# Patterns of Skeletal Scintigraphy and Their Relationship to Plasma and Urinary Histamine Levels in Systemic Mastocytosis

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**Scintigraphic findings in ten cases of systemic mastocytosis are described. Four radionuclide bone patterns were noted: normal, unifocal, multifocal, and diffuse. Compared with radiographic surveys, bone images were better able to show the widespread skeletal involvement in patients with diffuse disease, and to detect a greater number of focal lesions. Serum calcium, phosphorus, and bone-derived alkaline phosphatase, as well as urinary calcium, phosphorus, and hydroxyproline levels, were usually within normal limits even when the bone scintigrams were clearly abnormal. Plasma and urinary histamine levels were highest in patients whose bone images detected widespread skeletal involvement. In systemic mastocytosis, not only does scintigraphy document active bone disease more effectively than laboratory studies of bone metabolism and radiographs of bone, but it also appears to reflect the general severity of the disease process.**

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Systemic mastocytosis is a condition characterized by the presence of excessive numbers of mast cells in the skin, bone marrow, liver, spleen, gastrointestinal mucosa, and lymph nodes (*1*). The condition in which excess mast-cell numbers can be detected only in the skin is clinically more benign and is termed urticaria pigmentosa. In systemic mastocytosis, patients exhibit a variety of symptoms including pruritis, bone pain, flushing, abdominal pain, diarrhea, and syncope. These problems are associated with an excess production of such mast-cell-derived mediators as histamine (*2*), prostaglandin $D_2$ (*3*), and heparin (*4*).

The skeleton is one of the most frequently involved extracutaneous organs in mastocytosis (*5,6*). The radiographic osseous manifestations of systemic mastocytosis have been classified as either circumscribed or diffuse, with sclerotic, lytic, or mixed changes in the affected bones. The roentgenographic assessment of skeletal involvement usually requires a full skeletal survey. Several case reports have suggested that skeletal scintigraphy may be a better method to assess active skeletal disease in systemic mastocytosis. Bone images in these instances were reported as exhibiting either diffuse (*7,8*) or multifocal (*9,10*) patterns. To determine the usefulness of skeletal scintigraphy in assessing bone involvement in systemic mastocytosis, we performed bone scintigrams in ten patients with documented systemic mastocytosis. We noted four distinct bone-image patterns showing progressively severe skeletal disease. The scintigraphic degree of skeletal involvement was correlated with disease severity as determined by plasma and urinary histamine levels (*11,12*).

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## MATERIALS

Patients were evaluated for extent of disease by history, physical examination, laboratory studies, and radionuclide bone imaging. Radiographs were used to focus on symptomatic areas and on abnormal areas that had been detected with bone images. Three patients had complete radiographic bone surveys. When appropriate, the evaluation included radionuclide liver-spleen images and biopsies of bone marrow, liver, and skin. Multiple histamine determinations were performed on each patient over the 6-mo period of this study. Urinary hista-

**TABLE 1. CHARACTERISTICS AND SKELETAL DATA IN PATIENTS WITH SYSTEMIC MASTOCYTOSIS**

| Patient | General characteristics | | Osseous involvement by: | |
|---|---|---|---|---|
| | Age/sex | Sites of involvement | Tc-99m scintigram | Radiograph |
| 1 | 38/F | Skin,* marrow,* liver | normal | Focal area of sclerosis, left humerus |
| 2 | 64/M | Skin,* marrow,* gastrointestinal | normal | Generalized osteopenia |
| 3 | 52/F | Skin,* skeletal, liver, spleen | unifocal | Generalized osteopenia |
| 4 | 35/F | Skin,* skeletal* | unifocal | Normal |
| 5 | 43/F | Skin,* skeletal, gastrointestinal | unifocal | Normal |
| 6 | 48/F | Skin,* skeletal,* marrow gastrointestional | multifocal | Mixed lysis/sclerosis, spine and pelvis |
| 7 | 27/M | Skin,* skeletal, spleen | multifocal | Generalized osteopenia; healed fracture, right tibia and fibula |
| 8 | 33/F | Skin,* marrow,* liver, spleen, skeletal | diffuse | Mixed lysis/sclerosis of spine; focal defects, left iliac wing |
| 9 | 58/F | Skin,* marrow,* liver,* spleen, skeletal* | diffuse | Mixed lysis/sclerosis of spine; compression fracture, T12 |
| 10 | 63/M | Skin,* marrow,* liver, spleen, gastrointestional, skeletal | diffuse | Diffuse sclerosis, spine and ribs |

