Giant cell lesions

Central giant cell granuloma

Central giant cell granuloma (CGCG) (giant cell lesion or giant cell reparative granuloma) is a benign proliferation of fibroblasts and multinucleated giant cells within a well vascularized stroma that occurs almost exclusively within the jaws. The tumor typically presents as a solitary radiolucent lesion of the mandible or maxilla.

Etiology and Pathogenesis

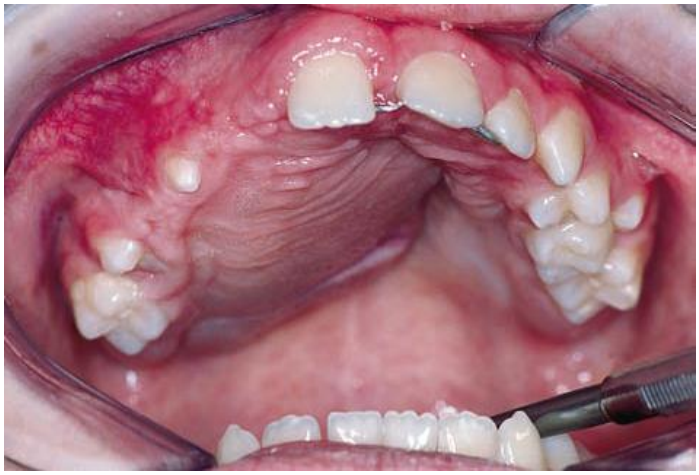
Initially was supposed to be a reparative response to intrabony hemorrhage and inflammation (the past name giant cell reparative granuloma). Because of its unpredictable and occasionally aggressive behavior, and because of its possible relationship to the giant cell tumor of long bones, CGCG is best considered a benign neoplasm. The primary tumor cells of CGCGs are fibroblasts (proliferative component which are responsible for recruitment and retention of monocytes and their subsequent transformation into multinucleated giant cells). Secondary cells, which are microscopically the most prominent, are multinucleated giant cells with osteoclast-like features. Accessory cells, seen in considerably smaller numbers, include macrophages, dendritic cells, and endothelial cells.

Clinical Features

CGCG found predominantly in children and young adults, with most cases (75%) presenting before 30 years of age. Females are affected more often than males in a ratio of 2:1.

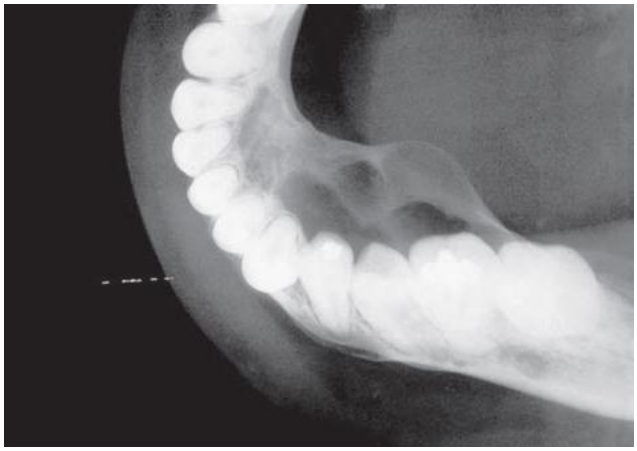
CGCG occurs almost exclusively in the maxilla and mandible. Lesions are seen more commonly in the mandible than in the maxilla. These lesions tend to involve the jaws anterior to the permanent molar teeth, with occasional extension across the midline.

CGCG typically produces painless expansion or swelling of the affected jaw with cortical plate thinning; and sometimes perforation with extension into soft tissues.



Radiographic features

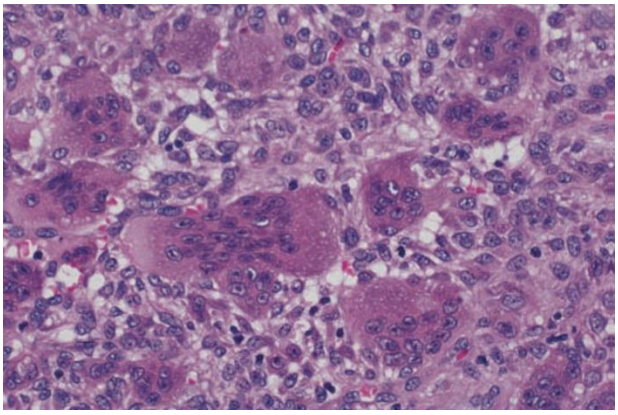
CGCG appears as multilocular or, less commonly, unilocular radiolucency of the bone. The margins of the lesion are relatively well demarcated, often presenting a scalloped border. In some instances, CGCG follows a more aggressive clinical and radiographic course. These "aggressive" CGCGs may cause pain or paresthesia with rapid growth, root resorption, perforation of cortical bone, and a higher recurrence rate.



