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Ossification of Mandibular Central Giant Cell Granuloma (CGCG) in Neurofibromatosis Type 1 Patients

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Abstract

Background/Aim: In patients afflicted with the autosomal dominant hereditary tumor predisposition syndrome neurofibromatosis type 1 (NF1), central giant cell granuloma of the jaw (CGCG) is observed in rare cases. In NF1, the lesion is caused by mutations in the *NF1* gene. The report summarizes the diagnosis, treatment and follow-up of 2 NF1 patients and provides a brief evaluation of case reports on NF1-associated CGCG.

Case Report: Both females with CGCG (age: 14 and 22 years) had either one or more jaw lesions. The lesions were removed with curettage to avoid dental injuries. In both cases, recurrences occurred, which led to re-ossification of the mandible through repeated surgical procedures after several years. The literature review based on 33 sufficiently documented cases shows clear differences between genders concerning the number of affected individuals in NF1. In addition, age at diagnosis of CGCG differed between NF1 patients compared to other RASopathies, namely Noonan syndrome. Cherubism-like lesions with tissue examination have only rarely been described in NF1 patients. In many reported cases surgical treatments were successful. However, in individual cases significantly mutilating interventions have been carried out, which raises questions about alternative treatment options. The proportion of purely diagnostic procedures without information about the further course is significant and limits information about the prognosis.

Conclusion: NF1-associated CGCG have predominantly been treated surgically. In these patients, CGCG can also be expected beyond adolescence. The examination of NF1 patients should include the assessment of potential facial manifestations with appropriately selected imaging. Long-term monitoring of the findings is mandatory.

Keywords: Neurofibromatosis type 1, central giant cell granuloma, RASopathy, dysembryoblastic neuroepithelial tumor, DNET, loss of heterozygosity, LOH.

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Introduction

Neurofibromatosis type 1 is an autosomal dominant tumor suppressor gene disorder that occurs at a frequency of approximately 1:2,500 live births (1). NF1 is characterized by neoplasms called neurofibromas that originate from nerve sheath cells of the peripheral nervous system. However, the genetic changes associated with *NF1* extend far beyond the anatomy and function of neurogenic structures. NF1 is also a bone disease (2). Bone tissue tumors and tumor-like lesions can arise in NF1 patients, for example non-ossifying fibromas (NOF), preferably in the long bones (3). Central giant cell granuloma (CGCG) of the jaws has morphological similarity to NOF and is assessed as the biological equivalent of this entity in the facial skeleton (4). CGCG (*a.k.a.*, central giant cell lesion, CGCL) of the jaw is registered much less frequently in NF1 than NOF (5). Case reports have shown that CGCG tumor cells in NF1 patients have a second mutation of the *NF1* allele in addition to the constitutive *NF1* mutation (5-8). There is little data on the treatment of NF1-associated CGCG. The purpose of this report is to document the course of surgically treated CGCG in NF1 patients and to provide a brief overview of previously published cases.

Methods. The analysis is based on the long-term follow-up of two NF1 patients who underwent surgical treatment for CGCG of the mandible at the Clinic for Oral and Maxillofacial Surgery, University of Hamburg. The surgical interventions were performed over a longer period and, following a follow-up examination several years later, showed therapeutic success, *i.e.*, extensive or even complete ossification of the lesions.

This experience prompted a literature search for CGCG in NF1 patients. Literature was searched for CGCG in NF1 patients using the keyword combinations "neurofibromatosis/neurofibromatoses", "neurofibromatosis type 1", "giant cell granuloma/giant cell granuloma of jaw", "giant cell lesion/ giant cell lesion of jaw", "epulis", "mandible", "maxilla", "bone", and "facial skeleton" in both medical and general databases. The studies used for evaluation were checked for further literature references on the topic, and additional studies were identified through this manual search. The main selection criteria for inclusion in the results were details in the reports that clearly indicated that the patients had NF1, met the currently valid diagnostic criteria for the entity, and had bone disease that met the diagnostic criteria of the CGCG. The following data were collected: age (at the time of CGCG diagnosis) and gender of the individuals, location of the lesion(s), therapy, and information on the course of the disease. Since the disease is classified as RASopathy, the data obtained was compared with published information on CGCG in other RASopathies. The evaluation of the literature showed that the only quantitatively usable comparison population was Noonan syndrome.

Case Report

Case 1. The female NF1 patient, who was 22 years old at the time of initial treatment, was initially treated surgically for an extensive plexiform neurofibroma encasing the thorax. The extended diagnosis included an examination of the dental status. OPG revealed a retromolar osteolysis of the mandibular right third and second molars region resembling a honeycomb outline (7). At the time of the first treatment, neither the wisdom tooth nor the second molar responded to adequately applied cold stimuli. Curettage of the bone lesion with extraction of the third molar was without complications at the age of 23 years (ys.). The histological diagnosis confirmed the suspicion of a CGCG. Subsequent molecular genetic testing identified both germline and somatic mutation of the *NF1* gene in the tumor cells of the bone lesion. In the further course of the disease, two interventions for recurrent osteolytic lesions at this site were necessary, localized at the root of the second molar and retromolar region. In every case, CGCG was confirmed histologically. Nine months after the last revision, at the age of 27 years, a complete ossification of the root of the second molar was found (Figure 1A-D). This tooth reacted to adequately applied cold stimuli.

