A Retrospective Analysis of Bone Scan Abnormalities in Mastocytosis: Correlation with Disease Category and Prognosis

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To investigate the usefulness of bone scintigraphy in systemic mastocytosis (SM), the scans of 73 patients were retrospectively reviewed and correlated with disease category. **Methods:** A modification of a previously described method for bone scan classification in this disease was used. In addition to the group as a whole, two subsets of patients with multiple bone scans were identified for closer analysis: those with (n = 13) and without (n = 12) scintigraphic evidence of progression of disease. **Results:** Overall, patients with more aggressive SM tended to have increasingly abnormal initial bone scans ($p2 = 0.0003$), although there was a considerable degree of overlap. Of patients undergoing serial studies, those with scintigraphic progression also tended to have more aggressive disease ($p2 = 0.006$) and a poorer prognosis than those with stable bone scans. **Conclusions:** Both the degree of abnormality on initial bone scan and progression of scintigraphic abnormalities with serial scanning appear to correlate with the presence of more aggressive systemic mastocytosis. Based on the patterns seen, in many cases this may be a reflection of bone marrow expansion, which in turn probably reflects increased marrow disease.

Key Words: mastocytosis; bone scan; bone marrow

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Systemic mastocytosis (SM) is a rare disorder of mast cell proliferation involving multiple organs. Most commonly affected are the skin, GI tract, liver, spleen, lymph nodes, bone and bone marrow. Systemic mastocytosis usually has an indolent course but may present with a more malignant process in some cases, most frequently with an associated hematologic disorder (*1*). Disease categorization and prognosis are based heavily on bone marrow biopsy and aspirate (bone marrow) results (*2–4*).

Radiographic bony involvement is seen in approximately 70% of patients with SM, with the skull, vertebrae, ribs and pelvis most commonly affected (*5*). On x-ray, abnormalities may be diffuse or circumscribed, and osteolytic, osteoblastic or mixed in character. Generalized osteopenia has been described (*6–8*). Technetium-99m-MDP bone scans also reflect skeletal involvement in SM, and often have a characteristic (albeit nonspecific) appearance. In order to further assess the clinical utility of bone scanning in this disease, records of SM patients were retrospectively reviewed focusing on patients who had multiple scans.

METHODS

Patient Population

All patients were enrolled in an ongoing prospective study of the natural history of SM. The diagnosis of SM was based on findings of increased mast cell numbers in one or more tissues including the skin, liver, spleen, lymph nodes and bone marrow. Systemic mastocytosis disease categories were assigned according to a classification system adopted by a consensus conference (*9*) with minor modifications (Table 1).

Bone scans performed between February 1980 and April 1992 on 76 SM patients were reviewed. Three patients whose scan interpretations were complicated by probable trauma were excluded from analysis. Of the remaining 73 patients, 25 had multiple scans. These patients were divided into two groups depending on whether their bone scans were stable (Group A) or demonstrated progression (Group B), and their medical records were reviewed in greater detail for the following information: sex, age at onset of disease, skin involvement, bone pain and bone marrow results. Age at onset of disease was defined as the age at which signs and symptoms of SM were reported to have first appeared, regardless of when the actual diagnosis was made. Bone pain was attributed to SM when no other cause was obvious. Bone marrow specimens were considered positive when characteristic lesions consisting of aggregates of mast cells often associated with eosinophilic and lymphocytic infiltrates were seen (*2,10*). Nondiagnostic and questionable marrow results were scored as negative for SM.

Bone Scans

Bone scans were performed approximately 3 hr following injection of ^{99m}Tc-MDP (25 mCi adult dose, 300 μCi/kg in children). Outside studies were also sometimes available. Scans were reviewed by two physicians blinded to the patients' clinical status, but not the diagnosis of SM, and any discrepancies were settled by consensus.

