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CLINICAL CASE SEMINAR

Tc^{99m}-Sestamibi Uptake in Osteitis Fibrosa Cystica Simulating Metastatic Bone Disease

MISHAELA R. RUBIN, VIRGINIA A. LIVOLSI, FRANCISCO BANDEIRA, GUSTAVO CALDAS, AND JOHN P. BILEZIKIAN

Departments of Medicine (M.R.R., J.P.B.) and Pharmacology (J.P.B.), Columbia University College of Physicians and Surgeons, New York, New York 10032; Department of Pathology and Laboratory Medicine, University of Pennsylvania Health System (V.A.L.), Philadelphia, Pennsylvania 19104; and Department of Medicine, Agamenon Magalhães Hospital, University of Pernambuco (F.B., G.C.), Recife, Brazil 2723

PRIMARY HYPERPARATHYROIDISM typically presents as an asymptomatic disorder of mild hypercalcemia (1). Severe parathyroid bone disease is rare since the advent of the multichannel autoanalyzer (1). However, *osteitis fibrosa cystica*, the classical bone disease of primary hyperparathyroidism (2), still occurs (3–9). The pathology involves excessive osteoclast resorption with destruction of cortical bone and creation of fibrous cysts. The marrow may be replaced by vascularized fibrous tissue and osteoclast-like giant cells. Blood pigment accumulates, imparting a reddish-brown hue and accounting for the term brown tumor (10). Occasionally, *osteitis fibrosa cystica* can be mistaken for a malignant lesion, even though it is reactive and clearly not neoplastic. On histological exam, the lesion may mimic a true giant cell tumor of bone (10). Radiologically, the multiple, osteolytic lesions may be indistinguishable from metastatic disease (11). Improvement and at times complete regression of the lesion occur after successful parathyroidectomy (12–14).

In parathyroid carcinoma, *osteitis fibrosa cystica* and other overt radiological signs of hyperparathyroid skeletal disease are much more common than in benign primary hyperparathyroidism (15–18). Although parathyroid carcinoma is a rare cause of PTH-dependent hypercalcemia (15, 19, 20), the associated hypercalcemia and bone disease are usually severe (21). As a result of the hypercalcemia, which can be marked, weakness, weight loss, anorexia, nausea, vomiting, polyuria, polydipsia, bone pain, and fracture frequently occur. Markedly high PTH and alkaline phosphatase levels are also found (22). As parathyroid cancer can metastasize to bone, it can be unclear in parathyroid carcinoma whether the bone lesions are from *osteitis fibrosa cystica* or metastatic parathyroid cancer.

In this report we describe a young man with severe hyperparathyroidism and bony lesions that were positively imaged by Tc^{99m}-sestamibi. As Tc^{99m}-sestamibi has high affinity for parathyroid tissue, the first impression was of metastatic parathyroid cancer. After successful parathyroidectomy, however, Tc^{99m}-sestamibi uptake in the skeletal lesions disappeared. Biopsy of the skeletal lesion confirmed the presence of a brown tumor. This case illustrates the potential of Tc^{99m}-sestamibi to image brown tumors in primary hyperparathyroidism. It documents that bone lesions of severe primary hyperparathyroidism can be reversibly taken up by Tc^{99m}-sestamibi, with disappearance after successful parathyroidectomy. This clinical case seminar also summarizes, for the first time, the cumulative, but rather limited, experience with Tc^{99m}-sestamibi in the context of positive imaging of benign skeletal lesions of primary hyperparathyroidism. When Tc^{99m}-sestamibi is taken up at nonparathyroid sites, one cannot conclude, therefore, that the tissue is parathyroid. Important management decisions follow as a result of this cautionary note.

Case Report

A 25-yr-old Brazilian man was evaluated because of generalized bone pain. He had been in good health until 1 yr before presentation, when he began to experience pain in the lower extremities and progressive difficulty walking. Weakness, anorexia, weight loss, and urinary frequency were also noted. A fracture involving the right femur was sustained after minimal trauma. A bone cyst was diagnosed at another hospital, and the pathology revealed changes compatible with brown tumor of hyperparathyroidism. There was no family history of parathyroid disease or other endocrinopathy. There was no history of urolithiasis, constipation, peptic ulcer disease, use of vitamins or calcium supplements, exposure to ionizing radiation, or use of tobacco or alcohol.