Central giant cell granuloma showing loculations and cortical expansion.

Histopathology

CGCG is composed of uniform fibroblasts in a stroma containing various amounts of collagen. Hemosiderin laden macrophages and extravasated erythrocytes are usually evident, although capillaries are small and inconspicuous. Multinucleated giant cells are present throughout the connective tissue stroma, and they may be seen in focal aggregates or patches (zonation phenomenon) or distributed evenly. Foci of osteoid may be present, particularly around the peripheral margins of the lesion. No microscopic features distinguish aggressive CGCGs from nonaggressive ones.



Differential diagnosis (histopathological)

1. Hyperparathyroidism

- Elevated serum parathormone and alkaline phosphatase
- Multiple bone lesions; loss of lamina dura

2. Aneurysmal Bone Cyst

- Blood-filled sinusoids present

3. Cherubism

- Symmetric lesions
- Family history
- Perivascular collagen cuffing

Treatment and Prognosis

Excision or curettage of the tumor mass followed by removal of the peripheral bony margins) with good prognosis and a low recurrence rate. Lesions with aggressive clinical features exhibit a tendency to recur, often necessitating more extensive surgical approaches, including resection. Intralesional injections of corticosteroids have been proposed, but results are varied and the basis of this therapy is questionable. Exogenous calcitonin administration may have some value in the treatment of aggressive lesions. Interferon-alpha has been proposed as an additional treatment modality on the basis of an antiangiogenic mode of action. Bisphosphonates (because of their inhibitory effects on osteoclasts) have been suggested as an alternative or adjunct to surgery.

Giant Cell Tumor

Giant cell tumors are true neoplasms that arise most commonly in long bones, especially in the area of the knee joint. These tumors exhibit a wide spectrum of biological behavior from benign to malignant. The relationship between this lesion and CGCG is controversial. Most regard the giant cell tumor as distinct from CGCG, acknowledging the very rare occurrence of giant cell tumor within the jaws. Giant cell tumors, although rare, have been reported in the jaws. Other sites of involvement in the head and neck include the sphenoid, ethmoid, and temporal bones. Giant cell tumors are most often seen in the third and fourth decades of life. Lesions exhibit slow growth and bone expansion, or they produce rapid growth, pain, or paresthesia.

Radiographically, the giant cell tumor produces a radiolucent image. Microscopically, this tumor is characterized by the presence of numerous multinucleated giant cells dispersed evenly among monocyte-macrophages and spindle cells. It has been proposed that the spindle cells represent the neoplastic cells in this tumor, and that the monocyte-macrophages are reactive, giving rise to giant cells through recruitment and induction factors (e.g., tumor necrosis factor [TNF]-alpha, macrophage colony-stimulating factor) secreted by the tumor spindle cells. Stromal cellularity is usually prominent, with minimal collagen production.

Giant cells in giant cell tumors are usually larger and contain more nuclei than the corresponding cells of CGCG. Significant variation is noted, however, such that any given lesion may present diagnostic difficulty because of considerable histologic overlap. Giant cell tumors may contain inflammatory cells and areas of necrosis while exhibiting a relative absence of hemorrhage and hemosiderin deposition. Osteoid formation is noted less often than in giant cell granulomas. Surgical excision is the treatment of choice for giant cell tumors. These lesions exhibit a greater tendency to recur after treatment than do giant cell granulomas. Although too few cases have been reported in the jaws to predict recurrence rates, it is noteworthy that 30% of lesions in long bones recur after curettage.

