Osteitis fibrosa cystica of mandible in hyperparathyroidism-jaw tumor syndrome: A rare presentation and review of literature

ABSTRACT
Brown's tumor, also referred as osteitis fibrosa cystica is a rare nonneoplastic diagnostically challenging consequence of hyperparathyroidism (HPT) which occurs due to increased parathormone secretions in blood, causing excessive calcium resorption from kidneys, bone resorption, and phosphaturia. Brown's tumor is a misnomer, presenting as cystic expansile lesions in bone, often misdiagnosed as neoplastic lesion or granuloma or abscess in bones. It can affect long bones, clavicle, ribs, and pelvis. According to literature, skeletal manifestations of Brown tumor is relatively rare and occurs in <2% of the cases of HPT. We present a case of a female 15-year-old patient who presented with bleeding gums and an expansile lesion in mandible whose previous investigations elsewhere suggested a malignant lesion. However, further investigations revealed it to be Brown’s tumor with primary HPT which is a rare genetic disorder, known as HPT-Jaw Tumor Syndrome (HPT-JT).

Keywords: Brown tumor, hyperparathyroidism jaw tumor, mandible, parathormone

INTRODUCTION

Parathyroids are four in number situated behind the thyroid gland. The function of Parathyroid hormone (PTH) is to maintain a proper calcium balance in the bloodstream and in tissues. PTH interacts with Vitamin D and its metabolites to regulate calcium absorption and excretion. Hyperparathyroidism (HPT) is a pathological condition characterised by elevated levels of parathormone in the blood due to overactivity of one or more parathyroid glands.[1] Primary lesion in parathyroid with excessive PTH secretion resulting into high PTH and high calcium is called primary HPT. Secondary HPT is due to Vitamin D deficiency or chronic renal failure, with high PTH and low calcium. Tertiary is with autonomic PTH secretion leading to high PTH and high calcium, with a history of chronic renal failure.[2] HPT caused by parathyroid adenoma causing increased osteoclastic activity in skeletal system presents as osteitis fibrosa cystica also known as Von Recklinghausen’s disease of bone. HPT can also present as a part of multiple endocrine neoplasia (MEN) I, IIA, and IIIb.[3]

Most of the patients with HPT remain asymptomatic and presents as an incidental diagnosis on biochemical testing with hypophosphatemia, hypercalcemia, and increased alkaline phosphatase levels in the blood.[1]

Brown tumor is a benign intraosseous, nonneoplastic lesion consisting of cellular fibrous tissue with multiple foci of mononuclear stromal cells mixed with hemorrhagic infiltrates, aggregations of multinucleated giant cells, hemosiderin deposits and occasionally trabeculae of woven bone. Radiologically, they present as solitary or multilocular soap bubble-like bone expanding radiolucencies.[3]
reported prevalence of Brown tumor is 0.1% with male:female ratio of 1:3 in age group <30 years. Its rare in facial bones but more common in the mandible than the maxilla.\textsuperscript{[4]} They mainly occur in patients with secondary HPT with renal insufficiency, and calcium malabsorption in facial bones, clavicle, ribs, pelvis, and femur are affected. Primary HPT with ossifying fibroma of the jaw, which represents HPT-Jaw Tumor syndrome (HPT-JT) is a rare variant.\textsuperscript{[5,6]}

We present a case report of a 15-year-old female with fibro-ossifying tumors of the mandible and multiple lytic lesions in skull, humerus, pelvis, femur, and other long bones with severe HPT.

CASE REPORT

A 15-year-old female patient referred from elsewhere was admitted in otorhinolaryngology department with slightly painful swelling in left side of the lower jaw, and bleeding from gums while brushing for the past 2 months. There was a history of abdominal pains with nausea, pain in limbs, and back every now and then for the last 3 years. She started limping in the past 2–3 months. There was no history of peptic ulcers, fractures, vitamin and calcium supplementation intake, urolithiasis, or any exposure to radiations.

On physical examination, there was a large 8 cm × 5 cm × 3 cm firm, slightly tender swelling in the left side of the mandible with the widening of the alveolar process. On palpation, no egg shell crackling was noted. On neck examination, no clinically palpable cervical lymph node detected. Rest of systemic examinations was normal [Figure 1].

