Endocrinology, Diabetes & Metabolism CASE REPORTS

D Gallo, S Rosetti and others | Brown tumors in primary hyperparathyroidism

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When primary hyperparathyroidism comes as good news

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Summary

Brown tumors are osteoclastic, benign lesions characterized by fibrotic stroma, intense vascularization and multinucleated giant cells. They are the terminal expression of the bone remodelling process occurring in advanced hyperparathyroidism. Nowadays, due to earlier diagnosis, primary hyperparathyroidism keeps few of the classical manifestations and brown tumors are definitely unexpected. Thus, it may happen that they are misdiagnosed as primary or metastatic bone cancer. Besides bone imaging, endocrine evaluation including measurement of serum parathyroid hormone and calcium (Ca) levels supports the pathologist to address the diagnosis. Herein, a case of multiple large brown tumors misdiagnosed as a non-treatable osteosarcoma is described, with special regards to diagnostic work-up. After selective parathyroidectomy, treatment with denosumab was initiated and a regular follow-up was established. The central role of multidisciplinary approach involving pathologist, endocrinologist and oncologist in the diagnostic and therapeutic work-up is reported. In our opinion, the discussion of this case would be functional especially for clinicians and pathologists not used to the differential diagnosis in uncommon bone disorders.

Learning points:

- Brown tumors develop during the remodelling process of bone in advanced and long-lasting primary or secondary hyperparathyroidism.
- Although rare, they should be considered during the challenging diagnostic work-up of giant cell lesions.
- Coexistence of high parathyroid hormone levels and hypercalcemia in primary hyperparathyroidism is crucial for the diagnosis.
- A detailed imaging study includes bone X-ray, bone scintiscan and total body CT; to rule out bone malignancy, evaluation of bone lesion biopsy should include immunostaining for neoplastic markers as H3G34W and Ki67 index.
- If primary hyperparathyroidism is confirmed, selective parathyroidectomy is the first-line treatment.
- In advanced bone disease, treatment with denosumab should be considered, ensuring a strict control of Ca levels.

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Background

Giant cell lesions belong to a heterogeneous group of skeletal tumors, characterized by osteoclastic-like giant cells and mononuclear stroma (1). The differential diagnosis could be challenging (1, 2). Differing from each other due to specific morphology, clinical and radiologic features, giant cell lesions include giant cell tumors of bone (GCTB), solid aneurysmal bone cysts, giant cell rich chondroblastoma, non-ossifying fibromas and brown tumors (BT). Demographic, anatomical and radiological features are crucial in the diagnostic work-up. Nevertheless, certain cases with unusual clinical presentation may be intricate to diagnose, especially in small biopsy specimen. So, the expertise of the pathologist is crucial in the pathological differential diagnosis (1, 2). Shortly, GCTB are rare lesions, with the potential to be locally aggressive, metastasize (10% of cases) and recur (20–55%) (1, 2). They account for the 5–6% of primary bone tumors, affecting young adult aged 20 to 40 years; cases in older patients have been described (2). They are classified on the basis of radiological appearance, local aggressiveness and risk of local recurrence (1, 2). Histologically, GCTB appear with a mixture of spindle mononuclear cells, osteoclast-like giant cells and non-neoplastic mononuclear cells. Although surgery is the elective treatment, in 2013, FDA approved the use of denosumab in unresectable GCTB (3).

Conversely, BT are rare, osseous lesions representing the ultimate expression of the bone remodelling process in prolonged hyperparathyroidism (3, 4, 5). BT pathogenesis involves the interaction between osteoclasts and stromal cells, expressing RANKL, a potent stimulator of osteoclast bone-resorbing activity (5). They preferentially develop in women, between their third and fourth decades of life (5). Typically, bone X-ray describes cortical thinning, generalized osteopenia and lytic well-defined border lesions with intralesional trabeculations. Bone scintigraphy shows increased uptake at the level of radiological lytic lesions (Fig. 1A, B, C and D) (5, 6). Grossly, BT appeared as well-circumscribed, hemorrhagic masses eroding the endosteum with consequent cortex remodelling (1). Intensely vascular fibrotic stroma (made by fibroblasts, extravasated red blood cells, macrophages) and multinucleated giant-cells constitute the histological structure (1). High Ca (Ca) and parathyroid (PTH) hormone levels are crucial to orientate clinical diagnosis (1, 5, 6).

