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Brown Tumors in Hyperparathyroidism: Pathophysiology, Diagnostic Challenges, and Therapeutic Approaches: A Review

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ABSTRACT

Brown's tumors are rare, benign, osteolytic lesions associated with excessive parathyroid hormone (PTH) secretion, typically occurring in untreated or advanced hyperparathyroidism (HPT). These lesions, although non-neoplastic, often mimic malignancies both clinically and radiologically, leading to diagnostic and therapeutic challenges. They are characterized by progressive bone resorption and fibrovascular tissue proliferation, often presenting as localized pain, swelling, or pathological fractures. Despite the decline in their incidence due to advancements in healthcare, their occurrence remains significant in regions with limited access to medical interventions. This review consolidates findings from 15+ peer-reviewed articles to provide a detailed overview of the pathophysiology, clinical features, diagnostic approaches, and comprehensive management strategies for Brown's tumors in the context of HPT.

Keywords: Brown tumor, Hyperparathyroidism, bone, CKD, osteolytic lesion

1. INTRODUCTION

Brown's tumors, also known as osteitis fibrosa cystica, represent a classic skeletal manifestation of advanced HPT [1]. Although musculoskeletal manifestations in patients with primary hyperparathyroidism (PTH) can reach 54.7%, the incidence of Brown tumors ranges from 1.5% to 4.5% [2]. These lesions arise due to persistent elevation of PTH, leading to localized bone destruction and replacement with fibrovascular tissue. The name "Brown's tumor" is derived from the hemosiderin deposits in the tissue, giving the lesions their characteristic coloration [3]. Brown tumors are gaint cell focal lesions associated with primary or secondary hyperparathyroidism; it may be invasive in some cases, but it is not potentially malignant [4]. Although these tumors are present in primary hyperparathyroidism, cases associated with chronic renal failure (CRF) are being reported with increaseing frequency. Brown tumor in CRF patients is an extreme form of osteodystrophy. These tumors are common in long borns, ribs and pelvis [5].

The epidemiology of Brown's tumors varies based on the underlying cause of HPT—primary, secondary, or tertiary. Primary HPT, often due to parathyroid adenomas, is the most common etiology in developed nations, while secondary HPT, associated with chronic kidney disease, predominates in areas with high rates of renal dysfunction [6]. Advances in diagnostic techniques and early intervention for HPT have reduced the incidence of Brown's tumors. However, delayed diagnosis or inadequate management of HPT can result in significant skeletal and systemic complications, underscoring the importance of early recognition and intervention [7]. This review on brown tumor helps understanding of pathophysiology, aids in accurate diagnosis, guides effective treatment, and raises awareness of this rare hyperparathyroidism-related bone lesion.

2. Pathophysiology

Brown tumors develop as a consequence of prolonged and severe hyperparathyroidism, where excessive parathyroid hormone (PTH) secretion disrupts normal bone remodeling. PTH increases osteoclastic activity by stimulating osteoblasts to produce receptor activator of nuclear factor kappa-B ligand (RANKL), which in turn activates osteoclasts. This results in excessive bone resorption, leading to the formation of lytic lesions [8]. Although PTH also stimulates osteoblasts to promote bone formation, chronic elevation of PTH tips the balance toward bone resorption, causing trabecular thinning, cortical porosity, and weakened bone structure. Within these lytic lesions, macrophages and multinucleated giant cells accumulate, creating a histological appearance similar to giant cell

tumors. The reddish-brown coloration of these lesions, from which the term "Brown tumor" is derived, results from hemosiderin deposition due to repeated microhemorrhages [9].

