Central giant cell reparative granuloma of the Jaws

Authors:

Erkan Orhan, MD,

assistant professor[1]

1) Namik Kemal University, Department of Plastic Surgery, Tekirdağ, Turkey

Correspondence Address:

Erkan Orhan, MD.

Reşat Nuri Sk 71/31 Y.Ayrancı

Çankaya/ ANKARA 06510

TURKEY

PHONE: +90 532 5004192

FAX: 0.282.250 9950

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Abstract

Central giant cell reparative granuloma (CGCRG) has been defined by The World Health Organization as a localized benign, however sometimes aggressive, osteolytic proliferation, consisting of fibrous tissue along with hemorrhage and hemosiderin deposits, with the presence of osteoclast-like giant cells and reactive bone formation. They are mostly localized in the maxilla and mandible, however lesions sourced from the orbit, paranasal sinuses, skull base, skull bones such as the temporal, sphenoid, ethmoid bones, and the small bones of the hands and feet, have also been published. CGCRG often presents itself as a painless swelling of the face or mouth and it is divided into 2 groups according to its clinical findings, as aggressive and nonaggressive type. Nonaggressive lesions are slow-growing, mostly asymptomatic lesions which don't cause perforation of the cortical bone and root resorption. Aggressive lesions however are fast-growing; larger than 5 cm in size; cause pain and paraesthesia, root resorption and cortical perforation; and commonly show recurrence after surgery. The differential diagnosis for CGCRG includes other giant cell lesions such as the true giant cell tumor of the bone, aneurysmal bone cysts, and chondroblastoma. The traditional treatment for CGCRG is surgical abortion and this treatment is sufficient in 80% of the cases. Alternative methods to surgery are; intralesional corticosteroid therapy, calcitonin treatment, interferon alpha-2a, and imatinib treatment.

1. Introduction

Central giant cell reparative granuloma (CGCRG) has been defined by The World Health Organization as a localized benign, however sometimes aggressive, osteolytic proliferation, consisting of fibrous tissue along with hemorrhage and hemosiderin deposits, with the presence of osteoclast-like giant cells and reactive bone formation (Orhan et al., 2010). The term central giant cell reparative granuloma was used in 1953 for the first time by Jaffe to identify a reactive lesion caused by intraosseous hemorrhage (Jaffe, 1953).

There is no consensus on whether CGCRG is a true neoplasm or a reactive lesion (Orhan et al., 2010). According to one view, it is accepted as a local reparative process occurring as a response to haemorrhage or inflammatory conditions caused by trauma (Alton et al., 2009), however there is no history of trauma in most patients (Orhan 2010). Another view is that CGCRG is a true neoplasm, an equivalent of the giant cell tumor (GCT) seen in long bones (Triantafillidou et al., 2011).

They are mostly localized in the maxilla and mandible (Üstündağ et al., 2002), however lesions sourced from the orbit, paranasal sinuses, skull base, skull bones such as the temporal, sphenoid, ethmoid bones, and the small bones of the hands and feet have also been published (Auclair et al., 1988). CGCG constitutes 7% of all benign masses in the jaw (O'Connell et al. 2013). Cases occur most frequently in the mandible, followed by the maxilla. 75% of the lesions occurring in the maxilla are located in the anterior, whereas the lesions occurring in the mandible are seen equally in the anterior and posterior (de Lange et al., 2005; Orhan et al., 2010).

CGCRG is more common in women, however when only the lesions in the mandible are taken into account, they have been reported equally in men and women. CGCRG may occur at any age,

yet 42% to 72% of the cases are seen before the age of 30 (Bataineh et al., 2002; de Lange et al., 2005; Orhan et al., 2010) and much less often after the age of 50 (Eisenbud 1998). The peak age range of incidence is 10-14 in men, and 15-19 in women (de Lange et al., 2004).

Isolated CGCRG is mostly unifocal (Ardekian et al., 1999). Multifocal lesions however are seen in patients with genetic diseases such as cherubism, Noonan syndrome (Edward et al., 2005), and neurofibromatosis type-1(NF-1) (Ruggieri et al., 1999) and systemic diseases such as fibro-osseous lesions, odontogenic fibroma (Ficarra et al.,1993), the brown tumor of hyperparathyroidism (Cohen 1998), fibrous dysplasia, ossifying fibroma (Penfold et al., 1993).

