Multiple brown tumors: Unusual presentation of parathyroid carcinoma

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ABSTRACT

Brown tumors represent the terminal stage of the remodeling process during hyperparathyroidism, and it is a rare clinical presentation of primary hyperparathyroidism. Parathyroid carcinoma is even more rare cause of primary hyperparathyroidism. This is a report of a multiple brown tumor caused by primary hyperparathyroidism secondary to parathyroid carcinoma. A 41-year-old woman, who was presented with a generalized bony pain and pathological fracture of left humerus. X-ray demonstrated lytic lesion in bilateral humerus and left ulna. Laboratory investigations showed hypercalcemia and hypophosphatemia with elevated parathyroid hormone level. Ultrasonography did not reveal any parathyroid lesion, whereas radionuclide Sestamibi scan delineated a focus of abnormal tracer uptake in the lower pole region of right lobe of thyroid, left maxilla, bilateral humerus, and left clavicle. She underwent right inferior parathyroidectomy, right hemithyroidectomy and central node dissection. Histological diagnosis confirmed parathyroid carcinoma. The rarity and the interesting clinical presentation of such association are discussed.

Key words: Brown tumor; multiple lytic lesions; parathyroid carcinoma

Introduction

When osteolytic lesions are identified, they are normally attributed to metastatic disease, frequently disregarding differential diagnosis such as metabolic bone disease. The main disease responsible for this is hyperparathyroidism (HPT). The skeletal changes of hyperparathyroidism are now rarely encountered, because hyperparathyroidism is currently being diagnosed and treated at an early stage. Brown tumors are benign, slow growing; giant cell granulomas represent the terminal stage of bone remodeling occurring as a result of peritrabecular fibrosis and osteoclastic activity in untreated HPT.[1] They occur in approximately 4.5% of patients with primary hyperparathyroidism (PHPT), but they rarely are the presenting feature. PHPT, 85% is caused by solitary parathyroid adenoma, 13% have hyperplasia, 1-2% has double adenoma, and 1% has carcinoma.[2] Involvement of the humerus resulting in fracture is a rare presentation of PHPT. We report an unusual case of parathyroid carcinoma presenting with HPT and brown tumors in the multiple bones.

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Case Report

A 42-year-old woman presented with generalized bony pain and pathological fracture of left humerus. Radiography revealed lytic lesions in the bilateral humeri [Figure 1], left ulna and mass in the left maxillary region. The serum level of calcium was 13.9 mg/dl, phosphorus was 1.1 mg/dl, PTH was 466 pg/ml, and serum alkaline phosphatase was 278 U/l. This supported the diagnosis of parathyroid adenoma. The HPT allowed the reinterpretation of the lytic lesions and found as brown tumors mimicking metastases.

Evaluation of the parathyroid glands was performed using ultrasound, which was normal. Parathyroid images were obtained after *i.v.* administration of 20 mCi of 99mTc-SESTAMIBI at 20 and 120 minutes. Subsequently thyroid scan was performed with 5 mCi of 99mTcO4. 99mTc-Sestamibi images revealed foci of abnormal tracer uptake in the left maxilla, proximal left humerus, head of right humerus, left clavicle and lower pole region of right lobe of thyroid, consistent with a parathyroid adenoma [Figures 2 and 3]. Microscopic examination revealed the presence of parathyroid carcinoma post right parathyroidectomy. Subsequently, she underwent right hemithyroidectomy and central node dissection.

