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Surgical treatment and reconstruction of central giant cell granuloma (CGCG) of the mandible of the aggressive type – case report and literature review

Leczenie chirurgiczne i rekonstrukcyjne centralnego ziarniniaka olbrzymiokomórkowego żuchwy o agresywnym przebiegu – opis przypadku i przegląd piśmiennictwa

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ABSTRACT:

Introduction: Central giant cell granuloma (CGCG) is a benign tumor-like lesion of a bone, mainly localized in the mandible. It usually occurs in children and young adults under 30 y/o., predominantly in females. The etiology of the disease remains unknown. Clinically, two types of CGCG have been distinguished – a non-aggressive one, in which the granuloma grows slowly, often asymptomatically, and aggressive type for which the following features are characteristic: increased bone destruction, severe pain, large size, rapid growth, high recurrence rate and complications such as root resorption, tooth displacement or cortical bone perforation. The treatment of CGCG depends on its type. In cases of granulomas of the aggressive type, the following therapeutic procedures have been proposed: intralesional corticosteroid injections, interferon and calcitonin therapy as well as immunotherapy with anti-bone resorptive human monoclonal antibody like denosumab. However, in most cases nonsurgical treatment is insufficient. Local curettage of the lesion also entails a high risk of relapse. Therefore, radical surgical resection, often combined with bone reconstruction, is the recommended way of treatment for aggressive CGCG.

Case report: The authors present a case of a 31-year-old female patient treated for central giant cell granuloma of the mandible at the Department of Oncological and Reconstructive Surgery, Maria Sklodowska Curie Memorial Cancer Centre and Institute of Oncology in Gliwice. The resection of CGCG localized in the mandible on the right side together with fibular free flap reconstruction has been performed, with satisfactory aesthetic effect. The immunohistochemical examination indicated a positive stain reaction for CD68 and CD31 and expression of Ki67 marker was 13%. No complications were reported in the postoperative period. The six-month follow up revealed no relapse.

Conclusions: The authors claim that radical surgical management should be performed in all patients with CGCG of the aggressive type. Fibular free flap is recommended for reconstruction in large bone defects. This allows tumor-free margins at the resection and satisfactory cosmetic outcome. Quality of life and facial appearance can be improved with dental implantation after a certain period of remission. A regular follow-up is essential as an element of holistic oncological process.

KEYWORDS: fibular free flap, giant cells, granuloma, mandible, reconstruction

STRESZCZENIE:

Wstęp: CGCG jest łagodną, guzopodobną zmianą kości, najczęściej lokalizującą się w obrębie żuchwy. Występuje ona głównie u dzieci i młodych dorosłych poniżej 30 r.ż., z przewagą płci żeńskiej. Etiologia schorzenia nie została do końca poznana. Klinicznie wyróżnia się dwie postacie CGCG: (1) nieagresywną, kiedy ziarniniak rośnie powoli, często bezobjawowo, oraz (2) agresywną, charakteryzującą się: nasilonym niszczeniem kości, dolegliwościami bólowymi, większymi rozmiarami guza, jego gwałtownym wzrostem i powikłaniami, takimi jak: resorpcja korzeni czy perforacja blaszki kostnej, oraz wysoką tendencją do nawrotów. Leczenie ziarniniaka zależy od jego postaci. W przypadkach CGCG o agresywnym przebiegu zastosowanie znajduje leczenie zachowawcze pod postacią sterydoterapii w infekcjach miejscowych, aplikacji interferonu, kalcytoniny czy denosumabu. Jednak w większości przypadków ta forma terapii bywa nieskuteczna. Również wyłyżeczkowanie zmiany niesie

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wysokie ryzyko nawrotu choroby. Stąd najlepszym sposobem postępowania jest radykalne chirurgiczne usunięcie zmiany, często wymagające operacji rekonstrukcyjnej ubytków kostnych.

