The Liver, Spleen, and Lymph Nodes in Mastocytosis

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In systemic mastocytosis the liver, spleen, and lymph nodes may be infiltrated by mast cells, with patterns of infiltration specific for each tissue. This may result in hepatosplenomegaly and enlarged lymph nodes. Extensive involvement with mast cells may also be associated with organ dysfunction. Specifically, in the case of liver, mast cell infiltration may result in fibrosis, portal hypertension, and abdominal ascites. Clinically significant involvement of the liver, spleen, and lymph nodes appears to be more common in patients with aggressive forms of mastocytosis, including those with a hematologic disorder. *J Invest Dermatol 96:45S–46S, 1991*

Irrespective of the category of mastocytosis into which a given patient is placed, the one constant is that over time patients with mastocytosis tend to increase their mast cell numbers in the skin, gastrointestinal tract, bone marrow, lymph nodes, liver, and spleen. Significant mast cell burdens are most obvious in those patients with long-standing indolent mastocytosis or with aggressive forms of the disease, such as seen in categories II and IV. Patients in these situations may exhibit a clinically relevant increase in the size of their lymph nodes, liver, and spleen.

In routine management of patients with mastocytosis, the lymph nodes, liver, and spleen are rarely biopsied and examined unless significant organ dysfunction has developed, or unless the concern is of a malignant process for which a biopsy is appropriate. Thus, existing data on the patterns of mast cell infiltrations and their consequences in the lymph nodes, liver, and spleen exhibit a bias for categories II and IV. Similarly, available information is insufficient to distinguish tissue-specific disease features typical for various categories of mastocytosis or to correlate the appearance of the mast cell within tissues and the category of disease. What is clear, however, is that an examination of lymph nodes, liver, and spleen from patients with mastocytosis does reveal significant pathology associated with mast cell infiltrates.

Two careful pathologic studies reveal the consequences of mastocytosis in the lymph nodes, liver, and spleen [1,2]. Anecdotal experience as reported by other groups [3] has helped substantiate these reports. In one report [1], a review of the records of a group of 58 mastocytosis patients revealed peripheral lymphadenopathy in 26% and central lymphadenopathy in 19% of patients at the time of diagnosis. Lymphadenopathy was more pronounced in patients with associated hematologic malignancies and aggressive nonleukemic mastocytosis. Within lymph nodes, mast cell infiltrates were most common in the paracortex, followed by the follicles, the medullary cords, and the sinuses (Table I). Early infiltrates were exemplified by clusters of mast cells.

Eosinophils accompanied mast cell infiltrates in lymph node tissues in approximately one half of the patients' lymph nodes. In two of 19 patients examined [2], there were dense eosinophilic abscess-like lesions near mast cells. Blood vessel proliferation was observed in four lymph nodes in the paracortical areas infiltrated by mast cells. Four of 19 patients exhibited extramedullary hematopoiesis. The authors noted that mast cell infiltrates in lymph node tissues could resemble T-cell lymphomas in their paracortical distribution, clear cytoplasm of the mast cells in some cases, and an associated vascular proliferation and eosinophilia. When mast cells replaced the lymphoid follicles, the pattern often bore a resemblance to follicular hyperplasia or lymphoma.

Another study, involving a review of hepatic material from 13 patients, documented the patterns of mast cell involvement in this organ system [2]. Patients in this series appeared to have more aggressive mastocytosis, as demonstrated by abdominal pain in six, significant diarrhea in seven, and ascites in five of 13 patients. The liver was clinically enlarged in 10 patients.

Hepatic fibrosis, the most frequent finding in the liver, was noted in all liver specimens examined (Table II). Fibrosis was minimal in one, mild in six, moderate in four, and severe in two patients. In the latter two patients, the presence of pseudo-lobes warranted the diagnosis of cirrhosis. Fibrotic patterns included a periductil pattern and portal to portal fibrosis. Five patients had fatty metamorphosis, and sinusoidal dilatation was noted in five. Inflammation was usually mild. The most common cellular infiltrate was mononuclear. Cholestasis was noted in only one patient. The usual liver test values (except for alkaline phosphatase) were often normal, despite significant hepatic involvement. Also, the severity of hepatic involvement did not correlate with the size of the liver or the liver function tests.

