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Clinical Case Seminar CCS3(1-11)

Brown tumors: an uncommon manifestation of bone disease in primary hyperparathyroidism

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Abstract

Bone involvement in primary hyperparathyroidism (PHPT) is characterized by decreased bone mineral density, bone resorption at both trabecular and cortical sites and bone erosions, up to brown tumors (BT) and cysts, the so-called osteitis fibrosa cystica (OFC). Signs and symptoms of OFC include bone pain, muscle weakness, skeletal deformities and pathological fractures. In recent years, PHPT has greatly changed its clinical expression, especially in Western countries. For these reason BT, a typical expression of OFC, are always less observed and often mistaken for malignancy. An integrated diagnostic approach, considering first a complete biochemical panel and a confirmation by functional imaging, is crucial for a correct diagnosis, mostly considering that such skeletal manifestations may be reversible after surgical cure of PHPT.

Key Words: osteitis fibrosa cystica, brown tumor, primary hyperparathyroidism, parathyroidectomy, hungry bone syndrome

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Introduction

Primary hyperparathyroidism (PHPT) is a disorder of bone metabolism consequent to the hypersecretion of parathyroid hormone (PTH) by one or more abnormally active parathyroid glands, with elevated serum calcium and elevated or inappropriately normal PTH (1). Its incidence increases with age and is 2 to 3 times higher in women, being PHPT mainly sporadic, while in 3-5% of patients it is part of an inherited syndrome (2). Sporadic PHPTcan derive from a single parathyroid adenoma (85% of cases), the hyperplasia of all four glands (10%), double adenomas (2-5%) or parathyroid carcinomas (<1%) (3-5).

Classical clinical manifestations of PHPTinclude skeletal disorders (osteitis fibrosa cystica – OFC, bone cysts and brown tumors – BT) and nephrolithiasis/nephrocalcinosis. Symptomatic

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PHPT also involves the neuromuscular system, the gastrointestinal tract, the cardiovascular system and the neurocognitive sphere (1). However, an overt involvement of the target organs has been observed only in 5% of cases in the United States and in Western Europe (6), where biochemical screening is routinely performed, and asymptomatic PHPT (high PTH with high/normal calcium levels) is the most common form of the disease at presentation (1). On the contrary, symptomatic disease is still present at diagnosis in countries like China or India, where biochemical screening is not a common practice (7).

OFC is characterized by bone pain and, radiologically, by subperiosteal reabsorption, osteolysis of the distal clavicles, "salt and pepper" aspect of the skull bones, bone cysts and BT (8, 9). BT represent the most typical feature of PHPT-relatedskeletal disorders, with an incidence of less than 5% (*versus* 13%in secondary hyperparathyroidism), and consist in benign, reactive lesions caused by disturbed bone remodeling related to long-standing increase in PTH levels (10). BT occur in single or multiple locations, most commonly the ribs, clavicle and pelvic girdle; the involvement of head and neck region (mainly mandible)is less frequent (11); spine involvement is unusual (10). Depending on their incidence and on their radiological appearance (lytic, multilobular cystic changes), BT can often be misdiagnosed on X-ray and CT scan as bone cysts, histiocytosis, leukaemia, bone metastases, osteosarcoma or giant cell tumors(8, 12, 13).

This article is aimed at reviewing the last 20 years' literature on BT in PHPT, starting from a unique case of appendicular osteolytic lesion in severe PHPT, that shows how a multidisciplinary approach can be effective and essential in these challenging diagnoses.

Patients and Methods

Case Presentation.

A 31-year-old man, truck driver, presented to our Orthopaedic Unit in January 2016 complaining of mild pain after a blunt trauma of the left forearm, in the absence of other symptoms. His past medical history was unremarkable. Standard anterior-posterior and lateral X-rays of the left forearm revealed an osteolytic lesion at the distal meta-epiphyseal junction involving the distal ulna, with a slight cortical breach without joint involvement (**Fig. 1 A and B**).

