


A Rare Manifestation of Secondary Hyperparathyroidism Due to Brown Tumors: A Case Report

Maria Boudina¹, Eleana Zisimopoulou¹, Pantelitsa Rakitzi¹, Sotirios Barbanis², Eleni Syndouka³, Chrysanthi Zouli¹, Aimilia Fotiadou¹, Mariana Stamati Stamati¹, Chrysanthi Balodimou¹, George Christantonidou¹, Alexandra Chrisoulidou¹

¹Department of Endocrinology, Theagenio Cancer Hospital, Thessaloniki, Greece; ²Department of Pathology, Theagenio Cancer Hospital, Thessaloniki, Greece; ³Department of Radiology, Theagenio Cancer Hospital, Thessaloniki, Greece

Correspondence: Maria Boudina, Department of Endocrinology, Theagenio Cancer Hospital, Thessaloniki, Greece, Email mariaboudina@gmail.com

Purpose: Brown tumors, also known as cystic fibrosa, are rare, benign, osteolytic, fibrotic lesions of the bones that occur secondary to hyperparathyroidism. They are caused by increased osteoclastic activity leading to an abnormal bone metabolism.

Case Description: Here, we present the case of a 58-year-old male, who presented with painful bony lesions, initially attributed to metastatic disease. After biochemical workout, imaging and biopsy, the nature of the lesions was revealed. We discuss the differential diagnosis and clinical management of the disease.

Conclusion: Patients with brown tumors should be assessed in the differential diagnosis of bony lesions and should always be tested for hyperparathyroidism. An early diagnosis is crucial for the successful treatment of such patients.

Keywords: brown tumor, hyperparathyroidism, chronic kidney disease, case report

Introduction

Hyperparathyroidism (HP) is a disorder in which there is an excess of parathyroid hormone (PTH) secretion. It can be classified, according to the origin of defect, into primary, secondary and tertiary.¹ Chronic renal failure is a common cause of secondary HP, triggered by hypocalcaemia, hyperphosphatemia or decreased active vitamin D. The prolonged stimulatory effect of parathyroid hormone on the skeleton causes increased bone turnover, resulting in resorption and replacement of the bone with fibrotic tissue, an entity called brown tumors.² The underlying pathophysiology has become more complex recently, due to the progressive awareness of the important role of fibroblast growth factor 23 (FGF23), α -klotho, as well as the Wnt-b-catenin signaling pathway. Firstly, during the early stages of chronic kidney disease, there is low bone turnover, due to resistance to the action of PTH, reduced calcitriol levels, malnutrition and uremia. High bone turnover disease (osteitis fibrosa) occurs only later on, when increased PTH levels are able to overcome skeletal PTH resistance, leading to the formation of brown tumors.³ Thus, big lesions appear, anywhere in the skeleton. The commonest locations of the lesions are mandible, clavicle, ribs and pelvis. They are rarely seen in clinical practice nowadays, due to the early detection of parathyroid abnormalities in biochemical laboratory tests. Brown tumors have been reported to occur in 1.5% to 4.5% of patients with primary or secondary HP.^{4,5} Patients with brown tumors should be assessed in the differential diagnosis of bony lesions and should always be tested for HP. An early diagnosis is crucial for the successful treatment of such patients.

Case Report

A 58-year-old male was referred to the primary care because of pleurodynia. He was an obese smoker with a heavy medical history of hypertension, chronic kidney disease stage III, obstructive pulmonary disease, heart failure and atrial fibrillation. He reported a two-year history of hyperthyroidism treated with methimazole. The patient underwent a thorax

CT, which revealed an extended goiter and extra pulmonary masses infiltrating the thoracic cage and the ribs (Figure 1). The masses were considered metastatic in origin, and the patient was referred to the oncology department of the hospital for additional imaging and staging. Bone scintigraphy indicated increased uptake in left scapula, ribs, left ileum and tibia. However, no primary tumor was identified from thorax, abdomen and brain CT. Biochemistry at the time revealed a correction for albumin calcium of 9.2 mg/dl (8.4–10.1), phosphorus at 2.38 mg/dl (2.5–4.5) and alkaline phosphatase 580 IU/L (30–120). The patient was then referred for an endocrine assessment. He was found to be clinically and biochemically euthyroid. Additional blood tests showed high PTH levels at 1184 pg/mL (15–65) and a mild vitamin D3 deficiency (17.3 ng/mL). The renal function was impaired (eGFR 50 – Stage 3A). Patient's characteristics are presented in Table 1.

