Are Gastrointestinal Mucosal Mast Cells Increased in Patients With Systemic Mastocytosis?

Sabine I. Siegert, MD,¹ Joachim Diebold, MD, PhD,¹ Dagmar Ludolph-Hauser, MD,² and Udo Löhrs, MD, PhD¹

Key Words: Mastocytosis; Mast cell count; Gastrointestinal mucosa

DOI: 10.1309/2880LF7Q6XH3HA3Q

Abstract

In patients with mastocytosis, gastrointestinal symptoms are a frequent phenomenon. However, there are only limited data about the quantity and distribution pattern of mast cells in the gastrointestinal mucosa. We stained gastroduodenal biopsy specimens from 27 patients with mastocytosis and 48 control subjects for mast cell tryptase, CD117, and CD25. The numbers of mucosal mast cells per high-power field showed wide variation in all groups and were decreased markedly in biopsy specimens of corpus and duodenum and statistically significantly decreased in antrum biopsy specimens from patients with systemic mastocytosis compared with patients with pure urticaria pigmentosa and with control subjects. Staining for tryptase showed highly significant correlation with staining for CD117. All mast cells were negative for CD25, which is expressed characteristically by neoplastic mast cells. Causes of the decrease of mucosal mast cells remain enigmatic, but our results show that gastrointestinal symptoms of patients with mastocytosis are most likely mediator-related and not due to an increase of local mast cells.

The term mastocytosis comprises a heterogeneous group of diseases characterized by accumulation and abnormal growth of mast cells in various organs and tissues. If only the skin is affected, the disorder is termed urticaria pigmentosa (UP). If other organ systems such as the bone marrow, gastrointestinal tract, or spleen and lymph nodes are involved, the term systemic mastocytosis is used. According to the World Health Organization classification of 2001, the major criterion for the diagnosis of systemic mastocytosis is the evidence of dense infiltrates of mast cells, ie, aggregates of 15 or more mast cells, in 1 or more extracutaneous organs.¹

About 25% of patients with any kind of mast cell disease and 70% of patients with systemic mastocytosis show gastrointestinal symptoms, including abdominal discomfort, nausea, vomiting, and diarrhea, when a careful history is obtained.² However, there are only limited data on small patient groups about the quantity and distribution pattern of mast cells in the gastrointestinal tract. Therefore, we performed a quantitative analysis of mucosal mast cells in the stomach and duodenum using biopsy specimens from patients with pure UP or systemic mastocytosis (diagnosed by bone marrow involvement) with or without skin involvement and from control subjects.

Materials and Methods

Two groups of patients were studied. The first group comprised 27 patients with mast cell disease, aged 23 to 65 years; 12 had pure UP, and 15 had systemic mastocytosis diagnosed by bone marrow biopsy. Of these 15 patients, 6 showed additional skin involvement. These patients had not been treated for...
mastocytosis at the time of biopsy. A second group of 48 subjects within the same age range served as the control group. Patients from both groups had a variety of gastrointestinal symptoms such as heartburn, nausea, vomiting, and abdominal discomfort and, therefore, underwent diagnostic endoscopy. A total of 152 mucosal biopsy specimens were obtained (59 from the gastric corpus, 68 from the gastric antrum, and 25 from the duodenum) Table II. None of the specimens showed more than low-grade chronic inflammation (according to the updated Sydney classification of gastritis).3

All paraffin-embedded specimens were stained by use of a monoclonal antibody for mast cell tryptase (clone AA1, Novocastra, Newcastle upon Tyne, England). After pretreatment with trypsin for 30 minutes at room temperature, the specimens were incubated with the antibody diluted 1:200 at room temperature for 60 minutes. The detection system used was biotinylated antibody + streptavidin (peroxidase-conjugated) from DAKO, Glostrup, Denmark, with amino-ethylcarbazole (AEC; BioGenex, San Ramon, CA) as the chromogen Image II.