As bone resorption progresses, the marrow space is replaced by vascularized fibrous tissue, composed of fibroblasts, giant cells, and areas of hemorrhage, further weakening the bone [10]. The associated biochemical imbalances, including hypercalcemia and hypophosphatemia, exacerbate bone demineralization and increase osteoclastic activity. Brown tumors most commonly occur in weight-bearing bones, such as the femur, pelvis, and vertebrae, but they can also affect the jaws, ribs, or other skeletal regions [11]. The systemic effects of prolonged hyperparathyroidism, such as fatigue, muscle weakness, nephrolithiasis, and neuropsychiatric symptoms, further contribute to the patient's clinical burden. Overall, Brown tumors represent the pathological endpoint of chronic dysregulation in bone metabolism caused by unregulated PTH activity, underscoring the need for timely treatment of hyperparathyroidism to prevent irreversible skeletal damage [12].

3. Clinical Presentation

The symptoms of Brown's tumors range from asymptomatic to severe, depending on the size, location, and number of lesions. Common clinical features include:

3.1. Localized Symptoms: Patients frequently report pain, swelling, or deformity in affected bones, often leading to functional limitations [13].

3.2. Maxillofacial Involvement: Lesions in the jaw are particularly distressing, causing facial asymmetry, dental instability, and difficulty chewing. These features can significantly affect quality of life and lead to social stigma [14].

3.3. Neurological Complications: Tumors in the spine can cause spinal cord compression, leading to neurological deficits such as radiculopathy, myelopathy, or even paraplegia in severe cases [15].

3.4. Pathological Fractures: The weakened structural integrity of bones predisposes them to fractures, even under minimal stress [16].

3.5. Systemic Features: Chronic HPT often presents with generalized bone pain, fatigue, and muscle weakness, further compounding the patient's symptoms [17].

These features necessitate a thorough evaluation to differentiate Brown's tumors from malignant bone lesions or other metabolic bone diseases.

4. Diagnostic Strategies

Accurate diagnosis involves a multimodal approach:

4.1. Biochemical Evaluation

- Elevated PTH Levels: A key diagnostic marker indicating hyper parathyroid activity [18].
- Serum Calcium: Hypercalcemia is common in primary HPT but may be absent in secondary HPT [19].
- Phosphate Levels: Typically low in primary HPT but elevated in secondary HPT due to renal dysfunction [20].
- Alkaline Phosphatase (ALP): Elevated levels indicate increased bone turnover [20].

4.2. Imaging Modalities

- X-rays: Show osteolytic lesions with well-defined margins, often described as "soap-bubble" lesions [21].
- CT Scans: Provide detailed structural information, particularly for complex anatomical regions [22].
- MRI: Useful for assessing soft tissue involvement and distinguishing Brown's tumors from malignancies [23].

- Sestamibi Scans: Highly effective for localizing parathyroid adenomas or hyperplasia. It is a nuclear medicine imaging test that uses a radioactive substance to detect overactive glands, heart disease, and breast cancer [24].

4.3. Histopathological Analysis

Histological examination confirms the diagnosis, revealing multinucleated giant cells, fibrovascular stroma, and hemosiderin deposits. The absence of malignant features differentiates Brown's tumors from neoplastic conditions such as osteosarcoma or giant cell tumors [25].

5. Management Strategies

5.1. Addressing the Underlying Hyperparathyroidism

The primary goal in treating Brown tumors is to correct the underlying hyperparathyroidism. In primary hyperparathyroidism (PHPT), surgical removal of the hyperfunctioning parathyroid gland(s) through parathyroidectomy is the definitive treatment [26]. Post-parathyroidectomy, normalization of parathyroid hormone (PTH) levels reduces osteoclastic activity, leading to the gradual regression of Brown tumors [27].

In secondary hyperparathyroidism (SHPT), commonly associated with chronic kidney disease (CKD), treatment includes managing hyperphosphatemia and hypocalcemia using phosphate binders, vitamin D analogs, and calcimimetics like cinacalcet [28]. In tertiary hyperparathyroidism, where hyperplasia becomes autonomous, parathyroidectomy is often necessary when medical management fails [29].

