Diagnosis of mastocytosis: general histopathological aspects, morphological criteria, and immunohistochemical findings

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Abstract

An increase in mast cell (MC) numbers in hemopoietic tissues may be associated with (a) primary neoplastic MC disease (mastocytosis); (b) non-mast cell lineage myelogenous disorders (myelodysplastic or myeloproliferative syndromes and myeloid leukemias); or (c) reactive, i.e. non-clonal states (MC hyperplasia and reactive mastocytosis). However, the histologic discrimination between hyperplastic states and neoplastic MC proliferative disorders is sometimes very difficult. MC hyperplasia is characterized by a diffuse increase in mature, round or spindle-shaped, metachromatic MC that are loosely scattered throughout the tissue and do not form dense focal infiltrates, even in states of marked hyperplasia. However, loosely scattered MC are also a prominent feature of many cases of myelodysplastic syndromes and acute leukemia involving the MC lineage. In contrast, the demonstration of dense, focal and/or diffuse MC infiltrates can be regarded as indicative of primary MC disease/mastocytosis. In addition to the highly diagnostic focal MC infiltrates, mastocytosis may also present with a predominantly diffuse or a mixed (diffuse and focal) infiltration pattern. The relatively rare diffuse pattern is usually dominated by atypical, often hypogranulated or even non-metachromatic MC and is associated with the aggressive or frankly malignant subtypes of systemic mastocytosis and MC leukemia. Although the demonstration of MC infiltrates in Giemsa-stained tissue sections is still very important for the diagnosis of mastocytosis, immunohistochemical techniques using antibodies against MC-associated antigens such as tryptase or c-kit (CD117) are essential for the identification of highly atypical, hypogranulated MC, especially in MC leukemia, and for the detection of small and even minute MC infiltrates. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Mast cells (MC) are a normal constituent of perivascular tissue and can be found throughout the body [1]. However, their numbers vary greatly depending on the tissue site. Although they are usually present in lymph node sinuses they are virtually absent from the normal spleen. An increase in MC numbers is either reactive (MC hyperplasia) or neoplastic (MC disease or mastocytosis). Because MC are difficult to identify in routine H and E-stained sections, an increase may easily be overlooked unless special metachromatic stains like giemsa or toluidine blue are applied [2,3]. Hematopathologists therefore use Giemsa stains to identify MC in lymph nodes and bone marrow sections. A marked increase in diffusely distributed MC is often associated with reactive, chronic inflammatory, and fibrogenic conditions but may also occur in various hematologic malignancies such as immunocytoma, chronic lymphocytic leukemia, myelodysplasia, and acute myeloid leukemia [4–6]. However, extremely large MC numbers are encountered almost exclusively in MC neoplasia, i.e. mastocytosis/MC disease and MC leukemia. Neoplastic MC may exhibit marked cellular atypia and therefore are sometimes extremely difficult to identify [7]. However, it has recently been shown that immunohistochemical staining with antibodies against tryptase, which is one of the two highly specific MC-associated serine proteases, is a powerful tool for the
The value of various histochemical involvement in MC proliferative disorders are described. In the following, the histopathologic patterns of tissue involvement in MC proliferative disorders are described. The value of various histochemical/immunohistochemical markers for the diagnosis of mastocytosis and its discrimination from other hematologic malignancies will also be discussed.

2. Patients and methods

The results of this study are based on the detailed clinical and histopathologic evaluation of more than 100 patients (mostly adults) with mastocytosis/MC disease (most cases with proven bone marrow involvement) and of more than 50 patients with a marked reactive increase in MC (mostly bone marrow trephine biopsy specimens). Serum tryptase levels were measured in certain of these patients. The length of the pre-diagnostic interval and the survival time were known for most patients. The most significant clinical findings such as hepatosplenomegaly, lymphadenopathy, osteolytic/-sclerotic lesions in the skeleton, skin lesions, etc. were recorded. The clinical features and histopathologic findings in these cases have been published during the past 15 years in a series of papers focusing on the various different tissue sites commonly involved in mastocytosis [9–13]. Tissue from these cases was routinely processed, i.e. fixed in 5% buffered neutral formalin, in the case of bone marrow trephine biopsy specimens also mildly decalcified overnight in edetic acid (EDTA), embedded in paraffin, cut at 4 μm, and stained by a variety of procedures including Giemsa/toluidine blue, naphthol AS-D chloroacetate esterase (CAE), anti-CD2, anti-CD68 (antibodies KP1 and PG-M1), anti-CD117 (c-kit), anti-chymase, and anti-tryptase [14–19]. Morphometric studies were performed using a computer-assisted video camera. For statistical analysis the t-test and the χ²-test were applied.

