Case Report

Maxillary brown tumor due to secondary hyperparathyroidism in a Hemodialysis patient: A case report and literature review

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Abstract

Hemodialysis is one of the commonly used renal replacement therapies in treating end-stage renal failure patients. Patients with long-term dialysis may develop frequently complications such as secondary hyperparathyroidism (SHPT), bone diseases, amyloidosis, endocrinal disturbances, cardiovascular complications and infections. Brown tumors (BTs) are erosive giant cell bony lesions that arise in some patients as a result of primary or SHPT. About 2% of all the reported cases showed involvement of facial skeleton, of which the mandible is the favorite site. A complete clinical, biochemical, radiological and histopathological correlation is required for definitive diagnosis. We report here a case of BT in 37-year-old female hemodialysis patient with SHPT.

Keywords: Brown tumor, giant cell lesions, hyperparathyroidism, osteitis fibrosa cystica, renal failure

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INTRODUCTION

The term "hyperparathyroidism" (HPT) refers to increased levels of secretion of parathyroid hormone (PTH) by the parathyroid glands. Based on its etiopathogenesis, HPT can be classified into primary, secondary and tertiary forms.[1] It was estimated that the incidence of some form of kidney diseases ranges between 8% and 10% of the adult population. Undetected/untreated chronic kidney disease (CKD) ultimately leads to kidney failure or end-stage renal diseases. These patients often require kidney transplant or regular dialysis treatment in order to survive. The later being the more readily available option. Patients with long-term dialysis often develop secondary HPT (SHPT).[2] Very rarely, SHPT can also be due to Vitamin D deficiency, calcitriol deficiency and increased phosphorous retention.[3] SHPT often leads to increased osteoclastic activity resulting in bone resorption, calciphylaxis, pruritis, cardiovascular diseases and many others.[4]

Oral health-care practioners should be aware of the consequences of elevated PTH levels on the maxillofacial skeleton-like Grave's disease, HPT – Jaw tumor syndrome, brown tumor (BT), Sagliker syndrome and osteitis fibrosa cystica (OFC) in order to establish proper diagnosis and

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subsequently their medical and dental management.[5] BTs were classic giant cell osteolytic lesions associated with HPT. They are considered to be reactive or reparative lesions rather than a true neoplasm. This giant cell granulomatous lesion was believed to occur as a result of rapid or imbalanced osteoclastic activity along with peritrabecular fibrosis. The characteristic brown-colored lesion was because of hemorrhage, hemosiderin deposition and hypervascularity and thus the name.[6]

BT usually occurs as asymptomatic, well-demarcated, expansile, unifocal or multifocal bone lesions. Their incidence remains as high as 58%–69% in underdeveloped countries in contrast to 1.5%–1.7% in developed countries.[7] Women are more commonly affected than men with varying degrees of aggressiveness and rate of recurrence. Most commonly it affects the axial skeleton such as long bones, tibia, pelvis, clavicle, spine and ribs.[8] As far as head-and-neck involvement is concerned, these lesions are reported in regions such as mandible, nasal, orbit, temporal, paranasal sinus, maxilla and palate. In the routine radiographs, it often appears as radiolucent lesions with well-defined borders. A complete clinical, biochemical, radiological and histopathological correlation is required for definitive diagnosis.

