

# Multifocal Central Giant Cell Granuloma of the Jaws: Case Report and Review of Literature

## Çenelerin Multifokal Santral Dev Hücreli Granüloması: Olgu Sunumu ve Literatür Derlemesi

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**ABSTRACT** Central giant cell granuloma (CGCG) is a fairly common lesion in the jaws aetiology of which is still completely unknown but thought to be of a reactive process to some unknown stimuli. CGCG is benign, nonodontogenic, and intraosseous lesion of the jaw and predominantly found in the mandible of young female patients with a variable clinical behavior. Histologically characterized by various numerous aggregations of multinucleated giant cells in fibrovascular stroma, hemorrhagic foci with hemosiderin pigments, and occasionally trabeculae of woven bone. CGCG of the jaw is usually unifocal. Therefore, multifocal CGCG is considered rare and strongly associated with several disorders. In this case report, the case of multifocal central giant cell which is seen an edentulous maxilla of a woman was presented. Literature review was also stated by using such keywords as granuloma, giant cell jaw and therapy that were used to review the related literature published between 1977 and 2014 in years PubMed.

**Key Words:** Granuloma, giant cell; jaw; therapy

**ÖZET** Santral dev hücreli granülom (SDHG), etiyolojisi halen tam olarak bilinmemekle birlikte bazı uyaranlara karşı gelişen reaktif süreçten kaynaklandığı düşünülen, çenelerin oldukça yaygın görülen lezyonlarıdır. SDHG, odontojenik olmayan, çenelerin intraosseöz lezyonudur ve ağırlıklı olarak da genç kadın hastaların mandibulasında değişik klinik özelliklerde görülmektedir. Histolojik olarak da, fibrovasküler stroma içerisine çok çekirdekli dev hücre agregasyonu, hemosiderin pigmentleri ile hemorajik odak ve bazen de kemik trabekülleri ile karakterize görüntü verir. SDHG sıklıkla tek odaklı olarak görülmektedir. Bu nedenle, multifokal SDHG nadirdir ve genellikle çeşitli bozukluklarla ilişkilidir. Bu olgu raporunda, dişsiz kadın hastanın maksillasında multifokal santral dev hücreli granülom vakası sunulmuştur. Granülom, dev hücre, çene, tedavi anahtar kelimeleri kullanılarak PubMed'ten yapılan 1977-2014 yılları arasındaki vakaların literatür derlemesi de yazımızda yer almıştır.

**Anahtar Kelimeler:** Granülom, dev hücre; çene; tedavi

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Central giant cell granuloma (CGCG) is a relatively rare nonneoplastic, intraosseous lesion first described by Jaffe in 1953, and it accounts for less than 7% of all benign maxillofacial bone lesions.<sup>1</sup> CGCG occurs more often in the mandible than in the maxilla, affects females more than males, and is commonly seen in individuals under the age of 30.<sup>2</sup>

The clinical behavior of CGCG varies and ranges from a slowly growing asymptomatic swelling to a tender aggressive lesion that causes local bone lysis, pain, root resorption, and displacement of teeth.<sup>3</sup> Clinicians have

proposed that CGCG of the jaw may be categorized into aggressive and nonaggressive lesions based on clinical and radiographic features, such as presence of pain, rapid growth, perforation of the cortex, and tendency to recur.<sup>4</sup> Most cases are non-aggressive and show little or no symptoms at all; slow growth without perforation of the cortical bone and root resorption of the teeth are involved.<sup>2</sup> Radiographically, all cases of CGCG appear as radiolucency osteolytic lesions. Radiologic features range from ill-defined destructive lesions to well-defined ones and small unilocular lesions to large multilocular lesions with displacement of teeth and tooth germs, root resorption, and cortical perforation.<sup>5,6</sup>

