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ORIGINAL ARTICLE

Brown tumor as a result of secondary hyperparathyroidism in chronic renal disease

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Abstract:

Introduction: Brown tumor is a focal lesion of giant cells that develops in association with hyperparathyroidism. **Objective:** To report a case of brown tumor that occurred in the mandibular symphysis region, associated with secondary hyperparathyroidism. **Case report:** A 45-year-old male patient with chronic renal failure exhibited increased volume with comorbid local paresthesia in the mandibular symphysis region. Radiographs showed a unilocular radiolucent area with partially defined edges in the anterior mandible region. The histopathological findings revealed connective tissue, rich in oval, notched cells and giant cells with hemosiderin pigments. Laboratory tests showed increased serum levels of parathyroid hormone. An attempt to control the hormone levels with medication while the patient awaited a kidney transplant was unsuccessful. Therefore, as a transplant was not imminent and injury continued to develop, the lesion was surgically excised. Three years later, the lesions recurred in the paranasal region. Following partial removal of the lesions, the patient is now under follow-up care. **Conclusion:** Correct diagnosis and effective treatment of brown tumor requires correlation of biochemical data with the patient's clinical, imaging, and histological profile.

Keywords: Hyperparathyroidism; Kidney Failure, Chronic; Giant Cells

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INTRODUCTION

Brown tumor is a focal lesion of giant cells without neoplastic potential that differentiates from other giant cell lesions via its association with hyperparathyroidism. The term brown tumor derives from the dark red appearance, observed macroscopically, from the bleeding and hemosiderin pigments present in this lesion[1, 2].

Increased serum parathyroid hormone (PTH) level is most often associated with a parathyroid adenoma, and commonly induces hypercalcemia. An imbalance between bone formation and resorption may cause bone lysis and subsequent formation of fibroelastic tissue that deforms the bone [3]. Clinically, these lesions have many symptoms such as pain, swelling, and pathological fracture [1]. In the early stages of systemic hyperparathyroidism, symptoms can be misdiagnosed as hypercalcemia; for example, pain may be attributed to urinary lithiasis[4]. Polyuria and gastrointestinal disorders may also occur[5,6].

Histological characteristics of brown tumor demonstrate highly vascular connective tissue with diffusely distributed multinucleated giant cells, and areas of hemorrhage and hemosiderin deposits [6]. Skeletal demineralization, resulting from elevated plasma calcium, leads to multinucleated giant cells or osteoclasts replacing bone[7,3].

The observation of central giant cell granuloma and aneurysmal bone cyst can indicate the differential diagnosis of brown tumor. However, clinical, histopathological, and imaging results are often insufficient to establish differences between this injury and other tumors[1]. The imaging profile typically reveals a well-demarcated radiolucent unilocular or multilocular osteolytic lesion, and rarely, root resorption or loss of lamina dura[6,8]. The correct diagnosis requires endocrine assessment in addition to clinical and imaging data.

In most cases, the preferred treatment includes the excision of the parathyroid gland-adenoma. In some cases of parathyroid hyperplasia, there may be tumor regression. Early diagnosis and treatment of hyperparathyroidism prevents the formation of brown tumors or sometimes allows spontaneous regression. However, if the tumor or associated symptoms persist, surgical excision should be performed [2,6].

The aim of this manuscript was to report a case of a brown tumor located in the mandibular symphysis, associated with secondary hyperparathyroidism due to chronic kidney disease.

CASE REPORT

A 45-year-old male patient sought treatment at the Maxillofacial Surgery Service, complaining of swelling in the mandibular symphysis region, associated with local paresthesia. The patient reported that this tumefaction had been present for 11 months. He also pointed out that he suffers from chronic kidney disease and hypertension. He received a right kidney transplant more than 10 years ago and has been undergoing hemodialysis since then. During the interview, The patient is a non-smoker and does not drink excessive alcohol or use illicit drugs. He was prescribed captopril (Captopril 25 mg, Medley, Campinas-SP, Brazil), clonidine hydrochloride (Atensina 0.600 mg, BoehringerIngelheim, Itapecerica da Serra-SP, Brazil), and Loniten (minoxidil 20 mg, Pfizer, Patheon Inc. Operations Whitby, Ontario, Canada).

