Giant Cell Lesions Associated with Primary Hyperparathyroidism

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Aims and Objective To evaluate the prevalence, clinical features, diagnostic laboratory values and treatment outcome of giant cell lesions (brown tumors) associated with primary hyperparathyroidism (PHPT) in oral and maxillofacial region. **Study Design** A 5 year retrospective data was analyzed wherein all histopathologically proven cases of giant cell lesions involving oral and maxillofacial region were evaluated. Out of these cases, those associated with PHPT were tabulated. Correlation was established with other concomitant clinical features and also with the laboratory values of altered serum calcium, phosphate, alkaline phosphate and parathormone. Follow up of these cases after the correction of PHPT was also noted.

Result Out of 85 cases of histopathologically proven giant cell lesions, five cases were associated with PHPT. There was involvement of maxilla and mandible in one case each. Only frontal bone was involved in two cases. Fifth case had multiple lytic lesions in maxilla and frontal bone. All patients consistently showed very high values of alkaline phosphate and parathormone. Hypercalcemia and hypophosphatemia was noted in four cases. All cases showed regression of the lytic lesion after parathyroidectomy obviating the need for surgical excision of the jaw lesions.

Conclusion Giant cell lesions (brown tumors) associated with PHPT in oral and maxillofacial region are rare clinical entities. The prevalence of PHPT associated giant cell lesions is 5.9 %. They are clinically, radiologically and histopathologically similar to any other peripheral or central giant cell tumor. Relevant history may alert the clinician and altered biochemical values may help in correlating the oral and maxillofacial findings with the underlying systemic disease. At times, the brown tumor maybe the only presenting sign leading to the diagnosis of PHPT.

Keywords Primary hyperparathyroidism · Brown tumor · Parathyroid hormone · Alkaline phosphatase · Giant cell lesion · Hypercalcemia

Introduction

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder [1], with varying clinical presentations, ranging from asymptomatic hypercalcemia detected during a routine biochemical testing to classic manifestations traditionally associated with the disease [2]. PHPT affects many organs, including bone, kidneys, soft tissues, the gastrointestinal tract, and the central nervous system [3]. As a part of systemic manifestation, the odontogenic tissue and the jawbones are also affected. Complete or partial loss of lamina dura (LD) and ground glass appearance of the jaw bones on radiographs are the most common findings [4, 5]. Rarely, lytic lesions in the jaws may present as reparative giant cell granulomas. These are called as brown tumors due to their appearance and are similar to any other giant cell lesion clinically, radiologically and histopathologically [6, 7]. The treatment of choice for a giant cell lesion not associated with PHPT is surgical excision though intralesional steroid

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injections have also been advocated with variable results [8]. But in a similar giant cell lesion associated with PHPT, surgical correction may not be needed or becomes secondary. Recurrence is inevitable when the underlying systemic cause of PHPT is missed or not corrected prior to surgery. The aim of this study was to evaluate the prevalence, clinical features, diagnostic laboratory values and treatment outcome of giant cell lesions (brown tumors) associated with PHPT in oral and maxillofacial region.

Study Design

A 5-year retrospective study was conducted at a single centre wherein 85 histopathological proven cases of giant cell lesion were evaluated for association with PHPT. Out of these 85 cases, details of five cases associated with PHPT were retrieved. History and clinical presentation with radiological features were evaluated and also correlation was established with concomitant clinical features and also with the laboratory values of altered serum calcium, serum phosphate, alkaline phosphatase (AP) and parathormone (PTH). All the five cases were associated with parathyroid adenoma. These cases were followed after curative parathyroidectomy. The patients were routinely put on Calcium and Vitamin D supplement by the Endocrinology unit. Serum calcium (8.6–10.2 mg/dl), inorganic phosphate (2.7–4.5 mg/dl), and alkaline phosphatase (3–13 KAU) were measured by autoanalyzer (Roche diagnostics, Modular P 800). Serum intact PTH (15–65 pg/ml) was measured by chemiluminescence assay (Roche, ELY-CYS 2010) and 25 (OH) D (11.1–42.9 ng/ml) was measured by radio immunoassay using commercially available kits (DiaSorin Inc., Stillwater, MN).