CASE REPORT

A 37-year-old female visited the outpatient department with the chief complaint of swelling over her left side face for 1 year. History of presenting illness revealed that the onset of the swelling was sudden on the extraoral region associated with weight gain. Patient noticed aggressiveness in its growing size both intra and extra orally for the past 3 months with the displacement of front tooth associated with the swelling with no history of pain and discharge. Patient also complains of difficulties in phonation and nasal obstruction for the past 3 months. No relevant history of trauma or facial paresthesia. Past medical history revealed the presence of Stage V chronic kidney disease for the past 8 years and under hemodialysis through A-V fistula on the right wrist. The patient was known hypertensive and under medication for the past 10 years. The patient had a history of hepatitis C diagnosed 7 years back and was treated for the same. The patient was diagnosed with HPT and under medication for the past 1½ years. Extraoral examination revealed a solitary localized swelling was present over left side anterior maxillary region of the face causing facial asymmetry. Skin overlying the swelling was intact and showed stretched out shiny appearance. All the vital signs were well within the normal limits. The swelling sized about 6 cm × 5 cm extends from 0.5 cm below the left side infraorbital margin superiorly up to the left side commissure inferiorly, and medially, it extends till to the right side ala of the nose and laterally till to the left side zygoma with notable deviation of the nasal tip, philtrum, left side ala of the nose and obliteration of left side nasolabial fold [Figure 1]. On palpation, the swelling was firm to hard in consistency, nontender, skin was pinchale with no rise in temperature. Bilateral submandibular lymph nodes are palpable.

Intraoral examination showed swelling over the upper alveolus measuring 8 cm × 6 cm in its greatest dimension extending from labial vestibule of 12 to 25 region on the labial aspect and from 16 to 26 region on the palatal aspect obliterating the labial vestibule. The overlying mucosa was intact and without any discharge. Displacement of teeth with Grade 1 mobility noted in relation to 11, 21, 22 and 23 region [Figure 2]. On palpation, the swelling was hard in consistency, nontender and nonfluctuant. Furthermore there was a palpable swelling on the lower labial vestibule region extending from 31 to 34 region. Orthopantomogram reveals multilocular radiolucency with well-defined margins involving the anterior maxilla. Reconstructed computed tomography shows 3.5 cm × 3.2 cm × 4.5 cm expansile lytic lesion from alveolar process with cortical expansion in left maxilla [Figure 3]. The lesion results in the displacement of the left side maxillary anterior teeth. Based on the clinical picture, medical history and radiological presentation, a provisional diagnosis of ameloblastoma, aneurismal bone cyst and giant cell lesion of the maxilla including the BT were considered.

Incisional biopsy was performed, and on the microscopic examination, the lesion was composed of numerous giant cells, more or less was uniform in size resembling osteoclasts in a fibrovascular cellular stroma that shows

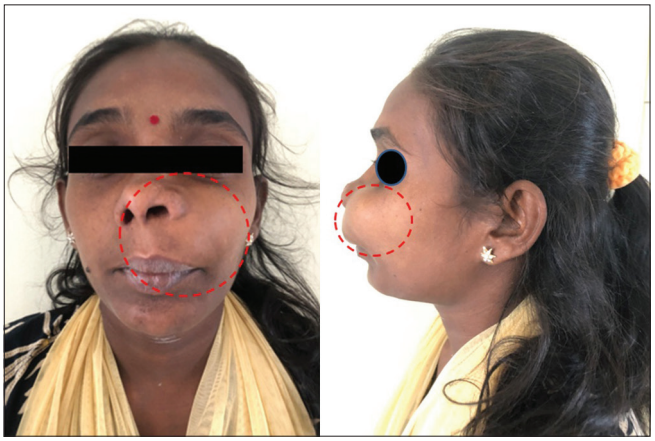

Figure 1: Clinical image that shows facial asymmetry involving the left anterior maxilla