Histologically, CGCG is characterized by the dense proliferation of oval or spindle-shaped mesenchymal cells as well as various numerous aggregations of multinucleated giant cells in fibrovascular stroma, hemorrhagic foci with hemosiderin pigments, and occasionally trabeculae of woven bone. The osteoclast-like giant cells have a patchy distribution and are usually associated with areas of hemorrhage. Round macrophages, extravasated erythrocytes, myofibroblasts, dystrophic calcification, and predominantly mononuclear inflammatory infiltrate, particularly surrounding the periphery of the lesion, are also found.<sup>4,7,8</sup>

The etiopathogenesis of CGCG is not completely understood, but it has been suggested that it is the result of an exacerbated reparative process related to previous trauma or inflammation and intraosseous hemorrhage.<sup>9,10</sup>

Surgical curettage has been applied in the conventional and traditional treatment of CGCG.<sup>11</sup>

Central giant cell granuloma of the jaw is usually unifocal. Multifocal CGCGs are considered rare and strongly associated with several disorders.<sup>5,12,13</sup>

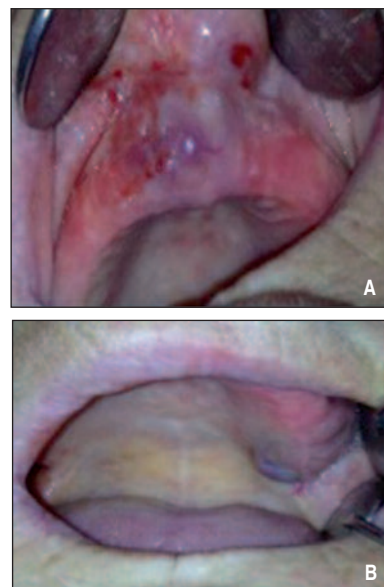
In the present paper, we report a case of multifocal CGCG in an edentulous patient and review the literature reports on this case in the last 37 years that from 1977 to 2014.

## CASE REPORT

A 61-year-old female patient visited our department with the complaint of swelling in the left

posterior region extending to the midline of the upper jaw for a year. It is understood that the swelling started as a small one and progressively increased to the present size for a period of one year. Intraoral examination showed dark-brown and normal mucosa color sessile lesions and buccal expansion was seen in the middle line and buccopalatal expansion in the left posterior maxillary alveolus (Figure 1). Previous trauma or surgery towards to the maxilla was not found, but the patient had a history of using totally dental prosthesis for the last 10 years. On the computerized tomography (CT), the lesions showed well defined osteolytic, unilocular radiolucencies in the maxilla (Figure 2). Either lesion measured more than 2 cm in dimensions. The patient's laboratory values for serum calcium, phosphate, alkaline phosphatase, and PTH were within normal limits. Blood chemistry, including calcium, alkaline phosphatase and inorganic phosphorus was normal.

An incisional biopsy from the posterior maxillary lesion was performed for histopathologic examination. The microscopic view of the lesion sections indicated a multinucleated giant cells, intermixed fibrohistiocytic stroma and multiple vas-



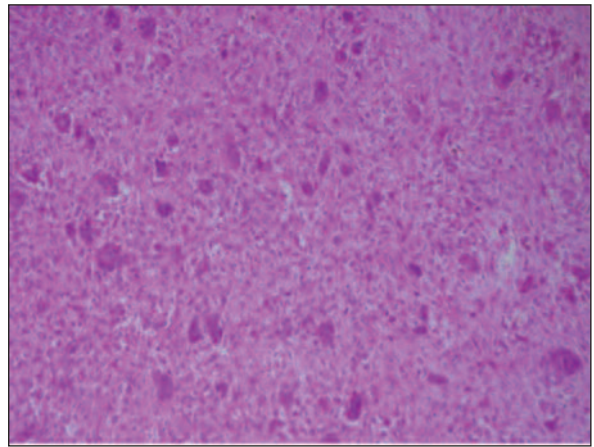
**FIGURE 1A, B:** Intraoral views. Intraoral examination showed dark-brown and normal mucosa color sessile lesions and buccal expansion was seen in the middle line and buccopalatal expansion in the left posterior maxillary alveolus.

cular channels (Figure 3). The diagnosis was compatible with CGCG.

