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Recurrent Mandibular Giant Cell Lesion in Neurofibromatosis Type 1: Second Hit Mutation on the *NF1* Gene in the Osseous Lesion

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Abstract. *Background/Aim: In the autosomal dominant hereditary disease neurofibromatosis type 1 (NF1), lesions of the jaw develop in isolated cases, which are diagnosed as central giant cell granuloma (CGCG). This study aimed to clarify the genetic basis of a bone lesion in a syndromic patient. Case Report: The NF1 patient had developed a CGCG that recurred after local excision. Blood and tumor tissue were studied for NF1 mutations using advanced molecular genetic methods. Examinations of blood and tumor tissue provided evidence of the constitutive mutation in both samples. A further mutation was detected in the tumor, which was interpreted as a somatic mutation. The detection of somatic mutation in the tissue was successful both on native and routinely fixed material. Conclusion: The study supports current assessments of CGCG as a benign neoplasm. In NF1 patients, the phenotype seems to imply bi-allelic loss of the NF1 gene. The detection of both mutations in routinely fixed tissue allows studies of archived tissue samples with this diagnosis.*

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Neurofibromatosis type 1 (NF1, MIM 162200) is an autosomal dominant inherited disease that causes a plethora of signs and symptoms. A regularly detected feature of the disease is a neoplasm arising from the cells that constitute the sheaths of peripheral nerves, the Schwann cells (1). The most prominent neoplasm arising in NF1 (2, 3), termed neurofibroma (1), mostly consists of tumor cells with Schwann cell differentiation. Neurofibromas are frequent cutaneous tumors in NF1 patients. However, tumors also develop in internal organs. Intraosseous neurofibroma is a well-known entity, which is also proven in the facial skeleton, particularly in the mandible (4, 5). However, NF1-associated intraosseous neurofibroma of the mandible is rare (6) and intraosseous lesions of the jaws are often not clearly diagnosed on radiological examination. In NF1 patients, in addition to the rare intraosseous nerve sheath tumors, other non-odontogenic (6) and odontogenic (7, 8) lesions must be considered as causes of osteolysis. A rare osseous lesion is the so-called central giant cell granuloma (CGCG), also called central giant cell lesion (9). Relatively rarely reported is the CGCG of the jaw in NF1 (10-19). Individual reports have reported germline and somatic mutations of the *NF1* gene in NF1-associated CGCG (15) and specifically in tumor cells of the lesions (18, 19). This report adds a further NF1-associated CGCG case and provides evidence of mutations in *NF1* in both alleles.

Case Report

The female patient, aged 22 years, presented at the Clinic of Oral and Craniomaxillofacial Surgery, University Hospital Hamburg-Eppendorf, for the treatment of an extensive

plexiform neurofibroma of the thoraco-abdominal region. The patient had numerous café-au-lait spots and axillary freckling of the integument. During routine diagnostics, an orthopantomographic view of the jaws (OPT) was taken (Figure 1A). On the radiograph, a sharply delineated radio-translucent lesion in the region of the right mandibular angle was detected, which had developed in topographical proximity to the molars. A multi-lobulated cyst of the jaw was suspected. Oral inspection revealed an intact, rosy mucosa with no apparent osseous pathology. The teeth of the 4th quadrant were firm, showed no bleeding after probing the periodontium, and responded adequately to cold stimuli, except for the third molar.

Due to the urgent treatment need of the very painful thoraco-abdominal tumor, the clarification of the oral findings was postponed. Six months after the first extensive tumor reduction of the trunk, the patient came for a follow-up examination. The OPT showed the known osteolytic findings unchanged. Under general anesthesia, the right side of the mandible was exposed through an angled muco-periosteal incision, and the cortical bone was trephined over the lesion. Underneath, a cavity filled with solid, gelatinous soft tissue of greyish color was exposed and the tumor tissue was excised. The roots of the third molar were not covered by bone, in direct contact with the soft tissue tumor, and had to be extracted. The uppermost layer of the bone bordering the lesion was removed with the drill, carefully sparing the exposed alveolar nerve (Figure 1B). The defect was filled with collagen and the wound was closed. The course of wound healing was uncomplicated.

Six months after the first intervention for the jaw lesion, the patient came back for a check-up of the trunk and jaw findings (Figure 1C). The osteolysis around the ramus and the third molar was re-ossified. However, well-demarcated radiolucency remained in the periapical area of the second molar, which was interpreted as a recurrence of the lesion. The patient did not appear until 15 months later for a re-investigation of the jaw findings. OPT of the jaws revealed some increase in size of the known mandibular periapical lesion (Figure 1D and Figure 2). Assuming a local recurrence, the *situs* was exposed in a procedure identical to the first intervention. A soft tissue lesion was present in the bone cavity, which was identical in texture and visual appearance to the primary findings. A second excision of the lesion was performed. The patient did not wish to have the molar extracted, which reached into the cavity with its roots and was in direct contact with the lesion. The healing process again was unremarkable. The serological findings showed no pathological parameters of the calcium metabolism during the entire treatment. The patient has consented in writing to the genetic examination of the samples and the publication of the examination and treatment results.

