reduce symptoms and complications (Molderings et al., 2011).

Exposition to triggers (animal venoms, extreme temperatures, mechanical irritation, alcohol, medications, etc.) should be avoided, but often no clear trigger may be identified, therefore active therapy must be considered (Valent et al., 2010).

Treatment in Mastocytosis may be symptomatic or cytoreductive. Symptoms could be managed with both non specific and tailored drugs. Cytoreduction should be considered if symptoms are refractory to basic therapy, rapidly worsening or life-threatening, or in the presence of complications (C-finding).

In summary, in CM and ISM therapeutic approach may be just symptomatic. In advanced forms of SM schedules must be personalized, depending on progression risk. In SSM and slowly progressing ASM IFNα and 2CdA may be appropriated. In rapidly progressing ASM, MCL and SM-AHNMD high intensity chemotherapy and allogeneic bone marrow transplantation represent the current therapeutic approach.

8.1 Symptomatic treatment

The so-called basic therapy consists in antihistaminic medications and MC membrane stabilizers. Usually relief occurs many days or weeks after the introduction of a new drug, therefore the persistence of symptoms does not justify an earlier shift to others therapeutic schedules. As each new drug can trigger a hypersensitive reaction, one drug at a time should be introduced (Quintas-Cardama et al., 2006).

When first line fails, immunomodulating agents may be considered, such as prednisone, cyclosporine, methotrexate, and azathioprine (Quintas-Cardama et al., 2006). IFNα might be combined with prednisone, but it generally represents the first line agent for cytoreduction in ASM.

Omalizumab, a humanized murine antibody targeted to IgE, is now available as an experimental option (Quintas-Cardama et al., 2006). It seems to control MC activation syndrome also in patients resistant to conventional fist line therapy. Recently, Molderings *et al.*, reporting their experience in four patients, showed its good risk-benefit profile. Two patients benefit a rapid remission, the third had a progressive improvement, only the fourth suffered from a worsening in MC-mediators syndrome (Molderings et al., 2011). Such isolated experience suggests that omalizumab could represent a new promising option.

Epinephrine on demand remains the gold standard during life-threatening anaphylactic or anaphylactoid episodes.

8.2 Cytoreductive treatment

Cytoreduction consists in single (IFNα and 2CdA) or multidrug (Fludarabine, Cytarabine, Mitoxantrone) approaches.

Usually IFNα represents the first line of treatment in slowly progressing variants. Cladribine is the second line, sometimes associated with novel agents (e.g. Imatinib).

In rapidly progressing variants Mito FLAG must be considered, with or without a previous treatment with 2CdA, in order to perform HSCT as soon as possible. In these cases BMT represents the only effective strategy to cure mastocytosis. If patient is ineligible, experimental trials remain the next option. Palliation is the last choice.

8.3 Novel agents

8.3.1 Tyrosine kinase inhibitors

Tyrosine kinase inhibitors have been under investigation since several years, particularly imatinib, dasatinib and midostaurin. Some clinical trials have been performed and many reports have been described. Target therapy has been observed to reduce both MC proliferation and infiltration, and sometimes to normalize BM histology. However, mediators related syndrome improved or got complete remission just in isolated reports.

8.3.1.1 Imatinib

Among the TK inhibitors, Imatinib is the most studied molecule. Low doses of Imatinib can inhibit wild type KIT. However, since D816V alters the kinase domain conformation, inhibiting steric interaction between the drug and the TK domain, efficacy of imatinib on *kit*D816V SM is still controversial. A phase II study conducted by Vega-Ruiz *et al.*, showed that imatinib has no significant clinical activity in patients carrying the D816V mutation. By contrast, in a different phase II trial Droogendij *et al.* observed an apparent remission in 11 *kit*D816V positive SMs (Droogendij et al., 2006). Some authors underline that concomitant use of prednisone may perhaps justify their results (Vega-Ruiz et al., 2009). Nevertheless, in some of these patients the observed reduction of symptoms was only transient. The case of SM with wild type kit or other sporadic mutations is different, since the conformational structure of the TK domain does not seem to be impaired. Moreover, these patients usually show an objective response, consisting in reduction of seric tryptase levels and bone marrow MC percentage (Vega-Ruiz, 2009). In summary, on one hand available data seem to suggest that imatinib is active against sporadic *kit* mutations, on the other hand the activity on *kit*D816V is not well established yet. Accordingly, in 2006 FDA approved the use of imatinib in adults with ASM without the D816V mutation.