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TABLE 1
Systemic Mastocytosis: Disease Categorization

Category	Description
1a	Indolent disease—skin disease only
1b	Indolent disease—systemic disease with/without skin involvement
2	Mastocytosis associated with a hematologic disorder
3	Aggressive disease with lymphadenopathy and eosinophilia

A modified version of the system described by Rosenbaum et al. (*11*) was used to classify bone scans (Table 2). Modifications included subdividing Type III scans to better reflect disease progression within this group, and the addition of a Type V scan (seen in 1 patient). Progression from one Type III subclassification to the next was sometimes based on mild changes, best appreciated by sequentially reviewing all of a patient's scans. A positive bone scan for SM was defined as Type II or greater. Heterogeneous increased skull uptake was scored as a single abnormality (Fig. 1), and findings characteristic of degenerative or arthritic disease were excluded for scoring purposes. Abnormalities attributable to known trauma were also excluded. Examples of Type IIIB and IV scans are provided (Figs. 2, 3).

Statistics

Mantel's test for trend in row by column (RxC) contingency tables (*12*) was employed for statistical analysis. For purposes of disease severity ranking, Categories 2 and 3 were combined since both represent different forms of aggressive SM. For analysis of subgroups A and B, disease categories at the time of the final bone scan (Group A), or at the time bone scan progression was first observed (Group B), were used.

TABLE 2
Bone Scan Classification System

Bone scan type	Description
I	Normal
II	Unifocal disease
IIIA	Multifocal disease
IIIB	Multifocal with diffuse features
IIIC	Same as IIIB with increased diffuse uptake
IV	Diffuse increased uptake (superscan)
V	Metastatic calcification

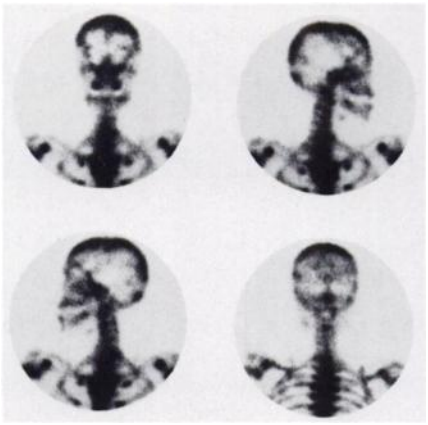

FIGURE 1. Heterogeneous skull uptake is scored as a single lesion for bone scan classification purposes.

RESULTS

The initial bone scan types, disease categories and ages at the time of the initial bone scan for 73 SM patients are shown in Table 3. In eight patients, bone marrow studies

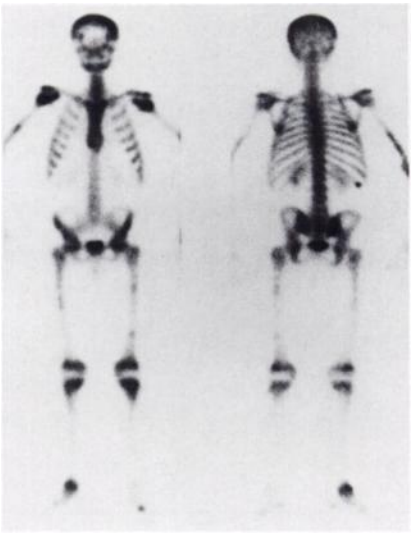

FIGURE 2. Example of a Type IIIB bone scan in 27-yr-old male with Category 1b SM showing multifocal abnormalities with moderately diffuse uptake, particularly in femurs. The focus in the right ankle is post-traumatic, as are probably the foci in the right posterior 11th rib and left foot.

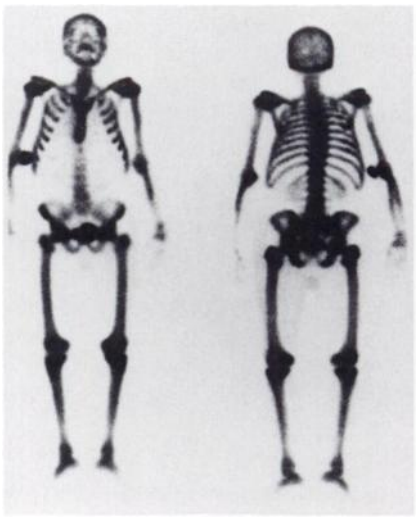

FIGURE 3. Example of a Type IV scan (superscan) in a 76-yr-old male patient with Category 1b SM. Evidence of dose infiltration is seen in right arm.

