

# Differential diagnosis between secondary and tertiary hyperparathyroidism in a case of a giant-cell and brown tumor containing mass. Findings by $^{99m}\text{Tc}$ -MDP, $^{18}\text{F}$ -FDG PET/CT and $^{99m}\text{Tc}$ -MIBI scans

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## Abstract

Brown tumor is one of the skeletal manifestations of hyperparathyroidism. It is a benign but locally aggressive bone lesion and its differential diagnosis with giant cell containing skeletal tumors or metastases may be complicated. *We present* a male patient with chronic renal failure who was initially misdiagnosed as having a giant-cell rich neoplasm of bone in his right thumb. Diffusely increased fluorine-18 fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) uptake in the axial and appendicular skeleton and multiple  $^{18}\text{F}$ -FDG avid lytic lesions suggesting multiple metastases were observed on the  $^{18}\text{F}$ -FDG positron emission tomography/computed tomography (PET/CT) scan. On the usual technetium-99m methylene diphosphonate ( $^{99m}\text{Tc}$ -MDP) bone scan we noticed diffusely increased uptake in the skeleton and two focuses with very much increased uptake, which suggested a metabolic bone disease rather than a multiple metastatic giant cell tumor or bone metastases. Additional investigation documented increased levels of parathyroid hormone. Parathyroid hyperplasia was finally diagnosed with  $^{99m}\text{Tc}$ -methoxyisobutylisonitrile (MIBI) parathyroid scintigraphy. Fluorine-18-FDG avid lytic lesions were attributed to hyperparathyroidism associated brown tumors instead of multiple metastases. *In conclusion*, we present a patient with chronic renal insufficiency, who suffered from secondary and later from tertiary HPT with polyostotic brown tumors, which were best shown by the  $^{18}\text{F}$ -FDG PET/CT than by the  $^{99m}\text{Tc}$ -MDP or the  $^{99m}\text{Tc}$ -MIBI scans.

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## Introduction

Renal osteodystrophy is a bone abnormality of patients with chronic renal failure. Osteitis fibrosa or hyperparathyroidism (HPT)-mediated high-turnover bone disease is a major type of renal osteodystrophy with increased serum phosphate and lack of active vitamin D, which both induce hypocalcemia. Hypocalcemia stimulates parathyroid glands to hyper produce parathormone (PTH), which is associated with bone loss, subperiosteal bone resorption and osteopenia. Apart from generalized bone manifestations, focal lytic lesions such as brown tumors may also appear [1].

Brown tumors associated with HPT are rare. Because of the rarity and the difficulty to clinically diagnose the above pathologic features, the diagnosis of brown tumors may be missed. Histopathologically, in the areas of bone resorption, the replacing fibroblastic tissue contains numerous osteoclast-like giant cells and this may lead to misdiagnosis of other giant cell containing lesions such as giant cell granuloma and aneurismal bone cysts [2]. Although giant cells containing tumors and brown tumors are characterized by identical giant cells and their histological appearance may be overlapping, some microscopic differences can be seen [3]. The differences refer to cell morphology and to the nuclei of the mononuclear cells [3]. In the giant cell tumors, giant cells are uniformly distributed while in brown cell tumors containing giant cells these giant cells are arranged in clusters [3]. The presence of HPT may support the differential diagnosis [4].

Adenomas and glandular hyperplasia are the main causes of primary HPT causing excessive secretion of PTH and hypercalcemia. Secondary HPT refers to the excessive secretion of PTH by the parathyroid glands in response to hypocalcemia and associated hypertrophy of the glands and is especially seen in patients with chronic renal failure [4]. During early secondary HPT, the blood calcium levels are normal or low, opposite to primary HPT.

Rarely, long standing secondary HPT may cause hyperplasia of one or more of the parathyroid glands, the system of normal inhibition of PTH secretion by calcium is inactive and PTH secretion persists even when the low calcium level is corrected. This event

is tertiary HPT, a state of excessive secretion of PTH after a long period of secondary HPT resulting in hypercalcemia.

