STATE-OF-THE-SCIENCE IN MAST CELL DISORDERS *

Hans-Peter Horny, M.D.

Institute of Pathology, Ansbach, Germany

*This lecture is mainly based on an article recently published in PATHOBIOLOGY (Vol. 74; pp 121): "MASTOCYTOSIS: STATE OF THE ART"

by H-P Horny, K Sotlar and P Valent

SUMMARY

Mastocytosis is a neoplastic disease involving mast cells and their CD34+ progenitors. Basically, mastocytosis should be separated from reactive states with mast cell (MC) hyperplasia. Symptoms in mastocytosis and mast cell hyperplasia are caused by inappropriate release of biological mediators from MC. A WHO consensus classification for mastocytosis exists, which is widely accepted and includes 3 major subvariants. 1. Cutaneous mastocytosis (CM), a benign disease in
which MC infiltration is confined to the skin, is preferentially seen in young children and exhibits a marked tendency to regress spontaneously. 2. Systemic mastocytosis (SM) which is commonly diagnosed in adults and includes four major categories: i. indolent SM/ISM (the most common form involving mainly skin and bone marrow); ii. a unique subcategory termed SM with an associated non-mast cell clonal hematological disease/SM-AHNMD: iii. aggressive SM/ASM usually presenting without skin lesions; and iv. MC leukemia/MCL, probably representing the rarest variant of human leukemias, and 3. The extremely rare localized extracutaneous MC neoplasms, either presenting as malignancy (MC sarcoma) or as benign tumor termed extracutaneous mastocytoma. Diagnostic criteria for mastocytosis include one major criterion (multifocal compact tissue infiltration by MC) and 4 minor criteria: 1. Prominent spindling of MC, 2. Atypical immunophenotype of MC with coexpression of CD2 and/or CD25 (antigens which have not been found to be expressed on normal/reactive MC), 3. Activating (usually somatic) point mutations of the c-kit proto-oncogene commonly involving exon 17, with the imatinib-resistant type D816V being most frequent, and 4. Persistently elevated serum tryptase level (>20 ng/ml). To establish the diagnosis of SM, at least one major and one minor criteria, or at least three minor criteria have to be fulfilled. The natural clinical course of mastocytosis is variable. Most patients, in particular those with CM and ISM, remain in an indolent stage over many years or even decades, while others, in particular those with ASM, SM-AHNMD, or MCL show a progressive course, usually with a fatal outcome. Mastocytosis may easily be confused with the rare and sometimes ill-defined myelomastocytic overlap
syndromes unless diagnostic criteria for mastocytosis are not strictly applied. The prototypic disease amongst "myelomastocytic overlaps" is the exceedingly rare myelomastocytic leukemia which is an acute myeloid leukemia with prominent signs of differentiation towards the mast cell lineage but not fulfilling diagnostic criteria for mastocytosis, in particular compact mast cell infiltrates are lacking.

DEFINITION
Mastocytosis is a very heterogeneous disease of bone marrow origin and characterized by abnormal growth and/or accumulation of clonal MC in one or more organs. In SM, at least one extracutaneous organ is involved. It cannot be overemphasized that mastocytosis basically must be diagnosed morphologically, by investigating biopsy specimens of skin (cutaneous mastocytosis) and/or bone marrow (to reveal or exclude SM). Cytomorphological diagnosis of SM in bone marrow smears is also possible in a minority of cases but is inevitable in all cases of MC leukemia.

MORPHOLOGICAL DIAGNOSIS
The diagnosis of mastocytosis can be established when multifocal compact MC infiltrates consisting of spindle-shaped MC, are detected in a given tissue. MC often show cytomorphological atypia with a reduced content of metachromatic granules. Usually, the compact MC infiltrates also contain varying amounts of intermingled eosinophils and lymphocytes. Compact lymphocytic infiltrates in the immediate vicinity of MC aggregates are commonly found in ISM and have been shown to be
reactive in nature in almost all cases. When compact infiltrates consist exclusively of round mature-appearing MC, other minor SM criteria must be fulfilled to achieve the definitive diagnosis of mastocytosis. In very rare instances there is a focal and/or diffuse collagen fibrosis of the bone marrow containing an abundance of loosely scattered spindle-shaped MC which lack both expression of CD25 and an activating point mutation of c-kit. This condition therefore must be regarded as reactive thus being an important mimicker of mastocytosis and might be tentatively be termed "fibromastocytic lesion".