Only a few cases with isolated multiple CGCRG of the jaw have been reported in literature. Hjorting-Hansen and Worsoe-Petersonz reported multiple isolated giant cell lesions in long bones and the jaw (Hjorting-Hansen and Worsoe-Petersen, 1967). Davis and Tideman published a case in which CGCRG was located in both the maxilla and mandible at the same time (Davis and Tideman, 1977). The lesion in the maxilla was detected 4 months after the one in the mandible. Cassatly et al. presented a case in which CGCRG was located in the mandible (Cassatly et al., 1988), whereas Smith et al. presented one with CGCRG located in both of the maxillary sinuses (Smith et al., 1990). Orhan et al. published a case which had no systemic and genetic diseases in the past, however, the patient had bilateral lesions in the mandible (Orhan et al., 2010).

The etiology of CGCRG is not fully known. Some genetically originated syndromes such as NF-1, cherubism, and Noonan were seen in the jaw with giant cell granuloma-like lesions (Triantafilidou et al., 2011). Some studies also identified chromosomal translocations in giant cell granuloma-like giant cell tumor (GCT) lesions of the long

bones. All of these findings suggest that the etiology of CGCRG is also genetically originated and that chromosomal abnormalities may be effective in its formation, yet this is controversial (Triantafilidou et al., 2011; O'Connell et al., 2013). Lange et al. suggested that the gene mutation responsible for causing CGCRG is either on or adjacent to the SH3BP2 gene region, which has an effect on osteoclastic activity (de Lange et al.,2007; Hyckel et al., 2005), however no SH3BP2 mutation was detected in children with isolated CGCRG (Idowu et al., 2008). Gomes et al. reported that there were H3F3A p.Gly34 Trp or p.Gly34 Leu mutations in sporadic cases (Gomes et al., 2014).

2. Histological Appearance

Histologically, CGCRG consists of highly cellular, plump, spindle-shaped cells with high mitotic rates, and fibrous stroma. Multinucleated giant cells line the stroma lengthwise and mostly aggregate in hemorrhage fields (Ficarra et al., 1993). These giant cells were found to originate from osteoclasts (Vered et al., 2006). Even though multinucleated giant cells may seem dominant, the proliferative cells of CGCRG were found to be fibroblasts, myofibroblasts, and inflammatory mononuclear cells (Schütz et al., 2010). Dystrophic calcifications and metaplastic ossifications are commonly seen and they are mostly at the periphery of the lesion (de Lange et al., 2004). The histological appearance of CGCRG is identical to the Brown tumors of hyperparathyroidism, cherubism, and aneurysmal bone cyst (Triantafilidou et al., 2011).

3. Radiological Appearance

The radiological appearances of CGCRG cases differ from small uniocular lesions to large multiocular lesions with ill-defined margins, which extend to the teeth and dental roots, causing cortical

expansion and perforation (de Lange et al., 2007).

In De Lange's series, it was found that 15.7% of the cases had a multiocular appearance, whereas 84.3% had a uniocular appearance (de Lange el al., 2005); however, in Whitake and Waldron's series, 61% was found to have a multiocular and 39% a uniocular appearance (Whitaker and Waldrom, 1993), and these findings were consistent with other studies in the literature (Güngörmüs and Akgül , 2003). The margins of the lesions were 56% well-defined, 30% ill-defined, and 14% continuous with the environment. The characteristics of the lesion can be better evaluated with tomography rather than plain film. The radiological appearance of the lesion isn't pathognomonic and may be confused with the other lesions of the jaw (Orhan et al., 2010).

4. Diagnosis

CGCRG often presents itself as a painless swelling of the face or mouth (de Lange 2005). Chuong et al. and Ficarra et al. divided CGCRG into 2 groups according to its clinical findings, as aggressive and nonaggressive type (Gomes el al, 2014).