* Increased mast-cell number documented by biopsy.

mine was measured by a method based on cation-exchange chromatography, organic solvent extraction, *o*-phthalaldehyde condensation, and comparison of the fluorescence with portions of each sample digested with diamine oxidase (*13*,*14*). Plasma histamine was measured by a modification of the single-emitter enzymatic assay involving extraction of tele-methylhistamine into chloroform and isolation of the 1-[$^3$H-methyl]histamine by thin-layer chromatography (*15*). Serum calcium, phosphorus, and alkaline phosphatase with bone fractionation, as well as urine calcium, phosphorus, and hydroxyproline levels were performed by standard laboratory procedures at our institution.

The bone scintigrams were obtained using a whole-body scanning camera or a rectilinear scanner, and a large-field-of-view gamma camera with a high-resolution collimator. The cameras were peaked at 140 keV with a 20% window. Whole-body anterior and posterior views, with multiple spot views were made 2–4 hr following i.v. injection of 10–20 mCi (370–740 MBq) of Tc-99m methylenediphosphonate (Tc-99m MDP) (0.15 mCi/kg). Assignment of scintigraphic findings into various categories was performed by a radiologist who was unaware of the patient's history, physical examination, or laboratory findings. The strength of the relationship between plasma and urinary histamine levels and the categorization of bone-image changes was determined with the Kendall rank correlation coefficient with p values for the one-tailed alternative hypotheses, assigning a value of 1.0 to normal, 2.0 to unifocal, 3.0 to multifocal, and 4.0 to the diffuse type of scintigram (*16*). When an individual had several plasma and urinary histamine determinations, the mean value was used in the calculation of the correlation.

## RESULTS

Demographic data on the patients studied is presented in Table 1 along with bone-imaging study and roent-

