Distribution of Hypertrophic Pulmonary Osteoarthropathy

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Radionuclide bone scanning is a sensitive detector of new bone formation. It offers the possibility of more complete description of the distribution of hypertrophic pulmonary osteoarthropathy. The scintigraphic findings in 48 confirmed cases of hypertrophic pulmonary osteoarthropathy (HPO) are described. Several new observations about the involvement of bones and distribution pattern have been made: the skull (mandible and/or maxillae) was involved in 42% of cases, the scapulae in 67%, and the patellae in 50%. Clavicles were involved in 33% of cases. With the exception of the humerus, the proximal and distal portions of each long bone were involved with equal frequency. Involvement of the extremities was invariably present, and disease almost always appeared more active in the lower than in the upper extremities. Asymmetric involvement of the extremities was noted in 17% of cases, and there was irregular involvement in 15%. Differentiation of metastatic disease from HPO by bone scanning is generally not difficult, since the most frequent patterns of distribution of these two conditions are entirely different.

Hypertrophic pulmonary osteoarthropathy (HPO) was first described by Bamberger [1] and Marie [2] in the late nineteenth century. The syndrome classically consists of clubbing of the fingers and toes, periosteal new bone formation in the tubular bones, painful swelling of limbs, arthralgia, and arthritis. Autonomic disturbances, such as sweating, flushing, and blanching of the skin also may be present [3].

The pathogenesis is uncertain. It is usually associated with malignant or inflammatory intrathoracic disease, although it occurs less commonly in congenital cyanotic heart disease, tumors of the esophagus, stomach, or liver, inflammatory bowel disease, and primary cholangitic cirrhosis [3–8]. Hypertrophic pulmonary osteoarthropathy in the absence of associated disease ("idiopathic" or "primary" HPO) is rarely reported [3].

Numerous individual case reports and several small series have described characteristic features of this entity on radionuclide bone scintigraphy [9–11]. These reports have emphasized diffuse, symmetrically increased uptake along the cortical margins of the diaphyses of the long, tubular bones, sometimes referred to as the "parallel tract" or "double stripe" sign. Rosenthal and Kirsch [9] noted that associated synovitis may produce increased uptake in juxtaarticular bone. They also described increased uptake in the distal phalanges associated with marked clubbing. Asymmetrical but otherwise characteristic involvement of the appendicular skeleton has been reported in two cases [9, 10].

We reviewed 48 cases of hypertrophic pulmonary osteoarthropathy (HPO) and have observed involvement of bones not previously described as being abnormal on bone scintigraphy: these include skull (particularly the maxillae and mandible), scapulae, patellae, ribs, and pubic and iliac bones. We have also observed asymmetric and irregular involvement of the long bones to be uncommon but far from rare.

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TABLE 1: **Basis for Diagnosis of Hypertrophic Pulmonary Osteoarthropathy**

Findings	No. Cases
Clinical only	15
Radiographic only	2
Remission or new appearance of scan finding only	6
Clinical and radiographic	17
Clinical and scan evolution	1
Radiographic and scan evolution	1
Radiographic, clinical, and scan evolution	6
Total	48

TABLE 2: **Associated Disease in 48 Cases of Hypertrophic Pulmonary Osteoarthropathy**

Disease	No. Cases
Neoplastic:	
Pulmonary or other intrathoracic:	
Primary lung tumor:	
Adenocarcinoma	16
Epidermoid carcinoma	10
Undifferentiated	5
Mixed cell type	1
Oat cell	1
Mesothelioma	1
No histology	1
Metastatic tumor in lung:	
Carcinoma of breast	2
Carcinoma of prostate	2
Renal cell carcinoma	1
Osteosarcoma	1
Angioblastic meningioma	1
Extrathoracic:	
Carcinoid tumor, disseminated (excluding lung)	1
Nonneoplastic disease:	
Pulmonary tuberculosis	1
Aspiration pneumonitis	1
Pulmonary abscess	1
More than one disease: Hepatoma and Pulmonary abscess	1
No known associated disease process ("idiopathic" HPO)	1

TABLE 3: **Grading Scale of Radionuclide Deposition in Bones**

Grade	Definition
0	Normal deposition of radiopharmaceutical
1	Subtle but definitely increased deposition
2	Moderately increased deposition, but less than lumbar spine
3	Deposition equal to lumbar spine
4	Markedly increased deposition: clearly in excess of lumbar spine

TABLE 4: **Regional Involvement of Skeleton by Hypertrophic Pulmonary Osteoarthropathy**

Region	No. Regions in Grades					Total Positive	% Positive
	0	1	2	3	4		
Skull	28	10	8	1	1	20	42
Clavicle	32	1	10	2	3	16	33
Scapula	15	8	20	2	3	32	67
Humerus, P	41	3	3	0	1	7	15
Humerus, D	18	11	13	3	3	30	63
Radius-ulna, P	8	5	21	6	8	40	83
Radius-ulna, D	7	6	20	10	5	41	85
Hands and carpus	6	8	29	3	2	42	88
Femur, P	13	2	16	10	7	35	73
Femur, D	6	4	16	13	9	42	88
Patella	24	7	10	7	0	24	50
Tibia-fibula, P	2	3	17	16	10	46	96
Tibia-fibula, D	3	5	12	13	15	45	94
Feet	9	11	16	7	5	39	81
Ribs	47	0	1	0	0	1	2
Pelvis	47	...	...	...	1	1	2

Note.—P = proximal; D = distal.