Opis przypadku: W niniejszej pracy autorzy przedstawiają przypadek 31-letniej chorej, leczonej w Klinice Chirurgii Onkologicznej i Rekonstrukcyjnej Centrum Onkologii – Instytutu im. Marii Curie-Skłodowskiej Oddziału w Gliwicach z powodu centralnego ziarniniaka olbrzymiokomórkowego żuchwy. U pacjentki wykonano operację resekcji fragmentu żuchwy po stronie prawej wraz z guzem z następową rekonstrukcją wolnym płatem strzałkowym, uzyskując zadowalający efekt kosmetyczny. Przebieg pooperacyjny był niepowikłany. W badaniu immunohistochemicznym wykazano dodatnią reakcję z przeciwciałami CD68 i CD31, a współczynnik Ki67 wyniósł 13%. W półrocznym okresie obserwacji nie odnotowano wznowy ziarniniaka.

Wnioski: Autorzy uważają, że radykalne leczenie chirurgiczne powinno być stosowane u wszystkich pacjentów z agresywną postacią centralnego ziarniniaka olbrzymiokomórkowego. Z uwagi na częste naciekanie kości w tych przypadkach, zalecają rekonstrukcję wolnymi płatami kostnymi z mikrozespoleniem naczyniowym. Pozwala to na uzyskanie radykalności onkologicznej w połączeniu z dobrym efektem kosmetycznym. Jakość życia i estetyka twarzy może być udoskonalona dzięki implantom zębowym, zastosowanym po odpowiednim czasie remisji choroby. W całościowym leczeniu onkologicznym ogromną rolę odgrywa ścisła, regularna kontrola w ośrodku prowadzącym.

SŁOWA KLUCZOWE: komórki olbrzymie, rekonstrukcja, wolny płat strzałkowy, ziarniniak, żuchwa

LIST OF ABBREVIATIONS

CD – cluster of differentiation
CGCG – central giant cell granuloma
CT – computed tomography
FFF – fibular free flap
HPF – high-powered field
MMP – methaloproteinase
MRI – magnetic resonance imaging
VEGF – vascular endothelial growth factor

INTRODUCTION

Central giant cell granuloma (CGCG) is a benign tumor-like bone lesion that accounts for approximately 7% of all benign tumors within the mandible [1]. CGCG was first described by Jaffe in 1953 [1]. It is mainly located in the maxilla and mandible, on its front surface [2]. It is estimated that the ratio of CGCG location in the mandible and jaw is between 2:1–3:1 [3, 4, 5]. Neville et al. report that this tumor can be found in the mandible with a frequency of 70% [6]. Other locations, such as the sphenoid or temporal bone, are rare [7, 8, 9]. CGCG occurs mostly in children and young people under the age of 30, more often in females. The etiology of this lesion remains unclear. The influence of such factors as injuries, repair processes after intra-articular inflammation or hemorrhages, transformation of hemorrhagic cysts and even genetic predisposition is suggested. Some association of CGCG development in patients with dental implants is also being considered [10, 11, 12].

Histologically, central giant cell granuloma is characterized by the presence of fibrous tissue with numerous hemorrhagic foci and giant multinucleated cells, preceded by bone tissue trabeculae [12, 13, 14].

The clinical course of CGCG varies – from asymptomatic slow-growing edema to painful, aggressive lesion causing bone lysis, root resorption and tooth displacement [1]. Most authors rely on Choung et al.'s division, who distinguish two types of central giant cell granuloma – aggressive and non-aggressive [15]. The non-aggressive type refers to cases in which the granuloma grows slowly, often asymptomatically. The aggressive type is characterized by increased bone destruction, pain, larger tumor size, its rapid growth, complications including root resorption, bone perforation and a high tendency to relapse [15]. Due to the described clinical course and proliferative activity of granuloma, some authors suggest a common pathogenetic basis for CGCG and other malignancies such as giant cell tumor [10, 16].

Among the likely predictive factors that may indicate the aggressive clinical course of CGCG, Souza et al. mention increased number and size of nucleogenic regions (AgNOR) and high values of Ki-67 proliferation factor [17]. Due to the fact that the process of osteolysis is accompanied with increased angiogenesis, a high value for the determination of VEGF and expression of metalloproteinase 9 (MMP-9) has been suggested as potential predictors of malignancy. Their increased activities are observed not only in the case of central giant cell granuloma, but also in giant cell tumor or aneurysmal bone cyst [18].

In the clinical trial, giant cell granuloma is a well-delineated, painless tumor, covered with unchanged mucosa, often causing facial deformity [19].