Histology. The bone biopsy of the right second mandibular molar revealed bone tissue with a lesion composed of spindle-shaped and polygonal cells with scattered osteoclast-type multinucleated giant cells, hemorrhage, and hemosiderin pigment (Figure 3A and B). The lesion was unencapsulated and infiltrated the adjacent bone that showed reactive changes (Figure 3C). Additionally, resorption of the dental roots was observed (Figure 3D and E). The findings were characteristic of CGCG. The second excision revealed a relapse of the same lesion (Figure 3F).

Peripheral nerve sheath tumors. Resection of the tumor from the trunk revealed nodular-plexiform neurofibroma. Further cutaneous neurofibromas were excised from the trunk and extremities (Figure 4).

Molecular genetics. Blood and native GCGG tissue as well as fixed tumor material from the bone lesion were examined for mutations in the *NF1* gene.

Fresh tumor sample analysis. For mutation analysis of native tissue DNA, the coding sequences and flanking intronic regions of the *NF1* gene (MIM 613113, ENST00000356175, exons 1-58) were enriched using a Nextera DNA Flex custom enrichment kit (Illumina, San Diego, CA, USA) and sequencing was carried out on the next-generation sequencing platform MiSeq (Illumina). The analysis of the sequence data was carried out with the help of the SeqNext module of the SEQUENCE Pilot software (JSI Medical Systems, Ettenheim, Germany). Variants with probable pathogenic importance within the sequence of the examined gene were independently validated by bidirectional Sanger sequencing on an ABI 3500 L sequencer (Thermo-Fisher, Waltham, MA, USA) after PCR amplification from the patient's DNA and purification of the PCR fragments. The bioinformatic deletion and duplication analysis was performed with varfeed 1.9.0 (Limbus Medical Technologies GmbH, Rostock, Germany). Analysis of the CGCG showed the pathogenic *NF1* mutation c.3942G>A (p.Trp1314*) in a heterozygous state. Furthermore, another pathogenic sequence change c.289C>T (p.Gln97*) of the *NF1* gene was detected in the tumor tissue DNA in a mosaic state with a variant allele frequency of 7.2%.

Analysis of formalin-fixed, paraffin-embedded tumor tissue. Independently from native tissue analysis, DNA extraction from the formalin-fixed and paraffin-embedded tumor material of the mandible was investigated for *NF1* mutations. Mutation analysis was done after next-generation sequencing (QIASeq Targeted DNA Panel CDHS-21330Z-424, Qiagen, Hilden, Germany). Analysis was performed with CLC Genomics Workbench 21 using the GRCh37 reference genome. The data set was filtered for non-synonymous exonic single nucleotide variants (SNVs) with an allele frequency of >5%, which are

