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Brown tumors: Iconographic review of 4 cases

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Abstract

With the advent of routine calcemia screening, hyperparathyroidism is usually discovered in the early stages and treated appropriately before significant skeletal changes occur.

Brown tumors represent a pathognomonic yet rare feature of hyperparathyroidism, and they can affect virtually any bone and manifest as pathological fractures, bone pain or remain asymptomatic.

Their imaging appearance is often non-specific, especially when they are multiple and consequently mistaken for malignancy, which is more commonly encountered in clinical practice.

Their diagnosis relies essentially on biology, with assessments of parathormone serum levels and phosphocalcic markers.

Over a period of 6 years, we have collected 4 cases of brown tumors, of which 3 were multiple and unique in one case affecting the maxillary bone, and we propose an iconographic review including different examinations (CT, MRI, PET-scan and scintigraphy) in order to approach the different imaging aspects of this entity and its etiologies.

Their treatment implicates mainly the treatment of the cause of hyperparathyroidism.

Keywords: Brown tumors; Hyperparathyroidism; Skeletal imaging; Parathyroidectomy; CT scan

1. Introduction

Brown tumors are focal bone lesions corresponding to bone remodeling as a response to the metabolic disorders caused by the chronic hypersecretion of parathormone or PTH-RP, a protein with the same metabolic effects as PTH [1].

It affects more females, with a sex ratio M/F of 1:3 and a peak of incidence in the sixth decade.

Brown tumors have been mainly reported in patients with primary hyperparathyroidism, seen in 3% of the cases, in contrast to 1.5–1.7% in patients with secondary hyperparathyroidism [2, 3]. The causes of primary hyperparathyroidism are pathologically divided into adenomas (85%), hyperplasia (15%) and carcinomas (<1%) [4].

We aim to present a pictorial review of brown tumors involving different bones.

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2. Case 1

A 42-year-old patient with no particular medical history presented to the emergency department for a left femoral diaphyseal fracture following a fall from stairs. She reported diffuse bone pain. A standard radiograph showed multiple osteolytic lesions of the left femur, hence the suspicion of a pathologic fracture.

NECT of the pelvis and the left thigh demonstrated multiple lesions of possible malignant tumoral origin, such as metastases or multiple myeloma, or benign tumors such as brown tumors considering the less aggressive nature of the lesions towards the adjacent soft tissues (***figure 1***).

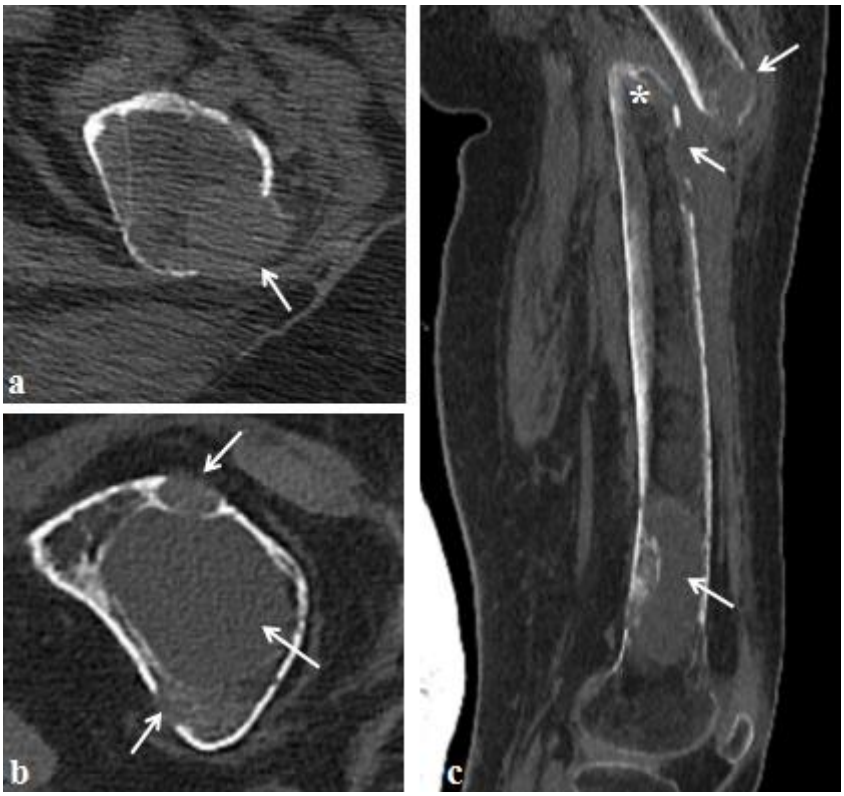

Figure 1 a and b Axial bone window slices showing expansive cortico-medullary and medullary left femoral osteolytic lesions (white arrows), responsible for discontinuity of the cortex, without periosteal reaction or invasion of the soft tissues. **c :** oblique reconstruction on the left femur showing the displaced fracture of the upper third of its diaphysis (asterisk) on an osteolytic lesion (red arrow)

It was decided to complete the investigations with a CCTAP CT to search for a primary tumor as well as phosphocalcic blood and urinary tests. The latter found hypercalcemia with corrected serum calcium measured at 140 mg/l [88 – 108 mg/l], hypophosphatemia at 19 mg/l [25-45 mg/l], parathormone > 2500 pg/ml [15 – 68 pg/ml] which is 36 times greater than its normal value [12-88 pg/ml], hypovitaminosis D at 10.5 ng/ml as well as normal renal function.

