Histiocytosis X: Comparison of Bone Scintigraphy and Radiography

Seoung Oh Yang, M.D., Eun Mi Koh, M.D., Myung Chul Lee, M.D., Chang-Soon Koh, M.D., In One Kim, M.D.*, Kyung Mo Yeon, M.D.*

Department of Nuclear Medicine and Pediatric Radiology,
Seoul National University Hospital

A retrospective analysis of concurrent bone scintigraphs and radiographs of 30 patients with histologically confirmed histiocytosis X was carried out to assess the pattern and distribution of bone lesion and the sensitivity of bone scintigraphy with reference to skeletal radiography. Totals of 41 regional and over 90 numeric bone lesions were found in all patients. Single bone lesions were seen in 15 patients and multiple lesions in 12 patients. Three patients had not revealed bone lesion. Distribution of lesions was skull, vertebrae, femur, ribs, mandible and the like, in the order of decreasing frequency. Unlike previous citations, the sensitivity of bone scan was relatively as high as over 85% and it showed two lesions of skull and clavicle which escaped from radiologic detection. Improvement of mechanical resolution and bone-seeking radiopharmaceuticals made it possible to detect bone lesions in histiocytosis X more accurately than previous decade. Bone scintigraphy could be the...
effective, helpful diagnostic procedure in the initial diagnosis as well as convenient follow-up method in histiocytosis X.

**Key Words:** Histiocytosis X, bone scintigraphy, radiography.

Histiocytosis X was introduced by Lichtenstein in 1953 to describe a clinical–radiologic–pathologic complex, which includes a spectrum of conditions that range from the benign eosinophilic granuloma through more disseminated chronic Hand–Schuller–Christian disease to the acute fulminating type of Letterer–Siwe disease. Radionuclide studies using bone–seeking radiopharmaceutical agents are an important and accepted method for documenting the presence and extent of skeletal involvement in a variety of disease processes. But bone scintigraphy had proved to be less sensitive than radiography in the detection of osseous lesions in histiocytosis X with disappointing results. However, with recent mechanical and radiopharmaceutical refinements, its sensitivity of detecting bone lesions in histiocytosis X has increased to over 80% with additional usefulness in the follow-up of the therapeutic response of the disease.

In this analysis, we collected pathologically-proven patients whose bone scintigraphs and radiographs were available from 1981 to June 1988 at the Seoul National University Hospital and Children’s Hospital. The purpose of this report is to assess the distribution and pattern of bone lesions and the relative sensitivity and role of bone scintigraphy and radiologic methods.

**Materials and Methods**

Thirty patients with an age range from 14 months to 45 years had been studied by bone scintigraphy and radiography before pathologic diagnosis was made. All had a 99m Technetium–Methylene-diphosphonate (MDP) bone scintigraphy using scintillation gamma cameras (Picker Dyna 415, ON 410 and Siemens Rota/ZLC 75). Liver scans with 99m Technetium–sulfur colloid were done in 4 patients and follow-up bone scintigraphy after therapy in 7 patients.

Only 3 of the 30 patients had radiographic skeletal surveys; others had radiographs of clinically or scintigraphically abnormal areas. Computed tomography (CT) of head was done in 6 patients and magnetic resonance imaging (MRI) in 2 patients to find intracerebral lesion. In one patient with irregular skull defect with mass formation, carotid angiography was performed to know the vascularity.

The clinical symptoms and signs at the initial admission are shown in Figure 2. Overall regional and cumulative counting of bone lesions was done according to the results of bone scintigraphs and radiographs.