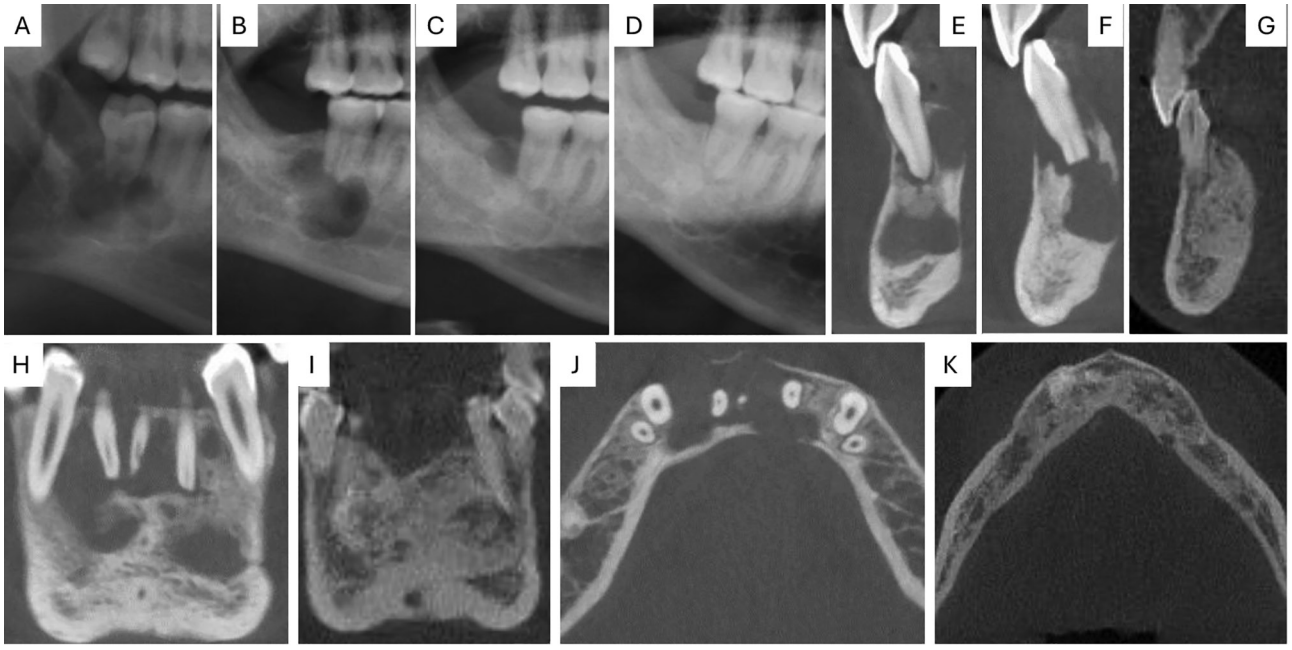

Figure 1. *Radiologic course of treated central giant cell granulomas (CGCG) in 2 patients with neurofibromatosis type 1 (NF1). Case 1: A-D; Case 2: E-K. Case 1: (A) Extensive CGCG with bone defect from the mandibular ramus to the second molar of the right mandible. (B) Two years after initial treatment, a peri-radicular recurrence around the second molar became apparent. Another two years later, the image (C) showed a recurrence distal to the root of the second molar. (D) Almost five years after initial treatment, the bony defect had been ossified. Figures A-D are cropped images of orthopantomograms. Case 2: Figures E-G show the changes in the central lower incisor over time (sagittal section, CBCT). (E) Periradicular osteolysis, (F) loss of the root tip, (G) ten years later, the bone had ossified, and the tooth had a bony coating. (H) and (I) Coronal view of the mandibular front at the start of treatment (H), and after ten years (I) (ossification). (J) and (K) Axial view of the osteolysis, particularly of the anterior mandible, at the start of treatment (J), and 10 years later (K). During this treatment period, the patient retained a complete set of teeth in the anterior mandible. Figures E-K are cropped images of cone beam computed tomograms (CBCT).*

Case 2. The patient was 14 years old at the start of oral surgical treatment (8). The diagnosis of NF1 had been made 1 year earlier. The patient had received a cranial MRI due to recurrent headaches, which showed a cerebral tumor. The suspected diagnosis at the time was dysembryoplastic neuroepithelial tumor (DNET). Lesions in the lower jaw were noticeable on the MRI, which justified the referral to the clinic for oral and craniomaxillofacial surgery for further clarification. Lesions were suspected to be of osseous origin. Curettage of the lesions was combined with application of hydroxyl-apatite. An impact of the known Hashimoto's thyroiditis on bone regeneration was excluded after detailed diagnostics. The filling of the cavities with bone replacement material was only stable after repeated curettage of recurrent CGCG that had caused oral fistulas. Marginal ossification of the bone lesions as well as new lesions were observed during treatment (Figure 1E-K). The last imaging following repeated interventions had suggested signs of marginal ossification of some lesions. The molecular tissue analysis of the CGCG identified the constitutive *NF1* mutation (detected in blood and tumor tissue) and a somatic mutation of the *NF1* allele in CGCG tumor cells (8).

Seven years later, the patient had a check-up on her own initiative. A few months earlier, she had had the brain tumor removed due to symptomatic epilepsy. The diagnosis of the entity agreed with the suspected diagnosis of the initial examination.

The overview image of the jaw showed the ossification of the mandibular lesions. In some areas small, dense, and bone-like, spherical structures were shown, which

were interpreted as residues of the previously inserted bone replacement material (Figure 1E-K). The cone beam computed tomography of the mandible depicted both the osseous densification zones within the previous lesions and the hydroxyl apatite particles embedded in the bone. The bony parts of the filled cavity outweighed those of the bone substitute material. Both substances were tightly packed together. The apical osteolysis of the anterior tooth treated with a root canal had been known since the previous surgical treatment. In summary, the x-ray findings showed the bony healing after repeated curettage of the CGCGs and partial defect filling with bone replacement material.

Ethics. All procedures performed in this study were performed following the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Before analysis, data were anonymized, and the investigators studying the radiographs were blinded to diagnosis and individual identity. The investigations into anonymized data were performed following Hamburgisches Gesundheitsdienstgesetz (Hamburg Health Services Act). This type of investigation does not require the approval of the local ethics committee. The examinations are part of a scientific thesis to fulfill the requirements for the attainment of a doctorate at the University of Hamburg (FKK). The patients have consented in writing to the publication of the examination results presented here.

Literature survey. Evaluation criteria. A literature survey was performed using the items "neurofibromatosis (type 1)", (central) giant cell granuloma" and "jaw" revealing 32 reports with histologically proven CGCG/CGCL (5-35) (Table I). Reports were excluded if it was not clear whether a tissue examination of a jaw lesion had been carried out and if the diagnosis of the syndrome could not be determined from the information provided. Cases diagnosed with "epulis" are previous names for connective tissue lesions that can be based on different pathogeneses. These reports were included in the evaluation if both a diagnosis of giant cell granuloma could be inferred from the report and the current diagnostic criteria for neurofibromatosis type 1 were met. The reports included in the evaluation either had extensive dissolution of the bone (9) and/or described the lesion as a giant cell granuloma in the text (11).