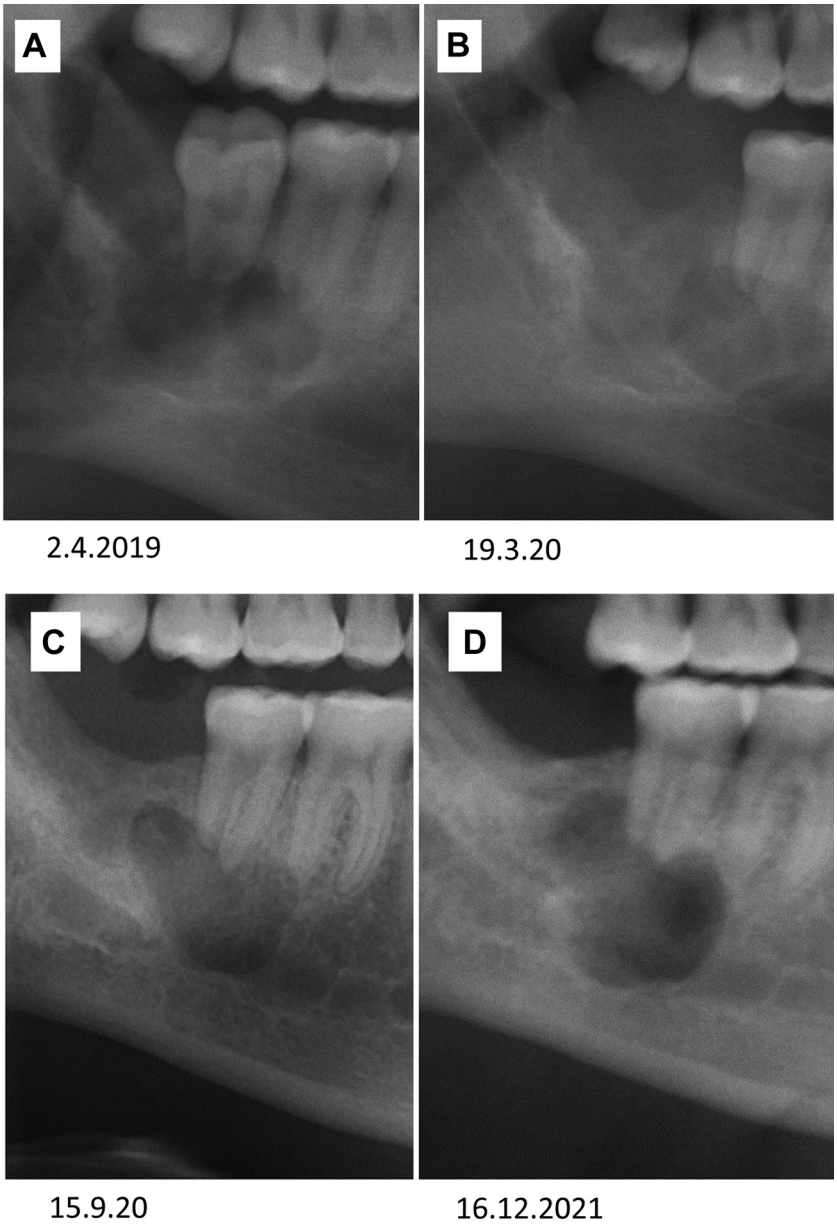

Figure 1. *Radiological representation (orthopantomography) of the bone lesion of the right angle of the jaw in a patient with neurofibromatosis type 1 (cropped images). A) Initial findings show multiple lobulated bone destruction extending both into the mandibular ramus and anteriorly to the apex of the adjacent molar. Bone destruction extends caudally to the mandibular canal. B) Findings after removal of the lesion and extraction of the molar. C) Approximately six months after removal of the giant cell lesion, the defect in the ramus has re-ossified. In contrast, a sharply demarcated, residual osteolytic lesion demarcates around the root of the second molar. D) This finding increases somewhat in the following 15 months (findings prior to excision of the recurrent tumor).*

stored in the 1,000-genome database as unknown polymorphisms. The following mutations were detected in the CGCG: 1. The *NF1* gene variant c.3942G>A, (p.Trp1314*), variant allele frequency 52%, coverage 3451. 2. The *NF1* gene variant c.289C>T, (p.Gln97*), variant allele frequency 11%, coverage 3584. Both mutations were considered relevant for tumor development.

The heterozygous mutation c.3942G>A (p.Trp1314*) has been repeatedly recorded as pathogenic in the databases LOVD (ID NF1_000419) and ClinVar (ID 849712). It is very likely the underlying germline *NF1* mutation in the patient. Also, the mutation has been described several times in the literature (20-23). In addition to the germline mutation, the mosaic nonsense mutation c.289C>T (p.Gln97*) was