Routine laboratory tests at admittance were in the normal range except for hypercalcemia (14.0 mg/dl, normal values 8.2-10.4), which prompted PTH assay.

As shown in **Table 1**, serum intact PTH was high (745 pg/ml, n.v. 8–76) with low 25-OH vitamin D levels (15.5 ng/ml; n.v. 21-80). Neck ultrasonography (US) and scintiscan of

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thyroid (^{99m}Tc- pertechnetate) and parathyroid glands (^{99m}Tc-sestamibi) showedsolid nodules at the lower pole of the thyroid and a parathyroid lesion(25 mm in maximum diameter) behind the right thyroid lobe (**Fig. 2**).

All data oriented for a diagnosis of PHPT with related skeletal disease. The patient underwent a whole-body bone scintigraphy with 99mTechnetium methylene-diphosphonate (99mTc-MDP), that displayed an abnormal uptake in the distal third of the left ulna, as well as in most parts of the body (front ribs, rear side of D10, right anterior iliac wing, pubic bones and right femur, kneecaps profiles, distal extremity of right fibula,**Fig. 3**).

The following percutaneous biopsy of the left ulna demonstrated, at histology, an osteolytic lesion replaced by proliferating fibroblastic cells, spindle cells and multinucleated giant cells, confirming the diagnosis of BT(**Fig. 4**).

In the meantime, serum levels of PTH and calcium rapidly raised up to 2352 pg/ml and 15.0 mg/dl, respectively. Right parathyroidectomy and total thyroidectomy (due to tracheal adherence) were performed in emergency.At the same time, a composed fracture revealed by X-rays in the bioptical site of the left ulna was stabilized by means of a k-wire. Histology demonstrated a benign parathyroid adenoma. Moreover, postoperative clinical course was complicated by a severe “Hungry Bone Syndrome” (HBS), presenting with numbness of face and muscular cramps at the limbs during the first week after surgery. HBS followed a rapid decrease of serum calcium levels (from 8.5 to 5.7 mg/dl) despite the appropriate calcium carbonate and calcitriol treatment, administered after surgery along with levothyroxine. Intravenous calcium infusions (3–5 g/day for a week) and later higher doses of oral calcium (1.2 g/day) and calcitriol (0.5 mg/day), finally led to biochemical stability. Ten months after surgery, imaging studies showed a substantial regression of the osteolytic lesions previously detected, while wrist movements were complete and painless (**Fig. 1 C and D**).

Blood tests reverted to normal values (calcium, 9.1 mg/dl; phosphorus, 2.7 mg/dl) with decreased PTH levels, 103 pg/ml (**Table 1**).The last X-ray, performed 10 months after k-wire removal, showed a complete healing of the ulnar lesion and a perfect recovery of wrist mobility.

Data source.

A systematic review of the literature was done among articles published in English through PubMed, Medline and Google Scholar, from January 1998 to January 2018. Terms used for the search (separately and in reciprocal conjunction) were: “Brown Tumor”, “Osteitis Fibrosa Cystica”, “Primary Hyperparathyroidism”, “Parathyroid adenoma”,

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"Parathyroidectomy", "Hungry Bone Syndrome".We focused on the epidemiology, natural history, clinical features, diagnosis and prognosis of this disease. To demonstrate the peculiar localization of BT in our patient, inclusion criteria were established as follows: 1) patients affected by primary hyperparathyroidism from a parathyroid adenoma or carcinoma with no other comorbidities; 2) appendicular skeleton localization of BT; 3) publications only in English.Exclusion criteria were: 1) axial localization of BT(facial and mandibular bones, ribs, pelvic girdle, spine); 2) multiple localizations.

From a total number of 246 papers, 200 papers not matching the inclusion criteria were excluded after abstract evaluation. Among the studies left, 19 became available for the review after full text evaluation.

