Case Report
Tumor/Infection
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SACRAL OSTEOSARCOMA ASSOCIATED WITH HYPERPARATHYROIDISM: A RARE CLINICAL ASSOCIATION

OSTEOSSARCOMA SACRAL ASSOCIADO AO HIPERPARATIREOIDISMO: UMA ASSOCIAÇÃO CLÍNICA RARA

OSTEOSARCOMA SACRO ASOCIADO A HIPERPARATIROIDISMO: UNA ASOCIACIÓN CLÍNICA POCO COMÚN

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ABSTRACT

Hyperparathyroidism is a condition characterized by excessive activity of the parathyroid glands, often resulting in lytic bone lesions and radiological features that can also be seen in giant cell tumors (GCT). The overlap in clinical, radiological, and histological findings between these entities can make accurate diagnosis challenging. This report describes the case of a patient presenting with an extensive lytic lesion involving nearly the entire sacrum. Although the coexistence of hyperparathyroidism and GCT was initially considered, histopathological analysis revealed a diagnosis of high-grade osteosarcoma, a rare finding in this clinical context. To the best of our knowledge, this is the first reported case of sacral osteosarcoma associated with hyperparathyroidism. ***Level of Evidence IV; Case Series.***

Keywords: Osteosarcoma; Hyperparathyroidism; Neoplasms; Diagnosis.

RESUMO

O hiperparatireoidismo é uma condição caracterizada por atividade excessiva das glândulas paratireoides, frequentemente resultando em lesões ósseas líticas e achados radiológicos que também podem ser observados em tumores de células gigantes (TCG). A sobreposição de achados clínicos, radiológicos e histológicos entre essas entidades pode tornar o diagnóstico preciso um desafio. Este relato descreve o caso de uma paciente com uma extensa lesão lítica envolvendo quase todo o sacro. Embora a coexistência de hiperparatireoidismo e TCG tenha sido inicialmente considerada, a análise histopatológica revelou o diagnóstico de osteossarcoma de alto grau, um achado raro nesse contexto clínico. Até onde sabemos, este é o primeiro caso relatado de osteossarcoma sacral associado ao hiperparatireoidismo. ***Nível de Evidência IV; Serie de Casos.***

Descritores: *Osteossarcoma; Hiperparatireoidismo; Neoplasias; Diagnóstico.*

RESUMEN

El hiperparatiroidismo es una condición caracterizada por una actividad excesiva de las glándulas paratiroides, que a menudo resulta en lesiones óseas líticas y hallazgos radiológicos que también pueden observarse en los tumores de células gigantes (TCG). La superposición de hallazgos clínicos, radiológicos e histológicos entre estas entidades puede dificultar un diagnóstico preciso. Este informe describe el caso de una paciente que presentaba una lesión lítica extensa que comprometía casi todo el sacro. Aunque inicialmente se consideró la coexistencia de hiperparatiroidismo y TCG, el análisis histopatológico reveló un diagnóstico de osteosarcoma de alto grado, un hallazgo poco frecuente en este contexto clínico. Hasta donde sabemos, este es el primer caso reportado de osteosarcoma sacro asociado con hiperparatiroidismo. ***Nivel de Evidencia IV; Serie de Casos.***

Descriptores: *Osteosarcoma; Hiperparatiroidismo; Neoplasias; Diagnóstico.*

INTRODUCTION

The parathyroid glands are typically four small glands located posterior to the thyroid. Parathyroid hormone (PTH) is a polypeptide with a short half-life (2–5 minutes), secreted in response to reduced levels of serum ionized calcium (Ca^{2+}) through a negative feedback mechanism.[1,2] PTH regulates calcium and phosphate homeostasis in organ-specific ways. Calcium-sensitive cells modulate the production of hormones that act on the skeleton, intestines, and kidneys. A decrease in plasma calcium stimulates PTH secretion, which increases calcium reabsorption in bone – raising serum levels – and in the kidneys – reducing urinary excretion. In bone, PTH promotes remodeling by mobilizing calcium and phosphate into the circulation.