Taking into consideration the laboratory results, the diagnosis of secondary HP was made. Since imaging was inconclusive about the nature of bony lesions, it was decided to undergo a bone biopsy. The examined specimen revealed a morphologically bland fibroblastic spindle cell proliferation admixed with numerous osteoclastic giant cells. According to pathology, despite the absence of evident hemorrhage, in context, the appearance of the lesion was suggestive of bone changes due to HP. Therefore, the diagnosis of brown tumors was confirmed by histological examination (Figure 2).

The patient received supplementation with calcium, vitamin D, vitamin D analogues and cinacalcet. There was a significant improvement in the laboratory tests with a striking reduction of PTH levels at 103 pg/mL. Moreover, 18 months after the initiation of the treatment, a thorax CT was repeated and revealed a regression of the tumors in the thoracic cage (4.7x3.9 to 4.3 × 2.8 cm) and the ribs. The lesions appeared well defined and ossification had started (Figure 3).

Discussion

The prevalence of HP has increased over the latest years because of the early detection of biochemical abnormalities on routine tests. However, in some cases, it remains under-diagnosed and physicians have to recognize and treat the underlying complications, before addressing the primary pathology.⁶



Figure 1 Thorax CT before treatment initiation. Intravenous contrast was administered prior to the exam. Extra pulmonary mass that infiltrates the thoracic cage and the ribs, as shown with the red arrow.

Table 1 Patient's Characteristics

Anthropometrics			
Age (years)	58		
Sex	Male		
Weight (kg)	128		
BMI (kg/m²)	39		
Biochemistry	Before treatment	After treatment	Normal values
Calcium	9.13	8.47	8.6–10.0 mg/dl
Phosphate	2.38	3.89	2.5–4.5 mg/dl
Creatinine	1.21	1.8	0.5–1.9 mg/dl
Alkaline phosphatase (ALP)	580	96	35–104 IU/L
25-OH Vitamin D	17.3 ng/mL		
Parathyroid hormone (PTH)	1184	103	15–65 pg/mL
TSH	0.03	1.17	0.2–4.2 IU/mL
FT4	1.1	1.07	0.9–1.6 ng/dl

Brown tumors represent a late event in untreated hyperparathyroidism. These tumors appear more often in primary HP, although they are also seen in secondary and tertiary HP.^{7,8} Clinically, a brown tumor presents as a slowly growing palpable mass and may cause bone pain or pathological fracture. Nonspecific general clinical features, such as weakness, polyuria, weight loss and recurrent nephrolithiasis, may also be associated with the accompanying HP. However, the suspicion of a brown tumor is based on radiological features either on plain film, computed tomography or MRI. If radiology is doubtful, as was in our case, biopsy of the bone tumor is recommended for the final diagnosis.⁹

The formation of brown tumors is the result of intense osteoclastic activity, fibroblast proliferation and bone resorption.^{10,11} The term is used because of reddish brown color caused by its vascularity, hemorrhage and deposits of hemosiderin.¹² Once brown tumors are diagnosed, the correction of the underlying endocrine disorder is the treatment of choice, leading to their regression.¹³ In cases of primary HP, radiological and scintigraphy investigation is suggested, and surgical removal of the parathyroid adenoma will lead to regression of symptoms and signs of the disease. In cases of

