Case Report

Multifocal osteolytic lesions of jaw as a road map to diagnosis of brown tumor of hyperparathyroidism: A rare case report with review of literature

Suchitra Gosavi[1], Harpreet Kaur[2], Pramod Gandhi[3]

[1]Department of Oral Pathology, Government Dental College and Hospital, [3]Department of Endocrinology and Diabteology, Kingsway Hospitals, Nagpur, Maharashtra, [2]Division of Oral Pathology, Centre of Dental Education and Research, All India Institute of Medical Sciences, New Delhi, India

Abstract

Brown tumor is unifocal or multifocal bone disease which represents terminal stage of hyperparathyroidism (HPT)-dependent bone pathology. It is recognized as a component of metabolic bone disease called osteitis fibrosa cystica generalisata or Von Recklinghausen disease of bone. HPT was first described by Von Recklinghausen in 1891. Brown tumor diagnosis nowadays is less frequently encountered because of early stage detection of HPT. This early detection is possible due to routine blood screening in asymptomatic adults or during evaluation of osteoporosis. Histologically, it may resemble any other giant cell lesion of the jaw that imposes diagnostic challenge and delay in treatment. We are introducing a case report of a 30-year-old female patient presented with multifocal osteolytic lesions in mandible with histopathology depictive of giant cell granuloma. Further biochemical investigations and X-ray skeletal changes raised the suspicion of primary HPT which was confirmed by parathyroid scintigraphy revealing parathyroid adenoma. The main purpose of this case report is to reinforce the role of oral examination in diagnosis of systemic diseases and to propose a diagnostic layout/algorithm when giant cells are present in biopsy specimen. Review of literature showing brown tumor of oral cavity associated with PHPT is discussed.

Keywords: Brown tumor, giant cell lesion, parathyroid adenoma, parathyroid scintigraphy, primary hyperparathyroidism

Address for correspondence: Dr. Harpreet Kaur, Division of Oral Pathology, Centre of Dental Education and Research, All India Institute of Medical Sciences, New Delhi - 110 023, India.
E-mail: hrprtarora@gmail.com
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INTRODUCTION

Shetty "the hyperparathyroidism is a disease in which there may be a complex, of biochemical, anatomic and clinical abnormalities"[1] Hyperparathyroidism (HPT) is caused by elevated parathyroid hormone (PTH) and classified into primary, secondary and least commonly tertiary types.[2] Additional hereditary form has been shown to be an autosomal dominant condition mapped to chromosome 1q21-q31, the location of the HRPT2 endocrine tumor gene.[3]

Primary HPT (PHPT) is the most common endocrine disorder after diabetes mellitus and thyroid dysfunction.[4]

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In PHPT, there is an autonomous overproduction of PTH, usually resulting from parathyroid adenoma (90%), parathyroid hyperplasia (3%), or less commonly an adenocarcinoma (3%) and rarely associated with Noonan type syndrome, MEN type 1 and 2A.[3] Secondary HPT is associated with compensatory hypersecretion of PTH in response to prolonged hypocalcemia commonly seen in renal failure. Tertiary HPT is due to persistent hypersecretion of PTH and it presents in patients with long-standing secondary HPT resulting in autonomous functioning of parathyroid gland.[2] The fourth type is an ectopic variant seen in patients with other malignancies.[5] To understand the pathogenesis of HPT, normal physiology of calcium and phosphorus homeostasis is depicted in Figure 1.[6]

Clinical picture in PHPT varies from asymptomatic to severe cases presenting with lethargy and coma. Severe