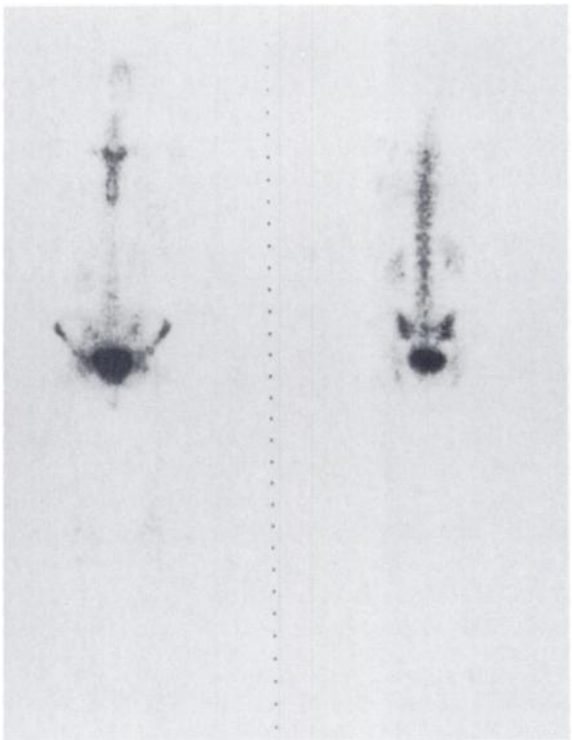

**FIG. 1.** Normal pattern of bone image (Patient 4 before development of focal rib lesion).

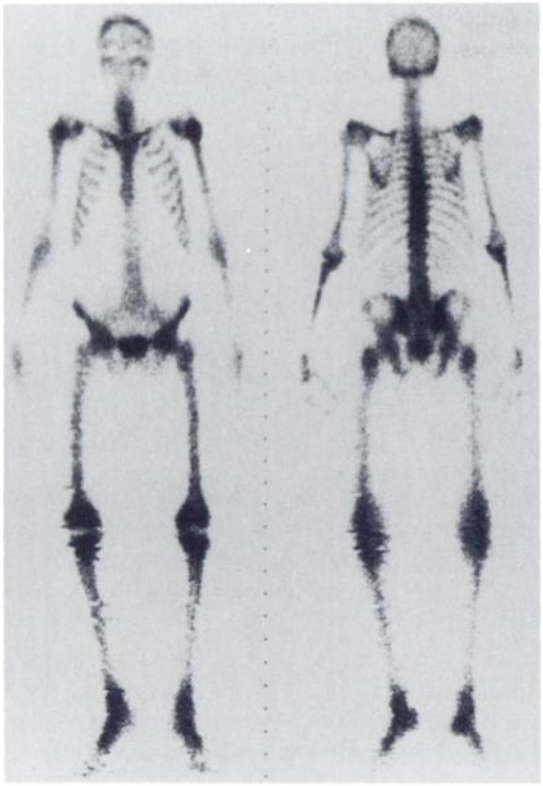

FIG. 2. Anterior (L) and posterior (R) whole-body images show uniformly increased skeletal activity (diffuse pattern, Patient 10).

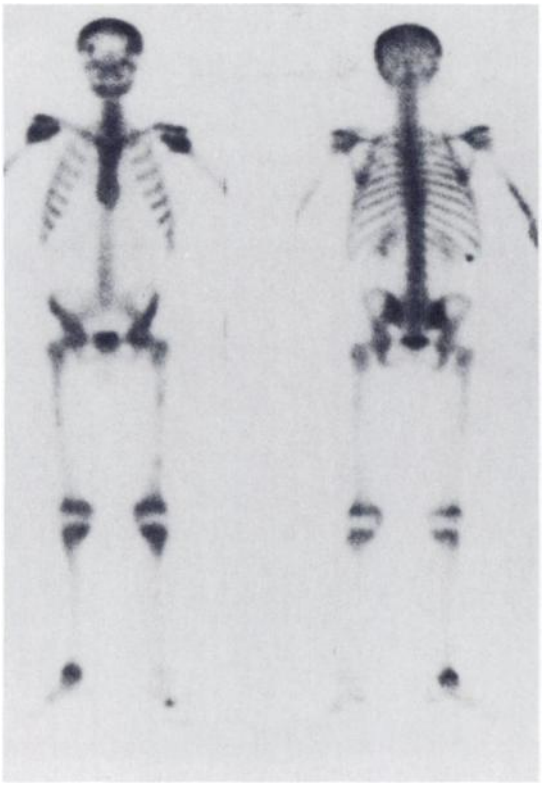

FIG. 3. Anterior (L) and (R) posterior whole-body images show multifocal areas of increased tracer accumulation (multifocal pattern, Patient 7).

genographic findings. Scintigraphic abnormalities, when present, were categorized as unifocal, multifocal, or diffuse. An example of a normal scintigram pattern is shown in Fig. 1. Scintigrams showing diffuse abnormalities were obtained from Patients 8, 9, and 10. The example in Fig. 2 shows an increased tracer accumulation that was evenly distributed throughout the axial and appendicular skeleton, combined with diminished soft-tissue and renal activity, reflecting extensive bone involvement ("superscan"). Patients 6 and 7 exhibited a pattern showing multiple abnormal foci along with a generally increased osseous-to-soft-tissue ratio that was not as intense or uniform as that seen in the diffuse pattern (Fig. 3). Three patients (Nos. 3, 4, and 5) had unifocal areas of increased tracer accumulation. Abnormal foci were located in the skull, humeri, femurs, ribs, and feet.