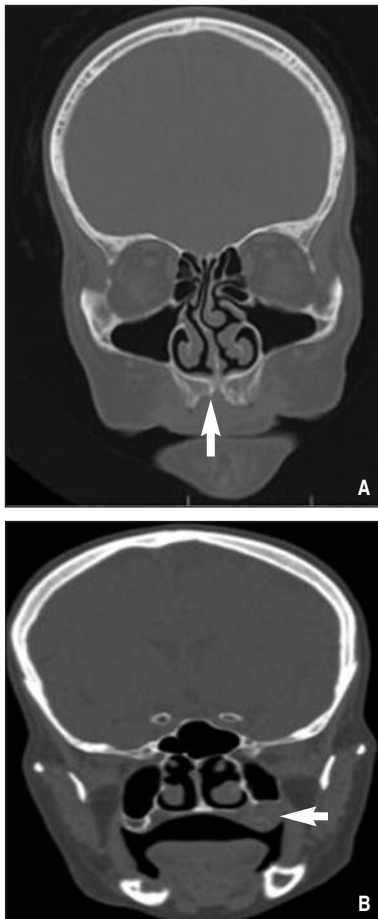
An informed consent was obtained from patient. The curettage of the lesion was performed under local anesthesia. The bone walls of the cavities were drilled with a round burr until healthy bone was encountered. The wound was closed with interrupted sutures. The postoperative course was uneventful (Figure 4). The histopathologic examination confirmed the diagnosis of a CGCG. Any evidence of clinical and radiological recurrence was observed during 12 months of follow-up.

## DISCUSSION

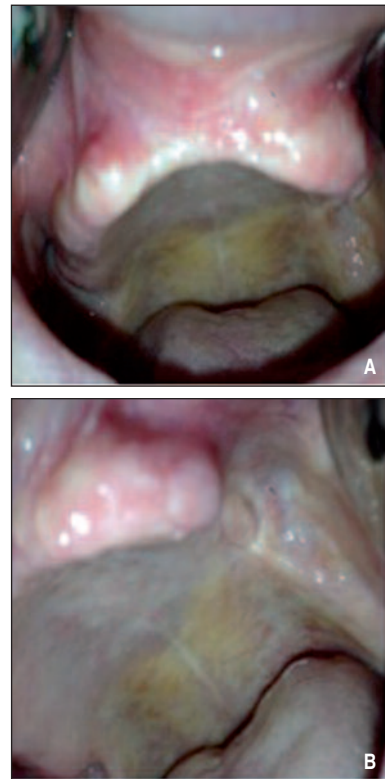
Multifocal CGCG in the jaw is usually associated with several disorders such as hyperparathyroidism, cherubism neurofibromatosis type I and



**FIGURE 3:** Histopathologically showing multinucleated giant cells (X200, H&E).



**FIGURE 2A, B:** The coronal CT scans shows multifocal osteolytic lesions in the maxilla (arrows).



**FIGURE 4A, B:** Intraoral views in the postoperative period.

Noonan syndrome.<sup>5,12,13</sup> While the histologic features of CGCG are indistinguishable from these diseases, but and are different clinical and radiologic features.<sup>2,5,14,15</sup> They have differential diagnosis of multifocal CGCG must be made with these diseases. Brown tumor, which is the bony lesion