Results

Data retrieved from this systematic review are summarized in **Table 2**. Analysing the 19 works retained, concerning 22 patients in total (8, 13-30), BT with appendicular localization occurred in female patients more than in males (13 *vs* 9); the average age was 43.2 years. Among these, in six subjects (27.3%) BT were localized in hip and femur, in three (13.6%) in tibias, in two (9%) in fingers and knees, respectively; patella, fibula, radius, clavicle and calcaneus were interested each in one case (4.5%); in four patients the humerus only was interested, while no ulnar localizations were found (**Table 2**).

Discussion

PHPT is one of the most common endocrine disorders. It mainly affects elderly females, with a prevalence of 21/1000 in women between 55 and 75 years-old, corresponding to 3/1000 in the general population (31). On the converse, PHPT and postoperative HBS are relatively rare conditions in young people (incidence of 2–5 in 100000, 8-9),being often the first manifestation of MEN1 syndrome (32). In the Western world, clinical presentation of the disease is dramatically changed in the last decades. Since the introduction of widespread screening in the United States (1970s), PHPT has been frequently diagnosed in asymptomatic forms, while in the early 2000s a growing number of patients had normocalcemic PHPT(1, 33, 34) with a tripled incidence in the years 1995-2010 (35). In China asymptomatic PHPT is now increasing, but in other Asian countries (India, Iran, Pakistan, Saudi Arabia and Thailand) PHPT remains for the most part a symptomatic disorder (1). For these reasons, clinical bone disease with bone pain, generalized osteoporosis and the typical radiological features of OFC is seen today in about 5% of cases (9). BT are localized in regions with particularly rapid bone loss, where granulation tissue

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and then fibrous tissue replace the normal bone marrow content. Brown coloration is due to hemosiderin deposition (36, 37). The radiological correlate of BT is typically a well-defined radiolucency causing cortical plate thinning and expansion (38). Common sites of occurrence are facial bones, pelvis, ribs, and femurs. In the literature, the most cases report a solitary lesion localized in the facial bones (39). Spine involvement is very rare and can require urgent surgery to prevent serious neurological complications. Cervical spine involvement is extremely rare and more frequent in secondary hyperparathyroidism(10). Along with their rarity, BT characteristics can create serious dilemmas in differential diagnosis, i.e. with bone metastases, aneurysmal bone cysts, Paget's disease, osteosarcoma, osteomyelitis and especially giant cell bone tumors. In fact, these last lesions can share with BT the typical radiolucency on x-ray. Even histology cannot guarantee the absolute certainty, since also BT contain giant cells and spindle-shaped cells (13). Therefore, the integration with a detailed clinical history and biochemical profile (hypercalcemia with normal/elevated PTH) is essential for diagnosis. Imaging with Tc-sestamibi, usually recommended as gold standard method for preoperative localization of pathological parathyroids, can demonstrate tracer uptake in BT (2, 13). It is important to highlight the fact that parathyroid surgery is generally curative towards PHPT complications (2, 40, 41).

HBS, first described by Albright and Reifenstein in 1950, is also a rare event today, because severe and prolonged post-operative hypocalcemia - exacerbated by suppressed PTH levels after parathyroidectomy - usually occurs in patients with severe PHPT and preoperative high bone turnover. The fall of PTH levels associated with osteoclastic reabsorption increases the calcium influxinto the bone, thus explaining these biochemical findings (42, 43). Some Authors have proposed treatment with bisphosphonates to prevent HBS in hyperparathyroidism, but such an approach remains controversial, and it may delay bone remodelling (44, 45).Pointing back at BT, as reported by Ruggeri et al. in 2010, the first-line therapy is represented by the treatment of primary disease that usually leads to tumor regression, while orthopaedic surgery should be considered if the mass does not regress after parathyroidectomy (or if pathological fractures occur) (46, 47). In our patient, the bone lesion decreased in size and recalcified after parathyroidectomy avoiding any additional orthopaedic procedure, while the osteosynthesis successfully achieved a complete recovery of wrist movements (**Fig. 1 C and D**).