3. Results

3.1. General histopathological aspects

Because very little information is available about normal MC numbers at different tissue sites, the diagnosis of a slight increase in MC, i.e. mild MC hyperplasia, often seems to be made arbitrarily. In a morphometric study, we found MC numbers of <4/100 mm² bone marrow in most normal/reactive states, while in myelodysplastic syndromes MC numbers usually were >5 but <100/mm². In MC neoplasia, however, the MC count in most cases was much higher than 100/mm², reaching a maximum of 2655/mm². The differences between MC numbers in normal/reactive bone marrow and bone marrow with myelodysplasia or mastocytosis were each statistically significant (P < 0.01). It is relatively easy to recognize a marked increase in MC numbers, especially when appropriate stains like Giemsa are used and the MC exhibit a mature phenotype with abundant, strongly metachromatic granules. Reactive conditions with marked and therefore easily recognizable MC hyperplasia include chronic inflammatory processes, hyperplasia being particularly prominent in tissue with collagen fibrosis. The stroma of certain benign and malignant tumors may also contain strikingly large numbers of MC. When there is an abundance of highly granulated MC it may be almost impossible to discriminate between MC hyperplasia and well-differentiated mastocytosis presenting as cutaneous mastocytosis or indolent systemic mastocytosis. In our experience, the major discriminative histological finding is the demonstration of at least one, even very small, dense focal tissue infiltrate consisting of cohesively aggregated MC. The presence of spindle-shaped MC in such infiltrates is of major diagnostic importance because very small aggregates of round or oval tryptase + cells can also be found in other myeloid neoplasms and even in reactive states. Dense focal MC infiltrates containing at least a minor proportion of spindle-shaped cells thus can be regarded as hallmark of MC disease/mastocytosis, while MC in hyperplastic conditions are almost always loosely scattered and evenly distributed. Dense MC infiltrates may consist of highly granulated and therefore strongly metachromatic MC, or of more atypical, often spindle-shaped, hypogranulated, or even non-metachromatic MC. It is sometimes very difficult to recognize the spindle-shaped cells as MC, even with stains like Giemsa and toluidine blue, since metachromatic granules are virtually absent in a considerable proportion of these cells. It should be emphasized, however, that the dense localized infiltrates of spindle-shaped cells in various hemopoietic tissues occur almost exclusively in mastocytosis and can be regarded as very strong evidence of MC disease. Compact MC infiltrates are sometimes very small and consist of only about 10 cells per section, but usually they are medium-sized and of a more granulomatoid appearance. Large or even coalescent MC infiltrates consisting mainly of spindle-shaped cells were found to be more common in the aggressive subtype of mastocytosis. In such cases, the diffusely infiltrating MC replace most of the pre-existing tissue, for example the bone marrow, which may lead to signs of organ impairment or even failure. Typically, the MC infiltrates are found in the immediate vicinity of blood vessels, with florid angioneogenesis in some cases, or in the bone marrow, in a predominantly peritrabecular position. MC infiltrates almost
always contain an abundance of reticulin fibers and, in the later stages of the disease, are accompanied by marked collagen fibrosis. Varying numbers of lymphocytes (both B and T cells), plasma cells, fibroblast-like cells, histiocytes, and eosinophilic granulocytes may be intermingled with the MC. The number of intermingled lymphocytes is sometimes high enough to obscure the underlying MC disease. In such cases, a diagnosis of low-grade non-Hodgkin’s lymphoma is often suspected initially.

3.2. Specific infiltration patterns in the bone marrow

In our experience, there are three major types of infiltration patterns in the bone marrow in systemic MC disease (Table 1):

1) The focal, dense or compact infiltrate, which is of varying size and cellular composition (Fig. 1). An admixture of lymphocytes is a common finding in patients with a more indolent or smouldering clinical course. The MC may be round or oval or may show prominent spindling. Spindle-shaped MC are often hypogranulated and contain very few metachromatic granules. Purely focal infiltration is found in about one half of all cases of systemic MC disease with proven bone marrow involvement and in the rare isolated bone marrow mastocytosis.