The corrected QT interval was measured at 387 ms [360 – 460 ms]. The patient was receiving per os and intravenous hyperhydration, then zoledronic acid.

CT revealed diffuse osteopenia and multiple osteolytic tissue lesions, located in both medullary and cortical bone (***figure 2***), fairly well limited, sometimes eroding the cortex, that enhanced intensely and heterogeneously after contrast, particularly at the ribs, without invasion of the soft tissues, and stigmata of an old fracture of the right upper humeral diaphysis.

Multiple non-obstructive bilateral renal calyceal urolithiases (***figure 3***) and a focal vein thrombosis of the left superficial and deep femoral veins were also observed.

A nodular lesion was detected next to the left wall of the oesophagus, with well-defined contours and enhancing homogeneously after contrast, measuring 15 x 11 x 33 mm (AP x Tr x Height), consistent with a mediastinal ectopic parathyroid adenoma (***figure 3***).

The final diagnosis retained was brown tumors complicating primary hyperparathyroidism.

The patient subsequently underwent open intramedullary nailing for her left femoral fracture, and is awaiting a parathyroid Sestamibi scan.

A bone biopsy came back positive for a giant cell tumor.

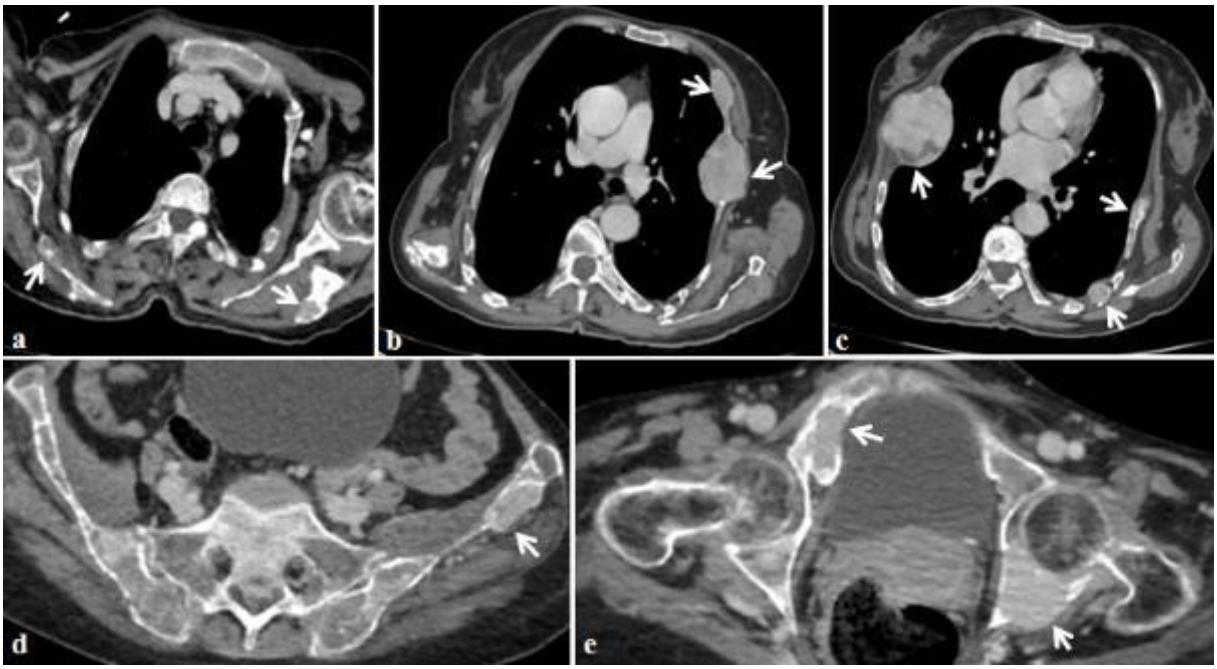

Figure 2 Axial CECT showing expansive osteolytic tissue lesions affecting the scapulae, ribs and pelvic bones, significantly thinning the cortical bone. The larger lesions present an intense and heterogeneous enhancement (**c**)

