

Invited Review

Systemic mast cell disease (mastocytosis). General aspects and histopathological diagnosis

H.-P. Horny, P. Ruck, S. Kröber and E. Kaiserling

Institute of Pathology, University of Tübingen, Tübingen, Germany

Summary. Systemic mast cell disease/mastocytosis (SMCD) is best defined as a multitopic proliferation of cytologically and/or functionally abnormal tissue mast cells (TMC). SMCD preferentially involves the bone marrow, skin, spleen, liver, and lymph nodes. The histopathological diagnosis of SMCD may be very difficult to make, and the disease is often not considered in the differential diagnosis of lymphoreticular neoplasia. In suspected cases of SMCD, basic dyes such as Giemsa and toluidine blue are useful to demonstrate the specific metachromatic granules of TMC. The naphthol AS-D chloroacetate esterase reaction has also proved to be very reliable for enzyme-histochemical identification of TMC.

Major diagnostic problems may arise in cases of malignant or «aggressive» SMCD exhibiting tissue infiltrates consisting predominantly of highly atypical, non-metachromatic TMC, which are usually also only weakly reactive for chloroacetate esterase.

Immunostaining with antibodies against the mast cell-specific proteases tryptase and chymase has proved to be of great value for establishing the correct diagnosis in such cases.

Anti-tryptase antibodies have major diagnostic significance due to their extremely high sensitivity and specificity. The classification of SMCD is controversial, but there is increasing support for the differentiation of at least two major subtypes that differ in prognosis: (i) a benign or «indolent» variant in which skin involvement (urticaria pigmentosa-like skin lesions) is usual, but associated malignant hematological disorders are rare; and (ii) a malignant or «aggressive» variant where skin involvement is usually absent but concomitant malignant hematological disorders (myelodysplastic and myeloproliferative syndromes and acute non-lymphocytic leukemias) are very common.

Preliminary molecular biological studies of a few cases of malignant SMCD using the recently developed HUMARA assay have yielded evidence that the disease is monoclonal.

Key words: Malignant mastocytosis, Mast cell, Mastocytosis, Systemic mast cell disease, Tryptase

Introduction

The term mastocytosis is used to denote a heterogeneous group of mast cell proliferative disorders. It must be emphasized that this term can, by definition, also be used to describe a reactive increase in TMC (mast cell hyperplasia). To avoid confusion, the terms generalized mastocytosis and systemic mastocytosis can be replaced by «systemic mast cell disease» (SMCD), which has become widely accepted in the Anglo-American literature for diseases with widespread tissue infiltration by abnormal TMC (Travis et al., 1988a). SMCD is a relatively rare disorder of presumed bone marrow origin that is characterized by an increase in the number of cytologically and/or functionally abnormal TMC, and can best be defined as a mast cell proliferative disorder with multitopic organ involvement. In the following, a critical discussion of the current systems of classification of mastocytosis will be followed by a description of the typical histopathological findings in SMCD. Particular emphasis will be placed on the immunohistochemical confirmation of the diagnosis in atypical cases of malignant SMCD using anti-tryptase antibodies. Recent molecular biological and genetic findings in SMCD will be outlined in the last section. This review is based principally on the clinical and histopathological findings of investigations performed on 88 archival cases of SMCD and a survey of an additional 172 published case reports. The main results of our studies were published in a series of papers each focusing on the histopathological findings in one of the organs/tissues frequently involved in SMCD (Horny et al., 1985, 1989, 1990, 1992, 1993a).

All available tissue from the archival cases was fixed in 4% formalin and embedded in paraffin. Sections were cut at 5 µm and stained with Giemsa and/or toluidine blue, hematoxylin&eosin, Gomori's silver impregnation, and the naphthol AS-D chloroacetate esterase reaction. As described in detail elsewhere, immunohistochemical investigations were performed by the standard ABC

Table 1. Classification of mastocytosis as proposed by Travis et al. (1988a) and modified by Metcalfe (1991).

<i>I. Indolent mastocytosis</i>
A. Skin only
Urticaria pigmentosa (UP)
Diffuse cutaneous mastocytosis
B. Systemic
Marrow
Gastrointestinal tract
±UP
<i>II. Mastocytosis with an associated hematologic disorder (±UP)</i>
A. Dysmyelopoietic disorders
B. Myeloproliferative disorders
C. Acute non-lymphatic leukemia
D. Malignant lymphoma
E. Chronic neutropenia
<i>III. Mast cell leukemia</i>
<i>IV. Lymphadenopathic mastocytosis with eosinophilia = aggressive mastocytosis (±UP)</i>

method with a broad panel of antibodies against a variety of antigens associated with mast cells (such as tryptase, chymase, and c-kit/CD117), leukocytes, and macrophages (Horny et al., 1987, 1993, 1997).

History and classification of mastocytosis

Mastocytosis is a disorder with an interesting history. In 1869, Nettleship and Tay were the first to describe the typical skin lesions of cutaneous mastocytosis, subsequently termed urticaria pigmentosa by Sangster (Nettleship and Tay, 1869; Sangster, 1878).

At about the same time, Paul Ehrlich described cells of the connective tissue possessing metachromatic intracytoplasmic granules, which he designated «Mastzellen» (i.e., overfed or overnourished cells) (Sagher and Even-Paz, 1967). Later, it was recognized that urticaria pigmentosa could be associated with symptoms that indicated generalization of the disease, but it was not until 1949 that Ellis reported internal organ involvement in a child with clinically recognized cutaneous mastocytosis (Ellis, 1949).

