Hematologic Aspects of Mastocytosis: II: Management of Hematologic Disorders in Association with Systemic Mast Cell Disease

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Individuals with systemic mast cell disease (SMCD) may develop various hematologic abnormalities, including cytopenias, myeloproliferative or myelodysplastic syndromes, lymphoproliferative syndromes, and primary or secondary leukemias. Management of those patients is often complicated by their associated hematologic abnormalities. In the case of non-malignant hematologic syndromes, the approach to management is supportive. At present, overt malignancies are managed with traditional chemotherapy. The presence of leukemia in patients with mast cell disease usually indicates a grave prognosis. *J Invest Dermatol 96:52S–54S, 1991*

Published series have consistently documented a number of hematologic abnormalities in patients with systemic mast cell disease (Table I) [1–5]. These abnormalities vary from mild cytopenias and cytoses noted on complete blood count (CBC) to more severe premalignant and overt malignant syndromes.

The most frequent hematologic abnormality is a mild-to-moderate anemia, occurring in a third to half of the patients demonstrated to have systemic disease.(Table II). The next most frequent abnormalities noted on CBC are thrombocytopenia and eosinophilia, which occur in up to one quarter of patients. In patients with eosinophilia, the circulating eosinophils are usually hypogranular with hypersegmented nuclei; the eosinophils appear quite similar to those seen in patients with the idiopathic hypereosinophilic syndrome. A variable monocytosis has also been documented in up to a fifth of patients. In lesser numbers of patients, leukopenia, basophilia and thrombocytosis have been reported. Surprisingly, circulating mast cells in the peripheral blood have been demonstrated in very few patients. The incidence of CBC abnormalities documented in "first-hand" clinical series [3–5] are similar to those cited in older series produced through literature review [1,2].

Various malignant or premalignant hematologic syndromes have been identified in patients with systemic mast cell disease (Table III). A small subgroup of adult patients with systemic mast cell disease have been documented to have myeloproliferative or myelodysplastic progression of their disease [1,3,5,6]. The peripheral blood picture may be consistent with that of either chronic myeloid leukemia (CML) or chronic myelomonocytic leukemia (CMML) and is associated with a poorer prognosis as defined by survival [6]. As with primary myeloproliferative and myelodysplastic syndromes, a secondary acute leukemia may develop in patients with systemic mast cell disease. In addition, there are reports of acute mast cell leukemia developing in nine patients with systemic mast cell disease [7]; those cases were characterized by the presence of large numbers of atypical-appearing mast cells in the peripheral blood, a leukocytosis/granulocytosis, and a compressed clinical course (survival, 2–9 months; mean, <6 months). At the National Institutes of Health, we have also seen eight patients with systemic mast cell disease who developed a lymphocytosis and lymphadenopathy syndrome suggestive of a malignant lymphoproliferative disorder. Tissue pathology could not support a diagnosis of non-Hodgkin's lymphoma, so we categorize this as a "lymphadenopathic" presentation of systemic mast cell disease. Such patients clinically resemble those described elsewhere as having "aggressive mastocytosis" [5]. Overt non-Hodgkin's lymphomas have also been reported to occur in patients with systemic mast cell disease [6]; whether those prior reports represent the same syndrome diagnosed at different points in the natural history of the disease remains to be determined.

In contrast to adult patients with systemic mast cell disease, our pediatric patients have few hematologic abnormalities. No pediatric patient in our series has demonstrated either a myeloproliferative or myelodysplastic peripheral blood picture. One has developed a significant granulocytopenia (<200 granulocytes/mm^3) with a mildly left-shifted, but adequate, marrow myeloid pool. A second patient, who has severe cutaneous involvement, exhibits a mild leukocytosis/granulocytosis without any dyspoeitic features. His episodes of granulocytosis appear to coincide with increased cutaneous manifestations and complications of his disease. We have seen no overt malignant or recognizable premalignant syndromes in our pediatric patients.

THERAPY

Systemic mast cell disease in the absence of an associated hematologic disorder is currently managed conservatively through the use of H1 and H2 antihistamines, cromolyn sodium, and, in advanced stages, corticosteroids. When systemic mast cell disease is associated with a leukemia or lymphoma, chemotherapy appropriate for that malignancy is indicated. Effective control of the malignancy through the use of chemotherapy can be accompanied by a regres-

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Abbreviations:
ANLL: acute non-lymphocytic leukemia
CBC: complete blood count
CML: chronic myeloid leukemia
CMML: chronic myelomonocytic leukemia

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Table I. Systemic Mast Cell Disease: Hematologic Manifestations

Cytopenias
Anemia
Thrombocytopenia
Leukopenia/granulocytopenia
Cytoses
Leukocytosis/granulocytosis
Eosinophilia
Monocytosis
Thrombocytosis
Lymphocytosis

Table II. Systemic Mast Cell Disease

	Travis [5]	Webb [3]	Brunning [4]
Number of patients	58	26	14
Cytopenias			
Anemia	47%	37%	36%
Thrombocytopenia	16	22	14
Leukopenia	16	15	21
Lymphopenia			
Cytosis			
Leukocytosis	19%	29%	21%
Eosinophilia	19	17	43
Basophilia	7	0	0
Monocytosis	16	17	0
Lymphocytosis	2		
Thrombocytosis	9		
Increased mast cells[a]			
<10%	2	2	0
>10%	2	2	0

[a] In periferal blood.

