Brown Tumors Mimicking Bone Metastases

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Brown tumors are rare skeletal manifestations of hyperparathyroidism (HPT) that may mimic cancer metastasis. Here, we present a 52-year-old woman with HPT and multiple foci of technetium uptake due to brown tumors on bone scintigraphy. Screening tests were negative for cancer and serum parathormon (PTH) measurement; parathyroid ultrasonography and scintigraphy suggested HPT. A chief cell adenoma in right and hyperplasia in the left parathyroid glands were surgically removed after which hungry bone syndrome emerged. Biopsy of the femur lesion during an open reduction with fixation operation due to a fracture established the diagnosis of a brown tumor. Brown tumors are important to consider in the evaluation of patients presenting with multiple foci of uptake on bone scanning and without an established primary neoplasm.

Key words: brown tumor ■ hyperparathyroidism ■ bone scintigraphy ■ cancer

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INTRODUCTION

Brown tumor is a rare clinical consequence of untreated severe primary or secondary hyperparathyroidism (HPT).[1] A "brown tumor" is not a true neoplasm but a term commonly used for osteitis fibrosa cystica. There may be multiple brown tumors, and they commonly arise in the pelvis, ribs, clavicles and extremities, though atypical locations have been frequently defined.[2-4] Bone metastases of cancer are also characterized with multiple focal lesions in similar locations on bone scintigraphy, a commonly used highly sensitive screening tool in oncology.[5,6] Here, we report a case with multiple brown tumors as a consequence of HPT without accompanying hypercalcemia mimicking cancer metastases on bone scintigraphy. Currently, brown tumors are an extremely rare clinical phenomenon in developed countries as a result of earlier diagnosis and treatment of HPT.[1] Such rare and multiple benign lesions constitute a real challenge for the clinician in the differential diagnosis of cancer.

CASE REPORT

A 52-year-old woman admitted for generalized musculoskeletal pain most remarkable on sacroiliac joints' movements. The patient had severe thoracic kyphoscoliosis. Three years ago, she was treated for a paravertebral tuberculosis abscess, and a thoracic 6–11 vertebral posterior fusion was performed. Complete blood count and serum biochemical analyzes, including blood urea nitrogen, creatinine, total protein, albumin, calcium (measured as: 9.0–9.4 mg/dL), phosphorus (measured as: 2.5 and 2.8 mg/dL), gamma glutamyl transpeptidase were in normal ranges, except that serum alkaline phosphatase was 198 (53–128) IU/L. Serum creatinine clearance was 72.0 (90–140) mL/min. Urinary spot and 24-hour calcium excretion measurements were 8.3 (8.4–10.2) mg/dL and 65 (80–250) mg/dL, respectively. Initial x-ray examinations showed multiple bone lesions, and a whole-body bone ^{99m}Tc-MDP scintigraphy showed foci of increased uptake

on the thoracic vertebral column, ribs, right femur neck and bilateral sacroiliac regions suggestive of metastatic lesions (Figure 1). Direct x-ray examinations of these foci revealed multiple lytic lesions (Figure 2). Computed tomography examinations of the chest, abdomen and pelvis, and mammography did not indicate a primary tumor. Serum CEA, CA 15-3 and CA 125 measurements were in normal limits. Serum intact parathormon (PTH) level was 1,234 (20–40) pg/mL, while osteocalcine was 163 (11–43) ng/mL. Thyroid function tests were within normal limits. Ultrasonography (USG) demonstrated two isoechoic nodules of 13 x 7 mm and 10-x-6-mm sized in the left posteromedial and right inferoposterior thyroid regions, respectively. Parathyroid subtraction ^{99m}Tc sestamibi (MIBI) scintigraphy showed extensive uptake in the right lower and the left upper neck regions consistent with parathyroid adenomas (Figure 3). Dual-energy x-ray absorptiometry (DXA) indicated diffuse severe osteoporosis with a L1-L4 z score of -4.4 g/cm^2 and a femoral neck Z-score of -3.0 g/cm^2. The patient had no history of urolithiasis, chronic constipation, renal and peptic ulcer diseases as well as use of vitamins or calcium supplements, and neck irradiation.