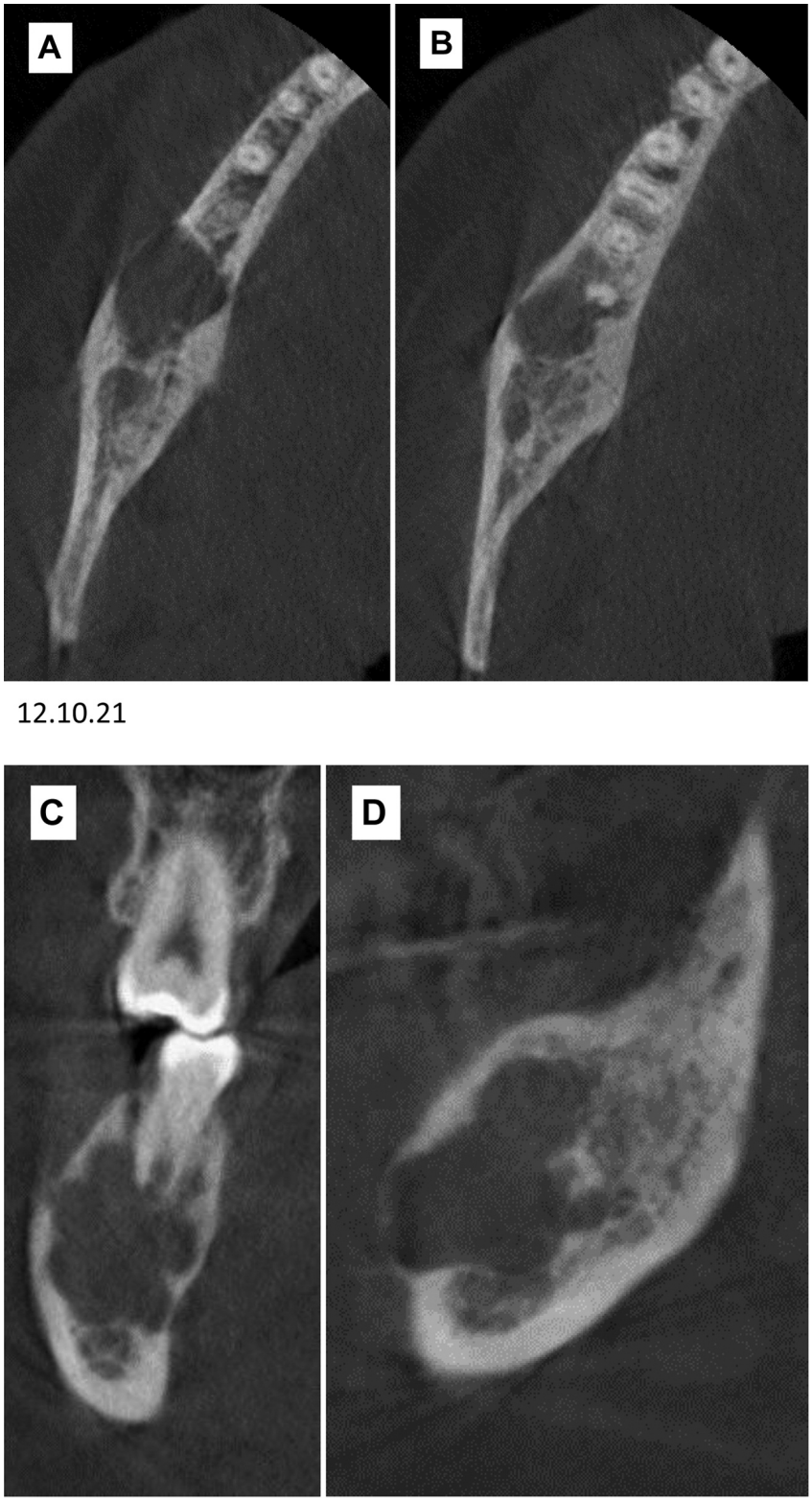

Figure 2. *Recurrence of a giant cell lesion of the lower jaw in neurofibromatosis type 1 in cone beam computed tomography (cropped images, right side of bone depicted). A) Osteolysis of the mandible with thinning of the vestibular cortical bones. B) Root apex of the second molar in the lesion (A and B: axial section). C) Multiple lobulated intraosseous lesion (coronal section). D) The lobulated lesion extends caudally to the nerve canal (sagittal section).*