It is conceptually reasonable to categorize mast cell diseases amongst disorders of the IgE mast cell/basophil effector system (associated with immediate hypersensitivity reactions), which also include atopic diseases and IgE myelomas. Current classification systems of the different types of mastocytosis, in particular of SMCD, are based on clinicopathological findings (Metcalfe, 1991).

At present, two different classification systems of mastocytosis are in use: one proposed by Travis et al. (1988a) and slightly modified by Metcalfe (1991) (Table 1); and the other suggested by the Kiel-Tübingen group of hematopathologists (Table 2). In the former, cases

Table 2. Classification of mastocytosis as proposed by Horny et al. (1985, 1989, 1993a).

<i>I. Cutaneous mastocytosis</i>
A. Urticaria pigmentosa (UP)
B. Diffuse cutaneous "erythrodermic" mastocytosis*
C. Telangiectasia macularis eruptiva perstans*
D. Solitary mastocytoma*
<i>II. Systemic (benign or indolent) mastocytosis,</i> usually with skin lesions of UP but no associated malignant hematological disorder (bone marrow involvement very common)
<i>III. Malignant (aggressive) mastocytosis,</i> usually without skin lesions of UP but with associated malignant hematological disorder (bone marrow involvement very common)
<i>IV. Mast cell leukemia*</i>
<i>V. Mast cell sarcoma*</i>

*: very rare.

with a more indolent clinical course are distinguished from those exhibiting an associated hematological disorder. In the first group (indolent mastocytosis) skin involvement is common, either in the form of pure cutaneous mastocytosis (urticaria pigmentosa or solitary skin mastocytoma) or as a manifestation of SMCD. The second group comprises cases with an associated hematologic disorder, usually a malignant myelogenous hemopathy (myelodysplastic and myeloproliferative disorders, or acute non-lymphatic leukemias), but it must be stated that aggressive mastocytosis is not always accompanied by an associated hematologic malignancy. SMCD with malignant lymphoma is also listed, but it should be noted that a reactive increase in TMC is very common in certain lymphoproliferative disorders, particularly immunocytoma, and it is easy to misinterpret this as an underlying SMCD. It is not clear why SMCD with associated (non-neoplastic) chronic neutropenia is listed here separately.

The basic principle of the Kiel-Tübingen system is the clear-cut distinction of defined entities similar to that applied to other tumors in general pathology. Pure cutaneous mastocytosis is classified separately because of its excellent prognosis, with spontaneous remissions in pediatric cases and an extremely indolent course in adults. When the diagnosis of SMCD has been established (usually on the basis of bone marrow histology), the presence or absence of urticaria pigmentosa-like, maculopapular skin lesions determines categorization into the two main subtypes, namely benign or indolent SMCD (with skin involvement) and malignant or aggressive SMCD (without skin involvement). More than 50% of patients with malignant mastocytosis exhibit an associated malignant hematological disorder that is myelogenous in nature. Nearly all the defined subtypes of myelodysplastic and myeloproliferative syndromes and acute non-lymphocytic leukemia have been described in association with SMCD (Horny et al., 1990). The overall prognosis of malignant SMCD is very poor and most patients die within 12

Systemic mastocytosis

months of diagnosis. As in the classification system of Travis et al. (1988a), the extremely rare mast cell leukemia (probably the rarest type of leukemia in man) is classified separately. However, no clear-cut definition of mast cell leukemia with respect to the number of circulating TMC has yet been established (Travis et al., 1986). Although only one case of true mast cell sarcoma in man has been reported we feel that this entity should be listed separately. It is interesting that in this case the patient presented with a solitary tumor of the larynx (a very uncommon site for mast cell neoplasia), later developed disseminated skin nodules (sarcomatosis), and finally died of mast cell leukemia (Horny et al., 1986).

Table 3 gives a hitherto unpublished proposed system of classification of mast cell tumors based mainly on path-anatomical findings according to the pattern of organ involvement. Localized (isolated) mast cell tumors are distinguished from variants with involvement of only one tissue/organ and the systemic or generalized subtypes of mastocytosis with multitopic organ involvement. As in other classification systems, mast cell leukemia is listed as a distinct entity (c.f. Tables 1, 2).

In summary, there is still no single, generally accepted classification system for mastocytosis. However, the assignment of patients to provisional categories based on prognosis, skin involvement, and associated hematologic disorders has substantially improved our ability to manage the disease and counsel patients.

Clinical diagnosis

Although the symptoms of SMCD are manifold, the typical clinical syndrome, with episodes of flushing, shortness of breath, nausea, and headache, is unique and not difficult to recognize. The symptoms result from the release of potent mediators (e.g., prostaglandin D₂, histamine, heparin, and tryptase) from TMC, and attempts have been made to establish the diagnosis of SMCD by biochemical demonstration of increased levels of such substances. In the absence of histological confirmation of excessive TMC proliferation, the diagnosis is referred to as inappropriate mast cell activation syndrome (IMCAS) (Travis et al., 1988a; Roberts and Oates, 1991). However, histological confirmation of abnormally increased numbers of TMC should be sought in all cases of suspected SMCD.

Histopathological diagnosis

The key finding for the diagnosis of SMCD is an increased number of TMC in certain tissues, particularly the bone marrow, skin, spleen, liver, and lymph nodes. As more than 90% of SMCD cases have bone marrow involvement and bone marrow trephine specimens are relatively easy to obtain, the diagnosis of SMCD is usually based on bone marrow findings (Parker, 1991a). The first step to establishing a diagnosis of SMCD is to think about it. The clinical information may provide the

Table 3. Classification of mast cell tumors according to the pattern of tissue involvement.