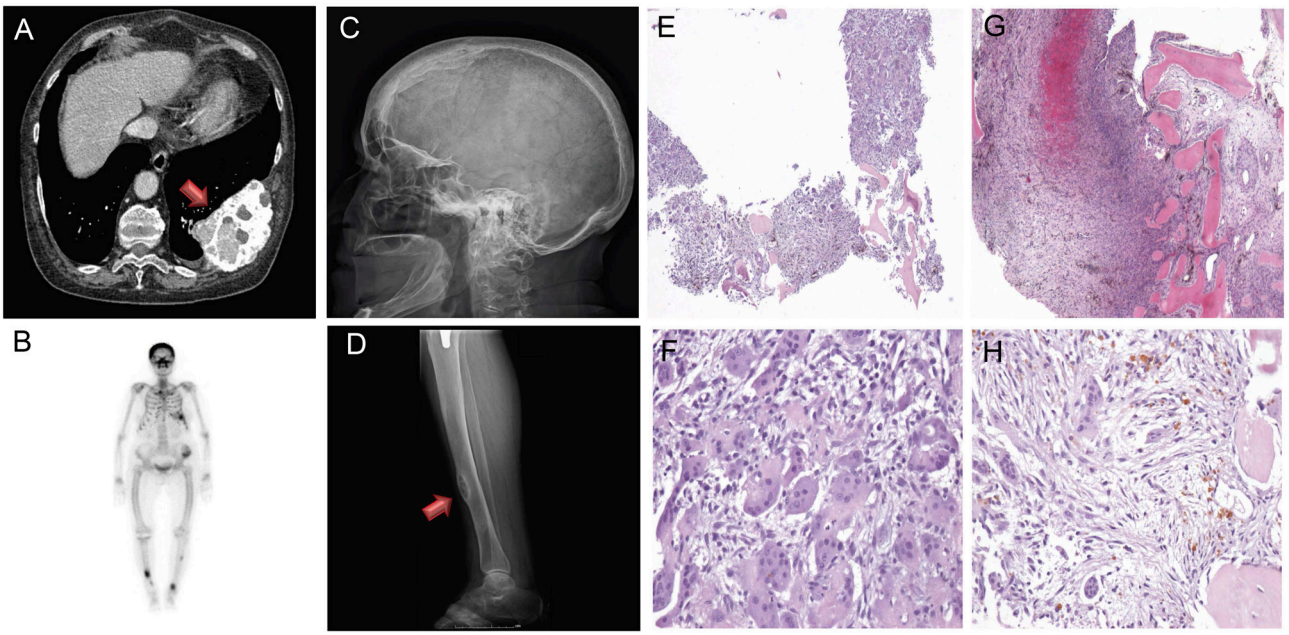

Figure 1
Bone lesions, due to hyperfunctioning parathyroid adenoma, described by different imaging techniques (A, B, C, D, E and F) and corresponding histologic specimens (E, F, G and H). In detail A, B, C, D, E and F: (A) Axial CT imaging of large chest mass; (B) Diffuse bone hypercaptation at ^{99m}Tc bone scintiscan; (C) Radiologic evidence of 'salt and pepper' shape of the skull and of trabecular rarefaction of left hemimandible; (D) Focal lesion of the tibia. (E and F) Histology of the left chest lesion; H&E stain; the tumor is hypercellular and composed of spindle cells admixed with numerous osteoclasts and reactive woven bone; (E) A×4 magnification; (F) A×20 magnification; (G and H) Histology of left iliac wing lesions; H&E stain; the tumor is composed of spindle cells with areas of extravasated red blood cells and is surrounded by a rim of reactive bone; (G) A×4 magnification; (H) A×20 magnification.