Materials and Methods

Case Selection

All bone scintigrams performed between January 1970 and March 1979 at Rush-Presbyterian-St. Luke's Medical Center and reported as demonstrating or possibly demonstrating HPO were retrieved, as were similar studies performed recently at Ohio State University Hospitals and Holy Family Hospital. The bone scintigrams, medical records and available skeletal radiographs of each patient were reviewed. A diagnosis of HPO was considered established if it could be confirmed by characteristic radiographic findings or if the patient exhibited characteristic clinical features [3] in the presence of a disease generally accepted as being associated with HPO [3]. Further, the disease was considered confirmed if previously absent, characteristic scintigraphic findings appeared on serial scintigraphy in the presence of disease known to be associated with HPO or disappeared on scans performed after definitive treatment of such disease. Cases in which findings were limited to the lower extremities and in which venous stasis and/or dependent edema of the lower extremities were present were excluded from the series. In this manner, a total of 48 confirmed cases were recovered (tables 1 and 2).

Bone Scintigraphy

Bone scintigraphy was performed with a variety of radiopharmaceuticals and imaging devices. Radiopharmaceuticals included fluorine-18 as sodium fluoride (^{18}F) in six cases, ^{99m}Tc-ethylene hydroxy diphosphonate in 24 cases, and ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) in 18 cases.

Imaging devices of six different designs were used including: (1) dual probe, 12.7 cm rectilinear scanners (Ohio Nuclear, Inc., model 84D), 20 cases; (2) an Anger, multiplane, tomographic scanner (Searle Diagnostics, Inc., Pho/Con), five cases; (3) an Anger scintillation camera with a 38 cm field of view coupled with a moving table (Searle Diagnostics, Inc., LFOV), 18 cases; (4) a prototype Anger camera with a 53.3 cm field of view in whole-body scanning mode (General Electric, Inc., model 535 camera), four cases; (5) a multicrystal, whole-body scanning device (Cleon), one case; and (6) an Anger camera with a 30.5 cm field of view (Picker Dynacamera 4/12). In some instances, stationary scintillation camera views (spot views) were taken.

Images were recorded on transparent film in all cases. Because of the variety of imaging devices and radiopharmaceuticals used and the relatively constant total imaging times used, count density and, hence, image quality varied greatly from patient to patient.