No changes related to his complaint were evident upon extra-oral examination (Figures 1a-b-c), but intraoral examination revealed an increase in anterior mandible volume with deletion of the vestibular sulcus (Figures 2a-bc).However, there were no changes to the bone or signs of cariogenic or periodontal disease in the area of the mandibular symphysis.

The panoramic radiograph showed a radiolucent image, unilocular with the lips, partially defined in the anterior region of the jaw associated with 44, 43, 42, 41, 31, and 32 roots. However, it did not compromise the basic portion of the jaw (Figure 3).

Axial slices obtained from computed tomography scans revealed buccal bone expansion, fenestration points, and considerable osteolysis in the anterior portion of the jaw (Figures 4a-bc).

Three presumptive diagnoses were determined from these findings: a central giant cell lesion associated with brown hyperparathyroidism tumor, a periapical cyst, or an odontogenic keratocystic tumor.

To distinguish between these diagnoses, an incisional biopsy of the lesion was performed. Histopathological examination of the surgical specimen revealed the presence of connective tissue, rich in oval, notched cells and multinucleated giant cells (Figure 5). Hemorrhagic foci and hemosiderin deposits were also observed. The histopathologic diagnosis was that of a giant cell lesion.

It was investigated whether there was systemic involvement correlating the observed giant cell lesion with brown tumor of hypothyroidism. Secondary hyperparathyroidism with chronic kidney disease

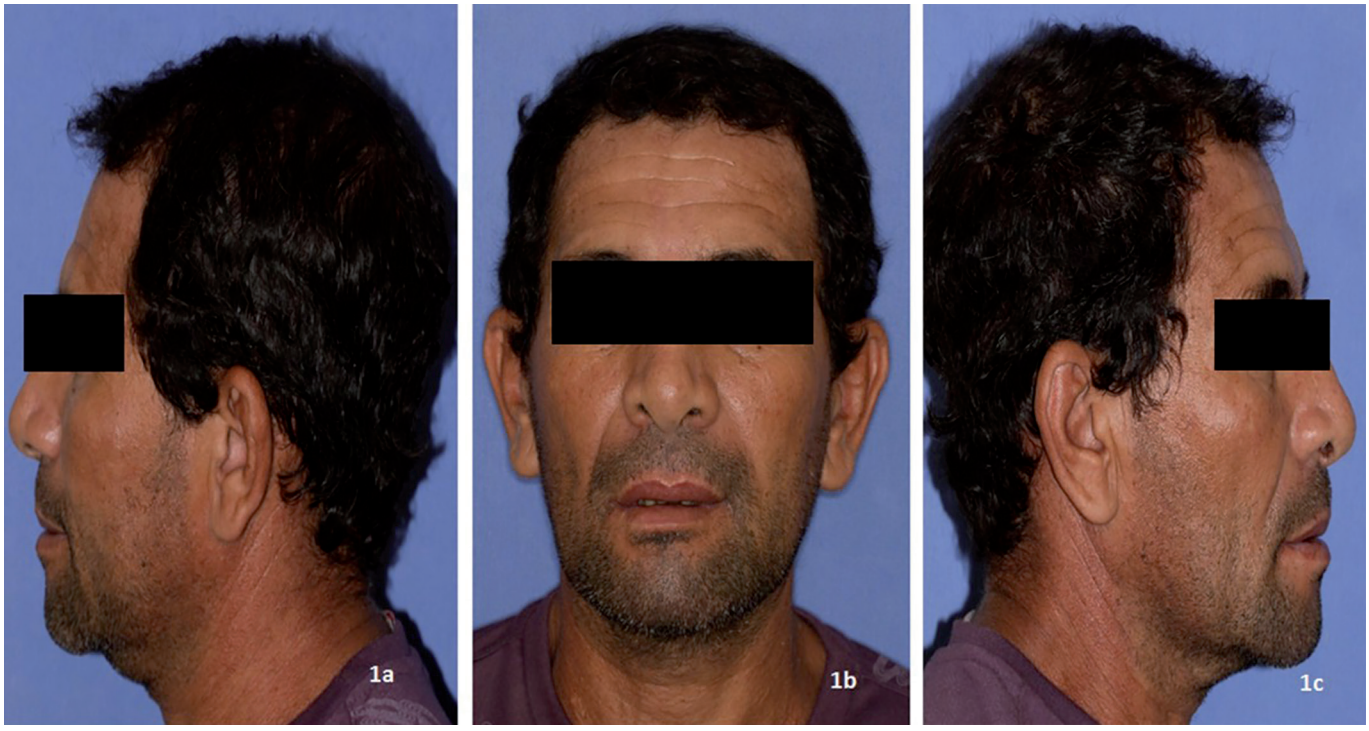
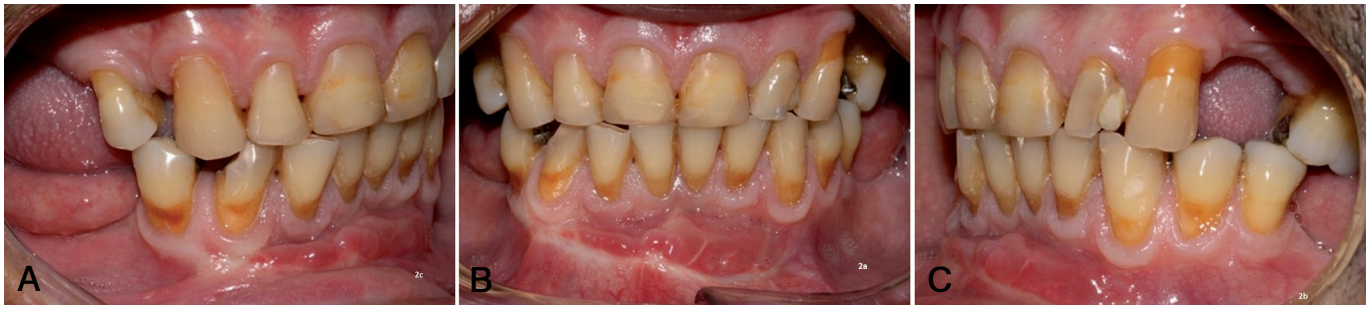