Blood tests demonstrated haemoglobin (14.1), total count (8580), elevated intact S. PTH (2269 pg/ml), raised S. Calcium (12.3 mg/dl), raised S. Alkaline Phosphatase (3319U/L), low Vitamin D3 (10.63 ng/ml), normal S. Prolactin (12.86 ng/ml) and normal S. Phosphorus (19.4). Urine calcium concentration was normal, 24 h urine for Phosphorus was low (291 mg/24 h), creatinine in urine was also low (408 mg/24 h).

- Fine-needle aspiration cytology showed: profuse Giant cells rich lesion-Giant cell reparative granuloma or Giant cell tumor of bone with scanty pus cells, no organism, acid-fast bacteria negative
- On HPE: vascularized fibrous tissue in vague storiform pattern, bony spicules and numerous osteoclastic cells with areas of hemorrhage and extravasated RBCs consistent with Brown tumor of HPT
- Contrast-enhanced computed tomography (CT) Face revealed: large destructive expansile lesion involving mandible-well defined, 7.0 cm × 5.2 cm × 5.0 cm with soap bubble appearance involving 2/3rd of the left side of body of mandible up to first molar tooth, to right side up to canine, medially involving the left genioglossus muscle with early obscuration of sublingual space [Figure 2]. Diffuse ground glass opacity in skull vault with lytic and sclerotic foci in vertebrae and head of left humerus
- X-ray skeletal survey: lytic with sclerotic lesions seen at the end of long bones with early deformity. Possible sclerosis seen on both SI joint. Bowing of both humeral neck regions
- USG Neck: Cystic SOL in left side of mandible and a possible cervicle lymph node near inferior part of left lobe of thyroid
- Sestamibi scan: left inferior parathyroid adenoma
- USG whole abdomen showed: Normal study.

She was initially on conservative management for treatment of HPT, MEN I was ruled out after consultation with Endocrinologist and Orthopaedic surgeon. Left parathyroid adenoma which was 2 cm × 1 cm in size was excised [Figure 3]. Preexcision serum PTH level was 1472 pg/mL, whereas, intraoperatively, postexcision level came to be 248 pg/mL.

After surgery, patient was on conservative management and advised for regular follow-up. Six months after initial management the patient had a minimal external deformity, no systemic manifestation and improved quality of life [Figures 4 and 5]. Repeat CT scan was done after 6 months and again after 1 year, [Figures 6 and 7] showing significant reduction of size of the lesion although complete bone remodeling will still take time.

DISCUSSION

Different bone expanding giant cell lesions that can arise in jaw bones include odontogenic cysts and tumors,
i.e., periodontal cyst, radicular cyst, or ameloblastoma, infectious diseases such as osteomyelitis or bone abscess, primary bone tumors, and cysts such as giant cell reparative granuloma or myxoma or simple bone cysts or odontogenic fibromas, metabolic bone disease, i.e., HPT or metastasis from a known or unknown primary such as lung, breast, kidney, or prostate.

Excessive PTH secretion causes osteoclastic activity to exceed the osteoblastic activity resulting into bone resorption, intraosseous bleeding and tissue degeneration, with the formation of a cystic lesion filled with hemosiderin loaded macrophages, giant cells, and fibroblasts. Hemosiderin deposits, hemorrhages and vascularization results into color and name BROWN TUMOR. It is difficult to differentiate brown tumor from any other jaw bone expansile lesion on the basis of histopathology or radiology, but the clinical correlation with HPT favours the diagnosis.

Histopathologically, it is very difficult to differentiate it from giant cell reparative granuloma, fibrous dysplasia or true giant cell tumors. Giant cell reparative granuloma is a localized lesion occurring mainly in young females but without HPT. True giant cell tumors will be more infiltrative and with some degree of cellular atypia histologically. Infectious diseases and other local cysts will also be localized and will lack the features of HPT.

