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

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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

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. 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. The fourth type is an ectopic variant seen in patients with other malignancies. To understand the pathogenesis of HPT, normal physiology of calcium and phosphorus homeostasis is depicted in Figure 1.

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

Multifocal brown tumor is rare complication of HPT with the prevalence of 0.1% in jaws. These bone lesions are classic skeletal manifestations of HPT, usually seen in severe forms with subperiosteal bone resorption. Brown tumors can affect the long bones, clavicle, scapula, ribs, pelvic bones, mandible, other craniofacial bones and the spine. 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.

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...
Incisional biopsy revealed highly cellular lesional connective tissue 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 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 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)

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)
Gosavi, et al.: Osteolytic lesions as road map to diagnose primary hyperparathyroidism

DISCUSSION

Recklinghausen (1891) was credited with the first description of HPT associated bone changes called osteitis fibrosa cystica. 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. However, Kar et al. has reported 40 cases of generalized bone involvement. Classical skeletal lesions which are bone resorption, bone cysts, brown tumors, generalized osteopenia are seen in <5% of cases. Brown tumor accounts for 10% of all skeletal lesions with a 0.1% incidence in jaws.

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. 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.

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. This may be attributed to hormonal imbalances which may be more common in females than males. 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. 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. 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.

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). 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.[8] [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.[9] Thus, excluding other differentials, PHPT diagnosis was made based on clinical, radiological and biochemical investigations.[8]

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: Contd...

| Central giant cell lesions        | Sex    | Age     | Site                     | Clinical features                                                                 | Radiographic                                      | Histopathology                                                                 | Serum calcium | Serum phosphorus | Serum ALP                                      |
|----------------------------------|--------|---------|--------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------|--------------------------------------------------------------------------------|---------------|------------------|------------------------------------------------|
| PHPT (present case)              | Female | Old age | Refer to text            | Refer to text                                                                      | Refer to text                                    | Refer to text                                                                      | ↑             | ↓                | N or osteolytic lesions                          |
| SHPT                             | male   | Old age | Same as PHPT             | Same as PHPT                                                                       | Same as PHPT                                     | Same as PHPT                                                                       | ↓             | ↑                | N or in osteolytic lesions                        |
| Cherubism - An AD disease        | Female | 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 Short stature, craniofacial dysmorphisms and congenital heart defects | Bilateral symmetrical multicocular radiolucent lesions in the jaw with thick sclerotic borders. Unerupted teeth -“Floating tooth syndrome” Multiocular 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) |
| Noonan like multiple giant cell lesion syndrome-AD | -      | Congenital anomaly       | -                                   | -                                                                                 | -                                               | -                                                                                   | -             | -                | -                                              |
| 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 | -                                                                                   | -             | -                | -                                              |

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