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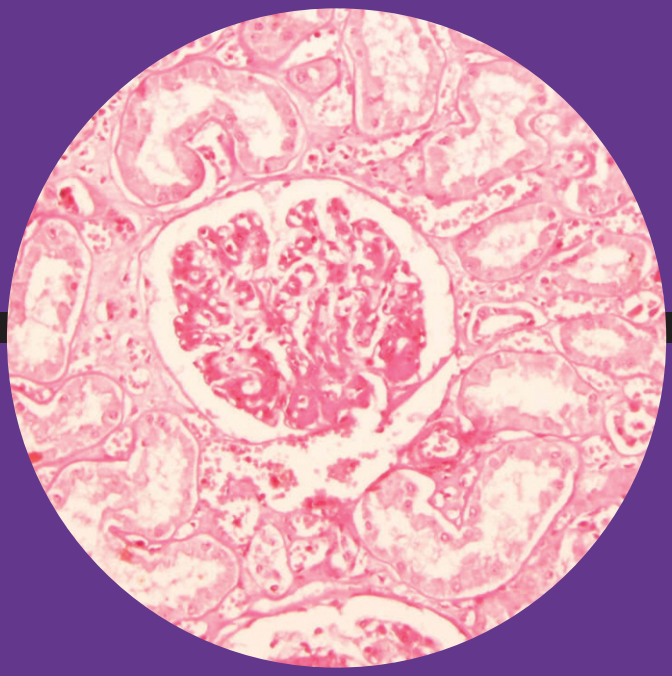

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Case Report

Brown tumor in mandible as a first sign of vitamin D deficiency: A rare case report and review

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ABSTRACT

Central giant cell granulomas (CGCGs) are uncommon but the most aggressive benign intraosseous tumors of jaws, with an unpredictable outcome. They account for less than 7% of all benign jaw lesions, with a female to male ratio of about 2:1. The classical "brown tumor" is commonly seen in the long bones, pelvis, and ribs. Facial bone involvement is rare and usually appears as solitary or multilocular soap bubble like radiolucencies. CGCGs are traditionally treated by both surgical and intralesional injection, with a variable recurrence rate. Here, we report a 12-year-old female patient with mandibular brown tumor as a first sign of secondary hyperthyroidism induced due to vitamin D deficiency and hypocalcemia.

Key words: Brown tumor, intraosseous lesions, secondary hyperparathyroidism, vitamin D deficiency

Introduction

Central giant cell granuloma (CGCG), first described by Jaffe in 1953,[1] is a benign intraosseous lesion consisting of cellular fibrous tissue that contains multiple foci of hemorrhage, aggregations of multinucleated giant cells, and occasionally trabeculae of woven bone that usually involves mandible than maxilla (2:1) before the age of 30 years.[2,3] Occurrences in other facial bones, such as the sphenoid and temporal, as well as in hand, foot, and humerus, have also been reported.[4-6] A clinically and histologically similar lesion occurs as a result of increased parathyroid hormone (PTH) levels which cause an imbalance between osteoclastic–osteoblastic homeostasis and calcium–phosphate regulation, leading to bone resorption with fibrous replacement of the marrow and thinning of the cortex.[7] Excessive PTH secretion may be due to problems in the glands themselves, in which case it is referred to as primary hyperparathryroidism and which leads to hypercalcemia. It may also occur in response to low calcium levels, as encountered in various situations such as vitamin D deficiency or chronic kidney disease; this is referred to as secondary hyperparathyroidism. Tertiary hyperparathyroidism has a high PTH and high serum calcium. It is differentiated from primary hyperparathyroidism by a history of chronic kidney failure and secondary hyperparathyroidism, as continuous stimulation of the parathyroids may result in adenoma formation and autonomous PTH secretion.

Often, multiple CGCGs are found to be associated with hyperparathyroidism.[8] There are no clinical, histological, cytometric, or immunohistochemical differences between the aggressive and nonaggressive CGCGs, and it is found that the giant cell tumors (GCTs) of long bones and the central giant cell tumors (CGCG) of jaws may be just variants of the same disease entity, with age- and site-specific features.[9]

In all cases, the raised PTH levels are harmful to bone and treatment is often needed. Recent evidence suggests that vitamin D deficiency/insufficiency plays a role in the development of hyperparathyroidism.[10] Here, we report on a rare case of vitamin D malabsorption and secondary hyperparathyroidism, presenting as an asymptomatic brown tumor of mandible, treated conservatively.