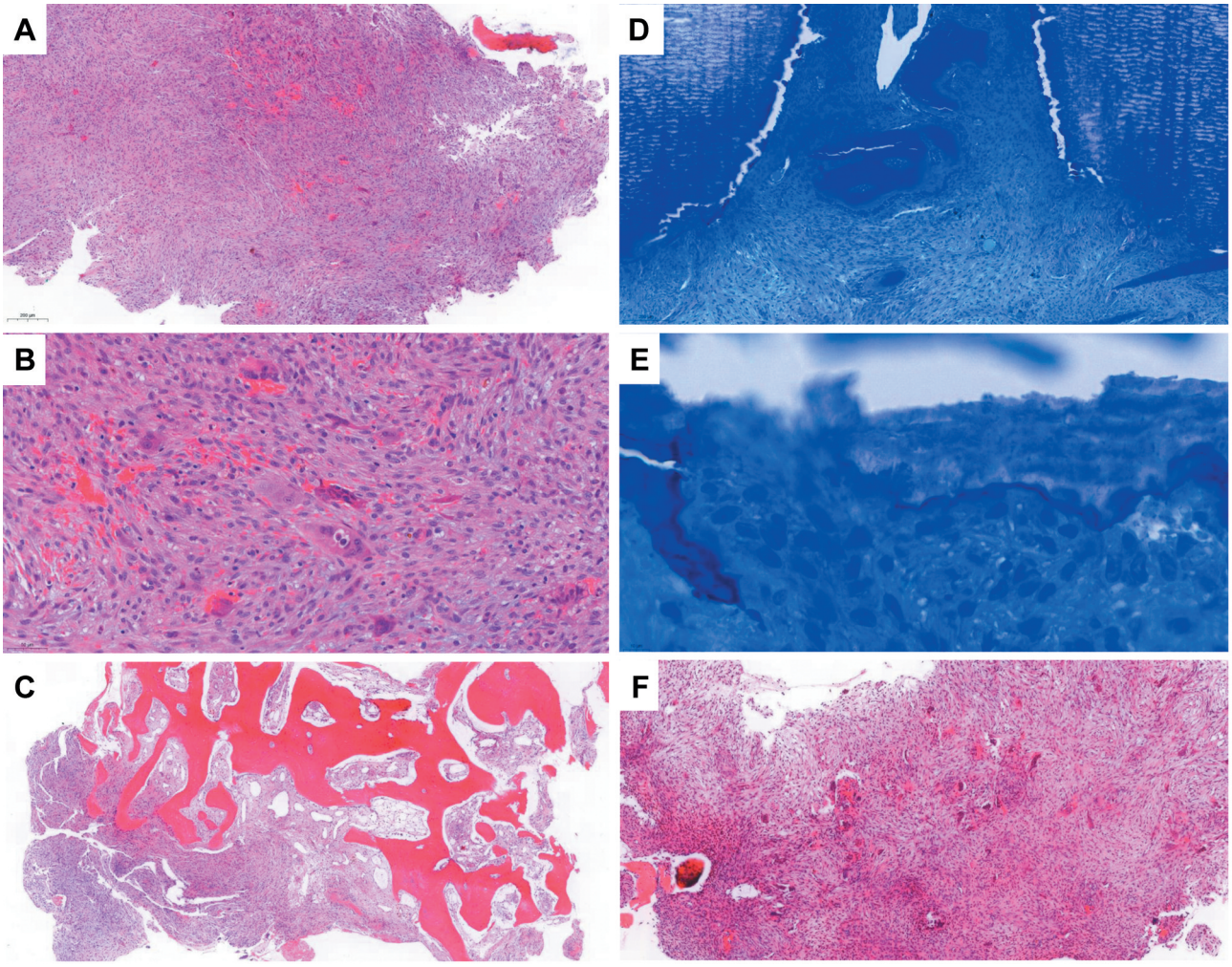

Figure 3. *Histology of giant cell granuloma in neurofibromatosis type 1. A) Spindle-shaped and polygonal cells with scattered osteoclast-type multinucleated giant cells [hematoxylin-eosin (HE) stain]. B) Higher magnification points out hemorrhage and hemosiderin pigment (HE stain). C) Infiltration of adjacent bone (HE stain). D) Resorption of dentin [undecalcified methylmethacrylate embedding (MMA), toluidine-blue stain]. E) Higher magnification of resorption site (MMA, toluidine-blue stain). F) Identical finding [central giant cell granuloma (CGCG)] in the second excision (HE stain). Scale bar: 200 μm.*

detected in tumor tissue. This alteration is interpreted as a second hit on the homologous allele of the CGCG tumor cells. The mutation is listed as pathogenic in ClinVar database (ID 818189) and is also described in the literature (23). Both variants are considered as causing loss of function alleles. The genetic tests therefore support the assumption that the CGCG of the mandible was a manifestation of NF1 and was driven by bi-allelic *NF1* defects in the tumor cells.

Discussion

So far, somatic mutations of the *NF1* gene in NF1-associated CGCG of the jaws have been demonstrated in native material of lesions and in cell culture (15, 18, 19). Elaborate conditioning and enrichment of the tumor cells of the CGCG in cell culture were necessary to isolate the tumor cells and detect the tumor specific *NF1* mutations (18, 19). We report here identical germline and somatic mutations in an NF1-associated recurrent CGCG after independent analysis of native and fixed specimens, which have been prepared from the same lesion. Current technical standards offer reliable analysis of archival material on this rare bone disease.

The radiological visualization of osteolysis of the jaws requires the differential diagnosis of numerous diseases, including cancer. NF1 is an autosomal dominant hereditary disease characterized primarily by tumors of the peripheral nervous system. Further tumors occur in the setting of NF1, which identify this disease as a multi-systemic tumor