Case presentation

A 70-year-old woman suffering from osteoarthrosis complained of diffuse arthralgias and increased walking difficulties, which forced her to use a wheelchair since a few weeks. To ameliorate her functionality, she was waiting for left knee replacement surgery. Unexpectedly, pre-operatory X-ray discovered a large chest mass of 8 cm associated to moderate hypercalcemia (serum Ca levels 13.8 mg/dL). Thus, the scheduled surgical treatment was postponed, and she was referred to the Oncologist. Her past medical history was unremarkable: she suffered from type 2 diabetes, primary hypothyroidism following total thyroidectomy for Graves' disease and mild chronic kidney failure.

Investigation

Biochemical tests documented moderate-to-severe hypercalcemia (ranging from 13.6 to 14.6 mg/dL, normal value 8.8–10.2 mg/dL) and increased alkaline phosphatase levels (262 U/L, 33–98 U/L) (Table 1). The thoracic CT scan described a mixed expansive mass of the left axillary region, infiltrating the thoracic cage bilaterally, the surrounding soft tissues and the ipsilateral lung (Fig. 1A). The mass was promptly biopsied, appearing as an osseous lesion with giant and stromal cells, hemorrhagic areas and new lamellar bone. These findings initially orientated to a differential diagnosis between GCTB and giant cell rich osteosarcoma. The patient and her family were informed of the severity of the situation. A re-examination of the bioptic material by a reference center described fragment of bone infiltrated by spindle stromal cells and numerous giant cells, overwhelming hemorrhagic component and hemosiderin pigment. This description orientated to GCTB or BT (Fig. 1E and F), but the material was insufficient for in-depth analysis. In the meantime, ^{99m}Tc (Technetium) bone scintiscan and total body CT scan detected focal lesions in the left iliac wing (about 10 mm large) and throughout the tibias (from 26 to 41 mm), bilaterally (Fig. 1B). The biopsies of two fragments from the left iliac wing lesions documented friable and hemorrhagic bone tissue. Microscopic analysis showed lamellar bone tissue, with abundant stromal spindle cells without cytological atypia, few giant cells and areas of extravasated red blood cells; the tumor was surrounded by a rim of reactive bone (Fig. 1G and H). Specimens exhibited a low proliferation index with Ki67 (methylation-inhibited binding protein 1 or MIB-1) and were not immunoreactive to S100 protein, MDM2, CD68, ERG and to keratin cocktail AE1/AE3 markers, ruling out the hypothesis of an aggressive lesion. Remarkably, the immunohistochemistry for H3G34W was negative, excluding the diagnosis of GCTB. It was at this time that serum PTH levels were first tested, resulting markedly elevated (PTH 562 pg/mL, normal value 5–39). This supported the diagnostic hypothesis of BT in primary hyperparathyroidism (pHPT). Low serum vitamin D levels (8.9 ng/mL) were also found. Possibly due to kidney failure, urinary Ca (103.2 and 103.7 mg/24 h) and phosphate (227–289 mg/24) daily excretion were at the low levels of reference range. The patient was referred to the Endocrine Unit for further evaluation. Bone x-ray was typical for osteometabolic disease, demonstrating osteostructural, lytic lesions of tibias and of the left iliac wing, vertebral somas reduction (D_{10}–D_{12}), diffuse osteopenia, trabecular rarefaction of the left hemimandible and 'salt and pepper' degranulation of the skull (Fig. 1C). Indeed, neck ultrasound (Fig. 2A) and ^{99}TcSestaMIBI parathyroid scintiscan showed a large mass in the anterior-right neck region, consistent with a hyperfunctioning parathyroid adenoma (Fig. 2B), thus supporting the suspicion of BT due to pHPT. Bone mineral densitometry showed secondary osteoporosis (neck of femur: BMD 0.4349 g/cm^2,

Table 1 Main biochemical parameters at baseline and after surgery.

Parameters	Reference range	Before surgery	After surgery		
			+2 weeks	+2 months	+6 months
Ca, mg/dL	8.8-10.2	13.6	8.4*	9.2*	9.6
Albumin, g/dL	3.5–5.2	4.6	4	3.88	3.7
Albumin corrected Ca, mg/dL		13.6	8.4	9.3	9.8
PTH, pg/mL	5-39	562	140	59	42
Creatinine, mg/dL	0.51–0.95	1.07	1.21	1.24	1.05
GFR, mL/min	≥ 90	53	46	45	54
ALP, U/L	33–98	262	-	-	18
25(OH) vitamin D, ng/mL		8.9	-	30†	27†

*During supplementation with Ca carbonate 1 g/day; †during supplementation with cholecalciferol 50 000 UI/month.
ALP, alkaline phosphatase; Ca, calcium; GFR, glomerular filtration rate; PTH, parathyroid hormone; 25(OH)vitamin D, calcifediol.