On physical examination, the patient appeared well. His blood pressure was 140/80 mm Hg. His temperature was 36.6 C, pulse was 100, and respirations were 20. A firm mass, 3 cm in diameter, was palpated near the left lobe of the thyroid gland. It moved with swallowing. The lungs, heart, and abdomen were normal. There was diffuse tenderness and warmth at the proximal left tibia and the mid third of the right tibia.

Initial laboratory data are shown in Table 1. Ultrasonography of the neck disclosed a 3.6-cm solid nodule posterior to the left thyroid lobe consistent with the mass felt on neck examination. A marked reduction in bone mass at all sites was measured by dual energy x-ray absorptiometry (Table 1), with T-scores at the lumbar spine (−3.84), femoral neck (−5.33), and distal radius (−4.93) in the markedly osteoporotic range. Skeletal x-rays revealed lytic lesions in the proximal left tibia and the mid third of the right tibia (Fig. 1), coinciding with areas of warmth and tenderness on physical examination. A whole body Tc^{99m}-sestamibi scan showed late uptake at the left neck and at the sites of the skeletal lesions in the lower extremities (Fig. 2A).

Alendronate (20 mg, orally) was administered daily for 1 month with no change in serum calcium. Subsequent surgical exploration of the neck revealed a well circumscribed 3.5-cm left lower lobe parathyroid mass.

TABLE 1. Laboratory data

	Preoperative	1–7 months postoperative (mean values)	Normal range
Serum calcium (mg/dl)	14.0	7.9	8.2–10.4
Serum phosphorus (mg/dl)	1.3	2.6	2.5–4.0
Intact PTH (pg/ml)	746	261	12–65
Alkaline phosphatase (IU/liter)	2820	1003	38–126
Urinary deoxypyridinoline (nmol/nmol creatinine)	28.8	14.3	4–19
24-h urinary calcium (mg)	67	40	80–250
L2-L4 (g/cm^2; T-score)	0.779 (−3.84)	0.810 (−3.58)[a]	
Femoral neck (g/cm^2; T-score)	0.430 (−5.33)	0.687 (−3.19)[b]	
Radius (g/cm^2; T-score)	0.409 (−4.93)	0.449 (−4.43)[c]	

[a] Four percent increase.
[b] Sixty percent increase.
[c] Ten percent increase.

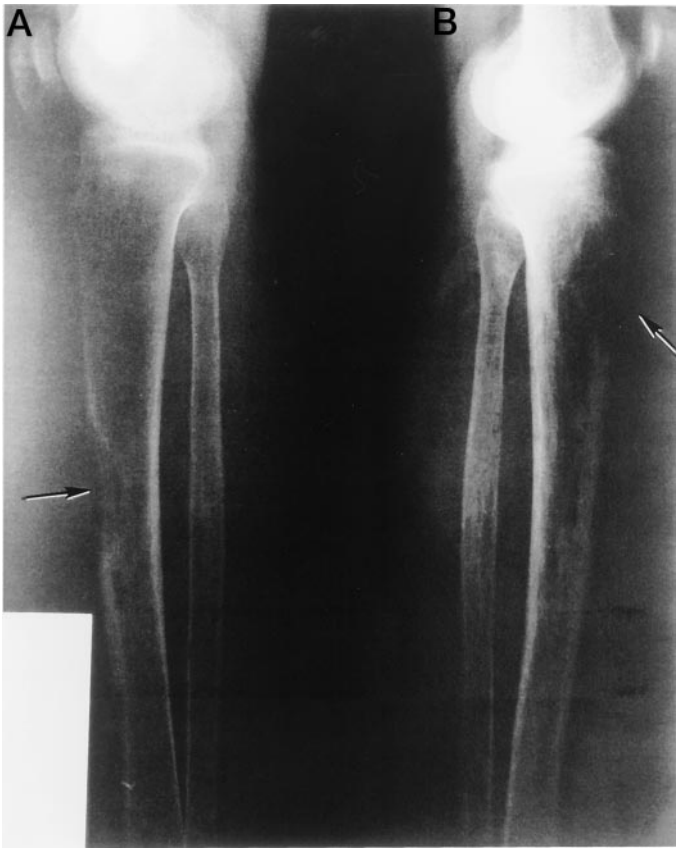

FIG. 1. Skeletal x-ray, with lytic lesions highlighted by *arrows*, in the upper third of the right tibia (A) and in the proximal left tibia (B). In the proximal left tibia (B), the abrupt loss of cortex defines the beginning of a large lytic lesion, which is best seen on the sestamibi image (Fig. 2).