Nonaggressive lesions are slow-growing, mostly asymptomatic lesions which don't cause perforation of the cortical bone and root resorption. Aggressive lesions however are fast-growing; larger than 5 cm in size; cause pain and paraesthesia, root resorption and cortical perforation; and commonly show recurrence after surgery (Chuong et al., 1986).

In Lange’s series, root resorption was seen in 13.5% of the cases, whereas tooth displacement was seen in 18% of the lesions (de Lange et al., 2005). As for Whitaker ve Waldron's series, it was reported that 43% of CGCRG cases had root resorption and 36% had tooth germ

displacement. The displacement of a tooth or teeth and root resorption is characteristically seen in aggressive lesions (Whitaker and Waldron, 1993).

Other symptoms include facial asymmetry, difficulty breathing, and pathologic fractures (Ustündağ et al., 2002). The calcaneus nature and thin cortical plans of the maxilla cause the lesion to expand much faster, therefore causing an earlier presentation of symptoms, than when in the mandible. The lesions of the maxilla may cause symptoms such as diplopia, epiphora, nasal obstruction, and epistaxis as a result of anterior expansion (Rawashdeh et al., 2006).

In some publications in the literature it has been stated that the aggressive type of CGCRG presents itself histologically with numerous giant cells, increased mitotic activity, and high fractional surface area (Kruse-Losler et al., 2006). However, in many other studies, it has been published that there is no difference between the aggressive and nonaggressive types of CGCRG in terms of histological appearance (Kauzman et al., 2004). Dewsnup et al. stated that there was increased expression of CD34 in clinically aggressive GCTs than in nonaggressive GCTs and with the immunohistochemistries fixation of CD34, the aggressiveness of the lesions could be detected (Dewsnup et al., 2004).

5. Differential Diagnosis

The differential diagnosis for CGCRG includes other giant cell lesions such as the true giant cell tumor of the bone, aneurysmal bone cysts, and chondroblastoma (Orhan et al., 2010). The differential diagnosis of giant cell tumor and CGCRG is very important in terms of treatment due to their different biological characters. The true giant cell tumor of the bone usually occurs in the epiphysis of long bones and rarely in the bones of the skull, however, CGCRG mostly occurs in the mandible and

maxilla. Both CGCRG and GCT are radiologically seen as lytic lesions and must be histologically differentiated (Orhan et al., 2010).

In histological examination, GCT consists of plump, round, and oval-shaped giant cells with several nuclei collected at the center of the cells, which are more uniformly distributed. GCT has more new bone formation focal areas and rarely hemorrhage, hemosiderin deposits or fibrosis, and has necrotic foci (Saw et al., 2009). Aneurysmal bone cysts are different from CGCRG in terms of microscopic appearance. Histologically, they are seen more as honeycomb networks filled with blood. Chondroblastoma has its own distinct histological appearance (Orhan et al., 2010).

6. Treatment

The traditional treatment for CGCRG is surgical abortion and this treatment is sufficient in 80% of the cases. Other surgical treatment options are peripheral osteotomy, en block resection, and reconstruction of the bone defect with either an autologous iliac bone graft or osseointegrated implant. Some authors have suggested laser or cryoprobe administrations to the margins of CGCRG (Orhan et al., 2010). Especially painful, fast-growing lesions larger than 3 cm are suitable candidates for surgical treatment (O'Connel et al., 2013).

CGCRG is a highly vascular lesion, therefore there may be significant blood loss during surgery and blood support may be required (Eisenbud et al., 1988). Apart from that, root damage and therefore tooth loss, facial deformities, and nerve damage may occur especially during en block resection and peripheral osteotomy due to CGCRG (Orhan et al., 2010; O'Connel et al., 2013). Alternative methods to surgery are recommended especially in non-aggressive, slow-growing lesions smaller than 3 cm

because of these complications (O'Connel et al., 2013).