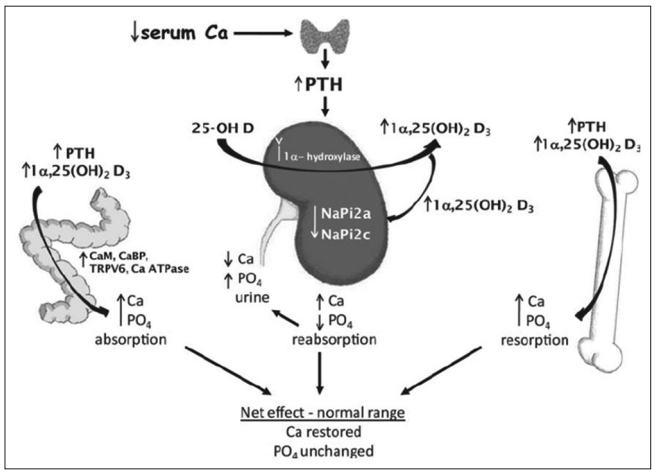

Figure 1: Traditional calcium, parathyroid hormone, and Vitamin D axis for the regulation of calcium homeostasis.[6] Under conditions of dietary calcium restriction, a decrement in serum calcium concentration induces release of parathyroid hormone from the parathyroid gland. Increased parathyroid hormone acts on the kidneys to stimulate renal 25(OH) D3-1α hydroxylase activity (1α-hydroxylase), which increases synthesis of the active form of Vitamin D (1α, 25-(OH) 2D3; calcitriol). Increased parathyroid hormone and 1α, 25-(OH) 2D3 target bone to induce a net resorption of calcium and phosphorus from mineralized tissue into circulation. Increased 1α, 25-(OH) 2D3 also targets the small intestine to stimulate active absorption of calcium and phosphorus through upregulation of proteins involved in calcium transport including calmodulin (calcium M), calbindin (calcium BP), transient receptor potential channel vanilloid 6 (TRPV6, also referred to as calcium transport protein 1) and calcium ATPase. The kidneys are ultimately required to restore serum calcium concentrations and maintain a calcium-to-phosphorus ratio. The increased 1α, 25-(OH) 2D3 stimulates renal calcium reabsorption through upregulation of calcium transport proteins and downregulation of phosphorus transport proteins (NaPi2a and NaPi2c). The net renal response results in a decreased excretion of calcium and an increased urinary excretion of P. Increased 1α, 25-(OH) 2D3 also serves as a feedback regulator to decrease 1α-hydroxylase activity. The net response to a decrement of serum calcium is a restoration of serum calcium with no effect on serum phosphorus

disease is classically described as "stones, bones, groans and moans" reflective of renal calculi, bone pathology, duodenal ulcers and confusion or dementia-like symptoms respectively.[7] Less frequent radiographic changes in jaws include the osteoporotic appearance of mandible or rarely maxilla (salt and pepper appearance), loosening of teeth, overall cortical plate thinning and partial loss of lamina dura.[7]

Multifocal brown tumor is rare complication of HPT with the prevalence of 0.1% in jaws.[8] These bone lesions are classic skeletal manifestations of HPT, usually seen in severe forms with subperiosteal bone resorption.[9] Brown tumors can affect the long bones, clavicle, scapula, ribs, pelvic bones, mandible, other craniofacial bones and the spine.[10] Histopathologically, it is identical to central giant cell granuloma (CGCG), and the name is derived from color of tissue specimen which is usually dark red-brown because of abundant hemorrhage and deposits of hemosiderin within the tumor. However, the word "tumor" is a misnomer as it is not a true neoplasm.

The diagnosis of PHPT on a giant cell picture in histopathology is classically been based on demonstration of increased serum PTH levels, hypercalcemia, hypophosphatemia and normal or highly increased (in widespread osteolytic lesions) alkaline phosphatase levels.[11]

We report a case of a 29-year-old female with punched out osteolytic lesions in mandible. Investigations revealed it to be a brown tumor associated with PHPT and parathyroid scintigraphy showed parathyroid adenoma as the cause of PHPT. This article presents diagnostic challenges associated with osteolytic lesions radiographically and differential diagnosis of giant cell lesions histopathologically with a proposal of diagnostic algorithm. Review of literature showing brown tumor of oral cavity associated with PHPT is discussed in the end [Table 1].