We also stained 24 biopsy specimens for CD117 (polyclonal rabbit antibody, DAKO): After pretreatment with TRS6 (Target Retrieval Solution, DAKO) for 15 minutes in a microwave oven, specimens were incubated with the antibody diluted 1:900 at room temperature for 60 minutes. The detection system used was the LSAB-kit (labeled streptavidin biotin; peroxidase-conjugated, DAKO) with AEC as the chromogen.

Three biopsy specimens were stained for CD25 (clone IL2 R, Quartett, Berlin, Germany). After pretreatment with Enhancer (Linaris, Munich, Germany) in the microwave oven for 30 minutes, the specimens were incubated with the antibody diluted 1:200 at room temperature for 60 minutes. The LSAB-kit was used as the detection system, and the chromogen was AEC.

P values were determined using the $\chi^2$ (Pearson) test.

## Results

We observed no mast cell aggregates in the biopsy specimens from patients with mastocytosis.

The numbers of mucosal mast cells per high-power field (HPF; objective, x40; ocular, 10/18; Laborlux D microscope, E. Leitz, Wetzlar, Germany) in patients with mastocytosis and control subjects showed wide variation Table II. The highest numbers were found in the control group. The numbers of mast cells in patients with systemic mastocytosis with and without skin involvement were statistically significantly decreased in the antrum ($P < .04$) and markedly decreased in corpus and duodenum without reaching statistical significance ($P < .6$ and $P < .13$, respectively). The mean and median numbers of mast cells per HPF in patients with pure UP were within the range of those for control subjects Table III and Figure 2I. The enumeration per HPF was used because it proved to be the most convenient unit for routine diagnostics; the numbers of mast cells per mm² are given in parentheses in Tables 2 and 3.

Staining for mast cell tryptase showed highly significant correlation with staining for CD117 ($r = 0.8; P < .001$) Figure 2I. The immunohistochemical reaction for CD25, which reportedly is expressed exclusively on the surface of neoplastic but not of normal mast cells, was negative in all specimens examined.

## Discussion

Mast cells have an important role in the normal gastrointestinal tract; many substances released by mast cells, such as histamine, serotonin, enzymes, and proteoglycans, regulate blood flow, gastrointestinal tract motility, and epithelial and endothelial permeability. In addition, the mast cell is considered an important agent in several gastrointestinal diseases such as chronic inflammatory bowel disease, gastrointestinal allergies, graft-versus-host-reaction, and bacterial and parasitic infections.4,7

In patients with mast cell disease, gastrointestinal symptoms such as epigastric discomfort, nausea, vomiting, and diarrhea are a frequent phenomenon. It is supposed that they are due more commonly to the release of the active mediators than to infiltration of the gastrointestinal tract by neoplastic mast cells.1 However, no detailed data are available about the quantity or distribution pattern of gastrointestinal mucosal mast cells in larger groups of patients with mastocytosis.

### Table II

<table>
<thead>
<tr>
<th>Total No. of Specimens (N = 152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
</tr>
<tr>
<td>25</td>
</tr>
<tr>
<td>14</td>
</tr>
</tbody>
</table>

## Table III

<table>
<thead>
<tr>
<th>Number of Biopsy Specimens Studied and Location of Sampling in Patients With Systemic Mastocytosis, Pure Urticaria Pigmentosa, or Systemic Mastocytosis With Skin Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic mastocytosis</td>
</tr>
<tr>
<td>Systemic mastocytosis with skin involvement</td>
</tr>
<tr>
<td>Urticaria pigmentosa</td>
</tr>
<tr>
<td>Control group</td>
</tr>
</tbody>
</table>
Staining for mast cell tryptase permits specific detection.\(^8\) Considering that mast cells might be negative for tryptase, for example after degranulation, we stained some of the biopsy specimens for the surface antigen CD117.\(^9\) The results of both stainings showed highly significant correlation, so that staining for mast cell tryptase alone apparently is sufficient.

