Bone Marrow Mast Cell Morphologic Features and Hematopoietic Dyspoiesis in Systemic Mast Cell Disease

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Abstract

Systemic mast cell disease (SMCD) cannot be distinguished from reactive mastocytosis (RM) by quantitation of mast cells in aspirate smears, and few studies have analyzed systematically the morphologic features of mast cells in SMCD vs RM. In addition, although SMCD is associated with myeloproliferative disorders/myelodysplastic syndromes (MPD/MDS), it is not known whether subtle signs of dysplasia or MPD can be found in SMCD, suggesting most cases are part of a dysplastic or myeloproliferative process. We compared 18 bone marrow specimens with SMCD with 10 bone marrow specimens from patients with RM. Mast cells in SMCD were more likely to show cytoplasmic hypogranularity, uneven granule distribution, and fusiform morphologic features. Eight cases of SMCD (44%) demonstrated MPD/MDS, and 9 cases (50%) showed subtle evidence of dyspoiesis, with megaloblastic change, nuclear budding of erythroid precursors, and/or atypical megakaryocytes. Mast cells in SMCD appear morphologically different from those in reactive proliferations. Dyspoietic features were present in most cases of SMCD, suggesting that SMCD is part of a spectrum of chronic myeloproliferative/myelodysplastic disorders.

Systemic mast cell disease (SMCD) is a rare disorder characterized by the accumulation of mast cells in a variety of organs including bone marrow, spleen, and liver, which may occur in association with skin involvement (urticaria pigmentosa).1-5 SMCD usually involves the bone marrow, characterized by mast cell lesions on core biopsy that show immunohistochemical positivity for chymase, tryptase, CD68, and CD117 (c-kit).5 Frequently, an increased number of mast cells on the aspirate smear is observed. An increase in aspirate mast cells also has been observed in numerous hematologic and nonhematologic disorders.3,4,6,7 One cannot distinguish systemic mast cell disease from reactive mastocytosis (RM) based solely on the quantity of mast cells in aspirate smears. While some investigators have commented on the morphologic appearance of mast cells in SMCD1,3,8-11 and suggested that nuclear atypia is associated with more aggressive disease,2,3,5,8 few attempts have been made to differentiate, in a systematic manner, the morphologic features of mast cells in SMCD vs RM.

SMCD is associated with myeloid disorders including myeloproliferative disease (MPD), myelodysplastic syndromes (MDSs), and acute myeloid leukemia.1-3,8-16 It is not known, however, whether more subtle signs of dysplasia or proliferation can be found in SMCD. Such findings may suggest more definitively that many cases of SMCD are part of a dysplastic or myeloproliferative process.

In the present study, the mast cell and bone marrow morphologic features of bone marrow specimens with SMCD are compared with cases of RM. The morphologic differences between mast cells in SMCD and reactive conditions are emphasized, as is the frequent occurrence of dyspoietic features in the other marrow lineages.
Materials and Methods

The pathology records from the University of Iowa Hospitals and Clinics, Iowa City, were searched for cases of SMCD with and without other hematologic malignant neoplasms. Eighteen bone marrow biopsy specimens from 17 patients with SMCD were identified, and the diagnosis of SMCD was reconfirmed in all cases. These were compared with 10 bone marrow biopsy specimens from patients with a variety of other hematologic disorders with increased mast cells on bone marrow aspirate. All bone marrow specimens were obtained from the posterior iliac crest under local anesthesia. Aspirates were obtained in all cases, fixed in methanol, and stained with Wright-Giemsa. Core biopsy specimens, fixed in B-5 fixative, decalcified, and stained with H&E, were obtained in 17 of the 18 SMCD cases and all of the cases with reactive mast cell proliferations; a clot section was available on the one case of SMCD without a core biopsy specimen.