Table III. Systemic Mast Cell Disease: Malignant/Premalignant Manifestations

Myeloproliferative disorder
Myelodysplastic syndrome
"Lymphadenopathic syndrome"
Non-Hodgkin's Lymphoma
Mast cell leukemia
(Secondary) acute leukemia

sion of the systemic mast cell disease. However, in patients with mast cell leukemia or other non-lymphocytic leukemias, response to conventional ANLL (acute non-lymphocytic leukemia) chemotherapy is usually transient at best and associated with significant morbidity. In patients with non-Hodgkin's lymphoma, response to chemotherapy is variable and appears to be related to the histologic subtype of the lymphoma [6]. For these reasons, aggressive treatment of systemic mast cell disease with conventional chemotherapeutic agents is not recommended except when an aggressive hematologic malignancy supervenes.

Currently, the approach to a patient with systemic mast cell disease and an overt hematologic disorder is to treat the hematologic manifestations conservatively, e.g., red blood cell or platelet transfusions as indicated, and antibiotics for infections. In a patient with clinically significant cytopenias and splenomegaly, splenectomy may result in some amelioration of the cytopenia and thereby reduce a patient's transfusion requirement or risk of bleeding or infection. The decision to perform splenectomy as well as the timing of that decision must be individualized for each patient, as there are no series investigating either the short- or long-term effects of splenectomy in systemic mast cell disease. In the future, other agents, such as biologic response modifiers and lymphokines, may be effective in the management of systemic mast cell disease patients with associated hematologic disorders; however, no data currently support their use.

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ROUNDTABLE

DR. AUSTEN: Thank you. Since you're a real hematologist, may I go back to that issue of basophils and mast cells in the circulation? I have two questions. Because the NIH experience has been with patients who certainly are as sick as anybody else's, and I'm not convinced that, let's say, the Mayo's experience involves any more severe disease, has your group ever seen mast cells in the circulation or basophils in the circulation?

DR. PARKER: We occasionally see basophils in the patients who have the myeloproliferative-type presentation. We're not surprised at that. Also you'll see basophils in the CMML category of the myelodysplastic syndromes. But I don't want to imply that they're part of the mast cell disease.

DR. AUSTEN: The point is, I think, that they have to be rechecked by modern criteria. In other words, because there have been reports of basophils in leukemic disorders and because I was curious as to what they were, we analyzed those basophils and, of course, found heparin, which has never been found in a real basophil, so I am not certain whether those basophilic leukocytes in leukemia are of the basophil lineage or whether they, in fact, are of the mast cell lineage and simply made it to the circulation early. It isn't that I know. I am very curious.

DR. PARKER: We have not looked with stains specific for mast cells in those patients.

DR. AUSTEN: Well, we isolated the proteoglycan. You can't fool around with staining, as far as I'm concerned, in part because the mucosal-type mast cell will have oversulfated chondroitin sulfates. We went to the trouble to sulfate-label and then characterize that they had some heparin. That doesn't mean I know how they should be classified. But in a myeloproliferative disorder I think it's worth at least not assuming they were basophils. We went after them on the assumption they were basophils because we wanted to get some chemical data on basophils and, when we were all done, decided we couldn't classify them.

DR. METCALFE: Well, we still don't know the lineage relationships, but let's talk about mast cells and basophils a moment. There is a paper by an electron microscopist reporting hybrid mast cells and basophils in basophilic leukemia. I've looked at it; there seem to be granules from both lineages. Now, that's against the prevailing notion that maybe mast cells are closer to monocytes. But, when you look at the problem the way hematologists do, which is by colony-forming units, the stem cells are totally at the whim of whatever growth factors you put in. At this point the only widely available growth factor for mast cells is really a general colony-stimulating factor, IL-3. So that if you don't see mast cells in colonies, it may be because we don't have the right growth factor. As soon as we get some growth factors that will encourage the proliferation of committed mast cell progenitors, we can begin to look and see if mast cells and basophils, or macrophages, or whatever, occur within the same colony-forming unit. Then I think we'll know the answer to this question.

There is one other observation that we made but have never been able to understand. When we tried to grow marrow from some patients with mastocytosis and myelodysplastic syndromes, we found large numbers of basophils and no mast cells. What's the lineage relationship of these two cells? At this point we don't know.

DR. AUSTEN: I have no objection to you finding basophils because the

eosinophils are there and they are really much closer to each other than they are to mast cells. Some Austrian investigators have clearly distinguished basophils from mast cells, based upon the monoclonal antibodies used for phenotyping at the cell surface, and put basophils in the myelocytic lineage and mast cells in the monocytic lineage.