1. <i>Localized</i>
(Benign) mastocytoma (skin, lung)
Mast cell sarcoma
2. <i>Disseminated (only one organ involved)</i>
Urticaria pigmentosa (skin)
Isolated mastocytosis of bone marrow
3. <i>Generalized/systemic</i>
Indolent systemic mastocytosis*
Malignant systemic mastocytosis**
4. <i>Leukemic</i>
Mast cell leukemia

*: usually with urticaria pigmentosa-like skin lesions and involvement of the bone marrow but without a concomitant hematologic malignancy;

** : usually with involvement of the bone marrow and a concomitant hematologic malignancy but without urticaria pigmentosa.

clue, but the hematopathologist also needs to have the necessary experience to be able to correctly interpret the sometimes confusing histomorphology of the disease.

In most cases, the histopathological findings are characterized by disseminated, dense clusters of pleomorphic, either spindle-shaped or ovoid, TMC (Webb et al., 1982; Brunning et al., 1983). More uniform dense infiltration does occur, but it is rare and encountered only in certain cases of malignant mastocytosis. Even when there is very extensive tissue infiltration, the basic pattern of disseminated TMC foci can still usually be detected. The histopathological picture is often obscured by intermingled lymphoreticular cells such as B and T lymphocytes, plasma cells, fibroblasts, histiocytes, and eosinophils and may be almost completely masked by a simultaneous hematologic malignancy, of which there is a high incidence in malignant SMCD (Horny and Kaiserling, 1988). In such cases, the clinical picture tends to be dominated by the coexisting hematologic malignancy and SMCD is not considered in the differential diagnosis (Travis et al., 1988b; Parker, 1991b).

As TMC are difficult to identify in hematoxylin & eosin-stained sections, even for the experienced investigator, additional stains are imperative for the diagnosis of SMCD. Giemsa and/or toluidine blue are recommended for demonstrating the metachromatic intracytoplasmic granules (Fig. 1). Although the naphthol AS-D chloroacetate esterase reaction (Leder's stain) stains all the cells of the neutrophil lineage, it can also be used for the identification of TMC. It is particularly helpful for the detection of more atypical, non-metachromatic TMC (Fig. 2). However, in some cases of malignant SMCD the TMC are very abnormal and do not stain for chloroacetate esterase or exhibit metachromasia. In such cases, immunostaining with antibodies against mast cell-specific antigens, such as tryptase or chymase, is necessary (Fig. 3). Tryptase is expressed very early in TMC maturation and anti-tryptase antibodies appear to have extremely high

Systemic mastocytosis

specificity and sensitivity, so that cells that do not express tryptase can be considered not to be TMC (Fig. 4) (own unpublished observations).

The organs most commonly involved in SMCD are, in decreasing order of frequency: bone marrow, spleen, liver, skin, and lymph nodes (all involved in at least 50% of patients). The presence or absence of skin infiltrates is of crucial importance for the discrimination of the two

main subtypes of SMC (indolent and aggressive) (Horny et al., 1983).

As mentioned above, irrespective of the organ involved, the tissue infiltrates of SMCD exhibit a basic pattern characterized by disseminated, sometimes granulomatoid, clusters of pleomorphic TMC. The TMC clusters are preferentially located in the perivascular and peritubercular areas in the bone marrow, the portal triads

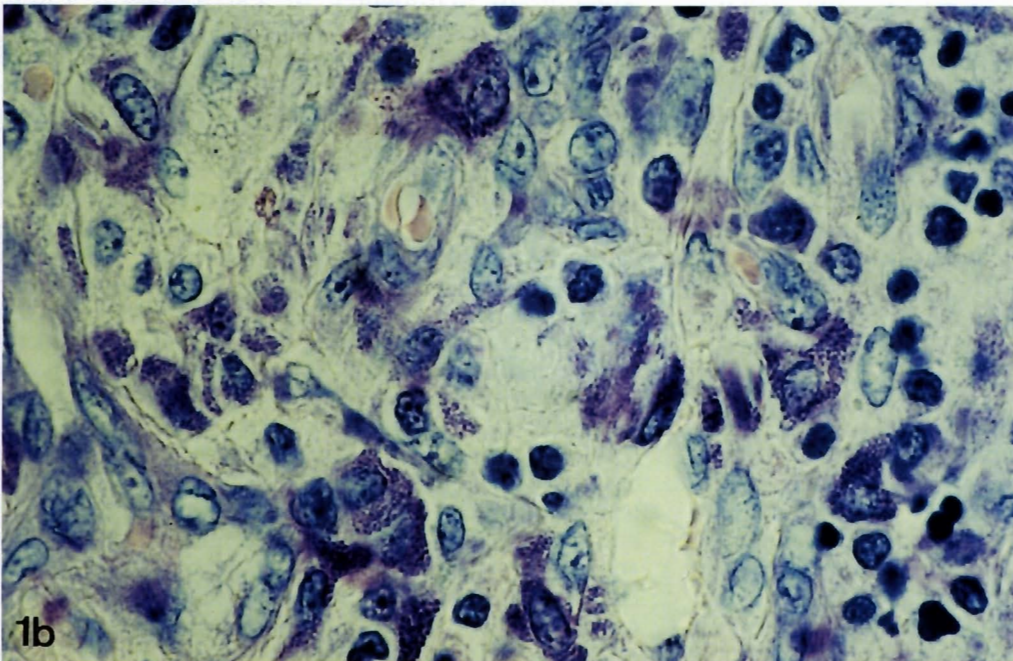
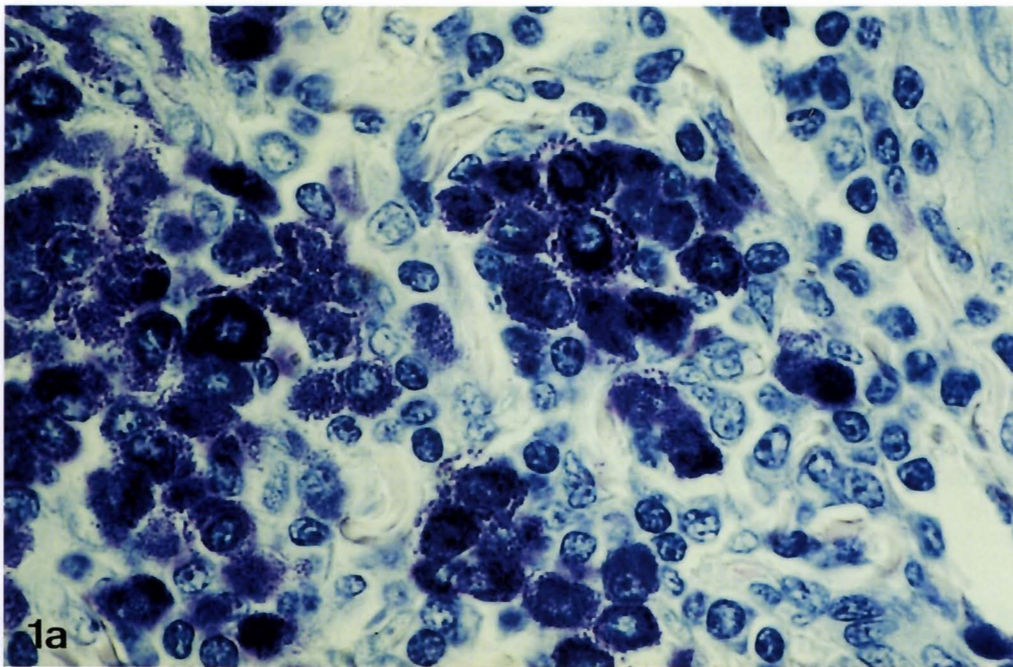


