



Multilevel brown tumors of the spine in a patient with severe secondary hyperparathyroidism

A case report and review of the literature

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Multilevel brown tumors of the spine in a patient with severe secondary hyperparathyroidism. A case report and review of the literature.

BACKGROUND. *The brown tumour is an extreme form of osteitis fibrosa cystica, representing a serious complication of the advanced primary or secondary hyperparathyroidism. It occurs in settings of high levels parathyroid hormone, like in primary or secondary hyperparathyroidism, with a frequency of 3-4% and 1.5-13% respectively, usually affecting young people.*

CASE REPORT. *The authors report a case of a 45 years old woman on long-term hemodialysis, with severe secondary hyperparathyroidism. The main clinical complaints were neck pain, lower thoraco-lumbar back pain, persistent left groin pain, and bilateral lower extremities weakness. The computed tomography scan revealed multiple spine brown tumors affecting the cervical, thoracic and lumbar level. After an initial partial response to the treatment of two years with Cinacalcet, a deterioration of the secondary hyperparathyroidism occurred (hypercalcemia, hyperphosphatemia) and the patient was referred for parathyroidectomy. The patient underwent total parathyroidectomy with auto-transplantation, with a positive postoperative result.*

CONCLUSIONS. *Secondary hyperparathyroidism can lead, during its course, to osteolytic bone lesions called brown tumors. If the medical treatment fails, the surgical removal of the parathyroid glands with autotransplant remains the only treatment of the bone lesions progression. Reviewing the relevant literature in English (until March 2015), we found 24 cases of symptomatic vertebral brown tumors. To the authors' knowledge, this is the first case which describes a multilevel spine involvement (more than two), and the fifth describing a cervical localization.*

KEY WORDS: Hypocalcaemia, Secondary hyperparathyroidism, Spine brown tumors

Introduction

The brown tumour (BT), presented as unifocal/multifocal lytic bone lesions, is an extreme form of

osteitis fibrosa cystica, representing a serious complication of advanced hyperparathyroidism (HPT). It occurs in settings of high levels of parathyroid hormone (iPTH), like in primary or secondary HPT (sHPT), with a frequency of 3-4% and 1.5-13% respectively ¹, usually affecting young people, especially females, with varying degrees of aggressiveness and risks of recurrence ². We report the case of a woman with end stage renal disease (ESRD) on long term hemodialysis, presenting a multi-level spine localization of brown tumors. We review the relevant literature, stressing the rarity of these benign tumors, especially the spine localization, and the importance of their consideration in dialysis patients with associated osteolytic bone masses.

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Case Report

The 45-year old woman with a 10-year history of hemodialysis for ESRD due to previous chronic glomerulonephritis, was admitted in our clinic for surgical treatment of severe sHPT. The main clinical complaints were neck pain, lower thoraco-lumbar back pain, persistent left groin pain, and bilateral lower extremities weakness.

She had been diagnosed with severe sHPT for more than five years, being treated conservatively with Alphacalcidol, phosphate binding drugs and bisphosphonates. Approximately two years ago, the treatment with Cinacalcet started due to the very high intact parathyroid hormone (iPTH) level and concomitant hypercalcemia. After an initial partial response to this therapy, an aggravation of sHPT occurred (hypercalcemia, hyperphosphatemia) and the patient was referred for parathyroidectomy.

Laboratory tests showed severe hyperparathyroidism, with extremely high parathyroid hormone level (iPTH) of 7900 pg/ml (reference range(rr): 15-68pg/ml), slightly elevated serum calcium level of 11,1mg/dl (rr: 8,5-10,5mg/dl), elevated serum phosphate level of 5,8 mg/dl (rr: 2,7-4,5mg/dl), and total serum alkaline phosphatase level (AlkPhos) of 714U/L (rr: 20-150U/L).

On the spine CT-scan, at cervical-thoracic and lumbar levels, we noticed diffuse prominent osteopenia and flattening of several vertebral bodies; two distinct expansile lytic lesions consistent with brown tumors are localized on the body of the 6th cervical and 10th thoracic vertebrae respectively, both including the right pedicle and transverse process. There are sclerosis of vertebral endplates ("rugged jersey spine"), subperiosteal resorption and Schmorl nodules. Another similar lesion is located on the body of the 2nd lumbar vertebra (L2) and spinous process of 3rd lumbar vertebra (L3), with posterior ver-