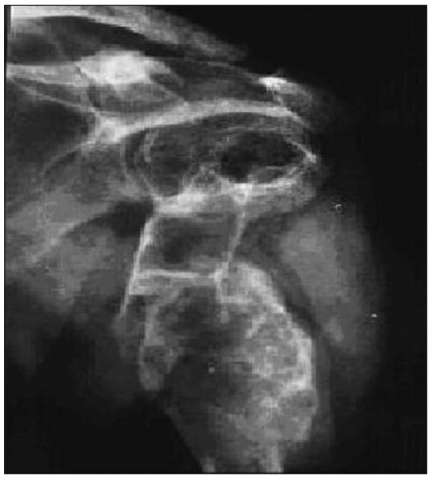

Figure 1: X-ray of left shoulder: Lytic area seen

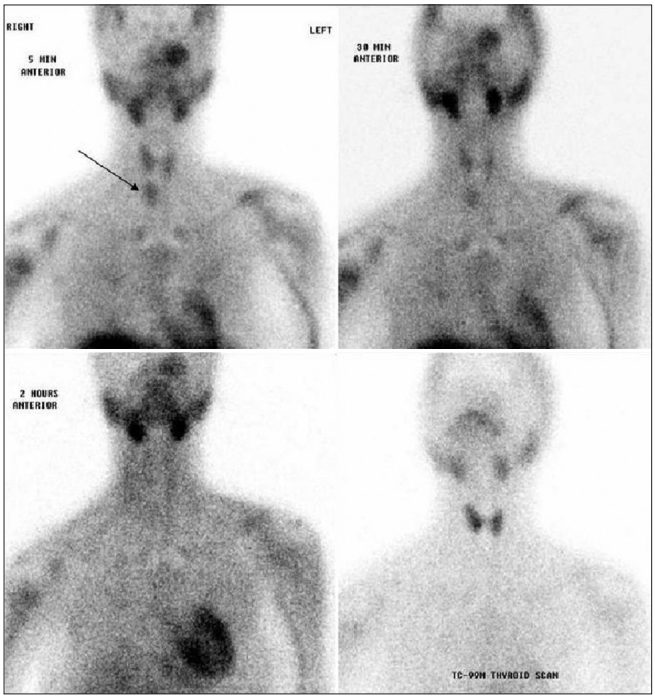

Figure 2: 99mTc-Sestamibi and 99m-Tc planar images: Abnormal tracer uptake in the lower pole region of right lobe of thyroid (arrow), proximal half of left humerus, head of right humerus, left clavicle, and left maxilla with normal 99m-Tc images

Discussion

Patients with undiagnosed HPT presenting with severe bone disease such as a brown tumor are becoming increasingly less common as a result of earlier diagnosis and improved treatment. The effects of PHPT on bone depend on the duration of disease and serum level of PTH. Increased PTH levels locally produced tumor necrosis factor and interleukin 1 (IL-1), which induce proliferation and differentiation of pluripotent bone marrow cells into osteoblasts. These cells produce granulocyte macrophage colony stimulating factor, IL-6, IL-11, and stem-cell factor that induce the migration and differentiation of monocytes into osteoclasts. Enhanced activity of osteoclasts and osteoblasts leads to bone resorption with an increased proliferation of fibrous tissue and extracellular matrix.[3] As the disease progresses, common findings include generalized osteopenia, bone pain, and pathologic fractures.[4] The earliest bone changes are typically visible in the hands, particularly in the phalanges, symphysis pubis, distal clavicle, vertebral bodies, lamina dura, and calvaria. The classic histologic appearance of long-standing PHPT in bone is "tunneling" resorption and peritrabecular fibrosis. In more severe cases, lytic lesions with cyst formation (osteitis fibrosa cystica) and/or with prominent multinucleated giant cells may be seen and are termed "brown tumors" due to their gross appearance of the brownish color caused by hemorrhagic debris, hemosiderin, and hypervascularity. They may cause tissue damage to adjacent structures and compressive manifestations.

Brown tumors develop in 3-4% of patients with PHTP, 1.5-1.7% of patients with secondary or tertiary hyperthyroidism.[5] They are more common in females between 30-50 years and incidence increases with age. They typically involve the ribs, pelvic bones, clavicle, and rarely the long bones and maxilla.[6] These patients also have additional manifestations associated with HPT with low serum phosphorus levels due to the phosphaturic effect of parathyroid hormone (PTH).

Radiographically, brown tumors appear as well-defined lytic lesions of the bone. Due to its rarity, brown tumors are often mistaken with giant cell tumor, giant cell granuloma aneurysmal bone cyst, disseminated malignancy. Diagnosis of brown tumor relies on finding of the multiplicity of these lesions and evidence of hyperparathyroidism.

Generally, high resolution USG, radionuclide imaging, computed tomography (CT) and magnetic resonance imaging (MRI) combinations are used for imaging of parathyroid pathology. One of the advantages of CT on USG is higher sensitivity (46-87%), better localization of the lesion and its ability to determine particularly ectopic parathyroid adenomas.[7] MRI is important for determination of hemorrhage, cystic component, and indirect estimation of fracture risk in brown tumor with a sensitivity of 65-80%.[8] In the radionuclide parathyroid imaging, Technetium (Tc) 99m Sestamibi scintigraphy and Tc99m pertechnetate are predominantly use for subtraction imaging due to their short half time, giving good image quality and low radiation risk. It is mainly indicated, if ectopic PTH producing adenoma is suspected or if the CT scan and the USG failed in localizing the PTH producing lesion with a sensitivity of 9O%. Tumor uptake of Tc99m-MIBI is related to increased perfusion, cell metabolism, ATPase pump activity and mitochondrial activity.[9] Localized bone remodeling induces increased blood flow and local metabolic activity that results in Tc-MIBI accumulation in brown tumors and bone fracture mimicking metastases.[9]