**Results**

Twenty-seven patients had bone involvement,
fifteen of which had single bone lesion, while 12 had multiple lesions. Table 1 and Figure 3 show the distribution of the bone lesions in single and multiple involvement as well as regional and numeric distribution. A total of 91 bone lesions (mean: 3) was found with the 41 regional distribution (mean: 1.4 anatomic region). Each four patients over 20 years of age had single bone lesion at ribs in 2, skull and scapula in 1. One out of 15 single lesions was missed on bone scintigraph and radiograph. Of 26 multiple anatomic lesions, 5 lesions were missed on bone scintigraphs and one clavicular lesion was positive on bone scintigraph before radiograph became abnormal. Two patients with multiple small punched-out skull defects and no evidence of marginal sclerosis or beveled edge showed no scintigraphic abnormality of skull (Table 2).

### Symptoms and Signs

![Symptoms and Signs]

**Fig. 2.** Symptoms and signs of histiocytosis X according to the pattern of bone lesion. (single: 15, multiple: 12, normal: 3)

<table>
<thead>
<tr>
<th>Location</th>
<th>Single (N=15)</th>
<th>Multiple (N=12)</th>
<th>Regional Total</th>
<th>Numeric Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skull</td>
<td>4</td>
<td>7</td>
<td>11</td>
<td>49</td>
</tr>
<tr>
<td>Vertebral</td>
<td>1</td>
<td>5</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Femur</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Ribs</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Mandible</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Clavicle</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Pelvic bone</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Scapula</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Humerus</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Metacarpal bone</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tibia</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1. Regional and Cumulative Numeric Distribution of Bone Lesions
Table 2. False Negative Bone Scans and Radiographs

<table>
<thead>
<tr>
<th>Location</th>
<th>Single Bone Lesion (15)</th>
<th>Multiple Bone Lesion (12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bone Scan</td>
<td>Radiograph</td>
</tr>
<tr>
<td>Skull</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Femur</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clavicle</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tibia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Numerical discrepancies were encountered mainly at calvarium with multiple small lytic lesions without sclerotic rim on radiographs, but there were some evidence of cold defects or surrounding rim of increased uptake (Fig. 4). On CT, low density lytic lesion was seen in the diploic space of the skull with rather smooth margin. In one case of right retrobulbar lesion, CT was of important complementary role to delineate the extent of soft tissue invasion (Fig. 5). Blood flow study with radioisotope was done in one case of skull defect which showed hyperemia at blood pool phase and cold lesion surrounded by rim of increased activity at delayed image (Fig. 6). Various locations of bone involvements were demonstrated in Figure 7. With the exception of skull and mandible, pattern of bone scintigraphic uptake was usually augmented. Seven patients had follow-up bone scintigraphy, and all abnormal uptake lesions became normalized in 2-20 months after therapy.

Two patients had evidence of hepatosplenomegaly on liver scan. In one patient with symptom of central diabetes insipidus, MRI detected suprasellar infiltrative lesion with good anatomic depiction but no specific diagnosis of histiocytosis X was made preoperatively (Fig. 8).

Discussion

The lesions grouped collectively as histiocytosis X are usually discovered by radiological investigation of a mass or painful area within bone. In the presence of destructive bone lesions on radiographs, it is relatively characteristic if not pathognomic of histiocytosis X to appear on bone scintigraphy as areas of decreased or increased uptake. Large lesions in particular will appear as cold area. Some will present as photon deficient areas, sometimes with a rim of increased activity around them. In this series,
pure cold defects on bone scintigraphy were limited at skull and mandibular large osteolytic lesion. It is known that bone scintigraphy is more effective in localizing involvement of ribs, spine, and pelvis. Bone scintigraphy is complemented with limited radiographic survey of clinically suspected area. Active early lesions of histiocytosis X can appear positive on bone scintigraphy while radiographs are normal. And this procedure can tell us whether the lesion is single or multiple and
Fig. 5. Five-year-old girl with exophthalmos.
A. Coronal CT shows well-margined right retrobulbar soft tissue density mass with benign nature.
B. Bone scintigraph shows increased activity around the right orbital region.