The radiological image of the central giant cell granuloma presents well or weakly delimited single- or multi-locular lumens with or without destruction of the cortical lamina [20]. In the case of larger changes, tooth separation may be observed [19]. Computed tomography is an extremely valuable diagnostic tool in the assessment of the extent of granuloma and the degree of bone tissue infiltration. MRI of the craniofacial area enables a better assessment of infiltration by soft tissue granuloma.

Treatment in most cases involves surgical removal of the lesion by curettage in the case of low-aggressive types of granuloma, and wide excision in more advanced cases [1, 4, 19]. However, sparing surgical treatment (currettage) is related to a greater risk of relapse than radical management [1, 21]. En bloc resection of large CGCG of the aggressive type is often associated with the necessity to restore bone defect, most often with a free flap with microanastomo-

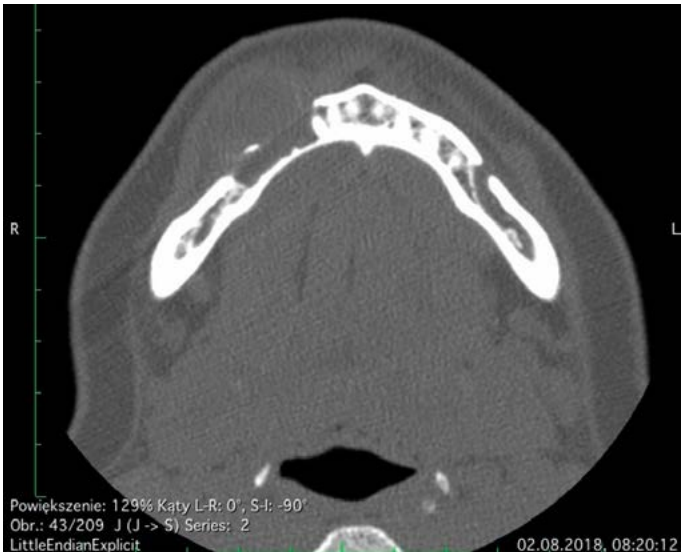

Fig. 1. Computed tomography of the mandible – transverse projection. Detailed description in the text.

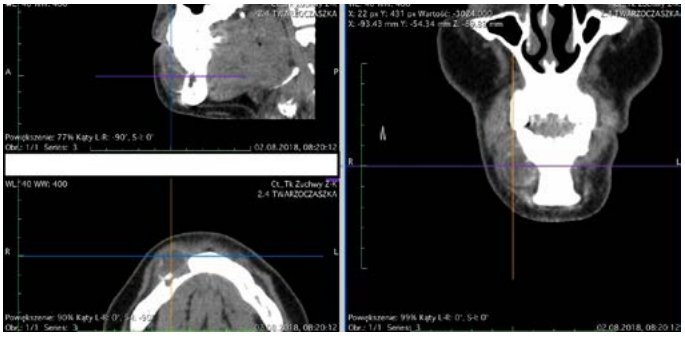

Fig. 2. Computed tomography – saggital, transverse and frontal projection. Detailed description of the tumor in the text.

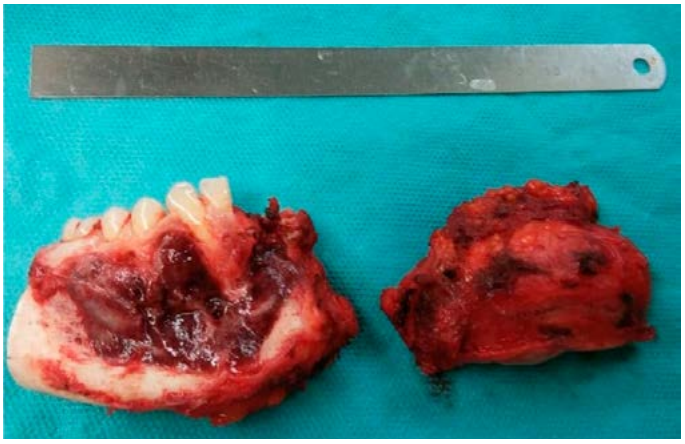

Fig. 3. Divided specimen of a tumor infiltrating the mandible. 'Skeletonized' fragment of the bone acted as a template for the reconstructive part of surgery. 15-cm-long model ruler.

sis' [1, 22]. An alternative to surgical treatment is local injectable steroid therapy, calcitonin, interferon alfa 2A, bisphosphonates or denosumab therapy [23, 24, 25, 26].