Calcitonin is a hormone produced in the C cells of the thyroid gland. Its function is to prevent bone resorption by inhibiting osteoclastic cells in bones, increase osteoblastic activity, and reduce the level of serum Ca. Borges et al. suggested that calcitonin treatment could be administered especially in young patients with advanced and aggressive lesions as an alternative to surgery (Borges et al., 2008). Harris published that complete remission of CGRGC occurred in 4 cases which had undergone synthetic human calcitonin treatment (Harris, 1993). Pogrel treated 10 CGRGC patients with subcutaneous salmon calcitonin injections and after an 18 month treatment period, complete remission was achieved in 8 patients (Pogrel, 2003). Triantafillidou et al. achieved success in 2 patients using calcitonin treatment (Triantafillidou et al., 2011). de Lange et al. and Kaban et al. reported that the growth of lesions couldn't be stopped with calcitonin treatment (de Lange et al., 2006; Kaban et al., 1999)

The mechanism of action of calcitonin treatment for CGRGC is not exactly known. The multinucleated giant cells in CGRGC have calcitonin receptors (Vered et al., 2006) and calcitonin inhibits the activity of these cells (Triantafillidou K). Although it may seem that the therapeutic effect of calcitonin is because it acts as an antagonist against osteoclastic bone resorption (Pogrel, 2003), its mechanism of action is unclear.

Human synthetic calcitonin or salmon calcitonin may be administered subcutaneously or as a nasal spray in calcitonin treatment (de Lange et al., 2007). The most important disadvantage of calcitonin treatment is that it takes too long. Therefore, calcitonin treatment is recommended for recurrences and multiple aggressive lesions. Calcitonin nasal spray has also been used to prevent

the formation of recurrence after surgery (Tabrizi, 2016). Calcitonin has been administered as 100 IU / day subcutaneously for 6 months-1 year or 200 IU / day intranasal between 6-28 months (Borges et al., 2008).

Another non-surgical treatment method is steroid treatment. In 1988 Flanagan et al. suggested intralesional corticosteroid treatment for CGRCG due to a theory based on dexamethasone inhibiting osteoclast-like cells in bone marrow cultures ((Flanagan et al., 1988; Pharoah et al., 1986). Jacoway et al. applied intralesional corticosteroid injections for the treatment of CGRCG for the first time (Jacoway et al., 1988). This was followed by the publications of Kermer et al. and Terry and Jacoway (Kermer et al., 1994; Terry and Jacoway, 1994). Terry and Jacoway performed steroid treatment on 4 patients in 1994. With weekly intralesional injections of triamcinolone acetonide for 6 weeks, full remission was achieved in 3 patients, 1 patient, however, needed additional surgery (Terry and Jacoway, 1994). Many other publications also reported cases in which successful results had been achieved with intralesional steroid therapy (Comert Eet al., 2006).

For the mechanism of action of the treatment, it has been suggested that is based on steroids inhibiting the extracellular production of bone resorbing lysosomal proteases (Kermer et al., 1994). The inducing impact of steroids on the apoptosis of osteoclast-like cells may also be influencing treatment (Dempster et al., 1997). Despite all of these explanations, the mechanism of action is unclear (O'Connell et al., 2013).

Another method is interferon treatment. Interferon is a cytokine with immunomodulator, antiviral, anti-angiogenic characteristics. During the early 1980s, it was shown in a series of lab experiments that interferon alfa (IFN-alpha)-2a inhibited angiogenesis (Sidky and Borden, 1987). Thanks to this

angiogenesis-inhibiting effect, interferon is used in the treatment of hemangioma and malignant tumors (Schütz et al., 2010).

The clinical appearance of CGCRG is a vascularized lesion, therefore it has been considered that CGCRG could be treated with an antiangiogenic treatment method such as IFN-alpha (Triantafillidou et al., 2011). Kaban et al treated CGCRG with interferon alpha for the first time (Kaban et al., 1999). de Lange et al. published 2 patients with CGCRG which were treated with interferon monotherapy in 2006 (de Lange et al., 2006). Interferon monotherapy prevents the rapid growth of lesions; however, it does not achieve total resolution. The reason for not achieving total remission has been explained as it not being able to directly inhibit fibrotic-originated proliferative tumor cells. Kaban et al. recommended that aggressive lesions be enucleated, the surrounding structures (nerves, teeth) be preserved, and IFN-alpha-2a treatment be administered 48-72 hours post op, instead of large en block resection (Kaban et al., 2002). Administration of IFN-alpha on aggressive CGCRG stops the rapid growth of the lesions and reduces their size; however, surgical intervention is still required (Triantafillidou et al., 2011). IFN alpha was administered subcutaneously as 3-6x106 IU / day of dose for 6-12 months in the study (Kaban et al., 2002).