Each bone marrow aspirate was examined for mast cell morphologic features, including number of mast cells with decreased granules and uneven distribution of granules, cell shape (round vs fusiform), and nuclear atypia. The abnormalities were quantitated as follows: “few” was defined as fewer than 25% of the cells showing the abnormality, “moderate” as between 25% and 50%, and “frequent” as greater than 50%. The number of mast cells per 10 high-power microscopic fields (×100) within aspirate particles was counted in the translucent areas of at least 4 separate marrow particles, and the results were analyzed using the Wilcoxon rank sum test. Three hundred cell differentials were performed on the aspirate smears. Evidence of dyspoiesis also was evaluated. Each core biopsy specimen was evaluated for cellularity, cellular atypia, architectural distortion, and the presence of mast cell lesions. The cases were examined by a second reviewer (N.S.R.) and the results confirmed. Immunohistochemical staining with antibodies to c-kit (CD117) (DAKO, Kyoto, Japan) was performed on 8 of the core biopsy specimens from the SMCD cases using an automated immunostainer (Ventana NexES, Ventana Medical Systems, Tucson, AZ). Cytogenetic analysis was performed on 2 SMCD cases following a standard method.17

Results

Eighteen bone marrow biopsy specimens from 17 patients were examined, all of which had mast cell lesions on the core biopsy specimens. These lesions were composed of predominantly paratrabecular and perivascular aggregates of mast cells with pale cytoplasm and variable numbers of admixed lymphocytes, plasma cells and eosinophils Image 1. Bone marrow involvement by mast cell lesions was focal (<10%) in 3 of 18 cases and extensive (>50%) in 4.

Clinical features of the patients with SMCD included a median age of 69 years (range, 34-86 years) and an almost equal male/female ratio (9 men and 8 women). Indications for bone marrow examination included splenomegaly, abdominal pain/diarrhea, fever, autoimmune hemolytic anemia, elevated liver function tests, and abnormal peripheral blood findings (anemia, leukopenia, thrombocytopenia). Skin involvement was not documented, although multiorgan involvement was present in 2 patients. Circulating mast cells were not seen in any of the cases. The control population consisted of 10 marrow specimens from 10 patients who were noted to have increased mast cells on bone marrow aspirate. The median age for RM patients was 60 years (range, 8-84 years); 5 men and 5 women were included in the study. These patients exhibited a variety of hematologic disorders, including pure red cell aplasia and leukemia/lymphoma; nonspecific marrow findings were identified in 2 of 10 patients. None had the classic symptoms associated with SMCD, and none of the core biopsy specimens demonstrated mast cell lesions.

The cytologic findings in the marrow mast cells in SMCD compared with RM are summarized in Figure 1 and Figure 2. Of 18 cases of SMCD, 17 (94%) had moderate or frequent numbers of mast cells with decreased cytoplasmic granules and uneven granule distribution compared with only 2 of 10 RM cases. No cases of RM demonstrated frequently decreased mast cell granularity or uneven granule distribution Image 2 and Image 3. Evaluation of the mast cell morphologic features revealed a preponderance of fusiform mast cells in 7 SMCD cases compared with only 1 RM case.

Image 1 Bone marrow core biopsy of systemic mast cell disease demonstrating a mast cell lesion (H&E, ×500).
The fusiform cells usually had long, polar cytoplasmic processes. Round mast cells were more frequent than fusiform ones in 5 of 18 SMCD marrow specimens, while 8 of 10 RM marrow specimens showed a preponderance of round cells. Round and fusiform cells were of approximately equal numbers in 6 SMCD cases vs 1 RM case. Nuclear features were difficult to evaluate on Wright-stained aspirates and were better visualized on H&E-stained cores. Irregular, lobulated mast cell nuclei were observed in 5 SMCD cases. Three of these cases had no associated MPD/MDS; 1 case had coexistent chronic myelomonocytic leukemia, and 1 had an unclassifiable myeloproliferative disorder. No nuclear atypia was identified in the RM cases.

The number of mast cells in aspirate particles counted in 10 high-power fields was highly variable on a case-to-case basis and demonstrated a wide range of values for both SMCD and RM cases. A mean number of 69.6 mast cells per 10 high-power fields (range, 27-160) was seen in SMCD cases. The RM cases demonstrated a mean of 56.7 mast cells per 10 high-power fields (range, 13-104). These differences were not statistically significant by the Wilcoxon rank sum test.
The evaluation of the dyspoietic features in the SMCD cases is given in Table 1. Dyspoiesis was identified in only 1 control case of RM, which showed 3% ringed sideroblasts but no other dyspoiesis. Of 18 SMCD cases, 8 (44%) demonstrated an associated myeloproliferative or myelodysplastic hematologic disorder. A chronic MPD was seen in 3 cases, including 1 case of essential thrombocythemia and 2 cases that could not be subclassified further. These 2 cases both showed hypercellularity and increased, atypical, clustered megakaryocytes on core biopsy; 1 also demonstrated granulocytic hyperplasia. Five cases of various MDSs were identified: 3 cases of chronic myelomonocytic leukemia (CMML); 1 case of refractory anemia with excess blasts in transformation (RAEB-T); and 1 case that could not be further subclassified but demonstrated marked myeloid proliferation, mild dyserythropoiesis, and megakaryocyte atypia.