Clinical characteristics. A total of 33 patients were included in the evaluation. The number of women clearly outweighed the number of men (female: *n*=22, male: *n*=11). Women were considerably older than men at the time of diagnosis and treatment (women: 27.8 years, range=7-53; men: 18.5 years, range=7-50). The proportion of patients under 18 years of age at first treatment in this group was 15 individuals (45.5%; mean age: 11.3), eight of whom were women and seven males (mean age of women=10.75, mean age of males=12). There was no gender difference between young CGCG patients. The high proportion of adult women with NF1-associated CGCG becomes clear when comparing affected men and women aged 30 years or older [11 women *vs.* 2 men; age of women: mean age=40.9 years, range=31-53; age of men: mean age=40 years (30 and 50)]. The proportion of women in this age group was 33.3% of the entire collective.

Age at time of diagnosis. Information on the timing of multiple lesions was recorded. Since both synchronous and metachronous findings could have been recorded in the case of multiple lesions in a patient, both temporal references could, in principle, occur in any case (metachronous: 7, synchronous: 14).

Imaging techniques. Orthopantomography dominated radiological imaging (*n*=20 cases). Especially in early examinations, the radiological findings were recorded using plain radiographs of a wide range of format (peri-apical radiograph to skeletal survey). Later, computed tomography (*n*=10) and cone beam computed tomography (*n*=7) predominantly were used as cross-

Table I. *Reports of NF1 patients with central giant cell granuloma of the jaw [including details of previous reports on the two patients presented here (8, 9)].*

Author(s)/ Year/ Reference ()	NF1[1]/Age at time of CGCG diagnosis[2]/ Sex	Localization/ Number of lesions (n) (previous data on CGCG diagnostics)	Temporal relationship of CGCG diagnoses in the case of multiple lesions	Jaw imaging	Diagnosis and treatment (Actions)[3]	Histology/ Genetics	Treatment/ Result	Follow-up after treatment[4]
Goetsch, 1955 (9)	Y/48/F	Maxilla (n=1)	N.a.	Plain radiographs (lesion covered retained premolar, extensive bone lesion)	Excision	Epulis	Several recurrences	N.d.
Daly *et al.*, 1970 (10)	Y/34/F	Mandible (multiple maxillary lesions of same type seen by oral examination)	Synchronous	Skeletal survey	Biopsy (mandible) Hyperparathyreodism, parathyroid adenoma removal, normal thyroid, Vitamin D substitution	Epulis	N.d.	3 years
Kerl and Schroll, 1971 (11)	Y/41/F	Mandible (33 years/history of epulis); Maxilla and mandible (41 ys)	Metachronous, later synchronous	Plain radiograph	Excision	Epulis, CGCG	N.d.	N.d.
Kaplan *et al.*, 1994 (12)	Y/51/F	Mandible (n=1)	N.a.	OPG	Biopsy	CGCG	N.d.	N.d.
Giese, 1995 (13)	Y/30/M	Maxilla (30 years), mandible (48 years)	Metachronous	OPG	Excision, tooth extraction	CGCG	Maxilla: No recurrence; Mandible: N.d.	Maxilla: 18 years Mandible: N. d.
Van Damme and Mooren, 1994 (14)	Y/11/M	Maxilla, mandible (multiple lesions)	Metachronous, later synchronous	OPG, periapical radiograph	Excisions, tooth extractions (no chemotherapy for CGCG; Growth hormone therapy to treat abnormally short statue at age 15 years)	CGCG	Recurrence (9 months), later: bone healing and new lesions	4 years (deceased)
Ardekian *et al.*, 1999 (15)	Y/38/F	Mandible (n=2, bilateral)	Synchronous	OPG, occlusal radiograph, CT	Curettage	CGCG	N.d.	N.d.
Ruggieri *et al.*, 1999 (16)	Y/11/F	Mandible (n=1)	N.a.	OPG	Curettage	CGCG	Rercurrence (12 months: curettage) no further recurrence	5 years
Krammer *et al.*, 2003 (17)	Y/11/F	Maxilla (n=1)	N.a.	CT	En-bloc removal; Genetic study (Blood)	CGCG; NF1 germline mutation: c.4268 A>G. No NF1 LOH in lesion*	N.d.	N.d.
Yazdizadeh *et al.*, 2004 (18)	Y/22/M	Maxilla (n=1)	N.a.	OPG	Resection	CGCG	No recurrence	1 year
De Lange and van den Akker, 2005 (19)[5]	Y/31/F	Maxilla, mandible (n=4 lesions, 2 each jaw)	Synchronous and metachronous	N.d.	Surgically removed	CGCG	Repeated recurrences	N.d.

Table I. *Continued*

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Author(s)/ Year/ Reference ()	NF1[1]/Age at time of CGCG diagnosis[2]/ Sex	Localization/ Number of lesions (n) (previous data on CGCG diagnostics)	Temporal relationship of CGCG diagnoses in the case of multiple lesions	Jaw imaging	Diagnosis and treatment (Actions)[3]	Histology/ Genetics	Treatment/ Result	Follow-up after treatment[4]
De Lange and van den Akker, 2005 (19)[5]	Y/17/M	Mandible (n=1)	N.a.	N.d.	Surgically treated	CGCG	No recurrence	N.d.
Martinez-Tello *et al.*, 2005 (20)	Y/11/M	Mandible (Cherubism-like lesions)	Synchronous	OPG, CT, MRI	Biopsy, curettage	CGCG	Slightly reduced jaw lesion	1.5 years
Edwards *et al.*, 2006 (21)	Y/12/M	Maxilla (n=1)	N.a.	CT	Hemimaxillectomy	CGCG	Recurrence (6 years), further maxillary resection, vascularized fibular bone graft ("aggressive CGCG")	1 year
Edwards *et al.*, 2006 (21)	Y/34/F	Maxilla, mandible (multilocular)	Metachronous	OPG	Mandibular ostectomy 10 years before (CGCG); Triamcinolone injection for local recurrence of CGCG surrounding dental implants failed radiographic improvement of bone lesion and justified debridement, bisphosphonate application	CGCG	"Aggressive" CGCG	N.d.
van Capelle *et al.*, 2007 (22)	Y/13/M	Mandible (Multilocular, cherubism-like)	Synchronous	OPG, MRI	Biopsy; Genetic study (Blood)	Osteoclast-rich lesion; NF1 germline mutation (exon 37; IVS37 + 1G>A)	N.d.	N.d.
Friedrich *et al.*, 2007 (6)	Y/7/F	Mandible (n=1) (Recurrence)	N.a.	OPG	Curettage; Genetic study (Blood, tissue of jaw lesion)	CGCG, NF1 LOH in tissue	No further recurrence; emergence of tumor-related impacted premolar	15 years
Chrcanovic *et al.*, 2011 (23)	Y/18/F	Mandible (n=2), bilateral lesions	Synchronous	OPG, CT	Enucleation, curettage, tooth extraction	CGCG	Advanced bone regeneration	7 months