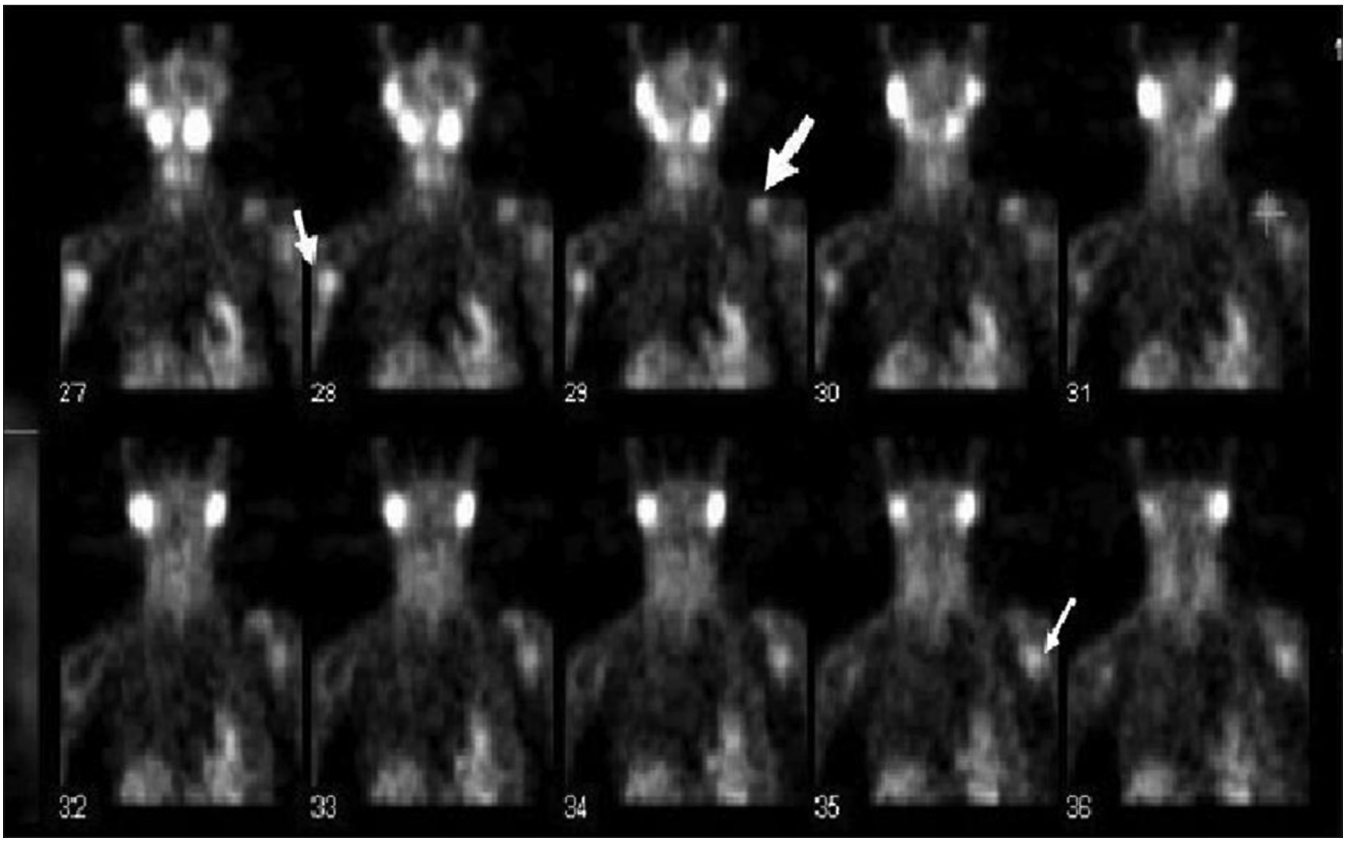

Figure 3: 99mTc-Sestamibi SPECT images, coronal view: Foci of abnormal tracer uptake in the proximal half of left humerus, head of right humerus, and left clavicle (thick arrow)

Treatment of HPT depends on the etiology of the condition. Once PHPT is diagnosed, the only cure is surgical removal of the parathyroid lesion. Medical treatment is reserved for patients who do not meet operative criteria. There is controversy regarding the appropriate management of brown tumors. Reporting on a series of 21 patients with brown tumors, Resendiz-Colosia and co-workers concluded that the natural history is spontaneous regression, either partial or complete after correction of PHTP.[10] Surgery is required under certain circumstances such as compressive neurologic symptoms, significant anatomical deformity, risk of a pathologic fracture, when the biopsy does not yield a clear diagnosis, when the symptoms or pain do not resolve despite adequate medical treatment and control of the hyperparathyroid state.[11]

In view of the histological appearance and similarity to other giant-cell tumors, brown tumor must always be considered in the differential diagnosis of lytic lesions and active steps are undertaken to exclude hyperparathyroidism. Identifying parathyroid carcinoma as a cause of PHPT is notoriously difficult to establish, as it is both rare and presents with a clinical-biochemical profile similar to benign parathyroid disorders. Therefore, the diagnosis is often made intraoperatively or postoperatively. The management of brown tumors is controversial, but a pragmatic approach is essential to a successful outcome. Tc-99m-MIBI may also be used to detect PTH secreting focus in patients of PHTP.

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