According to the latest World Health Organization classification of mastocytosis (Vienna, 2001), evidence of mast cell aggregates (ie, 15 or more mast cells) is the major criterion for the diagnosis of organ involvement. We observed no mast cell aggregates in our biopsy specimens, so that “involvement” per definition was not evident in our series. In general, infiltration of the gastrointestinal mucosa by abnormal mast

**Table 2**

Quantitative Assessment of Mast Cells in Stomach and Duodenum of Patients With Systemic Mastocytosis, Pure Urticaria Pigmentosa, or Systemic Mastocytosis With Skin Involvement and in Healthy Control Subjects\(^*\)

<table>
<thead>
<tr>
<th></th>
<th>Gastric Corpus</th>
<th>Gastric Antrum</th>
<th>Duodenum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic mastocytosis</td>
<td>42.5 ± 16.8 (265.6 ± 105.0)</td>
<td>28.8 ± 13.5 (180.0 ± 84.4)</td>
<td>31.6 ± 12.3 (197.5 ± 76.9)</td>
</tr>
<tr>
<td>Urticaria pigmentosa</td>
<td>53.7 ± 16.9 (335.6 ± 106.6)</td>
<td>44.0 ± 16.1 (275.0 ± 100.6)</td>
<td>45.0 ± 14.1 (281.3 ± 88.1)</td>
</tr>
<tr>
<td>Systemic mastocytosis with skin involvement</td>
<td>45.3 ± 15.9 (283.1 ± 99.4)</td>
<td>23.8 ± 6.9 (148.8 ± 43.1)</td>
<td>33.6 ± 12.7 (210 ± 79.4)</td>
</tr>
<tr>
<td>Control group</td>
<td>53.1 ± 20.5 (331.9 ± 128.1)</td>
<td>40.3 ± 176 (251.9 ± 110.0)</td>
<td>54.3 ± 24.3 (339.4 ± 151.9)</td>
</tr>
</tbody>
</table>

\(^*\) Mean value of mast cell counts per high-power field ± 1 SD; values in parentheses are the numbers of mast cell per mm\(^2\).
cells in systemic mastocytosis seems rare. It is mainly clinically described, for example, as small mucosal nodes or thickened folds in the small bowel or as exudative duodenitis, and rarely as duodenal ulcers or so-called bull’s-eye lesions.

Although measurements of urinary histamine secretion, gastric acid secretion, gastric emptying time, and small intestinal transit time have been performed in patients with mastocytosis, quantification of the numbers of mast cells has been reported only for small patient groups that included only a few patients with systemic mastocytosis. In our study, the numbers of mast cells per HPF showed wide variation in all study groups and in all 3 sampling locations. The highest numbers were found in the control group. The numbers of mucosal mast cells in the antrum of patients with systemic mastocytosis in comparison with healthy control subjects were statistically significantly decreased, and in the corpus and duodenum, they were decreased markedly. Compared with the median for healthy control subjects, mast cell counts for patients with systemic mastocytosis were lower in all 3 sampling regions. Some authors describe an increase in the gastrointestinal mast cell population in patients with mast cell disease. The interesting finding in the study by Ferguson et al using chloracetate esterase stain is that the 1 patient with systemic mastocytosis showed the lowest mucosal mast cell counts compared with the other 5 patients with pure UP. In our analysis, mast cell counts in patients with pure UP were within the range of healthy control subjects. Other studies described only minor histologic changes in the intestinal mucosa without quantitative changes in mast cells.

CD25 stains were completely negative in all cases examined. CD25 reportedly is expressed only on the surface of neoplastic but not of normal mast cells, so that we can presume that in our series, all cases contained normal reactive tissue mast cells.