Figure 1. Clinical features observed during the extraoral examination. No significant changes were observed in the patient's face



Figures 2. A: Erasing buccal groove in the anterior mandible region extending to the right premolars. **B:** rasing buccal groove in the anterior mandible region. **C:** Erasing buccal groove in the anterior mandible region extending to the left premolars.

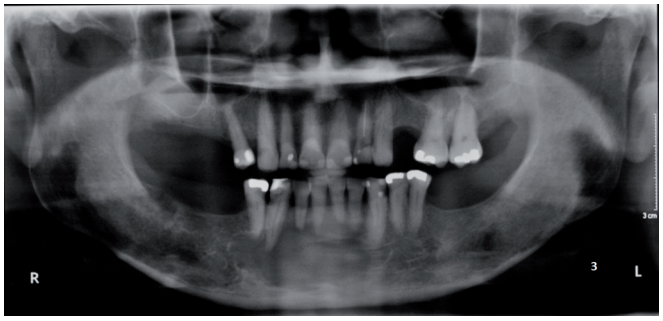


Figure 3. Extensive radiolucent lesion in the anterior mandibular bone.

was diagnosed, based on the serum levels of alkaline phosphate 459 U/L (36-14 U/L), parathyroid hormone 454.2 pg/ml (16-65 pg/ml), and calcium 2.38 mmol/L (2.10 to 2.55).

The parathyroid glands were not removed, as the PTH disorder was believed to be associated with chronic renal failure. An attempt was made to control the hormone levels medically, to resolve the parathyroid disorder, and stimulate tumor regression, while awaiting a second kidney transplant. However, it was not possible to control the PTH levels and the lesion continued to progress.