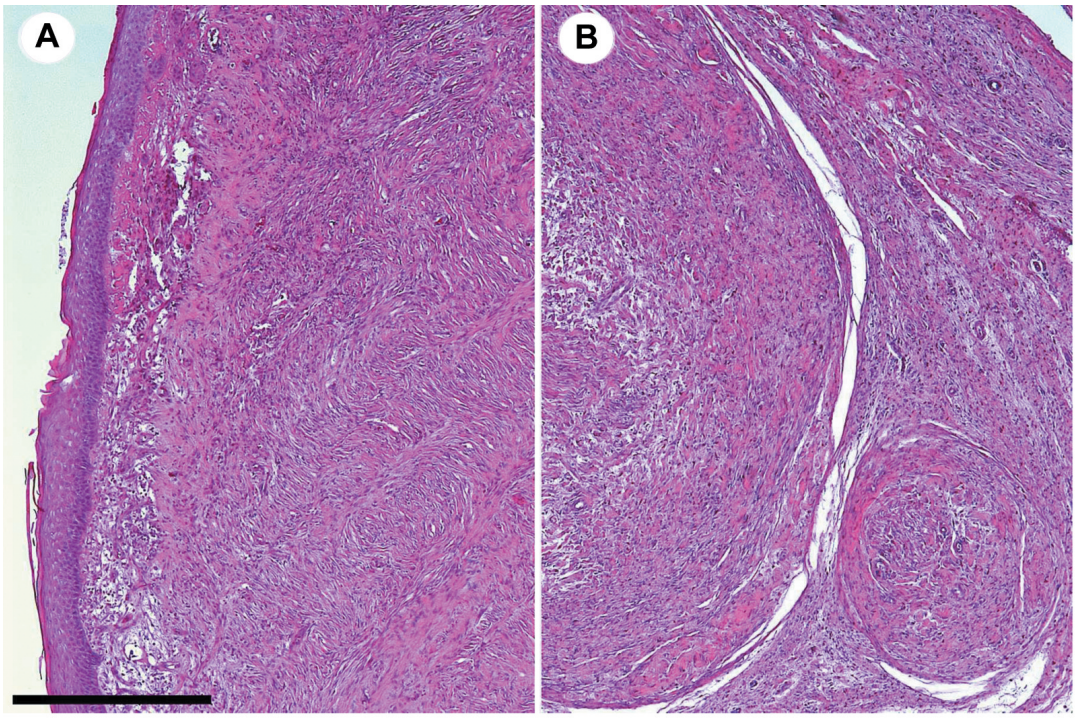

Figure 4. *Histology of neurofibroma in neurofibromatosis type 1 patient with central giant cell granuloma of the jaw. A) Cutaneous neurofibroma consisting of spindle shaped cells with intermingling collagen fibers. B) Diffuse plexiform neurofibroma with intraneural tumor portions with focal loose texture (left margin) and diffuse tumor growth between the encapsulated tumor areas (upper and lower right corner). Scale bar: 500 μm.*

predisposition syndrome (24). Indeed, NF1 is a relatively common genetic disorder that predisposes affected patients to cancer (25).

It is assumed that the tumors in NF1 originate primarily from derivatives of the neural crest (26, 27). Both Schwann cells and most of the skull bones are derivatives of the neural crest (28-30). Therefore, an association of certain neoplastic jaw lesions such as CGCG with the disease is presumptive for NF1 patients. Indeed, a connection between the CGCG and NF1 has been suspected earlier (18). However, while the CGCG tumor cell has been partially characterized, its origin is unknown. Until a few years ago, the causal (genetic) origin of CGCG was largely unknown. CGCG develops in NF1 and other syndromes, the common feature of which are causative mutations that affect the rat sarcoma homologue in human (RAS) pathway (24, 30). The syndromes caused by mutations in genes encoding components or modulators of the RAS pathway have been grouped together as RASopathies. The phenotypes of different RASopathies show significant overlaps. The overlaps of clinical findings make comprehensible that individual findings, for example CGCG of the jaw, cannot be reliably assigned to a distinct syndrome based on the histological diagnosis alone (30-33). Furthermore, the lesion is a sporadic finding well known in oral medicine (9). Recent studies revealed that somatic mutations in RAS pathway genes are the cause of sporadic non-syndromic CGCG cases (9). Evidence of RAS pathway mutations in CGCG provide arguments for defining CGCG as a neoplasm. However, in both sporadic and many syndrome-associated CGCG, the lesions already developed with evidence of constitutive RAS-mutations (9). In contrast, according to the few cases published on the subject in NF1, bi-allelic loss of *NF1* gene is necessary for the development of CGCG in this tumor predisposition syndrome (18, 19). CGCG of jaws in NF1 without evidence of the second hit can probably be attributed to methodological limitations (34, 35) or a pathogenesis of the lesion (cherubism-like tumorous expansion of facial bones) independent of somatic *NF1* mutations (35).

Conclusion

In NF1 patients, CGCG of the jaw is a neoplasm associated with somatic second-hit NF1 mutations in the tumor cells. After excision, the lesion has a tendency to local recurrence. Long-term control of the region after removal of the lesion is advisable.

Conflicts of Interest

The Authors declare that there are no conflicts of interest regarding this publication.

Authors' Contributions

Treatment of patient, conceptualization of the study: REF; genetic examinations: MZ, IW, US; histological examinations: CH, AML; literature research and evaluation, drafting of the manuscript: REF, FKK; final approval of manuscript: All Authors.

References

1 Von Recklinghausen FD: Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen. Berlin, Hirschwald, 1882.

2 Kluwe L, Friedrich R and Mautner VF: Loss of NF1 allele in Schwann cells but not in fibroblasts derived from an NF1-associated neurofibroma. Genes Chromosomes Cancer *24(3)*: 283-285, 1999. PMID: 10451710. DOI: 10.1002/(sici)1098-2264(199903)24:3<283::aid-gcc15>3.0.co;2-k

3 Kluwe L, Friedrich RE and Mautner VF: Allelic loss of the NF1 gene in NF1-associated plexiform neurofibromas. Cancer Genet Cytogenet *113(1)*: 65-69, 1999. PMID: 10459349. DOI: 10.1016/s0165-4608(99)00006-0

4 Blackwood HJ and Lucas RB: Neurofibroma of the mandible. Proc R Soc Med *44(10)*: 864-865, 1951. PMID: 14891790.

5 Prescott GH and White RE: Solitary, central neurofibroma of the mandible: report of case and review of the literature. J Oral Surg *28(4)*: 305-309, 1970. PMID: 4907056.