of hyperparathyroidism, is caused by increased circulating levels of the parathyroid hormone (PTH), which results in increased. PTH increased osteoclastic bone resorption primarily in the cortical bone.<sup>16</sup> With the increasing effect of PTH, hypercalcemia, hypophosphatemia, hypercalcuria, and hyperphosphaturia may be observed.<sup>17</sup> Cherubism is an autosomal dominant disorder characterized by large bilateral giant-cell lesions in the mandible and some times in the maxilla. Histologically, the lesions may be indistinguishable from CGCGs, so exact the diagnosis of cherubism should be made through the clinical and radiological symptoms.<sup>5</sup> Noonan syndrome is an autosomal dominantly inherited syndrome affecting the nervous system and is associated with short stature, various congenital heart defects, mild mental retardation, short and webbed neck, and hypertelorism.<sup>18</sup> Moreover, the differential diagnosis of CGCG should include another giant cell lesion, such as true giant cell tumor of the bone. Giant cell tumor (GCT) is considered truly neoplastic. While GCT occurs predominantly in the meta-epiphyseal regions of the long bones is rare in the skull, and CGCG usually appears in the mandible and the maxilla.<sup>11,19</sup> Malignant transformation in CGCGs is a rare phenomenon.<sup>2</sup>

In our case, endocrine examination showed no abnormal condition, no hyperparathyroidism or other disorders.

The etiopathogenesis of CGCG in the jaws remains controversial. Local and systemic factors are described in the literature. Trauma appertaining to the local factors, which produces intraosseous hemorrhage and the intraosseous reparative process. However, many patients with CGCG have no history of trauma.<sup>9,10</sup> The possible mutations described in exons 3, 4, 9, and 11 of SH3BP2 gene, neurofibromatosis type I, Noonan syndrome, cherubism, pregnancy, and hormonal disorders such as hyperparathyroidism are reported within systemic factors.<sup>5,8,20,21</sup>

In our case, no clear history of trauma was evident, and swelling increase developed gradually. However the patient has used dental prosthesis for

10 years. The occurrence of local trauma depending on the long-term use of dental prosthesis could be a probable etiologic factor. There was no clear etiologic factor resulting in multifocal CGCG. Although multifocal CGCGs not associated with systemic disorders and syndromes in the jaws are rare, only 15 cases have been reported since 1977 (Table 1).

Various studies have shown that the CGCG occurs in the mandible more than in the maxilla.<sup>5,8,22-25</sup> As shown in the multifocal CGCG cases in Table 1, similar to the results reported on unifocal CGCG, five of the cases were seen only in the mandible, and 10 in the maxillo-mandibular region. However, the lesions in our case were seen only in the maxilla.

The CGCG usually occurs in the first three decades of life.<sup>2,23,25</sup> The mean age of the 15 previously reported multifocal CGCG cases was 29.46 years. Eight cases occurred in patients under the age of 30 years,<sup>5,10,26-30</sup> and seven of them occurred in patients above the age of 30 years (Table 1).<sup>5,31-36</sup> The age of the present case was 62 years.

Previous investigations have reported a significant female preponderance, and hormonal influences have been suggested as a possible causative factor in CGCG development.<sup>37</sup> Based on 15 multifocal CGCG case reports summarized in Table 1, the incidence is clearly higher in women (n=11) than in men (n=4).

Miloro and Quinn have been suggested dividing multifocal CGCGs into synchronous or metachronous lesions. According to their opinion, metachronous lesions are more likely to demonstrate a recurrence because of inadequate initial treatment, whereas synchronous lesions are more likely to demonstrate true multifocality.<sup>35</sup>

However, when we examined previously reported metachronous cases, secondary lesions were seen in a different location from the primary lesion located in the jaw (Table 1).<sup>5,32,33,36</sup> Therefore, the recurrence of a treated lesion is expected to occur in the primary focus. If the recurrence reveals a different focus from the primary focus, it is considered independent or metastatic. Therefore, in

**TABLE 1:** Literature review of the Multifocal CGCG nonassociated with systemic disorders and syndrome in the jaws in subjects.