The side effects of interferon are; fever, flu-like symptoms, nausea, lethargy, post-nasal drip, skin rash, hair loss, neutropenia, thrombocytopenia, elevated liver enzyme, spastic diplegia, drug-induced lupus erythematosus, and pancreatitis (O'Connel et al., 2013).

Another alternative method of treatment is imatinib (de Lange et al., 2009). Imatinib is a tyrosine kinase inhibitor protein and is used for the treatment of chronic myeloid leukemia and gastrointestinal tumors (Druker et al.,

1996). It has been shown that Imatinib inhibits the activity of osteoclasts and is used in the treatment of skeletal diseases with excessive osteoclast activity such as CGCRG. Imatinib was used as 400 mg / day dose in the studies (de Lange et al., 2009).

7. Recurrence

An average of 11-49% recurrence is seen after CGCRG treatment (Triantafillidou et al 2011). Recurrence is more commonly seen in aggressive lesions which especially perforate the cortical plate and invade surrounding soft tissues (Minic and Stajcic, 1996). Chuong et al. and Ficarra et al. reported a recurrence of 72% in clinically aggressive types and 3% in non-aggressive types (Chuong et al.,1986; Ficarra et al., 1993), Whitaker and Waldron reported a recurrence of 46.1% in aggressive lesions (Whitaker and Waldron, 1993).

Whitaker and Waldron determined an average time period of 21 months post treatment for recurrence. Recurrence is rarely seen after 2 years (Whitaker and Waldron, 1993), however, a case which showed recurrence after 22 years was reported in literature (Horner, 1989).

The patient's age affects recurrence in male patients (Orhan et al., 2010). Recurrence occurs more often in young males and is seen in the earlier stages of life (Triantafillidouet al., 2011), however age doesn't affect recurrence in females (de Lange et al., 2004).

Whitaker and Waldron stated that the incidence of recurrence was more common in lesions larger than 3 cm (Whitaker and Waldron, 1993). According to Lange et al, although there is no difference between the maxilla and mandible in terms of recurrence, other studies have shown that incidence of recurrence is higher in the maxilla than in the mandible (%28,6-%23,2). A simple explanation for this difference is that surgical curettage is more difficult in the maxilla (de Lange et al., 2005).

In order to prevent recurrence it is recommended that aggressive GCG be removed with 0.5 cm healthy tissue (Bataineh et al., 2002).

8. Conclusion

CGCRG's are mostly localized in the maxilla and mandible; however, lesions can be seen on the orbit, paranasal sinuses, skull base, skull bones such as the temporal, sphenoid, ethmoid bones, and the small bones of the hands and feet. Treatment option for aggressive lesions which are fast-growing, larger than 5 cm in size, cause pain and paraesthesia, root resorption and cortical perforation, is surgery, but for nonaggressive lesions, which are slow-growing, mostly asymptomatic, and which don't cause perforation of the cortical bone and root resorption, alternative methods to surgery should be kept in mind.

9. References

- Alton DM, Anavi Y, Calderón S. Central giant cell lesion of the jaw: nonsurgical treatment with calcitonin nasal spray. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009 Jun;107(6):811-8. doi: 10.1016/j.tripleo.2009.02.013.

- 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 Jul;57(7):869-72. PMID: 10416639

- Auclair PL, Cuenin P, Kratochvil FJ, Slater LJ, Ellis GL A clinical and histomorphologic comparison of the central giant cell granuloma and the giant cell tumor. Oral Surg Oral Med Oral Pathol. 1988 Aug;66(2):197-208. PMID: 3174054

- Bataineh A, Al-Khateeb T, Rawashdeh M . The surgical treatment of central giant cell granuloma of the mandible. J Oral Maxillofac Surg. 2002 Jul;60(7):756-61. PMID: 12089688

- Borges HO. Machado RA, Vidor MM. Beltrao RG, Heitz C, Filho MS. Calcitonin: a non-invasive giant cells therapy, Int J Pediatr Otorhinolaryngol. 2008 Jul;72(7):959-63. doi: 10.1016/j.ijporl.2008.03.016.