Imatinib is also a potent competitive inhibitor of PDGFR and has been demonstrated to be either active or effective in FIP1L1/PDGFRA related HES. Consequently, SM patients with blood eosinophilia are recommended to be screened for this fusion protein. However, cardiogenic shock has been reported in patients with HES after the start of therapy with imatinib. Such an adverse event could be easily avoided by concomitant administration of corticosteroids during the first one or two weeks of treatment, mostly in case of echocardiographic abnormalities or high serum troponin levels at baseline.

Nilotinib is another TK inhibitor that has shown an in vitro activity against *kit* similar to imatinib, but no clinical experiences have been reported yet (Quintas-Cardama et al., Cancer 2006).

8.3.1.2 Dasatinib

Dasatinib is a dual SRC/ABL kinase inhibitor that is more potent than imatinib also against KIT. Preliminary data from either preclinical or clinical studies seemed to suggest a key role

in SM, independently on mutational state of *kit* (Shah et al., 2006). However, data are too limited to draw any conclusion and the efficacy of dasatinib still remains controversial. Some authors described long lasting histological responses (Verstovsek et al, 2007) and both groups of patients with wild type and *kit*D816V improved in symptoms and quality of life. Wild type kit and *kit*D816V improved in symptoms and quality of life. It has been proposed a weekly dose escalation from 20 mg QD up to 100 mg QD during the first month of therapy (Rondoni et al., 2007). The proportion of responses may increase administering a dose of 120 mg QD in case of suboptimal or no response after three months of therapy. Based on this, the GIMEMA group is conducting an Italian multicenter phase II study in which subjects with SM are treating with a continuous regimen of dasatinib at a starting dose of 20 mg once daily. The primary endpoint is the evaluation of clinical response in terms of proportion of subjects experiencing a regression in B/C findings and mediator-related symptoms. The secondary endpoints include duration of response, progression free survival and time to response (GIMEMA, 2008).

8.3.1.3 Midostaurin

Midostaurin is a multi-kinase inhibitor with a demonstrated *in vitro* activity against KIT, but there are only sporadic observations of effectiveness *in vivo*. Gotlib *et al.* reported a case of MCL associated with MDS/MPD who received a transient benefit from administration of midostaurin (Gotlib et al., 2005). More interestingly, midostaurin seems to exhibit a synergic activity with nilotinib (Quintas-Cardama et al., 2006), suggesting a more attracting role of these small molecules, as useful tools to combine in multidrug strategies in order to avoid the resistance to single agent approaches.

8.3.1.4 Other TK inhibitors

Several more small molecules have been identified as potential agents against MC diseases: e.g. ATP analogs (OSI-930, MLN518, PD180970, PD180970, PD173955, AP23464 and AP23848), indolinone-based products (SU11652, SU11654 and SU11655) or quinoxaline derivatives (AGL2043). To date there are no data on clinical tolerability and efficacy yet (Quintas-Cardama et al., 2006).

8.3.2 Monoclonal antibodies

Monoclonal antibodies might play a crucial role in the future. The antiCD25 antibody conjugated with the pseudomonas exotoxin-A generates a potent immunotoxin with proapoptotic activity, associated with a significant reduction in the number of MCs (Valent et al., 2004). The effect is similar to that reported by other authors after in vitro exposure to Ontak, also known as denileukin diftitox, consisting in recombination of CD25 ligand and diphtheria toxin. Based on data on Ontak preclinical activity as well as clinical effectiveness in cutaneous T-cell lymphoma, there are ongoing phase II trials to test Ontak also in SM patients.