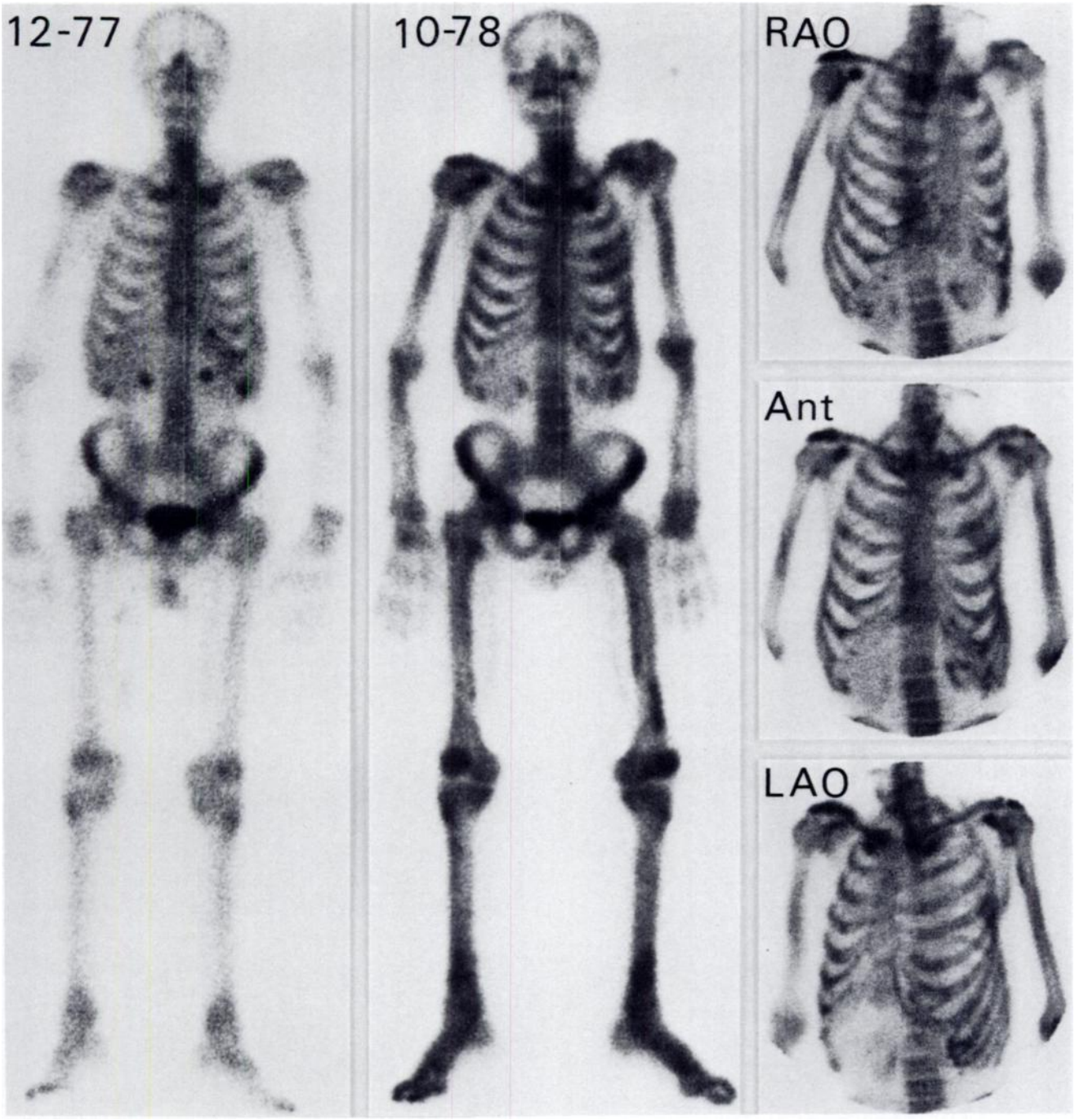

Fig. 1.—71-year-old man, status post resection of carcinoma of lung. Bone scintigram normal 12-77. Recurrence of lung tumor 10-78; bone scan demonstrates hypertrophic pulmonary osteoarthropathy. Malar bones, ribs, and extremities are involved.

Count densities ranged from about 25 counts/cm^2 in the region of the spine when using the dual probe, 12.7 cm rectilinear scanner and ^{18}F to about 1,000–2,000 counts/cm^2 ("average" count density) when using the prototype, 53.3 cm scintillation camera and ^{99m}Tc-MDP.

Scintigram Interpretation

The scintigrams of the 48 patients considered to have confirmed HPO were reviewed by two observers (A. A. and E. W. F.). The long bones of the extremities, the bones of the hands and feet, the scapulae, clavicles, skull, ribs, and patellae were graded for radiopharmaceutical accumulation by consensus according to the five category rating scale outlined in table 3. The presence or absence of symmetry (equal involvement of corresponding right and left extremities) and irregularity (marked variation in intensity of uptake over short distances along the long bones) were noted, as was the relative overall involvement of the upper versus the lower extremities. When the distribution of uptake was asymmetric or irregular, the grade of involvement was taken as that of the side or location