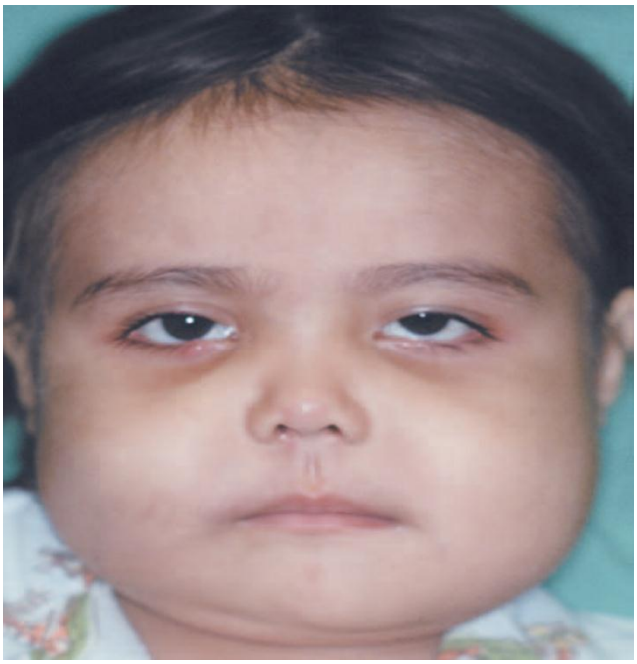
Cherubism

benign hereditary condition that affects the jaws only and is transmitted as an autosomal-dominant trait with high penetrance (100% in males and 50% to 75% in females). some investigators regard it as a genetically determined chronic noninfectious inflammatory disorder). The mutation involves SH3BP2 gene on chromosome 4 which encodes protein which activate osteoclasts resulting in disrupted jaw morphogenesis.

Clinical Features

Cherubism characterized by bilateral symmetrical asymptomatic involvement of the maxilla and/or mandible (mostly mandibular involvement) usually found in children.

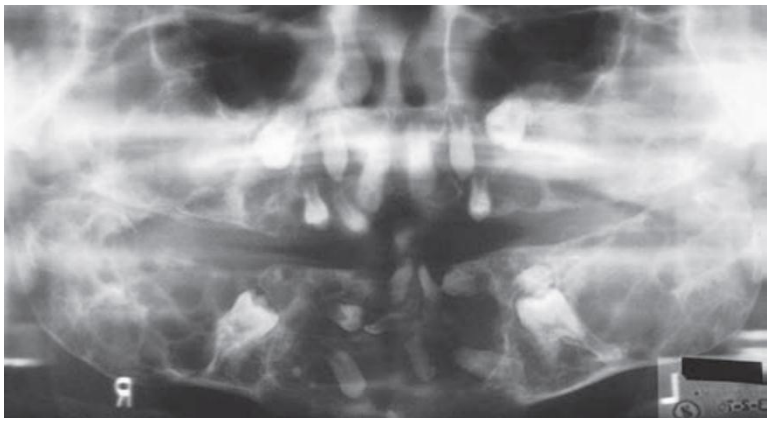
The term cherubism has been used to describe patients with a bilaterally symmetric swelling of the lower third of the face, marked fullness of the jaws, cheeks, and upwardly gazing eyes. The mandibular angle, ascending ramus, retromolar region, and posterior maxilla are most often affected. The coronoid process can also be involved, but the condyles are always spared. Early loss of deciduous teeth and ectopic eruption or impaction of permanent teeth. Submandibular and upper cervical lymphadenopathy are common usually subsides after 5 years of age. Serum calcium and phosphorous levels are within normal limits, but alkaline phosphatase levels may be elevated.



Cherubism. This young girl shows the typical cherubic facies resulting from bilateral expansile mandibular and maxillary lesions.

Radiographical features:

characterized by numerous well-defined multilocular radiolucencies of the jaws. expansion and thinning of the cortical plate with occasional perforation. An occlusal radiograph of the maxilla may give a soap bubble appearance, with maxillary antrum obliteration. Unerupted teeth are often displaced and appear to be floating in the cyst-like spaces.



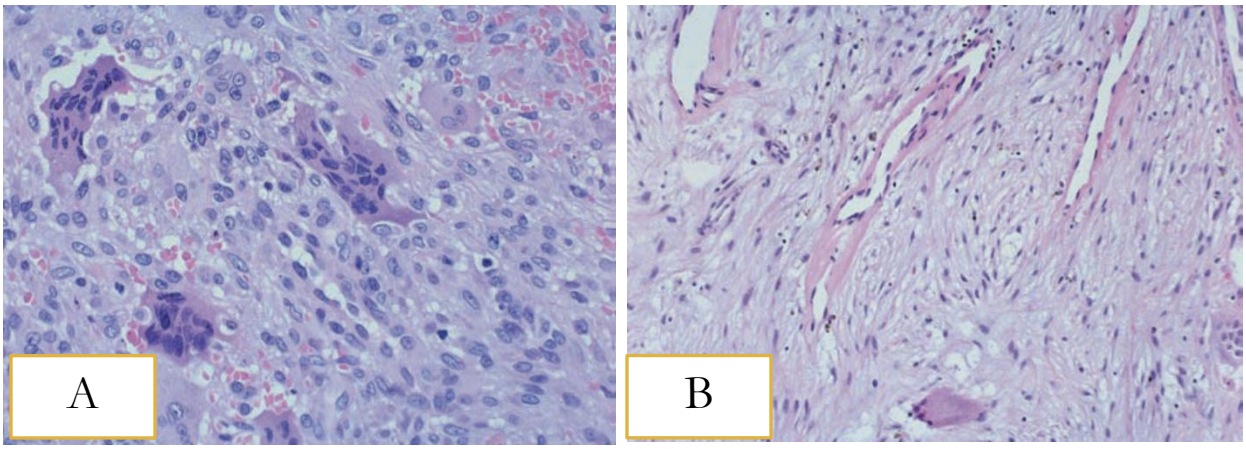
Cherubism: all four quadrants are involved

