Bone Scintigraphy in Growth Hormone-Secreting Pulmonary Cancer and Hypertrophic Osteoarthropathy

Hiromichi Uchisako, Kazuyoshi Suga, Nobuyuki Tanaka, Kazuya Nishigauchi, Tsuneo Matsumoto, Naofumi Matsunaga and Takashi Nakanishi

Department of Radiology, Yamaguchi University School of Medicine, Ube, Japan and Department of Radiology, Saiseikai Shimonoseki General Hospital, Shimonoseki, Japan

Hypertrophic osteoarthropathy was detected in a 55-yr-old man with pulmonary squamous-cell cancer by bone scintigraphy using ^{99m}Tc-hydroxy methylene diphosphonate (HMDP). Intense symmetrical uptake was demonstrated in the distal portions of the long bones as was the parallel tract sign, accompanied by markedly elevated serum growth hormone levels. After chemoradiotherapy for pulmonary cancer, the arthralgia disappeared and scintigraphic findings and serum growth hormone levels improved, suggesting that ectopic production of growth hormone in the pulmonary tumor had been associated with hypertrophic osteoarthropathy. These findings indicate that bone scintigraphy is useful for detecting hypertrophic osteoarthropathy, and assessing alterations in hypertrophic osteoarthropathy activity post-treatment.

Key Words: bone scintigraphy; growth hormone; pulmonary cancer; hypertrophic osteoarthropathy

J Nucl Med 1995; 36:822–825

Hypertrophic osteoarthropathy is a characteristic clinical syndrome of osteoarthropathy due to various pulmonary and nonpulmonary disorders. Hypertrophic osteoarthropathy is most commonly associated with pulmonary cancer, because the incidence of hypertrophic osteoarthropathy in patients with pulmonary cancer is approximately 10% (*1*). Although the exact mechanism and causes of hypertrophic osteoarthropathy remain unknown, endocrine substances such as estrogen, adrenocorticotropin (ACTH) and growth hormone excreted by pulmonary cancers are considered possible causes. Bone scintigraphy using ^{99m}Tc-phosphate complexes is a sensitive method for detecting hypertrophic osteoarthropathy, and its characteristic findings have been reported (*1–6*).

In the present paper, we report bone scintigraphic findings obtained in an extremely rare case of hypertrophic osteoarthropathy associated with ectopic growth hormone-secreted by pulmonary cancer. We also report alteration of the findings after successful treatment of the tumor.

Received Apr. 18, 1994; revision accepted Nov. 7, 1994.

For correspondence or reprints contact: Hiromichi Uchisako, MD, Department of Radiology, Yamaguchi University School of Medicine, Kogushi 1144, Ube, Yamaguchi, 755, Japan.

CASE REPORT

A 55-yr-old man was admitted to the hospital on June 24, 1992. For 2 yr prior to admission, he had felt arthralgia in the left knee joint. In the preceding two months, he developed severe pain in both knee joints and could not stand. He also felt pain in the right elbow at the time of admission. On physical examination, the patient had marked clubbing of the fingers and toes, but there was no acromegaly in his facial features.

Chest x-ray (Fig. 1A) and a CT scan (Fig. 1B) revealed a large mass in the left lower lobe with slight pulmonary effusion. Bronchoscopic examination revealed a reddish tumor obstructing the left lower bronchus, and squamous-cell carcinoma was diagnosed by biopsy specimen.

Bone scintigraphy (Fig. 2) was performed because of the arthralgia to assess bone metastasis. Intense symmetrical uptake was demonstrated in the distal portions of the long bones, patellae, feet and phalanges of the hands. A linear increase in ^{99m}Tc-HMDP uptake along the cortical margins of the distal femora was also found. X-ray findings of the extremities showed an obvious periosteal reaction with subperiosteal bone formations corresponding to lesions showing linear uptake of ^{99m}Tc-HMDP (Fig. 3). These bone scintigraphic and x-ray findings were consistent with typical findings in hypertrophic osteoarthropathy. Serum growth hormone was measured on the assumption that hypertrophic osteoarthropathy might be caused by ectopic growth hormone secretion from the pulmonary tumor (*7*). The fasting serum growth hormone level was markedly elevated: 14 ng/ml (normal level <0.42 ng/ml). All other serum hormone levels, including ACTH, antidiuretic hormone, parathyroid hormone, calcitonin, prolactin and human chorionic gonadotropin, were within normal ranges. MRI of the pituitary gland did not show pituitary adenoma or hyperplasia.