Other monoclonal antibodies are under investigation in Mastocytosis: the antiCD25 Daclizumab and Basiliximab, the antiCD33 Gemtuzumab with the toxic compound calicheamicin and the antiCD87 and antiCD45 antibodies, conjugated to $_{131}$I radioisotope or diphtheria toxin (Quintas-Cardama et al., Cancer 2006).

8.3.3 mTor inhibitors

mTor inhibitors have been tested since it has been demonstrated, both *in vitro* and *in vivo,* that the mTor pathway is active in SM and contributes to MC survival, growing and proliferation (Kim et al, 2008). Preclinical observations suggest that mTor inhibitors act against clonal MCs. Particularly, rapamycin inhibits selectively the mTor pathway, either in fresh MCs collected from KITD816V patients or in KITD816 cell lines. Hence, everolimus was tested in a clinical trial, but it did not show any apparent significant effectiveness. Perhaps some more experiences must be collected to determine whether mTor inhibitors may play any role in SM (Quintas-Cardama et al., 2006).

8.3.4 Future perspectives in SM therapy

Apoptosis still remains an attractive way to be investigated. Several drugs have shown some activity on Bcl-2 family members, as bortezomib, obatoclax and geldanamycin. The first one acts promoting Bim expression, the second one is known as BH3-mimetic (Aichberger et al., 2009), the last one inhibits the hsp90-bcl2 complex (Quintas-Cardama et al., 2006).

9. Conclusion

SM is a rare disorder, but its prevalence might be underestimated. Afar from drafting a complete and exhaustive review on mastocytosis, the aim of this chapter was to remark the relevance of SM. Clinical suspicion is really important and multimodality approaches must be considered to get the right diagnosis. Then, treatment must be personalized for each patient, accordingly with a careful and complete characterization of the disease.

Prospectively, two major challenges still have to be faced in SM research: first, the molecular and cellular pathogenesis; second, the definition of new strategies of treatment. About the former goal, we do believe that reporting new cases may be of great usefulness and is needed to better understand the nature of the disorder. In order to this, the case we described may perhaps represent a paradigmatic example. Referring to treatment, several novel agents are under investigation. However, preliminary clinical data seem to suggest that the use of a single drug may be insufficient. That means that a multidrug strategy is needed within a multitarget approach.

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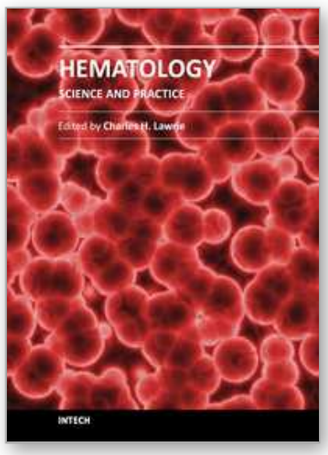

Hematology - Science and Practice

Edited by Dr. Charles Lawrie

ISBN 978-953-51-0174-1
Hard cover, 596 pages
Publisher InTech
Published online 02, March, 2012
Published in print edition March, 2012

Hematology encompasses the physiology and pathology of blood and of the blood-forming organs. In common with other areas of medicine, the pace of change in hematology has been breathtaking over recent years. There are now many treatment options available to the modern hematologist and, happily, a greatly improved outlook for the vast majority of patients with blood disorders and malignancies. Improvements in the clinic reflect, and in many respects are driven by, advances in our scientific understanding of hematological processes under both normal and disease conditions. Hematology - Science and Practice consists of a selection of essays which aim to inform both specialist and non-specialist readers about some of the latest advances in hematology, in both laboratory and clinic.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Antonia Rotolo, Ubaldo Familiari, Paolo Nicoli, Daniela Cilloni, Giuseppe Saglio and Angelo Guerrasio (2012). Systemic Mastocytosis: An Intriguing Disorder, Hematology - Science and Practice, Dr. Charles Lawrie (Ed.), ISBN: 978-953-51-0174-1, InTech, Available from: http://www.intechopen.com/books/hematology-science-and-practice/mast-cell-disease

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