

Recurrent Diffuse Neurofibroma of the Mandibular Anterior Lingual Alveolar Process Associated With Dental and Skeletal Changes in Neurofibromatosis Type 1

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Abstract

Background/Aim: Neurofibromatosis type 1 (NF1) is a tumor predisposition syndrome and a bone disease. Dystrophic facial skull often is topographically related to diffuse neurofibromas (DNFs). The report traces the diagnosis and treatment of an oral DNF that was registered in adolescence and describes associated bone findings. The aim of the investigation was to illustrate and specify the interplay of tumor-associated and dysmorphic changes of the facial skull in NF1.

Case Report: This 14-year-old patient with NF1 had developed a solid tumor arising from the mandibular anterior lingual alveolar process. Histological examination of the tumor identified a DNF. Imaging showed a funnel-shaped vertical defect of the alveolar process between incisors, asymmetry of bony chin and vertical position of mental foramina. The chin showed irregular, bi-cortical connected bone canals suspected to indicate enlarged neurovascular channels. Thirteen years later, the patient developed a local tumor recurrence (DNF). Meanwhile, the anterior bone defect had become larger. However, the bony chin appeared considerably sclerosed. In contrast, mandibular shape and surface were unchanged.

Conclusion: DNF can affect the position of teeth, invade the bone, and cause enlarged bone channels. Surface erosion and trophic effects of the mandible may arise adjacent to the neurogenic lesion. DNF of the oral cavity can recur. It is becoming apparent that the tumor-associated skeletal and dental changes in the mandible correlate with the time of development of the peripheral nerve sheath tumor. The findings could be useful as indications for an expanded tumor search in the affected area.

Keywords: Neurofibromatosis type 1, oral neurofibroma, mandible, dysplasia, dental surgery.

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Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant hereditary tumor predisposition syndrome. The phenotype is highly variable, with almost complete penetrance. The cause of the monogenic disease is attributed to a mutation on chromosome 17q11.2 (1). The *NF1* gene product is called neurofibromin. Neurofibromin inactivates the rat sarcoma (RAS) protein. As a result, proliferative and mitogenic processes of the cell are activated (2). The increased risk of developing neoplasia in NF1 individuals is attributed to the somatic loss of the second *NF1* allele (3). The characteristic appearance of patients with NF1 is caused by neurogenic tumors of the skin, the neurofibromas. The tumor cells are Schwann cells/Schwann cell precursors with biallelic loss of *NF1* (3). Sporadic oral neurofibroma is a rare diagnosis of oral lesions (4, 5) and occasionally observed in patients with NF1 (6–19). The location, size and histological type of oral neurofibroma is variable (20, 21).

Overall, oral neurofibromas usually are reported as cases and are not considered in clinical studies of patients with NF1 (22–25). However, a recent study has indicated that careful examination of the oral cavity of patients with NF1 registers neurofibromas far more frequently than previously assumed (21). But in most cases these tumors do not require treatment (21). Furthermore, intraosseous nerve sheath tumors are more often schwannomas than neurofibromas, and sporadic lesions have been reported more frequently in intraosseous neurogenic tumors of the jaws than those with a syndromic background (26). The intraosseous mandibular neurofibroma of the patient with NF1 is a rarity (for review: 27). Malignant degeneration of oral neurofibromas is rare (28). Presently, it is not possible to determine whether there are differences in the frequency of oral MPNST between sporadic and NF1-associated cases. This report describes the diagnosis and treatment of an oral nerve sheath tumor in a patient with NF1 and identifies associated skeletal changes, characteristic for invasive tumor growth.

Case Report

Medical history. This male patient presented as a child of a father with confirmed NF1. The patient was diagnosed with NF1 in the first year of life. The child had multiple cafe-au-lait spots and axillary freckling. One of two half-siblings (female) also had NF1, as well as a brother.

During childhood, several support measures were implemented to compensate for his global developmental disorder. The child developed multifactorial epilepsy, which was treated with various medication regimens. At the age of 10 years, the patient developed visual field defects because of a progressive chiasmatic optic glioma, which was successfully treated with chemotherapy according to International Society of Pediatric Oncology (Société internationale d'oncologie pédiatrique, SIOP) standards for treatment of low grade glioma (LGG) [SIOP-LGG 2004 (29)]. The first surgical measures were necessary at the age of 8 years to remove symptomatic gluteal plexiform neurofibroma (PNF).