In the differentiation, giant cell tumor, ameloidoma, cherubism, aneurysmal bone cyst, or brown tumor in the course of hyperparathyroidism should be taken into account [7]. It is advisable to determine the level of calcium, phosphorus and parathyroid hormone in the blood serum in order to avoid an incorrect diagnosis.

The authors present the case of a 31-year-old patient who was treated surgically for central giant cell granuloma of the jaw at the Department of Oncological and Reconstructive Surgery, Maria Sklodowska Curie Memorial Cancer Centre and Institute of Oncology in Gliwice.

CASE REPORT

A 31-year-old patient to the Maria Sklodowska Curie Memorial Cancer Centre and Institute of Oncology in Gliwice in September 2018 due to a tumor of the alveolar part of the mandible on the right side. The lesion appeared in February 2018. In March 2018 initial curettage was performed in the dentist's office in the patient's place of residence. In histopathological examination, giant cell epulis was diagnosed. After two months, the tumor has grown and expanded dynamically. Topical steroid therapy was used without a therapeutic effect. In August 2018 computed CT of the mandible was performed. The presence of a solid focal lesion with density from 25 to 80 HU and dimensions 22 x 16 mm was observed, covering the soft tissues forward and on the right side of the mandible as well as bone of the mandibular body, in which bone lysis was observed at a length of about 17 mm (Fig. 1.–2.).

In September, a tumor biopsy was performed, based on which the diagnosis made after surgery (curettage) was confirmed.

At the first visit to the Cancer Centre in September 2018 an irregular, hard tumor of a diameter of about 3cm was found within the alveolar part of the mandible on the right side, in the vestibule of the mouth, making the skin of the submental area bulge. The histopathological and cytological tests previously obtained were again verified at the Cancer Pathology Department of the Institute of Oncology in Gliwice. Based on the obtained images in correlation with the clinical condition and radiological image of the tumor, the central giant cell granuloma of the mandible was finally diagnosed. The patient was qualified for surgical treatment. In January 2019, the patient underwent surgery of segmental resection of the mandible with a tumor on the right side from tooth 32 to 47 and reconstruction with a fibular free flap harvested from the left lower limb. The operating specimen contained a 7 x 4 x 2 cm tumor covered with a fragment of mucosa (5 cm long and 0.9 cm wide). On the cross-section, the tumor was embellished, brown-gray in color with hemorrhage and cartilage foci. The tumor infiltrated the mandible bone in the area of 5 x 2.5 cm. The margins of healthy tissue were: anterior – 1cm, posterior – 1.5 cm (Fig. 3.).

There were no complications in the perioperative course. A satisfactory cosmetic effect was obtained (Fig. 4a.–b.), no complications within the donor site were observed.

Pathomorphological examination confirmed the diagnosis of central giant cell granuloma and radical resection of the lesion (Fig. 5.). In additional immunohistochemical studies, a positive stain reac-

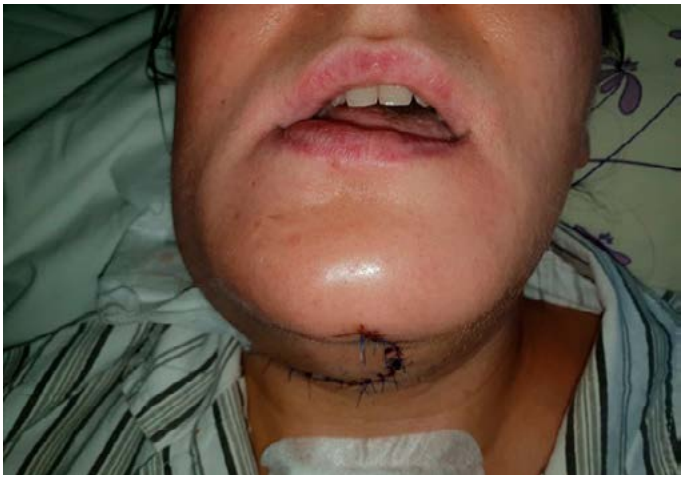

Fig. 4a. The 3rd postoperative day. Mild edema of the right side of reconstructed mandible and sutures on the neck.