Result

Out of 85 cases of histopathologically proven giant cell lesions, five cases were associated with PHPT (5.9 %). Four were females and the age range was 26–38 years. Single jaw involvement was seen in two cases, one in maxilla and one in mandible. Two cases showed involvement of frontal bone and the fifth case showed multiple lytic lesion in maxilla and frontal bone. Four cases reported to the oral surgery clinic directly with the chief complaint of abnormal growth whereas only one was referred from the department of endocrinology for evaluation of the lesion. All the lesions were slow growing and painless. Three patients had concomitant generalized bone pains and one had a history of renal stones. One patient had hypertension as the only associated feature. All patients showed very high values of PTH and AP. The increased values of serum PTH ranged from 592.6 to

2,075 pg/ml. Similarly serum AP varied from 217.2 to 621.0 KAU. 25-hydroxyvitamin D (25-OHD) showed decreased values in three patients ranging from 10.8 to 44 ng/ml. Hypercalcemia was seen in four out of five cases, the value of serum calcium ranging from 9.6 to 15.5 mg/dl. Serum phosphate showed decreased values in the same four out of five cases, the values ranging from 1.5 to 4.1 mg/dl. All the patients underwent parathyroidectomy which was followed by regression in the size of the lesion. No surgical intervention for maxillofacial lesions was required in any patient (Table 1 with Figs. 1, 2, 3, 4).

Discussion

This study reports a prevalence of 5.9 % of giant cell lesions associated with PHPT. At times the oral and maxillofacial manifestations can be the only presenting feature and the presence of a histologically proven giant cell lesion should alert the maxillofacial surgeon to rule out PHPT. Parathyroidectomy is the primary treatment modality in diagnosed cases of giant cell lesion associated with PHPT. Once the parathyroid hormone levels return to their normal range, there is marked improvement in the osteolytic lesions in context of pain, tenderness and new bone formation.

Earlier we had correlated the osteogenic and odontogenic changes with high levels of AP and PTH. Loss of lamina dura, reduced cortical width of mandible and ground glass appearance of jaw bone on conventional radiographs was related to the severity of PHPT. With high PTH and AP values, absence of LD was more frequent. A moderate rise in PTH or AP did not alter the odontogenic tissue, and thus it appeared that the odontogenic signs and symptoms were manifestation of the advanced stages of PHPT [5].

Brown tumor is a misnomer. It is a non-neoplastic giant cell lesion which is slow growing and locally destructive. Its vascularity, hemorrhage, and deposits of hemosiderin impart the characteristic brown color. It results from direct effect of PTH on bone. PTH is the most important regulator of calcium. It is secreted in response to low serum calcium level. Circulating PTH elevates serum calcium by following methods: (1) stimulates osteoclastic resorption of bone (2) increases conversion of vitamin D to active Vitamin D (1,25-dihydroxycholecalciferol). (3) increases distal tubular reabsorption of calcium. Brown tumor is formed because of an imbalance of osteoclastic and osteoblastic activity causing bone resorption with fibrous replacement of the marrow and thinning of the cortex.

The patients presenting with brown tumors may also be having other signs and symptoms of PHPT. The typical

Table 1 Clinical and radiological features and biochemical values of five patients of giant cell lesions associated with PHPT