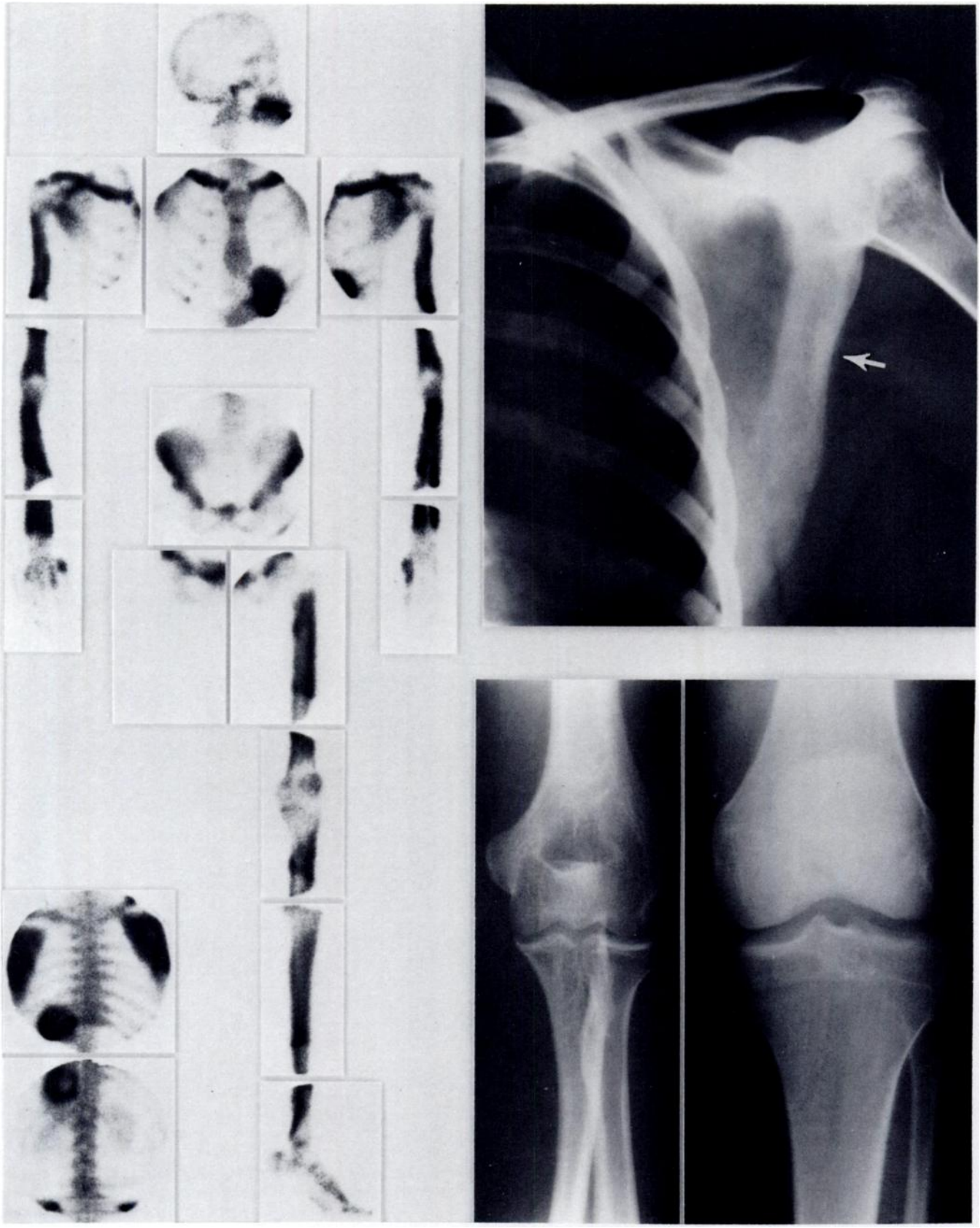

Fig. 2.—18-year-old-man, status post right hip disarticulation for osteosarcoma, now with lung metastases. Intense radionuclide uptake in long bones, clavicles, scapulae, mandible, and superior alveolar ridge. Lesser involvement in pubic, iliac, and metacarpal bones. Cause of intense gastric uptake undetermined. Periosteal new bone formation barely visible along lateral aspect of scapula (*arrow*) and long bones.

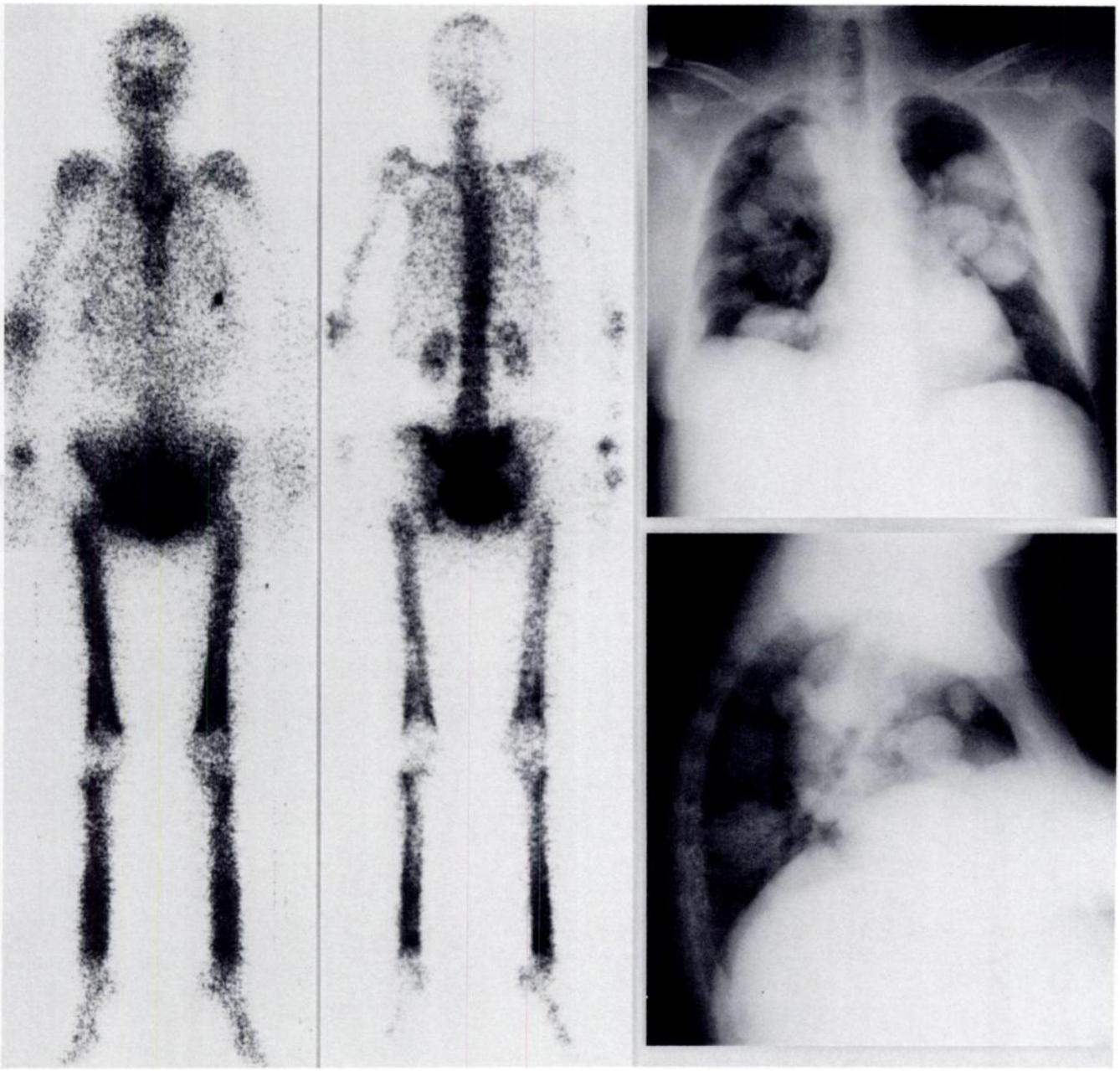

Fig. 3.—Angioblastic meningioma, metastatic to lungs and liver. HPO distribution symmetrical and regular, limited to periosteum of long bones of lower extremities: epiphyses appear spared.

of greatest radioactivity. The bones of the spine and pelvis were not explicitly graded for uptake, but the scintigrams were observed for evidence of involvement of these bones.