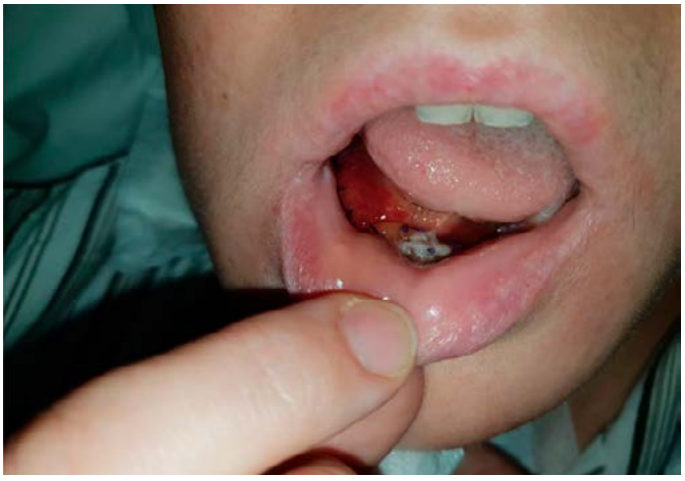

Fig. 4b. The 3rd postoperative day. Vestibule of the mouth. Suture line is visible in the photo.

tion was obtained for CD68 (98 multinucleated cells / 10 HPF) and CD31 (64 vessels/10 HPF) antibodies, and the Ki67 marker was 13%. In addition, no metastases were found in the intraoperative biopsy of the cervical lymph nodes of the right side.

In the six-month follow-up, no relapse of CGCG was found either in the clinical trial (Fig. 6.) or on the basis of a follow-up CT scan (Fig. 7.). Satisfactory aesthetic appearance was obtained in the patient, as well as good functioning in terms of chewing, talking and swallowing.

DISCUSSION

Central giant cell granuloma is a benign tumor. Despite this, in some cases certain features may indicate an aggressive nature. They include the clinical course and the characteristic histopathological picture.

As already mentioned in the introduction to this article, the aggressive type of CGCG is evidenced by its rapid growth, tendency to relapse, and increased bone destruction. In the described case, all the above-mentioned features were observed. The granuloma quickly increased after the initial curettage. In August 2018, the tumor was about 2 x 1.5 cm, a month later its diameter was about 3 cm, and the size of the surgical material in January 2019 was rated at 7 x 4 x 2 cm. It can therefore be assumed that in 5 months the granuloma's size almost tripled. Such growth dynamics clearly addresses in favour of the aggressive character of CGCG. In addition, imaging studies demonstrated intensive infiltration of the mandible (bone lysis of approximately 17 mm in length), which was confirmed pathomorphologically in the surgical material (infiltration in the area of 5 x 2.5 cm) (Fig. 5.). All these clinical features are evidence of the aggressive nature of the described case.

The histopathological result may also indicate an aggressive type of granuloma. In the case, a typical image was obtained for the central giant cell granuloma with a characteristic richly vascularized fibrocellular stroma with small oval and spindle-shaped mononuclear cells and clusters of multinucleated cells (Fig. 8.). This corresponds to numerous data from literature. Amaral et al. report

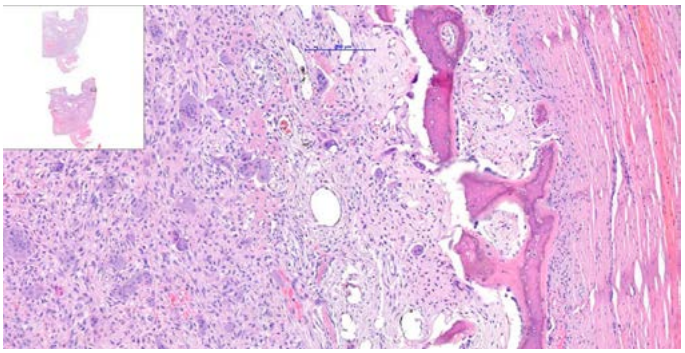

Fig. 5. Central giant cell carcinoma. The mandible bone infiltrated by CGCG, destruction of the bone. Tumor margins free from neoplastic tissue. Magnification x10.

that central giant cell lesions are characterized by multinucleated giant cells similar to osteoclasts surrounded by mononuclear cells. Papanicolaou et al. observe numerous multinucleated giant cells on a well vascularized fibroblastic bedwith the presence of oval and spindle-shaped cells forming a heterogeneous population of macrophages and fibroblast-like cells [10, 28].