TABLE 3
Patients in Each Disease Category versus Initial Bone Scan Type

Disease category	Type I	Type II	Initial Bone Scans: Type IIIA	Type IIIB	Type IIIC	Type IV
1a	5	3	1	0	0	0
1b	7	3	9	11	8	5
2	0	1	1	4	1	1
3	0	0	0	3	1	1
nbm*	3	2	1	1	1	0
Total	15	9	12	19	11	7
Mean age (yr)	25	36	44	50	52	61
(range)	(<1–64)	(25–52)	(29–62)	(25–74)	(27–76)	(36–76)

*nbm = no bone marrow studies obtained.

were not performed and their disease category could not be ascertained. Patients with more advanced SM tended to have increasingly abnormal initial bone scans (p2 = 0.0003), although, as can be seen in Table 3, there was a considerable degree of overlap between groups.

Of the subgroup of 25 patients with multiple bone scans, 12 had stable scan findings (Group A) while 13 demonstrated progression (Group B). One unusual patient progressed from a Type IV superscan to a Type V scan, in which there were areas of abnormal soft tissue uptake and marked absence of activity in bone, consistent with metastatic calcification and a terminal hypercalcemic state.

The clinical characteristics, disease categorization and mortality data for Groups A and B are presented in Table 4. Data on bone scan and bone marrow studies is presented in Table 5. Overall, Group B patients were referred earlier (relative to onset of disease) and more frequently than those in Group A for both bone scan and bone marrow studies. These patients tended to have the more aggressive forms of disease (p2 = 0.006), although the distribution of initial scan types in both groups was similar (p2 = 0.62) (Table 5). In addition, 5/13 (38%) Group B patients had Category 2 or 3 SM, with four patients dying within 1.7–6.4 yr of their first bone scan (mean = 3 yr). This is in contrast to Group A, none of whom have developed more than Category 1b disease. Lengths of follow-up (from the date of initial bone scan) were comparable, with means of 9 and 7.5 yr for Groups A and B, respectively.

Overall, 9/12 (75%) patients in Group A had positive bone scans and 10/12 (83%) have had bone marrow findings consistent with SM. Only one pediatric patient had both negative bone marrow and bone scan studies. In Group B, all patients eventually had positive bone scan and bone marrow findings documented. Unfortunately, adequate data for determining the chronological sequence with

TABLE 4
Clinical Characteristics of Patients with Multiple Bone Scans

	Group A (n = 12)	Group B (n = 13)
Male/Female	5/7	3/10
Mean age at onset of SM	27.8 yr	37 yr
(range)	(2–54)	(16–66)
Age ≤ 18 at onset of SM	4 (33%)	1 (8%)
Skin disease	12 (100%)	9 (69%)
Bone pain	6 (50%)	10 (77%)
SM disease category		
1a	2 (17%)	0
1b	10 (83%)	8 (62%)
2	0	2 (15%)
3	0	3 (23%)
Mortality to date	0	4 (31%)

TABLE 5
Scan and Bone Marrow Data for Patients with Multiple Bone Scans

	Group A (n = 12)	Group B (n = 13)
Mean number of bone scans	2.6	4.1
(range)	(2–5)	(3–8)
Initial bone scan type		
I	3 (25%)	2 (15%)
II	1 (8%)	2 (15%)
IIIA	3 (25%)	1 (8%)
IIIB	2 (17%)	6 (46%)
IIIC	3 (25%)	1 (8%)
IV	0	1 (8%)
Mean time between bone scan 1 and last bone scan (range)	4.2 yr (1–10)	3.8 yr (1–8)
Mean duration of SM at bone scan 1 (range) (range)	13.4 yr (0–30)	5.4 yr (0–15)
Mean duration of SM at 1st pos bone scan (range)	16.9 yr (4–30)	6.1 yr (0–18)
Mean duration of SM at bone marrow 1 range	12.8 yr (0–30)	5.1 yr (0–16)
Mean duration of SM at 1st pos bone marrow (range)	14.9 yr (2–34)	5.6 yr (0–16)

* Bone scan 1 = initial bone scan; bone marrow #1 = initial bone marrow; pos = positive.

which bone scan and bone marrow studies became positive in most patients was unavailable. This was usually because both studies were positive the first time they were obtained (5/12 Group A and 10/13 Group B), or because they were not performed concurrently. Of the cases in which a chronological sequence could be determined, however, three patients had positive bone scans with concurrently negative bone marrows (documented for up to 4.5 yr in one patient). Conversely, four patients have had negative bone scans with up to a 3-yr history of positive bone marrow examinations.