Total surgical removal of the lesion ensued, with enucleation, curettage, peripheral osteotomy, and extraction of the element involved (Figures 6a-b-c). The excision required an intraoral incision in the vestibular portion to the boundary of the lesion and mucoperiosteal detachment with delimitation of the visible edges of the pathological tissue. Curettage, extraction of affected

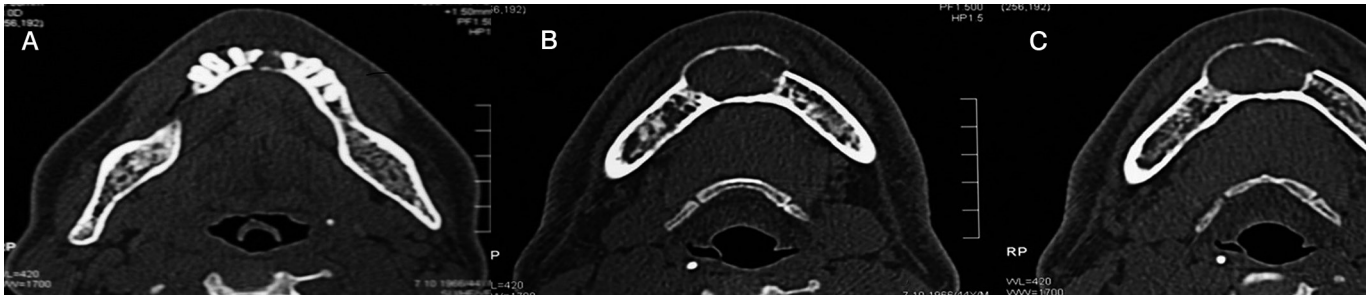


Figure 4. A: Hypodense lesion on the mandibular symphysis region with partially defined limits. **B-C:** Hypodense lesion on the mandibular symphysis region with partially defined limits (arrows).

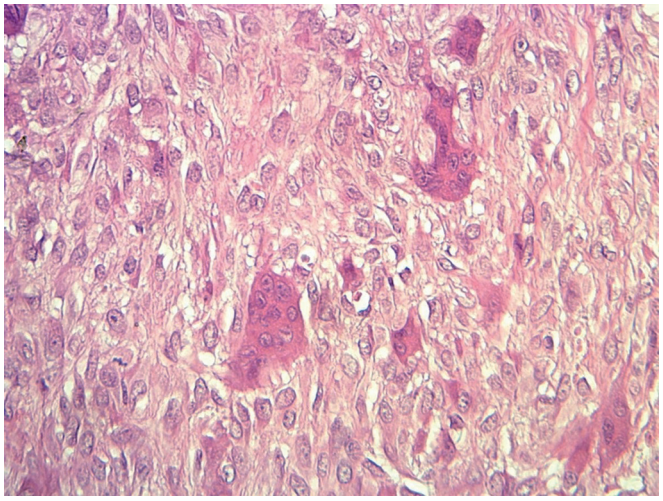


Figure 5. Multinucleated giant cell in the stroma. Hematoxylin-eosin (HE), 400X.

units, ostectomy, irrigation, and suturing of the edges were performed following the excision.

After 6 months of follow-up, hormone levels (PTH 28.1 pg/mL) and bone metabolism were medically controlled (calcitriol, 0.25 mcg daily [Rocaltrol, Catalent Germany GmbH Eberbach, Eberbach, Germany]), allowing oral rehabilitation by the use of implants.

Three years following surgery, radiographies showed bone formation and absence of relapse (Figure 7), clinically showed good healing (Figure 8) and he continued rehabilitation with prosthetic implants (Figure 9; 10 a-b).

During this follow-up period, serum PTH levels fluctuated, reaching 699 pg/mL in 2013, and 3 years after surgery, the patient presented again with a single bone lesion in the paranasal region, which was excised. The patient is now under follow-up and awaiting a new kidney transplant, which may normalize PTH levels.