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Dysregulation or deficiency of PTH may lead to hypocalcemia, hyperphosphatemia, and hypercalciuria.[1,3,4] In oncologic contexts, hypercalcemia of malignancy may arise in the setting of a substantial tumour burden.

Brown tumours are focal bone lesions caused by increased osteoclastic activity and fibroblast proliferation in the setting of hyperparathyroidism. Although they can develop in any skeletal site, they most commonly affect the ribs, clavicles, extremities, and pelvic girdle.[5] These lesions are characterized by numerous osteolytic, often cystic areas, particularly in long bones and the jaw. Brown tumours are considered a serious complication of hyperparathyroidism. Therefore, although histological findings may be suggestive, accurate diagnosis requires integration of clinical, radiological, and laboratory data to avoid misdiagnosis.[6]

Osteosarcoma, by contrast, is a primary malignant bone tumor with an estimated global incidence of 3.4 cases per million per year.[7] It predominantly affects children and adolescents, with peak incidence in the second and third decades of life. The most common anatomical sites include the distal femur, proximal tibia (knee region), and proximal humerus (shoulder region). Five-year survival rates for conventional osteosarcoma have improved from 20% to 50% over the last century, primarily due to the introduction of adjuvant chemotherapy and advancements in early diagnosis.[8,9] For any suspected bone lesion, preoperative imaging should include radiographs, which typically reveal an ill-defined lesion with osteoblastic and/or osteolytic features, periosteal reaction, and a soft tissue mass.[8]

Experimental studies have shown that PTH modulates osteoblast activity and may influence osteosarcoma cell behaviour in both animal and human models.[10–13] However, few clinical reports have suggested a potential link between hyperparathyroidism and osteosarcoma. For instance, Betancourt et al. described a 69-year-old female with primary hyperparathyroidism (PTH > 1,000 pg/mL) and a malignant tumor of the right proximal femur. Histological examination revealed a high-grade fibroblastic osteosarcoma, and she subsequently underwent curative resection of a large left parathyroid adenoma.[14] One year later, another case reported a 56-year-old woman initially diagnosed with a brown tumor of the tibia, which was later reclassified as osteosarcoma based on histopathology, leading to appropriate oncologic treatment.[15]

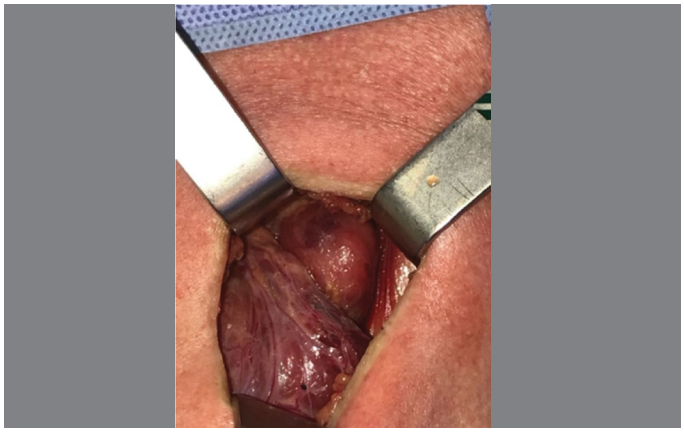
In a broader context, Jimenez et al. (2005) reviewed a cohort of 1,234 patients with osteosarcoma and found only three cases with concurrent hyperparathyroidism and fibroblastic osteosarcoma.[16] These findings suggest that hyperparathyroidism is not more prevalent among patients with osteosarcoma than in the general population. However, the authors emphasized that hyperparathyroidism may alter the histological and cytological features of osteosarcoma.[16] The present study aims to report and discuss a rare clinical case of sacral osteosarcoma in a patient with coexisting hyperparathyroidism, contributing to the limited literature on this potential association and highlighting the importance of considering endocrine disorders in the differential diagnosis and pathological interpretation of osteogenic tumours.