- Cassatly MG, Greenberg AM, Kopp WK. Bilateral giant cell granulomata of the mandible: report of case. J Am Dent Assoc. 1988 Nov;117(6):731-3. PMID: 3198881

- Chuong R, Kaban LB, Kozakewich H, Perez-Atayde A. Central giant cell lesions of the jaw: a clinicopathologic study J Oral Maxillofac Surg. 1986 Sep;44(9):708-13. PMID: 3462363.

- Cohen MA, Hertzanu Y. Radiologic features, including those seen with computed tomography, of central giant cell granuloma of the jaws. Oral Surg Oral Med Oral Pathol. 1988 Feb;65(2):255-61. PMID: 3422730.

- Comert E, Turanli M, Ulu S. Oral and intralesional steroid therapy in giant cell granuloma. Acta Otolaryngol. 2006 Jun;126(6):664-6. DOI: 10.1080/00016480500468976

- Davis GB, Tideman H. Multiple recurrent central giant cell granulomas of the jaws. Case report. J Maxillofac Surg. 1977 Jun;5(2):127-9. PMID: 267702.

- de Lange J, van den Akker HP, Klip H. Incidence and disease free survival after surgical therapy of central giant cell granulomas of the jaws in The Netherlands; 1990–1995. Head Neck. 2004 Sep;26(9):792-5. DOI: 10.1002/hed.20069.

- de Lange J, Van den Akker HP. Clinical and radiological features of central giant-cell lesions of the jaw. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005 Apr;99(4):464-70. DOI: 10.1016/j.tripleo.2004.11.015.

- de Lange J, van der Akker HP, van der 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 Nov;104(5):603-15. DOI: 10.1016/j.tripleo.2007.04.003.

- de Lange J, van Rijn RR, van den Berg H, van den Akker HP. Regression of central giant cell granuloma by a combination of imatinib and interferon: a case report. Br J Oral Maxillofac Surg. 2009 Jan;47(1):59-61. doi: 10.1016/j.bjoms.2008.05.013.

- Dempster OW, Moonga BS, Stein LS, Horbert WR, Antakly T. Glucocorticoids inhibit bone resorption in isolated rat osteoclasts by inducing apoptosis. J Endocrinol. 1997 Sep;154(3):397-406. PMID: 9379116.

- Dewsnup NC, Susarla SM, Abulikemu M, Faquin WC, Kaban LB, August M. Immunohistochemical evaluation of giant cell tumors of the jaws using CD34 density analysis. J Oral Maxillofac Surg. 2008 May;66(5):928-33. doi: 10.1016/j.joms.2008.01.033.

- Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, Zimmermann J, Lydon NB. Effects of a selective inhibitör of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med. 1996 May;2(5):561-6. PMID: 8616716.

- Edwards PC, Fox J, Fantasia JE, Goldberg J, Kelsch RD.Bilateral central giant cell granulomas of the mandible in an 8-year-old girl with Noonan syndrome (Noonan-like/multiple giant cell lesion syndrome). Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005 Mar;99(3):334-40. DOI: 10.1016/j.tripleo.2004.08.021.

- Eisenbud L, Stern M, Rothberg M, Sachs SA.Central giant cell granuloma of the jaws: experiences in the management of thirty-seven cases, J Oral Maxillofac Surg. 1988 May;46(5):376-84. PMID: 3163371.

- Ficarra G, Sapp P, Eversole LR. Multiple peripheral odontogenic fibroma, World Health Organization type, and giant cell granuloma: a report of an unusual association. J Oral Maxillofac Surg. 1993 Mar;51(3):325-8. PMID: 8445478.

- Flanagan AM, Nui B, Tinkler SM, Horton MA, Williams DM, Chambers TJ. The multinucleate cells in the giant cell granulomas of the jaw are osteoclasts. Cancer. 1988 Sep 15;62(6):1139-45. PMID: 2457425.