In all cases of suspected mastocytosis a limited panel of antibodies against at least three antigens should be applied: i. anti-tryptase which is highly specific and sensitive (with the exception of both neoplastic tryptase+ myeloblasts and basophils), and therefore allows screening for both the number of loosely scattered MC and immediate detection of even small compact MC infiltrates. In extramedullary tissues (e.g. mucosa of the gastrointestinal tract), non-specific background-staining of anti-tryptase may easily lead to overestimation of MC numbers and misinterpretation as mastocytosis; ii. antibodies against KIT (CD117) should therefore also be applied to reconfirm the presence of MC in such cases. Although anti-KIT antibodies are highly non-specific because KIT is also expressed on hemopoietic stem cell, melanocytes, germ cells, and CAJAL cells, they have been found to be of superior sensitivity allowing verification of tryptase+ cells as MC without significant background-staining. iii. antibodies against CD25 which is also a very non-specific antigen which is expressed on activated T cells but also on
certain B-cell malignancies like hairy cell leukemia, should also be applied in all cases of suspected SM because neoplastic MC coexpress CD25 whereas normal and reactive MC are CD25-negative. CD25 immunohistochemistry is of particular diagnostic value in the bone marrow where CD25+ lymphatic cells are found only in very small number or virtually are absent and the CD25-reactivity of megakaryocytes can be easily used as internal control. The diagnostic value of anti-CD2 antibodies is limited because of a lower sensitivity for detection of atypical MC and the presence of CD2+ T cells in almost all tissue infiltrates of mastocytosis.

WHO CLASSIFICATION OF MASTOCYTOSIS

Based on significant advances in mastocytosis research, an updated consensus classification for mastocytosis has been proposed in 2001. This classification system was fully adopted by the WHO and has now become widely accepted because it provides both criteria to discriminate between SM and MC hyperplasia and between SM and CM. Moreover, it even allows separation of SM from related myeloid disorders with signs of MC differentiation. Three major subgroups of the disease were defined: i. Cutaneous mastocytosis (CM); ii. Systemic mastocytosis (SM) including ISM, ASM, SM-AHNMD, and MCL; and iii. extracutaneous mastocytoma.

CM is an indolent disease and, by definition, can only be diagnosed when SM is excluded by appropriate investigations. Most patients are children, whereas only a minority of adult patients have pure cutaneous mastocytosis. In adults, a trephine
biopsy specimen including immunohistochemical and molecular analyses must always be investigated to assess or exclude SM. The most common subvariant of CM presents as disseminated macular or maculopapular rash, and has been descriptively termed urticaria pimentosa. Diffuse cutaneous mastocytosis is much less frequent and usually seen only in very young children. The solitary or localized mastocytoma (of the skin) is also rare, and has a totally benign clinical course. Most MC tumors of the skin show a benign course or even resolve spontaneously at puberty. However, more recently, a unique case of a primary cutaneous mast cell sarcoma (with secondary infiltration of the bone marrow) has been detected (own unpublished observation).

ISM is the most common variant of SM comprising about two thirds of all cases. Usually, ISM involves both skin and bone marrow. The bone marrow infiltration may be difficult to detect in some cases and then can only be diagnosed when appropriate immunohistochemical stains including an anti-CD25 antibody and molecular (D816V) studies, are performed. ISM shows a prolonged clinical course in almost all patients with survival times of two decades and more. However, in a small group of patients, transformation into another disease category, such as aggressive SM, or SM with an associated hematological malignancy (SM-AHNMD) occur.

ASM is by far much less common than ISM comprising only about 5% of all SM patients. Clinically, ASM may present with hepatosplenomegaly and/or generalized
lymphadenopathy, but usually without skin lesions. ASM is often revealed only by histological examination, but not suspected by the clinician. ASM is characterized by progressive MC infiltration of various organs with clinically significant impairment of their function including severe cytopenia, malabsorption, bone fractures, and signs of hepatopathy with loss of liver function. Such findings are termed C-findings. MC infiltration leading to marked organomegaly should not be regarded as a C-finding unless accompanied by signs of impaired organ function. Significant organomegaly is also found in patients with an indolent or a smouldering course, and then represent B-findings. A rare subvariant of ASM with prominent eosinophilia of blood and tissues and generalized lymphadenopathy (clinically mimicking malignant lymphoma) has been described as lymphadenopathic mastocytosis with eosinophilia.