CASE REPORT

A 45-year-old male patient was referred from another hospital to a leading Brazilian orthopaedic reference center with a diagnosis of giant cell tumor (GCT) of the sacrum, previously confirmed by percutaneous biopsy. The patient's main symptoms included local axial and radicular pain, progressive bilateral sciatica over the course of one year, and muscle weakness, without neurological deficits. Initial imaging studies (Figure 1) revealed an extensive lytic lesion involving nearly the entire sacrum, with magnetic resonance imaging demonstrating a predominantly left-sided mass. (Figures 1E and 1F)

As part of the standard institutional protocol, a second needle biopsy was performed to confirm the diagnosis. Concurrently, laboratory tests were requested to rule out a brown tumor secondary to hyperparathyroidism, which is often histologically indistinguishable from GCT. Laboratory evaluation revealed primary hyperparathyroidism, with elevated serum calcium levels of 14.49 mg/dL (reference range: 8.5–10.2 mg/dL) and markedly increased parathyroid hormone (PTH) levels of 392.0 pg/mL (reference range: 10–65 pg/mL), prompting further endocrine investigation. Cervical ultrasonography revealed a 2.9 cm hypoechoic nodule adjacent to the right parathyroid gland. Parathyroid scintigraphy demonstrated a focal area of increased radiotracer uptake in the lower pole of the right thyroid lobe, suggestive of parathyroid hyperplasia or adenoma, with no other abnormal foci identified. Based on these findings, the patient underwent parathyroidectomy, and histopathological examination of the resected tissue confirmed the diagnosis of parathyroid adenoma. (Figure 2)

Unexpectedly, histological examination of the sacral lesion revealed a bone-forming high-grade malignant neoplasm**,** composed of neoplastic mononuclear cells and multinucleated giant cells exhibiting marked anaplasia and pleomorphism,



Fonte: Author's own case.

Figure 2. Open resection of parathyroid adenoma.

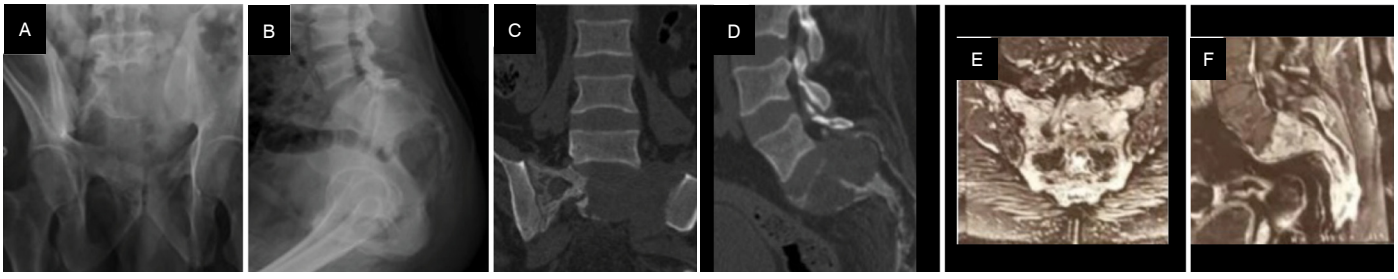


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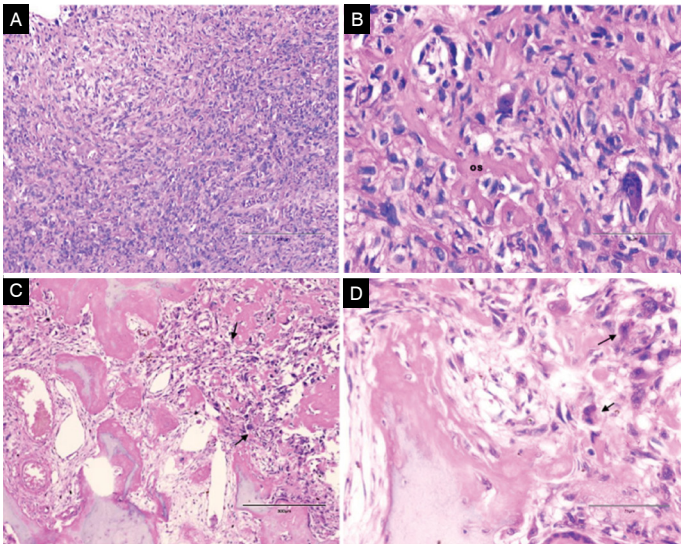
Figure 1. Patient's preoperative radiologic features. (A) Anteroposterior and (B) lateral pelvic radiographs showing a large lytic lesion predominantly extending to the left of the midline; (C) Coronal and (D) sagittal CT images demonstrating extensive destruction of the sacrum with involvement of the spinal canal; (E) Axial and (F) sagittal T1-weighted MRI with contrast, revealing a hyperintense and heterogeneous lesion.