DISCUSSION

Bone scanning provides an efficient, noninvasive method of assessing and following active bone and bone marrow involvement in patients with SM. The degree of bone scan involvement in SM has been previously shown to correlate with urinary and plasma histamine levels and therefore, presumably, with disease activity (*11*). Likewise, in the present series, patients with more aggressive SM tended to have increasingly abnormal initial bone scans.

Of our 73 patients, 79% of initial bone scans were positive with changes presumably due to SM. This compares to the approximately 70% of SM patients with radiographic bone disease (*5*) and the 74% with positive bone marrow studies (*4*) reported in other series. However, bone scan findings do not always correlate with x-ray (*11,13,14*) or bone marrow (*4*) results. In the present series, patients with positive bone marrows and negative bone scans were identified, as were those with negative bone marrows and positive scans. These discrepancies are likely due in part to the random nature of bone marrow sampling and the high sensitivity and nonspecific nature of bone scan findings.

Rosenbaum et al. (*11*) grouped bone scans by degree of involvement, which progressed from normal to focal to diffuse as the extent of disease increased. We similarly found that disease progression on serial bone scans involved a general shift from focal to diffuse disease, and that it was helpful to subdivide the multifocal Type III category to reflect these changes (Table 2). In addition to advancing bony disease, the shift to diffuse findings may be due in part to secondary bone marrow expansion as bone marrow involvement increases. Bone scan findings characteristic of marrow expansion include diffuse increased tracer uptake in areas such as the skull and distal long bones (*15, 16*), and marrow expansion in SM has been documented using radionuclide marrow scans (*13,14,17*).

In this study, patients in whom progression of bone scan abnormalities occurred were referred for bone scan and bone marrow studies an average of 8 yr earlier than those with stable scans, presumably reflecting the aggressive nature of the disease in these patients such that their clinical status prompted earlier evaluation. Similar differences in disease duration at the time of the first positive bone scan or bone marrow studies were seen, although this may also be a result of earlier testing. (Had Group A been studied earlier, their results may also have been positive.) The aggressive nature of the SM in Group B is also evident in that 5/13 (38%) of these patients had Category 2 or 3 disease, with four patients dying of disease-related complications to date. In contrast, all patients in Group A have had an indolent course with no fatalities, despite longer durations of disease.

Recently, Lawrence et al. (*4*) published the results of a prospective study of 46 patients from this institution focusing on bone marrow pathology. Dividing their patients into those with and without SM of the marrow, they found that a positive bone marrow (Category 1b, 2 or 3) carried a poor prognosis, with 10/32 (31%) of such patients dying during follow-up, compared to 0/14 patients who had negative marrows (Category 1a). Positive bone scans were found in similar percentages of both groups and did not correlate with prognosis, but were not further categorized.

Taken together, the results of these two studies suggest that after first identifying a poor prognosis group with positive bone marrow findings, serial bone scans may then help to further identify those most likely to have an accelerated course. Also, in patients with negative bone marrows, progression of bone scan abnormalities may identify a subgroup in whom repeat bone marrow study and closer clinical follow-up should be considered.

CONCLUSION

Bone scanning provides an efficient, noninvasive method of assessing and following active bone and bone marrow involvement in patients with SM. In some instances, the bone scan will be abnormal despite a negative bone marrow. As the disease progresses, abnormalities on bone scan tend to become increasingly diffuse in nature, probably reflecting secondary bone marrow expansion as a result of increasing bone marrow involvement. Both the degree of abnormality on initial bone scans and progression of scintigraphic abnormalities with serial scanning appear to correlate with the presence of increasingly advanced systemic mastocytosis. Further study with periodic, concurrent performance of both bone scans and bone marrows is needed to clarify the role of these studies in managing these patients.

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