5.2. Surgical Intervention for Tumor Lesions

Although Brown tumors are benign and often regress after correction of hyperparathyroidism, large or symptomatic lesions may require direct surgical intervention [30]. Indications for tumor surgery include:

- Severe pain.
- Pathological fractures.
- Structural compromise (e.g., spinal instability).
- Orthopedic procedures such as curettage, bone grafting, or internal fixation may be performed depending on the location and extent of the lesion [31].

5.3. Pharmacological Support

Adjunctive therapy with bisphosphonates can help inhibit bone resorption and support bone mineral density recovery [32]. Their use is particularly beneficial in preventing further osteoclastic activity while waiting for the effects of definitive hyperparathyroidism treatment [33]. Denosumab, a monoclonal antibody, has been explored in cases where bisphosphonates are contraindicated or ineffective [34].

5.4. Rehabilitation and Monitoring

Post-treatment rehabilitation involves calcium and vitamin D supplementation to support bone healing and prevent hypocalcemia caused by the "hungry bone syndrome" following parathyroidectomy [35]. Regular monitoring with imaging, serum calcium, phosphate, and PTH levels is crucial to ensure tumor regression and identify potential recurrence [36].

5.5. Management of Advanced or Refractory Cases

In cases where hyperparathyroidism treatment does not resolve Brown tumors, or in patients who cannot undergo parathyroidectomy, long-term medical therapy and palliative orthopedic interventions may be necessary [37]. Multidisciplinary care involving endocrinologists, orthopedic surgeons, and nephrologists is essential in these complex cases [38].

6. Discussion:

Brown tumors, though benign, represent a significant complication of prolonged, untreated hyperparathyroidism (HPT), particularly in resource-limited settings where late presentations are more common. These lesions underscore the skeletal consequences of chronic PTH excess, manifesting as painful, destructive, and sometimes deforming bone lesions. The pathogenesis highlights the critical balance between osteoclastic and osteoblastic activity, disrupted by sustained PTH elevation. While early diagnosis of HPT has reduced the incidence of Brown tumors in developed regions, secondary and tertiary HPT—especially in chronic kidney disease—remain significant contributors globally. Differentiating Brown tumors from malignant bone lesions is essential to avoid misdiagnosis and inappropriate interventions. Treatment requires addressing the underlying HPT, with parathyroidectomy offering excellent outcomes in primary disease, while pharmacologic management is vital in secondary forms. Adjunctive surgical and supportive therapies may be needed in severe or symptomatic cases. Overall, multidisciplinary management ensures optimal patient outcomes and highlights the importance of early HPT detection and intervention.

7. Conclusion

Brown's tumors underscore the systemic implications of untreated or advanced hyperparathyroidism. While their incidence has declined with improved diagnostic and therapeutic strategies, their presence signals the need for urgent and targeted intervention. Timely diagnosis and management of HPT, coupled with appropriate treatment of skeletal complications, are pivotal to preventing morbidity and enhancing patient outcomes. A multidisciplinary approach remains the cornerstone of care for this rare but impactful condition.

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9. Table: **Fig**: selected case reports on brown tumors, including patient demographics, tumor locations, underlying causes, and references.

Patient Demographics	Tumor Location(s)	Underlying Cause	Reference
34-year-old female	Mandible	Secondary hyperparathyroidism due to chronic kidney disease	Brown Tumors: A Case Report and Review of the Literature
45-year-old male	Multiple bones	Primary hyperparathyroidism due to parathyroid carcinoma	Multiple Brown Tumors in Primary Hyperparathyroidism
50-year-old female	Multiple bones	Primary hyperparathyroidism	Multiple bone brown tumor secondary to primary hyperparathyroidism
60-year-old female	Maxillary sinus	Primary hyperparathyroidism	Brown tumor of the maxillary sinus in a patient with primary hyperparathyroidism
40-year-old female	Mandible	Secondary hyperparathyroidism due to systemic lupus erythematosus and chronic kidney disease	A Case Report with 5 Years Follow-Up and Review of the Literature

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