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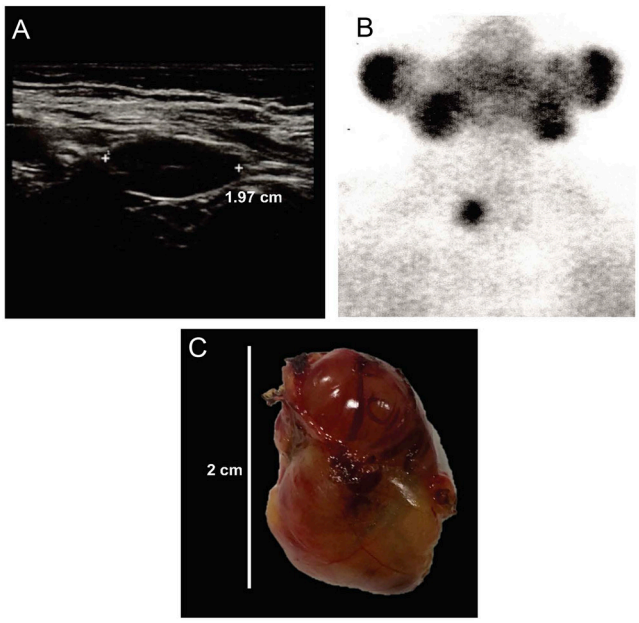

Figure 2
(A and B) Hyperfunctioning parathyroid adenoma, described by different imaging techniques. (A) Sonographic image in the longitudinal plane demonstrated a 9 × 15 × 20 mm, hypoecoic lesion, lodged at the right-inferior thyroid bed and suggestive of parathyroid adenoma or thyroid residual tissue; (B) TC-SestaMIBI scintiscan described a focal hypercaptation at right-inferior thyroid bed, confirming the nature of the lesion. (C) Gross photograph of the right-inferior parathyroid adenoma, surgically removed. The mass measured 22 × 17 × 6 mm. Notice the area of parathyroid hypotrophic tissue at periphery. When sliced, it appeared as a solid and whitish mass with brown spots.

T-score −3.7). Biochemical screening (including baseline pituitary function tests, gastrin, calcitonin and metaneprhines) ruled out a multiple endocrine neoplasia syndrome.

Treatment

Since the first histological report orientated to malignant extended lesions, surgical resection was judged not feasible. Palliative therapy with monthly s.c. injection of denosumab 120 mg associated to i.v. rehydration seemed reasonable. Due to low vitamin D_3 levels, oral cholecalciferol treatment (50 000 UI monthly) was associated. Treatment with denosumab 120 mg was discontinued after the acquisition of more complete histological and clinical information. At this point, given the diagnosis of pHPT, selective mini-invasive parathyroidectomy was performed (Fig. 2C). Histological specimen was diagnostic for a 22-mm parathyroid adenoma, with oxyphilic degeneration. Postoperatively, the patient experienced transient and mild hypocalcemia (8.4 mg/dL), requiring oral Ca carbonate (500 mg b.i.d) supplementation. Treatment with cholecalciferol was continued. To improve bone mineral density, s.c. denosumab 60 mg injection every 6 months was associated.

Outcome and follow-up

Two months after parathyroidectomy, serum Ca levels normalized (9.2 mg/dL) and serum PTH concentration significantly decreased (59 pg/mL). Ca supplementation was stopped. Monthly biochemical follow-up, advisable in case of chronic kidney failure, confirmed normal serum Ca levels (Table 1). The patient progressively improved, with regression of fatigue and joint pain enough to regain the ability to walk.