Splenic involvement is also common in mastocytosis, being seen in 28 (48%) of one group of 58 patients [1]. The authors of this study reviewed the pathologic features of 16 spleens. All but one of the spleens showed a paratrabecular distribution of mast cell infiltrates: 10 (64%) perifollicular, two (14%) follicular, and one (7%) diffuse (Table III). Various degrees of trabecular fibrosis were present in biopsies examined, as were eosinophilic infiltrates. Seventy-one percent of biopsies showed extramedullary hematopoiesis.

Grossly, the spleen often appeared to have a thickened capsule due to fibrosis. Cross sections of the parenchyma showed multiple 1–2-mm nodular areas attributed to fibrosis or infiltrations. Again, mast cell infiltrates in the spleen were seen to produce a lesion that could be confused with T-cell lymphoma, follicular hyperplasia and lymphoma, Kaposi's sarcoma, or a granulomatous process. Particularly in the spleen, mast cell infiltrates could resemble a myeloproliferative disorder or hairy cell leukemia. Markedly increased splenic weights (greater than 700 g) generally occurred in patients who fit into unfavorable categories of mastocytosis, for example, aggressive

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Abbreviation:

TGF-beta: transforming growth factor-beta

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Table I. Lymph Node Pathology: Mast Cell Distribution

Sinusoidal
Follicular
Perifollicular
Paracortical

Table II. Liver Pathology

Mast Cell Distribution
Sinusoidal
Portal
Other
Tissue Eosinophilia
Fibrosis

Table III. Spleen Pathology

Mast Cell Distribution
White Pulp: Follicular, Perifollicular,
Perivascular
Red Pulp: Perivascular, Diffuse
Fibrosis
Trabecular, Paratrabecular

mastocytosis and mastocytosis with an associated hematologic disorder.

In summary, the lymph nodes, liver, and spleen are common sites of involvement in mastocytosis. These organs appear particularly susceptible in cases where the disease is aggressive or associated with a hematologic disorder. Particular attention must be directed toward the proper identification of lesions within these organs as due to mast cells and associated pathology rather than to other malignant conditions. Fibrosis associated with mast cell proliferation and eosinophilic infiltrations are common accompaniments of the disease process.

It is interesting to speculate on the association between mast cells and fibrosis. Fibrosis accompanies mast cell infiltrates, particularly in lymphoid tissues and in the bone marrow. Mast cells themselves may produce certain connective tissue components, and mast cells do synthesize TGF-β and other agents that may promote fibrosis. Ultimately, in the case of liver disease, the fibrosis may lead to ascites, which requires aggressive therapy (see Metcalfe, page 55).

The association of mast cells and lymphoid tissues may reflect either regional overproduction of growth factors for mast cells, or a predisposition for mast cells at certain sites within the body, particularly the lymph nodes, liver, and spleen.

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ROUNDTABLE

DR. AUSTEN: Thanks very much, Dr. Metcalfe. Is the fibrosis in the lymph nodes as dramatic as in the liver, spleen, and bone marrow?

DR. METCALFE: No, it is present but it's less dramatic.

DR. AUSTEN: Is there any information on the relative degrees of maturity of the mast cells in the organs in which fibrosis is or is not present?

DR. METCALFE: I know what you're getting at. A couple of years ago you suggested to me that immature mast cells might be associated with fibrosis. In fact, in these tissues, the mast cells associated with fibrosis may be primitive.

DR. MINER: I'm not sure I understand what the patient population is and how it's been obtained.