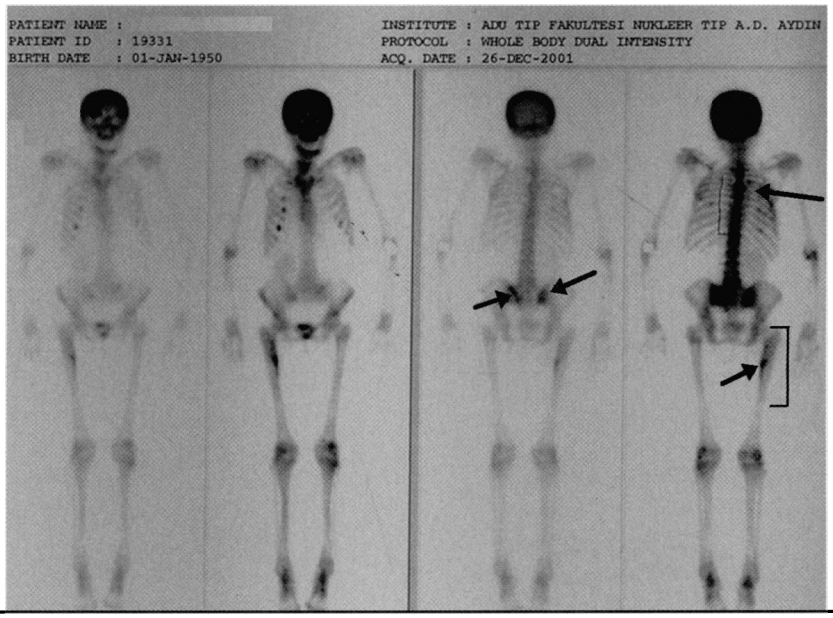
The day before the neck surgery she admitted to the emergency department for a fracture of proximal one-third right femur due to falling down on the floor. An open reduction with fixation was performed with parathyroidectomy. Biopsy of the femur lesion revealed a dense infiltration of the marrow by reactive fibroblastic tissue with scattered multinucleated giant cells, hemorrhage and increased osteoblastic activity (Figure 4). Parathyroidectomy specimens revealed a chief cell adenoma in right and hyperplasia in the left parathyroid gland. The patient experienced persistent hypocalcemia requiring calcium and vitamin-D replacement in the postoperative follow-up period that was diagnosed as "hungry bone syndrome" by the endocrinology department. For the time, she is doing well at the second year of the follow-up with a serum PTH level of 3.2 pg/mL, and under calcium and vitamin-D replacement therapy.

DISCUSSION

Isolated skeletal metastasis of unknown origin is a relatively rare entity. About 90% of patients with skeletal metastases present with multiple lesions, and the probability of reflecting metastases increases related to the number of abnormal foci on the bone scan.[6,7] A focus of increased uptake on scintigraphy may represent metastasis in approximately 50% of patients with an established cancer diagnosis. The probability of representing metastatic disease of a new detected focus is 53% in spine, 15% in skull, and 12% in extremities and sternum. Although the ribs constitute the most common locations of new lesions, they correlate with metastasis in only 35% of the cases. Metastatic involvement is directly related with the skeletal blood flow and occurs predominately in well-vascularized parts of the skeleton, particularly the axial skeleton (80%), including the ribs, vertebral column and pelvis as well as the proximal ends of the long bones.[5] Existence of multiple increased foci of technetium uptake was also consistent with metastases in our patient. Breast, prostate, thyroid, lung, kidney and pancreas neoplasms constitute the underlying malignity in >80% of such presented cases. Primary tumor can be diagnosed by medical history; physical examination; routine laboratory analysis; plain radiographies of the involved bones and the chest; and the computed tomographies of the chest, abdomen and pelvis in 85% of the patients who present with bone metastasis.[8-10] These screening tools did not reveal a primary tumor in our patient.