Fig. 1. Systemic mast cell disease; lymph node. An abundance of mast cells with strongly metachromatic granules is easily visible in Giemsa stains. The lymphoreticular tissue is effaced. Note that all the mast cells in (a) are round, but a considerable proportion of those in (b) are spindle-shaped. Giemsa. x 560

in the liver, the perifollicular areas in the spleen, perivascular and periadnexal areas in the skin, and the sinuses and pulp cords in the lymph nodes (Horny et al., 1985, 1989, 1992, 1993a).

Cytologically, the TMC in SMCD are medium-sized to large histiocyte-like cells that may assume a fusiform or round to ovoid shape. They have relatively well-defined margins and, in hematoxylin&eosin stains, pale granular cytoplasm. In Giemsa and toluidine blue stains, the TMC of indolent or benign SMCD (with skin involvement) always exhibit metachromatic granules, although they may be sparse in a considerable proportion of the cells. Most TMC are also strongly reactive for chloroacetate esterase. At least a small proportion of TMC in all cases of so-called aggressive or malignant mastocytosis (without skin involvement) exhibit cellular atypia, with only weak or even absent metachromasia and chloroacetate esterase reactivity. Irrespective of the diagnosis, the nucleus may be round or indented (i.e., monocytoïd) and relatively small, sometimes even pyknotic with condensed chromatin. Nucleoli are inconspicuous. Mitoses are rarely seen.

Origin and immunophenotype of mast cells

Although the origin of TMC was a matter of speculation for nearly a century, there is now increasing evidence that these cells originate in the bone marrow and are closely related to the myelomonocytic lineage (Lennert and Parwaresch, 1979). Today, the hypothesis

that human TMC derive from a pluripotent CD34+ hemopoietic stem cell is generally accepted (Kirshenbaum et al., 1991). TMC express a variety of antigens, which are acquired at different stages of maturation. Among those already expressed very early during differentiation are c-kit (CD117), tryptase, and histamine, while heparin and chymase have been shown to belong to the «late» antigens (Valent, 1995).

Although TMC share some striking phenotypic similarities with the circulating basophil, in particular the presence of metachromatic granules, there are fundamental differences that suggest a clear distinction between these two cell types (Agis et al., 1996). For example, basophils derive from granulocytopoietic cells, whereas TMC probably differentiate as a separate lineage. Moreover, TMC contain proteolytic enzymes such as tryptase and chymase, while basophils lack immunohistochemically-detectable amounts of these substances. Highly enriched cultures of basophils do not produce TMC, a finding that can be regarded as almost definitive proof that TMC belong to a separate cell lineage.