CASE REPORT

A 29-year-old female patient presented to the Department of Oral Pathology and Microbiology, Government Dental College and Hospital, Nagpur, with the chief complaint of pain and swelling in the left posterior region of lower jaw since 6–7 months. When the patient entered our department, a waddling gait was observed. Proper history revealed vague intermittent bone pain with acquired gait change over a period of few months. Intraoral examination revealed mild obliteration of buccal vestibule [Figure 2]. Orthopantomogram showed multifocal osteolytic lesions

Table 1: 10 years review of literature of brown tumor of jaw associated with primary hyperparathyroidism till 2018

Year and author	Age/ sex (years)	Clinical presentation	Radiological features	Serum calcium	Serum phosphorus	Serum ALP	Serum PTH	Cause of PHPT	Treatment
Proimos E 2009	42/ female	Facial pain and deformity	Round osteolytic lesion in anterior part of right maxillary sinus invading floor of orbit, anterior ethmoid sinus and nasal cavity	13.2 mg/dl (N: 8.5-10.5 mg/dl)	1.9 mg/dl (N: 2.50-4.50 mg/dl)	227 U/L (N: Upto 115.00)	920 pg/ml (N: 10-60.00 pg/ml)	Parathyroid adenoma	Referred to det of endocrinology
B. Chami *et al*. 2011	43/ female	Swelling in anterior palate approximately 4 cm × 3 cm	Palatal radiolucent destructive bone Lesion extending to the floor of nasal cavity and expanding the cortical plate	148 mg/l (normal: 86-105)	17 mg/l (normal: 25-50)	-	8608 pg/ml; normal: 9-55	Parathyroid adenoma	Surgical removal of mass
Soundarya, *et al*. 2011	60/ male	B/L maxillary swelling	Well-defined lytic lesion in maxilla, subperiosteal resorption of index finger	7.7 mg/dL	2.9 mg/dl	747 U/L	121 pg/ml	-	Complete resection of tumor
Elbuken G 2014	50/ male	Sessile swelling on the anterior region of the maxilla (peripheral location	-	10.6 mg/dl	1.9 mg/dl	430 U/L	355 pg/mL	Parathyroid adenoma	Surgical removal of parathyroid mass
Shetty AD *et al*. 2014	22/ female	Diffuse hard, tender swelling over left side of face	Unilocular radiolucency wrt 34-36 region with associated root resorption	12.5 mg/dl		762 U/L	452.5 pg/ml	Parathyroid hyperplasia	Surgical removal of parathyroid mass and curettage of bony lesions
Abhishek Ranjan Pati *et al*. 2014	34/ male	Massive painful swelling in right maxilla	Osteolytic lesion in anterior part of right maxillary sinus invading floor of orbit, anterior ethmoid sinus and nasal cavity	12 mg/dl	6.7 mg/dl	283 U/L	314 pg/ml	Parathyroid adenoma	-
Rao *et al*. 2016	55/ female	Asymptomatic with intraoral diffuse swelling in left mandible	Well defined, multilocular radiolucency in the left body of the mandible with resorption of roots irt 34, 35 and 36	11.3 mg/dl	-	134 U/L	210 pg/ml	Parathyroid adenoma	Partial parathyroidectomy
B. Gogolewski 2017	27/ female	Expansile mass in maxilla	Multifocal osteolytic lesions in maxilla and mandible	1.8 mmol/L (N: 0.98-1.21 mmol/L	-	-	653 pg/ml	Parathyroid adenoma	Right inferior parathyroidectomy
Kalapala L. 2016	42/ female	Swelling over left side of face with I/O swelling in mandibular 34-37 region	Multilcular radiolucent lesion in posterior mandible, in skull parietal and osteolytic areas	13.1 mg/dl	10 mg/dl	-	711 pg/ml	Parathyroid adenoma	-
Marcelo P 2017	35/ male	Expansile lesion in left mandible	Unilocula radioluceny in left side of mandible	-	-	-	502.8 pg/ml	-	Enucleation of the lesion, dental extraction of 36 element, curettage and synthesis of the region
Manoharan *et al*. 2017	46/ female	Expansile, hard mass in right and left nasolabial fold	Multiloculated osteolytic lesioninvolving both maxillae	12.9 mg/dl	2.1 mg/dl	-	1900 pg/ml	Parathyroid adenoma	Surgical excision of lesion
Ojha SS 2018	62/ female	Firm to hard swelling in anterior mandible	Expansile lytic lesion in midline of the mandible	3.16 mmol/L	-	-	516 pg/ml	Parathyroid adenoma	Surgical excision of lesion

B/L: Bilateral, ALP: Alkaline phosphatase, PTH: Parathormone, PHPT: Primary hyperparathyroidism

on anterior mandible, left posterior body region of mandible and right ramus of the mandible which were more clearly appreciated in cone-beam computed tomography (CT) images [Figures 2-4]. The differential diagnosis of CGCG, HPT, multiple myeloma and metastatic carcinoma was considered.

