Case series

Are brown tumours a forgotten disease in developed countries?

I tumori bruni: patologia dimenticata nei paesi sviluppati?

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SUMMARY

Brown tumours (BT), an expression of osteitis fibrosa cystic due to primary hyperparathyroidism (pHPT), can occasionally be mistaken for malignancy. Among 615 patients who underwent parathyroidectomy for pHPT in our institution, the medical records of three patients affected by BT were reviewed. The first patient underwent surgical removal of the orbital mass for a suspected lachrymal gland neoplasm. The remaining two patients underwent, respectively, leg amputation and femur resection for a suspected bone malignancy. Final histology showed a BT in three cases. All three patients were admitted to our Division and underwent successful parathyroidectomy for parathyroid adenoma in two cases and for parathyroid carcinoma in the remaining case. When faced with an osteolithic bone lesion, complete evaluation of medical history, biochemical and radiographic findings can help to reach a correct diagnosis and avoid unnecessary bone resections.

KEY WORDS: Brown tumour • Osteitis fibrosa cystica • Primary hyperparathyroidism • Giant cells tumour

RIASSUNTO

I tumori bruni (BT), rara manifestazione dell'iperparatiroidismo primitivo (pHPT), possono talvolta essere misdiagnosticati come tumori maligni dell'osso. Su un totale di 615 pazienti sottoposti a paratiroidectomia abbiamo analizzato tre pazienti affetti da BT. Il primo paziente è stato sottoposto a un'orbitotomia per una sospetta neoplasia della ghiandola lacrimale. Gli altri due pazienti sono stati sottoposti, rispettivamente, a un'amputazione di gamba e ad una resezione di femore. L'esame istologico definitivo ha confermato in tutti i casi un tumore bruno dell'osso ed i pazienti sono stati successivamente sottoposti a paratiroidectomia per un adenoma paratiroideo in due casi, e per carcinoma paratiroideo nel rimanente caso. La nostra esperienza dimostra che un corretto inquadramento diagnostico dei pazienti affetti da pHPT può evitare inutili resezioni ossee.

PAROLE CHIAVE: *Tumore bruno • Osteite fibroso-cistica • Iperparatiroidismo primitivo • Tumore a cellule giganti*

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Introduction

Brown tumours (BT), or lesions resembling a giant cell tumour of the bone, are one of the complex pathologic expressions of osteitis fibrosa cystica (OFC). BT represent focal bone lithic lesions often developing at multiple sites including the maxilla, mandible, orbit, clavicle, ribs, tibia, femur and pelvic bones [1-5]. Radiographic findings can mimic bone malignancy, while the synchronous involvement of multiple skeletal segments can be interpreted as diffuse metastatic disease [6-11]. Since BT are a bone expression of pHPT, the main goal of treatment should be cure of the underlying endocrine disorder. Once successful parathyroidectomy has been performed, total or partial BT regression is often achieved [6 12-14], and unnecessary mutilating bone resections can be prevented [15]. Indeed, most authors suggest parathyroid resection and clinical observation of bone remodelling as the gold standard of treatment in cases of BT [6 12-20].

In this study, we reviewed the experience with BT in a third care referral centre of a Western country, with the aim of determining if the rarity of the disease may lead to a delay in the diagnosis or to inappropriate treatment of pHPT.

Methods

Among all patients who underwent parathyroid surgery for pHPT between May 1998 and June 2012 at our institution [21], complete medical records of patients affected by BT were collected and reviewed. Demographic, clinical preoperative and postoperative data were assessed. Parathyroid tumour size was determined as the longest dimension measured during surgery. Follow-up was obtained by direct patient phone contact and outpatient consultation.

Statistical analysis was performed using a commercially available statistic software package (SPSS 10.0 for Win-

Table. I. Patient characteristics.