Results

The results of regional grading of the bone scintigrams are described in table 4. Bones of the torso (excluding the clavicles and scapulae) appeared definitely affected in only two patients: in one case scintigrams gave evidence of moderate rib involvement (fig. 1), and in the second case the pelvis (pubic and iliac bones) appeared diseased (fig. 2). The spine was not clearly diseased in any patient.

Involvement of the extremities was invariably present. The pattern of radionuclide uptake in the long bones was similar to that previously described [9, 11, 12]. Generally, there was diffuse uptake along the cortical margins of the long bones, frequently involving only those regions of the cortex covered by periosteum (fig. 3), but sometimes affecting epiphyseal bone as well (fig. 4). Involvement was usually regular (85% of cases) and symmetric (83% of cases). Disease almost always appeared more active in the lower than in the upper extremities (98% of cases) (figs. 3–6). Further, activity was usually greater in the long bones distal to the knees and elbows than in the long bones proximal to these joints (fig. 5). The tibiae and fibulae were more com-

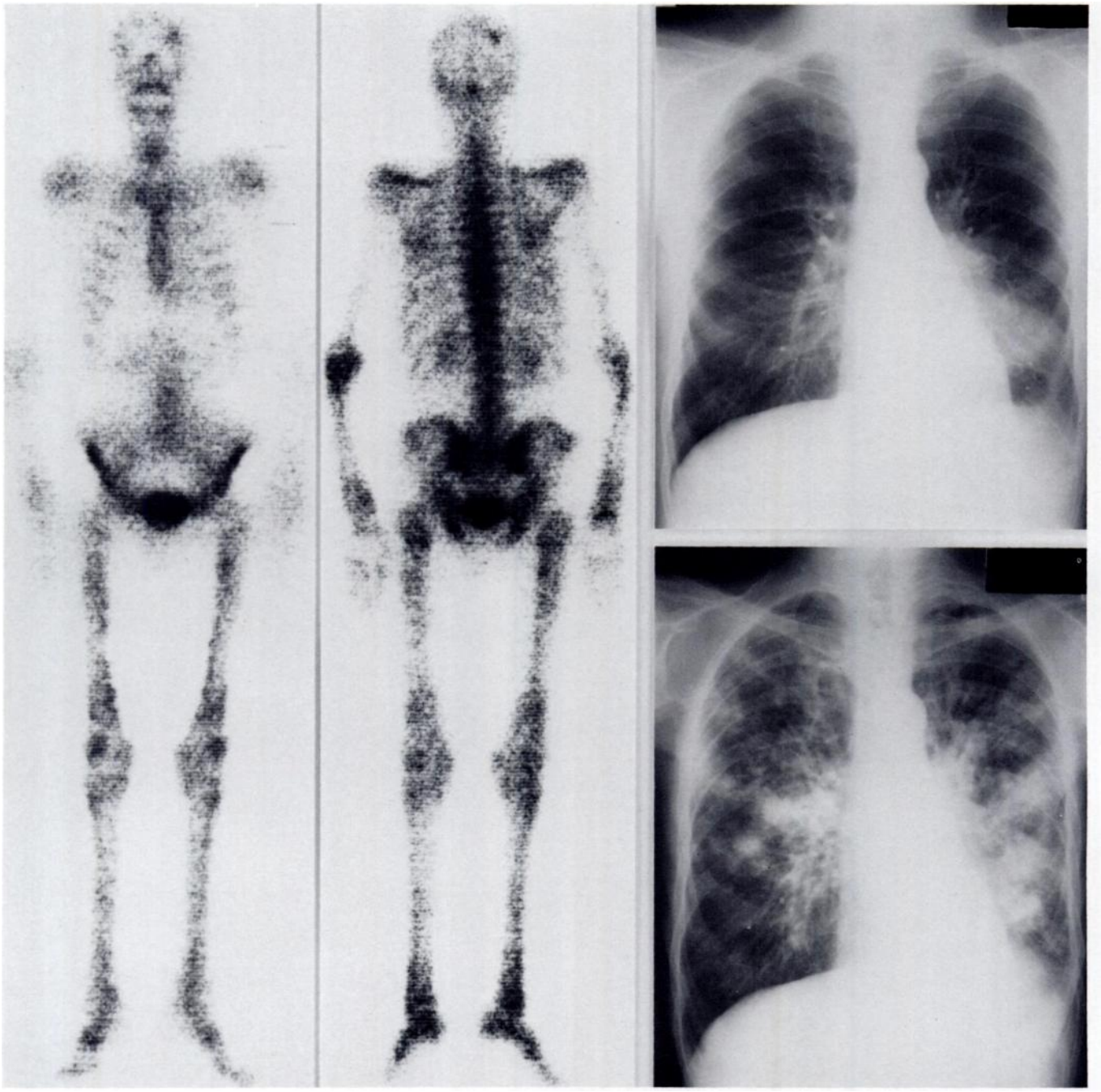

Fig. 4.—Chronic aspiration pneumonitis. No tumor at autopsy. Symmetrical, irregular long bone distribution of HPO, involving epiphyses as well as periosteum.