Table I. *Continued*

Table I. *Continued*

Author(s)/ Year/ Reference ()	NF1[1]/Age at time of CGCG diagnosis[2]/ Sex	Localization/ Number of lesions (n) (previous data on CGCG diagnostics)	Temporal relationship of CGCG diagnoses in the case of multiple lesions	Jaw imaging	Diagnosis and treatment (Actions)[3]	Histology/ Genetics	Treatment/ Result	Follow-up after treatment[4]
Hachach-Heram *et al.*, 2011 (24)	Y/14/F	Maxilla, mandible (multilocular, cherubism-like)	Synchronous	OPG, CT	Debulking procedure, bone augmentation	Osteoclast-rich lesion, genetically proven cherubism; evidence of cutaneous neurofibroma; family history of NF1 and cherubism	Consolidation of bone, aesthetic improvement, dental implants for prosthesis	3 years
Kumar *et al.*, 2012 (25)	Y/50/M	Mandible (n=1)	N.a.	OPG	Biopsy	CGCG	No recurrence	1 year
Stewart *et al.*, 2014 (5)	Y/18/M	Maxilla, mandible (at least n=2)	N.d.	N.d.	Genetic study (Blood, tissue)	CGCG; NF1 germline mutation; NF1 somatic mutation in cell culture of jaw lesion (1721+5_1721 + 20dupinsAluSb1)	N.d. (syndrome-associated lesions were assessed as "aggressive")	N.d.
Stewart *et al.*, 2014 (5)	Y/43/F	Maxilla, mandible (at least n=2)	N.d.	N.d.	Genetic study (Blood, tissue)	CGCG; NF1 germline mutation; NF1 somatic mutation in cell culture of jaw lesion [c.5234C>G, p.S1745* (germline); c.3916C>T p.R1306* (somatic)]	Recurrence of lesion(s) in both jaws (syndrome-associated lesions were assessed as "aggressive")	N.d.
Trindade *et al.*, 2015 (26)	Y/42/F	Maxilla, mandible (n=1 each)	Synchronous	CT	Curettage, marginal ostectomy	CGCG	No recurrence	3 years
Friedrich *et al.*, 2016 (8)[6]	Y/14/F	Mandible (multifocal)	Synchronous	OPG, CBCT, MRI	Curettage, bone substitute material; Genetic study (Blood, tissue of jaw lesion)	CGCG; NF1 germline mutation, NF1 somatic mutation in cell culture of jaw lesion [c.1527 + 1187 C>G (germline); c.952del (somatic)]	Recurrences, later: re-ossification	8 years
Latifi *et al.*, 2017 (27)	Y/35/F	Maxilla (n=1)	N.a.	OPG, CBCT	Biopsy	CBCG	Recurrence, tooth extractions ("aggressive lesion")	1 year

Table I. *Continued*

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Author(s)/ Year/ Reference ()	NF1[1]/Age at time of CGCG diagnosis[2]/ Sex	Localization/ Number of lesions (n) (previous data on CGCG diagnostics)	Temporal relationship of CGCG diagnoses in the case of multiple lesions	Jaw imaging	Diagnosis and treatment (Actions)[3]	Histology/ Genetics	Treatment/ Result	Follow-up after treatment[4]
Tosios *et al.*, 2019 (29)	Y/53/F	Maxilla, mandible, (Multilocular, cherubism-like)	Synchronous	OPG, CBCT (first radiograph taken at 36 years already showed lesions)	Biopsy; Radiotherapy (Maxilla)	CGCG	N.d.	N.d.
Santos *et al.*, 2019 (30)	Y/13/F	Maxilla, mandible (n=2)	Metachronous	OPG	Mandible: subtotal mandibulectomy (13 years), maxilla: curettage (26 years later)	CGCG	No recurrence ("aggressive behavior of CGCL")	26 years (mandible) 3 years (maxilla)
Vanelli *et al.*, 2020 (31)	Y/11/M	Mandible (n=1)	N.a.	CT	Biopsy; Surgical removal; Genetic study (Blood)	CGCG; NF1 germline mutation (c.2789_2791delATC; p.Tyr930_Pro931delinsSer)	N.d.	6 years
Friedrich *et al.*, 2021 (32)	Y/16/F	Maxilla, mandible, (Multilocular, cherubism-like)	Synchronous	OPG, CBCT, MRI	Osteotomy; Genetic study (Blood, tissue of jaw lesion)	CGCG; NF1 germline mutation (c.99delA; p.Val34Serf*10); no second NF1 hit in jaw lesion detected	Stable disease (both jaws affected)	10 years
Friedrich *et al.*, 2022 (7)[6]	Y/22/F	Mandible (n=1)	N.a.	OPG, CBCT	Curettage, tooth extraction; Genetic study (Blood, tissue of jaw lesion)	CGCG: NF1 germline mutation and NF1 somatic mutation in jaw lesion [c.3942G>A; p.Trp1314* (germline), and c.289C>T; p.Gln97* (somatic)]	Recurrences (n=2); follow-up: bone completely reossified	5 years
Dogan and Gunaydin, 2023 (33)	Y/7/F	Maxilla, mandible (n=2)	Metachronous	CT	Excision including adjacent bone	CGCG	No recurrence	3 years
Sarantou *et al.*, 2024 (34)[7]	Y/9/M	Maxilla, zygoma, mandible (Multilocular, cherubism)	Synchronous	CT	Biopsy; Genetic study (Blood)	CGCG; SH3BP2 and NF1 germline mutation (c.2205T>A; p.Tyr735*)	N.d.	N.d.