Incisional biopsy revealed highly cellular lesional connective showing proliferation of exceedingly vascular granulation tissue with numerous endothelial lined blood vessels, abundant areas of hemorrhage in the background. There were focal aggregates of multinucleated giant cells (pale eosinophilic cytoplasm and centrally placed 8–10 nuclei)

distributed diffusely throughout the section. The picture was suggestive of giant cell lesion [Figure 5] and histopathology

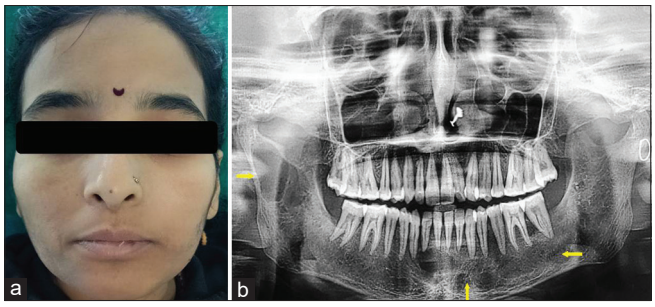

Figure 2: Extraoral and intraoral presentation of patient. Normal facial symmetry (a) and multifocal osteolytic lesions in anterior mandible, left posterior body, and right ramus of mandible (b)

differentials were all giant cell lesions such as CGCG, HPT, giant cell tumor, cherubism and aneurysmal bony cyst. Excisional biopsy revealed the similar picture. Skeletal survey showed multiple discrete radiolucencies in skull, pelvis, chest, spine and tibia [Figure 4]. Blood analysis is depicted in Table 2. Thus, in view of multifocal osteolytic lesions, giant cell granuloma on biopsy, hypercalcemia and raised PTH levels, the final diagnosis of brown tumor of PHPT was rendered. Parathyroid scintigraphy showed parathyroid adenoma in midline anterior neck inferior to the thyroid gland as a cause of PHPT [Figure 6].

Endoscopic removal of parathyroid mass was done. The lesion was histopathologically diagnosed with