In additional immunohistochemical tests, a positive reaction for CD31 and CD68 antibodies was observed. CD68 is a highly expressed glycoprotein in macrophage, human monocytes, osteoclasts or histiocytes (Fig. 9.). According to Sargolazaei et al., its presence in multinucleated giant cells reaches 100% in the case of CGCG, while it is significantly higher in non-aggressive than aggressive type of granuloma [29].

In turn, CD31 is the main intercellular endothelial protein. Due to the rich vascularization of the stroma in CGCG, the expression of this protein is also worth analyzing (Fig. 10.). Razavi et al. demonstrated higher CD31 activity in aggressive forms of giant cell granuloma compared to non-aggressive forms. Similar observations concerned the Ki67 cell proliferation marker [30], which in our case was 13% (Fig. 11.). If the presented immunohistochemical tests are performed at the stage of tumor diagnosis, they can help in determining the nature of CGCG, and thus will be of key importance in making the decision about the appropriate treatment of the patient. If non-aggressive CGCGis demonstrated, less

Tab. I. Advantages and disadvantages of different methods of conservative treatment of central giant cell granuloma.

TYPE OF CONSERVATIVE TREATMENT	ADVANTAGES	DISADVANTAGES
Local steroid therapy (e.g. triamcinolone for 4 weeks)	Easy administration; low invasiveness; short treatment time; least side effects	Suppression of the adrenal cortex, contraindications to therapy for comorbid diabetes, gastric ulcer and immunodeficiency
Calcitonin by nasal spray or subcutaneously	An effective alternative in the case of contraindications for surgical treatment	High price; daily drug administration; long-term therapy (1–1.5 yrs); side effects in the form of nausea, vomiting, dizziness, rash
Denosumab administered subcutaneously	Increased bone mineralization; effective for small changes	Side effects: pain, impaired healing
Bisphosphonates	Supportive action for other forms of treatment	Risk of osteonecrosis – dependant on the route of administration, duration of treatment and supporting factors, such as past injuries, dental procedures or inflammation of the teeth and periodontitis

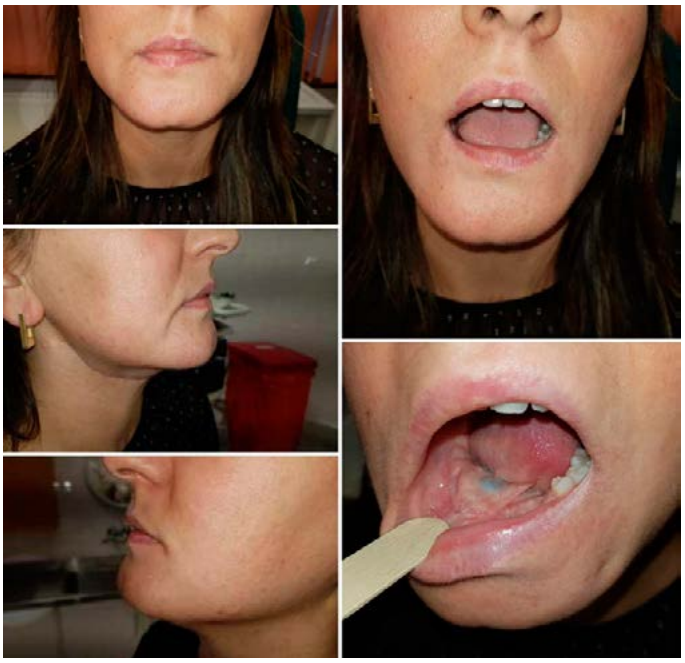

Fig. 6. Clinical picture of the patient in 6-month follow-up. No relapse of CGCG was observed.