Table I. *Continued*

Table I. *Continued*

Author(s)/ Year/ Reference ()	NF1[1]/Age at time of CGCG diagnosis[2]/ Sex	Localization/ Number of lesions (n) (previous data on CGCG diagnostics)	Temporal relationship of CGCG diagnoses in the case of multiple lesions	Jaw imaging	Diagnosis and treatment (Actions)[3]	Histology/ Genetics	Treatment/ Result	Follow-up after treatment[4]
Barut *et al.*, 2024 (62)	Y/29/F	Mandible (a second mandibular lesion proved neurofibroma of alveolar process on the contralateral side), Assessment of craniofacial MRI performed two years before diagnosis revealed evidence and growth of the lesion	N.a.	Bite wings (not informative), OPG, CBCT, (MRI)	Biopsy, extirpation of lesion, triamcinolone injection for local treatment of CGCG failed reduction of bone lesion and justified resection of the lesion (alveolar process resection)	CGCG: NF1 germline and NF1 somatic mutation in jaw lesion (c.3871-2 A>G and p. Q786fs*30)	Recurrence: 14 months after extirpation, bone defect	1 year

*Authors point out that up to that time, LOH detection of the NF1 gene in CGCG had not been achieved in NF1 patients.[1]A case was included in the evaluation, if the report contains sufficient information on clinical findings for the diagnosis of "NF1" to be made according to the revised diagnostic criteria (36) or refers to an already established diagnosis of the disease. The third case of reference 19 was first reported in reference 14. [2]Age refers to the author's/authors' initial examination for a jaw lesion (CGCG/epulis). In individual cases with significant findings that suggested an earlier diagnosis of the bone lesion, this finding was noted. [3]Biopsy is marked with a question mark if the publication does not specify which examination technique was used for the histological findings referred to. [4]The information on the course of events is a reproduction of the authors' reports. For patients with repeated interventions for CGCG, the follow-up time after the last intervention was estimated in individual reports. [5]The report describes a third case of NF1-associated CGCG, which has already been published by van Damme and Mooren (1994) (14). [6]Includes information about the two reported cases already detailed in earlier reports of the principal author. [7]Report describes genetically confirmed cherubism and NF1 in one patient. CGCG/CGCL: Central giant cell granuloma/lesion; F: female; M: male; Y: yes; N.a.: not applicable; N.d.: no data; NF1: neurofibromatosis type 1; NF1: NF1 gene; SH3BP2: SH3 domain-binding protein 2 gene; CT: computed tomography; CBCT: cone beam computed tomography; MRI: magnetic resonance imaging; OPG: orthopantomogram.

sectional imaging techniques, occasionally supplemented by magnetic resonance imaging (*n*=5) (no information: 5 patients).

Cherubism-like CGCG in NF1. Based on the radiological findings, five cases were described as cherubism-like. An earlier report detailed the extensive surgical treatment of cherubism in a young patient with a family history of both cherubism and neurofibromatosis. The patient had cutaneous neurofibromas and café-au-lait spots. Genetic evidence of the SH3BP2 mutation was obtained (Table I). One recently published case had genetically proven the coincidence of NF1 and cherubism in an individual (Table I).

Treatment and follow-up. References to biopsies were obtained from 17 patients. Surgical procedures were documented in 24 patients (72.7%) (previous biopsies were not considered in this assessment). The spectrum of procedures ranged from local excision to the subtotal removal of a jaw. Descriptions of the surgical procedures varied [excision *n*=6, curettage/enucleation *n*=12; osteotomy/(en-bloc-) resection *n*=5, extensive jaw resections/debulking *n*=3]. In 3 cases only 'surgical

removal' or 'treatment' was reported. External radiation therapy was used in only one case to treat a maxillary CGCG. If the reports describe treatment beyond biopsy evidence of the lesion, the reports describe predominantly surgical measures (Table I). However, two case reports documented the failure of local cortisone application to cure the lesion. In another case vitamin D was substituted (Table I).

Recurrences occurred in 11 cases (31.4%). No recurrence/bone healing could be derived from the reports of 12 cases. The evaluation also includes cases that documented healing of the CGCG at one point and then reported a new lesion at another site (multiple mentions). There was no information in ten cases about the course of the disease with regard to the CGCG.

Discussion

The course of the two cases described here indicates that surgical treatment of the lesions can be carried out successfully. However, in both cases the treatment was only successful after multiple surgical interventions which had been carried out over a longer period. Follow-up checks on NF1 patients with CGCG are essential to assess treatment results.

Frequency of CGCG. Information on the frequency of CGCG in NF1 is currently missing. Table I summarizes some findings from reports of CGCG reported in patients with NF1. The data are based on case reports or individual cases identified from larger analyses of NF1-associated lesions. The highest number of patients in a report is three (19). An earlier literature review of jaw findings in published NF1 cases mentioned 3 of 174 individuals were affected by CGCG or epulis (1.72%) (13). In another study of 48 NF1 patients one case with mandibular CGCG was recorded (3.57%) (37). A proportion of over 3% of CGCG identified on orthopantomograms NF1 patients (and histologically verified) refers to the data analysis of a clinic that is a supra-regional center for the treatment of NF1 patients with tumor manifestations of the head and neck region. A conclusion on the frequency of the lesion in patients with this RASopathy cannot be drawn from the records.