2) Diffuse infiltration, which varies in density and has only a slight tendency to form compact infiltrates. In these cases, MC exhibit varying degrees of cellular atypia. Diagnostic problems are much greater than with the focal infiltration pattern, especially when round MC predominate. Immunostaining for MC markers, in particular tryptase, is essential in such cases. Diffuse infiltration alone is relatively rare. The differential diagnosis includes myelodysplastic syndromes and tryptase + AML, which, in rare instances, also shows a diffuse increase of atypical, often blast-like, round to oval (but never spindle-shaped) tryptase + cells that are

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**Table 1**

Bone marrow infiltration patterns in mastocytosis

<table>
<thead>
<tr>
<th>Type</th>
<th>Main morphologic findings</th>
<th>Associated disease</th>
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<tbody>
<tr>
<td>1 Compact</td>
<td>Granulomatoid, sharply demarcated granulomatoid</td>
<td>Indolent mastocytosis, Smouldering mastocytosis</td>
</tr>
<tr>
<td>2 Diffuse</td>
<td>Loosely scattered MC</td>
<td>MC hyperplasia (MDS, AML, MPS), Urticaria pigmentosa</td>
</tr>
<tr>
<td>2A Interstitial</td>
<td>Hemopoiesis normal or abnormal</td>
<td>Mast cell leukemia, Myelomastocytic leukemia</td>
</tr>
<tr>
<td>2B Dense</td>
<td>MC atypia pronounced</td>
<td>Mast cell leukemia, Myelomastocytic leukemia</td>
</tr>
<tr>
<td>3 Mixed</td>
<td>Compact and diffuse (2A or 2B)</td>
<td>Aggressive mastocytosis, Smouldering mastocytosis, Indolent mastocytosis</td>
</tr>
</tbody>
</table>

a MC, Mast cell(s).
usually detected after microwave pretreatment. There are two subtypes of the diffuse infiltration pattern. First, the so-called interstitial pattern (type 2A) in which the MC are more loosely scattered (Fig. 2), and secondly, the cellular or dense pattern (type 2B), in which there is effacement of the pre-existing hematopoietic bone marrow (Fig. 3). The interstitial pattern is seen mainly in reactive states (MC hyperplasia), for example in lymphoplasmacytic immunocytoma or hairy cell leukemia, but it is also found in the bone marrow of many patients with cutaneous mastocytosis (urticaria pigmentosa) without focal or compact MC infiltrates. The dense pattern is strongly associated with primary MC disease, particularly the malignant subtype of systemic mastocytosis (aleukemic MC leukemia) and 'true' MC leukemia.

(3) Combination or mixed patterns, in which there are focal, dense MC infiltrates and marrow areas that are more diffusely involved. In some of these cases, the focal infiltrates are large and irregular, and have a tendency to merge. This infiltration pattern is often seen in patients with long-standing indolent disease or the aggressive subtype of systemic mastocytosis. In cases of indolent mastocytosis the architecture of the remaining bone marrow may be quite well preserved (type 3A), while in MC leukemia it is usually widely effaced (type 3B).

Sarcomatous infiltration, in which there is destruction of pre-existing tissues, has not yet been identified in the bone marrow. The extremely rare, localized MC sarcoma consists of sheets and strands of highly atypical, usually hypogranulated or even non-metachromatic MC that are only recognizable by immunophenotypical analysis using a panel of antibodies including anti-tryptase and/or anti-c-kit (CD117). This tumor has been found at tissue sites that are not normally involved by systemic mastocytosis. The four confirmed MC sarcomas described so far were located in the larynx, the dura mater, the large bowel (ascending colon), and the gingiva.

3.3. Infiltration of extramedullary tissue

It must be emphasized that criteria for the histopathological diagnosis of primary MC disease must be based on the site involved. Because bone marrow is the tissue most commonly involved in systemic mastocytosis and is relatively easy to obtain for investigation, the infiltration patterns at this site are described, but also apply in principle to extramedullary sites. The following should be considered when MC disease is diagnosed in tissue other than the bone marrow (Table 3):

Spleen: Because MC are virtually absent from both normal and hyperplastic splenic tissue, the presence of even a few loosely scattered MC may be indicative of primary MC disease. When a diagnosis of mastocytosis has been confirmed in extrasplicenic tissue, the demonstration of tryptase-positive spindle-shaped cells in a normal-sized spleen can be regarded as compatible with involvement by systemic MC disease. In typical cases of systemic MC disease (indolent, aggressive, or malignant), however, the spleen is markedly enlarged and histologic investigation reveals dense disseminated infiltrates consisting of round and/or spindle-shaped MC, predominantly located in the red pulp.
Liver: MC are virtually absent from the normal liver but their number may be increased in the portal tracts in chronic inflammatory states with florid fibrosis and/or cirrhosis. The presence of even a few loosely scattered MC within the sinusoids is, in our experience, seen only in systemic mastocytosis. However, dense focal MC infiltrates are also seen within enlarged and fibrotic portal tracts in all cases of liver involvement by MC disease.