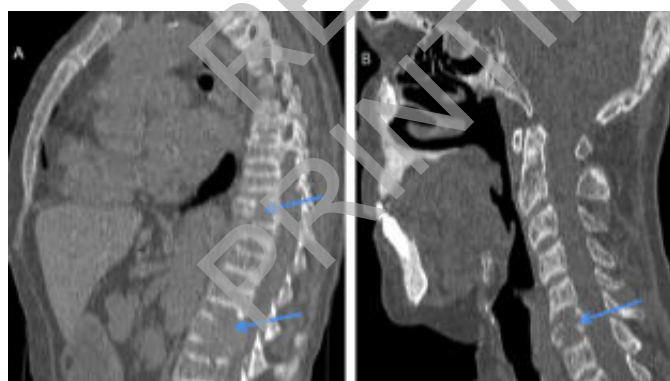


Fig. 1: A - Multiplanar reconstruction sagittal view thoraco-lumbar spine, window for soft tissues (width 350, level 40). Diffuse prominent osteopenia of entire spine with sclerosis of the endplates, flattening of several vertebral bodies, expansile lytic lesions at the L2 body level, L3 spinous process consistent with brown tumors. The osteopenia and sclerosis of the endplates creates the characteristic aspect of "rugged jersey" spine. B - Same as previous, cervical spine. Expansile well defined lytic lesion in the C6 body - brown tumor.

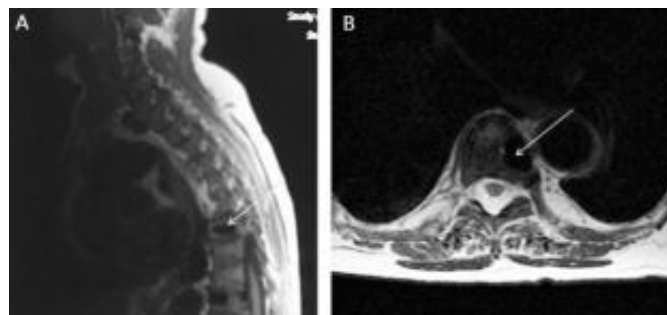


Fig. 2: The sagittal T2 weighted sequence of the thoracic and lumbar spine shows, at the Th 10th body level, an expansile lesion with heterogeneous signal. Axial T2 weighted image at the Th10th level, brown tumour in the Th 10th vertebrae body.

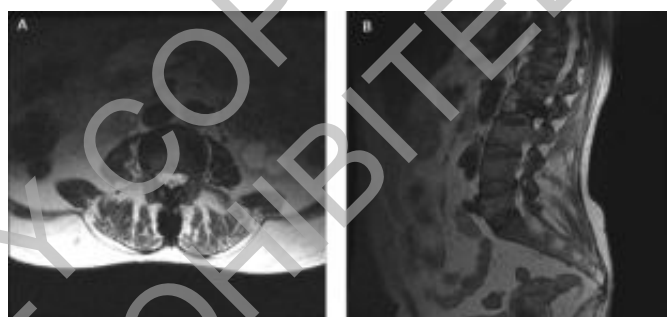


Fig. 3: The sagittal T2 weighted sequence of the lumbar and sacral spine shows, at the L2 level, a large expansile lesion with heterogeneous signal, high signal small cavities associated with low signal hemosiderin deposits, and also low signal lesions of the L3 and S1 spinous processes, and of the L5 body. Axial T2 weighted image at the L2 level, brown tumour of the L2 body.

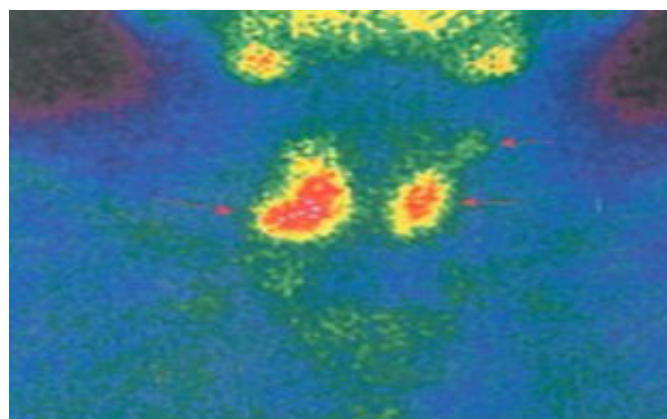


Fig. 4: (99Tc-MIBI) showed an abnormal tracer uptake compatible with hyperfunctioning parathyroid glands.

tebral wall lytic destruction and lumbar canal stenosis at this level. (Figs. 1 A, B).

The magnetic resonance imaging (MRI), sagittal and axial weighted sequences, confirmed the presence of several expansile lesions at cervical, thoracic and lumbar levels, consistent with brown tumors (Figs. 2 A, B Fig. 3 A, B). The cervical ultrasonography revealed three cervical

hypoechoic masses with augmented doppler signal; the scintigraphic study with technetium Tc 99 methoxyisobutyl isonitrile (⁹⁹Tc-MIBI) showed an abnormal tracer uptake compatible with hyperfunctioning parathyroid glands at the level of the masses identified by ultrasonography (Fig. 4).