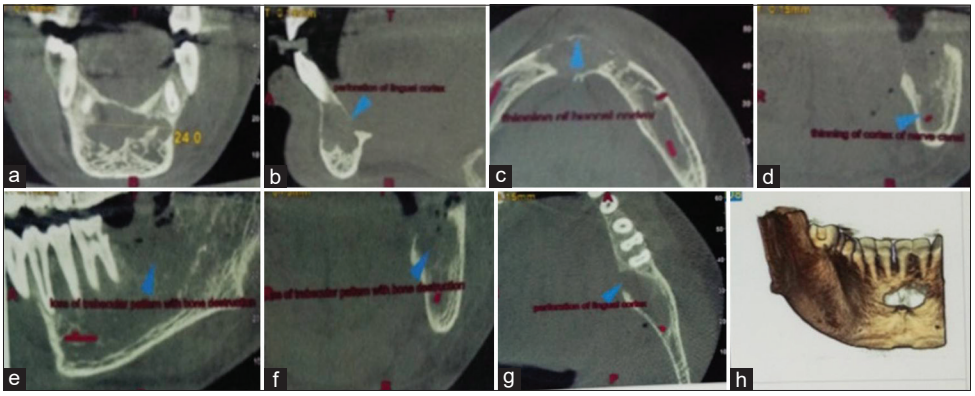

Figure 3: Cone-beam computed tomography showing radiolucencies in the mandibular anterior region and left posterior region. In anterior region, radiolucency is measuring about 13.5 mm × 11.3 mm extending till periapical region from 32 to 42, with round to oval in shape. Periphery of pathology is well defined with scalloped and corticated borders. No cortical expansion is seen. Perforation of lingual cortex and thinning of buccal cortex seen with irregular bone destruction in some areas is seen. No root resorption. (a-d). In the posterior region, radiolucency is measuring approximately 23.4 mm × 16.6 mm in length involving edentulous region of 37 and 38. Superior-inferiorly, it is extending from crest of alveolus to involve the inferior border of mandible. Periphery is ill-defined noncorticated with irregular shape. The presence of irregular bone destruction with loss of trabecular pattern. Thinning of cortex of the nerve canal in missing tooth space of 37 (e-g). (h) The 3D image of the affected site showing destruction of the bone

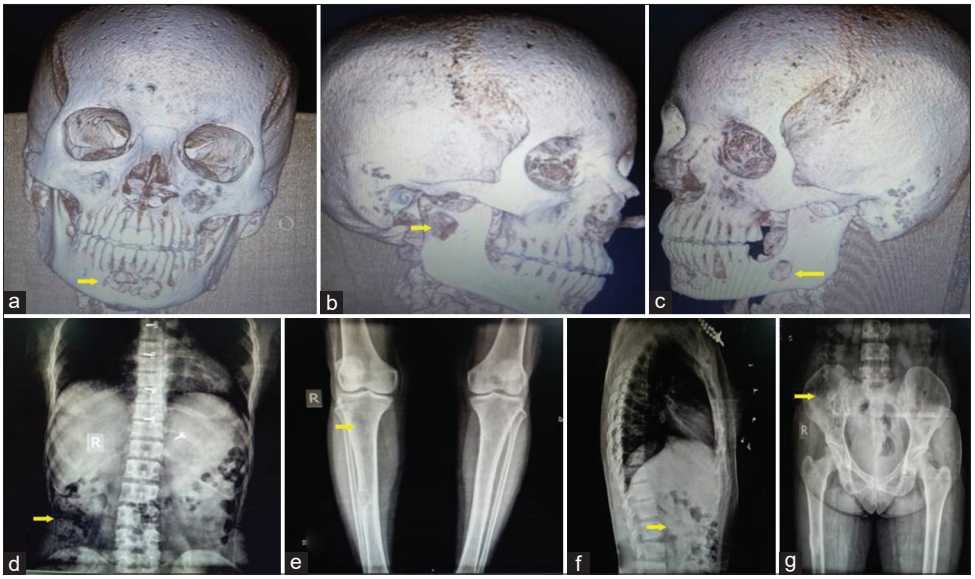

Figure 4: Three-dimensional re-construction of cone-beam computed tomography images and skeletal survey. Osteolytic lesions on right ramus, left postbody, and anterior region of mandible (yellow arrows a-c). Multiple discrete osteolytic lesions on spine, tibia, chest, and pelvis (d-g)

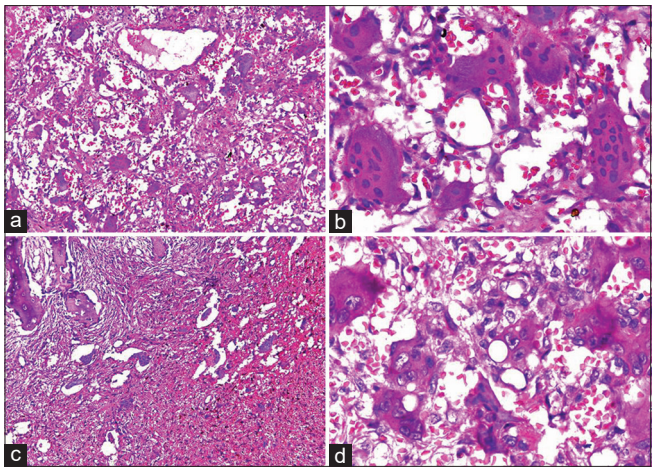

Figure 5: Histopathology of lesion. Incisional biopsy showed multinucleated giant cells in the background of abundant hemorrhage (a and b). Excisional biopsy revealed similar picture (c and d)