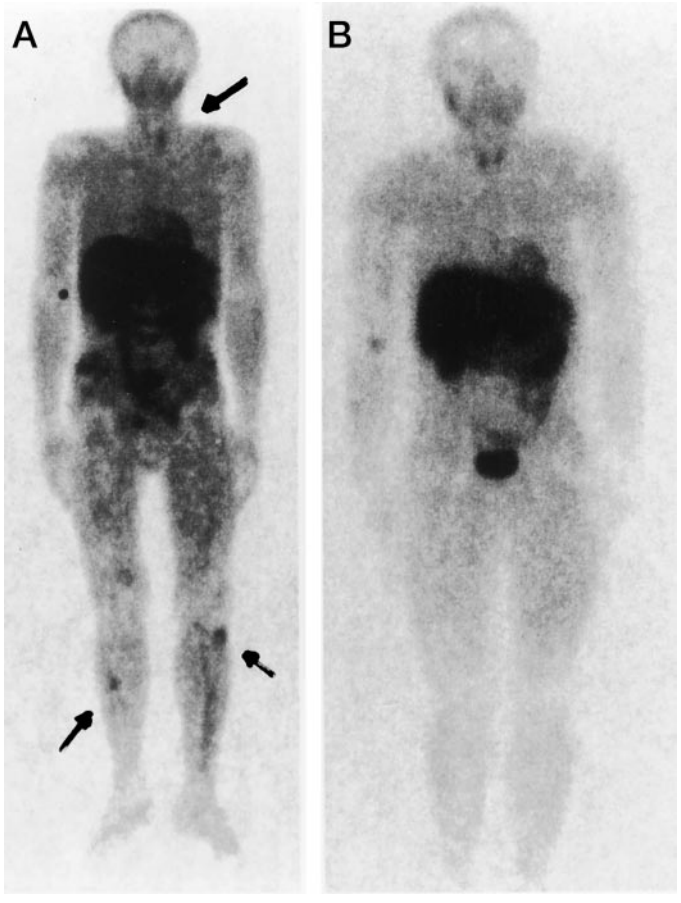

FIG. 2. Tc^{99m}-sestamibi uptake was performed preoperatively (A) and 6 months after surgery (B). The *arrows* highlight the areas of tracer uptake in the neck (parathyroid region), left tibia, and right tibia. The *black dot* in the right antecubital fossa is probably an artifact from the tracer injection.

Histological examination revealed features suspicious for parathyroid carcinoma, including easily identified mitotic figures and marked cellular uniformity. There was no evidence of vascular invasion at the tumor periphery. There was no adjacent lymphadenopathy. Twenty-four hours after surgery, serum calcium and PTH returned to normal at 10.0 mg/dl and 24 pg/ml, respectively. Seven days after surgery, serum calcium fell further to 7.6 mg/dl. Alkaline phosphatase activity decreased to 1003 IU/liter, and urinary deoxypyridinoline decreased to 14.3. The patient was discharged on supplemental calcium (1 g daily) and ergocalciferol (800 U daily).

Six weeks after surgery, serum calcium was 7.9 mg/dl, phosphorus was 2.6 mg/dl, and PTH was 240 pg/ml. Twenty-four-hour urinary calcium excretion fell to 40 mg. A whole body Tc^{99m}-sestamibi scan continued to show uptake in both legs.

Six months after surgery, serum calcium was 8.6 mg/dl, and PTH was 364 pg/ml. 25-Hydroxyvitamin D was 14 ng/ml (normal, 10–55). Seven months after surgery, serum calcium was 7.7 mg/dl, and PTH was 180 pg/ml. The persistent elevation of PTH was thought to be consistent with both a secondary hyperparathyroidism and the anabolic role of PTH in remineralizing the enlarged bone remodeling space after parathyroidectomy. Bone densitometry revealed increases at the lumbar spine (4%), femoral neck (60%), and distal radius (10%; Table 1). On

repeat Tc^{99m}-sestamibi scan, there was no longer any uptake in the neck or at skeletal sites (Fig. 2B). The patient provided informed consent.