According to the results of studies on isolated cells, normal/reactive mature TMC express both widely-distributed and unique antigens, amongst them cell surface receptors, such as the high affinity IgE binding sites and the mast cell growth factor receptor (c-kit/CD117), and cell adhesion molecules, such as CD29 (common β chain of the β 1 integrins), CD44 (Pgp-1 homing receptor), CD49d (alpha-4 integrin chain), and

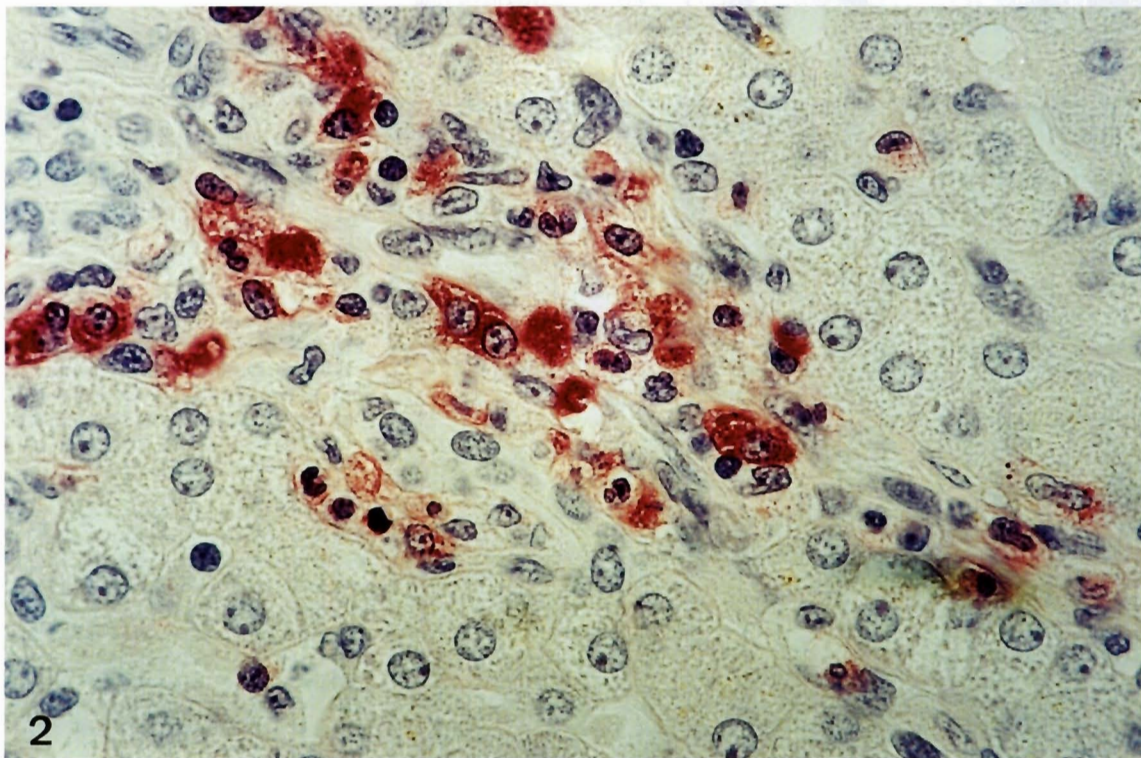


Fig. 2. Systemic mast cell disease; liver. The connective tissue of the portal triad is heavily infiltrated by mast cells. All the tumor cells exhibit strong reactivity for chloroacetate esterase, indicated by red staining of the cytoplasm. Naphthol AS-D chloroacetate esterase reaction. x 450

Systemic mastocytosis

CD54 (ICAM-1) (Sperr et al., 1994).

Most studies of TMC in SMCD have been performed on routinely processed tissue (usually formalin-fixed and paraffin-embedded). Neoplastic TMC have been found to express a variety of antigens. Most are also found on/in normal TMC: for example, the common leukocyte antigen (CD45); CD68, a macrophage-associated antigen detected by the antibodies KP1 and PG-M1; CD117 (c-

kit); vimentin; and the granule-associated enzymes chymase and tryptase, the latter being of greater diagnostic value (Horny et al., 1987). It is also of diagnostic relevance that the macrophage-related antibodies PG-M1 (CD68) and Ki-M1P show more reactivity with the atypical TMC of malignant mastocytosis than the well-differentiated TMC of indolent mastocytosis (Horny et al., 1993b).