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Case Report

A 12-year-old female patient reported with the chief complaint of swelling in the right mandibular angle region since 8 months [Figure 1]. The swelling was slowly growing, bony hard in consistency, and not associated with any symptoms, non-tender, and not mobile. There were no neurosensory deficits or cervical lymphadenopathy evident. Mouth opening was normal with full complement of teeth present except third molars. Diffuse obliteration of right mandibular buccal vestibule, retromolar trigone, and expansion of lingual cortex distal to mandibular right second molar was evident. None of the mandibular right quadrant teeth were tender or mobile. All mandibular teeth were vital. Radiograph revealed tooth bud of third molar, unilocular radiolucency extending from apical and distal of mandibular right second molar to ramus, with sclerotic border at the body region anteriorly and scalloped at the ramus, expanded, leaving thin cortices toward the lower and posterior border of mandible, the third molar apparently pushed upward when compared with the left mandibular third molar, and no evidence of root resorption [Figure 2]. Fine needle aspiration cytology (FNAC) was done with positive aspiration of little frothy appearing blood. Meanwhile, an open curettage biopsy was performed and sent for histopathologic evaluation. The histopathology reported it as CGCG with sections showing fibrocellular connective tissue stroma with numerous plump fibroblasts and multinucleated giant cells, few osteoblasts, and numerous blood vessels [Figure 3].

Considering the histological diagnosis of a giant cell lesion, the patient was subjected for PTH estimation, renal function tests (RFT), and complete blood investigation. The PTH was 635.5 (14.0−72.0) pg/ml, alkaline phosphatase 421 (33−96) U/l, total calcium 7.8 (8.7−10.2) mg/dl and phosphorous was 4.10 (2.5−4.3) mg/dl. Complete skeletal radiographs ruled out the presence of any bony lesions. Serum Vitamin D was not measured due to resource limitations. The patient was treated conservatively with surgical debridement alone using modified Brosch's procedure, sacrificing the third molar and preserving the inferior alveolar nerve [Figure 4], followed by maxillo-

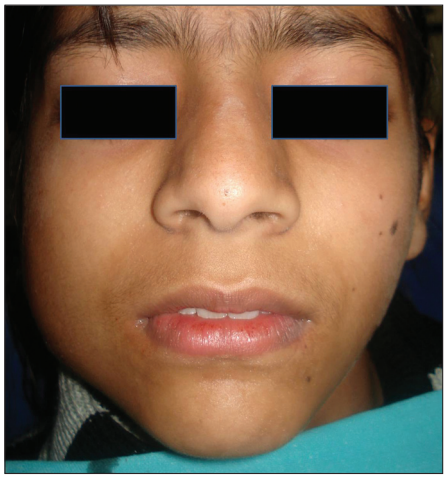


Figure 1: Preoperative view – swelling at the right mandibular angle region

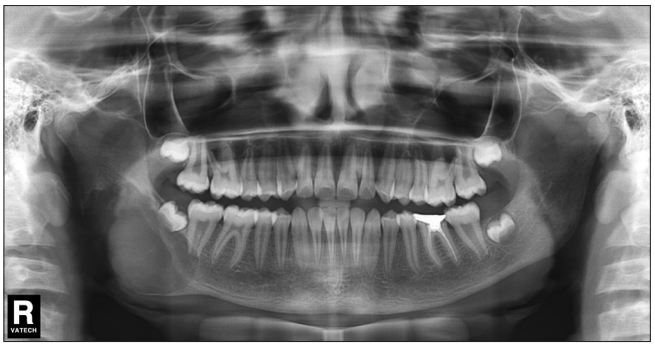


Figure 2: Pre op orthopantomogram showing radiolucency at right angle and ramus of mandible with upward displacement of third molar bud