mononuclear oval-to-spindle-shaped fibroblastic cells, with interstitial hemorrhage, increased vascularity and focal deposits of hemosiderin. Based on her past medical history and along with the histopathological observation, a diagnosis of BT was arrived [Figure 4]. Other significant biochemical findings of the patient includes serum creatinine 8.7 (NR 0.7–1.3 mg/dl), PTH assay 1423 (NR 12–88 pg/ml), blood urea 159 (NR 20–40 mg/dl), alkaline phosphatase (ALP) 287 (NR up to 115 IU/l) and glomerular filtration rate by Modification of Diet in Renal Disease formula 8 (NR >90 ml/min). As the tumor results in the respiratory distress, facial disfigurement, displacement and malocclusion of teeth and considering the extent of the tumor with the underlying uncontrolled disease, surgical intervention was opted after discussing with the nephrologist. A complete excision of tumor was done, and while grossing the excised specimen shows well-encapsulated lesion sized about 6 cm × 4.5 cm × 5.5 cm in size, the cut sections reveal numerous patchy areas of brownish black regions throughout the specimen representing the zones of hemorrhage and hemosiderin pigmentation [Figure 5]. Microscopic examination of the different regions of the specimen shows similar picture as it is in the Incisional biopsy [Figure 6]. Correlating the clinical, radiological, biochemical and histopathological observation, a final diagnosis of BT due to SHPT was arrived. The patient follow-up was satisfactory, and the postoperative healing was well within the normal limits [Figure 7].

DISCUSSION

The parathyroid glands were first identified by Sir Richard Owen in 1850, are comprised of 4 small endocrine glands located in the posterior aspect of the thyroids. Parathyroid hormone/Parathormone (PTH) secreted by these glands were responsible for maintaining the serum calcium and phosphate homeostasis, which is necessary for the muscle, nerve functions and the normal physiology of the bone.[9] The term "HPT" was coined by Henry Dixon *et al.* refer to the increased level of PTH, and it is of utmost importance to evaluate the various etiopathogenesis for proper patient management. HPT may occur in one of the following forms [Table 1].

Primary HPT (PHPT) is the third most frequent endocrine disorder to occur after diabetes and thyroid dysfunction. The estimation of serum calcium and phosphorous is the basic laboratory procedure used to distinguish the PHPT from SHPT. Autonomous overproduction of PTH in PHPT due to the reasons mentioned in the table results in hypercalcemia and hypophosphatemia, whereas the *vice versa* happens in SHPT.[13] Levels of ALP vary among the patients and depend on the level of osteolysis.

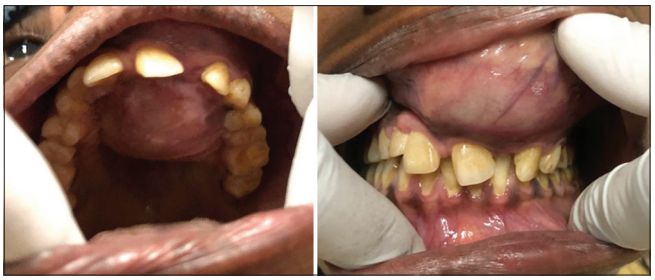

Figure 2: Intraoral view that shows the extent of the swelling till to the molar region, obliterating the labial vestibule with the displacement of anterior teeth

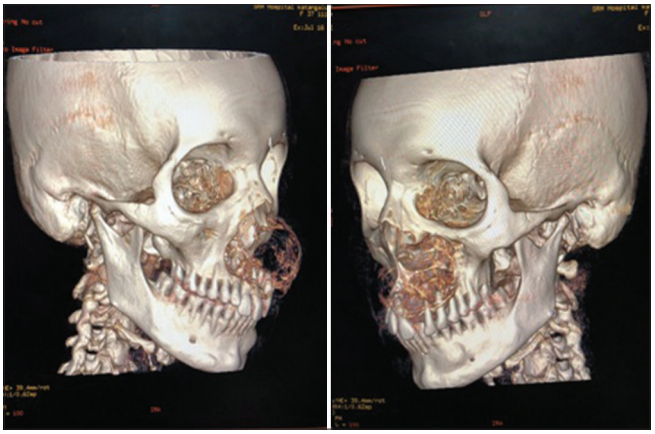

Figure 3: Three dimensional reconstructed computed tomography scan shows the osteolytic lesion involving the anterior maxilla

Figure 4: Well-encapsulated lesion and the cut section reveal numerous patchy areas of brownish black regions representing the zones of haemorrhage