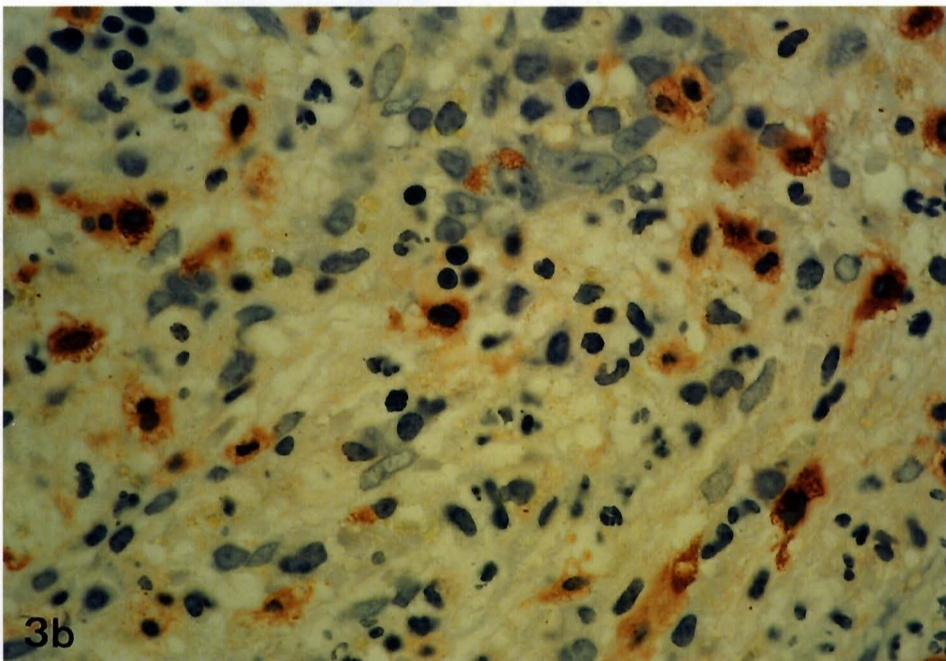
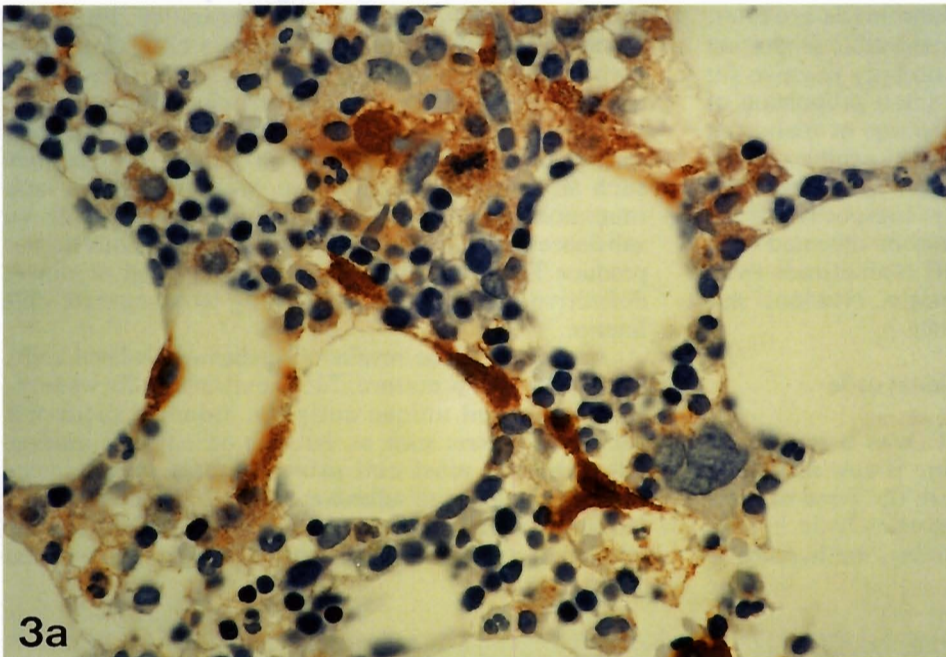


Fig. 3. Systemic mast cell disease; bone marrow. **a.** Bone marrow with intact architecture and normal distribution of hemopoietic cells is seen. Note that the number of mast cells is abnormally increased. Mast cells can easily be identified by the brown granular staining of their cytoplasm for tryptase. This case followed an indolent clinical course. **b.** Bone marrow from a case of malignant mastocytosis with an associated myeloproliferative disorder. The marrow is extremely hypercellular and its normal architecture is obliterated. Mast cells are again easily identifiable by their reactivity for tryptase. ABC method; AA1 (anti-tryptase). x 350

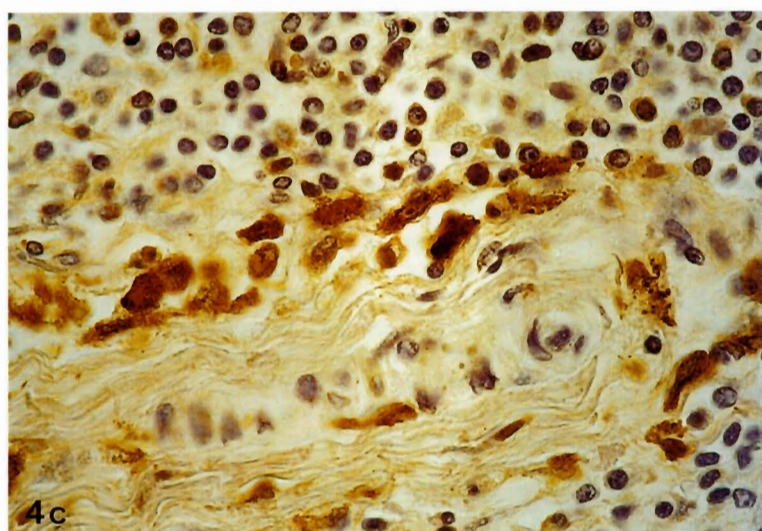
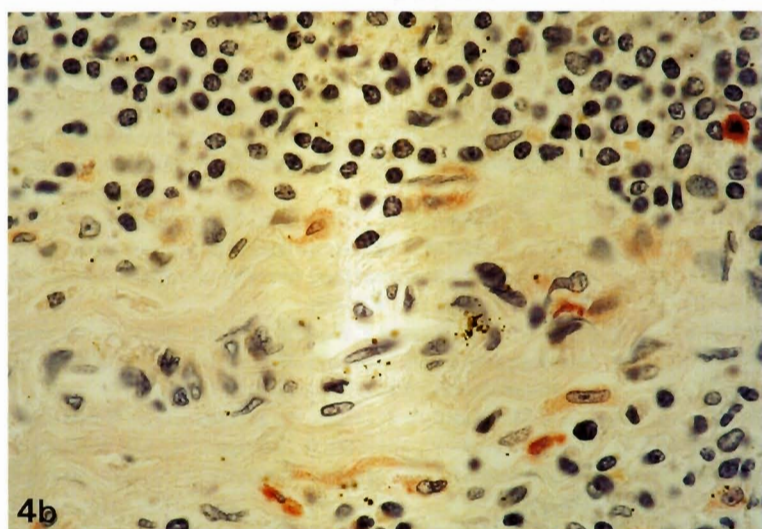
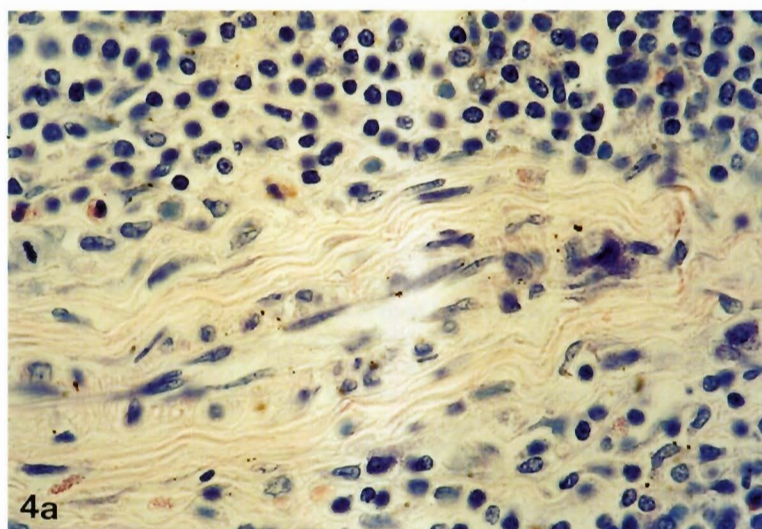