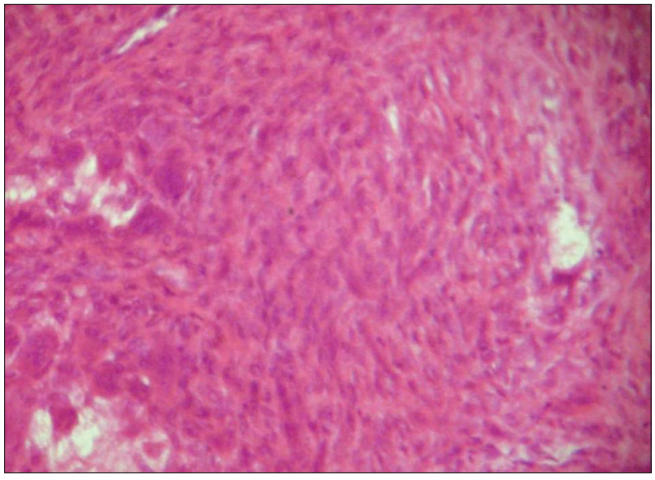


Figure 3: Histopathology showing fibrocellular connective tissue stroma with fibroblasts, giant cells, osteoblasts and blood vessels

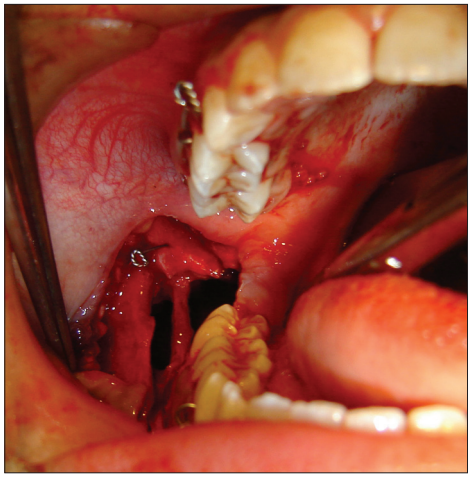


Figure 4: Intra operative view showing post debridement site using Brosch procedure and preserved inferior alveolar nerve

mandibular fixation for 6 weeks. On endocrinologist's reference, the patient was diagnosed to be suffering from hypocalcemia/secondary hyperparathyroidism, the cause being nutritional or vitamin D deficiency. She was advised Tab. calcium carbonate, chewable, thrice daily, with cholecalciferol sachet 60 000 U once a week, after a stat dose of Inj. Arachitol 6 lakh unit along with calcium rich diet, and suggestion to increase sunshine exposure through outdoor activities.

The patient was reviewed 6 months postoperatively, and a series of immediate, 2-week, 8-week, and 6-month post-op radiographs [Figures 5a-c] showed satisfactory evidence of bone formation. A repeat blood examination reported PTH as 27 (14.0−72.0) pg/ml, total calcium as 9.7 mg% (8.7−10.2 mg/dl), phosphorous to be 4.5 mg% (2.5−4.3 mg/dl), and alkaline phosphatase activity as 212 (33−96) U/l, and clinically no neurological deficits were present.