A comprehensive molecular genetic study recruited tissue samples of bone lesions collected by a very large research group (5). The researchers represented institutions that had genetically and clinically examined NF1 patients from national reference centers. In the study group, several NOF of long bones and three patients with CGCG of the jaw were analyzed. Only two individuals fulfilled diagnostic criteria of NF1 (5). There is therefore reason to suspect that CGCG is a lesion that is rarely noticed in NF1 patients. At least, the lesion is rarely studied in NF1. At present, meta-analyses on the diagnosis and treatment of CGCG are not helpful for assessing frequency and characteristics of the lesions in NF1. A detailed analysis of 2270 published CGCG cases explicitly excluded syndromic patients with this finding from the analysis and therefore those results cannot be used to systematically assess the diagnosis, treatment, and prognosis of NF1-associated CGCG (38). However, CGCG is generally a rare finding in dental diagnostics. The evaluation of incidental findings on 6,252 panoramic radiographs from a Canadian general dental practice revealed only one patient with CGCG (0.016%) (39). A study on the frequency and characteristics of CGCG in the Dutch population recorded 96 patients with CGCG (40). This is the only population-based study to date on the frequency of CGCG. The incidence was reported as 0.00011%. The authors calculated CGCG incidence to be 1.05 per 10^6 person-years for males and 1.25 for females. The first population-based evaluation of CGCG did not report syndrome-associated cases. A subsequent report based on 83 patients of the same study group identified 3 patients with NF1 (3.61%) (19) (Table I). The overview (Table I) shows that the germline mutation of an NF1 patient with CGCG has been identified in at least four cases. A further seven cases (including one case with LOH detection) describe both the germline and somatic mutations of the respective NF1 cases with CGCG.

Number and timing of CGCG. An earlier review of CGCG described multilocular jaw lesions in 50% of cases (n=16)

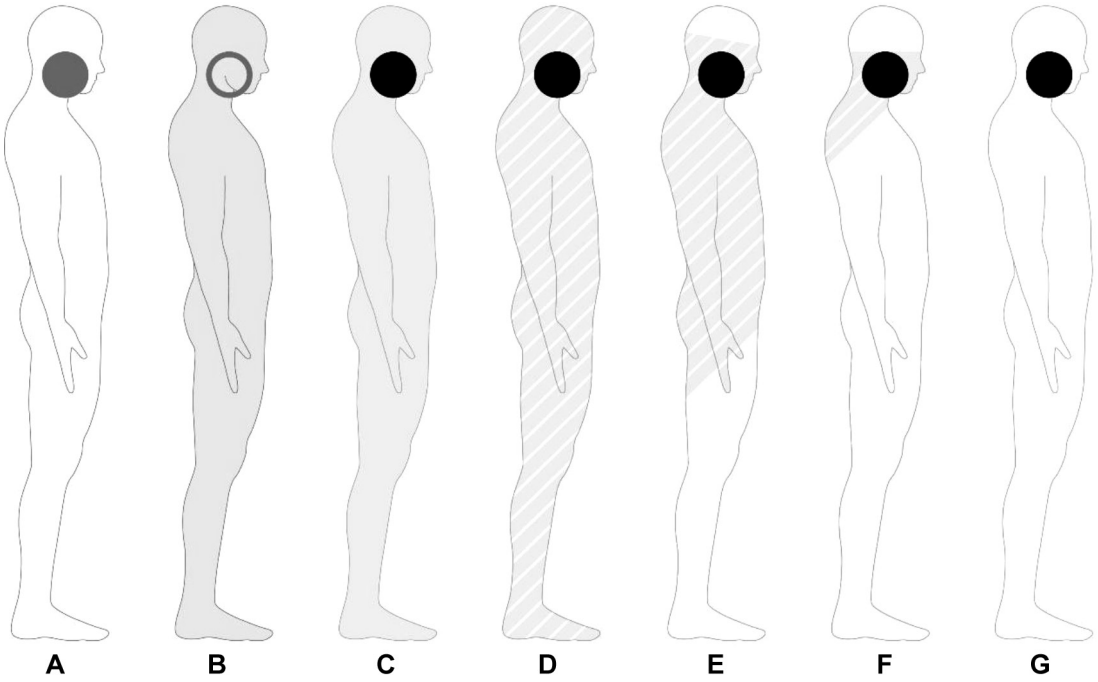

Figure 2. *Schematic representation of the genetic basis of central giant cell granuloma of the jaw. (A) In a healthy patient, a mutation arises in cells of the jaws that causes a CGCG (sporadic lesion). For these cases, mutations in the KRAS, FGFR1 and TRPV4 genes were identified in the tumor cells (46). There are no mutations in the NF1 gene in sporadic CGCG (49). (B) In a patient with RASopathy - with a few exceptions - the genotype is defined by an autosomal dominant mutation. This mutation can initiate a CGCG under circumstances that are still unclear. According to current knowledge, a second mutation is not necessary for the development of CGCG in these patients. The ring here merely illustrates the region of tumor manifestation; the genetically highlighted status in the tumor area is unchanged with respect to the mutation of the RAS-controlling genes compared to the organism as a whole. (C) Patients with NF1 have a germline mutation of the NF1 gene. A CGCG occurs when the function of the NF1 allele is lost in the jaw's tumor cells (second hit). (D) The germline NF1 mutation can occur post-zygotically (genetic mosaic) but can be detected in large areas of the body. The sketches (E) and (F) illustrate that the NF1 mutation mosaic may only affect parts of the body (segmental neurofibromatosis). In individual cases, only a circumscribed region (here the jaw and surrounding area) is affected (E). Up to now, CGCG has not been described to have occurred in cases of mosaic (in this case: segmental) NF1 (D-F). (G) Theoretically, the LOH of the NF1 gene could cause a CGCG to develop exclusively in the tumor cell of the jaw. The phenotype would correspond to that of a sporadic CGCG as shown in (A). Previous reports (49) give no reason to suspect that this phenotype has been realized.*

but gives no information on the general medical history of the patients (41). The authors of the Dutch study provided a literature survey showing that multiple lesions are rare and often associated with a syndrome (42). However, their own cases (*n*=2) with *synchronous* multiple lesions were unrelated to a syndrome (42). On the other hand, multifocal CCGGs recently were considered a sure sign that calls for the discovery of syndromic causes (28). As the second case of the present report shows, the reverse conclusion does not apply, because solitary CGCG can also occur with a known syndrome (Table I). Since metachronous lesions have been noted relatively frequently (19, 40, 42) when treating unilocular lesions, it is important to thoroughly examine both jaws during follow-up.