monly involved by HPO than any other bones: either the tibiae or the fibulae were involved in every case. With the exception of the humerus, the distal and proximal portions of each long bone were involved with equal frequency. On the other hand, the distal humerus exhibited typical changes of hypertrophic pulmonary osteoarthropathy far more frequently (63% of cases) than the proximal part of that bone (15% of cases). The patellae were reported as exhibiting definite involvement in 50% of cases. However, the great variation in radiopharmaceutical uptake by normal patellae made interpretation of patellar involvement difficult, casting doubt on the accuracy of this estimate.

Scapular involvement was present in 67% of cases, but was confirmed radiographically in only one case (fig. 2).

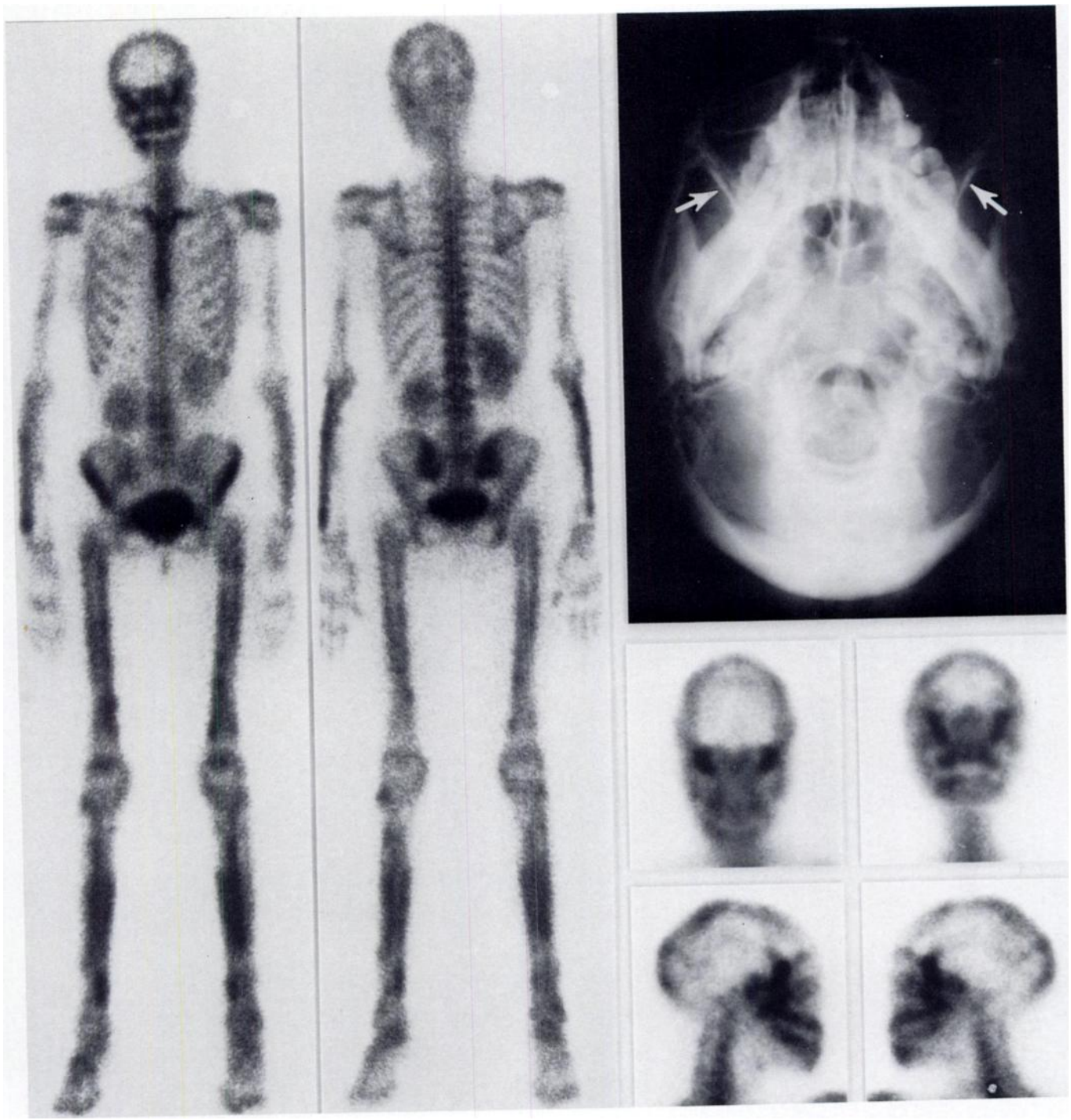

Fig. 5.—43-year-old woman with carcinoma of lung. Intense radionuclide uptake seen in maxillae, especially frontal and zygomatic processes. Confirmed radiographically (*arrows*). Mandible also appears involved. Typical long bone disease with bones distal to elbows and knees more intensely involved than humeri and femora.