Histopathology

the lesions are composed of a vascularized fibrous stroma containing multinucleated giant cells, resembling central giant cell granuloma (Mature lesions exhibit a large amount of fibrous tissue and fewer giant cells). A distinctive feature that is often present is eosinophilic perivascular cuffing of collagen surrounding small capillaries throughout the lesion.

Differential diagnosis:

Central giant cell granuloma, giant cell tumor, fibrous dysplasia, and Paget's disease of bone.



Cherubism: multinucleated giant cells in fibroblastic stroma. Note eosinophilic perivascular cuffing in B

Treatment and Prognosis

The prognosis is relatively good, particularly if the disease is limited to one jaw, especially the mandible. After a rapid pace of bone expansion, the disease is usually self-limiting and regressive. spontaneous regression begins at puberty, with relatively good resolution by age 30. Surgical intervention must be based on the need to improve function, prevent debility, and satisfy esthetic considerations. If necessary, conservative curettage of the lesion with bone recontouring may be performed.

Hyperparathyroidism

Hyperparathyroidism may be one of three types:

- Primary
- Secondary
- Hereditary

Primary hyperparathyroidism is characterized by hypersecretion of parathyroid hormone from (hyperplastic parathyroid glands (3%), a parathyroid adenoma (90%), or less commonly, an adenocarcinoma (3%)).

Characteristic laboratory findings include

- elevated calcium level
- elevated alkaline phosphatase level

Secondary hyperparathyroidism occurs as a compensatory response to hypocalcemia, as in renal failure and in patients undergoing renal dialysis (renal osteodystrophy), as well as in those with intestinal malabsorption syndromes. In these patients, vitamin D3, which is activated in the kidney, is reduced. Vitamin D3 is required for calcium absorption and metabolism.

The hereditary form has been shown to be an autosomal-dominant condition mapped to chromosome 1q21-q31, the location of the HRPT2 endocrine tumor gene.

Clinical Features

The disease spectrum of primary hyperparathyroidism ranges from asymptomatic cases (diagnosed by routine serum calcium determinations) to severe manifesting as lethargy and occasionally coma. The incidence increases with age (usually those older than age 60) and is greater in postmenopausal women.

Early symptoms include fatigue, weakness, nausea, anorexia, arrhythmias, polyuria, thirst, depression, and constipation. Bone pain and headaches are often reported.

Several clinical features are associated with primary form of this disease, classically described as **"stones, bones, groans, and moans,"** reflective of renal calculi, bone pathology, duodenal ulcers, and confusion or dementia-like symptoms, respectively. The renal component of stones or calculi or, more rarely, nephrocalcinosis is related to hypercalcemia, the metabolic marker of excess parathormone activity. Gastrointestinal manifestations include peptic ulcer resulting from the increase in gastric acid, pepsin, and serum gastrin levels. Rarely, pancreatitis may develop as a result of obstruction of the smaller pancreatic ducts by calcium deposits.

Neurologic manifestations coma or parathyroid crisis may occur. Loss of memory and depression are common, and rarely, true psychosis may appear. Some of the neurologic findings may be attributed to calcium deposits in the brain. Severe osseous changes (called in the past, osteitis fibrosa cystica) are the result of significant bone demineralization, with fibrous replacement producing radiographic changes that appear cyst-like. In the jaws, these lesions microscopically resemble central giant cell granuloma, or so-called "brown tumor," reflective of the brownish hue derived from accumulated intralesional hemosiderin pigment and erythrocyte extravasation. The histopathological features are identical to CGCG.