The patient received chemoradiotherapy. The pulmonary tumor was irradiated with a total dose of 60.6 Gy. Chest CT after treatment showed that the tumor shrank to half its pretreatment diameter. Severe arthralgia of the knee joints disappeared within 2 wk after treatment. A bone scan obtained 5 wk after treatment showed improvement in the intense ^{99m}Tc-HMDP uptake in the extremities and patellae (Fig. 4). The growth hormone serum level also decreased to the normal range. At this time, however, x-ray

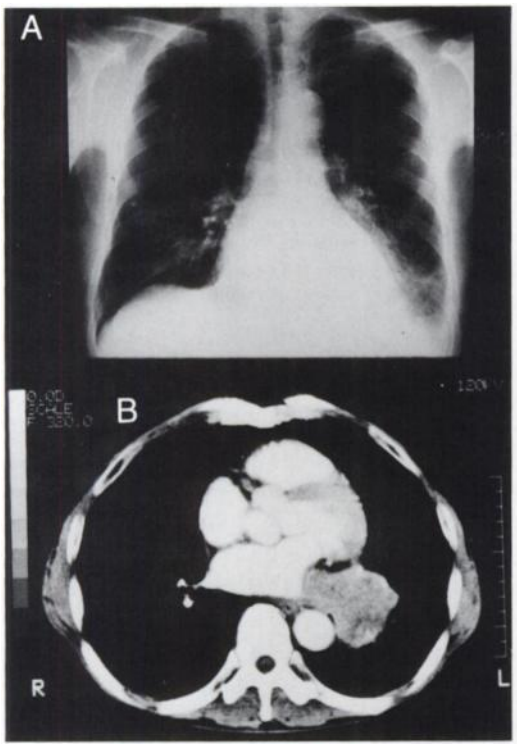

FIGURE 1. (A) Chest PA x-ray on admission revealed an infiltrative shadow in the left lower lung field and disappearance of the left line of the descending aorta. (B) Chest CT scan revealed a large mass invading the left lower pulmonary vein in the left lower lobe.

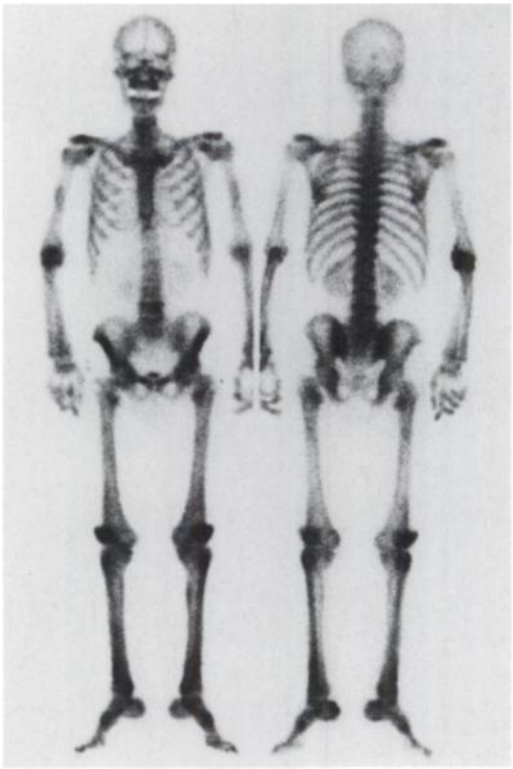

FIGURE 2. Anterior and posterior bone scintigrams of the whole body reveal diffuse, symmetrically increased uptake along the pericortices of the long bones and increased tracer localization at both patellae, hands, feet, knee joints and right elbow joints. Scintigrams were obtained before chemoradiotherapy for pulmonary cancer.

findings of the lower extremities showed no alterations and abnormal subperiosteal bone formations remained.

DISCUSSION

Hypertrophic osteoarthropathy is clinically characterized by several or all of the following abnormalities: clubbing of the digitis, periosteal new bone formation in the tubular bones, painful swelling of limbs, arthralgia and arthritis (*8*). It is usually associated with malignant or inflammatory intrathoracic disease, although it occurs less commonly in extrathoracic disease such as liver or inflammatory bowel disease (*9*). The most common disease associated with hypertrophic osteoarthropathy is pulmonary cancer, which occurs in 80% of patients (*10*).

The exact etiology of hypertrophic osteoarthropathy in patients with pulmonary cancer remains uncertain, however, vagal nerve stimulation (*11*) or endocrine substances (*7,12–14*) produced by tumors, such as estrogen, ACTH, growth hormone and other vasodilative substances may be factors. In our patient, hypertrophic osteoarthropathy may have been associated with ectopic growth hormone secretion from pulmonary cancer, since simultaneous improvement in clinical symptoms and serum growth hormone level was observed following treatment, with accompanying improvement in bone scintigraphic findings. Growth hormone producing pulmonary cancer is extremely rare and only 14 cases have been previously reported (*7,15–20*). Eight of them were complicated by hypertrophic osteoarthropathy, and all cases showed parallel improvement of clinical symptoms and the serum growth hormone level following treatment, as observed in our present patient. Bone imaging was not performed on these patients.