Of note, our patient lacked general or local disease-related symptoms despite disseminated bone lesions and altered biochemical profile. In fact, the radiological finding of an

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osteolytic lesion was accidental, since he went to the Orthopaedic Unit after an apparently post-traumatic fracture. An important contribution to clinical success was due to diagnostic timeliness and multidisciplinarity, involving orthopaedic surgeons, nuclear physicians, endocrinologists, anesthesiologists, diagnostic radiologists and pathologists

Conclusion

PHPT has greatly changed its clinical expression along the years, especially in Western countries. For these reasons, OFC and BT as typical features of skeletal involvement are always less observed. Since BT are benign lesions but they resemble malignant tumors – namely giant cell tumors – in many of their characteristics, an integrated and multidisciplinarydiagnostical approach (with a complete biochemical panel first, and a possible confirmation by functional imaging) is crucial for a correct diagnosis. Finally, compared with the other cases we have searched for in the literature, our patient presented with a unique appendicular localization.

Table 1. Serum and urinary biochemical data at admittance, one day before surgery and in the post-operative period (1 day, 15 days, 1 month, 6 months and 1 year after surgery) and normal ranges. *Bold characters indicate altered values

			Post-operative					
	Admittance	Pre-operative	1 day	15 days	30 days	6 months	1 year	Normal Values
Serum calcium [mg/dL]	**14***	**15**	10	**5.7**	**8**	9.3	9.5	8.2-10.4
Ionized calcemia [mg/dL]	4.8		**2.8**			**4.3**	**4**	4.5-5.3
Serum phosphate [mg/dL]	2.7			3.3	3.3	4.1	2.8	2.5-4.6
Serum magnesium [mg/dL]	1.9		**1**	**1.45**	1.9	**1.32**	1.81	1.5-3.8
Serum creatinine [mg/dL]	1.3		1.2			1.3		0.5-1.4
PTH [pg/mL]	**745**	**2352**	**784**	**103**	**243**	16	18	8-76
Serum albumin [g/dL]	4.75						4.47	4.02-4.76
Vitamin D [ng/mL]	**15.5**					45.7	21	21-80
Alkaline phosphatase [U/L]	62					62	**194**	0-130
Urinary calcium [mg/day]	60					60		100-300
Urinary phosphorus [mg/day]	**735**					49		400-1000
TSH [μUI/mL]	2.11					**7.86**	1.43	0.3-4.2
Total proteins [g/dl]	8					7		6-8.2

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Table 2. Demographic, clinical characteristics and musculoskeletal manifestations of patients with primary hyperparathyroidism and brown tumors described in literature since 1997.

Reference	Year	Median Age	Sex	Localisation
Diamanti-Kandarakis et al.	2007	42	F	Fibula
Juarez-Leon et al.	2015	18	F	Humerus
Wang et al.	2014	22	*1M*/1F	Humerus
Velayutham et al.	2017	43	F	Finger tip
Misiorowski et al.	2017	46	*2M*/1F	Clavicle, knee, Humerus
Vaishya et al.	2017	25	F	Tibia
Jervis et al.	2017	58	F	Knee
Park SH et al.	2016	57	F	Femur
Penhoat et al.	2017	65	*M*	Tibia
Basaran et al.	2016	38	*M*	Hip
Sathyakumar et al.	2016	28	F	Hip
Phulsunga et al.	2016	42	F	Tibia
Ouzaa et al.	2015	66	F	Radio
Das et al.	2015	35	*M*	Femur
Irie et al.	2015	31	F	Patella
Radulescu et al.	2014	69	*M*	Femur
Younes et al.	2004	48	*M*	Femur
Dogan et al.	2004	50	F	Calcaneal
Nagaraj et al.	2012	39	*M*	Thumb

Figure 1. X-ray evidence of an expansive osteolytic lesion of the left metadiaphyseal ulna, on anteroposterior view (A) and side view (B). After surgery, subsequent X-rays show the progressive regression of the ulnar osteolytic lesion: four months (C) and twelve months (D) after surgery.