More subtle dyspoiesis, not meeting diagnostic criteria of MPS/MDS, was seen in an additional 9 (50%) of 18 cases. In the erythroid lineage, this included dyserythropoietic changes (nuclear budding, abnormal lobation of erythroid precursors, and megaloblastic change) as well as mild open chromatin. Atypical megakaryocytes with hypolobate or hyperlobate forms, separate nuclear lobes, and increased numbers of megakaryocytes with clustering were identified on core biopsy. Four cases also demonstrated granulocytic hyperplasia, with giant bands and metamyelocytes noted in 1 case. Of these 4 cases, 3 also had atypical megakaryocytes, and 2 showed dyserythropoiesis. Only 1 had no other associated dyspoietic changes. One of the 17 cases had moderate dyspoiesis involving all 3 lines on the original diagnostic biopsy but no definitive MPD/MDS; repeated biopsy 2 years later showed CMML.

The cellularity of SMCD cases also was assessed on the marrow particles of the aspirate and/or core biopsy specimen: 13 of 18 marrow specimens were hypercellular, including 7 of 8 cases with MPD/MDS. Although this number includes 3 of the 4 cases with extensive (>50%) marrow involvement by mast cell lesions, the residual marrow was, of itself, also hypercellular.

Cytogenetic analysis of the bone marrow specimen was normal in 2 cases studied, 1 with moderate dyspoiesis and 1

**Table 1**

<table>
<thead>
<tr>
<th>Associated Hematologic Disorder</th>
<th>No. (%) of Marrow Specimens (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic myeloproliferative disorders</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Essential thrombocythemia</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Not classifiable</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Myelodysplastic syndromes</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia</td>
<td>3 (17)</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Not classifiable</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Mild to moderate dyspoiesis</td>
<td>9 (50)</td>
</tr>
<tr>
<td>Dyserythropoiesis</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Megaloblastic change</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Atypical megakaryocytes</td>
<td>8 (44)</td>
</tr>
<tr>
<td>Increased or clustered megakaryocytes</td>
<td>6 (33)</td>
</tr>
<tr>
<td>Granulocytic hyperplasia</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Hypercellular marrow</td>
<td>6 (33)</td>
</tr>
<tr>
<td>No dyspoiesis</td>
<td>1 (6)</td>
</tr>
</tbody>
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RAEB-T, refractory anemia with excess blasts in transformation.

**Image 4** Mild dyserythropoiesis in a patient with systemic mast cell disease but without myeloproliferative disorder/myelodysplastic syndrome (Wright, ×1,000).

**Image 5** Clustered, atypical megakaryocytes on core biopsy specimen in systemic mast cell disease (H&E, ×100).
with RAEB-T. Flow cytometric analysis was not performed on any of the study cases, but immunohistochemical stains for c-kit (CD117) were pursued in 8 cases. Of these, strong positivity for c-kit was noted in only 2 cases, while 2 cases showed weak and focal positivity. No c-kit staining was seen in the mast cell lesions of 3 cases, and no mast cell lesions could be identified in the sections on 1 case.

Clinical follow-up was available for 5 patients. Of the patients with mild to moderate dyspoiesis, clinical follow-up was available for 3. One died of complications of SMCD (hepatic involvement with acute gastrointestinal bleeding) 4 years after initial diagnosis; the other patient was alive 3 years after diagnosis. Neither of these patients demonstrated progression to a diagnostic MPD/MDS. As previously mentioned, the third patient later developed CML and died of complications of this disorder. Both of the other patients diagnosed with MPD/MDS (1 with CML and 1 with acute myeloid leukemia) died of these diseases within 1 year of diagnosis.