DISCUSSION

Brown tumor, also known as cystic fibrous osteitis, is a rare metabolic bone disease that can develop in advanced stages of primary, secondary, or tertiary hyperparathyroidism[6]. It is considered a rare finding and is only found in advanced stages of hyperparathyroidism[5,9] This injury occurs more often in the mandible than the maxilla and is three times more common in women over 50 years[10]. It may appear in any bone, but is often found in the bones of the face and jaw, especially in cases of longstanding disease[1]. In this case, the lesion was located in the mandibular symphysis region, a fact consistent with the literature[1,7,11,12].

Among other giant cell lesions that cause bone expansion, there are the reparative granuloma of giant cells, cherubism, and brown tumor[2]. Radiographically and histopathologically, the latter resembles other bone injuries that occur on the face. The differential diagnosis

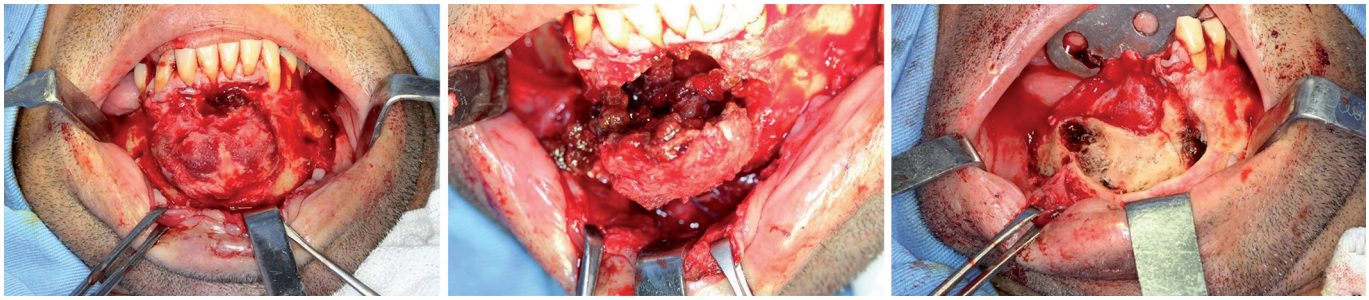


Figure 6. A: Surgical approach with lesion visualization. **B:** Surgical approach with lesion visualization. **C:** Aspects of bone store after lesion removal

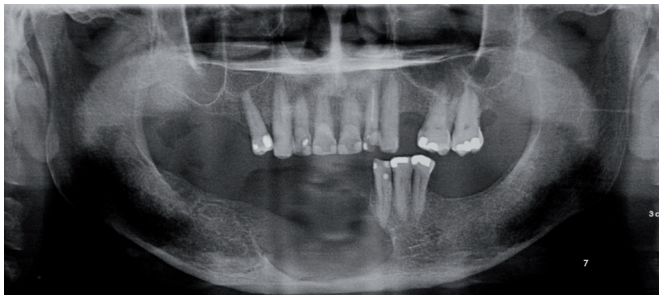


Figure 7: New bone formation in the area previously occupied by the lesion.

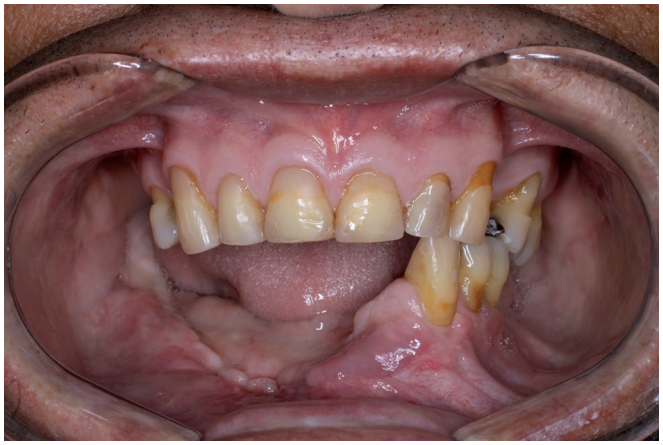


Figure 8: Post-surgical after 07 months.