SHPT is an adaptive mechanism that occurs in response to deteriorating kidney function with decreased glomerular filtration, impaired phosphate excretion, raised serum phosphorous, reduced extracellular ionized calcium and the inability to bioactivate Vitamin D results in increased PTH

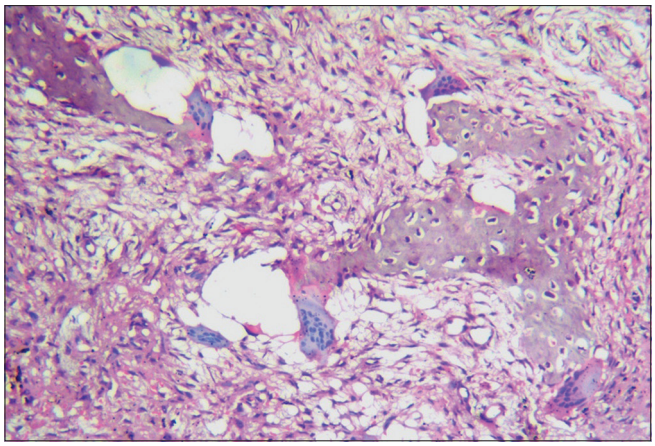

Figure 5: Incisional biopsy. Histopathological image shows multinucleated giant cells in fibrovascular stroma (H&E stain, X 10 magnification)

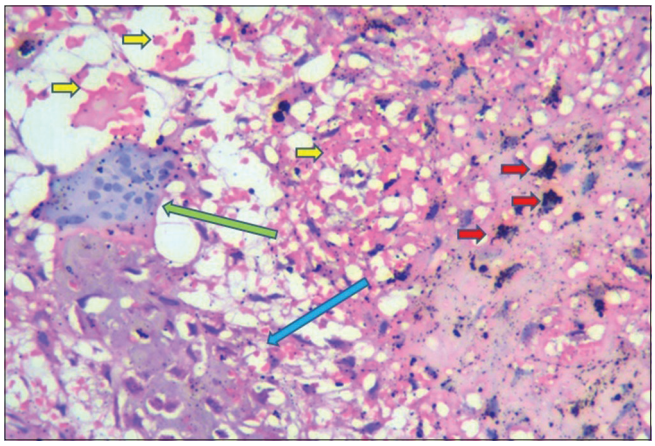

Figure 6: Excisional Biopsy. Histopathological image shows multinucleated giant cells (green arrow) associated with the bony spicule (blue arrow), extravasated red blood cell (yellow arrow) and focal deposits of hemosiderin (red arrow) (H&E stain, X 100 magnification)

Figure 7: Postoperative follow-up of the patient

production and its release. Furthermore, it was in CKD, the increased fibroblast growth factor-23 expression inhibits residual renal 25(OH)-1-hydroxylase, exacerbates the calcitriol deficiency and serving as an additional catalyst of SHPT. Under expression of the calcium-sensing receptor and Vitamin D receptor in varying levels in CKD patients worsen the situation further, preventing parathyroid cells from responding properly to ambient calcium and/or calcitriol. All the abovementioned mechanisms are believed to play a significant role in the development of SHPT in CKD patients.[14]

Table 1: Etiological factors underlying various forms of hyperparathyroidism

Types of HPT	Underlying mechanism/etiology
PHPT	Adenoma, hyperplasia, carcinoma of parathyroids, syndromes such as noonan, multiple endocrine neoplasia type 1/2A
SHPT	CRF, hypocalcemic conditions such as rickets, oseteomalacia, Vitamin D deficiency and pregnancy, Sagliker syndrome[10]
THPT	Long-term secondary HPT
Ectopic HPT	Patients with other malignancies[11]
Hereditary HPT	HPT jaw tumor syndrome-inhibition of parafibromin protein as a result of mutations in HRPT2/CDC73 in 1q25-q31 chromosome[12]

HPT: Hyperparathyroidism, PHPT: Primary HPT, SHPT: Secondary HPT, THPT: Tertiary HPT, CRF: Chronic renal failure