	Patient 1 57 years, male	Patient 2 67 years, female	Patient 3 59 years, male
First admission	Ophthalmology Division (University Hospital)	Orthopaedic Division (Rural Hospital)	Orthopaedic Division (University Hospital)
Bone lesion	Suspected right lachrymal gland neoplasm	Suspected right tibia malignancy	Spontaneous left femur, tibia and fibula fractures
Type of bone resection performed	Right lateral orbitotomy and resection	Right leg amputation	Segmental left femoral resection
PTH (pg/ml)	1330	1813	1638
Serum calcium (mg/dl)	11.2	11.9	13.2
Serum alkaline phosphatase (UI/L)	1754	1654	780
Type of surgery	Left inferior parathyroidectomy + Total thyroidectomy for MNG*	Right superior parathyroidectomy + completion thyroidectomy for recurrent MNG*	Right superior parathyroidectomy
Final parathyroid histology	Parathyroid adenoma (2.5 cm - 3.4 grams) Papillary thyroid microcarcinoma (0.1 cm) follicular variant	Parathyroid carcinoma (2 grams) Benign goitre	Parathyroid adenoma (2.2 cm - 2.5 grams)
Length of follow-up (months)	48	39	32
Follow-up	Radiographic complete resolution of bone disease. No recurrence of HPT† nor DTC‡	Improvement of bone demineralization. No recurrence of parathyroid carcinoma	Complete resolution of bone demineralization. No recurrence of HPT*

** Multinodular goitre; † Hyperparathyroidism; ‡ Differentiated thyroid carcinoma.*

dows; SPSS Inc., Chicago, Ill). The χ^2 test was used for categorical variables, and a *t* test was used for continuous variables. A p value < 0.05 was considered statistically significant.

Results

Among 615 patients who underwent parathyroidectomy at our institution between May 1998 and June 2012, 3 patients (0.5%) had BT. Mean preoperative serum calcium and PTH levels were 12.1 ± 1.0 mg/dl and 1593 ± 245 pg/ml respectively. Mean serum alkaline phosphatase was 1396 ± 536 UI/L. Demographic and clinical characteristics of patients are reported in Table I.

Patient 1

A 57-year-old man was admitted to the Ophthalmology Division for a superior right palpebral intumescence associated with a hard mass, enophtalm, lateral right blepharitis and mild conjunctivas hyperaemia. Cranium CT scan and MRI showed an expansive, hypervascularized, 2 cm lesion of the right lateral angle of the orbital with epicentre on the lachrymal gland, with bone scalloping (Fig. 1). The patient complained of polyuria, stypsis, weight loss and chronic diffuse bone pain.

He underwent lateral right orbitotomy. Frozen section examination of the mass revealed a giant cell tumour of the bone. The subsequent whole body bone scintigraphy showed diffuse uptake (skull, scapulohumeral articulations, ribs, pelvis, right femur and tibias, left radius and III/IV left metacarpus), confirmed by CT scan and lower limb x-ray (Fig. 2).

Final histology confirmed the diagnosis of bone giant cell tumour, consistent with BT. On the basis of these findings, the patient underwent laboratory and imaging evaluation for pHPT. Laboratory findings showed high serum calcium levels (11.2 mg/dl), low serum phosphorus levels (1.7 mg/dl), high alkaline phosphatase levels (1754 UI/L) and high PTH levels (1330 pg/ml). Urinary calcium and phosphorus were within normal range (134 mg/l and 450 mg/l, respectively). Neck ultrasound showed a voluminous multinodular goitre and a hypoechoic nodule close to the left inferior thyroid lobe consistent with hyperplasic parathyroid (Fig. 3). Sesta-MIBI scintiscan confirmed a wide area with marked enhancement and slow washout caudal to the left inferior thyroid pole.

The patient underwent left inferior parathyroidectomy and concomitant total thyroidectomy. Final histology showed a 2.5 cm principal cell parathyroid adenoma (3.4 g in weight) and a follicular variant of papillary thyroid microcarcinoma (0.1 mm in diameter). The postoperative course was uneventful. On the first post-operative day, the PTH level was 33.8 pg/ml and serum calcium level was 8.1 mg/dl. At 48 months follow-up evaluation, PTH and serum calcium levels were within the normal ranges. Radiographic examination showed complete resolution of bone disease.