6 Friedrich RE and Scheuer HT: Non-odontogenic intraosseous radiolucent lesions of the mandibular body are rare findings on panoramic views of patients with neurofibromatosis type 1. Anticancer Res *39(4)*: 1971-1985, 2019. PMID: 30952741. DOI: 10.21873/anticanres.13308

7 Visnapuu V, Pienihäkkinen K, Peltonen S, Happonen RP and Peltonen J: Neurofibromatosis 1 and dental caries. Clin Oral Investig *15(1)*: 119-121, 2011. PMID: 19727860. DOI: 10.1007/s00784-009-0341-x

8 Friedrich RE and Reul A: Decayed, missing, and restored teeth in patients with Neurofibromatosis Type 1. J Clin Exp Dent *10(2)*: e107-e115, 2018. PMID: 29670726. DOI: 10.4317/jced.54561

9 Gomes CC, Diniz MG, Bastos VC, Bernardes VF and Gomez RS: Making sense of giant cell lesions of the jaws (GCLJ): lessons learned from next-generation sequencing. J Pathol *250(2)*: 126-133, 2020. PMID: 31705763. DOI: 10.1002/path.5365

10 Kerl H and Schroll K: [Multiple giant-cell granuloma of the jaw associated with Recklinghausen's neurofibromatosis]. Wien Klin Wochenschr *83(52)*: 938-941, 1971. PMID: 5002595.

11 Ruggieri M, Pavone V, Polizzi A, Albanese S, Magro G, Merino M and 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 *87(1)*: 67-72, 1999. PMID: 9927083. DOI: 10.1016/s1079-2104(99)70297-0

12 Ardekian L, Manor R, Peled M and 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 *57(7)*: 869-872, 1999. PMID: 10416639. DOI: 10.1016/s0278-2391(99)90833-9

13 Edwards PC, Fantasia JE, Saini T, Rosenberg TJ, Sachs SA and Ruggiero S: Clinically aggressive central giant cell granulomas in two patients with neurofibromatosis 1. Oral Surg Oral Med Oral Pathol Oral Radiol Endod *102(6)*: 765-772, 2006. PMID: 17138179. DOI: 10.1016/j.tripleo.2005.10.038

14 van Capelle CI, Hogeman PH, van der Sijs-Bos CJ, Heggelman BG, Idowu B, Slootweg PJ, Wittkampf AR and Flanagan AM: Neurofibromatosis presenting with a cherubism phenotype. Eur J Pediatr *166(9)*: 905-909, 2007. PMID: 17120035. DOI: 10.1007/s00431-006-0334-6

15 Friedrich RE, Mautner VF and Scheuer HA: Loss of heterozygosity in tumor cells of a recurrent mandibular giant cell granuloma in neurofibromatosis type 1. Anticancer Res *27(4A)*: 2079-2083, 2007. PMID: 17649825.

16 Chrcanovic BR, Gomez RS and Freire-Maia B: Neurofibromatosis type 1 associated with bilateral central giant cell granuloma of the mandible. J Craniomaxillofac Surg *39(7)*: 538-543, 2011. PMID: 21071237. DOI: 10.1016/j.jcms.2010.10.014

17 Jyothi SK, Pushpanjali M, Chandrasekhar R and Devarampatti N: Central giant cell granuloma in a patient with neurofibromatosis type 1: a case report. International Journal of Oral-Medical Sciences *11(3)*: 223-228, 2021. DOI: 10.5466/IJOMS.11.223

18 Stewart DR, Brems H, Gomes AG, Ruppert SL, Callens T, Williams J, Claes K, Bober MB, Hachen R, Kaban LB, Li H, Lin A, McDonald M, Melancon S, Ortenberg J, Radtke HB, Samson I, Saul RA, Shen J, Siqveland E, Toler TL, van Maarle M, Wallace M, Williams M, Legius E and Messiaen L: Jaffe-Campanacci syndrome, revisited: detailed clinical and molecular analyses determine whether patients have neurofibromatosis type 1, coincidental manifestations, or a distinct disorder. Genet Med *16(6)*: 448-459, 2014. PMID: 24232412. DOI: 10.1038/gim.2013.163

19 Friedrich RE, Grob TJ, Hollants S, Zustin J, Spaepen M, Mautner VF, Luebke AM, Hagel C, Legius E and Brems H: Recurrent multilocular mandibular giant cell granuloma in neurofibromatosis type 1: Evidence for second hit mutation of NF1 gene in the jaw lesion and treatment with curettage and bone substitute materials. J Craniomaxillofac Surg *44(8)*: 1054-1060, 2016. PMID: 27316856. DOI: 10.1016/j.jcms.2016.05.010

20 Upadhyaya M, Osborn MJ, Maynard J, Kim MR, Tamanoi F and Cooper DN: Mutational and functional analysis of the neurofibromatosis type 1 (NF1) gene. Hum Genet *99(1)*: 88-92, 1997. PMID: 9003501. DOI: 10.1007/s004390050317

21 Toliat MR, Erdogan F, Gewies A, Fahsold R, Buske A, Tinschert S and Nürnberg P: Analysis of the NF1 gene by temperature gradient gel electrophoresis reveals a high incidence of mutations in exon 4b. Electrophoresis *21(3)*: 541-544, 2000. PMID: 10726756. DOI: 10.1002/(SICI)1522-2683(20000201)21:3<541::AID-ELPS541>3.0.CO;2-L