More than 90% of patients undergoing hemodialysis for CKD/chronic renal failure (CRF) will develop renal osteodystrophy. Abnormal metabolism of bone in these patients leads to the occurrence of BT.[15] Friedrich von Recklinghausen in 1891 was the first person to describe the bone changes associated with the HPT referred to as "Osteitis Fibrosa Cystica". Max Askanazy in 1904 was the first person to report a patient with skeletal disease and a tumor involving the parathyroid gland.[16] Jaffe coined the term "BT" to describe the bony lesions found in HPT. BT normally considered as the delayed manifestations in HPT. The terms such as osteoclastoma were used in the past and preferably should be avoided.

BTs are uncommon lesions with an overall prevalence of 0.1% in the jaws seen in both PHPT and SHPT. The incidence of BT with SHPT is comparatively less when compared with PHPT. Women are frequently affected than men, and the incidence increases with age, especially in the postmenopausal women probably attributed to the hormonal imbalances. Clinically, these tumors present as well circumscribed, exophytic, hard, palpable, uni or multilocular swellings with or without facial deformities. Depending on the size, extent and location of the lesion, symptoms vary among the patients with few elicit painful lesions and the rest are asymptomatic. In the present case, the age of the patient was relatively young and presented as asymptomatic but features such as facial disfigurement, displacement and loosening of tooth, nasal obstruction and difficulty in chewing were her major concern.

Mandible is more frequently involved as far as the maxillofacial skeleton is considered and was explained by the fact that the osteoclastic activity by the circulatory PTH was more in the cortical bone. This fact is in contrast with our present case and shows maxillary involvement. Routine radiographic interpretation includes well-defined, uni or multilocular punched out radiolucency with cortical thinning and reactive bone formation. Very rarely, the margins show scalloping. Correction of the PTH levels by medical or surgical management in both PHPT and SHPT will reduce the burden in the bone. Generalized loss of lamina dura, narrow pulp chamber and medullary ground glass appearance are some of the other findings.

Microscopic observation of this lesion was not unique and resembles other giant cell lesions. Central giant cell granuloma should be ruled out by comparing with the biochemical profile such as serum calcium and phosphate levels. Giant cell tumor or osteoclastoma shows cellular atypia, more infiltrative with larger giant cells with more than 40–60 nuclei, and the absence of hemorrhage. Characteristic cherub faces, occurrence in very young age, symmetrical involvement and perivascular eosinophilic cuffing differentiates this from cherubism. Aneurysmal bone cyst shows typical blood soaked sponge description intraoperatively along with blood-filled spaces without endothelial lining differentiates from BT. Special stains including PAS, GMS, Congo red and along with that chest radiographs are required to rule out microbial and other granulomatous conditions.

Management of BT varies from patient to patient. In case of PHPT, underlying pathology of the parathyroid gland has to be identified and should be treated accordingly. Investigations such as ultrasound and technetium scan are often used and found to be helpful in patients with PHPT. The management of BT in SHPT was centered around in controlling the underlying CRF/CKD. Often the procedures such as hemodialysis and dietary phosphorous restrictions; calcimimmetic drugs such as cinacalet, Vitamin D sterols, phosphate binders, bisphosphonates and intralesional steroid therapy were mentioned in the literature with varying success rate. Health-care provider should customize the treatment for each patient and should be aware of the short- and long-term complications of the abovementioned drugs. Surgical corrections are opted for refractory cases and patients with poor compliance to medical therapy, also in patients who need functional and esthetic restoration. Recurrence is rare if the underlying renal disease is not controlled postoperatively.

CONCLUSION

SHPT is a chronic condition that affects people with chronic kidney disease and has severe health effects, leading to bone disease frequently which will have a negative impact on morbidity and mortality. BT was more likely to occur in patients with uncontrolled and untreated HPT. The primary goal of this case study is to emphasize the importance of oral evaluation in diagnosing the underlying systemic diseases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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