### Table 3
Quantitative Assessment of Mast Cells in Stomach and Duodenum of Patients With Systemic Mastocytosis, Pure Urticaria Pigmentosa, or Systemic Mastocytosis With Skin Involvement and in Healthy Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Gastric Corpus</th>
<th>Gastric Antrum</th>
<th>Duodenum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic mastocytosis</td>
<td>39.8 (248.8)</td>
<td>25.4 (158.8)</td>
<td>23.6 (1475)</td>
</tr>
<tr>
<td>Urticaria pigmentosa</td>
<td>52.9 (330.6)</td>
<td>46.3 (289.4)</td>
<td>50.3 (314.4)</td>
</tr>
<tr>
<td>Systemic mastocytosis with skin involvement</td>
<td>38.0 (2375)</td>
<td>23.8 (148.8)</td>
<td>32.8 (205.0)</td>
</tr>
<tr>
<td>Control group</td>
<td>51.1 (319.4)</td>
<td>37.5 (234.4)</td>
<td>56.5 (353.1)</td>
</tr>
</tbody>
</table>

*Median of mast cell counts per high-power field; values in parentheses are the numbers of mast cells per mm².

Figure 1 Comparison of mast cell numbers in control subjects and in patients with systemic mastocytosis (SM), urticaria pigmentosa (UP), or systemic mastocytosis with skin involvement (SM + UP), taking as a basis the median mucosal mast cell count of the control subjects (marked by thick line). Whereas in the control group the mast cell numbers above and below the median are almost equal, mast cell numbers in most of the biopsy specimens with SM with and without skin involvement are below the median in all 3 regions of sampling (box plots with mean marked by thin line: A, corpus, \( P < .6 \); B, antrum, \( P < .04 \); C, duodenum, \( P > .13 \)). Mast cell numbers of patients with pure UP are within the range of control subjects.
A decrease of mast cells in the gastrointestinal tract also is described for other diseases, such as celiac disease in children. In a study by Suranyi et al., mast cell counts in the small bowel mucosa of children with active, untreated celiac disease were highly significantly decreased compared with the counts in healthy control subjects. On a gluten-free diet the counts increased but never reached the counts of the healthy control subjects. It was speculated that this was due to unidentified toxic agents. In our study, this reason is not likely because we observed no other damage or structural change in the mucosa, and our patients had not been treated for mastocytosis at the time of biopsy.

Thus, the cause of the decrease of mucosal mast cells in the stomach and duodenum of patients with mastocytosis remains enigmatic. In this regard, a study by Ammann et al. is noteworthy. These investigators studied 4 patients with systemic mastocytosis with regard to the histologic changes in the intestinal mucosa, serum gastrin and histamine levels, and tissue histamine content. There was no increase in mucosal mast cells, but there was a markedly increased histamine content in the gastric tissue. Therefore, it can be speculated that the decrease of mast cells might be due to a negative feedback mechanism in which normal tissue mast cells are reduced as a consequence of high histamine levels in the tissue, which, in turn, are derived from the increased and neoplastic mast cells in the bone marrow and other tissues.

Conclusions

We examined a large series of patients with systemic and cutaneous mastocytosis using tryptase immunohistochemical analysis for mast cell counting in gastroduodenal biopsy specimens, which proved to be a reliable and easy-to-use diagnostic tool. Our results show that the gastrointestinal symptoms of patients with mastocytosis most likely are mediator-related and not due to an increase of local mast cells. Our findings suggest that endoscopy of the upper gastrointestinal tract might not be mandatory in the routine workup for the diagnosis of systemic mastocytosis.

Another study dealing with mucosal mast cell numbers in colonic biopsy specimens is in progress. Preliminary data on a very small group of patients with systemic mastocytosis compared with control subjects show similar tendencies to those pointed out in the present study, without considering differences between anatomic colonic segments so far.

Figure 21 Comparison of mast cell tryptase and CD117 immunohistochemical analysis for the quantification of mucosal mast cells. Median numbers of positive cells per high-power field are given. Mast cell numbers show highly significant correlation in staining for mast cell tryptase compared with staining for CD117 ($r = 0.8$; $P < .001$).

References