Lymph nodes: Because MC may be present in relatively large numbers in chronic lymphadenitis, mainly within the sinusoids, it is often very difficult to confirm or exclude lymph node involvement by systemic mastocytosis. In positive cases, however, dense MC infiltrates in the pulp cords or the paracortical areas are typical findings. As at other tissue sites, MC infiltrates are commonly accompanied by varying numbers of eosinophilic granulocytes and by reticulin fibrosis.

Gastrointestinal tract: MC numbers are often increased in the mucosa in various reactive conditions. Therefore, the only proof of involvement by primary MC disease is the presence of dense infiltrates within the lamina propria, often in the deeper parts or even in the immediate vicinity of the muscularis mucosae.

3.4. Immunohistochemical findings

There is now definitive evidence that MC are of myelogenous origin. They derive from a CD34-positive progenitor cell and thus belong to the large family of CD45-expressing hematopoietic cells. Normal/reactive MC exhibit almost unique immunophenotypical features. Irrespective of their stage of maturation and location, normal MC invariably strongly express the serine protease tryptase and the receptor for c-kit (receptor for MC growth factor or stem cell factor = CD117). Therefore, in all the cases we analyzed, including reactive and neoplastic states, antibodies against tryptase produced granular cytoplasmic staining of MC (Figs. 1–3). In routinely processed (formalin-fixed, paraffin-embedded) tissue, MC were also shown to express macrophage-related antigens, such as CD68. Whereas the anti-CD68 antibody KP1 produces marked staining of normal, reactive, and neoplastic MC, PG-M1 (anti-CD68R) has a more restricted specificity and reacts mainly with neoplastic MC in cases of systemic aggressive and malignant MC disease. The T cell-associated antigen CD2 has been found to be specifically expressed by neoplastic MC but is not expressed in all cases. Of the antigens that are important for the diagnosis of hematologic malignancies in routinely processed tissue, the following have been found never to be expressed by normal/reactive or neoplastic human MC: myeloperoxidase, elastase, CD15, CD34, and the lymphocyte-related antigens CD3, CD5, CD10, CD20, CD30, and CD43. The specificities and sensitivities of the markers relevant to the diagnosis of MC disease/mastocytosis are listed in Table 2.

As already stated, the diagnosis of MC disease/mastocytosis in routinely processed tissue specimens after fixation in formalin and embedding in paraffin should be based on immunohistochemical investigations. Anti-tryptase antibodies (e.g. AA1 from DAKO Diagnostika, Hamburg, Germany) are the markers of choice for the identification of all MCs, even highly atypical, hypo-

Fig. 3. Mastocytosis: diffuse (‘cellular’) bone marrow infiltration. Extremely hypercellular bone marrow with subtotal depletion of fat cells and blood cell precursors. Note the diffuse cellular infiltrate consisting of strongly immunoreactive mast cells. The picture is typical of mast cell leukemia (aleukemic and leukemic). ABC method, AA1 (anti-tryptase).
granulated or non-metachromatic cells, which may be the dominant cell population in aggressive mastocytosis, MC leukemia, and MC sarcoma, all of which are very rare. To avoid underestimation of MC numbers, the degree of infiltration and/or the percentage of MC should always be assessed with the help of anti-trypase immunostaining. This is also especially useful for screening tissue specimens like bone marrow trephines for the diagnostic dense/compact MC infiltrates in patients with clinically proven cutaneous mastocytosis (usually urticaria pigmentosa). We make a diagnosis of systemic MC disease in patients with cutaneous mastocytosis when at least one dense aggregate of at least 10–15 tryptase-expressing cells, i.e., MC, is detected in bone marrow sections.