Patient 2

A 67-year-old female patient was admitted to the Orthopaedic division of a rural hospital for a suspected right leg bone malignancy (preoperative cytology consistent with "giant cell bone tumour") (Fig. 4). She had underwent previous subtotal thyroidectomy for goitre. The patient complained of chronic diffuse bone pain and osteoporosis. A right leg amputation was performed. Final histology showed a focal giant cell tumour, consistent with BT.

On the basis of the final histological report, she underwent biochemical tests and imaging studies for pHPT. Biochemically examinations revealed hypercalcaemia (11.9 mg/dl), high levels of alkaline phosphatase (1654 UI/L) and high PTH levels (1813 pg/ml). Sesta-MIBI scintiscan showed a hyperfunctioning right parathyroid lesion. Four months after the right leg amputation, the patient was admitted to our division with a diagnosis of pHPT. She underwent bilateral neck exploration with the findings of enlargement of the right superior parathyroid gland. The parathyroid gland was strictly adhering to the thyroid lobe and presented a suspicious morphology. A superior right parathyroidectomy was performed with "*en bloc*" resection of residual thyroid gland because of the suspicion of malignancy and the concomitance of large multinodular parathyroid recurrent goitre. Final histology showed 2 g parathyroid carcinoma with focal vessel infiltration (2% positivity for Ki-67 with 8-10% spikes of expression). The thyroid nodules were benign.

The post-operative course was characterized by transient moderate hypocalcaemia treated with medical therapy. PTH on second post-operative day was 7.4 pg/ml. After 39-months of follow-up, the patient showed no sign of recurrent parathyroid carcinoma. Serum calcium and PTH were within the normal range. Bone densitometry showed improvement of the diffuse demineralisation.

Patient 3

A 59-year-old male patient was admitted to the Orthopaedic Division of our Hospital for prosthetic left coxo-femoral joint replacement due to pathologic spontaneous left femur fracture. He had a history of kidney and gall bladder stones, and diffuse osteoporosis. A segmental femur resection was performed. Final histology showed multiple brownish cystic focal areas heterogeneous in diameter, refilled by fibrous tissue with a large number of giant and tapered cells organized in clusters with low mitotic activity. Four months later the patient experienced another pathologic fracture involving the left tibia. Total body X-ray showed diffuse osteopenia, mostly in long bones, with spongiosis transformation of the cortical bone associated with multiple diffuse osteolithic lesions. Final histology showed a mass of fibroblastic and macrophage cells consistent with BT. Since the suspicion of pHPT was raised, the patient underwent laboratory and imaging evaluation for pHPT. High PTH (1638 pg/ml) and serum calcium levels (13.2 mg/dl), low serum phosphorus (2.3 mg/dl) and high alkaline phosphatase (780 UI/L) were found. Sesta-MIBI scan showed a large hyperfunctioning right parathyroid gland.

The patient then underwent mini-invasive bilateral neck exploration and superior right parathyroidectomy. Final histology showed a 2.2 cm parathyroid adenoma, 2.5 g in weight. The patient developed severe post-operative hypocalcaemia treated with medical therapy that was discontinued 6 months after parathyroidectomy.

At 32 months follow-up, PTH and calcium values were within normal range. Bone densitometry showed complete resolution of bone demineralisation.

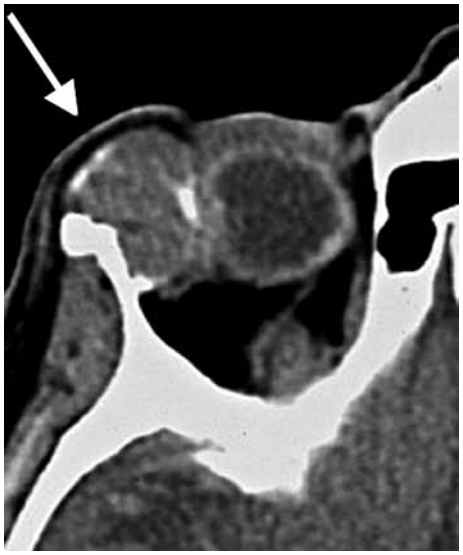

Fig. 1. Patient 1. Right orbit: suspected lachrymal gland neoplasm.