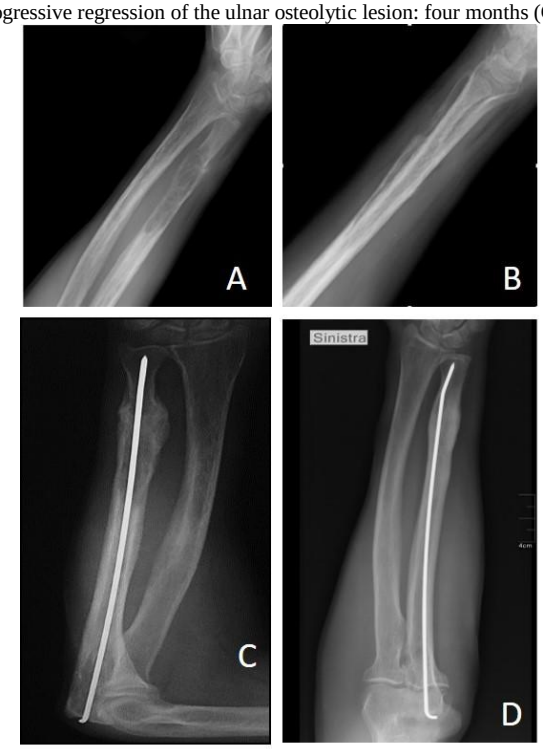

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Figure 2. Neck ultrasound reveals the presence of a solid nodule contiguous to the lower pole of the thyroid, measuring 25 mm in maximum diameter (A). Parathyroid scintigraphy with ^{99m}Tc-MIBI demonstrates pathological and intense uptake of the tracer in a definite area localized over the jugulum (B, C), corresponding to the US finding.

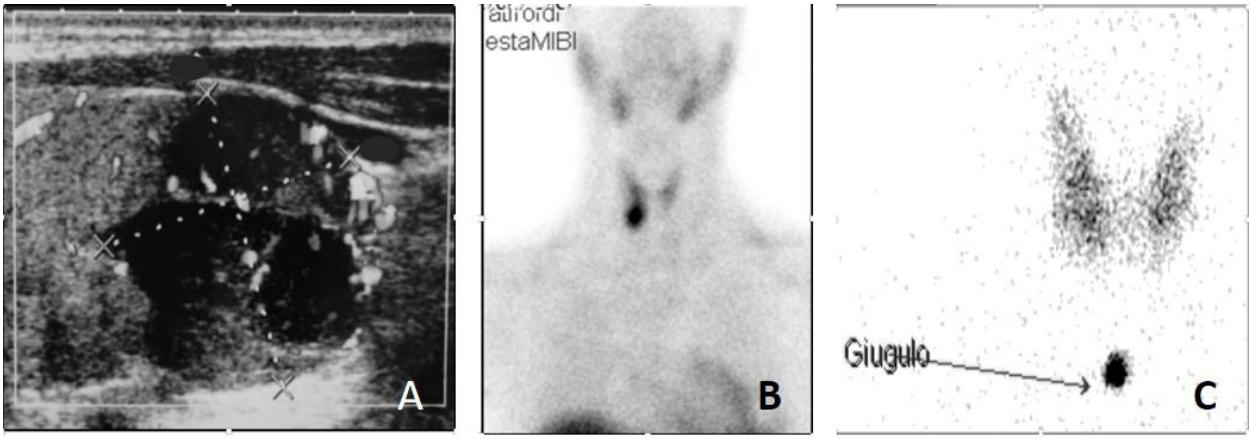

Figure 3. Whole-body bone scintigraphy with ^{99m}Tc-MIBI, showing an abnormal uptake in the distal third of the left ulna, as well as in most parts of the body, especially in the front ribs, rear side of D10, right anterior iliac wing, pubic bones, right femur, in the profiles of the kneecaps and in the extremity of right distal fibula.