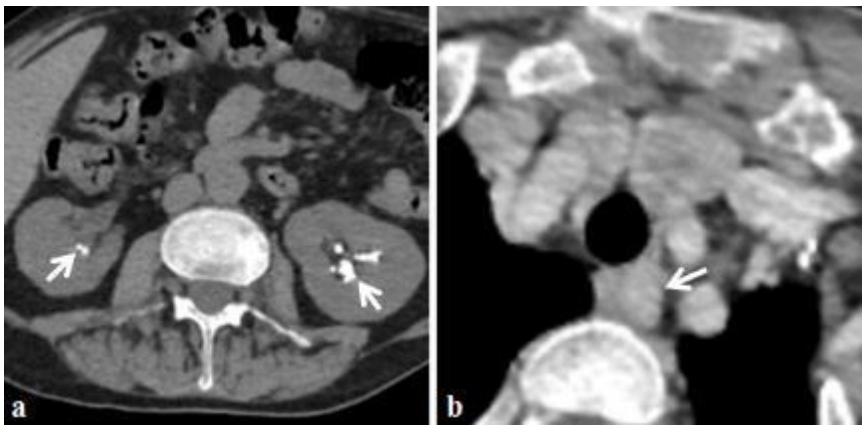

Figure 3 a NECT shows bilateral non obstructive urolithiases complicating hyperparathyroidism **b.** CECT scan showing the parathyroid adenoma

3. Case 2

A 60-year-old woman, who had a history of rectal adenocarcinoma resection and was monitored for chronic renal failure, presented with diffuse bone pain.

The attending physician requested a TAP CT, which found osteolytic lesions involving the bones of the pelvis and the right femur, raising suspicion of bone metastases from her rectal tumor. In addition, there was no local recurrence of her tumor or suspicious lymph nodes, liver or lung metastases.

After a multidisciplinary consultation meeting, the patient had a PET-CT which showed avid fixation of the osteolytic lesions (***figure 4***).

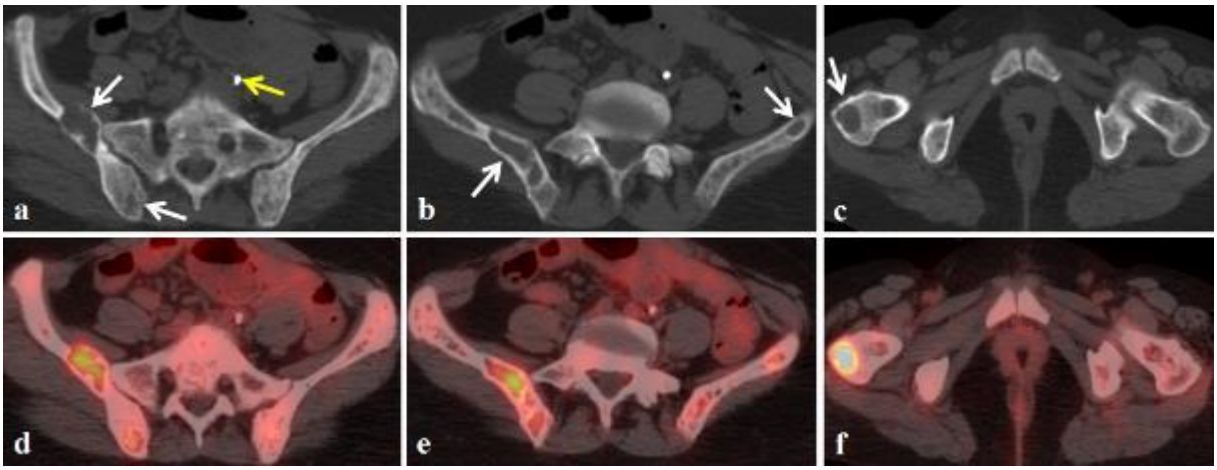

Figure 4 a, b and c NECT shows multiple osteolytic lesions of the bones of the pelvis and the right femur, mostly medullary, thinning the cortex of the right iliac bone (**a**). We also noted a left JJ stent, indicated by the yellow arrow. **d, e and f :** Axial PET-scan sections superimposed on the abnormalities noted on conventional imaging, showing the uptake of 18-FDG by the bone lesions.

A bone biopsy was proposed to the patient (***figure 5***) and the anatomopathological result was in favor of a giant cell tumor without evidence of malignant cells.

Laboratory tests found increased PTH serum levels and normal calcemia.The diagnosis of brown tumors complicating hyperparathyroidism was made, and the patient was started on medical treatment with good improvement.