with interspersed unmineralized osteoid matrix, consistent with the diagnosis of high-grade osteosarcoma (Figures 3A and 3B). The patient was subsequently treated with neoadjuvant chemotherapy, which resulted in incomplete tumor regression (Figures 3C and 3D)

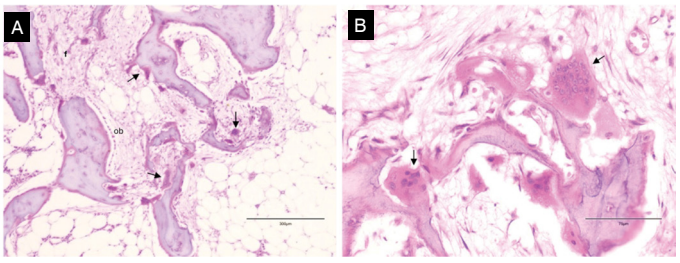
Following chemotherapy, the patient underwent an *en bloc* sacral resection with lumbopelvic reconstruction using a combination of fibular autograft and structural allograft (Figure 4). The reconstruction was performed using the characteristic "cathedral configuration" of lumbopelvic instrumentation. Histological analysis of bone tissue adjacent to the tumor revealed morphological features consistent with hyperparathyroidism, including irregularly sized trabeculae**,** increased osteoclastic activity associated with reactive bone remodeling, numerous prominent osteoblasts lining the trabeculae, well-defined cement lines, and intertrabecular fibrosis. (Figure 5)

Ethical approval was obtained from the National Institute of Traumatology and Orthopedics (INTO, Rio de Janeiro, Brazil) Human Ethics Committee (CAAE: 24670519.7.0000.5273).



Fonte: Author's own case.

Figure 3. High-grade osteosarcoma. (A) Bone-forming hypercellular malignant neoplasm; (B) Neoplastic mononuclear cells and multinucleated giant cells displaying marked anaplasia and pleomorphism, with interspersed areas of unmineralized osteoid matrix (os); (C) Post-chemotherapy specimen showing residual viable tumor cells (arrow); (D) Persistent residual neoplastic cells (arrow), indicating incomplete tumour regression and a partial response to treatment. Hematoxylin and eosin staining; (A) and (C) are at 100x magnification, whereas (B) and (D) are at 400x magnification.



Fonte: Author's own case.

Figure 5. Post-chemotherapy sacral resection specimen. (A) Irregularly sized bone trabeculae with numerous prominent osteoblasts (ob) lining their surfaces, along with increased osteoclastic activity (arrows) associated with bone marrow fibrosis (f); (B) Higher magnification showing the trabecular surface with multinucleated osteoclasts (arrows) actively resorbing bone. Hematoxylin and eosin staining.