A bone biopsy performed at L2 vertebrae body level showed scattered groups of osteoclast-like multinucleate cells in a brownish-granular material, confirming the diagnosis.

The patient underwent total parathyroidectomy with auto-transplantation. At the time we did not benefit from an intra-operative iPTH sample, but the immediate post-operative serum iPTH (10 hours) was of 6,3 pg/ml (rr: 15-68pg/ml). The postoperative period was uneventful. One year after surgery, the patient had mild hypocalcaemia, normal phosphorus and iPTH level and no clinical complaints. A written informed consent was obtained for this publication.

Discussion

Our case illustrates the importance of taking brown tumors into account for patients on long-term hemodialysis for ESRD and associated bone disease. Failure to establish the correct diagnosis may lead to further unnecessary diagnosis procedure with surgery delays or, on the contrary, to extensive surgery.

Generally, the osteoarticular symptoms are among the main manifestations of sHPT, especially in long-term hemodialysis patients, and can alternate from a generalized osteopenia, bone demineralization, leading to cystic lesion and brown tumour^{1,2}. The latest, also called osteoclastoma, is considered a reparative cellular process, rather than a real neoplasia, as its name suggests³. Thus, the brown tumor, despite its name, is not a malignant condition. It represents a consequence of functional primary or secondary hyperparathyroidism, consisting in osteoclastic lesions with mineral substance lost, due to the action of very high increased levels of the parathyroid hormone. In western countries, routine screening laboratory tests for hyperparathyroidism diagnosis or early transplant therapy in patients with ESRD, reduce these tumours' occurrence. Unfortunately, in developing countries, bone lesions are still frequent, especially in patients with long-term dialysis with severe sHPT but, not surprisingly, even in primary HPT. The first case reporting a brown tumor, published in 1953, described a frontal ethmoid appearance⁴. Any bone may be affected, but the ribs, clavicles, pelvic girdle and the mandible are the most frequently reported localizations². Spine involvement is extremely rare. While searching MEDLINE, the English language literature (until March 2015), we found only 24 cases of patients with renal HPT and symptomatic vertebral brown tumors (Table I)⁵⁻²⁸.

Table 1 - Symptomatic vertebral brown tumors in literature.

Author	Year	Vertebral localization	Symptoms
1.Ericsson <i>et al.</i> (7)	1978	Cervical	Paresis
2.Bohlman <i>et al.</i> (8)	1986	Thoracic	Back pain, paraplegia
3.Pumar <i>et al.</i> (9)	1990	Thoracic	Paraplegia
4.Barlow, Archer (10)	1993	Cervical	Neck pain, neuralgia
5.Mourelatus <i>et al.</i> (11)	1998	Thoracic	Back pain
6.Fineman <i>et al.</i> (12)	1999	Thoracic	Incipient paraplegia
7.Azria <i>et al.</i> (13)	2000	Thoracic	Back pain
8.Masutani <i>et al.</i> (14)	2001	Thoracic	Paraplegia
9.Paderni <i>et al.</i> (15)	2003	Lumbar	Back pain
10.Vandenbussche <i>et al.</i> (16)	2004	Thoracic	Back pain, incipient paraplegia
11.Tarrass <i>et al.</i> (17)	2006	Sacral	Cauda equina compression
12.Kaya <i>et al.</i> (18)	2007	Thoracic	Brachialgia
13. Wiebe <i>et al.</i> (19)	2008	Thoracic	Paraparesis
14.Ren <i>et al.</i> (20)	2008	Thoracic	Incipient paraplegia
15.Noman <i>et al.</i> (21)	2009	Thoracic	Back pain
16. Mak <i>et al.</i> (22)	2009	Thoracic	Back pain, incipient paraplegia
17.Kampschreur <i>et al.</i> (23)	2010	Thoracic	Back pain
18. Gheith <i>et al.</i> (24)	2010	Lumbar	Back pain, incipient paraparesis
19.Resic <i>et al.</i> (25)	2011	Cervical	Neck pain
20.Mateo <i>et al.</i> (26)	2011	Cervical	Neck pain
21.Low <i>et al.</i> (27)	2011	Thoracic	Back pain, incipient paraplegia
22.Araujo <i>et al.</i> (28)	2012	Thoracic + sacral	Back pain, paraplegia
23.Fargen <i>et al.</i> (29)	2013	Lumbar	Acute paraparesis
24. Arsalanizadeh, Westacott (30)	2013	Thoracic	Back pain
26. Present case	2014	Cervical + thoracic + lumbar	Neck pain, backpain

To our knowledge, this is the first case describing a multilevel spine involvement and the fifth describing a cervical localization. Spine brown tumors sometimes remain oligosymptomatic, with patients complaining only of intermittent, unspecific back pain, as in our case. In other cases, they may cause neurologic compromise, even with acute-onset paraparesis, requiring emergent decompressive neurosurgery in order to preserve the neurologic function^{6,7,14}.