Author, year	Age	Gender	Location of lesions	Metachronous/Synchronous	Treatment
Davis and Tideman, 1977 <sup>33</sup>	31	F	1. Right mandibular body 2. Left maxilla	Meta-2. lesions identified 4 months and 1 year after lesion 1.	Surgical Curettage
Weldon and Cozzi, 1982 <sup>29</sup>	22	F	1. Left maxilla, 2. and 3. Bilateral mandibular premolar region	Syn	Enucleation
Cassatly et al., 1988 <sup>26</sup>	27	F	1. and 2. Mandibular parasymphysis and body	Syn	Excised (Curettage)
Smith et al., 1990 <sup>36</sup>	41	F	1. Right mandibular ramus, 2. Left maxillary sinus, nasal bone, orbit and right maxillary sinus	Meta-2. lesions identified 9 years after lesion 1.	Surgical Curettage
Loukota, 1991 <sup>28</sup>	25	F	1. Right mandible, 2. Left maxilla	Meta-2. lesion identified 10 months after lesion 1.	Surgical Curettage
Wise and Bridbord, 1993 <sup>30</sup>	23	M	1. Left mandibular body, 2. and 3. Left and right nasomaxillary areas	Syn	Excisional Curettage
Miloro and Quinn, 1995 <sup>35</sup>	37	F	1. Left posterior maxilla, 2. Anterior mandible.	Syn	Surgical Excision
Curtis and Walker, 2005 <sup>32</sup>	62	M	1. Left angle of the mandible, 2. Right mandibular body, 3. Right maxilla	Meta- 2. lesion identified 16 year after lesion 1. -3. lesion identified 1 year after lesion 2.	Partial Maxillectomy
De Lange, 2005 <sup>5</sup>	12	M	1. Left 3 <sup>rd</sup> molar region (2 syn), 2. Left premolar region, 3. and 4. left 2 <sup>nd</sup> molar region and left ramus mandible	Meta (2 syn)- 2. lesion identified 3 years after lesion 1. - 3. and 4. both lesions simultaneously diagnosed 4 years after lesion 1.	Surgical Curettage
De Lange, 2005 <sup>5</sup>	20	F	1. and 2. Left ramus mandible	Syn	Surgical Curettage
De Lange, 2005 <sup>5</sup>	36	F	1. Right anterior region maxilla, 2. Left anterior region maxilla, 3. Right anterior region mandible	Meta- 2. lesion identified 1 year after lesion 1. - 3. lesion identified 3 years after lesion 1.	Surgical Curettage
Martins et al., 2007 <sup>34</sup>	35	F	1. Left anterior maxilla, 2. Right mandibular molar.	Syn	Surgical Curettage
Bilodeau et al., 2009 <sup>31</sup>	42	F	1. Left mandible, 2. Left maxilla	Syn	Enucleated
Kang and Kim, 2010 <sup>27</sup>	17	M	1. Right nasomaxillary area, 2. and 3. bilateral posterior mandible	Syn	There is no detail information about the treatment
Orhan et al., 2010 <sup>10</sup>	12	F	1. and 2. Bilateral ramus mandible	Syn	Surgical Curettage

metachronous case, the fact that secondary lesions thought as recurrences of the primary lesion were seen as a remote possibility by the author of this article.

Synchronous lesions were reported in 9 out of the 15 cases, Among these cases, five had lesions occurring metachronously and one case had both synchronous and metachronous lesions

(Table I). The present case featured synchronous lesions.

All CGCG cases are initially treated by local excision or curettage. However, applications of non-surgical methods have been recommended in the literature, such as intra-lesional corticosteroid injections, systemic administration of calcitonin, and administration of alfa-interferon.<sup>11</sup> Moreover, en-bloc resection has been suggested for the removal of more aggressive CGCG and for providing the lowest recurrence rate.<sup>1,4,38</sup> Laser or cryosurgery

has been suggested in several reports.<sup>10,38</sup> In the literature, the recurrence rates of CGCG ranges from 11.0% to 49.0% or higher, depending on the type and/or treatment.<sup>2,4,5,8,23,39-41</sup>

Consequently, we could not find any case knowledge in the literature about the etiopathogenesis of patients with multifocal CGCG not associated with systemic disorders or syndromes in the jaws. In presented case, local trauma caused by dental prosthesis could be a probable etiologic factor.

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