Herein, we report a case of a male, with chronic renal insufficiency patient and multiple brown tumors, who was at first pathologically misdiagnosed as having giant-cell bone tumor. The patient developed secondary and then tertiary HPT. Clinical, biochemical and multimodality imaging and biopsy findings supported the diagnosis.

## Case report

A 53 years old man presented with generalized bone pain for 1 year and also swelling in his right thumb and left ribs for 3 months. He was admitted to our orthopedic clinic. Magnetic resonance imaging of his hand and computed tomography of the thorax showed expansile lytic lesions on the 2<sup>nd</sup> phalanx of the right thumb and the anterior ends of both right and left 7<sup>th</sup> ribs which were suspicious for metastases. Bone biopsy of the tumor of the thumb (Fig. 1a) showed a giant cell-rich neoplasm (Fig. 1b). The patient's further work-up included technetium-99m methylenediphosphonate (<sup>99m</sup>Tc-MDP) bone scintigraphy and fluorine-18-fluorodeoxyglucose (<sup>18</sup>F-FDG) positron emission tomography/computed tomography (PET/CT) whole body scan. Bone scintigraphy was performed after the intravenous (i.v.) administration of 740MBq <sup>99m</sup>Tc-MDP with a gamma camera (Siemens, Ecam-Signature, Germany) equipped with low energy high resolution collimator. Whole body bone imaging with <sup>99m</sup>Tc-MDP, revealed diffusely increased uptake in the calvarium, the cortex of the long bones, the sternum, the vertebral column and also a focal increased uptake on the anterior end of the 7<sup>th</sup> right rib and also on the left pubic bone. Radiotracer excretion was observed neither in the bladder nor in the kidneys, demonstrating the classical findings of "super scan" pattern which occurs secondarily to metabolic or metastatic bone disease (Fig. 2a-b). Since giant-cell tumor of bone can metastasize and suspicious metastatic lesions were reported in the <sup>99m</sup>Tc-MDP scan, whole body <sup>18</sup>F-FDG PET/CT imaging was arranged to evaluate these lesions. A dose of 370MBq <sup>18</sup>F-FDG was injected i.v. in a fasting state, with an integrated scanner (Siemens, Biograph, mCT, Germany). This scan depicted <sup>18</sup>F-FDG avid focal lytic lesions throughout the skeleton including the right thumb and also diffusely increased <sup>18</sup>F-FDG uptake in the vertebral column, the pelvic bones and also in cortical regions of the appendicular skeleton (Fig. 2c and 3). Radiotracer excretion was also not observed in the kidneys and the urine bladder.

In spite of the biopsy report, because of the discordance between the bone scans by <sup>99m</sup>Tc-MDP and by <sup>18</sup>F-FDG PET/CT and the absence of any primary neoplasm, metabolic bone disease was considered for diagnosis. The patient suffered from chronic renal failure and was under haemodialysis treatment for 8 years. High serum calcium and PTH levels were noticed in his 2 years earlier biochemical files (11.4mg/dL, n: 8.4-10.2mg/dL, and 2160pg/mL, n: 12-65pg/mL, respectively). He was on calcimimetic treatment and was receiving orally tablets of cinacalcet, 30mg/day. Serum calcium, phosphorus and PTH levels were 9.7mg/dL (normal: 8.4-10.2mg/dL), 3.5mg/dL (normal: 2.3-