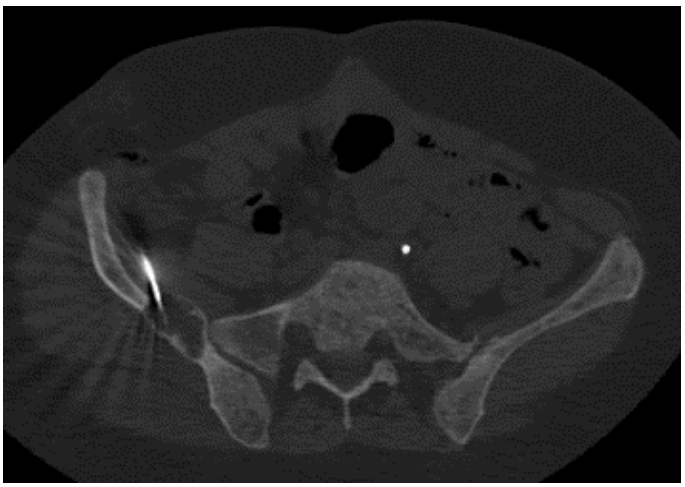

Figure 5 Axial image of a NECT of the pelvis showing the bone biopsy procedure of the right iliac lesion

4. Case 3

A 28-year-old patient consulted the traumatology department for pain in the right ankle that started a month ago. The clinical examination was unremarkable, and an x-ray of the ankle revealed an osteolytic lesion of the right fibula, responsible for a rupture of the cortex.

CT and MRI of the right ankle were performed to characterize the lesion (***figure 6***) and found a delimited osteolytic lesion rupturing the fibular cortex, described as T1 hypointense, hyperintense in PD sequence, enhancing intensely and homogeneously after contrast injection, limited on its upper pole by osteosclerosis.

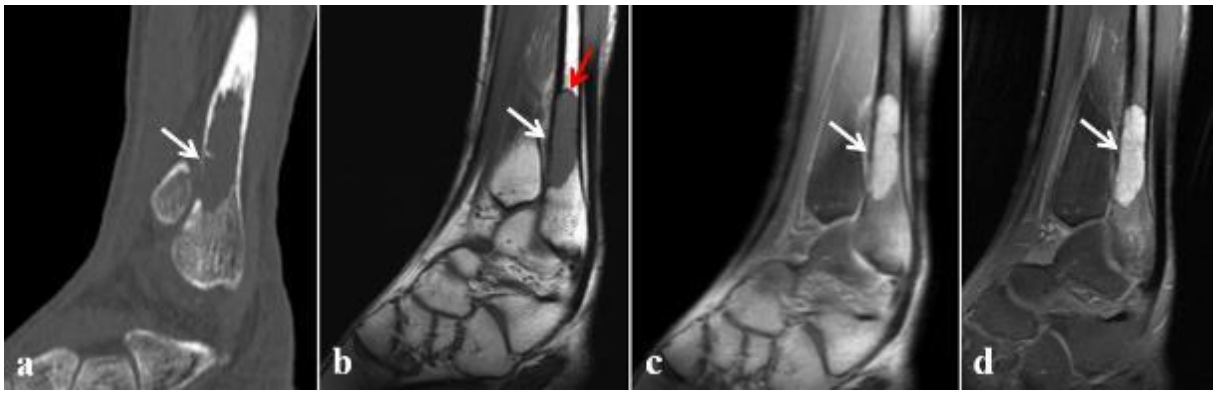

Figure 6 a. Oblique reconstruction of a NECT scan showing a central osteolytic lesion responsible for the thinning of the right fibular cortex (white arrow). **b, c and d. :** Sagittal T1 (b), DP (c) and T1 FATSAT after injection of gadolinium (d) show the same lesion, surrounded by a border of sclerosis at its upper pole (red arrow)

A biopsy of the fibular bone lesion was performed and came back in favor of a giant cell tumor.

With the multiplicity of bone lesions objectified on additional X-rays, the absence of neoplastic background and the laboratory tests showing hypercalcemia with corrected calcemia measured at 123 mg/l, a mild hypophosphatemia at 24 mg/l, a serum parathormone at 1287 pg/ml (14 times its normal value), as well as correct renal function, the diagnosis of brown tumors was made.

The corrected QT interval was normal, and the patient was put on oral and intravenous hyperhydration.

Complementary low-dose whole-body CT (***figure 7***) shows medullary or juxta-cortical lesions of the bones of the pelvis and lower limbs with the same semiological characteristics as those of the right fibular lesion, some of which were classified as Lodwick IA and IB.

A cervical ultrasound found a nodule facing the postero-inferior pole of the thyroid gland, well limited, homogeneously hypoechoic and hypervascular on color Doppler, measuring 13 x 6 x 13 mm, compatible with a parathyroid adenoma. A Sestamibi scan detected the same abnormality (***figure 8***).

The parathyroid nodule was resected, and histopathological examination of the parathyroid nodule revealed an adenoma.

Laboratory tests then showed normalization of the PTH levels, and follow-up imaging (***figure 9***) demonstrated restoration of the ruptured cortex and mineralization of the osteolytic lesion.