The clavicles were diseased in 33% of cases (fig. 2). Finally, the skull was involved in 42% of cases. In almost all instances, skull involvement appeared limited to the maxillae and/or mandible (fig. 5). In one case, however, the entire skull appeared diseased.

Discussion

Hypertrophic pulmonary osteoarthropathy has long been considered a disease which predominantly affects the appendicular skeleton [3]. Our experience supports this

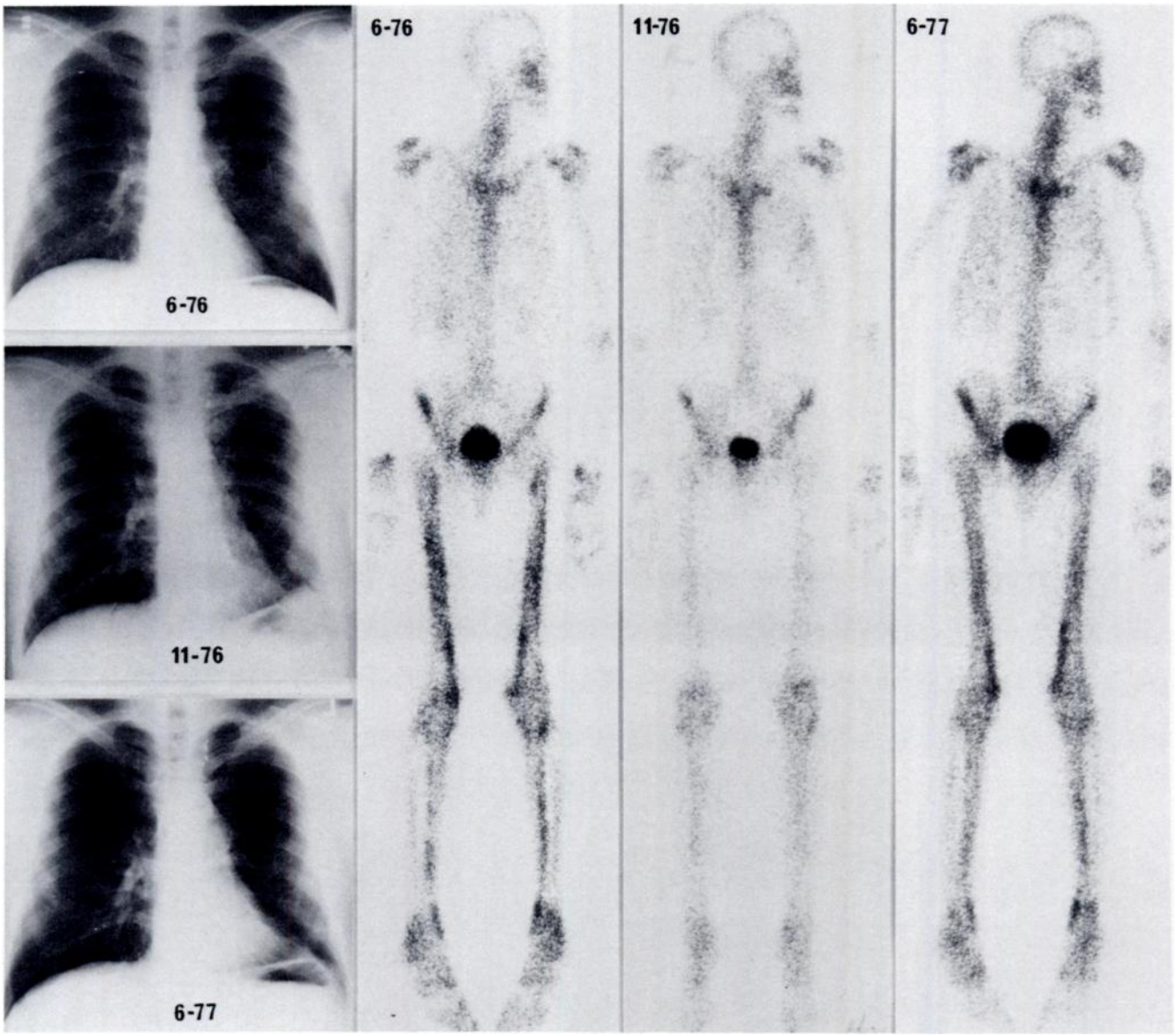

Fig. 6.—52-year-old man with carcinoma of left pulmonary apex. Scintigram on 6-76 demonstrates HPO, lower extremities only, irregular in distribution. 5-months after resection (11-76) scintigram is normal. 1 year after resection (6-77) chest radiograph demonstrates recurrence in left hilum. Scintigram shows recurrence of HPO.

impression. In our series, bones of the extremities exhibited typical changes of HPO in every case. In addition to universal involvement of the long tubular bones, the superior image quality attainable through use of ^{99m}Tc-labeled radiopharmaceuticals and efficient, high resolution Anger camera imaging systems allowed demonstration of involvement of the diaphyses and metaphyses of the metacarpal and metatarsal bones, the calcanei, and the distal phalanges with great regularity (fig. 7). Hypertrophic pulmonary osteoarthropathy is generally thought to affect the distal portions of the long bones more frequently than the proximal parts [3]. We found this to be true only of the humerus. However, the observation of others that the long bones distal to the elbows and knees are involved more commonly than the bones proximal to these joints [3] is borne out by our data.