**Table 2**

<table>
<thead>
<tr>
<th>Marker*</th>
<th>Specificity</th>
<th>Sensitivity</th>
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<tbody>
<tr>
<td>Tryptase</td>
<td>b</td>
<td>c</td>
</tr>
<tr>
<td>Chymase</td>
<td>c</td>
<td>a</td>
</tr>
<tr>
<td>c-kit/CD117</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>CD68/CD68R</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>CD2</td>
<td>d</td>
<td>a</td>
</tr>
<tr>
<td>Chloroacetate esterase</td>
<td>b</td>
<td>b</td>
</tr>
<tr>
<td>Glemsa/toluidine blue</td>
<td>b</td>
<td>b</td>
</tr>
</tbody>
</table>

*Low.

b Moderate.

c High.

d Expression of CD2 in mast cells seems to be specific to mastocytosis, normal or reactive mast cells being CD2 negative.

e Essential markers are highlighted.

metrical evidence of CD2 expression by neoplastic MC, and measurement of the serum tryptase level, may help to confirm or exclude the diagnosis of mastocytosis [22–26]. In a few cases, the investigation of blood and bone marrow smears may be extremely helpful for the detection of atypical MC with bilobed or monocytoid nuclei, and circulating MC. The finding of unusually large numbers of MC in bone marrow smears can be regarded as strong evidence of the malignant, aleukemic subtype of mastocytosis, or MC leukemia.

The overproduction and subsequent increase of MC with single or multiple organ involvement can be divided into completely benign, reactive processes (MC hyperplasia), and neoplastic conditions (mastocytosis or primary MC disease). Because pure cutaneous mastocytosis often resolves spontaneously during adolescence, especially when it occurs in young children, it cannot be stated with certainty whether all subtypes of mastocytosis are in fact truly neoplastic [27,28].

Chronic inflammatory processes, especially those with marked fibrosis, and certain benign and malignant tumors of hemopoietic and non-hemopoietic origin, are a common cause of marked tissue MC hyperplasia. In some of these tumors, there are often large numbers of MC. The MC in such cases seem to be an integral part of the cellular reaction to the tumor, and are especially abundant in lymphoplasmacytic immunocytoma (Waldenström’s macroglobulinemia), neurogenic tumors, and liposarcoma. A few years ago, we observed a unique spindle-cell tumor that had arisen in an inguinal lymph node of a male patient without clinical signs of MC disease [29]. The tumor consisted of two major cellular components: fibroblast-like cells expressing vimentin but no hemopoietic antigens, and large, round to ovoid, strongly metachromatic MC without recognizable atypia. Because MC made up about 30–40% of the tumor cells, the lesion was designated fibromastocytic tumor of lymph node origin and not as MC disease with a spindle cell component.

A crucial factor for the development of MC hyperplasia and neoplasia seems to be an elevated concentration of functionally active c-kit ligand (MC growth factor/MGF or stem cell factor/SCF) which can be produced not only by fibroblasts and histiocytes but possibly also by the neoplastic cells of tumors with a marked reactive increase in MC. In neoplastic states the autonomous MC proliferation may be induced by activating mutations of c-kit [30–37].

According to our findings in bone marrow trephine biopsy specimens, the demonstration of at least one dense MC infiltrate is sufficient to establish a diagnosis of MC disease/mastocytosis, especially when a significant proportion (> 25%) the lesional MC are spindle-shaped. It has also been shown that immunostaining for tryptase is the most reliable stain for screening of tissue sections to detect even very small MC infiltrates
which, in rare cases, may consist of only 10–15 cells. By contrast, a few cases of myelodysplastic syndromes or acute myeloid leukemia may also contain increased numbers of tryptase-expressing tumor cells/blast cells, which sometimes form small cell clusters. However, these cells are round or ovoid and never spindle-shaped. Such immunohistochemical findings should not, by definition, be termed MC disease/mastocytosis. Because some patients with myelodysplastic syndromes and increased numbers of tryptase-positive cells in bone marrow sections also show elevated numbers of circulating MC, we feel that a designation such as ‘myelomastocytic leukemia’ would be more appropriate [38]. Interestingly, a minority of cases of acute myeloid leukemia exhibits relatively large numbers of tryptase-expressing blast cells, which, in conventional stains, cannot be differentiated from the other tumor cells. In our opinion, such cases could be termed ‘tryptase + AML’. On the other hand, a few cases in which there is co-existence of ‘true’ mastocytosis with focal bone marrow involvement and AML have also been reported [39].