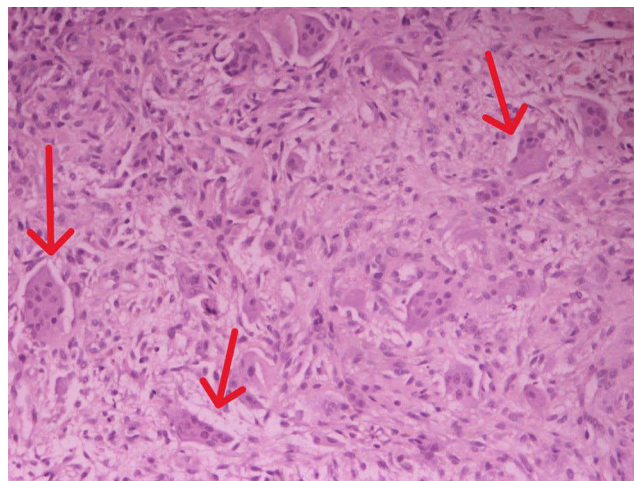


Figure 2 Biopsy from one of the osteolytic rib lesions shows bland fibroblastic spindle cell proliferation admixed with numerous osteoclastic giant cells (arrows), findings which in context are most suggestive of bone changes due to hyperparathyroidism (hematoxylin-eosin, x200).

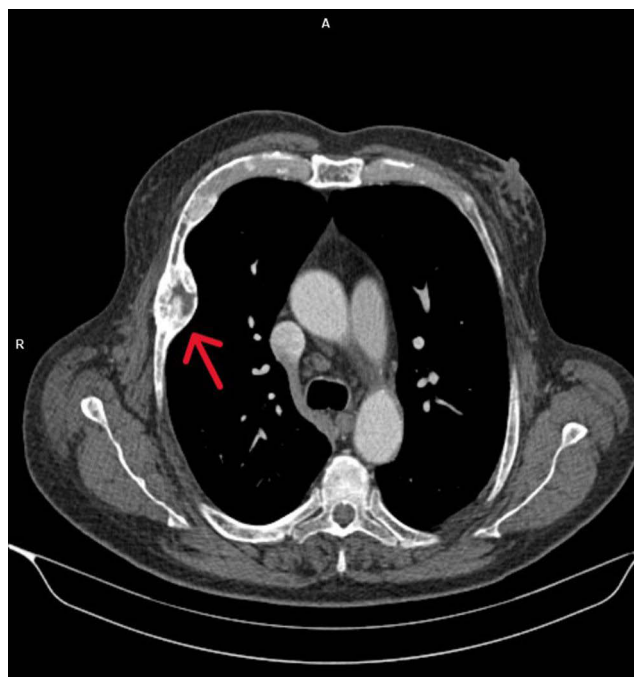


Figure 3 Thorax CT after i.v contrast, 18 months post treatment showed regression of the tumor in the thoracic cage (from 4.7×3.9 to 4.3×2.8 cm) and the ribs, as shown with the red arrow.

secondary HP, identification of the underlying disorder, most commonly vitamin D deficiency or chronic renal failure, will be necessary. In any case, the optimal treatment aims at the reduction of PTH levels and improvement of phosphorus levels.

The differential diagnosis of a lytic bone tumor, such as a brown tumor, includes bone metastasis or myeloma, simple bone cyst, infection (osteomyelitis) or infarction (bone infarction), eosinophilic granuloma, osteoblastoma, chondroblastoma or non-ossifying fibroma^{14,15} (Box 1). In our case, the patient presented with painful bone lesions that initially were considered bone metastases, which represents the main differential problem in these cases. Thorough medical history and clinical examination are mandatory to reveal signs and symptoms, in addition to biochemical, hormonal, radiologic and scintigraphic evaluation in these patients. Differential diagnosis is important, as it will define the treatment of choice and the overall prognosis of the patient.

Box 1 Differential Diagnosis of Bone Lesions

Giant cell tumor
Metastatic carcinoma
Brown tumors
Chondrosarcoma
Chondroblastoma
Osteosarcoma
Osteomyelitis
Aneurysmal bone cyst
Eosinophilic granuloma
Infarction
Infection
Non-ossifying fibroma

Despite the rarity of the disease, clinicians should include brown tumors in the differential diagnosis of bony lesions and should always test for HP. Nowadays, due to high accessibility of diagnostic tools and especially biochemical tests, high PTH levels should be further assessed, in order to classify the hyperparathyroidism and be alert to its complications. A high index of suspicion will lead to an early diagnosis. More case studies are needed in order to differentiate bone lesions.

Ethical Approval and Consent for Publication

Institutional Review board (IRB) approval for this study was not required. The patient gave his consent for the publication of information related to his medical condition.

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Disclosure

The authors declare they have no competing interest for this study.

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