4.7mg/dL) and 1808pg/mL (normal: 12-65pg/mL), respectively. Serum alkaline phosphatase level was 874 U/L (normal: 40-100 U/L). The possibility of brown tumors with HPT was considered and parathyroid scintigraphy was scheduled. Early planar, late planar and single photon emission tomography (SPET) <sup>99m</sup>Tc-methoxyisobutylisonitrile (MIBI) scan were performed 20 and 120min after the i.v. injection of the radiopharmaceutical. Quite increased uptake consistent with parathyroid hyperplasia, was observed in the parathyroid glands, which were lying as projected in both the right and left lower poles and also in the left upper pole of the thyroid gland (Fig. 4). The high levels of PTH and calcium suggested that after a period of secondary HPT, tertiary HPT had evolved perhaps 2 years earlier. Thus, the diagnosis of HPT with multifocal brown tumors instead of multiple metastases was established. Since brown tumors can be polyostotic, whole body <sup>99m</sup>Tc-MIBI scan was also performed to look for multifocal disease which might had been missed on the PET/CT scan due to non <sup>18</sup>F-FDG avid lesions. However, only right and left patellar <sup>99m</sup>Tc-MIBI accumulation was observed in this whole body scan (Fig. 5).

The patient is still on medical treatment, refused to be operated and is receiving phosphate binding drugs and calcium mimetics.



**Figure 1.** a: The patient was suffering from swelling of his right thumb for 3 months b: Pathologic examination revealed bone lesion with multinucleated giant cells (white arrow), mono nuclear stromal cells, osteoblastic and osteoclastic areas and deposits of hemosiderin (black arrow) Hematoxylin and eosin stain, x200.

## Discussion

Brown tumors develop as a complication of long-standing primary or secondary HPT [1]. They are not actual tumors but result from excessive osteoclastic activity. They can be seen in monostotic or polyostotic forms [5]. Despite their benign characteristics, they can behave aggressively and can be destructive. The differential diagnosis between brown tumors and bone metastases may be challenging, especially in patients with an unknown primary tumor [6].

The incidence of brown tumors has been reported to be 3% in patients with primary HPT, in contrast to 1.5%-1.7% in patients with secondary HPT [5]. In the present case, brown

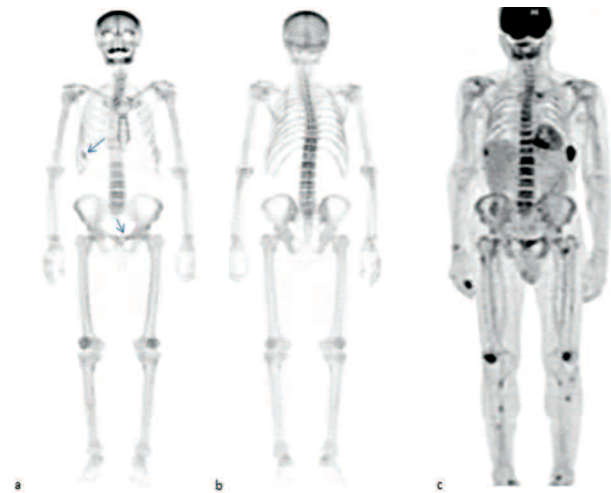
tumors were observed in a patient with tertiary HPT, after a long period of secondary HPT. The patient was receiving cinacalcet, which increases the sensitivity of calcium receptors of the parathyroid cells, reduces PTH levels and thus decreases serum calcium levels. We thought that the normocalcemic state of the patient was secondary to his medical treatment.

Discrepant uptake among radiotracers of  $^{99m}\text{Tc}$ -MIBI,  $^{99m}\text{Tc}$ -MDP and thallium-201 in brown tumors has been reported in the literature [7]. Changing manifestations of brown tumors examined with  $^{18}\text{F}$ -FDG,  $^{99m}\text{Tc}$ -MIBI and  $^{99m}\text{Tc}$ -MDP have also been described [5, 8-10]. On the bone scan decreased uptake in brown tumors is caused by the expansile character of these lesions [11]. A pattern of increased uptake may also be seen because of the reactive osteoblastic bones, surrounding the lesion [11]. Dinauer et al (1996) reported brown tumors uptake of  $^{99m}\text{Tc}$ -MIBI in a patient with parathyroid adenoma [9]. However, no focal uptake of  $^{99m}\text{Tc}$ -MIBI in the brown tumors of a similar patient was reported by Zanglis et al (2006) [10]. Lack of mitochondria in brown tumors was thought to be responsible for their non accumulation of the radiotracer.