Table 2: Biochemistry report of patient

Test	Patient's findings	Normal range
Serum creatinine	0.70 mg%	0.60-1.40 mg%
Blood urea	14.40 mg%	20.00-40.00 mg%
Serum sodium	138 mg/L	135-145.00 mg/L
Serum potassium	4.10 mg/L	3.50-4.50 mg/L
GFR by MDRD formula	105	≥60 mll/min/173 m^2
Serum calcium	12.40 mg/dl	9-11 mg/dl
Serum phosphorus	1.40 mg/dl	2.50-4.50 mg/dl
ALP	2182 IU/L	Upto 115.00
PTH assay	706.04 pg/ml	12-88.00 pg/ml

PTH: Parathormone, GFR: Glomerular filtration rate, ALP: Alkaline phosphatase, MDRD: Modification of diet in renal disease study

parathyroid adenoma and the patient was kept under regular follow-up.

DISCUSSION

Recklinghausen (1891) was credited with the first description of HPT associated bone changes called osteitis fibrosa cystica.[12] Bone involvement is the late manifestation of the HPT. The incidence of bone lesions has decreased from 80% in the past to 15% in the present. This may be attributed to biochemical monitoring of serum calcium levels.[8] However, Kar *et al.* has reported 40 cases of generalized bone involvement.[13] Classical skeletal lesions which are bone resorption, bone cysts, brown tumors, generalized osteopenia are seen in <5% of cases.[5] Brown tumor accounts for 10% of all skeletal lesions with a 0.1% incidence in jaws.[8]

Brown tumors are nonneoplastic lesions resulting from abnormal bone metabolism in HPT. The name "brown tumor" for bony lesions seen in HPT was first coined by Jaffe.[14] They have been described in both primary (4.5%) and secondary HPT (1.5%–1.7%) as resulting from an imbalance of osteoclastic and osteoblastic activity with bone resorption exceeding the bone formation.[15]

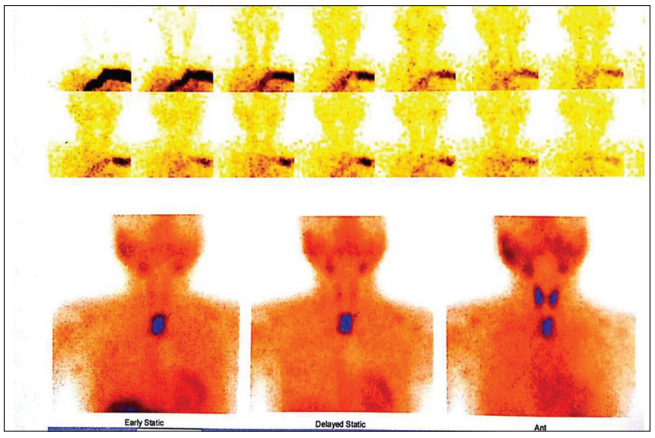

Figure 6: Parathyroid scintigraphy. The Tc-99M-tetrofosmin scan reveals abnormal large focus of intense tracer uptake in midline anterior neck, inferior to both lobes of the thyroid gland. Significant washout of tracer from thyroid gland is seen on delayed images with persistently seen focal tracer activity

There is female predominance as compared to males in brown tumor. The incidence increases with age with most cases reported in more than 50 years and greater in postmenopausal women.[7] This may be attributed to hormonal imbalances which may be more common in females than males.[8] The present case was a relatively young 29-year-old female.

Clinical symptoms of brown tumor can be an asymptomatic swelling or a painful exophytic mass with associated symptoms of hypercalcemia ("bony pain/bone fractures, renal stones, abdominal groans and psychic moans"). Our case presented with only bone pain as a symptom of hypercalcemia that may be attributed to slightly raised serum calcium levels above normal (12.4 mg/dl in the present case).