Using data from a reference center for hematopathology, in about one fourth to one third of the patients with SM, an AHNMD is diagnosed thus making SM-AHNMD the second most frequent subtype of SM. Regarding patients from a dermatological clinic, however, the incidence of indolent SM would be significantly higher. To establish a diagnosis of SM-AHNMD WHO criteria for both SM and the AHNMD must be fulfilled. SM-AHNMD is a unique disorder amongst hematological neoplasms in that it combines two completely different histologies and disease-categories into one defined entity of SM. The vast majority (about 80 to 90%) of "AHNMDs" are myeloid disorders including almost all defined disease entities: myelodysplastic syndromes (MDS), myelodysplastic/myeloproliferative syndromes
(MDS/MPS), myeloproliferative syndromes (MPS), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML). Most common amongst myeloid malignancies are disorders of the MDS/MPS group, usually termed chronic myelomonocytic leukemia (CMML). Of special importance is the clear-cut separation of chronic eosinophilic leukemia (CEL) containing loosely scattered CD25+ abnormal MC but not fulfilling the criteria of SM, and SM-CEL with multifocal compact diagnostic mast cell infiltrates and criteria for both SM and CEL. Associated lymphatic malignancies comprise only about 10 to 20% of all "AHNMDs" with plasma cell myelomas being most frequent within this group. Rare cases of acute and chronic lymphatic leukemia as well as hairy cell leukemia have also been reported. To identify CD25-expressing atypical mast cells in hairy cell leukemia may be challenging because the neoplastic B cells usually strongly express CD25. Clinical picture and prognosis of SM-AHNMD patients are mainly determined by the "AHNMD". Rarely, infiltrates of SM have been detected only after successful chemotherapy of an AML. The compact blast cell infiltrates of AML in such cases obscure the mast cell infiltrates of SM but CD25-expressing loosely scattered mast cells sometimes forming distorted small compact infiltrates and the activating point mutation D816V are detected retrospectively. This condition is tentatively termed "occult mastocytosis". SM-AHNMD may present with three histomorphological pictures: i. extremely hypercellular marrow with multifocal infiltrates of SM and the diffuse-compact infiltrates of "AHNMD"; ii. normo- or even hypocellular marrow usually seen in patients with plasma cell myeloma or chronic lymphatic leukemia both exhibiting a multifocal but minor infiltration with widely intact hemopoiesis; and iii. "occult"
mastocytosis which is revealed only after chemotherapy because diffuse-compact blast cell infiltrates obscured SM.

MCL is extraordinarily rare and characterized by leukemic infiltration of various organs by atypical MC. MCL is the only subvariant of mastocytosis diagnosed cytologically in smear preparations: MC numbers in bone marrow smears must exceed 20% of all nucleated cells. The cut-off level of 20% for bone marrow MC only refers to the cytological assessment in smears, but not to the percentage of MC in the histological analysis. In most cases with MCL, circulating MC are found. In typical MCL, MC make up more than 10% of blood cells, while aleukemic variants of MCL are rare. The prognosis of patients with MCL is grave. The most important differential diagnosis to be considered is myelomastocytic leukemia.

Localized MC proliferations are also extremely rare and include both the extracutaneous mastocytoma (of the lung) and the "true" MC sarcoma of which less than five published cases have been published. Since cytomorphological atypia of MC sarcoma is usually very high (according to a grade 3 sarcoma), it is impossible to achieve the correct diagnosis without appropriate immunohistochemical stainings. It is noteworthy that most reported MC sarcomas occurred in tissues not commonly involved by SM (larynx, colon, meningeal site). All cases showed rapid progression and generalization with a terminal phase resembling ("secondary") MC leukemia.
RARE SUBVARIANTS OF MASTOCYTOSIS AND DIFFERENTIAL DIAGNOSES WITH SPECIAL EMPHASIS ON MYELOMASTOCYTIC OVERLAP SYNDROMES

MYELOMASTOCYTIC OVERLAP SYNDROMES:

By definition, myelomastocytic overlap syndromes include a variety of myeloid malignancies, some of them still being ill-defined, with prominent signs of differentiation towards the mast cell lineage but not fulfilling criteria for mastocytosis. It is of importance to note that myelomastocytic overlap syndromes cannot be detected unless immunohistochemical markers related to mast cell antigens are applied, namely tryptase, chymase, CD117 (KIT), and, of superior value to assess an atypical immunophenotype of mast cells, CD25. The myelomastocytic overlap can be detected at an immunohistochemical and/or a molecular level. Recently, it could be shown that clonal mast cells expressing the typical activating point mutation D816V for KIT also carry the activating point mutation V617F for JAK-2. The prototypic disorder amongst these rare neoplasms is the myelomastocytic leukemia. Other diseases that may be placed under the heading of a myelomastocytic overlap include: tryptase+ AML, myeloid neoplasms with D816V (KIT), myeloid neoplasms with CD25+ mast cells, FIP1L1-PDGFR-alpha+ eosinophilic leukemia, SM-AHNMD, and "occult" mastocytosis. In our own experience all cases of D816V+ myeloid malignancies (usually AML) proved to be occult mastocytosis (SM-AHNMD) when appropriate immunohistochemical analyses were performed.
The following subcategories of disorders are described in more detail and either represent rare subvariants of mastocytosis not yet included in the WHO classification system (1.-4.) or are disorders closely related and therefore often confused with "true" mastocytosis usually within the spectrum of myelomastocytic overlap syndromes (5.-8.):

1. **SMOULDERING MASTOCYTOSIS (SSM)**: SSM is a defined subcategory of ISM that clinically assumes an intermediate position between ISM and ASM, with a high degree of tissue infiltration including the bone marrow, a high serum tryptase level (>200 ng/ml), and organomegaly, e.g. lymphadenopathy or splenomegaly (B-Findings). By definition, C-findings are not detected in SSM.

2. **WELL-DIFFERENTIATED SYSTEMIC MASTOCYTOSIS (WDSM)**: WDSM is another subcategory of ISM. Compact tissue infiltrates of mastocytosis consisting exclusively of round mature-appearing hypergranulated MC belong to the spectrum of the so-called tryptase-positive round cell infiltrate (of the bone marrow), preliminary termed TROCI-bm. TROCI-bm may present with both localized or diffuse infiltration patterns, and WDSM is included within the differential diagnostic spectrum of localized TROCI-bm. Morphologically, WDSM can be separated from "common" SM by the absence of both CD25 expression on MC and the typical exon 17 point mutations. The only published case of WDSM reported on a unique point mutation of c-kit within the transmembranous domain (F522P) which did not lead to imatinib-resistence seen in patients carrying the typical D816V mutation. In addition, a unique case of WDSM was recognized within the spectrum of SM-
AHNMD presenting with an associated monoblastic leukemia (own unpublished observation).

3. MONOCLONAL MAST CELL ACTIVATION SYNDROME: This disorder comprises a group of patients clinically presenting with recurrent episodes of anaphylaxis, no skin lesions, and only one or two minor diagnostic criteria for SM but lacking the major criterion of a compact infiltrate. In this subdiagnostic condition, MC may display cytomorphological atypia, aberrant expression of CD25 or the presence of D816V but all three features (which would be sufficient for the diagnosis of SM) are not detectable. A follow-up of such patients may reveal SM, whereas progression into high grade SM seems unlikely and has not described so far.

4. OCCULT MASTOCYTOSIS: Occult mastocytosis presents in two different variants. On the one hand, it can be a rare occurrence within the spectrum of SM-AHNMD and is detected after eradication of the "AHNMD" by adequate chemotherapy and then, retrospectively, may be also found in the initial biopsy specimens where it was obscured by the widespread neoplastic non-MC clone. This can only be achieved after appropriate immunohistochemical and molecular analysis. Despite complete hematological remission infiltrates of SM usually persist or even progress signaling that still one part of the neoplastic process is still present. On the other hand, it was possible to analyse tissues which had been removed years before the diagnosis of SM was established. Although there was no morphological evidence of a tissue infiltrate of SM, molecular analysis yielded the
presence of an activating c-kit mutation up to 10 years before morphological manifestation of SM.

5. **MYELOMASTOCYTIC LEUKEMIA (MML):** MML represents a rare advanced myeloid neoplasm (usually a myelodysplastic syndrome of RAEB type or even AML by WHO criteria) exhibiting more than 10% metachromatic immature cells (often metachromatic blasts) in a bone marrow or blood smear but not fulfilling criteria for diagnosis of SM. Probably, most cases of MML are cytomorphologically misdiagnosed as acute basophilic leukemia without adequate histopathological and immunophenotypical analysis of a bone marrow trephine specimen. Histologically, there is an abundance of tryptase (or rarely, chymase) expressing cells but there are no compact MC infiltrates, there is no aberrant phenotype of MC with coexpression of CD25 and there is no activating point mutation of c-kit. In most cases of MML a significant increase in CD34+ progenitor/blast cells is detected. Tentatively, MML is best categorized as a subgroup within the MDS/MPS overlap syndromes.