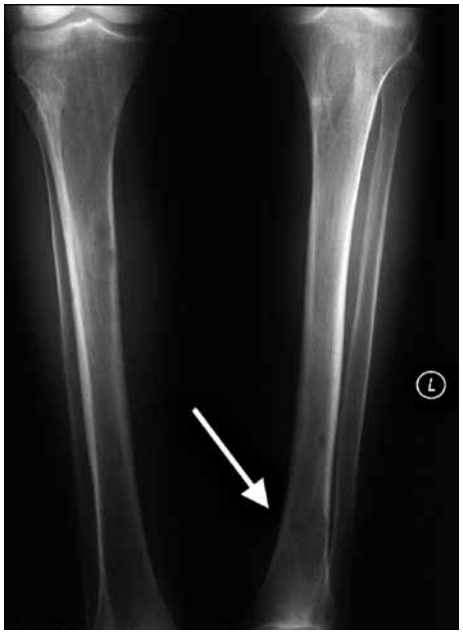

Fig. 2. Patient 1. Left tibia lesion (preoperative X-ray).

Discussion

After the introduction of routinely measurement of serum calcium levels as a part of biochemical screening in current clinical practice in the early 1970s, a large cohort of previously unrecognized hypercalcaemic patients was uncovered [1-3 22]. As a consequence in developed countries, where biochemical screening was widespread, a sharp increase in the incidence of primary hyperparathyroidism (pHPT) was registered [22]. On the other hand, the recog-

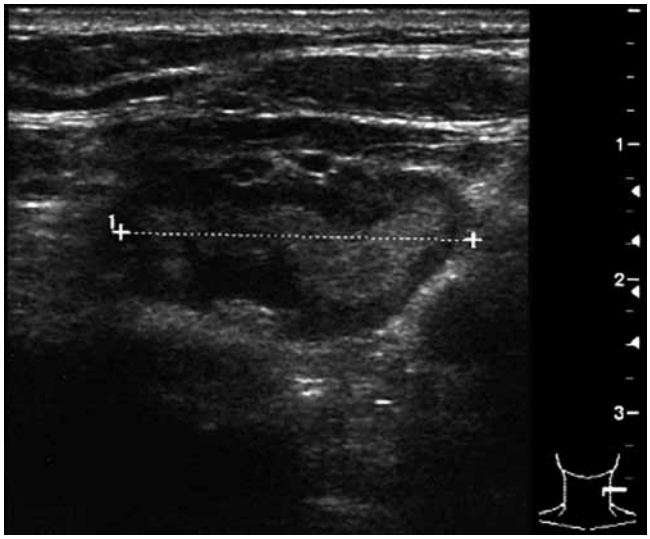

Fig. 3. Patient 1. Left inferior parathyroid adenoma (preoperative ultrasonography).

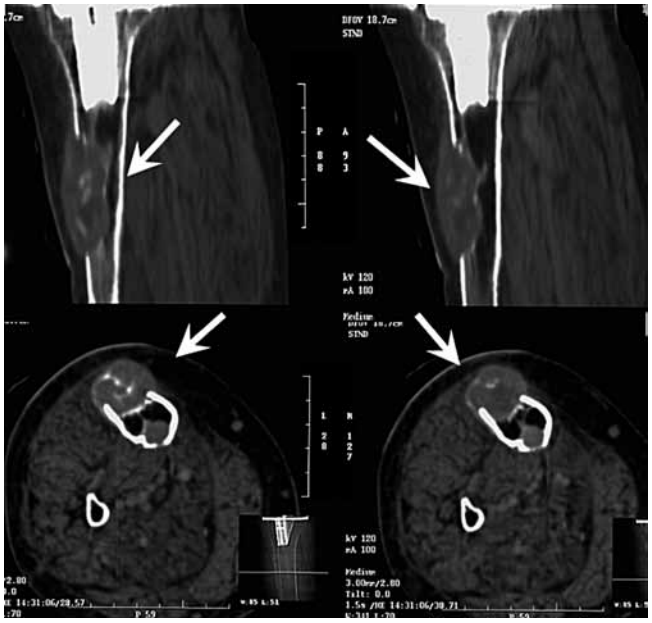

Fig. 4. Patient 2. Right tibia lesion (preoperative CT scan).