- Gomes CC, Diniz MG, Amaral FR, Antonini Guimarães BV, Gomez RS. The highly prevalent H3F3A mutation in giant cell tumours of bone is not shared by sporadic central giant cell lesion of the jaws. Oral Surg Oral Med Oral Pathol Oral Radiol. 2014 Nov;118(5):583-5. doi: 10.1016/j.

- Güngörmüs M , Akgül HM . Central giant cell granuloma of the jaws: a clinical and radiologie study. J Contemp Dent Pract. 2003 Aug 15;4(3):87-97. PMID: 12937599.

- Harris M. Central giant cell granulomas of the jaws regress with calcitonin therapy Br J Oral Maxillofac Surg. 1993 Apr;31(2):89-94. PMID: 8471587.

- Hjorting-Hansen E, Worsoe-Petersen J.Recurrent benign giant cell lesions of the jaws with metastasis?. J Laryngol Otol. 1967 Sep;81(9):1033-44. PMID: 6050979.

- Horner K. Central giant cell granuloma of the jaws: a clinico-radiological study, Clin Radiol. 1989 Nov;40(6):622-6. PMID: 2598590.

- Hyckel P, Berndt A, Schleier P, Clement JH, Beensen V, Peters H, Kosmehl H. Cherubism - new hypotheses on pathogenesis and therapeutic consequences. J Craniomaxillofac Surg. 2005 Feb;33(1):61-8. DOI: 10.1016/j.jcms.2004.07.006.

- Idowu BD, Thomas G, Frow R, Diss TC, Flanagan AM. Mutations in SH3BP2, the cherubism gene, were not detected in central or peripheral giant cell tumors of the jaw. Br J Oral Maxillofac Surg. 2008 Apr;46(3):229-30. DOI: 10.1016/j.bjoms.2007.04.014.

- Jacoway JR. Howell FV, Terry BC. Central giant cell granuloma: an alternative to surgical therapy. Oral Surg Oral Med Oral Pathol 1988:66:572.

- Jaffe HL. Giant-cell reparative granuloma, traumatic bone cyst, and fibrous (fibroosseous)dysplasia of the jawbones, Oral Surg. Oral Med. Oral Pathol. 1953; 6 (1): 159–175. doi:10.1016/0030-4220(53)90151-0.

- Kaban KB, Mulliken JB, Ezekowitz RA, Ebb D, Smith PS, Folkman J. Antiangiogenic therapy of a recurrent giant cell tumour of the mandible with interferon alpha-2a. Pediatrics. 1999 Jun;103(6 Pt 1):1145-9. PMID: 10353921.

- 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 Oct;60(10):1103-11. PMID: 12378481.

- Kaffe I, Ardekian L, Taicher S, Littner MM, Buchner A. Radiologic features of central giant cell granuloma of the jaws, Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1996 Jun;81(6):720-6. PMID: 8784905.

- Kauzman A, Li SQ, Bradley G, Bell RS, Wunder JS, Kandel R.Central giant cell granuloma of the jaws: assessment of cell cycle proteins, J Oral Pathol Med. 2004 Mar;33(3):170-6. PMID: 15128059.

- Kermer C, Millesi W, Watzke IM. Local injection of corticosteroids for central giant cell granuloma. A case report. Int J Oral Maxillofac Surg. 1994 Dec;23(6 Pt 1):366-8. PMID: 7699277.

- Kruse-Lösler B, Diallo R, Gaertner C, Mischke KL, Joos U, Kleinheinz J.Central giant cell granuloma of the jaws: a clinical, radiologic, and histopathologic study of 26 cases, Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006 Mar;101(3):346-54. DOI: 10.1016/j.tripleo.2005.02.060.

- Minic A, Stajcic Z. Prognostic significance of cortical perforation in the recurrence of central giant cell granulomas of the jaws. J Craniomaxillofac Surg. 1996 Apr;24(2):104-8. PMID: 8773892.