Discussion

Imaging by scintigraphy, such as thallium (TR^{201}) and sestamibi (Tc-^{99m}-sestamibi), helps to identify eutopic and ectopic parathyroid tissue. Useful in the past, earlier imaging agents such as thallium have been replaced by Tc^{99m}-sestamibi, the most sensitive and specific imaging agent for parathyroid tissue (23, 24). The application of Tc^{99m}-sestamibi scanning to the preoperative localization of abnormal parathyroid tissue has improved the success rate of surgery, especially in patients who have undergone previous neck surgery (23, 25, 26). The clinical setting becomes more complicated in patients with severe primary hyperparathyroidism in whom the differential diagnosis is often between benign and malignant disease. When Tc^{99m}-sestamibi images bony lesions, there is a high suspicion for parathyroid cancer with metastatic parathyroid tissue in bone (27). This is a particularly important clinical point, because the histological diagnosis of parathyroid cancer by direct examination of the tissue removed in the neck, as illustrated by this patient, is not always clear. Thus, the presence of a sestamibi-visualized lesion in bone favors the diagnosis of parathyroid cancer. Not so widely appreciated, however, is the finding that Tc^{99m}-sestamibi can also be taken up by skeletal brown tumors, mimicking metastatic parathyroid cancer (28–33). The case reported here and the few others reported in the literature introduce an important caution in the interpretation of bony lesions taken up by Tc^{99m}-sestamibi in patients suspected of harboring parathyroid cancer.

Two cases of Tc^{99m}-sestamibi uptake in brown tumors associated with parathyroid cancer have been reported. Lu *et al.* (28) described a 44-yr-old woman with recurrent parathyroid carcinoma and multiple areas of Tc^{99m}-sestamibi uptake in bone lesions. The sites of Tc^{99m}-sestamibi uptake correlated with cystic lesions on computed tomography that were radiographically consistent with brown tumors. After surgical removal of the carcinoma, serum calcium and PTH decreased. However, a bone biopsy or a follow-up Tc^{99m}-sestamibi scan was not reported. Another case report described a 37-yr-old woman with parathyroid carcinoma and a biopsy-proven brown tumor in her right lower extremity (29). Serum PTH normalized after parathyroidectomy. In this case, a follow-up Tc^{99m}-sestamibi was performed 9 months later and revealed complete resolution of the bone lesion. Here, as with our patient, it is clear that the lesion was due to hyperparathyroidism and not metastases from parathyroid carcinoma.

Tc^{99m}-sestamibi uptake in a brown tumor associated with a parathyroid adenoma has also been reported. A 44-yr-old man with a parathyroid adenoma and Tc^{99m}-sestamibi uptake in a maxillary tumor was recently described (30). Ginsberg *et al.* (31) reported Tc^{99m}-sestamibi uptake in the rib of a 28-yr-old man with renal failure and secondary hyperparathyroidism. In another case, a 34-yr-old woman with a mediastinal parathyroid adenoma and Tc^{99m}-sestamibi uptake in lytic extremity lesions was described (32). However, bone pathology and follow-up Tc^{99m}-sestamibi scans were not reported in any of these cases. An additional case report described a 68-yr-old man with a parathyroid adenoma and Tc^{99m}-sestamibi uptake at the site of a left lower extremity fracture through a brown tumor (33). In this case, a bone biopsy proved the presence of osteitis fibrosa cystica, although a follow-up Tc^{99m}-sestamibi scan after parathyroidectomy was not reported.

Although severe primary hyperparathyroidism and parathyroid carcinoma are rare, our case and a review of the literature provide insight into the potential of Tc^{99m}-sestamibi to detect brown tumors of hyperparathyroidism. In severe primary hyperparathyroidism, Tc^{99m}-sestamibi uptake may indicate osteitis fibrosa cystica, rather than metastatic parathyroid disease. The precise mechanisms for the increased uptake of sestamibi in a brown tumor have yet to be elucidated, but it is likely to occur because of increased perfusion, metabolism, and osteoclastic activity (29, 33). Finally, this case and others reviewed here document the point that in severe primary hyperparathyroidism, the presence of uptake by Tc^{99m}-sestamibi in the skeleton cannot be equated with the presence of metastatic parathyroid disease.

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Address all correspondence and requests for reprints to: John P. Bilezikian, M.D., Department of Medicine, Columbia University College of Physicians and Surgeons, 630 West 168th Street, New York, New York 10032. E-mail: jpb2@columbia.edu.

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