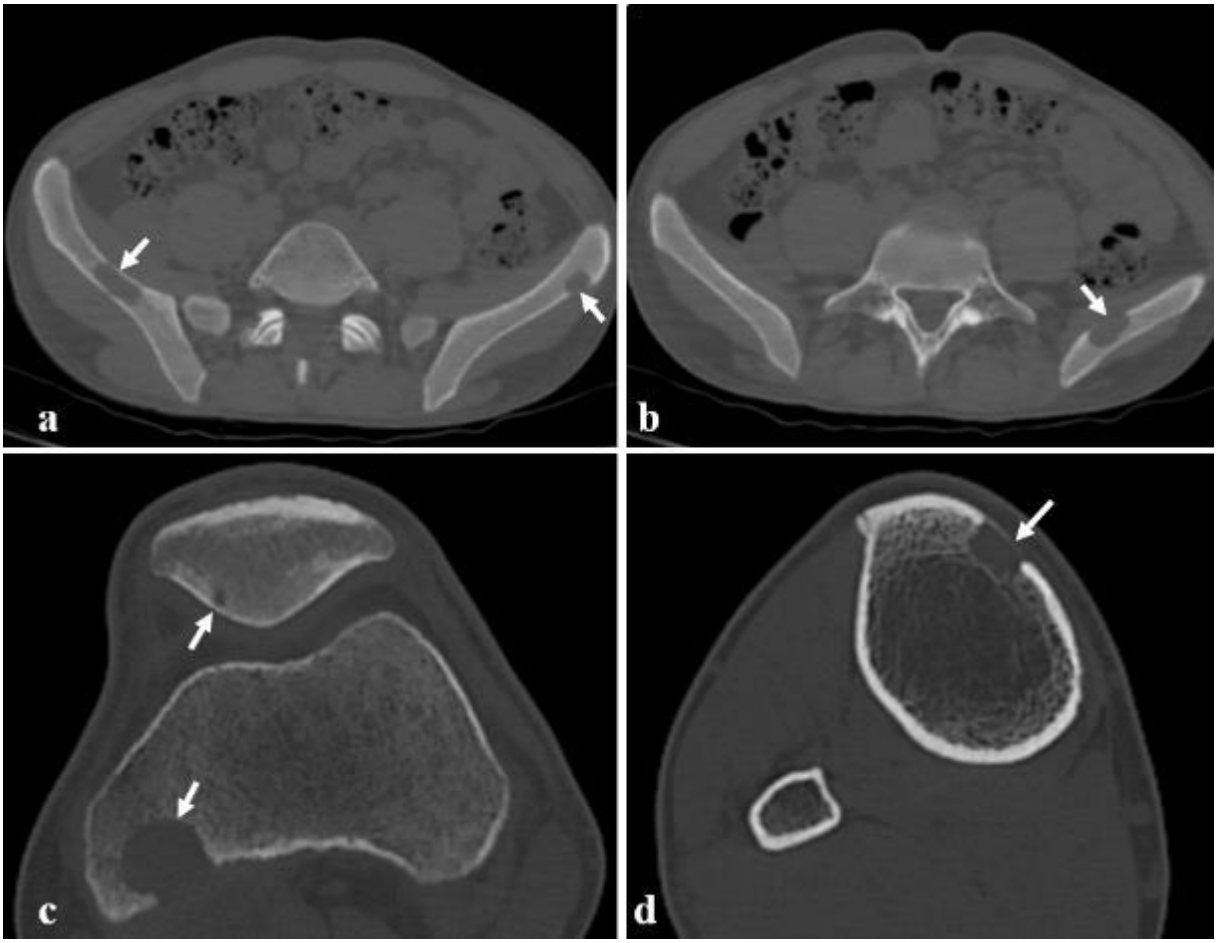

Figure 7a and b Axial CT slices show well-marginated osteolytic lesions of the pelvic bones, responsible for the rupture of the cortex of the left iliac bone. **c.** and **d.** : Juxtacortical osteolytic lesions of the left femoral condyle and patella (c) and right tibia (d), with a discontinuity of the femoral cortex and thinning the tibial cortex

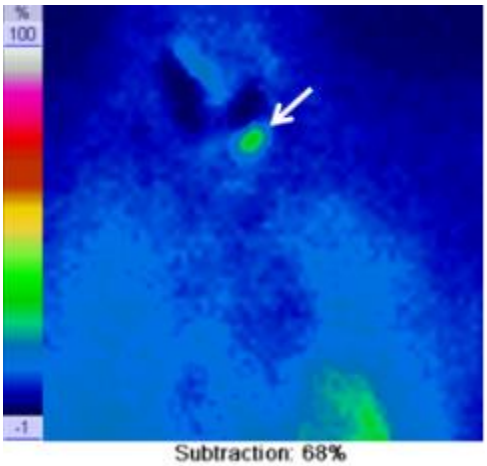

Figure 8 Coronal image of the MIBI scintigraphy showing fixation under the left thyroid lobe, corresponding to the left inferior parathyroid adenoma