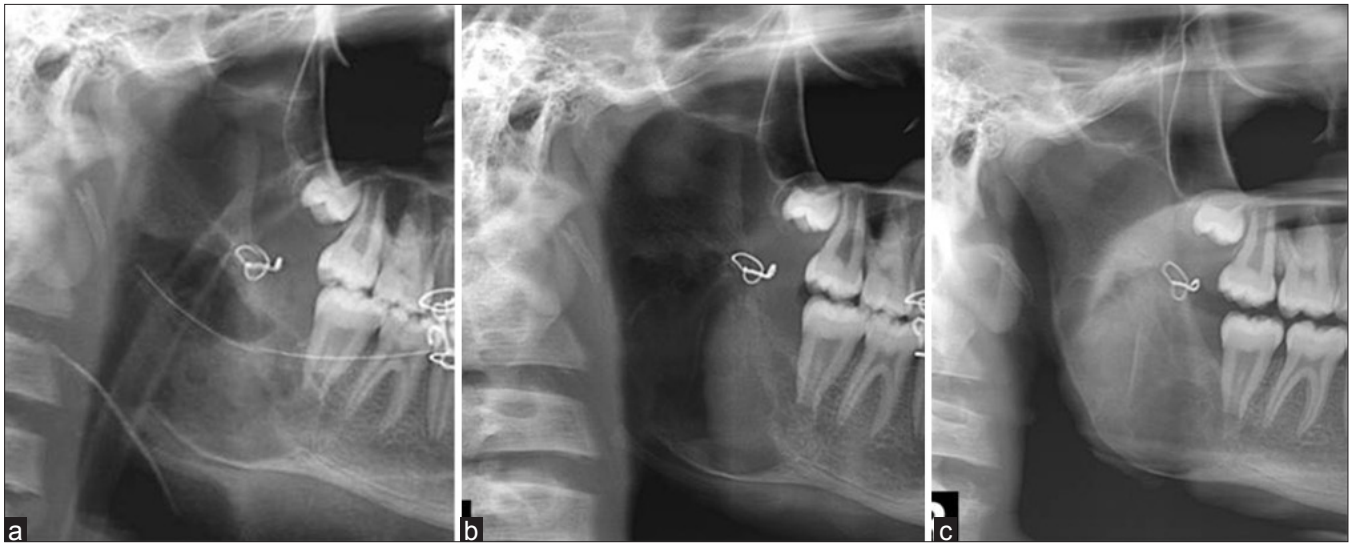
Discussion

The parathyroid glands, situated behind the thyroid, are not regulated by the pituitary gland, but respond directly to changes in serum ionized calcium concentrations. PTH is a single-chain polypeptide of 84 amino acids, which is synthesized by the chief cells and released in response to a fall in serum ionized calcium concentration. This hormone interacts with vitamin D and its metabolites in regulating calcium absorption and excretion. PTH has direct effects which promote reabsorption of calcium from renal tubules and also has indirect effects, mediated by increased conversion of 25-hydroxycholecalciferol (i.e. vitamin D) to the more potent hormone 1,25-dihydroxycholecalciferol, which results in increased calcium absorption from food and enhanced mobilization of calcium from bone [Figure 6].

Vitamin D deficiency can be caused by conditions that result in little exposure to sunlight, such as living in northern latitudes, dark skin, infants or elders having less chance to go outside, and covering one's face and body mainly due to religious reasons. Particularly, women may acquire vitamin D deficiency, even though they live in a sunny climate.

PTH plays a central role in regulating calcium homeostasis because vitamin D and dietary calcium are rarely deficient. Moreover, 99% of the total body calcium is in bone, but this pool is in dynamic equilibrium with the extracellular fluid by processes of bone resorption and deposition. The initial effect of PTH on bone is to stimulate osteolysis, returning calcium from bone to extracellular fluid. Prolonged exposure of bone to PTH is associated with increased osteoclastic activity, extensive bone remodeling, and osteoblastic repair. In some species, calcitonin, a hormone secreted from the parafollicular C cells of the thyroid gland, also regulates calcium metabolism. However, although calcitonin is a useful tumor marker in medullary carcinoma of thyroid, it is of no clinical relevance to calcium homeostasis in humans.

It is customary to distinguish three categories of hyperparathyroidism [Table 1]. In *primary hyperparathyroidism*, there is usually autonomous secretion of PTH by a single parathyroid adenoma varying in size from a few millimeters to several centimeters in diameter, and seen in postmenopausal women. Rare causes include carcinoma of the parathyroids. *Secondary hyperparathyroidism* is present when there is hyperplasia



Figures 5: (a-c) composite picture showing Immediate/8weeks/6months postoperative orthopantomogram

with increased PTH secretion in an attempt to compensate for prolonged hypocalcemia caused by chronic renal failure or prolonged dialysis, or severe malabsorption. In a very small proportion of cases of secondary hyperparathyroidism, continuous stimulation of the parathyroids may result in adenoma formation and autonomous PTH secretion. This is known as *tertiary hyperparathyroidism*.[11,12]

Primary hyperparathyroidism is the most common of the parathyroid disorders, with a prevalence of about 1 in 800. It is 2–3 times more common in women than men and 90% of the patients are over 50 years of age. It also occurs in all of the familial multiple endocrine neoplasia syndromes. The incidence of primary hyperparathyroidism is 0.2% in patients older than 60 years and the estimated prevalence is over 1%, including undiscovered symptomatic patients. [11,13] In the present case, primary hyperparathyroidism was ruled out by the absence of adenoma or a glandular hyperplasia.

The various reasons are listed out [Table 2], which need to be considered as the differential diagnosis in hypocalcemia.[12] Subtotal thyroidectomy for Graves' disease causes transient hypocalcemia in 10% of patients, 12–36 hours following surgery. Idiopathic hypoparathyroidism may develop at any age, and is sometimes associated with autoimmune disease of the adrenal, thyroid, or ovary, especially in young people. Pseudohypoparathyroidism is usually an autosomal dominant syndrome in which there is tissue resistance to the effects of PTH. The PTH receptor is normal, but there is a defective post-receptor mechanism. In our patient, the lack of dietary calcium and vitamin D deficiency activated the excessive secretion of PTH, which then is known to mobilize calcium from body skeleton, and in the case discussed here, the mandible was involved.