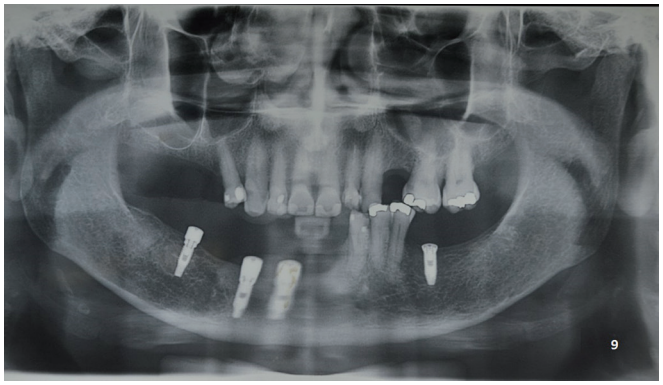


Figure 9: Radiography showing rehabilitation with osteointegrated implants.

is determined from the PTH, calcium, and alkaline phosphatase levels in the blood[11].

Chronic renal failure is the main cause of secondary hyperparathyroidism[3] Ninety two percent of patients undergoing dialysis develop secondary hyperparathyroidism and about 1.5%, develop brown tumors[1]. Chronic renal failure results in impaired vitamin D metabolism, hyperphosphatemia, hypocalcemia[13] and leads to hyperplasia of the parathyroid gland that responds to demand by increasing synthesis and secretion of PTH. Similar findings were noted in this case. Indeed, increased levels of PTH may affect bone tissue and potentially promote the differentiation of osteogenic cells such as osteoblasts and osteoclasts. As a matter of fact, osteoid can be formed within a vascular tissue [13]. PTH can also change the balance between the intra- and extra-cellular calcium levels, increasing bone resorption, reducing its density and inducing calcium deposits in soft tissues[10].

Leal et al [14] described a patient with chronic renal failure, who underwent dialysis for 9 years and developed a large, rapidly growing brown tumor. Furthermore, she had skeletal deformities and reabsorption in the distal phalanges of the fingers. In our case, the development time of the injury was 11 months. In most cases, injury is only noticeable when clinically detectable or when it affects the patient's pain perception. Therefore, the time course of the disease reported by the patient may be underestimated, although it ratifies existing data in the literature indicating that the development of brown hyperparathyroidism tumor can range from as little as 1 month[3,5] to longer periods, such as 3 years[1]. The average development time found in the literature is 10 months.

Patients with hyperparathyroidism may have nonspecific symptoms, including weakness, rapid fatigue, and depression. The symptoms may be related to tumor size and location, but in most cases, these tumors are not painful[5,14,16]. However, Pinto MC et al [10] reported pain associated with the symptoms of brown tumor. In our case, the patient complained of paresthesia. This symptom could relate to the proximity of the inferior alveolar neurovascular bundle. In some cases, the size and location of the lesion may induce difficulty in swallowing, breathing[14] epistaxis, and even septal deviations[5].

A study by Eufrazino et al. [15] showed that patients treated in the public health service had higher levels of serum calcium and PTH than those treated privately, which could suggest a late medical assessment with delayed diagnosis. Brown tumors are late manifestations of hyperparathyroidism, and its incidence could be reduced through early diagnosis.

Radiographically, brown tumors are described as well-demarcated, circumscribed, and osteolytic lesions[17,16]. In this case, computed tomography revealed fenestration and expansion of the bone pubis region. Lessa et al. 2005[5] reported loss of cortical bone and decreased trabecular bone and skeletal changes that may represent early stages of the disease.