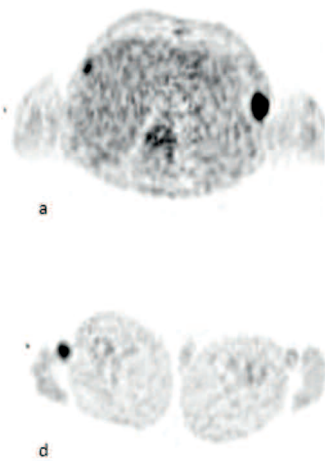
Increased  $^{18}\text{F}$ -FDG uptake has been shown in osteoclastic like giant cells containing lesions, including brown tumors [5]. The intracellular glucose metabolism of the giant cells macrophages has been suggested to partly explain the increased  $^{18}\text{F}$ -FDG uptake [5].

In our patient, the  $^{99m}\text{Tc}$ -MDP bone scan and the  $^{99m}\text{Tc}$ -MIBI scan failed to depict all lesions while the  $^{18}\text{F}$ -FDG PET/CT scan detected them all. The bone scan and the  $^{18}\text{F}$ -FDG PET/CT scan showed a superscan pattern. Brown tumors located in the left pubis, in both tibia and in ribs did not display radiotracer accumulation on the  $^{99m}\text{Tc}$ -MIBI scan. We thought that differences in cellularity and mitochondrial content among brown tumors could be the reason for localizing them or not by  $^{99m}\text{Tc}$ -MIBI.

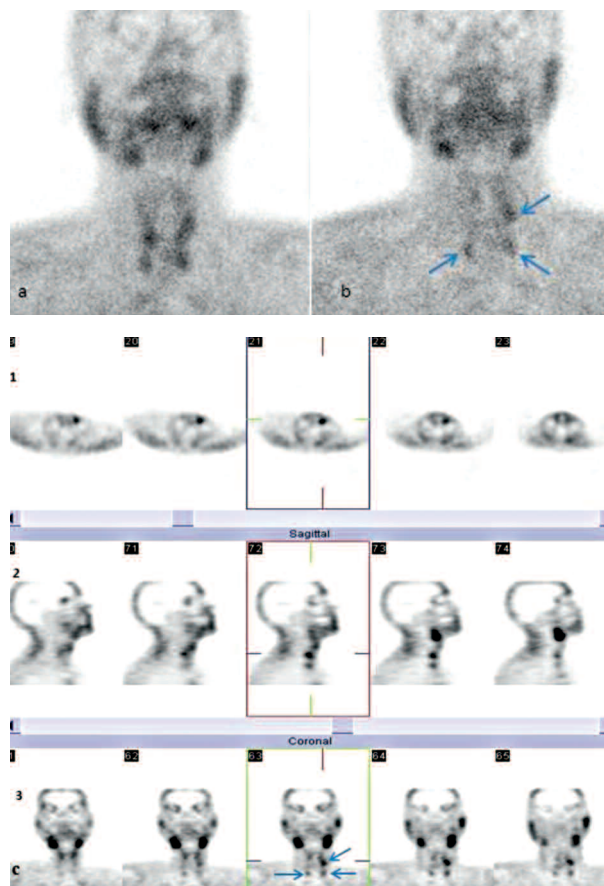
Our findings are concordant with other researchers' results. Multiple brown tumors without focal  $^{99m}\text{Tc}$ -MDP or  $^{99m}\text{Tc}$ -MIBI uptake were reported in a patient with a spontaneous humerus fracture [10]. Diffusely enhanced  $^{18}\text{F}$ -FDG