nition of a significantly higher disease prevalence based on screening laboratory results led to an essential change in the presentation of pHPT. Whereas prior to the 1970s, pHPT was a disease of recurrent kidney stones, OFC, neuromuscular dysfunction [23] and symptomatic hypercalcaemia, it has now become an asymptomatic or mildly symptomatic disease detected by incidental finding of hypercalcaemia [22 24 25]. Nowadays, in most of developed countries, symptomatic pHPT with involvement of the skeleton is the exception rather than the rule [1], and it has recently been reported that less than 5% of pHPT patients display evidence of OFC [3]. Nonetheless, one should keep in mind that in advanced pHPT the entire skeleton can be involved [3]. Indeed, in the developing countries most of patients (58-69% in recent reports) affected by pHPT present symptomatic OFC, severely decreased bone densitometry and BT [5 26].

The challenging patterns in pHPT manifestations influence the confidence of clinicians with obsolete unusual symptoms. Moreover, the resemblance of BT with primitive bone neoplasm and the characteristic multisegmental involvement simulating metastatic disease can confuse clinicians in the correct diagnostic and therapeutic management. BT are non-neoplastic lesions representing a reparative cellular phenomenon that involves areas with intense bone re-absorption due to the effect of high circulating PTH levels [27]. Giant cells refill the osteolithic defect as fibroblasts and can deform the bone profile, mimic a neoplasm or cause pathological fractures [28]. In these cases, the delayed diagnosis of pHPT may result in unnecessary bone resections and mutilation.

Moreover, also from an histological point of view, differential diagnosis between BT, giant cell granuloma and giant cell bone tumour may be very difficult without correct and complete clinical preoperative evaluation, as also reported in our series [9 29].

In the present small series, BT involved different bone segments. A revision of previous reports shows a large variability in skeletal distribution of such lesions even if in most experiences craniofacial localization was prevalent [6 8 12 14 16 18-20 29-33]. Nonetheless, the site involved does not aid in directing diagnosis. We observed that the three patients presenting with BT had a median age ranging from 57 to 67 years. This could be of some importance if we consider that primitive bone malignancies are more frequent seen in a younger age. Therefore, in case of a suspected bone lesion arising in a patient of middle age in a Western country, exclusion of pHPT is mandatory.

Most authors [6 12-20 34-35] agree that the best treatment of BT is the cure of the underlying pHPT. When a successful parathyroidectomy for pHPT is performed, partial or even total recovery of the OFC patterns has been described [6 12-20 32 34]. This was partially observed in our experience, since most of the bone lesions associated with the BT were recovered after the resolution of the pHPT. Unfortunately, we could not evaluate the eventual regression pattern of BT after successful parathyroidectomy, because in all the cases in this series bone lesions were removed before definitive diagnosis and treatment of pHPT. Similarly to other experiences [6 12-20 32 34], probably, also in our series, most of the invalidating bone resections would have been prevented after successful parathyroidectomy. Indeed, extensive bone resection has been deemed necessary only in the case of fractures or compressive symptoms [28 36].

Since the time required achieving a BT regression after successful parathyroidectomy is widely variable, in the case of late bone recovery some authors propose a completion small bone resection [15 31-33].

In all the cases of our series, after an initial mistake in clinical interpretation, a diagnosis of pHPT was easily achieved. Surgical cure of pHPT was obtained in all cases.

Conclusions

This series demonstrates that BT represent a very rare manifestation of pHPT in developed countries (< 1% of all cases in our experience). When facing with osteolithic bone lesion, especially in middle-aged patients with diffuse osteopenia, clinicians should keep in mind this unusual presentation of pHPT, while the similarity with primary bone tumours can mislead diagnosis. A complete evaluation of medical history, biochemical and radiographic findings can aid in achieving correct diagnosis and avoid unnecessary bone resections.

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