Scintigraphy is a highly sensitive method for the detection of the altered local bone metabolism; however, it lacks specificity since a variety of diseases causing increased bone turnover such as trauma, infections and metabolic bone diseases may result with increased foci of uptake besides cancer metas-

Figure 1. Whole-body bone scintigraphy: note the increased technetium uptake on the thoracic vertebral column, ribs, right femur neck and bilateral sacroiliac regions suggestive of metastases (arrows)



tases.[5] Benign disorders should always be researched in patients with and without an established cancer.[11] There are several reported cases presenting with brown tumors mimicking bone metastases in the literature.[12-16] The radiographic presentations and the histological findings on bone biopsy were important for differential diagnosis of underlying diseases in all these reports. A patient reported by Hsieh et al.[15] had also admitted with pathologic fracture of the distal femur like ours.

Besides HPT, we detected osteoporosis according to criteria of International Society for Clinical Densitometry in our patient.[17] Bones are the primary target of PTH, and in HPT the earliest changes are seen on x-ray examinations, where subperiosteal erosions can be detected. Brown tumors usually develop in the third to fourth decades of life, and females are more frequently affected. The brownish appearance results from hypervascularity, hemorrhage and hemosiderin accumulation. The lesions contain fibrous tissue with giant cells, hemosiderin-laden macrophages and fibroblasts that fill the lytic areas. Eighty percent of brown tumors arise as a complication of parathyroid adenoma. Of the remaining, 50% are due to primary hyperplasia. Rarely, more than one of the glands are hyperfunctioning.[18,19] Our patient had two hyperfunctioning parathyroid glands—a chief cell adenoma in the right and hyperplasia in the left. Coexistence of parathyroid adenoma and hyperplasia is an extremely rare entity.[20] In patients with parathyroid adenoma, atrophy is seen in the remaining parathyroid glands. Parathyroid hyperplasia is generally seen in all four glands, and no uptake is observed in MIBI scan. There are few reported cases for coexistence of concurrent parathyroid hyperplasia and parathyroid adenoma.

Figure 2. Brown tumor on the right proximal femur

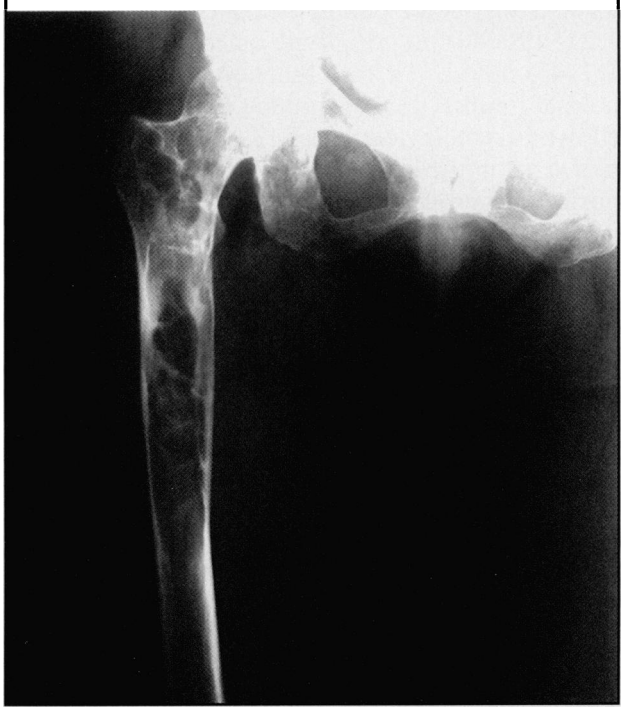


Figure 3. Abnormal uptakes of Tl^{201} on parathyroid scan (arrows)