**Discussion**

SMCD is characterized by a proliferation of mast cells and the formation of characteristic mast cell lesions. Normal bone marrow mast cells are round to oval, with densely packed, uniform cytoplasmic granules and a nonlobulated nucleus. Mast cells in SMCD vary in morphologic features from fairly typical mast cells to larger, fusiform cells with loosely but uniformly scattered fine granules. Nucleoli and nuclear lobulation have been reported in SMCD by some investigators. Previous studies have not attempted to quantify these morphologic distinctions.

No statistical difference in mast cell numbers was seen between the SMCD and RM cases, supporting previous observations that numerous mast cells can be seen in a variety of hematologic disorders and malignant neoplasms. However, mast cells in SMCD were much more likely to have decreased cytoplasmic granules and uneven granule distribution within the cytoplasm. While occasional RM cases had a preponderance of fusiform or spindle-shaped mast cells, SMCD cases were much more likely to demonstrate these morphologic features. Several of the SMCD cases showed nuclear lobulation, but this finding was clearly present in only 5 cases (28%), although this is a higher percentage than the 12% (3/26) reported by Lawrence et al. There was no clear association between nuclear lobulation and the presence of an associated MPD/MDS. Immunohistochemical staining with c-kit emphasized the mast cell lesions on core biopsy sections but was strongly positive in only a minority of cases. Overall, although previous studies have emphasized mast cell cytologic atypia as a criterion for “aggressive mastocytosis,” we found morphologic abnormalities in almost all of the SMCD cases examined.

Frequent concurrence of SMCD with other hematologic disorders was identified, as in previous studies, with 8 (44%) of 18 cases demonstrating associated MPD/MDS. This percentage was somewhat higher than identified in several previous series (21%, 24%, 33% ) but not considerably greater than the 40% demonstrated by Horny et al in their archival material. MDSs, diagnosable by French-American-British criteria, were present more commonly than MPDs, similar to the cases described by Travis et al.

We also found dyspoietic changes of the other bone marrow elements in SMCD. Nine of 10 cases not involved by MPD/MDS showed at least mild dyserythropoiesis and/or megakaryocytic atypia; proliferative changes (granulocytic hyperplasia, hypercellularity) also were present in a proportion of these cases. These dysplastic/proliferative changes suggest that there is a more widespread marrow defect present in cases of SMCD than has been recognized previously and are supportive of the generally recognized neoplastic nature of SMCD, which has been recently demonstrated by studies showing mutations in the c-kit proto-oncogene. These findings more definitively suggest that SMCD is one aspect of a hematologic disorder involving multiple bone marrow lineages. Under the proposed World Health Organization classification, SMCD is subclassified according to the presence or absence of an associated hematologic disorder. It is possible that most cases of “systemic mast cell disease without associated hematologic disorder” actually have a concurrent hematologic defect, albeit one below current diagnostic thresholds. The clinical relevance of our findings is unclear, since limited clinical follow-up of the study patients was available. However, disease in 1 of 3 patients with more subtle dyspoiesis for whom follow-up was found progressed to a diagnostic MPD/MDS.

It is not clear why some dyspoietic processes largely involve the mast cell lineage, with only mild effects on the other cell lines, and why others produce a concurrent MPD/MDS or do not significantly affect the mast cell lineage. It would be of interest to examine cases of MPD/MDS without SMCD to see whether dysplastic changes are present in the mast cells of these lesions and whether they occur as frequently as in SMCD cases. Of note, some MPD/MDS cases can have a mild, diffuse increase in mast cell numbers, unassociated with SMCD, which may be part of the clonal marrow proliferation.

We have shown that although bone marrow mast cells in SMCD do not differ numerically from those in RM, they preferentially show decreased and uneven cytoplasmic granulation, as well as a more frequent fusiform shape. The presence of mast cell cytologic atypia on aspirates should alert
the observer to the possibility of SMCD, necessitating a careful review of the core biopsy sections and consideration of step sections and immunohistochemical stains (such as c-kit) to identify mast cell lesions. Similarly, the presence of atypical fibrous lesions on core biopsy, combined with mast cell atypia on aspirate, should be regarded as very suggestive of SMCD and prompt further evaluation, including rebiopsy if necessary. We found a frequent (44%) concurrence of MDSs and MPDs and a surprisingly high incidence of more subtle dyspoietic changes in the marrow elements of the remaining cases. These findings suggest that SMCD may be associated with an underlying marrow disorder in a large percentage of cases.

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References