DR. METCALFE: Well, as I've said, there's a clear population selection in the papers cited in this report. These studies are biased for people with severe, advanced, and probably aggressive disease, often associated with a hematologic malignancy.

DR. AUSTEN: On the other hand, a very substantial fraction of our patients, some of whom we've followed for almost a decade, have marked, rock-hard hepatosplenomegaly and, at the moment, they behave no differently than anybody else in our series. In fact one patient now has a large liver and didn't a year ago.

DR. METCALFE: I don't know what to say about that, except that we have started a prospective study to look at liver fibrosis. We set very stringent criteria for evidence of liver disease. We've been applying those criteria to our patient population for the past year, and we've biopsied three or four livers. In other words. I also believe that patients with indolent disease get mast cells in the liver and spleen; they may get some enlargement and probably some degree of fibrosis. The really dramatic cases, however, are those from which tissue is obtained.

DR. SOTER: I have been intrigued by the absence of skin fibrosis, and yet in scleroderma there are increased mast cells in skin and you get incredible changes. Do we know the maturity of those mast cells in scleroderma?

DR. METCALFE: No, I don't think we do. We do know that some of them apparently are degranulated. Clearly the pathology in scleroderma skin is not solely dependent on mast cells, otherwise we would see it in mastocytosis, so that must depend upon specific inflammatory triggers, which turn on these cells to make the changes of scleroderma.

DR. PARKER: I just want to go back to Dr. Miner's point. I think one of the problems in going through literature reviews and trying to figure out the pathology is that the pattern we now recognize as fulminant mastocytosis, if I may introduce another word, wasn't recognized as mast cell disease 20 years ago. A patient with more of a myeloproliferative or a myelodysplastic picture was not reported as having systemic mast cell disease. Therefore, the physician wouldn't have reported the myelofibrosis or the organ fibrosis consequences of systemic mast cell disease. Current authors recognize those findings as being part of the spectrum of systemic mast cell disease. We'll see more reports, such as the one out of the Mayo Clinic, showing extensive fibrosis in end-organs in the aggressive mast cell syndromes.

DR. AUSTEN: My only problem is with the word "aggressive" mast cell disease. Our patients with palpable hepatosplenomegaly and portal hypertension do not have an aggressive mast cell disease. We have a nomenclature problem.

DR. METCALFE: Well, let me say two things. The first is that the data I presented on liver and spleen disease should not be taken as representative of all patients. These are highly selected data. You don't put somebody in an aggressive category based upon this kind of supposition. Secondly, we still are faced with a problem in category I, which is that it is still too diffuse. My own bias is that if we can figure out a way to better divide patients into clear categories, that will someday be followed by a recognition that those categories actually represent distinctly different lesions — perhaps overproduction of IL-5 in one instance, overproduction of IL-3 in another case, stem cell growth factor in still another.

DR. AUSTEN: We will struggle more with it at the end of the day.

DR. MINER: In your patients who have large livers and spleens, when you biopsy their livers, do you see increased mast cells?

DR. AUSTEN: In the periportal spaces, to the best of my recollection, there's fibrosis, some mast cells and some eosinophils, and the eosinophils are probably more striking than the mast cells.

DR. MINER: I'm not impressed by the fact that mast cells are highly concentrated there. Let me just shake your paradigm a little bit. In a well-described entity in which there is fibrosis of the liver, patients have huge numbers of mast cells in their terminal ileum. This implies that perhaps the fibrotic factors are being released in the gastrointestinal tract, being cleared in the liver and, with a very efficient high pass, you have injury to the liver without systemic effects.

DR. AUSTEN: In a sense I can't tell you you're wrong, but Dr. Metcalfe showed you the pathology.

DR. METCALFE: There really is no discrepancy here between what Dr. Austen is saying and what's presented here. We see patients that have large liver and spleens but don't get into the kind of problems that lead to biopsies. Occasionally such patients will come in to us with a liver biopsy, and they have some increase in mast cells.