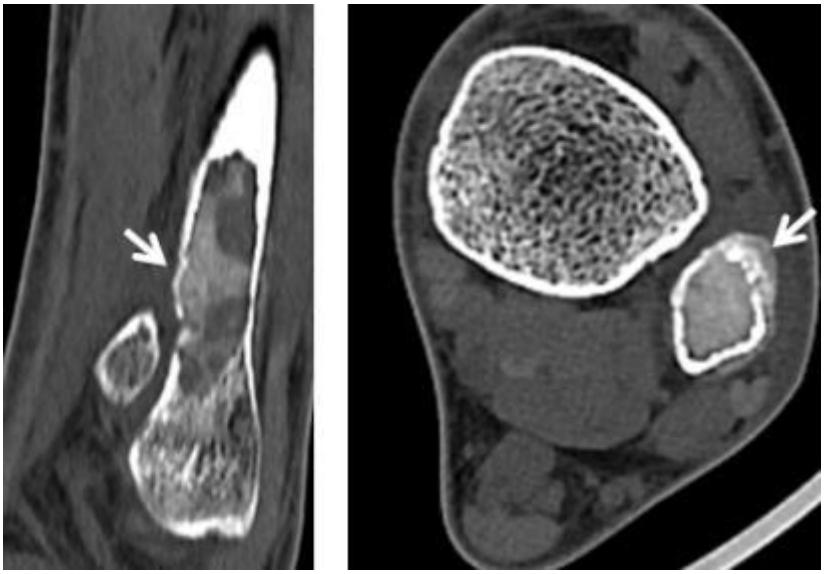

Figure 9 Oblique sagittal and axial CT showing bone mineralization of the right fibula one month after the adenoma resection

5. Case 4

A 51-year-old female patient was complaining of an ongoing polyuro-polydipsic syndrome, which started a month before her admission.

The clinical examination was normal, and the biological assessment found hypercalcemia with corrected serum calcium at 140 mg/l, low hypophosphatemia at 15 mg/l, hypovitaminosis D at 8 µg/l and high parathormonemia at 845 pg/ml.

A cervical ultrasound and CT scan (***figure 10***) showed a hypervascular nodule behind the posterior pole of the thyroid, measuring 24 x 14 x 29 mm, suggesting a parathyroid adenoma. The CT scan also found an osteolytic and expansive lesion of the maxilla, thinning the cortex and protruding into the lumen of the ipsilateral maxillary sinus, strongly enhancing after contrast administration, without associated osteolysis of the adjacent dental roots or extension to the soft subcutaneous tissues, suggestive of a brown tumor (***figure 11***).

The patient underwent excision of the parathyroid nodule with a simple postoperative course.

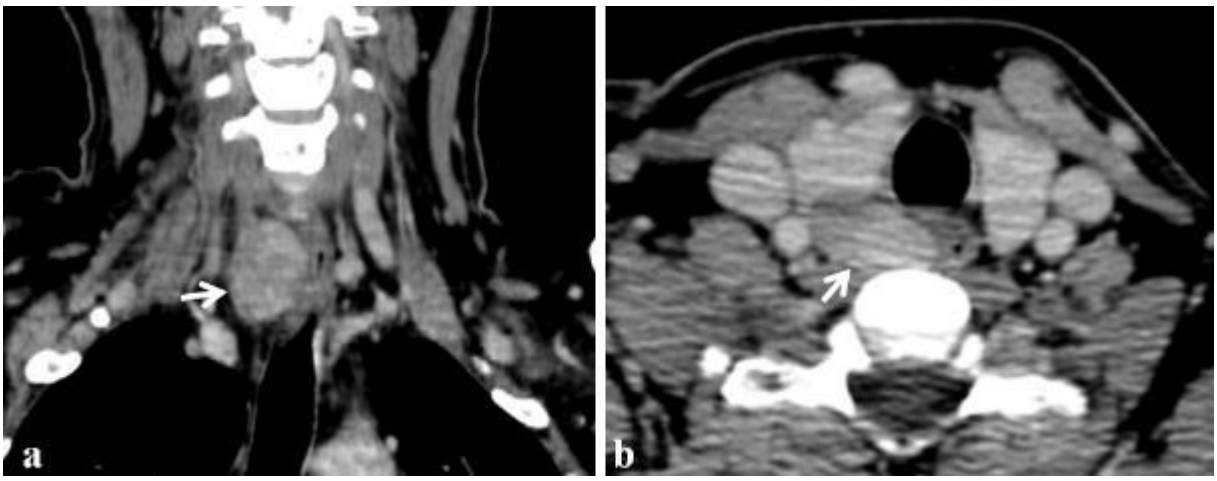

Figure 10 Coronal and axial images of a CECT show the right posterior and inferior parathyroid adenoma