S No.	Age/ Sex	Clinical presentation	Relevant history and presentation	Radiology	Laboratory values	Treatment	Follow up (1 year)
1	35/F	Firm oval painless nontender intraoral swelling since 2.5 years (Fig. 1a)	Treatment for renal stones 5–6 years back	Saucer shaped osteolytic defect extending up to the lower border on the left side of mandible in O.P.G. (Fig. 1b)	PTH: 727.7 pg/ml 25-OHD: 11.39 ng/ml AP: 217.17 KAU serum calcium: 9.6 mg/dl serum phosphate: 4.1 mg/dl	Parathyroidectomy	Regression of lytic lesions in the mandible. (Fig. 1c)
2	42/M	Firm painless nontender slow growing firm mass on the left anterior maxillary alveolus since 1 year	Bone pains	CT scan depicts osteolytic mass in the frontal bone (Fig. 2)	PTH: 616.7 pg/ml 25-OHD: 18.5 ng/ml AP: 300 KAU serum calcium: 13.60 mg/dl serum phosphate: 2.4 mg/dl	Parathyroidectomy	Regression of lytic lesions in the maxilla and the frontal bone.
3	38/F	Firm painless nontender slow growing globular mass on the left posterior maxillary alveolus since 2 years (Fig. 3)	Hypertension	Lateral skull radiograph shows oval lytic lesion in left posterior maxilla	PTH: 592.60 pg/ml 25-OHD: 10.8 ng/ml AP: 300.0 KAU serum calcium: 11.20 mg/dl serum phosphate: 2.40 mg/dl	Parathyroidectomy	Reduction in size of alveolar growth
4	33/F	Firm painless slow growing globular mass on the forehead since 3.5 years	Bone pains	A coronal CT scan showing lytic lesion in the frontal bone (Fig. 4a)	PTH: 2,075 pg/ml 25-OHD: 32 ng/ml AP: 621.0 KAU serum calcium: 13.70 mg/dl serum phosphate: 2.0 mg/dl	Parathyroidectomy	Regression of growth on the forehead. (Fig. 4b, c)
5	26/F	Bony swelling in forehead since 2 years	Bone pains	Lateral skull × radiograph showing lytic lesion in the frontal bone	PTH: 1,321.3 pg/ml 25-OHD: 44 ng/ml AP: 329 KAU serum calcium: 15.5 mg/dl serum phosphate: 1.48 mg/dl	Parathyroidectomy	Regression of growth on the forehead

PTH reference range 15–65 pg/ml, 25-OHD reference range 11.1–42.9 ng/ml, AP reference range 3–13 KAU, serum calcium reference range 8.6–10.2 mg/dl, serum phosphate reference range 2.7–4.5 mg/dl

Fig. 1 **a** A giant cell lesion representing as an intraoral mass in the posterior mandible in patient 1 **b** O.P.G. depicting osteolytic lesion (Encircled) **c** O.P.G. depicting regression and calcification of the osteolytic lesion post-treatment in patient 1

Fig. 2 Coronal CT scan depicting an osteolytic lesion in the frontal bone in patient 2

Fig. 3 Intra-oral picture showing a globular firm mass on the buccal cortex in patient 3

pentad of “bones, stones, moans, groans and fatigue overtones” may be visible in variable proportions [9]. Generalized weakness, anemia, abdominal pain because of gastric ulcer, pancreatitis, renal or gall bladder stones are

common features. Osteoporosis, skeletal deformities, pathological fractures may be additional presentations in moderate to severe cases. Detailed history taking should include queries regarding all these conditions. Vitamin D deficiency is endemic in Indian population which seldom shows hypercalcemia. Normocalcemic PHPT is quite common in the subcontinent [10]. Hence abnormal serum calcium level may be misleading. A minimum of three tests for serum calcium at different time intervals should be taken to pick up the disease. Raised AP and PTH are the

Fig. 4 **a** Coronal CT scan showing lytic lesion in the frontal bone in patient 4 **b** Lateral skull view showing the protruding growth in patient 4 **c** Lateral skull view after parathyroidectomy showing complete regression of the growth in patient 4

two significant laboratory tests that must be advised before going for local surgical intervention. An ultrasound of the parathyroid glands followed by a biopsy confirms parathyroid adenoma. Additional radiological finding of reduced cortical width in an O.P.G., loss of LD in a dental radiograph or rarely solitary or multiple lytic lesions may be suggestive of the underlying systemic cause. At times, these accidental findings by a dentist may lead to the diagnosis of PHPT.

The treatment of giant cell lesion not associated with PHPT requires complete excision with low rate of

recurrence. But in case of any giant cell pathology associated with PHPT, surgical excision is a relative contraindication. The main concern of the clinician must be to correct the underlying disease. Parathyroidectomy is the primary treatment modality in diagnosed cases of PHPT. Once the parathyroid hormone levels return to their normal range, there is marked improvement in the osteolytic lesions in context of pain, tenderness and new bone formation. None of the cases in our series required surgery for the jaw lesions.

To our knowledge, this is first indian study to analyze the prevalence of brown tumor in oral and maxillofacial region in a contemporary population. We conclude that each case of histopathologically proven giant cell lesions should be screened for PHPT. It is important to be aware of endocrine cause of these common clinical and radiological features to avoid unnecessary local surgical intervention.

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