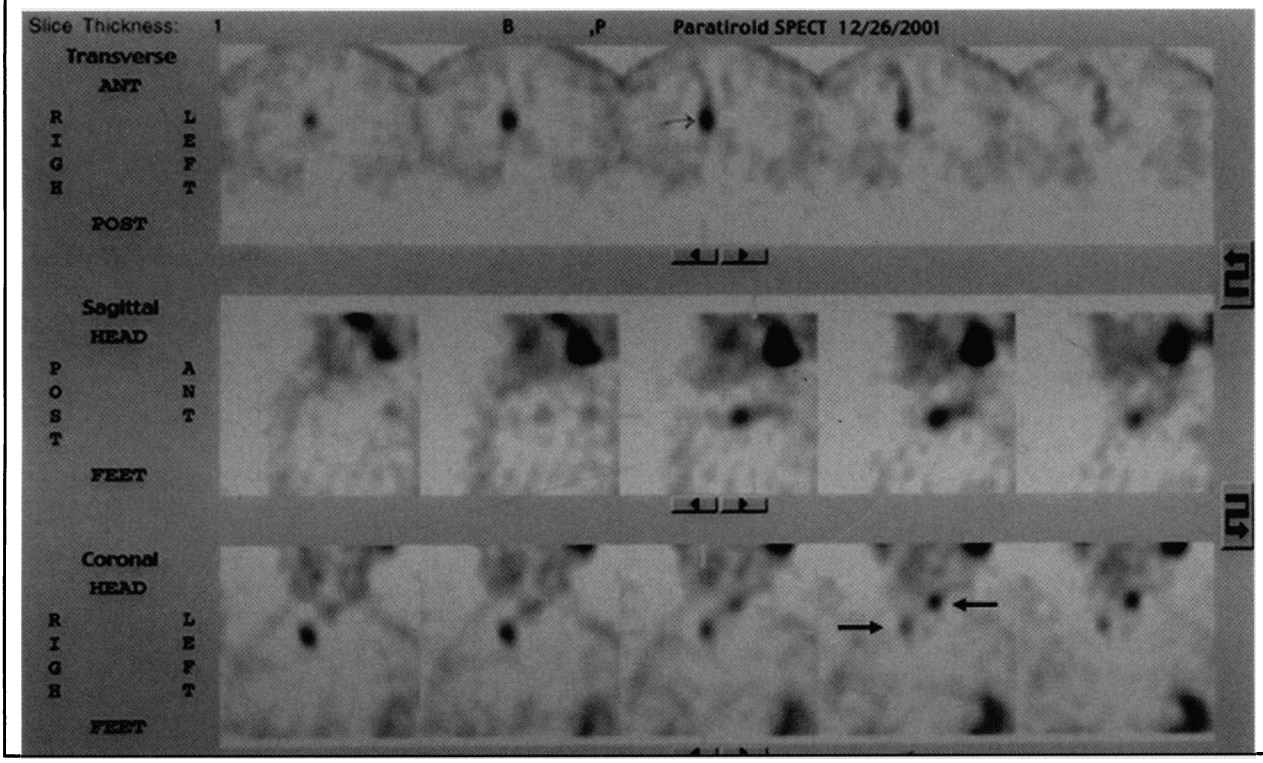
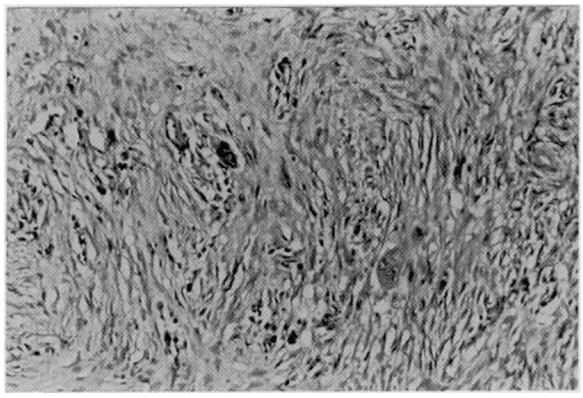


Figure 4. Spindle cells, numerous osteoclast-type giant cells and abundant hemosiderin on right femur curettage specimen (H.E. x200)



The association of hyperplasia and adenoma could be explained by an initial hyperplasia of one gland and subsequent transformation of another into adenoma. As vitamin-D levels were not measured in our patient, it was not possible to determine whether this case had a normocalcemic primary HPT due to long and severe disease or a coincidence of primary HPT with vitamin-D deficiency.

The patient developed persistent hypoparathyroidism after parathyroid adenomectomy, and she is still under calcium and vitamin-D replacement therapy.

CONCLUSION

Though rare, HPT-causing brown tumor(s) is an important differential diagnosis in the evaluation of patients presenting with multiple foci of uptake on bone scanning and without an established primary neoplasm, especially in underdeveloped countries. Serum PTH measurement, parathyroid ultrasonography and scintigraphy are helpful diagnostic tools, whereas bone biopsy may help to rule out an accompanying malignancy.