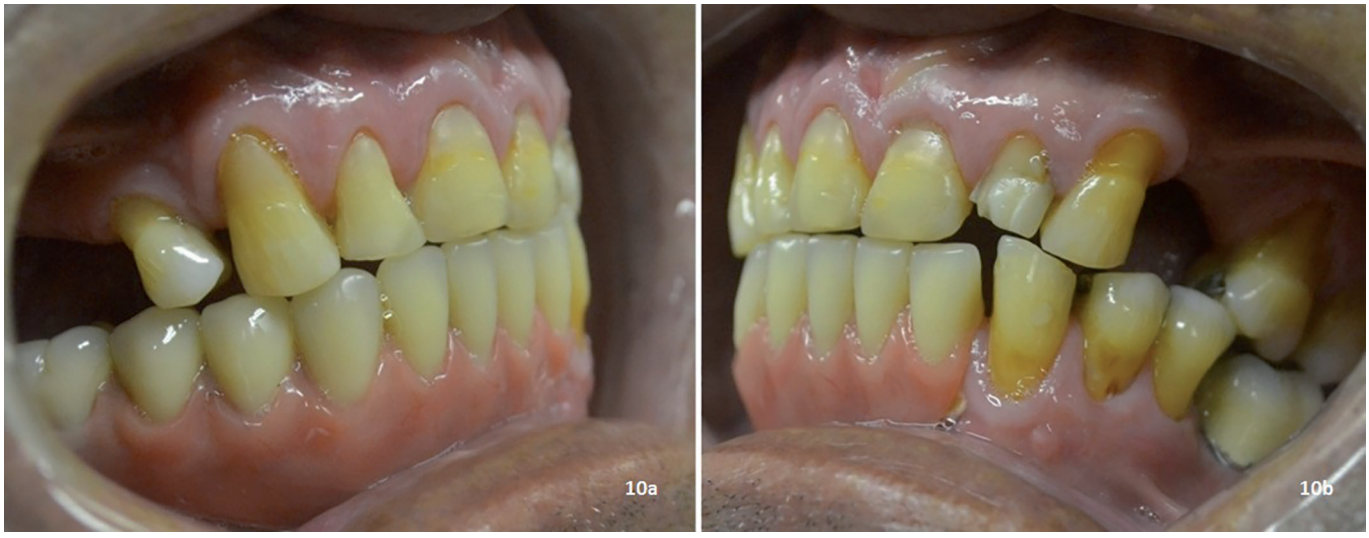


Figure 10. A-B: Rehabilitation with prosthetic implants.

Brown tumors do not show pathognomonic histological changes[5]. Histological reports of injured tissue describe connective tissue rich in notched oval cells in which giant cells, hemorrhagic foci and hemosiderin can be observed. These histopathologic features were described similarly by Lessa et al 2005[5]; Monteiro 2009[13]; Wang et al 2014[16]; Shetty, Namitha, James, 2015[6]). Additionally, microfractures, osteoid tissue, and cystic areas of degeneration can also be found[5].

Initial treatment involves correction of hyperparathyroidism, which usually leads to tumor regression[5]. Tumor preventive treatment objectives for patients with chronic renal failure include normalizing blood levels of calcium and phosphate[14,10]. The use of oral chelators and calcitriol supplements have been described by Leal et al 2006[14]. Calcitriol replacement to normalize serum PTH was the treatment of choice. However, when there is an adenoma in the parathyroid gland[14,10,6,18] some authors recommend parathyroidectomy as the preferred therapy. Indeed, Monteiro 2009[13] recommended removal of the parathyroid even in the absence of an adenoma. However, in the present case PTH deregulation was associated with chronic renal failure; therefore, parathyroidectomy would be ineffective.

Surgical resection of brown tumors is generally not recommended[16], and their surgical removal is determined by their sequelae. These may include adverse effects of bone expansion on chewing, speech, breathing, and aesthetics, or, when the tumors occur in other bones, functional disorders with involvement of joints. Symptomatic tumors or pathological fracture risk are also indications for excision[16]. With calcitriol replacement and surgical excision of the tumor lesion, it was possible to restore normal levels of PTH. Moreover, paresthesia reported by patients has also resolved following tumor removal.

The patient has been under follow up for 3 years waiting for a new kidney transplant that may allow regression of serum PTH, which reached 699 pg/mL in 2013. In early 2015, the patient presented with recurrent lesions in the paranasal region, verified by incisional biopsy. Definitive treatment can only be performed after renal transplantation and normalization of PTH levels.

CONCLUSION

Patients with chronic renal insufficiency may develop secondary hyperparathyroidism. In advanced stages of the disease, the presentation of brown tumors is possible. Biochemical findings support the diagnosis and may decide the patient's prognosis. Treatment is based on reducing the levels of PTH, either through medical management, parathyroidectomy or kidney transplantation.

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