22 Sabbagh A, Pasmant E, Imbard A, Luscan A, Soares M, Blanché H, Laurendeau I, Ferkal S, Vidaud M, Pinson S, Bellanné-Chantelot C, Vidaud D, Parfait B and Wolkenstein P: NF1 molecular characterization and neurofibromatosis type I genotype-phenotype correlation: the French experience. Hum Mutat *34(11)*: 1510-1518, 2013. PMID: 23913538. DOI: 10.1002/humu.22392

23 Zhu G, Zheng Y, Liu Y, Yan A, Hu Z, Yang Y, Xiang S, Li L, Chen W, Peng Y, Zhong N and Mei H: Identification and characterization of NF1 and non-NF1 congenital pseudarthrosis

of the tibia based on germline NF1 variants: genetic and clinical analysis of 75 patients. Orphanet J Rare Dis *14(1)*: 221, 2019. PMID: 31533797. DOI: 10.1186/s13023-019-1196-0

24 Legius E, Marchuk DA, Collins FS and Glover TW: Somatic deletion of the neurofibromatosis type 1 gene in a neurofibrosarcoma supports a tumour suppressor gene hypothesis. Nat Genet *3(2)*: 122-126, 1993. PMID: 8499945. DOI: 10.1038/ng0293-122

25 Rauen KA, Huson SM, Burkitt-Wright E, Evans DG, Farschtschi S, Ferner RE, Gutmann DH, Hanemann CO, Kerr B, Legius E, Parada LF, Patton M, Peltonen J, Ratner N, Riccardi VM, van der Vaart T, Vikkula M, Viskochil DH, Zenker M and Upadhyaya M: Recent developments in neurofibromatoses and RASopathies: management, diagnosis and current and future therapeutic avenues. Am J Med Genet A *167A(1)*: 1-10, 2015. PMID: 25393061. DOI: 10.1002/ajmg.a.36793

26 Wallace MR, Marchuk DA, Andersen LB, Letcher R, Odeh HM, Saulino AM, Fountain JW, Brereton A, Nicholson J and Mitchell AL: Type 1 neurofibromatosis gene: identification of a large transcript disrupted in three NF1 patients. Science *249(4965)*: 181-186, 1990. PMID: 2134734. DOI: 10.1126/science.2134734

27 Bolande RP: Neurofibromatosis – the quintessential neurocristopathy: pathogenetic concepts and relationships. Adv Neurol *29*: 67-75, 1981. PMID: 6798844.

28 Trainor PA, Melton KR and Manzanares M: Origins and plasticity of neural crest cells and their roles in jaw and craniofacial evolution. Int J Dev Biol *47(7-8)*: 541-553, 2003. PMID: 14756330.

29 Jessen KR and Mirsky R: The origin and development of glial cells in peripheral nerves. Nat Rev Neurosci *6(9)*: 671-682, 2005. PMID: 16136171. DOI: 10.1038/nrn1746

30 Martik ML and Bronner ME: Riding the crest to get a head: neural crest evolution in vertebrates. Nat Rev Neurosci *22(10)*: 616-626, 2021. PMID: 34471282. DOI: 10.1038/s41583-021-00503-2

31 Sinnott BP and Patel M: Giant cell lesion of the jaw as a presenting feature of Noonan syndrome. BMJ Case Rep *2018*: bcr2017224115, 2018. PMID: 29848529. DOI: 10.1136/bcr-2017-224115

32 Zenker M: Clinical manifestations of mutations in RAS and related intracellular signal transduction factors. Curr Opin Pediatr *23(4)*: 443-451, 2011. PMID: 21750428. DOI: 10.1097/MOP.0b013e32834881dd

33 Yazdizadeh M, Tapia JL, Baharvand M and Radfar L: A case of neurofibromatosis-Noonan syndrome with a central giant cell granuloma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod *98(3)*: 316-320, 2004. PMID: 15356469. DOI: 10.1016/S10792 10404000654

34 Krammer U, Wimmer K, Wiesbauer P, Rasse M, Lang S, Müllner-Eidenböck A and Frisch H: Neurofibromatosis 1: a novel NF1 mutation in an 11-year-old girl with a giant cell granuloma. J Child Neurol *18(5)*: 371-373, 2003. PMID: 12822827. DOI: 10.1177/08830738030180051901

35 Friedrich RE, Zustin J, Luebke AM, Rosenbaum T, Gosau M, Hagel C, Kohlrusch FK, Wieland I and Zenker M: Neurofibromatosis type 1 with cherubism-like phenotype, multiple osteolytic bone lesions of lower extremities, and Alagille-syndrome: case report with literature survey. In Vivo *35(3)*: 1711-1736, 2021. PMID: 33910856. DOI: 10.21873/invivo.12431

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