Ossifying fibroma of the jaw (brown tumor) with primary HPT, as in our case, is a relatively rare autosomal dominant disorder with incomplete penetrance and variable expressions and is known as HPT-JT. Pathogenesis of HPT-JT involves an activation of HRPT2 gene (located on 1q25) which codes for a 531 amino acid protein called parafibromin. Tumor suppressor role is also suggested here for the allelic loss of 1q24–q32. There is reduced penetrance in females. HPTJT which is considered more aggressive as compared to sporadic HPT due to the risk of developing parathyroid carcinomas (10%–15% of affected individuals) and frequent
multiglandular involvement. Single gland involvement occurs in 89% of cases. Treatment for HRPT2 related HPT is surgery. Radiologically, the unique parathyroid lesion is excised and so is a grossly enlarged gland. Recurrent cases need revision surgery. Single gland disease may also be confirmed by intraoperative PTH assay which should decrease by more than 50% in 10 min after excision. Long-term follow-ups in these patients is mandatory.

Brown tumors usually regress after normalization of S. PTH levels. Cystic brown tumors will not show radiographic ossification after parathyroidectomy. Bone lesion need not to be operated on. There are possibilities of remodelling after normocalcemia level is achieved, but in case of persistent bony lesion even after 6 months of metabolic control, curettage and enucleation is recommended.[13]

CONCLUSION

Primary HPT with Vitamin D deficiency, hypercalcemia and brown tumor in mandible-HPT-JT syndrome is a relatively rare now, especially after recent improvements in analytical technologies which usually detects HPT in asymptomatic stage. At present, in Asian population, Primary HPT is three times more common than diabetes mellitus. It’s presentation as osteitis fibrosa cystica is rarer, <2% of the population. Serum PTH level and levels of Vitamin D3, calcium, phosphorus, and alkaline phosphatase in blood is mandatory for planning management of any bone expansile lesion cases. Excision of parathyroid adenoma and achievement of normocalcemic level with long-term follow-ups proves to be the treatment of choice in these cases. Curettage and enucleation should be considered in cases where primary bone lesion expands or does not regress even after 6 months of primary management.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the author.

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 initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Rosenberg EH, Guralnick WC. Hyperparathyroidism: A review of 220 proved cases, with special emphasis on findings in the jaw. Oral Surg Oral Med Oral Pathol 1962;15:84-94.
2. Ahmed R, Ahmed JM. Primary secondary, tertiary hyperparathyroidism. Otolaryngol Clin North Am 1996;17:407-10.
3. Som PM, Lawson W, Cohen BA. Giant-cell lesions of the facial bones. Radiology 1983;147:129-34.
4. Whitaker SB, Waldron CA. Central giant cell lesions of the jaws. A clinical, radiologic, and histopathologic study. Oral Surg Oral Med Oral Pathol 1993;75:199-208.
5. Proimos E, Chimona TS, Tamiolakis D, Tzanakakis MG, Papadakis CE. Brown tumor of the maxillary sinus in a patient with primary hyperparathyroidism: A case report. J Med Case Rep 2009;3:7495.
6. Okada H, Davies JE, Yamamoto H. Brown tumor of the maxilla in a patient with secondary hyperparathyroidism: A case study involving immunohistochemistry and electron microscopy. J Oral Maxillofac Surg 2000;58:233-8.
7. Keyser JS, Postma GN. Brown tumor of the mandible. Am J Otolaryngol 1996;17:407-10.
8. Merz MN, Massich DD, Marsh W, Schuller DE. Hyperparathyroidism presenting as brown tumor of the maxilla. Am J Otolaryngol 2002;23:173-6.

9. Kar DK, Gupta SK, Agarwal A, Mishra SK. Brown tumor of the palate and mandible in association with primary hyperparathyroidism. J Oral Maxillofac Surg 2001;59:1352-4.

10. Teh BT, Färnebo F, Twigg S, Höög A, Kytölä S, Korpi-Hyövölä E, et al. Familial isolated hyperparathyroidism maps to the hyperparathyroidism-jaw tumor locus in 1q21-q32 in a subset of families. J Clin Endocrinol Metab 1998;83:2114-20.

11. Carpten JD, Robbins CM, Villablanca A, Forsberg L, Presciuttini S, Bailey-Wilson J, et al. HRPT2, encoding parafibromin, is mutated in hyperparathyroidism - jaw tumor syndrome. Nat Genet 2002;32:676-80.

12. Yamazaki H, Ota Y, Aoki T, Karakida K. Brown tumor of the maxilla and mandible: Progressive mandibular brown tumor after removal of parathyroid adenoma. J Oral Maxillofac Surg 2003;61:719-22.