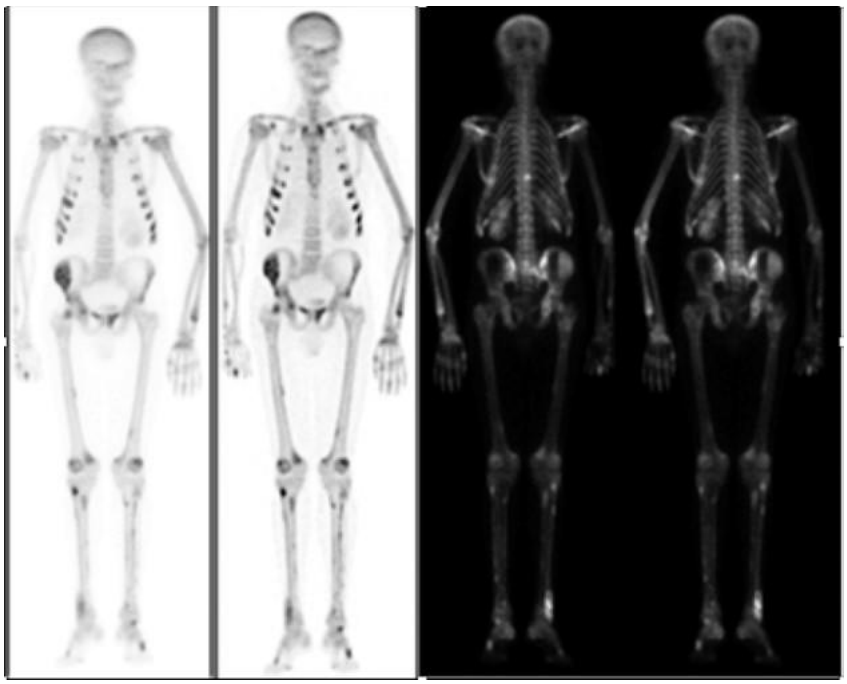

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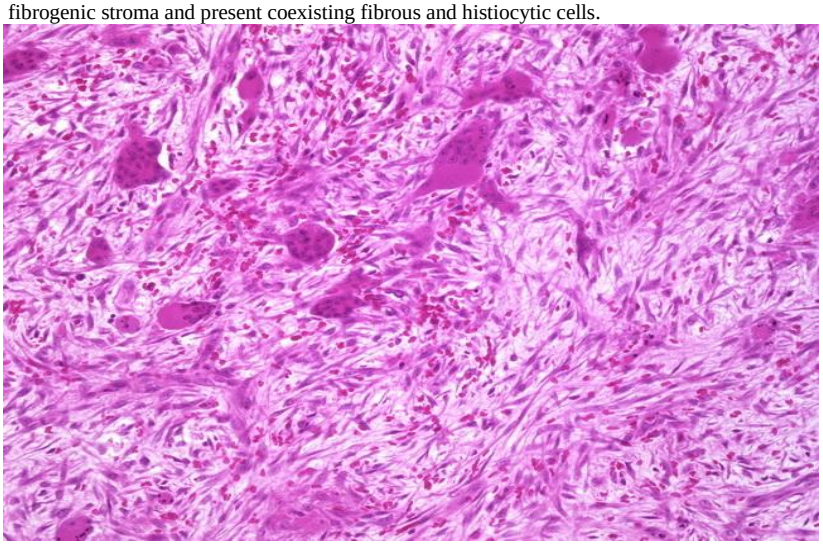
Figure 4. Immunohistochemical analysis of the ulnar lesion demonstrated several osteoclast-like giant cells in the context of the replacing fibroblastic tissue occupying the areas of bone resorption. Without an integrated evaluation of clinical, biochemical and imaging data, this finding may be misdiagnosed as a giant cell tumor. However, giant cell tumors usually lack fibrogenic stroma and present coexisting fibrous and histiocytic cells.



Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant

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