CGCG and hyperparathyroidism. Multifocal CGCG has been described for NF1, but hyperparathyroidism should always be excluded (15). However, the coincidence of NF1, hyperparathyroidism and CGCG is rare (10). The NF1 patient's medical history can contribute significantly to the differential diagnosis of tumor-associated and endocrine-related jaw lesions of this type (43).

CGCG vs. neurofibroma of jaws in NF1. Mandibular neurofibromas arising from the inferior alveolar nerve`s branches are rare in NF1 and cannot be differentiated from CGCG on plain radiographs (44). Surgical exploration is recommended in these cases (45). Histological confirmation of the diagnosis is mandatory. Non-odontogenic osseous lesions of the jaws are rare in NF1 patients (44). Coincidence of neurofibroma and CGCG in NF1 has been noted and both lesions were spatially separated (Table I).

Genetics and RASopathy. In CGCG, a mutation is often detected in the tumor cells that influences the control of 'RAS', *i.e.*, the human analogue of the *rat s*arcoma virus gene (46). In several neoplasms and in some inheritable syndromes different mutations of genes were identified that control RAS. These mutations cause reduced suppression of RAS, so that cell proliferation is increased. Impaired control of RAS signal transduction is a key factor in the development and persistence of neoplasms. An important genetic cause of several syndromes are constitutive mutations that reduce RAS regulation. The syndromes are collectively classified as "RASopathies". Rasopathies are rare diseases, have considerable phenotypic variability, and occasionally develop CGCG (47). The phenotype of sporadic and syndromic CGCG does not differ clinically, radiologically or in the histological assessment. Information on the prevalence of RASopathies varies considerably and is based on estimates, recently preferably derived from clinical studies, meta-analyses, and reviews (1, 47, 48). NF1 is the most common RASopathy. Clinical and genetic studies have shown that in some patients with RASopathy, the causal mutation is present in only part of the body's cells (mosaic status). This genetic variability also applies to NF1. Whether genetic mosaics occasionally identified in RASopathies are associated with CGCG is unknown (Figure 2). Apparently, studies on sporadic CGCG excluded any *NF1* mutation (49). It is unknown whether sporadic CGCG cases also include patients who have a higher burden of genetically modified cells beyond the local findings ('segmental' RASopathy). At the present state of knowledge, this theoretically possible diagnostic group (mosaic RASopathy with CGCG) is based on pathogenetic speculation that cannot be substantiated or at least discussed from current reviews (38). Molecular genetic diagnostics decoded the sporadic CGCG as a neoplasm caused by mutations involved in the control of RAS (TRPV4, KRAS, and FGFR1) (46). According to current knowledge, the genetic basis of CGCG in NF1 differs from other syndromic CGCGs because in NF1 both alleles of the tumor suppressor gene are defective in the bone lesion (5, 6). In contrast, in syndromic CGCG of the jaws arising in other RASopathies, the loss of one allele is apparently sufficient to trigger or promote the development of a neoplasm, *e.g.*, CGCG (4) (Figure 2). This genetic finding was identified also in implant-related peripheral giant cell granuloma (50, 51). Apparently, the diagnosis of oral giant cell granuloma (both central and peripheral) encompasses several mutations in genes controlling RAS-dependent signaling pathways. Figure 2 presents a schematic representation of some known and potential genetic constellations that could cause a CGCG.

CGCG, RASopathies and NF1. A recent literature review on syndrome-associated and sporadic CGCG of the jaw considered reports on 22 patients with NF1 (52). The authors point out that the epidemiological data are primarily determined by the numerically dominant Noonan syndrome-associated CGCG. The mean age at the time of CGCG diagnosis was calculated at 10.5 years, significantly below that of the analysis presented here, which only took NF1 patient data into account. The sex ratio determined by Luna *et al.* (52) with a slightly more common manifestation in males (1.15:1 M/F ratio) contrasts with our own evaluations, which show that this lesion is found much more often in females. The authors confirm the previously made assumption (28) that multiple CGCG should raise suspicion of a syndromic disease and recall difficulties in distinguishing a solely radiological/clinical identified RASopathy-related bone lesion (20) from cherubism (31, 52). The review by Luna

et al. points out some differences between syndrome-associated and sporadic CGCG (age, sex ratio, number of lesions) but emphasizes the wide range of overlapping findings (52).

Cherubism and cherubism-like lesions in NF1. Multiple and expansive CGCG with symmetrical localization and extension are a hallmark of cherubism. This disease is caused by a mutation of sarcoma (Src) homology 3 domain (SH3)-binding protein 2 gene (*SH3BP2)*. *SH3BP2* mutations do not occur in sporadic CGCG of the jaw (53). However, cherubism can be oligosymptomatic and, in rare cases, only occur on one side and thus resemble the radiological findings of a CGCG [reviewed at (54)]. Some cases of RASopathies may develop a cherubism-like phenotype due to multifocal CGCG or even complete formation of the characteristic facies in extensive bimaxillary lesions (32). Recently, a molecular genetic study has shown one case where NF1 and cherubism may coexist (34). Different RASopathies can have different mutations that affect RAS control and generate the same bone tumor phenotype. The overlapping phenotypes of genetically different RASopathies suggest that the finding of a CGCG of the jaw should prompt a careful examination of the affected individual (20). The phenotypic similarity of initial cherubism with extensive CGCG may complicate clinical differentiation of the pathogenesis of the lesion(s), particularly in children and adolescents (32, 54). In cherubism, the involution of bone lesions in adolescence is to be expected in many cases. Surgical intervention is recommended only in patients with significant disfigurement and/or limitation of vital functions due to the lesion (54). For sporadic and syndrome associated CGCG, the course of the disease is difficult to predict (54). Large lesions can destroy considerable parts of the facial skull and the risk of recurrences following surgery is unpredictable. The present review identified no case of spontaneous regression in a case of NF1-associated CGCG/cherubism-like lesion. The range of therapeutic measures for NF1-associated CGCG is wide (Table I). Our two cases presented in more detail show that local treatment measures are successful in the early stages and lesions with limited bone defects. However, the re-ossification was only evident after several years of follow-up. In a previous case with LOH detection of the NF1 gene in the CGCG, the one-time intervention to treat the recurrence was sufficient to bring the bone to healing and to initiate regular tooth replacement (6) (Table I). On the other hand, extensive lesions with life-threatening complications can be controlled through appropriate surgical measures, including providing patients with implant-supported prosthetics (24).