Fig. 6. Thirteen-year-old boy with toothache and fever.
A. Small ovoid low density lesion is seen in the diploic space of the right temporal bone.
B. Blood pool image shows hot uptake at the same site.
C. Delayed image shows central cold defect with surrounding rim of increased activity.

the early response of the lesion after treatment including surgery and chemotheraphy.

Although bone scintigraphy is generally more sensitive and become positive prior to radiographs in bone lesions, their use in histiocytosis X has been in dispute3-7,11). Previous report of poor scintigraphic sensitivity in detecting histiocytosis X should be reconsidered in accordance with development of mechanical devices and effective radiopharmaceuticals. And it is still imperative that high resolution or magnification image of specific sites should be obtained to improve diagnostic
Fig. 7. Various locations of bone involvement.
A. A well-circumscribed osteolytic lesion at ilium with differential destruction and beveling of the medial margins.
B. Slightly extensive hot activity at the same lesion of A.
C. A 45-year-old man with C.C. of chest mass shows purely lytic lesion and hot activity at left 1st rib.
D. A 2-year-old infant with hand swelling. Expanse lesion with inner sequestra at 3rd metacarpal bone.
E. A 2-year-old infant with spine deformity. Characteristic shape of vertebra plana and increased uptake(arrows) of L1.
accuracy. Table 3 lists the sensitivity of bone scintigraphy in comparison to radiography according to the literature. As many bone lesions of histiocytosis X are purely osteolytic without evident osseous reaction, a certain percentage of cold and false negative lesions has to be expected in bone scintigraphy. False negative lesions on bone scintigraphy can be explained by their size and the absence or presence of normal bone. Other factors influencing the sensitivity of bone scintigraphy are the equipment and technique used.

The distribution of bone lesions in our series was not dissimilar to the literature in the order of skull, spine, femur, and ribs\textsuperscript{1,2,9,12}. More single lesions were seen in our series compared to the findings of Schaub et al. If one excludes the four adult patients of single bone lesion, the pattern would be similar to their children's series. The ratio of male and female was 2:1 in our series same as Senac's series.

Liver scans can give information about hepatosplenic involvement and additional pulmonary uptake of sulfur colloid by increased phagocytic function in the lungs. CT is preferred in the assessment of CNS, orbital and mastoid lesions can be precisely distinguished from intracranial lesions\textsuperscript{13,14}.

The detailed information in the hypothalamic and sella region would be obtained much better by MRI, thus the application of MRI in histiocytosis X will expand.

The indication for a diagnostic procedure to individual case is determined by the prognostic value of the suspect pathologic findings and the clinical necessities. Although recent studies stress the self limited course of the disease\textsuperscript{15}, an initial work-up is done by bone scintigraphs and radiographs of clinically suspect areas to identify possible hidden orthopedic and neurologic sequelae in children\textsuperscript{16,17}. The follow-up of single lesions after surgery can be done by radiographs. However it should be kept in mind that a patient presenting with single lesion initially, can develop other

Table 3. Sensitivity of Bone Scan in Histiocytosis X according to Literature

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>Lesions on</th>
<th>X-ray sensitivity</th>
<th>Bone Scan Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siddiqui et al.</td>
<td>21</td>
<td></td>
<td>95%</td>
<td>63%</td>
</tr>
<tr>
<td>Kumar et al.</td>
<td>7</td>
<td></td>
<td>92%</td>
<td>72%</td>
</tr>
<tr>
<td>Schaub et al.</td>
<td>20</td>
<td>98%</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>Yang et al.</td>
<td>30</td>
<td>95%</td>
<td>85%</td>
<td></td>
</tr>
</tbody>
</table>

* Radiographs of clinical and/or scintigraphic suspect area.
bone lesions later9). In case of multiple lesions follow-up bone scintigraphy will show the effects of the treatment as well as the appearance of new lesions. Bone scintigraphy proved of much benefit to the diagnosis of bone lesions in histiocytosis X along with appropriate radiologic examination.

REFERENCES