The following main types of infiltration pattern can be recognized in MC disease: (i) ‘MULTIFOCAL- DENSE’, which is the predominant pattern in indolent systemic MC disease with skin involvement; (ii) ‘DIFFUSE-DENSE’, which is the predominant pattern in MC leukemia; (iii) ‘DIFFUSE-INTERSTITIAL’, which is the predominant finding in MC hyperplasia; and (iv) ‘MIXED’, which is a combination of the focal and diffuse infiltration patterns.

While pure diffuse infiltration is relatively rare, the predominantly focal and the mixed infiltration patterns are common, and are found in the overwhelming majority of patients with systemic MC disease. Focal and mixed infiltration patterns are highly characteristic bone marrow findings in such patients and, especially when cutaneous mastocytosis (urticaria pigmentosa) has already been established, pose no problems for the hematopathologist. The occurrence of clusters of spindle-shaped cells in such histological settings is pathognomonic for MC disease, even when metachromatic granules are virtually absent. Nevertheless, we strongly recommend the application of at least one anti-tryptase antibody even in such cases to provide definitive evidence that the spindle cells are of MC origin.

However, diffuse infiltration of the bone marrow, in which there is usually a marked preponderance of spindle cells and which occurs in the rare leukemic mastocytosis, may pose considerable diagnostic difficulties. In most cases, the majority of the atypical MC are almost devoid of diagnostic metachromatic granules. It is therefore necessary to perform additional immunostains before a final diagnosis can be established. Other antibodies in addition to anti-tryptase should be applied. It has been demonstrated that the detection of CD2 expression by the neoplastic MC is extremely helpful for the diagnosis of malignant mastocytosis [40,41]. The evaluation of bone marrow and blood smears in such cases enables the easy recognition of marked cytological atypia of the MC. Of special importance here is the demonstration of MC with immature, bilobed, or monocytoid-appearing nuclei. Such nuclear atypia is rarely, if at all, seen in patients with indolent MC disease [42].

It is not clear from our findings, however, whether the demonstration of just one small MC infiltrate in tissues other than the bone marrow is also enough for a definitive diagnosis of MC disease/mastocytosis. Because normal/reactive splenic tissue is nearly devoid of MC, even a slight diffuse increase in MC in the red pulp can be regarded as highly suspicious of MC disease/mastocytosis. Rare cases of cutaneous mastocytosis, in particular teleangiectasia macularis eruptiva perstans, may show only a mild perivascular increase in MC that is almost undetectable without special stains [43,44]. When the gastrointestinal tract is involved, MC numbers are usually markedly elevated but the MC are often distributed evenly throughout the mucosa, without forming dense infiltrates. However, in the extramedullary tissues commonly involved by MC disease, such as skin, lymph nodes, and liver, a few dense granulomatoid infiltrates can usually be detected in most of the cases.

Table 3
Histologic diagnosis of mastocytosis in extramedullary tissues

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Normal MC number</th>
<th>Histologic signs of mastocytosis</th>
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<tbody>
<tr>
<td>Spleen</td>
<td>Virtually absent</td>
<td>Slight increase in MC numbers</td>
</tr>
<tr>
<td>Liver</td>
<td>Very few</td>
<td>Intrasinusoidal MC</td>
</tr>
<tr>
<td>Lymph node</td>
<td>Varies</td>
<td>Dense MC infiltrates</td>
</tr>
<tr>
<td>GI Tract</td>
<td>Varies</td>
<td>Dense MC infiltrates</td>
</tr>
</tbody>
</table>

5. Conclusions

A diagnosis of MC disease/mastocytosis is not always easy to establish on the basis of morphology alone. According to our findings in a large series of cases the following points should be observed:

1. **Tissue sections** should always be investigated because the cytologic evaluation of bone marrow smears may yield false-negative results.

2. **Bone marrow** should be **immunostained for tryptase** in all cases of suspected primary (or secondary) MC disease because atypical (hypogranulated or even non-metachromatic) MC may easily escape detection when only metachromatic dyes like Giemsa or toluidine blue are used.
3. The discrimination of MC disease from hyperplastic states should be based on the detection of at least one dense focal MC tissue infiltrate. This is especially true for the bone marrow. The presence of spindle-shaped, often hypogranulated cells in a dense MC infiltrate, even if it consists of only about 10 cells, can be regarded as morphological proof of primary MC disease (mastocytosis). The detection of such small infiltrates and the identification of spindle-shaped cells as MC is very much facilitated by immunostaining for tryptase.

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References