Imaging. The imaging used in the analyzed case reports represents the development of radiological technology over time and thus the improved representation of the bone in currently available cross-sectional images based on computed tomographic techniques. The importance of MRI cannot be determined due to the few application reports. However, craniofacial MRI analysis can be used successfully to identify CGCG (Table I). On plain radiographs and CT images, the predominant radiological feature of CGCG is marked, homogeneous osteolysis of the jaws. The boundaries of the lesion are usually sharply defined, with a variable and nonspecific outline. Resorption of tooth roots is occasionally observed (23, 38). A specific radiological pattern of CGCG cannot be derived from the imaging. Surgical exploration to confirm the diagnosis is an essential part of the consultation and treatment of patients (Table I). The radiological images of hereditary cherubism and cherubism-like lesions are similar.

Treatment of CGCG. CGCG treatment is mainly surgical (52). However, various drug therapies have been applied and recommended (32, 42). Indications for drug therapies are potentially large lesions whose surgical treatment could have a mutilating effect (55). CGCG recurrences are relatively common and apparently independent of the classification of the lesion as a sporadic or syndrome-associated event. Long-term monitoring of treated lesions is recommended. Information on the treatment and success of syndrome-associated CGCG in RASopathies is sparse (56).

The treatment measures of syndrome-associated lesions apparently do not differ from cases of non-syndromic CGCG (52). The presented literature review shows that previous interventions for NF1-associated CGCG have been predominantly surgical (Table I). Extensive resections have been used in cases diagnosed as aggressive CGCG (21, 30). Regarding the biology of syndromic CGCG, some authors suspect that these lesions can more often be assigned to the aggressive phenotype (52). The evaluation presented here summarizes some reports in which the authors assessed the NF1-associated CGCG as "aggressive". However, a classification based on a diagnostic standard for this judgment is not documented. The "aggressive" courses described in this way show, in individual cases, significant destruction of the bones and recurrence of the lesion. However, only a few reports made such a judgment (Table I). In summary, the presented overview does not provide sufficient information on the proportion of aggressive CGCG in this syndrome. The term has been used by some authors without providing a definition or classification for this diagnosis.

For example, Stewart *et al.* (5) examined CGCG and NOF for evidence of *NF1* mutation in their review of the consistency of Jaffe-Campanacci syndrome as a *sui generis* entity or variant of NF1-associated phenotype. Most patients were affected by NF1. A clinical summary of the study is the indication that many lesions were classified as "aggressive". The authors do not present a definition that allows the application of this judgement (5). General overviews on CGCG assume that aggressive lesions are only found in a small proportion of affected patients (40, 42). Overall, a relatively large number of CGCG have been cured in NF1 patients, often after several procedures. Cherubism-like lesions can also be classified histologically as an aggressive form of CGCG (24). The few reports on cherubism-like CGCG in NF1 patients do not provide sufficient information on the course of treatment. Only one paper describes successful surgical interventions and a course that documents the partial regression of CGCG (24). In our own patient, the clinical-radiologic findings of cherubism were unchanged until the third decade of life. The honeycomb-like expansion of the facial bones reached the orbit. The facial changes were less noticeable than described for cherubism (and were slightly asymmetrical). The very small number of reported cases prevents assessment of the course of cherubism-like CGCG in NF1 based on literature and our own experience.

The analysis of the data on the treatment of NF1-associated CGCG documents the paucity of knowledge on the use of chemotherapeutic agents in this indication. Only few case reports document the use of cortisone in the treatment of CGCG (Table I). Larger reviews on the medical treatment of CGCG do not provide any information on syndrome-associated therapeutic concepts or therapeutic concepts adapted to this diagnosis regarding chemotherapy. For example, de Lange *et al.* mention intralesional therapy with calcitonin without it being evident from the reports whether an NF1 patient had been treated with this drug (19). Reviews of CGCG therapy describe the use of calcitonin, corticosteroids, drugs that affect the proliferation of osteocytes, immunomodulators or anti-angiogenic drugs (40). None of the reviews address whether there are differences in the efficacy of these drugs in syndromes, e.g. NF1 or other RASopathies, and sporadic cases. One comprehensive review explicitly excludes syndrome-associated CGCG from the analysis (38). From the reports to date, no assessment can be made as to whether chemotherapy of NF1-associated CGCG will be successful. In these cases, not only the genetic disposition of the patients must be considered, but also co-morbidities that may influence patient compliance (8, 35).

Prognosis. The prognosis of syndrome associated CGCG is complicated by the variety of underlying diseases capable of developing the neoplasm [multifaceted etiology and pathogenesis (49)] and the incompletely understood characteristics of the CGCG's tumor cells. The tumor cells have the characteristics to drive osteoclasts (57) and the ability to form osteogenic matrix (58). Osteogenic capability may be a prerequisite for the spontaneous resolution of CGCG after incisional biopsy, which has been reported anecdotally (59, 60). It is unknown whether the

spontaneous involution of bone lesions known in cases of cherubism occurs similarly in cases of cherubism-like lesions/CGCG in NF1. The currently available case reports on cherubism-like NF1 do not provide any data that would suggest such a course.

Conclusion

In most cases, the identification of individual CGCG is probably the result of a sporadic mutation in an often narrowly defined region, *i.e.*, a lesion arising in and confined to a part of the jaws (38). Individuals with multifocal findings should have extended examinations (28, 61, 62). CGCG should be considered in the diagnosis of jaw lesions in NF1 patients of all ages and irrespective of number of lesions. Imaging the skull is included in whole-body MRI examinations and provides a diagnostic basis for the early detection of CGCG (62). General guidelines for tumor follow-up should be applied to CGCG, both in sporadic and syndrome-associated cases.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Reinhard E. Friedrich: Treatment of patients, project, administration, conceptualization, investigation, methodology, writing – original draft, writing – review and editing. Felix K. Kohlrusch: Conceptualization, methodology, writing – review and editing. Martin Gosau: Supervision and editing. Christian Hagel: writing, review and editing. All authors approved the final version of the article.

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