Table 1: Classification of hyperparathyroidism

Type	Serum calcium	Parathyroid hormone
Primary	Raised	Not suppressed
Single adenoma (90%)		
Multiple adenomata (4%)		
Nodular hyperplasia (5%)		
Carcinoma (1%)		
Secondary	Low	Raised
Chronic renal failure		
Malabsorption		
Osteomalacia & rickets		
Tertiary	Raised	Not suppressed

An increased PTH level in the patient created imbalance in osteoclastic-osteoblastic homeostasis and calcium–phosphorous regulation [Figure 7], which presented as CGCG of mandible as a first sign of hyperparathyroidism, which is rare. However, brown tumors in the mandible are diagnosed in 4% of all cases of hyperparathyroidism. The true incidence and prevalence of brown tumor, however, must be higher and the most likely explanation is that in most patients, the jaw lesions are never diagnosed and will spontaneously disappear when the PTH and calcium levels are corrected.[7]

The recurrence rate of CGCGs after initial conservative surgical therapy (curettage) is reported as 12−37%; repeat curettage usually prevents further recurrence.[14] But in cases of vitamin D deficiency and secondary hyperparathyroidism, the lesion usually resolves after surgical debridement and replacement therapy.[10]

Rubio *et al*.[15] treated two cases with enucleation which included removal of teeth involved in the lesion and the surgical site treated with tricloroacetic acid 50% and cryosurgery, and bone stabilized using reconstruction plate. Bone regeneration has been excellent as the ages of patients were 26 and 9 years, respectively.

Other treatment modalities tried for treating CGCG include intralesional injection of corticosteroids,[16-19] calcitonin,[20-22] cryotherapy,[15] antiangiogenic therapy with interferons.[23,24] In a recent review of literature by Lang *et al*.,[25] they tested the RANK and RANKL (an essential cytokine for

Table 2: Differential diagnosis for hypocalcemia

	Total serum calcium concentration	Ionized serum calcium concentration	Serum phosphate concentration	Serum parathyroid hormone concentration
Hypoalbuminaemia	↓	→	→	→
Alkalosis	→	↓	→	↑
Respiratory, e.g. hyperventillation				
Metabolic, e.g. Conn's syndrome				
Vitamin D deficiency	↓	↓	↓	→ or ↑
Chronic renal failure	↓	↓	↑	↑
Hypoparathyroidism	↓	↓	↑	↑
Post-surgical				
Idiopathic				
Infantile				
Pseudohypoparathyroidism	↓	↓	↑	↑
Acute pancreatitis	↓	↓	→ or ↓	↑