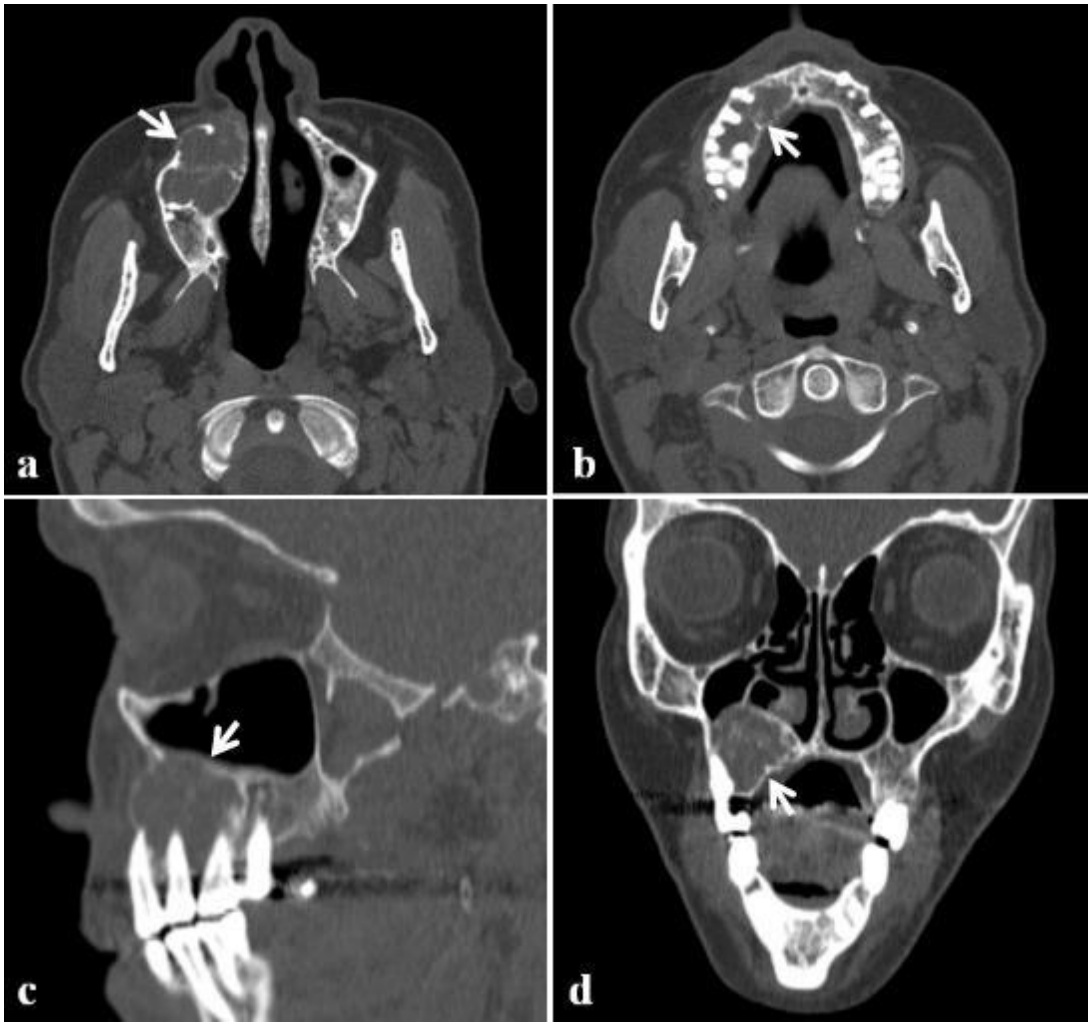

Figure 11 Axial NECT images (a and b), sagittal (c) and coronal (d) show the right maxillary osteolytic lesion

6. Discussion

Hyperparathyroidism can be asymptomatic or reveal itself through the symptoms of hypercalcemia : diffuse bone pain, dehydration, arterial hypertension, polyuria and polydipsia, constipation, abdominal pain, urolithiasis and arrhytmias.

Other manifestations of hyperparathyroidism affect the kidneys (urolithiasis and nephrocalcinosis secondary to hypercalciuria), joints (chondrocalcinosis by deposition of microcrystals of calcium pyrophosphate) and bones.

Brown tumors exhibit slow growth and are not a neoplastic proliferation as their name suggests, but rather a response of the bone to its excessive and prolonged resorption induced by the action of parathormone. They correspond on the microscopic level to areas of intense bone resorption where giant cells are found, an abundant fibro-vascular stroma and hemorrhage, the latter being responsible for the deposition of hemosiderin which gives these tumors their characteristic brownish color.

Only the biological assessment, including serum parathormone and phosphocalcic markers, often makes it possible to distinguish these tumors from giant cell tumors because of their significant histological similarity.