In hypertrophic osteoarthropathy, there is an initial inflammatory reaction with round cell infiltration and prolif-

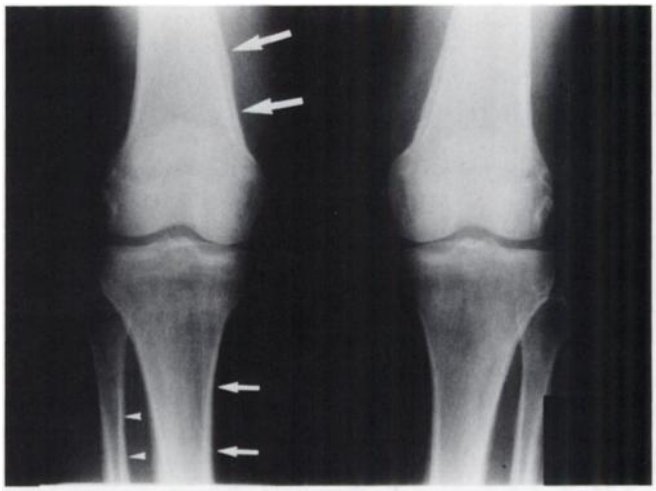

FIGURE 3. X-ray of the bilateral knee joints before treatment shows subperiosteal bone formation of the femora (large arrows), tibiae (small arrows) and fibulae (arrowheads).

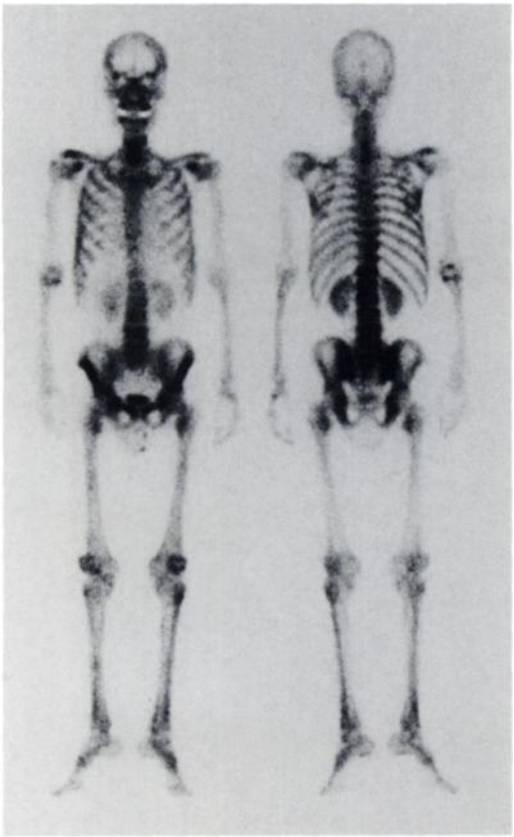

FIGURE 4. Bone scintigrams obtained 5 wk after treatment reveal markedly decreased uptake in the extremities and show improvement of hypertrophic osteoarthropathy.

eration of vascular connective tissue followed by osteoid formation and calcification. Technetium-99m-phosphate accumulates and reflects the elevation of bone blood flow and osteoblastic activity (*21*). Therefore, bone scanning is a sensitive method for detecting hypertrophic osteoarthropathy.

Typical bone scan findings in hypertrophic osteoarthropathy are symmetrically increased uptake along the cortical margins of the long, tubular bones (*1–6*), which are seen more frequently in the distal portions than the proximal parts (*9*). When intense uptake in the cortical portions of the bones seems to form two different linear accumulations, it is called the "parallel tract" or "double stripe" signs. Increased uptake in juxta-articular bone due to arthritis and in the distal phalanges with clubbing are additional characteristic findings (*4*). In our patient, bone scanning disclosed these typical, characteristic patterns, and the scintigraphic findings contributed to the diagnosis of hypertrophic osteoarthropathy. Asymmetric involvement of the extremities and irregular involvement may occur, but it is less common, appearing in 17% and 15% of patients, respectively (*4*). Since our patient had bone scan findings typical of hypertrophic osteoarthropathy, there may be no characteristic pattern for hypertrophic osteoarthropathy associated with ectopic growth hormone.

Like hypertrophic osteoarthropathy, pachydermoperiostitis, thyroid acropachy and unusual cortical reaction with venous insufficiency also show periosteal new bone formation (*22,23*). Hypertrophic osteoarthropathy should be differentiated from these entities with clinical and laboratory findings.