DR. PARKER: We do see two relatively distinct populations of cells with deep basophilic granules. We have ones that look like classical, traditional basophils on light microscopy, and we'll call those basophils. Then we see those that look more like monocytes with basophilic granules; I believe those are circulating mast cells.

DR. AUSTEN: But a preleukemic bone-marrow abnormality is less interesting to me than what you find in your other 60% of patients who can have very substantial mastocytosis. To the best of my knowledge, nobody has seen increased mast cells in the circulation, nobody has seen basophils in the circulation, but about a third will have eosinophils.

DR. METCALFE: On a number of occasions, we've looked at patients who had very severe mastocytosis, in the aggressive or indolent category, and we have never found more than maybe a rare mast cell in the circulation after looking at thousands of cells. They look like what Dr. Parker just mentioned but you don't see them to any number.

DR. AUSTEN: Now, Dr. Parker, if mast cells come from bone marrow and, in fact, we all now believe they do, and if we have patients with urticaria pigmentosa and mast cells in bone marrow, why are we not finding them in the blood and how are we getting all these peripheral lesions?

DR. PARKER: There are two potential ways that they can get there: through the blood and through the lymphatics. If bone marrow were the only site of production, then I would say that they've got to be going through the blood. But we know that some cells that are primarily produced in the marrow were produced elsewhere in fetal life, or precursors were formed elsewhere and then they migrated to what became the bone marrow, but that there are rests of those cells in extramedullary sites. I don't know enough about mast cells to give you an intelligent answer, but it's conceivable that that could be happening.

DR. WEIDNER: I have a different question. How did you decide that there are no mast cells in the circulation? You said you counted thousands of cells. Maybe the way to go would be to use flow cytometry.

DR. METCALFE: Well, first of all, I didn't say there weren't any. I said they were rare. And there's a big difference. If you assume that a mast cell lives three months or more, you don't have to have very many mast cells migrate to a tissue. So if you only saw one per thousand white blood cells, that may be all that's necessary to populate peripheral tissue.

DR. PARKER: If I may draw an analogy between mast cells and megakaryocytes: megakaryocytes are produced in the marrow. You can also find them in the lungs, but they are not produced in the lungs. There's been a big controversy about this. In a rare normal peripheral blood sample, you will find a megakaryocyte. That's all it takes. One will occasionally exit the marrow into the blood, and end up in the lungs. These are long-lived cells, so you don't need very many out there to spread them around. And to support what Dr. Metcalfe said, that may be enough, a rare mast cell may be enough.

DR. METCALFE: There's another possibility, too. They may not be recognizable as mast cells by the standard morphologic criteria. It may be that they don't have granules yet; they may look like a large lymphocyte.

DR. PARKER: Or they could look like a regular monocyte or a slightly dysplastic monocyte.

DR. METCALFE: Recently, we published that you can sort cells from murine marrow on the basis of an IgE receptor. Some of the positive cells didn't look like mast cells, yet when we cultured them with murine IL-3, they matured into mast cells. This is also along the line of what Thomas Huff has shown at the Medical College of Virginia. Through his technique, he can get what he calls a committed mast cell progenitor. He believes that a second mast cell factor is a granule-maturation factor, which is in the periphery. Either one of those, or a combination, would explain what we see.

DR. KETTELHUT: In the pediatric literature, there have been reports of occasional circulating mast cells. And these children seem to do well.

DR. PARKER: I want to point out a potential hematologic problem not related to marrow histopathology. Mast cells contain heparin, and in someone with a large mast cell burden there is the theoretical risk that if they degranulate mast cells, the cells will release enough heparin to cause a bleeding diathesis. To my knowledge, a systemic bleeding diathesis has never been documented in a mast cell patient, although local bleeding clearly occurs.

A case in point was the young boy Dr. Kettelhut presented. He was about two months of age. He had a massive cutaneous infiltration with mast cells, and he bled significantly when we biopsied his marrow. Local procedures can be associated with increased local bleeding, but as far as a disseminated systemic hemorrhagic diathesis, I'm not aware of that happening, and I don't think people taking care of mast cell patients should be overly concerned with that possibility.

DR. ROBERTS: We draw a lot of partial thromboplastin time (PTT), and people with horrible attacks will have a doubling, tripling of the PTT, and then it goes back to normal again. But, it takes an enormous amount of mast cell activation to make an abnormal PTT.

DR. KETTELHUT: Some young infants, when they have bullous eruptions and a shock-like state and gastrointestinal bleeding, also have some abnormalities of the clotting system, to the point that it's been suggested that they should be given protamine. That's never been done, and the circulating anticoagulant has yet to be unequivocally identified as heparin.

DR. PARKER: I wouldn't argue that you can't get very high local levels, for example, children who have bullous eruptions and bleed into the bullae certainly can have very high local levels of heparin. But I'm talking about a disseminated intravascular coagulation type of picture: primary, de novo, as a consequence of systemic mast cell degranulation.

DR. AUSTEN: It's important to keep in mind that not all proteoglycans are heparin.