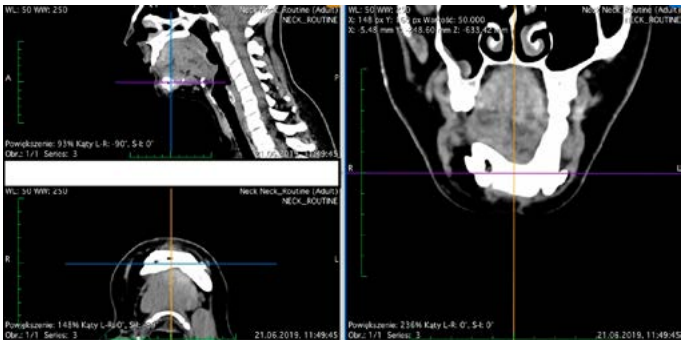

Fig. 7. Computed tomography of the maxillo-facial complex in 6-month follow-up. The bony part of the fibular free flap is marked. No features of CGCG relapse were observed.

radical methods of therapy may be considered, including conservative treatment, e.g. local steroid therapy. The aggressive type of CGCG should be treated as radically as possible and as soon as possible after diagnosis.

Among the various forms of CGCG treatment, surgical and non-surgical methods should be mentioned. The first include subcutaneous calcitonin injection or its nasal spray application. The action of calcitonin in this disease entity is based on inhibiting bone resorption and osteoblast stimulation [31]. Kaban et al. and Tarsitano et al. propose subcutaneous uses of interferon 2a in single daily doses due to its anti-angiogenic effect or increased bone production [25, 32]. Local steroid therapy is also being attempted. This treatment is especially recommended for young people. Non-surgical methods help to avoid disfiguring scars and deformations. The efficacy of denosumab, a monoclonal antibody that inhibits bone resorption, has also been proven. According to Bredell et al., continuation of immunotherapy should last 12 months [33].

Some authors also mention the beneficial effects of bisphosphonates, such as aledronic or zoledronic acid [26]. They both inhibit osteoclasts. However, their possible side effects, undoubtedly related to the intravenous route of administration, should be kept in mind (Tab. I.) [34]. Like all types of treatment, the ones presented above have their pros and cons. They were presented in the form of a table (Tab. I.).

Most authors agree that in the aggressive type of giant cell granuloma, the most effective treatment method is radical resection, especially after ineffective healing of the lesion. In order to avoid facial deformities and maintain a good quality of life, more conservative surgery is possible, provided that it is supplemented with additional therapy [35], e.g. topical administration of the steroid [36]. Rachmiel et al. proposed a six-week local steroid therapy followed by a surgery with a good end result and a 5-year relapse-free period [37].

Due to frequent bone infiltration (especially of the mandible) in the case of aggressive CGCG and the associated need for bone fragment resection, it is essential to plan the reconstruction in advance. The authors recommend the use of bony free flaps based on vascular microanastomosis, such as the fibular free flap or iliac crest free flap. A similar solution was presented by Tosco et al. in 2 patients treated for CGCG, in whom the mandible bone could not be preserved [1]. Shirani et al. also considered reconstruction using iliac crest free flap in a 13-year-old female patient with giant cell granuloma of the mandible, however, due to the risk of massive bleeding and the lack of group-compatible blood for transfusion, they decided to use a titanium plate [2].

Long-term follow-up of patients with CGCG is a key element of comprehensive treatment. Lange et al. report that relapses in non-aggressive types occur in 11–49% of cases, and in the aggressive type CGCG reach as much as 72% [21]. In the absence of relapse,

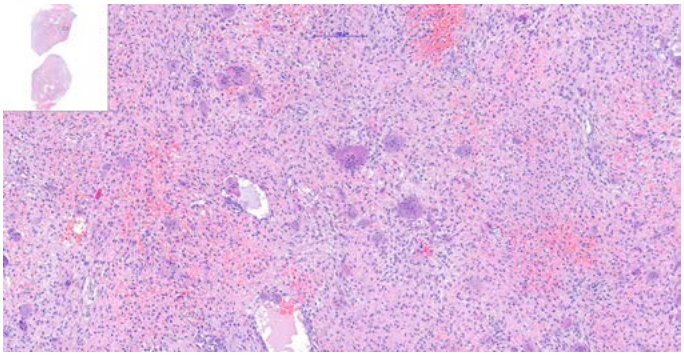

Fig. 8. Central giant cell granuloma. Fibromuscular stroma with small, oval and fusiform cells, multinuclear cells, thin-walled vessels and extravasations. Magnification 10x.