Aneurysmal Bone Cyst

Aneurysmal bone cysts are pseudocysts because they appear radiographically as cyst-like lesions but microscopically exhibit no epithelial lining. This lesion represents a benign lesion of bone that may arise in the mandible (mostly), the maxilla, or other bones.

Etiology and Pathogenesis

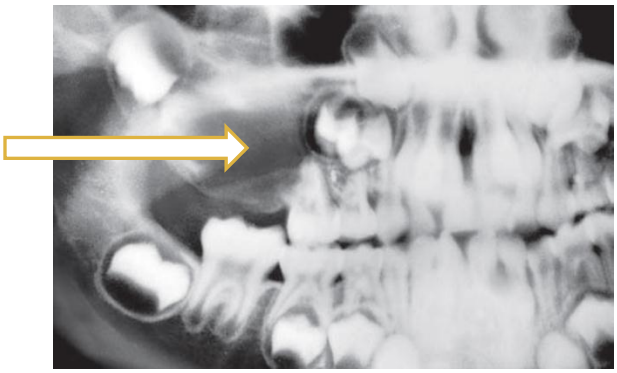
The pathogenesis of the aneurysmal bone cyst is not well understood. Some evidence suggests a reactive process, and other evidence suggests a tumor. Supporting the tumor concept is the identification of translocation of the TRE17/ USP6 locus, resulting in TRE17 overexpression in more than 60% of ABC cases in long bones. An unrelated precursor primary lesion of bone, such as fibrous dysplasia, central giant cell granuloma, chondroblastoma, and other primary bone lesions, is believed to initiate a vascular malformation, resulting in a secondary lesion or aneurysmal bone cyst.

Clinical Features

Aneurysmal bone cysts typically occur in persons younger than 30 years. When the mandible and the maxilla are involved, the more posterior regions are affected, chiefly the molar areas. Pain is described in approximately half of cases, and a firm, non-pulsatile swelling is a common clinical sign. On auscultation, a bruit is not heard, indicating that blood is not located within an arterial space; on firm palpation, crepitus may be noted.

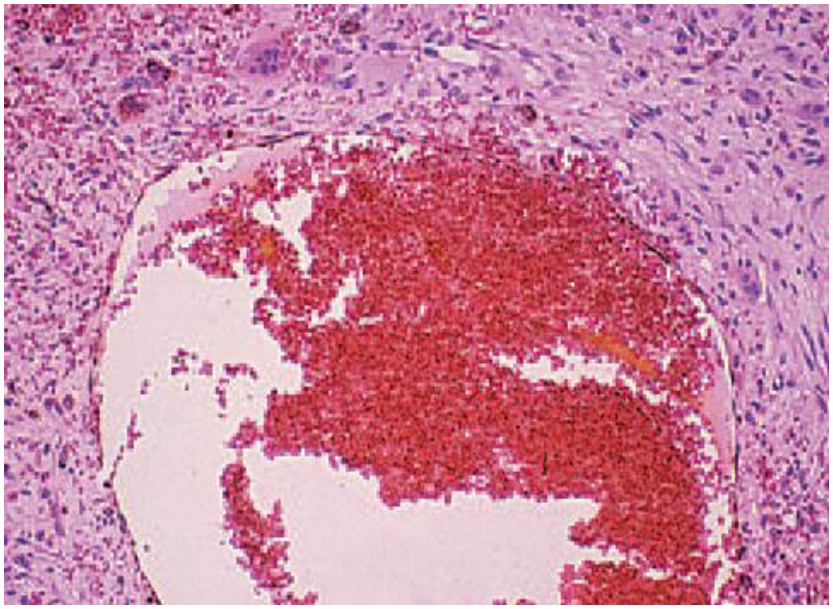
Radiographic features:

Destructive or osteolytic process with slightly irregular margins. A multilocular pattern is noted in some instances. When the alveolar segment of the mandible and the maxilla is involved, teeth may be displaced with or without concomitant external root resorption.



Histopathology

A fibrous connective tissue stroma contains variable numbers of multinucleated giant cells. Sinusoidal blood spaces are lined by fibroblasts and macrophages. With the exception of the sinusoids, the aneurysmal bone cyst is similar to central giant cell granuloma. Reactive new bone formation is commonly noted.



Differential Diagnosis

- OKC/KCOT
- central giant cell granuloma
- Ameloblastic fibroma should be included in the differential diagnosis.

Ameloblastoma and odontogenic myxoma could be included, although these lesions more typically appear in older patients

Treatment and Prognosis

A relatively high recurrence rate has been associated with simple curettage. Excision or curettage with supplemental cryotherapy is the treatment of choice.