Bone scintigrams indicating active disease were not well correlated with roentgenographic changes. Patient 1, with a bone image revealing no abnormalities, had a small, ill-defined area of sclerosis in the proximal metaphysis of the left humerus. Patient 6, with multifocal scintigraphic changes, showed diffusely mixed sclerotic and lytic changes on radiographs of the vertebral column and pelvis (Fig. 4), but focal scintigraphic abnormalities in the femurs were not seen by radiograph. Patient 7, whose multifocal image changes showed generalized osteopenia, also exhibited healed traumatic fracture sites in the right distal tibia and fibula that corresponded to

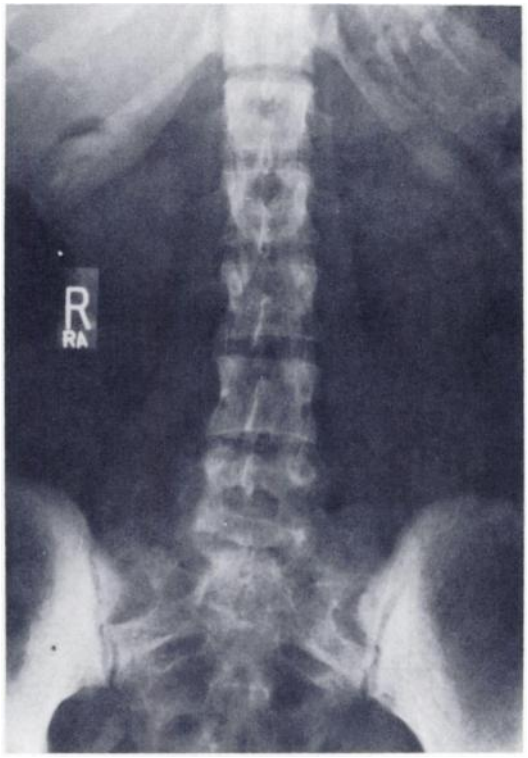


FIG. 4. Mixed sclerotic and lytic changes seen throughout lumbosacral spine and pelvis (Patient 6).

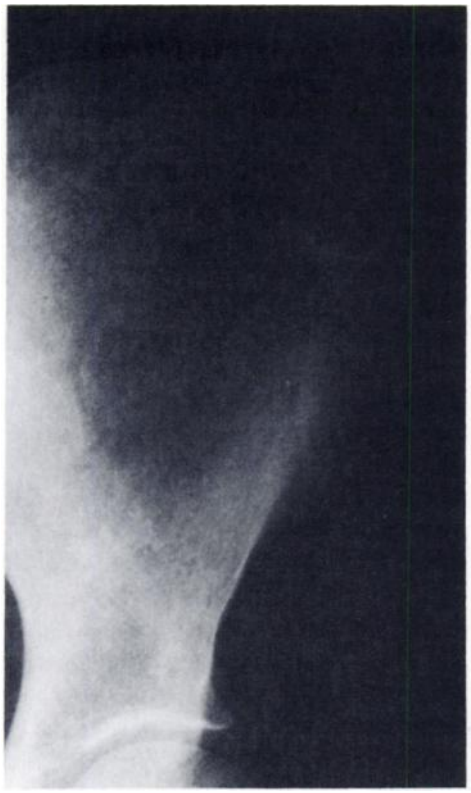

FIG. 5. Well-defined, lytic area with surrounding sclerosis in left iliac bone (Patient 8).

one of 11 areas of focally increased scintigraphic activity. However, other patients with focal scintigraphic changes (15 sites) did not demonstrate any corresponding radiographic changes. Radiographs from Patient 10, who exhibited uniform diffusely increased skeletal tracer uptake, showed generalized increased bone density throughout the vertebral column and ribs. Two patients (Nos. 8 and 9) with a diffuse type of bone image, demonstrated mixed sclerotic and lucent areas in the spine and pelvic bones by radiograph. In Patient 8, in addition, a well-circumscribed 2-cm lytic defect with a thin, well-defined sclerotic rim was present in the left iliac wing (Fig. 5). No corresponding focal abnormality was seen in the scintigram. In Patient 9, a compression fracture of T-12 was seen.

There appeared to be some value in repeating scintigrams to document skeletal disease. One patient (No. 4), suspected of having systemic mastocytosis, had an initial bone-image showing no abnormalities (Fig. 6, left). On a subsequent scintigram 22 mo later (Fig. 6, right), she showed an abnormal posterior right eighth-rib focus; it was biopsied and showed increased granulated cells compatible with systemic mastocytosis. Rib radiographs made before the biopsy indicated no abnormalities.

demonstrate skeletal disease in systemic mastocytosis. None of the patients studied have abnormal levels of serum calcium or phosphorus. Urinary values for calcium, phosphorus, and hydroxyproline were normal. Bone-derived serum alkaline phosphatase was somewhat elevated in two of the three patients with the diffuse type of scintigrams.