Fig. 4. Systemic mast cell disease; spleen. (a), (b), and (c) show the same peritrabecular area in different stains. Note that Giemsa staining (a) does not reveal any cells with metachromatic granules. However, chloroacetate esterase staining (b) reveals some loosely scattered spindle-shaped mast cells with weak reactivity of the cytoplasm. The diagnostic value of immunostaining for tryptase is demonstrated by (c), in which an unexpected abundance of mast cells is seen. a, Giemsa; x 350; b, Naphthol AS-D chloroacetate esterase; x 350; c, ABC method; AA1 (anti-tryptase); x 290

Molecular biology and genetics of SMCD

Only a few molecular biological studies of SMCD have been published. Recently, Nagata et al. (1995) demonstrated a point mutation in the catalytic domain of the proto-oncogene c-kit (CD117 or SCF/MGF receptor) in peripheral blood mononuclear cells of patients with mastocytosis with an associated hematologic disorder, but not in patients with other variants of SMCD or hematologic neoplasms without morphological evidence of involvement of the TMC lineage. Longley et al. (1996) detected a somatic c-kit activating mutation in TMC of patients with urticaria pigmentosa and aggressive mastocytosis. Zhang et al. (1984) described a patient with SMCD exhibiting a neoplastic cell clone in the bone marrow with the rarely detected translocation (X;8) (q27;q21.3). Increased levels of the soluble form of the stem cell factor (SCF), also known as mast cell growth factor (MGF), have been found in the skin of some patients with cutaneous mastocytosis. Since alterations in transcription of the gene encoding MGF were not detected, an aberration in the metabolism of MGF was suspected, and this finding was then regarded as strong evidence to support classification of cutaneous mastocytosis as a reactive or hyperplastic process rather than a neoplastic disease (Longley, 1993). In summary, it has not yet been established whether the various types of mastocytosis are reactive/hyperplastic conditions or true neoplastic disorders. We have recently investigated this problem by subjecting tissue specimens from female patients with SMCD to the assay for analysis of clonality at the human androgen receptor (HUMARA) locus. In both spleen samples from patients with aggressive mastocytosis (but without associated hematological disorders) the HUMARA assay revealed monoclonality (Kröber et al., 1997). To the best of our knowledge, this is the first molecular biological evidence to suggest that at least some variants of SMCD are monoclonal hemopathies.

Acknowledgements. The authors wish to thank Dr. M. Ruck for help in preparation of the manuscript.