Given the emphasis in the literature on the predominantly peripheral distribution of HPO, we were surprised at the frequency with which we observed increased radiopharmaceutical uptake in the scapulae (67% of cases), the clavicles (33% of cases), and the skull (42% of cases) (figs. 2 and 5). The maxillae and mandible were commonly involved, but in one instance HPO appeared to affect the entire skull. The clavicles and the scapulae have been generally thought affected only in the most severe cases of HPO [3, 13]. We are unaware of previous reports of demonstration by radionuclide scintigraphy of involvement of the skull or scapulae.

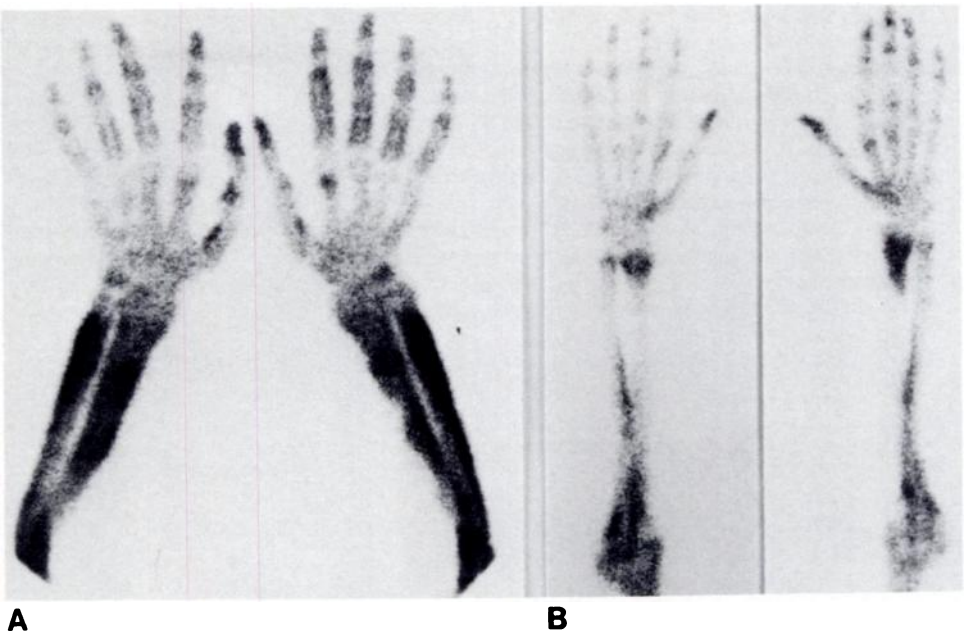

Fig. 7.—Classical patterns of HPO in hands. Common diaphyseal (**A**) and more common metaphyseal (**B**) involvement of metacarpals and phalanges. Activity is not periarticular but limited to one side of joint; pattern clearly distinct from arthritis. Also consistent increased uptake at distal phalanges.

The ribs of one patient (fig. 1) and the pelvis (ilium and pubis) of another (fig. 2) appeared moderately affected by HPO, a finding not previously reported. In no case were we able to detect evidence of involvement of the spine or sacrum. We recognize that the method of grading may have introduced a bias against detection of disease in the spine and pelvis. Nonetheless, involvement of the pelvis, spine, or ribs by scintigraphically detectable HPO must be considered rare. This is consistent with published data regarding the histologic distribution of HPO [3].

In six cases, increased radioactivity in a periosteal distribution suggestive of HPO was confined to the lower extremities. Caution should always be exercised when attributing such findings to HPO, since similar hypertrophic changes in bone may result from venous stasis and dependent edema of any cause [14].

Several reports have suggested that differentiation of HPO from osseous metastases may be difficult [7, 12]. We believe this difficulty has been exaggerated. In fact, differentiation of metastatic tumor from HPO on bone scintigraphy is generally easy, because the distributions of these conditions are entirely different. Metastatic tumor almost always involves the central skeleton in an irregular, focal, asymmetric pattern. When long bones are involved it is the medullary cavity which is primarily affected. On the other hand, HPO primarily affects cortical bone of the extremities in a regular, diffuse, symmetrical fashion, usually sparing the spine, pelvis, and ribs.

Clinical symptoms, signs, and radiographic and radionuclide image findings may diminish or even disappear after appropriate therapy of the associated disease process (fig. 6) [9, 10, 15, 16]. In our series, eight patients with HPO underwent serial scanning following treatment. Five patients showed complete remission of bone scan evidence of disease within 2–6 months after completion of therapy; three patients showed only partial remission. In one of the latter cases, a patient with carcinoma of the lung treated by radiation therapy showed partial remission by 2 months after treatment. In a second case, scans of a patient with carcinoma of the breast metastatic to the lungs exhibited fluctuating intensity of uptake by the lesions of HPO over several years in response to variations in antitumor chemotherapy.

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