Imaging typically finds one or more well-demarcated osteolytic lesions, of a solid, cystic or mixed nature, expansive, of variable location but more frequently affecting the bones of the face, the clavicles, the ribs, the bony pelvis and the long bones [5], that can result in pathological fractures. The lytic lesions may be trabeculated, with a multiloculated appearance [6].

They can also present as an ill-defined lesion, a mixed osteolytic and condensing lesion, or with involvement of the adjacent soft tissues, thus mimicking metastases [7, 8]. In these cases, histological confirmation is recommended [9].

Other radiological manifestations of hyperparathyroidism include subchondral bone resorption, diffuse osteopenia, cortical thinning, resorption of the tufts of distal phalanges and the radial border of the hand phalanges [6, 10].

MRI may show heterogeneous signal intensity, with hypointensity suggesting the presence of hemosiderin [6]. Fluid-fluid levels may be seen in the cystic components [6].

The differential diagnosis of solitary brown tumors includes solitary bone cyst, aneurysmal bone cyst, giant cell tumor, and giant cell reparative granuloma.

A giant cell tumor is usually an eccentric arising from the epiphysis and extending to the metaphysis in its evolution. It never arises in a diaphyseal location, rarely affects children and occurs once skeletal maturity has been reached. Multiple locations are practically never seen [6].

A giant cell granuloma has sharp margination and may sometimes be classified as a Lodwick IA lesion. Fine or coarse trabeculations may be seen, and the cortex may be expanded or thinned, but is usually not permeated [6].

When it involves the mandible, the differential diagnosis includes benign conditions such as a simple bone cyst, an odontogenic keratocyst, other odontogenic cysts (radicular cyst, lateral periodontal cyst, and medial mandibular cyst), bone abscess, focal osteomyelitis and eosinophilic granulomas, as well as malignant tumors represented mainly by ameloblastoma, metastasis, primary plasmacytoma, and giant-cell lesions [11].

The differential diagnosis of facial bone involvement in chronic renal failure includes fibrous dysplasia and uremic leontiasis ossea [12]. The latter most often affects the maxilla and mandible, followed by the bones of the base of the skull [13], and is expansive and symmetric with a typical pattern of succession of hyperdense and hypodense lines.

Multiple brown tumors can be confused with metastases, multiple myeloma or multiple bone cysts [14].

It is important to remain cautious when faced with the diagnosis of a brown tumor in a patient known and followed for hyperparathyroidism. Indeed, Xie and Al [9] reported the case of a 54-year-old patient who consulted for a painful and solitary bone lesion of the proximal tibial metaphysis, with discovery of hyperparathyroidism. The anatomopathological study of the bone biopsy was in favor of a low-grade chondrosarcoma.

In the same context, Panagopoulos et al [15] reported the case of a 53-year-old patient who underwent surgery for giant cell tumors of the left radius and ulna, which was deemed a posteriori useless in view of the subsequent discovery of multiple osteolytic lesions, which were brown tumors secondary to a parathyroid carcinoma.

Ouzaa et al. [16] described an osteolytic lesion involving the metaphyseal–epiphyseal junction of the distal radius in a 66-year-old woman diagnosed with primary hyperparathyroidism, initially thought to be a brown tumor. The patient underwent a resection of a benign parathyroid adenoma but was still complaining of wrist pain a year later. The radiograph showed progression of the radial lesion and the patient had a biopsy followed by surgery for a giant cell tumor.

The treatment of brown tumors consists of treating the etiology of hyperparathyroidism since they regress and transform into condensing lesions. The time required for bone repair varies from a few months in young patients to several years in older patients [17].

Pathologic fractures require fixation, and in some cases, curettage and grafting of the brown tumor are indicated [6]. Surgical decompression may be indicated when there is a severe neurological deficit [18].

7. Conclusion

The diagnosis of brown tumors can be difficult since they can mimic malignancy, and the correlation of imaging features with laboratory data is necessary for an accurate assessment.

An overview of relevant clinical history and available laboratory investigations, mainly the phosphocalcic markers, should preferably precede image interpretation as their radiological appearance is nonspecific. However, this is often not the case in developing countries, where hyperparathyroidism is diagnosed in advanced stages or during complications, in contrast to the western world, where it is usually detected incidentally in routine biochemical screening including serum calcium.

Based on the imaging findings, further imaging and laboratory investigations may be suggested to ascertain the diagnosis; the main priority is to exclude a malignant primitive tumor or hematologic malignancy, followed by meticulous research for other manifestations of hyperparathyroidism and its etiology.

Abbreviations

- 18-FDG: 18-fluoro-deoxy-glucose
- CCTAP: cerebral, cervical and thoraco-abdomino-pelvic
- CECT : contrast-enhanced computed tomography
- CT : computed tomography
- MRI : magnetic resonance imaging
- NECT : non-enhanced computed tomography
- PD : proton density
- TAP : thorax, abdomen and pelvis
- PET : positron emission tomography
- PTH : parathyroid hormone

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no competing interests.

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