The clinical findings of the initial tumor and the recurrence are demonstrated in Figure 1. Figure 2 shows the radiological findings on panoramic view (PV) and cone beam computed tomography (CBCT). Figure 3 shows the initial findings on magnetic resonance images (MRI). Figure 4 shows the three-dimensional imaging of the mandibular bone surface. Figure 5 shows the tumor recurrence on CBCT and MRI, and Figure 6 documents the histological findings.

Oral tumor. The 14-year-old male patient presented for evaluation of a recently noticed mass arising from the lingual side of mandibular frontal teeth' alveolar process that extended to the floor of the mouth. It was not possible to determine when the tumor had been first noted. The dentition was complete including the anlage of the four wisdom teeth. The medical history gave no indication of disorders of tooth replacement and the placement of the permanent teeth in the dental arch. Except for the tumor-associated positional disorders, the teeth were placed symmetrically and without pre-contacts in occlusion. The

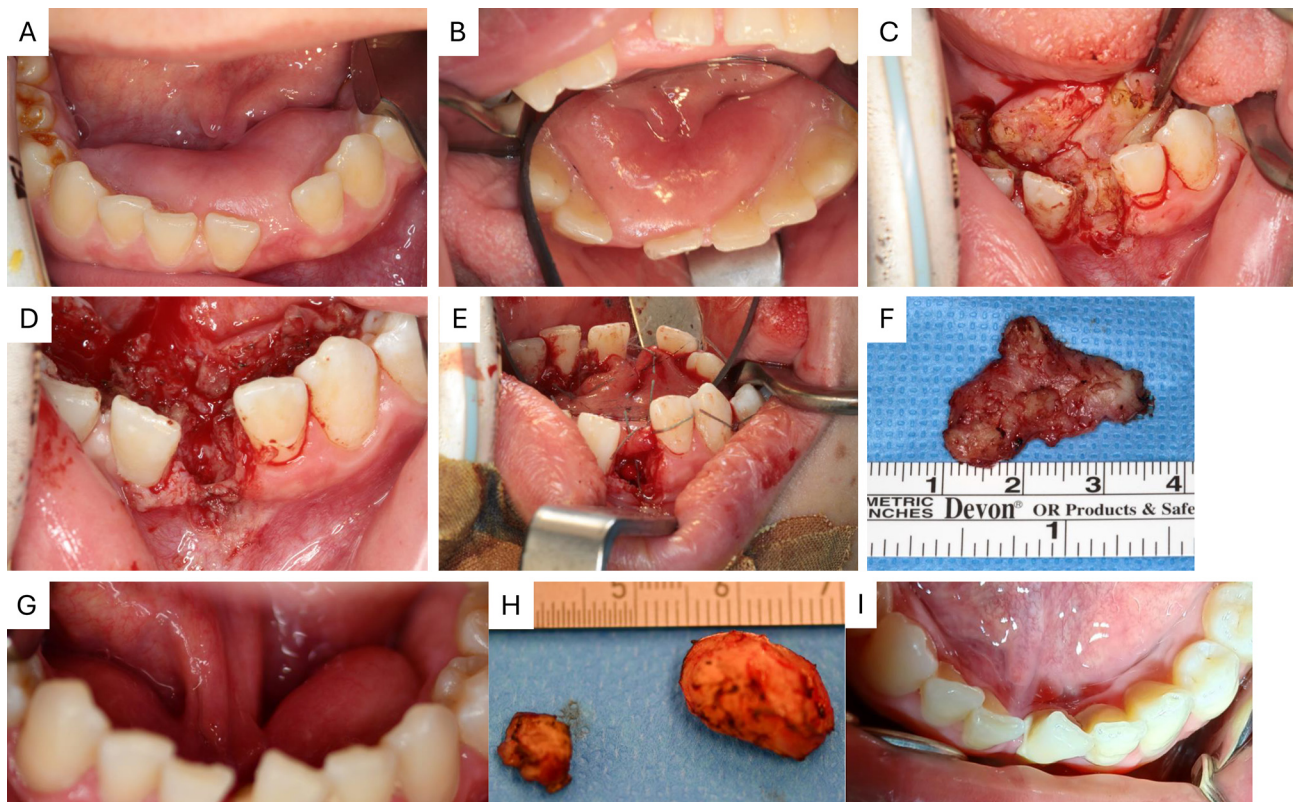


Figure 1. Clinical findings at first treatment (A-F) and recurrence (G-I). (A) Displacing soft-tissue tumor of the lingual alveolar process with protrusion into the floor of the mouth. (B) The tumor has displaced the left central and lateral incisors (mirror image). In addition, the central incisor has lost proximal contact with the antimer. The remaining anterior dental arch has hardly been altered by the space-occupying lesion. (C) Removal of the covering mucosa from the rough mass. The slightly bleeding tumor is firmly attached to the alveolar process. (D) Defect situation of the floor of the mouth after tumor excision. (E) Covering of the defect with mucosa of the floor of the mouth. (F) Main resected specimen. (G) Local recurrence of diffuse neurofibroma originating from both sides of the lingual alveolar process. (H) Main resected specimen of the recurrent tumor. (I) Complete wound healing three months after surgery.

oral examination revealed a solid tumor originating predominantly from the lingual alveolar process of the mandible that protruded cushion-like into the floor of the mouth and somewhat restricted the excursion of the tongue (Figure 1A and B). The covering mucosa of the painless tumor was pale pink, evenly supplied with blood and completely intact. The displacing effect of the tumor on the position of the mandibular anterior teeth was striking. A wide diastema had developed between the left central and lateral incisor. The gap between the teeth was filled by fibrously thickened gingiva. The clinical aspect justified the descriptive designation as epulis. Although the aspect only allowed the assumption that a fibroma had

developed at this site, a neurogenic tumor was suspected due to the genetic predisposition. However, the alternative diagnosis of gingival hyperplasia induced by antiepileptic drugs or giant cell granuloma could not be ruled out by clinical investigation (30-32).