Discussion

An excessive, uncontrolled secretion of PTH from one (80%) or more (15–20%) parathyroid glands causes the common disorder of mineral metabolism called pHPT (3). Depending on severity and duration of serum hypercalcemia, clinical manifestations of pHPT include bone loss, kidney stones (nephrolithiasis and nephrocalcinosis), neuropsychiatric symptoms (anxiety and depression), muscle pain and weakness (3). Osteitis fibrosa cystica is a rare, but pathognomonic manifestation of skeletal involvement in severe pHPT. Radiological features are skull thinning with 'salt and pepper shape', diffuse demineralization, bone erosion, phalanges subperiosteal resorption, cysts and, rarely, BT (5, 6). Nowadays, due to the introduction of serum Ca determination in routine biochemical tests, primary hyperparathyroidism is generally diagnosed when asymptomatic or mild (3). Since BT are unexpected, these large lytic lesions are often misdiagnosed as primary or metastatic cancer and referred to Oncologists.

Much more lobulated appearance of BT has been suggested as possible key to differentiate it from CGTB (2). Additionally, BT commonly arise in pelvis, ribs, clavicles and extremities, while CGTB develop in the metaphysis of long bones (distal femur, distal radius proximal tibia) (1). Indeed, immunohistochemistry can be crucial, especially when clinical appearance does not allow a clear-cut diagnosis. Recently, a single driver mutation at position 34 of H3F3A (H3 histone family member 3A) gene coding for the histone variant H3.3 (H3.3-G34W) has been identified to be highly specific for GCTB (7). This mutation is restricted to neoplastic stromal cells. The mutation H3F3A is present in the majority of GCTB and is, therefore, useful for confirming diagnosis

(7, 8). In this case, the histological reevaluation by expert pathologists finally allowed the correct diagnosis. The evidence of reactive bone tissue surrounding the tumor was suggestive for a non-malignant lesion. Negative immunostaining for neoplastic markers, H3G34W and low Ki67 proliferation index supported the hypothesis of BT (7, 8, 9). Certainly, histology has a key role in the classification of giant cells lesions. The clinical suspicion, as well, is indispensable to orientate the pathologist. It can readily be imagined that the diagnosis of non-treatable bone cancer profoundly worried the patient, who was relieved by the second histological response. The proper diagnosis could seriously modify the treatment, as well as the impact of the disease on patient's life. CGTB are burdened by the unpredictable risk of local recurrence and lung metastasis, while BT have a benign clinical course. Moreover, while treatment of CGTB is surgical curettage of the bone lesion, BT typically have a good prognosis after resolution of the underpinning metabolic disorder. Definitively, early diagnosis of BT is definitively crucial to avoid unnecessary medical/surgical treatment. Denosumab therapy has been approved, with different administration regimens and doses, for the treatment of unresectable CGTB, as well as for osteoporosis in pHPT (10). Denosumab 120 mg injection once every 4 weeks is indicated as prevention of skeletal-related events in adults with advanced bone malignancies (3). On the other hand, Eller-Vainicher *et al*. demonstrated the protective effect of denosumab 60 mg once every 6 months in the prevention of fracture in pHPT-related osteoporosis (10). According to FDA, 'highlights of prescribing information' due to the risk of hypocalcemia serum Ca levels should be tested before denosumab administration.

In our opinion, this case is interesting, first, because it represents a 'real life situation'. Although not innovative, the description provides practical information for the clinical approach to bone disorders. Furthermore, it offers a detailed and updated description of the histological and molecular tests suggested by a group of skilled pathologists. Hyperparathyroidism and its skeletal consequences are still overlooked. Indeed, such severe manifestations are actually rare because diagnosis is usually early, thanks to routine biochemical tests. In addition, evaluation of bone lesions should routinely include markers of mineral metabolism taking advantage of automated biochemical screening. Then, results should be critically evaluated and interpreted. In this case, hypercalcemia emerged during the first biochemical tests, but due to the extension of bone lesions it was misdiagnosed as the consequence of the remodelling process in advanced metastatic bone disease. This also explains the reason why denosumab 120 mg was started as soon as possible, while waiting for additional clinical information. This case underlines and reinforces the importance of a multidisciplinary work-up. Endocrine evaluation, biochemical tests including serum PTH and Ca levels and expert pathologist evaluation should be the key for a proper management.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent for publication of the clinical details and clinical images was obtained from the patient.

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