REFERENCES

1. Yilmazlar S, Arslan E, Aksoy K, et al. Sellar-parasellar brown tumor: case report and review of literature. *Skull Base.* 2004;14:163-168.

2. Kanaan I, Ahmed M, Rifai A, et al. Sphenoid sinus brown tumor of secondary hyperparathyroidism. *Neurosurgery.* 1998;42:1374-1377.

3. Mourelatus Z, Goldberg H, Sinson G, et al. Case of the month: March 1998–48 yr old man with back pain, weakness. *Brain Pathology.* 1998;8:589-590.

4. Blinder G, Hiller N, Gatt N, et al. Brown tumor in the cricoid cartilage: an unusual manifestation of primary hyperparathyroidism. *Ann Otol Rhinol Laryngol.* 1997;106:252-253.

5. Rybak LD, Rosenthal DI. Radiological imaging for the diagnosis of bone metastases. *Q J Nucl Med.* 2001;45:53-64.

6. Jacobson AF, Stomper PC, Jochelson MS, et al. Association between number and sites of new bone scan abnormalities and presence of skeletal metastases in patients with breast cancer. *J Nucl Med.* 1990;31:387-392.

7. Tumeh SS, Beadle G, Kaplan WD. Clinical significance of solitary rib lesions in patients with extra skeletal malignancy. *J Nucl Med.* 1985;26:1140-1143.

8. Alcalay M, Azais I, Brideon B, et al. Strategy for identifying primary malignancies with inaugural bone metastases. *Rev Rhum Engl Ed.* 1995;62:632-642.

9. Brage ME, Simon MA. Evaluation, prognosis, and medical treatment considerations of metastatic bone tumors. *Orthopedics.* 1992;15:589-596.

10. Rougraff BT, Kneisl JS, Simon MA. Skeletal metastases of unknown origin. *J Bone Joint Surg Am.* 1993;75:1276.

11. Barutca S, Yurekli Y, Erdogan S, et al. Parathyroid adenoma-related hypercalcaemia in breast cancer: a critical diagnosis in clinical oncology. *Int J Clin Pract.* 2003;57:729-730.

12. Bassler T, Wong ET, Brynes RK. Osteitis fibrosa cystica simulating metastatic tumor. An almost-forgotten relationship. *Am J Clin Pathol.* 1993;100:697-700.

13. Joyce JM, Idea RJ, Grossman SJ, et al. Multiple brown tumors in unsuspected primary hyperparathyroidism mimicking metastatic disease on radiograph and bone scan. *Clin Nucl Med.* 1994;19:630.

14. Sugden CJ, Laird BJ. Hammers and nails: a report. *Palliat Med.* 2004;18:734-736.

15. Hsieh MC, Ko JY, Eng HL. Pathologic fracture of the distal femur in osteitis fibrosa cystica simulating metastatic disease. *Arch Orthop Trauma Surg.* 2004;124:498-501.

16. Chuang TC, Chang JM, Hwang SJ, et al. A patient of primary hyperparathyroidism with full-blown bone changes simulating malignancy. *Kaohsiung J Med Sci.* 1998;14:584-589.

17. Lewiecki EM, Watts NB, McClung MR, et al. For the International Society for Clinical Densitometry. Official positions of the International Society for Clinical Densitometry. *J Clin Endocrinol Metab.* 2004;89:3651-3655.

18. Gupta A, Horattas MC, Moattari AR, et al. Disseminated brown tumors from hyperparathyroidism masquerading as metastatic cancer: a complication of parathyroid carcinoma. *Am Surg.* 2001;67:951-955.

19. Heath H III, Hodgson SF, Kennedy MA. Primary hyperparathyroidism: incidence, morbidity, and potential economic impact in a community. *N Engl J Med.* 1980;302:189-193.

20. Berland Y, Olmer M, Lebreuil G, et al. Parathyroid carcinoma, adenoma and hyperplasia in a case of chronic renal insufficiency on dialysis. *Clin Nephrol.* 1982;18:154-158. ■