In brown tumors, jaw involvement is rare with mandible is (4.5%) more commonly involved than maxilla.[11,16] Radiographically, brown tumor does not show any characteristic features as it presents as osteolytic lesions. The present case also showed multifocal osteolytic lesions in mandible, skull, pelvis, ribs, spine and tibia [Figure 4]. These bone lesions are explained on the basis of increase in levels of circulatory PTH that lead to increased osteoclastic bone resorption primarily in cortical bone. This may explain why mandible preponderance over maxilla as in the present case.[17]

Various entities benign and malignant can appear as bone expanding or lytic lesions in the facial bones. Most likely differential diagnoses are odontogenic cysts and tumors, infectious diseases (bone abscess and osteomyelitis), metabolic bone disease (HPT), metastasis

from unknown primary, multiple myeloma, primary bone tumor and cysts (simple bone cysts, eosinophilic granuloma, Langerhans cell histiocytosis and giant cell lesions).[16] The present case presented with bone pain and multifocal osteolytic lesions led to radiological differential diagnosis of HPT, multiple myeloma and metastatic carcinoma from unknown primary.

The histopathological picture was similar to other giant cell lesions of jaw [Table 3] thereby excluding multiple myeloma and metastatic carcinoma from an unknown primary. It should be differentiated from other true giant cell tumors of bone, and it represents reparative granuloma rather than a true neoplastic process[18] [Table 3].

There is a familial form of HPT associated with jaw tumors in which the histology of the jaw tumor shows an ossifying fibroma (associated with HRPT2 gene mutation). This can be readily distinguished from brown tumors on histological grounds.[19] Thus, excluding other differentials, PHPT diagnosis was made based on clinical, radiological and biochemical investigations.[5]

Ultrasound, CT scan, or technetium scan techniques can also be used to detect the diseased parathyroid gland.[8] The parathyroid technetium scintiscan is one of the most preferred imaging modalities to localize diseased parathyroid glands prior to surgery.[18] In the present case, parathyroid scintigraphy showed parathyroid adenoma in midline anterior neck.

The treatment of HPT is the first step in the management of brown tumor. There is agreement as to the treatment of choice for PHPT being parathyroidectomy; however, opinions are divided as to the treatment of bone lesions. Authors such as Scott *et al*. believe that bone lesions disappear spontaneously following removal of the diseased parathyroid gland;[20] Martínez-Gavidia *et al*. recommend initial treatment with systemic corticosteroids to reduce the tumor size followed by surgical removal of the residual lesion.[21] In the case of large destructive cysts, or in cases where the lesions continue for more than 6 months, or there is disruption of the function of the affected organ, or growth despite adequate metabolic control, Yamazaki *et al*. recommend curettage and enucleation.[22] In our case, endoscopic removal of the parathyroid mass was done with regular monitoring of serum calcium and PTH levels.

CONCLUSIONS

Although with advancing era, diagnosis of HPT is usually done in the asymptomatic adults on the basis of routine

Table 3: Differential diagnosis of giant cell lesions

Central giant cell lesions	Age	Sex	Site	Clinical features	Radiographic	Histopathology	Serum calcium	Serum phosphorus	Serum ALP
CGCG (nonneoplastic lesion)	<30 years	Female > male	Exclusively in jaws Anterior mandible crossing midline	Asymptomatic, seen during routine radiographic examination, nonaggressive form-painless expansion of affected bone, aggressive form-pain, cortical perforation and root resorption	Expansile, well demarcated, scalloped border, noncorticated multilocular, less commonly unilocular radiolucency	Loose fibrillar connective tissue with many interspersed proliferating fibroblasts, hemosiderin laden macrophages and extravasated RBCs, capillaries-snmall and inconspicuous, multinucleated giant cells are in focal aggregates or patches (zonation phenomenon) or diffusely scattered	N	N	N
Giant cell tumor (osteoclastoma)-benign but locally destructive neoplasm	3rd–4th decade	Male > female	Rare in skull, preferential sites-sphenoid, ethmoid and temporal bones	Pain, swelling and pathological fracture	Radiolucent with poorly defined and irregular margins	Stromal cellularity is prominent, minimal collagen production. Mitotic figures may be found. Giant cells in larger, 40-60 nuclei than CGCG, more homogenous pattern of distribution. May contain inflammatory cells and areas of necrosis but relative absence of hemorrhage and hemosiderin pigment	N	N	N

Contd...