- O'Connell JE, Kearns GJ. Aggressive giant cell granuloma of the jaws treated with interferon alpha: a report of two cases. Ir J Med Sci. 2013 Jun;182(2):163-70. doi: 10.1007/s11845-012-0858-x.

- Orhan E, Erol S, Deren O, Sevin A, Ekici O, Erdoğan B.I diopathic bilateral central giant cell reparative granuloma of jaws: a case report and literature review. Int J Pediatr Otorhinolaryngol. 2010 May;74(5):547-52. doi: 10.1016/j.ijporl.2010.02.006.

- Penfold CN, McCullagh P,Eveson JW, Ramsay A. Giant cell lesions complicating fibro-osseous conditions of the jaws, Int J Oral Maxillofac Surg. 1993 Jun;22(3):158-62. PMID: 8340626.

- Pharoah MJ, Heersche JN. Dexamethasone inhibits formation of osteoclast-like cells in bone-marrow cultures. J Dent Res. 1986 Jul;65(7):1006-9. PMID: 3458750.

- Pogrel MA. Calcitonin therapy for central giant cell granuloma, J Oral Maxillofac Surg. 2003 Jun;61(6):649-53. DOI: 10.1053/joms.2003.50129.

- Rawashdeh M, Bataineh A, Al-Khateeb T. Long-term clinical and radiological outcomes of surgical management of central giant cell granuloma of the maxilla. Int J Oral

Maxillofac Surg. 2006 Jan;35(1):60-6. DOI: 10.1016/j.ijom.2005.03.005.

- Ruggieri M, Pavone V, Polizzi A, Albanese S, Magro G, Merino M, Duray PH.Unusual form of recurrent giant cell granuloma of the mandible and lower extremities in a patient with neurofibromatosis type 1. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999 Jan;87(1):67-72. PMID: 9927083.

- Saw S, Thomas N, Gleeson MJ, Bódi I, Connor S, Hortobágyi T. Giant cell tumour and central giant cell reparative granuloma of the skull: do these represent ends of a spectrum? A case report and literature review. Pathol Oncol Res. 2009 Jun;15(2):291-5. doi: 10.1007/s12253-008-9124-y.

- Schütz P, El-Bassuoni KH, Munish J, Hamed HH, Padwa BL. Aggressive central giant cell granuloma of the mandible. J Oral Maxillofac Surg. 2010 Oct;68(10):2537-44. doi: 10.1016/j.joms.2009.06.042.

- Sidky YA, Borden EC. Inhibition of angiogenesis by interferons: effects on tumour- and lymphocyte-induced vascular responses. Cancer Res. 1987 Oct 1;47(19):5155-61. PMID: 2441862.

- Smith PG, Marrogi AJ, Delfino JJ. Multifocal giant cell lesions of the maxillofacial skeleton: a case report. J Oral Maxillofac Surg. 1990 Mar;48(3):300-5. PMID: 2303939.

- Tabrizi R. Re: Can calcitonin nasal spray reduce the risk of recurrence of central giant cell granuloma of the jaws?-a response. Int J Oral Maxillofac Surg. 2016 Aug 20. pii: S0901-5027(16)30152-7. doi: 10.1016/j.ijom.2016.07.008.

- Terry BC, Jacoway JR. Management of central giant cell lesions: an alternative to surgical therapy. Oral Maxillofac Surg Clin North Am 1994:6:579-601.

- Triantafillidou K, Venetis G, Karakinaris G, Iordanidis F. Central giant cell granuloma of the jaws: a clinical study of 17 cases and a review of the literature. Ann Otol Rhinol Laryngol. 2011 Mar;120(3):167-74. PMID: 21510142.

- Ustündağ E, Iseri M, Keskin G, Müezzinoğlu B. Central giant cell granuloma. Int J Pediatr Otorhinolaryngol. 2002 Sep 2;65(2):143-6. PMID: 12176185.
- 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 Aug;35(8):756-60. DOI: 10.1016/j.ijom.2006.02.014.
- Whitaker SB. Waldron CA. Central giant cell lesions of the jaws. A clinical, radiologie, and histopathologic study. Oral Surg Oral Med Oral Pathol. 1993 Feb;75(2):199-208. PMID: 8426719.