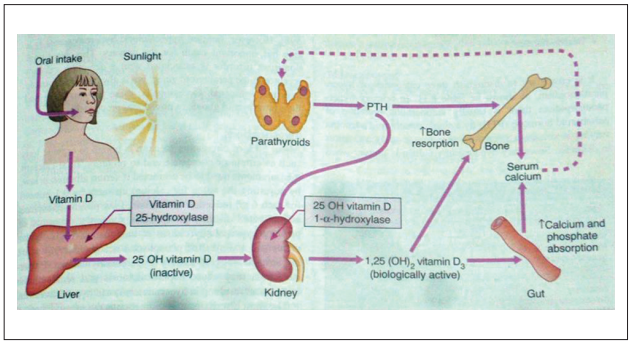


Figure 6: Normal functioning of parathyroid glands

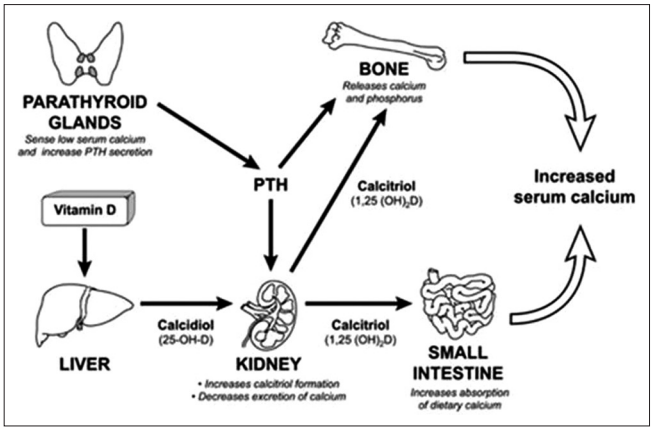


Figure 7: Effect of increased parathyroid hormone and homeostasis

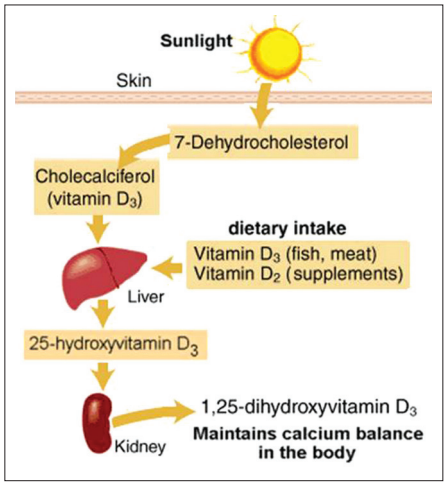


Figure 8: Vitamin D synthesis

osteoclastogenesis, demonstrated in CGCG) inhibitors such as osteoprotegrin (OPG) and monoclonal antibody to RANKL, AMG 162, with promising results when tried with caution. Theoretically, OPG/AMG 162 and calcitonin could be synergistic since OPG/AMG 162 inhibits the formation of osteoclast-like cells, while calcitonin hampers their function. Since RANK and RANKL modulate NF-kappa-B activity, which has a key role in regulation of the immune response, cell growth, differentiation, and apoptosis, the side effects, especially in systemic treatment, warrant careful attention. *Imatinib*, a protein tyrosine kinase inhibitor used to treat chronic myeloid leukemia (CML) and gastrointestinal stromal tumors, is found to be an effective anti-osteolytic agent and could therefore be useful in the treatment of skeletal disease involving excessive osteoclast activity, such as CGCG.[25]

Based on clinical, radiological, and histopathologic findings[26,27] of our patient, we categorized the condition under nonaggressive type of CGCG and decided for conservative treatment. A modified Brosch's procedure[28,29] was performed with lateral mandibular cortex based on the periosteum and thorough surgical debridement was done. The ramus was stabilized using a 24-G wire and water-tight closure achieved with a tube drain in place. The patient was put on maxilla–mandibular fixation for 6 weeks and started on medical line of treatment as described above [Figure 8]. A 6-month postoperative PTH assay, calcium, phosphorous, and alkaline phosphatase levels showed remarkably reduced values, with homogenous bone opacification at the ramus and body regions.

Conclusion

Vitamin D deficiency, secondary hyperparathyroidism, hypocalcemia, and CGCG as a first presentation in the mandible is relatively a rare combination reported in the literature. There is a possibility of spontaneous regression of lesion once the deficiency is corrected, which could be the reason for less number of reports in the literature. A parathyroid estimation, calcium and phosphorous, alkaline phosphatase levels should be made a mandatory investigation in all cases of CGCG. Though the case treated with conservative surgical debridement and replacement therapy yielded satisfactory results in 6 months, long-term follow-up is necessary to understand the tumor behavior.

References

1. Jaffe HL. Giant-cell reparative granuloma, traumatic bone cyst, and fibrous (fibro-osseous) dysplasia of the jaw bones. Oral Surg 1953;6:159-75.
2. Whitaker SB, Waldron CA. Central giant cell lesions of the jaws. Oral Surg Oral Med Oral Pathol 1993;75:199-208.
3. Stavropoulos F, Katz J. Central giant cell granulomas: A systematic review of the radiographic characteristics with the addition of 20 new cases. Dentomaxillofac Radiol 2003;31:213-7.
4. Ratner V, Dorfman HD. Giant cell reparative granuloma of the hand and foot bones. Clin Orthop 1990;260:251-8.
5. Shafer WG, Hine MK, Levy BM, editors. A text book of oral pathology. New York: Saunders; 1983. p. 146-9.
6. Thomas IH, Chow CW, Cole WG. Giant cell reparative granuloma of the humerus. J Pediatr Orthop 1988;8:596-8.
7. Lange DJ, Akker HP. Clinical and radiological features of central