Table 3: Contd...

Central giant cell lesions	Sex	Age	Site	Clinical features	Radiographic	Histopathology	Serum calcium	Serum phosphorus	Serum ALP
PHPT (present case)	Female > male	Old age	Refer to text	Refer to text	Refer to text	Refer to text	↑	↓	N or osteolytic lesions
SHPT	Female > male	Old age	Same as PHPT	Same as PHPT	Same as PHPT	Same as PHPT	↓	↑	N or in osteolytic lesions
Cherubism - An AD disease SH3BP2 mutation on chromosome 4	Female > male	2-4 years, regresses after puberty	Mandible and maxilla	Characteristic renaissance cherub faces with rounded jaws, vertical displacement of orbital floor 'eyes upturned to heaven appearance', Submandibular and cervical lymphadenopathy-common	Bilateral symmetrical multilocular radiolucent lesions in the jaw with thick sclerotic borders. Unerupted teeth -"Floating tooth syndrome"	Numerous giant cells in a collagenous stroma, containing abundant fibroblasts. Perivascular eosinophilic cuffing is specific for the lesion	N	N	N (in active growth period there may be physiological increase in ALP)
Noonan like multiple gaint cell lesion syndrome-AD	-	Congenital anomaly	-	Short stature, craniofacial dysmorphisms and congenital heart defects	Multilocular radiolucency	Numerous giant cells in a collagenous stroma, containing abundant fibroblasts. Perivascular eosinophilic cuffing is specific for the lesion	N	N	N (in active growth period there may be physiological increase in ALP)
Aneurysmal bone cyst	Male=female	<20 years	Nearly every part of skeleton, long bones, vertebral column- common Mandible > maxilla	Painful firm swelling Two clinicopathologic forms: Primary lesion/a secondary lesion (arising in other neoplastic/nonneoplastic osseous conditions)	Multilocular radiolucency with honeycomb or soap bubble appearance, eccentrically ballooned	Cavernous or sinusoidal blood filled spaces without endothelial lining. Giant cells (patchy distribution similar to CGCG) along with varying amounts of hemosiderin pigment are present	-	-	-

↑: Increase downward arrow decrease. ALP: Alkaline phosphatase, CGCG: Central Giant cell granuloma, PHPT: Primary hyperparathyroidism, SHPT: Secondary hyperparathyroidism

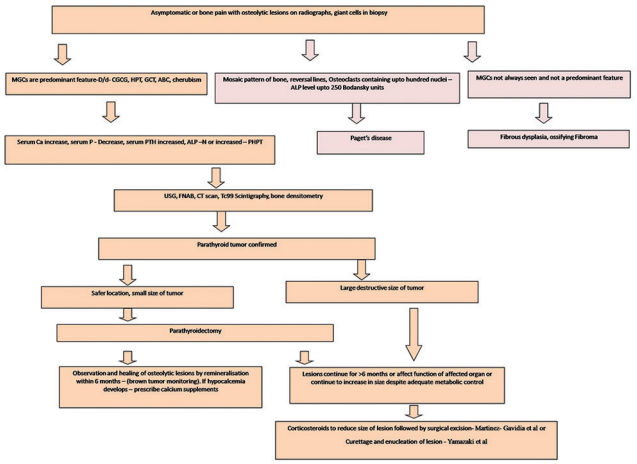

Figure 7: Algorithm for diagnosis and treatment of primary hyperparathyroidism and exclusion of other giant cell lesions

biochemical investigations, however, in rare cases, HPT can present as osteolytic bone lesions. Thus, HPT should be kept in the differential diagnosis of such osteolytic lesions. Further, giant cells in biopsy report must be confronted with the results of the clinical examination, laboratory tests and diagnostic imaging. Otherwise, diagnostic errors or a delay in diagnosis may ensue.

A diagnostic key/approach is shown in Figure 7 when we get osteolytic lesion radiographically and giant cells in biopsy.

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Conflicts of interest

There are no conflicts of interest.

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