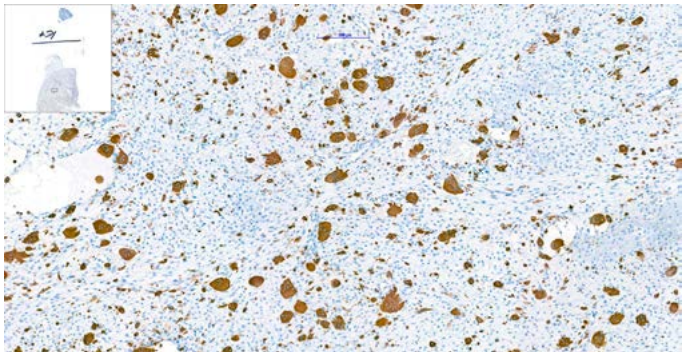

Fig. 9. Central giant cell granuloma. CD68 expression in giant cells. Magnification x10.

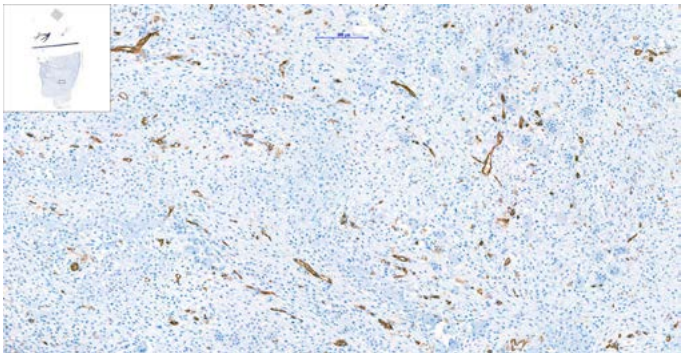

Fig. 10. Central giant cell granuloma. CD31 expression in blood vessels. Magnification x10.

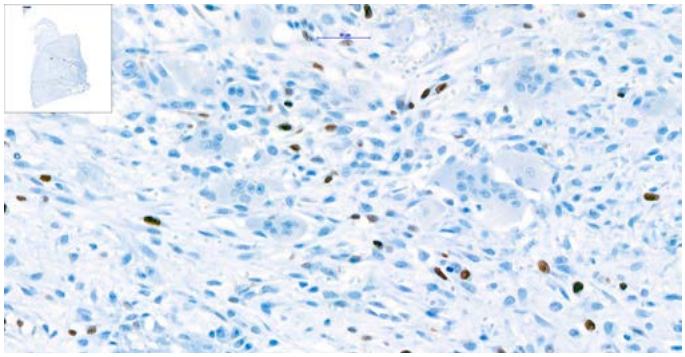

Fig. 11. Central giant cell granuloma. Ki67 expression. Magnification x40.

implantation of dental implants is an important aspect to maintain full functionality and aesthetics of the oral cavity. In the described case, the patient is being prepared for this stage of treatment.

CONCLUSIONS

Central giant cell granuloma may exhibit local malignancy, which consists of a specific clinical picture (rapid growth dynamics, tendency to relapse and increased destruction of the infiltrated bone) and a characteristic histopathological image imitating other malignant tumors with similar morphology. Therefore, complementary research and search for effective markers are needed to allow early differentiation of both forms and appropriate treatment planning.

If an aggressive type of CGCG is diagnosed, radical surgical treatment is recommended (after prior acceptance of the patient and taking into account the age of the patient). According to the authors, the surgery of aggressive type of CGCG of the mandible should involve segmental resection of the mandible with free flap reconstruction with vascular microanastomosis (preferably iliac crest or fibular flap). This allows complete excision of the lesion with a satisfactory functional and aesthetic effect, with the option of implanting dental implants in the event of a longer relapse-free period.

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