giant-cell lesions of the jaw. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;99:464-70.
8. Ardekian L, Manor R, Peled M, Laufer D. Bilateral central giant cell granulomas in a patient with neurofibromatosis: Report of a case and review of the literature. J oral Maxillofac Surg 1999;57:869-72.
9. Aragão Mdo S, Piva MR, Nonaka CF, Freitas Rde A, de Souza LB, Pinto LP. Central giant cell granuloma of the jaws and giant cell tumor of long bones: An immunohistochemical comparative study. J Appl Oral Sci 2007;15:310-6.
10. Zink AR, Panzer S, Fesq-Martin M, Burger-Heinrich E, Wahl J, Nerlich AG. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: Consequences for bone loss and fractures and therapeutic implications. Endocr Rev 2001;22:477-501.
11. Rosenberg EH, Guralnick WC. Hyperparathyroidism, A review of 220 proved cases with special emphasis on findings in the jaws. Oral Surg Oral Med Oral Pathol 1962;15 Suppl 2:84-94.
12. Haslett C, Chilvers ER, Hunter JA, Boon NA. Davidson's Principles and Practice of Medicine. 18th ed. Churchil Livingstone; 2000. p. 575-9.
13. Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL. Harrison's Principles of Internal Medicine. 15th ed. New York: McGraw Hill; 2001. p. 2209-13.
14. Greenberg MS, Glick M. 10th ed. Burkets Oral Medicine Diagnosis and Treatment. BC Decker Inc.; 2003. p. 143.
15. Rubio E, Pezza V, Ratinoff M, Giannunzio G, Ferreria JL. Central giant cell granuloma-A conservative approach. Int J Oral Maxillofac Surg 1997;26:89.
16. Kremer C, Millesi W, Watzke M. Local injections of corticosteroids for central giant cell granuloma. Int J Oral Maxillofac Surg 1994;23:366-8.
17. Carlos R, Sedano HO. Intralesional corticosteroids as an alternative treatment for central giant cell granuloma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;93:161-6.
18. Abdo EN, Alves LC, Rodrigues AS, Mesquita RA, Gomez RS. Treatment of a central giant cell granuloma with intralesional corticosteroid. Br J Oral Maxillofac Surg 2005;43:74-6.
19. Vered M, Buchner A, Dayan D. Immunohistochemical expression of glucocorticoid and Calcitonin receptors as a tool for selecting therapeutic approach in central giant cell granuloma of the jaw bones. Int J Oral Maxillofac Surg 2006;35:756-60.
20. Harris M. Central giant cell granulomas of the jaws regress with Calcitonin therapy. Br J Oral Maxillofac Surg 1993;31:89-94.
21. Dominguez CL, Martinez GC, Plasencia DJ, Suner M. Intranasal Calcitonin therapy for central giant cell granuloma. J Craniomaxillofac Surg 2004;32:244-5.
22. Lange JD, van den Akker HP, Zanten GO, Engelshove HA, Berg H, Klip H. Calcitonin therapy in central giant cell granuloma of the jaw: A randomized double-blind placebo-control study. Int J Oral Maxillofac Surg 2006;35:791-5.
23. Kaban LB, Troulis MJ, Ebb D, August M, Hornicek FJ, Dodson TB. Antiangiogenic therapy with interferon alpha for giant cell lesions of the jaws. J Oral Maxillofac Surg 2002;60:1103-11.
24. Lange JD, van den Akker HP, Van den Berg H, Richel DJ, Gortzak RA. Limited regression of central giant cell granuloma by interferon alpha after failed Calcitonin therapy: A report of two cases. Int J Oral Maxillofac Surg 2006;35:865-9.
25. Lange JD, van den Akker HP, van den Berg H. Central giant cell granuloma of the jaw: A review of the literature with emphasis on therapy options. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;104:603-15.
26. Kaban BL, Chuong R, Kozakewich H, Atayde AP. Central giant cell lesions of the jaws: A clinicopahologic study. J Oral Maxillofac Surg 1986;44:708-13.
27. Kaffe I, Ardekian I, Taicher S, Littner MM, Buchner A. Radiologic features of central giant cell granuloma of the jaws. Oral Surg Oral Med Oral Pathol 1996;81:720-6.
28. Sokler K, Sandev S, Grgurevic J. Surgical treatment of Large mandibular cyts. Acta Stomatol Croat 2001;35:253-7.
29. Williams TP, Connor FA Jr. Surgical management of the odontogenic keratocyst: Aggressive approach. J Oral Maxillofac Surg 1994;52:964-6.

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