Several investigators reported the usefulness of bone scintigraphy in addition to bone x-rays in monitoring improvement in hypertrophic osteoarthropathy (*1–6*). In the present case, the subperiosteal bone formation seen on radiography before treatment did not resorb clearly after treatment, although improvement of the bone scan was clearly observed.

Rosenthall et al. (*2*) reported a patient who showed radionuclide regression of pericortical uptake of hypertrophic osteoarthropathy 1 yr after removal of the pulmonary tumor. The precise time at which the bone scan normalized could not be ascertained in that patient. In our patient, improvement was obtained 5 wk after radiation therapy, indicating that radionuclide regression was obtained relatively early after treatment.

Concomitant improvement of bone scan findings and serum growth hormone levels after treatment were observed despite the lack of change in x-ray findings, which indicates that bone scans are useful in detecting hypertrophic osteoarthropathy and monitoring it after treatment.

REFERENCES

1. Donnelly B, Johnson PM. Detection of hypertrophic pulmonary osteoarthropathy by skeletal imaging with ^{99m}Tc-labeled disphosphonate. *Radiology* 1975;114:389–391.
2. Rosenthall L, Kirsh J. Observation of radionuclide imaging in hypertrophic pulmonary osteoarthropathy. *Radiology* 1976;120:359–362.
3. Charkes ND. Mechanisms of skeletal uptake. *J Nucl Med* 1979;20:794–795.
4. Ali A, Telalman MR, Fordham EW, et al. Distribution of hypertrophic pulmonary osteoarthropathy. *AJR* 1980;134:771–780.
5. Spencer RP, Daju JA. Bilateral lower limb uptake of bone scanning agents. *Semin Nucl Med* 1980;10:314–316.
6. Kroon HM, Pauwels EK. Bone scintigraphy for the elevation and follow-up of hypertrophic pulmonary osteoarthropathy. *Diag Imag* 1982;51:47–55.
7. Steiner H, Dahlback O. Ectopic growth hormone production and osteoarthropathy in carcinoma of the bronchus. *Lancet* 1968;1:783–785.
8. Hansen-Flaschen J, Nordberg J. Clubbing and hypertrophic osteoarthropathy. *Clin Chest Med* 1987;8:287–298.
9. Howell DS. Hypertrophic osteoarthropathy. In: McCarthy DJ, ed. *Arthritis and allied disorders*. Philadelphia: Lea & Febiger; 1979:977–982.
10. Coury C. Hippocratic fingers and hypertrophic osteoarthropathy. *Br J Dis Chest* 1960;54:202–209.
11. Flavel G. Reversal of pulmonary hypertrophic osteoarthropathy by vagotomy. *Lancet* 1956;1:260–262.
12. Ginsberg J, Brown JB. Increased estrogen excretion in hypertrophic pulmonary osteoarthropathy. *Lancet* 1961;2:1274–1276.
13. Fusco FD, Rosen SW. Gonadotropin producing anaplastic large cell carcinomas of lung. *N Engl J Med* 1966;275:507–515.
14. Leung FW, Williams AJ. Indomethacin therapy for hypertrophic pulmonary osteoarthropathy in patient with bronchogenic carcinoma. *Clin Med* 1985; 142:345–347.
15. Dupont B, Hoyer I. Plasma growth hormone and hypertrophic osteoarthropathy in carcinoma of the bronchus. *Acta Med Scand* 1970;188:25–30.
16. Sparagana M, Phillips G, Hoffman C. Ectopic growth hormone syndrome associated with lung cancer. *Metabolism* 1971;20:730–736.
17. Greenberg PB, Beck C, Martin TJ. Synthesis and release of human growth hormone from lung carcinoma in cell culture. *Lancet* 1972;1:350–352.
18. Beck C, Burger HG. Evidence for the presence of immunoreactive growth hormone in cancer of the lung and stomach. *Cancer* 1972;30:75–79.
19. Mukherjee SK. Growth hormone secreting carcinoma of lung and hypertrophic osteoarthropathy. *Age Aging* 1975;4:95–98.

20. Gropp C, Havemann K, Sheuer A. Ectopic hormones in lung cancer patients at diagnosis and during therapy. *Cancer* 1980;46:347–354.
21. Gall EA, Bennett GA, Bauer W. Generalized hypertrophic osteoarthropathy; pathologic study of seven cases. *Am J Pathol* 1951;27:349–381.
22. Scalon GT, Clemett AR. Thyroid acropachy. *Radiology* 1964;83:1039.
23. Ediken J, Hodges PJ. New bone production and periosteal reaction. In: *Roentgen diagnosis of diseases of bone.* Baltimore: Williams & Wilkins, 1973:39–54.