On medical imaging, brown tumors appear as a lytic solitary or multifocal lesion, with thinned cortical bone²⁹; our case also demonstrates other described bone structure changes that suggest renal osteodystrophy: osteopenia with osteosclerosis of the vertebral endplates ("rugger jersey spine" aspect), "salt and pepper" bone appearance, subperiosteal bone resorption and disappearance of the lamina dura²⁹. ⁹⁹Tc-MIBI parathyroid scintigraphy has low sensitivity in detecting hyperplastic glands in sHPT²⁷ and, since the surgeon would perform total or subtotal parathyroidectomy, irrespective of the scan results, the rationale for using this test is questionable. Despite the fact that it is not routinely performed, the ⁹⁹Tc-MIBI scintigraphy was preferred in this case, due to our desire to examine the case more profoundly.

The bone biopsy histologically confirms the diagnosis; its diagnosis role could be debatable but it should be considered when differential diagnosis with other bone lytic lesions i.e. regenerative granuloma, giant cell granuloma, giant cell tumor, aneurysmal bone cyst, cherubism, Paget's disease is deemed necessary³.

Brown tumors treatment relies on definitive control of the underlying hyperparathyroid status. Our patient had a long history of severe sHPT, treated conservatively for a too long period; the treatment with Cinacalcet, started two years ago, succeeded only partially and temporarily in reducing the very high iPTH level. The presence of severe bone structure changes with multiple brown tumors, along with huge preoperative serum iPTH and very high level of total serum alkaline phosphatase, betray an old hyperparathyroid status, an intensive osteoclast-fibroblastic bone activity, and even the surgery delays.

All the patients unresponsive to medical treatment or those presenting severe sHPT, need parathyroidectomy²; after surgery, the bone lesions usually cease to grow, and eventually ossify without further consequences for the patient^{1,3,14,21}. Direct approach to the bone lesions is avoided, unless they provoke complications: compressive neurologic symptoms, significant anatomical deformity, risk of a pathologic fracture^{8,9}. In our case, we performed a total parathyroidectomy with auto-transplant; intra-operatively we discovered significantly increased and even "macroscopically" nodular parathyroids, which also betray the long evolution of the sHPT. The final histopathologic report confirmed the nodular hyperplasia.

We presented a case with interesting particularities: i. a woman with longstanding history of hemodialysis for

ESRD and extremely rare multilevel spine localization ii. massively preoperative raised serum iPTH level showing a severe secondary hyperparathyroid status, unresponsive to medical treatment.

Conclusions

Secondary hyperparathyroidism can lead during its course to osteolytic bone lesions called brown tumors. If the medical treatment fails, surgical removing of the parathyroid glands with auto-transplant remains the only treatment of the bone lesions progression. Reviewing the relevant literature in English (until March 2015), we found 24 cases of symptomatic vertebral brown tumors. To the authors' knowledge, this is the first case which describes a multilevel spine involvement (more than two), and the fifth describing a cervical localization.

Riassunto

Il tumore bruno è una forma estrema dell'osteite fibroso-cistica, che rappresenta una complicazione grave della forma avanzata di iperparatiroidismo primitivo o secondario. Può indorgere nel caso che si sviluppino elevati livelli di paratormone, come si verifica nell'iperparatiroidismo primitivo e secondario con una frequenza rispettivamente del 3-4% e del 1,5-13% , e colpisce per lo più l'età giovanile.

Gli Autori presentano il caso di una donna di 45 anni in trattamento dialitico da molto tempo, che presentava un iperparatiroidismo grave. I principali sintomi clinici erano rappresentati da dolori cervicali, dolori al tratto toraco-lombare dorsale, e debolezza ad entrambi gli arti inferiori.

La TC ha messo in evidenza la presenza di tumori bruni a livello delle vertebre cervicali, toraciche e lombari. Dopo un parziale successo al trattamento per due anni con Cinacalcet si è verificato un deterioramento dell'iperparatiroidismo secondario (ipercalcemia ed iperfosfatemia) ed è stata indicata ed eseguita la paratiroidectomia con autotrapianto, cui ha fatto seguito un risultato postoperatorio positivo.

In conclusione l'iperparatiroidismo secondario può comportare lo sviluppo di lesioni osteolitiche ossee indicate come "tumori bruni". Se il trattamento medico fallisce, l'unico rimedio alla progressione della patologia è rappresentato dalla paratiroidectomia con autotrapianto.

Dopo revisione della abbondante letteratura in lingua Inglese (fino a marzo 2015) si rilevano 24 casi di tumori bruni sintomatici a livello vertebrale. A conoscenza degli Autori questo è il primo caso che descrive una diffusione vertebrale a più livelli, ed il primo che segnala una localizzazione al tratto vertebrale cervicale.

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