It was our impression that more extensive skeletal involvement was observed in patients with severe mastocytosis. It is probable that the degree of mast-cell infiltration in a given tissue is reflected in the histamine content of that tissue (*17*,*18*). As expected, the quantity of histamine or its metabolites found in the urine appears to increase with the clinical severity of systemic mastocytosis (*11*,*12*). We thus compared the bone-image pattern with average urine and plasma histamine values determined for each patient with systemic mastocytosis (Table 2). There were correlations between the pattern of bone image and the levels of plasma and urinary histamine [$\tau = 0.56$ ($p = 0.014$) and 0.369 ($p = 0.0023$), respectively]. Patients with diffusely positive scintigrams had the highest histamine levels, and those with multifocal images consistently had the next highest levels.

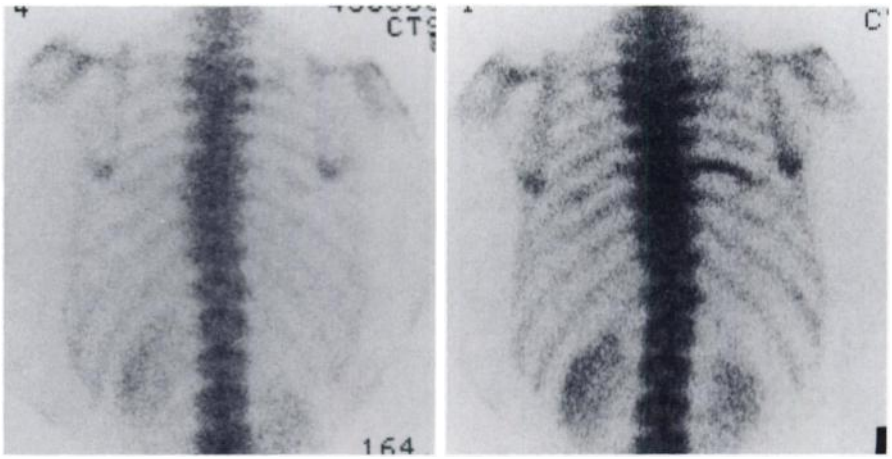

FIG. 6. Left-normal posterior scintiphoto of chest. Right-22 mo later, focally increased activity is present in medial portion of right eighth of right eighth rib (focal pattern, Patient 4).

**TABLE 2. COMPARISON OF BONE SCINTIGRAPHIC PATTERNS AND PLASMA AND URINARY HISTAMINE DETERMINATIONS**

| Patient | Image pattern value* | Plasma histamine pg/ml (N)† | Urinary histamine ng per mg creatinine/ml (N) |
|---|---|---|---|
| 1 | 1 | 891 (6) | 32 (5) |
| 2 | 1 | 1570 (3) | 63 (4) |
| 3 | 2 | 863 (5) | 48 (5) |
| 4 | 2 | 202 (1) | 139 (24) |
| 5 | 2 | 1222 (5) | 60 (5) |
| 6 | 3 | 1521 (4) | 135 (5) |
| 7 | 3 | 2440 (1) | 142 (1) |
| 8 | 4 | 2907 (5) | 143 (7) |
| 9 | 4 | 2691 (5) | 561 (2) |
| 10 | 4 | 2660 (1) | 651 (1) |

* See Materials section.

† Average value for N determinations. Normal plasma histamine levels are 318.4 ± 25 pg/ml (*15*). Normal urinary histamine levels are 12.2 ± 0.8 ng per mg of creatinine/ml (*14*).

Patients with normal or unifocal scintigrams had similar plasma and urinary histamine levels.