6. **TRYPTASE+ ACUTE MYELOID LEUKEMIA:** Tryptase+ AML is also a rare finding and characterized by strong expression of tryptase and less frequently also of KIT (CD117) by myeloblasts in an otherwise morphologically unremarkable AML (often subtypes FAB M1, M2, or M4-eo). Tryptase+ AML lacks criteria for diagnosis of SM. The separation of tryptase+ AML from MML is possible by counting metachromatic cells in blood and/or bone marrow smears: presence of more than 10% metachromatic cells with signs of MC differentiation argues for the diagnosis of MML.
7. **EOSINOPHILIC LEUKEMIA (EL):** Mutated (FIP1L1-PDGFR-alpha) EL could be shown to exhibit a significant increase in atypical spindle-shaped CD25-positive mast cells in more than 50% of the cases. Initially, this finding led to an erroneous interpretation of EL being a subtype of mastocytosis. In a minority of cases with EL mast cells form small non-diagnostic aggregates not fulfilling the major criterion for diagnosis of tissue infiltration by mastocytosis. However, a few EL cases show features indistinguishable from mastocytosis with formation of compact dense infiltrates consisting of CD25+ mast cells allowing a diagnosis of SM-AHNMD (SM-EL) to be established. Interestingly, such cases lack the point mutation D816V (KIT), a finding clearly contrasting to all other subtypes of SM-AHNMD that carry D816V in almost all cases.

8. **BASOPHILIC LEUKEMIA (BAL):** BAL is an extremely rare subvariant of myeloid leukemias and until now could not be diagnosed histologically in bone marrow trephine biopsy specimens. BAL also belongs to the spectrum of TROCI (diffuse type) since it could be shown that neoplastic basophils do express immunohistochemically detectable amounts of tryptase. Definitive diagnosis of BAL is only possible when basophil-related antibodies like 2D7 and/or BB1 are used for immunohistochemical analysis of a trephine biopsy specimen. In contrast to MC granules, metachromatic granules of basophils are water-soluble and therefore cannot be detected in routinely processed formalin-fixed tissues. In most published cases of BAL, the underlying disease was classified as Ph+ CML. Recently, a unique case of secondary basophilic leukemia in a patient with Ph+ CML with associated SM was diagnosed retrospectively in an analysis of almost 200 cases of
CML using antibodies against 2D7 and BB1, respectively (own unpublished observation).
SELECTED REFERENCES


Table 1

**WHO criteria for Diagnosis of Systemic Mastocytosis**

<table>
<thead>
<tr>
<th><strong>Major:</strong>*</th>
<th>Multifocal compact infiltrates of MCs in bone marrow or other extracutaneous organ(s) (&gt;15 MCs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minor:</strong>*</td>
<td>a. MCs in bone marrow or other extracutaneous organ(s) show an abnormal spindle-shape morphology (&gt;25%)</td>
</tr>
<tr>
<td></td>
<td>b. c-kit mutation D816V in extracutaneous organ(s)**</td>
</tr>
<tr>
<td></td>
<td>c. MCs in the bone marrow express CD2 or/and CD25</td>
</tr>
<tr>
<td></td>
<td>d. Serum tryptase &gt;20 ng/ml (does not count in patients who have an associated hematopoietic clonal non MC lineage disease (= AHNMD))</td>
</tr>
</tbody>
</table>

* if at least one major and one minor criterion or three minor criteria are fulfilled, the diagnosis SM can be established