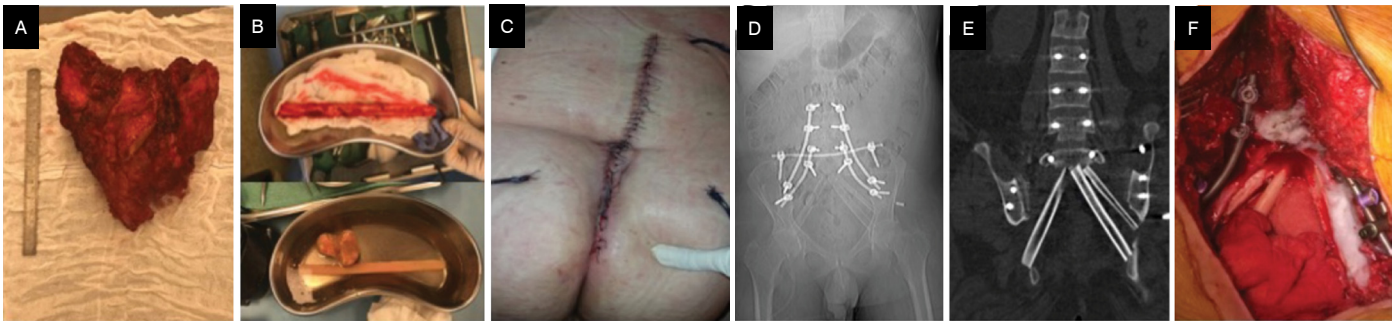
DISCUSSION

This report represents a rare and diagnostically challenging scenario in which a high-grade sacral osteosarcoma was identified in a patient with confirmed primary hyperparathyroidism. The initial biopsy suggested a GCT, a common differential diagnosis due to histological overlap with brown tumours – non-neoplastic, osteolytic lesions caused by excessive PTH activity. The markedly elevated serum calcium and PTH levels initially supported this diagnostic hypothesis. However, a second biopsy, combined with comprehensive histopathological assessment, confirmed the diagnosis of high-grade osteosarcoma, characterized by neoplastic osteoid production, cellular atypia, and multinucleated giant cells.

This case underscores the critical importance of integrating clinical, radiological, biochemical, and histological data to prevent misdiagnosis – particularly in skeletal lesions occurring in patients with endocrine disorders such as hyperparathyroidism.

Although preclinical studies have demonstrated that PTH may modulate osteoblast proliferation and influence osteosarcoma cell behaviour, clinical reports describing the coexistence of osteosarcoma and hyperparathyroidism remain exceedingly rare. The present case contributes to the sparse body of literature on this association. Previous reports, including those by Betancourt et al. (2003) and Jutte et al. (2004), described high-grade osteosarcomas in patients with hyperparathyroidism.[14,15] A retrospective review by Jimenez et al. (2005), involving more than 1,200 osteosarcoma cases, identified only three patients with coexisting hyperparathyroidism, suggesting no significant increase in incidence. Nevertheless, the authors emphasized that parathyroid dysfunction may modify the histological features of osteosarcoma.[16]

More recently, a 2023 case study reported the coexistence of



Fonte: Author's Own Case.

Figure 4. Intraoperative and postoperative images. (A) En bloc resection of the sacrum; (B) Lumbopelvic reconstruction using fibular autograft and structural allograft; (C) Midline wound closure following reconstruction; (D) Anteroposterior lumbosacral radiograph demonstrating lumbopelvic instrumentation in the characteristic "cathedral" configuration; (E) Coronal CT scan showing the position of pedicle screws and structural bone grafts; (F) Intraoperative posterior view highlighting the "cathedral" configuration of the reconstruction.

primary hyperparathyroidism and sarcoma, raising the possibility that prolonged PTH exposure may represent a rare risk factor for bone sarcomas.[17] These observations highlight the potential for tumour-promoting effects of chronic hormonal dysregulation, warranting further investigation into a possible – but likely uncommon – pathogenic link.

Although *in vitro* and *in vivo* studies have suggested that elevated PTH levels may contribute to sarcomagenesis, clinical evidence in humans remains limited.[18] Nonetheless, the present case supports the hypothesis that chronic endocrine disturbances could influence tumour microenvironment and cellular behaviour. Furthermore, this report emphasizes the diagnostic complexity of bone lesions in anatomically challenging locations such as the sacrum, where overlapping clinical and pathological features may obscure accurate classification.

CONCLUSION

This rare case of sacral osteosarcoma in the setting of primary hyperparathyroidism contributes meaningful evidence to a scarcely documented association. Case reports such as this are essential to raise awareness among clinicians and pathologists regarding the potential diagnostic pitfalls posed by overlapping features of hyperparathyroidism-related bone disease and primary bone malignancies. Accurate diagnosis is crucial to ensure appropriate therapeutic decision-making and to avoid delays or errors in management. Future studies are needed to understand better the potential interplay between hormonal dysregulation and osteogenic tumorigenesis.

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