References

- Agis H., Füreder W., Bankl H.C., Kundi M., Sperr W.R., Wilhelm M., Boltz-Nitulescu G., Butterfield J.H., Kishi K., Lechner K. and Valent P. (1996). Comparative immunophenotypic analysis of human mast cells, blood basophils and monocytes. *Immunology* 87, 535-543.
- Brunning R.D., McKenna R.W., Rosai J., Parkin J.L. and Risdall R. (1983). Systemic mastocytosis, extracutaneous manifestations. *Am. J. Surg. Pathol.* 7, 425-438.
- Ellis J.M. (1949). Urticaria pigmentosa: a report of a case with autopsy. *Arch. Pathol.* 48, 426-435.
- Horny H.-P. and Kaiserling E. (1988). Lymphoid cells and tissue mast cells of bone marrow lesions in systemic mastocytosis: a histological and immunohistological study. *Br. J. Haematol.* 69, 449-455.
- Horny H.-P., Parwaresch M.R. and Lennert K. (1983). Klinisches Bild und Prognose generalisierter Mastozytosen. *Klin. Wochenschr.* 61, 192-197.
- Horny H.-P., Parwaresch M.R. and Lennert K. (1985). Bone marrow findings in systemic mastocytosis. *Hum. Pathol.* 16, 808-814.
- Horny H.-P., Parwaresch M.R., Kaiserling E., Müller K., Olbermann M., Mainzer K. and Lennert K. (1986). Mast cell sarcoma of the larynx. *J. Clin. Pathol.* 39, 596-602.
- Horny H.-P., Reimann O. and Kaiserling E. (1987). Immunoreactivity of normal and neoplastic human tissue mast cells. *Am. J. Clin. Pathol.* 89, 335-340.
- Horny H.-P., Kaiserling E., Campbell M., Parwaresch M.R. and Lennert K. (1989). Liver findings in generalized mastocytosis. A clinicopathologic study. *Cancer* 63, 532-538.
- Horny H.-P., Ruck M., Wehrmann M. and Kaiserling E. (1990). Blood findings in generalized mastocytosis: evidence of frequent simultaneous occurrence of myeloproliferative disorders. *Br. J. Haematol.* 76, 186-193.
- Horny H.-P., Ruck M.T. and Kaiserling E. (1992). Spleen findings in generalized mastocytosis. A clinicopathologic study. *Cancer* 70, 459-468.
- Horny H.-P., Kaiserling E., Parwaresch M.R. and Lennert K. (1993a). Lymph node findings in generalized mastocytosis. *Histopathology* 21, 439-446.
- Horny H.-P., Ruck P., Xiao J.-C. and Kaiserling E. (1993b). Immunoreactivity of normal and neoplastic human tissue mast cells with macrophage-associated antibodies, with special reference to the recently developed monoclonal antibody PG-M1. *Hum. Pathol.* 24, 355-358.
- Horny H.-P., Kaiserling E., Sillaber C., Walchshofer S. and Valent (1997). A case of bone marrow mastocytosis associated with an undifferentiated extramedullary tumor of hemopoietic origin. *Arch. Pathol. Lab. Med.* 121, 423-426.
- Kirshenbaum A.S., Kessler S.W., Goff J.P. and Metcalfe D.D. (1991). Demonstration of the origin of human mast cells from CD34+ bone marrow progenitor cells. *J. Immunol.* 146, 1410-1455.
- Kröber S.M., Horny H.-P., Ruck P., Kämmerer U., Geiselhart A., Handgretinger R., Griesser H., Menke D.M. and Kaiserling E. (1997). Mastocytosis: reactive or neoplastic? *J. Clin. Pathol.* 50, 525-527.
- Lennert K. and Parwaresch M.R. (1979). Mast cells and mast cell neoplasia: a review. *Histopathology* 3, 349-365.
- Longley J. (1993). Is mastocytosis a mast cell neoplasia or a reactive hyperplasia? Clues from the study of mast cell growth factor. *Ann. Med.* 26, 115-116.
- Longley B.J., Tyrrell L., Lu S.Z., Ma Y.S., Langley K., Ding T.G., Duffy T., Jacobs P., Tang L.H. and Modlin I. (1996). Somatic c-kit activating mutation in urticaria pigmentosa and aggressive mastocytosis: establishment of clonality in a human mast cell neoplasm. *Nat. Genet.* 12, 312-314.
- Metcalfe D.D. (1991). Classification and diagnosis of mastocytosis: current status. *J. Invest. Dermatol.* 96, 2S-4S.
- Nagata H., Worobec A., Oh C.K., Chowdury B.A., Tannenbaum S., Suzuki Y. and Metcalfe D.D. (1995). Identification of a point mutation in the catalytic domain of the protooncogene c-kit in peripheral blood mononuclear cells of patients who have mastocytosis with an associated hematologic disorder. *Proc. Natl. Acad. Sci. USA* 92, 10560-10564.
- Nettleship E. and Tay W. (1869). Rare forms of urticaria. *Br. Med. J.* 2, 323-324.

Systemic mastocytosis

- Parker R.I. (1991a). Hematologic aspects of mastocytosis. I: bone marrow pathology in adult and pediatric systemic mast cell disease. *J. Invest. Dermatol.* 96, 47S-51S.
- Parker R.I. (1991b). Hematologic aspects of mastocytosis. II: management of hematologic disorders in association with systemic mast cell disease. *J. Invest. Dermatol.* 96, 52S-54S.
- Roberts L.J. II and Oates J.A. (1991). Biochemical diagnosis of systemic mast cell disorders. *J. Invest. Dermatol.* 96, 19S-25S.
- Sagher F. and Even-Paz Z. (1967). Mastocytosis and the mast cell. Year book Publishers. Chicago.
- Sangster A. (1878). An anomalous mottled rash, accompanied by pruritus, factitious urticaria and pigmentation, «urticaria pigmentosa (?)». *Trans. Clin. Soc. London* 11, 161-63.
- Sperr W.R., Bankl H.C., Mundigler G., Klappacher G., Großschmidt K., Agis H., Simon P., Laufer P., Imhof M., Radaskiewicz T., Glogar D., Lechner K. and Valent P. (1994). The human cardiac mast cell: localization, isolation, phenotype, and functional characterization. *Blood* 84, 3876-3884.
- Travis W.D., Li C.-Y., Hoagland H.C., Travis L.B. and Banks P.M. (1986). Mast cell leukemia: report of a case and review of the literature. *Mayo Clin. Proc.* 61, 957-966.
- Travis W.D., Li C.-Y., Bergstralh E.J., Yam L.T. and Swee R.G. (1988a). Systemic mast cell disease. Analysis of 58 cases and literature review. *Medicine* 67, 345-368.
- Travis W.D., Li C.-Y., Yam L.T., Bergstralh M.S. and Swee R.G. (1988b). Significance of systemic mast cell disease with associated hematologic disorders. *Cancer* 62, 965-972.
- Valent P. (1995). Mast cell differentiation antigens: expression in normal and malignant cells and use for diagnostic purposes. *Eur. J. Clin. Invest.* 25, 715-720.
- Webb T.A., Li C.-Y. and Yam L.T. (1982). Systemic mast cell disease: a clinical and hematopathologic study of 26 cases. *Cancer* 49, 927-938.
- Zhang Y., Schlegelberger B., Weber-Matthiesen K., Grote W. and Bartels H. (1994). Translocation (X;8) (q27;q21.3) in a case of systemic mastocytosis. *Cancer Genet. Cytogenet.* 78, 236-238.