## DISCUSSION

The presence of skeletal disease in systemic mastocytosis has been well documented. Approximately 70% of the patients with the disease have radiographically detected changes in bone formation (*17*). Sagher and Even-Paz described and categorized the bone lesions in systemic mastocytosis (*18,19*). Their descriptive classification of generalized and localized radiographic readings appears to be applicable as well to the spectrum of radiographic findings seen in the patients reported here (Table 1). As in most other disorders affecting the skeleton, radionuclide scintigraphy appears to be more sensitive than radiography in detecting and locating active lesions, especially since many may be asymptomatic and escape detection even on skeletal surveys. Bone scintigrams may show more widespread involvement in patients with diffuse disease and detect a greater number of focal lesions.

The scintigraphic findings in the ten cases of mastocytosis reported in this paper could be divided into four distinct patterns: normal, unifocal, multifocal, and diffuse (Table 1). The diffuse type of scintigraphic findings ("superscans") in systemic mastocytosis are grossly indistinguishable from those of patients with other metabolic diseases such as hyperthyroidism, hyperparathyroidism, renal osteodystrophy, and osteomalacia of other origins (*20,21*). The appearance and distribution of focal scintigraphic defects is also nondiagnostic. Inadvertent misdiagnosis (before bone biopsy) of a malignant osteoblastic metastasis has been reported in a patient with systemic mastocytosis (*22*).

The association of skeletal scintigraphic patterns with extent of disease as assessed by histamine levels (Table 2) is of particular interest. Patients with diffusely positive bone images had the highest mast-cell burden as reflected in plasma and urinary histamine values (Table 2). These patients also complained of severe bone pain and generally required intermittent pain medication. Those patients with multifocal and unifocal lesions had progressively lower levels of histamine in plasma and urine, consistent with our general impression of more moderate disease. Thus the scintigraphic classification of systemic mastocytosis patients may prove to have value in indicating the overall severity of the disease.

In general, the osseous uptake of Tc-99m phosphorus compounds appears to be related to their binding at crystal surfaces and to immature collagen, and is influenced by blood flow and reactive bone formation (*20*). Previous reports have ascribed scintigraphic changes in systemic mastocytosis to bone-marrow mast-cell aggregates that give rise to local bone resorption and reactive formation of new bone, which appears as active areas on skeletal scintigrams (*23*). Histopathologic studies, using undecalcified iliac-crest biopsy specimens from patients with systemic mastocytosis, have shown excess numbers of mast cells, unusual marrow "granulomas," which consist in large part of spindle-shaped mast cells, and histologic evidence of associated accelerated bone turnover and peritrabecular fibrosis (*24*).

The means by which mast cells might influence bone formation has not been explored. The association of severe bone involvement with high levels of plasma and urinary histamine noted in this report leads us to speculate that histamine may be playing some direct role in disturbing normal bone turnover, but the mechanism is unknown. There is some evidence to suggest that the osteopenia associated with mastocytosis is mediated by the chemical products of mast cells. Long-term therapy with heparin—another prominent component of mast cells—has been shown to result in osteopenia (*25*). Heparin is a potent in vitro bone-resorbing agent. Senile osteoporosis has also associated with the presence of increased numbers of mast cells (*26*). Regardless of the pathophysiology, radionuclide bone imaging appears to reflect the severity and extent of bone involvement in mastocytosis.

## ACKNOWLEDGMENTS

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## Erratum

In the article entitled, "Tc-99m Galactosyl-Meoglycoalbumin: In Vitro Characterization of Receptor-Mediated Binding," Vol. 25, July 1984, pp. 779-787, please note the following corrections.

Page 779, right column, line 11 should read:
After screening several labeled muscarine derivatives, he selected 3-quinuclidinyl-4-iodo-benzilate (4-Iodo QNB). . .

Page 780, right column, line 12, value should read: (280 nm, $a_m = 4.0 \times 10^4\ M^{-1}\ cm^{-1}$).

Page 780, under **In vivo simulations,** fifth line, word is "Simulation" not "Stimulation."

Page 785, under **Specificity: molecular,** left column, last paragraph, reference in line 5 should be *(26)*, line eight should be *(43)*.

Page 785, right column, last line, reference is *(45)*.

Page 785, please delete last paragraph in Acknowledgments.

Heading Table 2 should read: Galactose density (moles/mole)