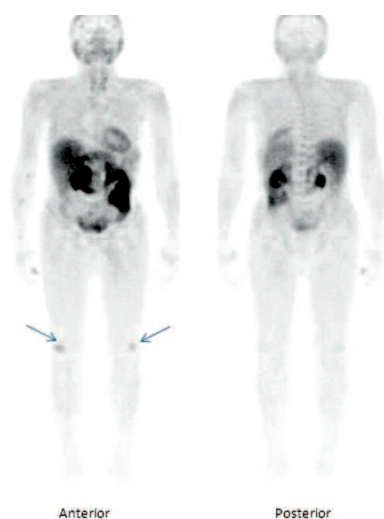
**Figure 2.** Anterior (a) and posterior (b) view of the  $^{99m}\text{Tc}$ -MDP bone scans, demonstrated diffusely increased uptake in the calvarium, in the cortex of the long bones, the sternum, the vertebral column. Focally increased uptake in the anterior end of the 7<sup>th</sup> right rib and in the left pubic bone was also observed (arrows). Absence of the radiotracer excretion in the urine bladder and kidneys was noticed. (c) Whole body maximum intensity projection (MIP) images from  $^{18}\text{F}$ -FDG PET/CT scan showed increased  $^{18}\text{F}$ -FDG uptake in the vertebral column, the pelvic bones and also in the cortical regions of the appendicular skeleton. Focuses of increased  $^{18}\text{F}$ -FDG uptake throughout the skeleton were also recognized. Excretion of  $^{18}\text{F}$ -FDG was also not observed in the urine bladder and in the kidneys.



**Figure 3.** Transaxial PET (a, d), CT (b, e) and fused (c, f) images of the  $^{18}\text{F}$ -FDG PET/CT scan. The CT components of the fused image demonstrated  $^{18}\text{F}$ -FDG avid lytic lesions (arrows) including the one located in the patient's right thumb (e).



**Figure 4.** Dual phase planar  $^{99m}\text{Tc}$ -MIBI parathyroid scan was performed a: at 20min and b: at 120min after injection. Imaging by SPET c. 1: transaxial 2: sagittal 3: coronal slices were performed at the late phase. Focuses consistent with parathyroid hyperplasia were observed at the right and left lower poles and also the left upper pole of the thyroid gland in both the late planar and the SPET images (arrows).



**Figure 5.** Anterior and posterior  $^{99m}\text{Tc}$ -MIBI whole body imaging showed radio-tracer accumulation in both patellas (arrows). Although patellar radio-tracer uptake is nonspecific especially for bone scan,  $^{18}\text{F}$ -FDG PET/CT also depicted  $^{18}\text{F}$ -FDG accumulation and lytic lesions in both patellas. Right patellar uptake of  $^{99m}\text{Tc}$ -MIBI could be attributed to a brown tumor. The patient was operated in his left knee, so post-operative changes could not be ruled out in the left patella.

uptake in the axial and appendicular skeleton without renal and bladder activity, has been also reported in the PET/CT scan in renal osteodystrophy [12] and it was postulated to be due to increased metabolism and accelerated bone turnover. Like in our patient, coexistence of focal areas of  $^{99m}\text{Tc}$ -MDP and  $^{18}\text{F}$ -FDG accumulation accompanied by diffusely increased axial and appendicular uptake has been reported by other researchers [8, 13]. However, compared to  $^{18}\text{F}$ -FDG PET, the usual technique for the detection of in situ and ectopic parathyroid disease is still scintigraphy with  $^{99m}\text{Tc}$ -MIBI with sensitivity of 85%-100% and specificity close to 100% in cases of parathyroid adenomas [6].

*In conclusion*, we present a patient with chronic renal insufficiency, who suffered from secondary and later from tertiary HPT with polyostotic brown tumors, which were best shown by the  $^{18}\text{F}$ -FDG PET/CT than by the  $^{99m}\text{Tc}$ -MDP or the  $^{99m}\text{Tc}$ -MIBI scans. It is our opinion that the overall radiopharmaceutical choice for the detection of in situ and ectopic parathyroids is still  $^{99m}\text{Tc}$ -MIBI.

*The authors declare that they have no conflicts of interest.*

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