** other activating mutations at codon 816 of c-kit also count as a minor criterion

MCs, mast cells
<table>
<thead>
<tr>
<th>Variant - Subvariants</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous Mastocytosis</td>
<td>CM</td>
</tr>
<tr>
<td>- Maculopapular CM*</td>
<td>MPCM</td>
</tr>
<tr>
<td>- Diffuse CM</td>
<td>DCM</td>
</tr>
<tr>
<td>- Mastocytoma of skin</td>
<td></td>
</tr>
<tr>
<td>- (Mast cell sarcoma of skin)</td>
<td></td>
</tr>
<tr>
<td>Indolent Systemic Mastocytosis</td>
<td>ISM</td>
</tr>
<tr>
<td>- Smouldering SM</td>
<td>SSM</td>
</tr>
<tr>
<td>- Isolated bone marrow mastocytosis</td>
<td>BMM</td>
</tr>
<tr>
<td>Systemic Mastocytosis with an associated clonal hematologic non mast cell lineage disease</td>
<td>SM-AHNMD**</td>
</tr>
<tr>
<td>Aggressive Systemic Mastocytosis</td>
<td>ASM</td>
</tr>
<tr>
<td>- lymphadenopathic SM with eosinophilia***</td>
<td></td>
</tr>
<tr>
<td>Mast Cell Leukemia</td>
<td>MCL</td>
</tr>
<tr>
<td>- Typical MCL</td>
<td></td>
</tr>
<tr>
<td>- Aleukemic MCL****</td>
<td></td>
</tr>
<tr>
<td>(Extracutaneous) Mast Cell Sarcoma</td>
<td>MCS</td>
</tr>
<tr>
<td>Extracutaneous Mastocytoma</td>
<td></td>
</tr>
</tbody>
</table>

* also termed urticaria pigmentosa; ** the subtype of the "AHNMD" has to be defined by WHO criteria as well; *** in a subgroup of these patients, the FIPL1-PDGFR fusion gene is detectable; **** circulating mast cells are <10%.
### Table 3

**Diagnostic Work up in Patients with Suspected Mastocytosis**

<table>
<thead>
<tr>
<th>Initial Sign/Symptom</th>
<th>Recommended Diagnostic Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>UP-like skin lesions in pediatric cases</td>
<td>1. Skin biopsy (with analysis of c-kit D816V) &amp; serum tryptase (monitoring)*&lt;br&gt;Bone marrow investigation in cases with suspected hematologic disease / SM</td>
</tr>
<tr>
<td>UP-like skin lesions in adult patients</td>
<td>1. Bone marrow examinations, skin biopsy &amp; serum tryptase (&gt;20 ng/ml in most cases)&lt;br&gt;2. In case of SM → complete staging:&lt;br&gt;GI tract, osteodensitometry, y-ray of bones, ultrasound of abdomen, complete blood count, serum chemistry, coagulation parameters, c-kit mutations</td>
</tr>
<tr>
<td>Reported mediator symptoms but no skin lesions (UP)**</td>
<td>1. Serum tryptase, if &gt;20 ng/ml → 2.&lt;br&gt;2. Bone marrow examination, if SM → 3.&lt;br&gt;3. SM – Staging**</td>
</tr>
<tr>
<td>Severe unexplained allergic reaction / anaphylaxis at presentation</td>
<td>1. Serum tryptase, if &gt;20 ng/ml → 2.&lt;br&gt;2. Repeat serum tryptase a few weeks later: if then, serum tryptase is &gt;20 ng/ml → 3.&lt;br&gt;3. Bone marrow examination, if SM → 4.&lt;br&gt;4. SM – Staging**</td>
</tr>
</tbody>
</table>

* In young infants, a serum tryptase level slightly exceeding 20 ng/ml is not regarded as safe indicator for systemic mastocytosis. Therefore, it is recommended to wait and to monitor the serum tryptase level over time in these patients (but do not perform a bone marrow puncture) unless other signs for a systemic hematologic disease are found (organomegaly, osteolyses, severe cytopenias, others).

** Especially in patients with aggressive mast cell disorders, skin lesions are absent. Therefore it is of pivotal importance to know the subtype of SM in these patients as soon as possible. In aggressive SM the serum tryptase level is usually higher than in patients with isolated bone marrow mastocytosis (often <20 ng/ml), a benign mast cells disease in which skin lesions are also absent.
Table 4

**MYELOMASTOCYTIC OVERLAP SYNDROMES**

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelomastocytic leukemia</td>
</tr>
<tr>
<td>SM-AHNMD</td>
</tr>
<tr>
<td>Eosinophilic leukemia</td>
</tr>
<tr>
<td>&quot;Occult&quot; mastocytosis</td>
</tr>
<tr>
<td>Tryptase+ AML</td>
</tr>
<tr>
<td>KIT$^{D_816V}$-positive myeloid malignancy</td>
</tr>
<tr>
<td>Myeloid malignancy with CD25+ mast cells</td>
</tr>
</tbody>
</table>