X-ray. The panoramic X-ray examination of the jaws showed a V-shaped, caudally narrowing mandibular osteolysis below the interdental soft tissue lesion, starting at the limbus alveolaris and reaching the root tip of the left central incisor (Figure 2A). The lesion projected around the root of the left central incisor (tooth 31). However, the boundaries of the lesion were blurred in the cranial region,



Figure 2. Radiological findings at the time of the first treatment of the oral tumor [panoramic view (PV) (A) and cone beam computed tomography images (B-D)]. (A) The PV shows an asymmetric bone in the chin area with a plus on the right side. A soft tissue slough is shown between the crowns of the two lower left incisors, which rises to the incisal edge level. A zone of osteolysis can be seen around the left central incisor. There is a cranially and laterally blurred hyperdense zone on the left paramedian side distant to the central incisor's apex that is continuously merging into the mandibular basal cortical margin. The right mental foramen is considerably enlarged, the left one is barely delineated. In addition, there is an approximately circular radio-translucency below the root of tooth 31, which does not appear to be in contact with the periodontal osteolysis. Neither the shape of the remaining mandible nor the nerve canals appear deformed or enlarged. (B) The axial section shows the transition of the additional foramen into the bone canal. (C) The coronal section through the chin region shows the intraosseous canals. The canals met in cross-section show a continuous, circular hyperdense boundary. (D) The axial slice [cranial to (B)] shows the extensive circular bone loss around the root of the left central incisor. The neighboring teeth are displaced from the periodontally affected tooth while maintaining the physiologic axial position [see also (A)]. The shape of the dental arch is physiologically formed.

so that the V-shaped boundary line was only visible in the caudal part. Caudal to the peri-radicular osteolysis, a blurred hyperdense region of the left-sided chin region was conspicuous, without a specification being possible in the overview image. The medial border of the hyperdense region, which ended where the caudal extension of the right chin region merged into the less prominent level of the left side of the chin, was conspicuous.

The right mental foramen was positioned more caudally than the antimer of the opposite side. The right

foramen had a significantly larger diameter on the plain view. The left mental foramen was barely visible on this projection. A perforation of the vestibular mandibular cortical was seen caudally and in perpendicular relation to the extensive bone defect of the alveolar process of the left lower incisor region and localized in the base of the mandible. This bone defect was reminiscent of an additional foramen. The tomographs of the chin region showed the connection of the defect to the reticular canal system of the bone. Ramus and articular processes were

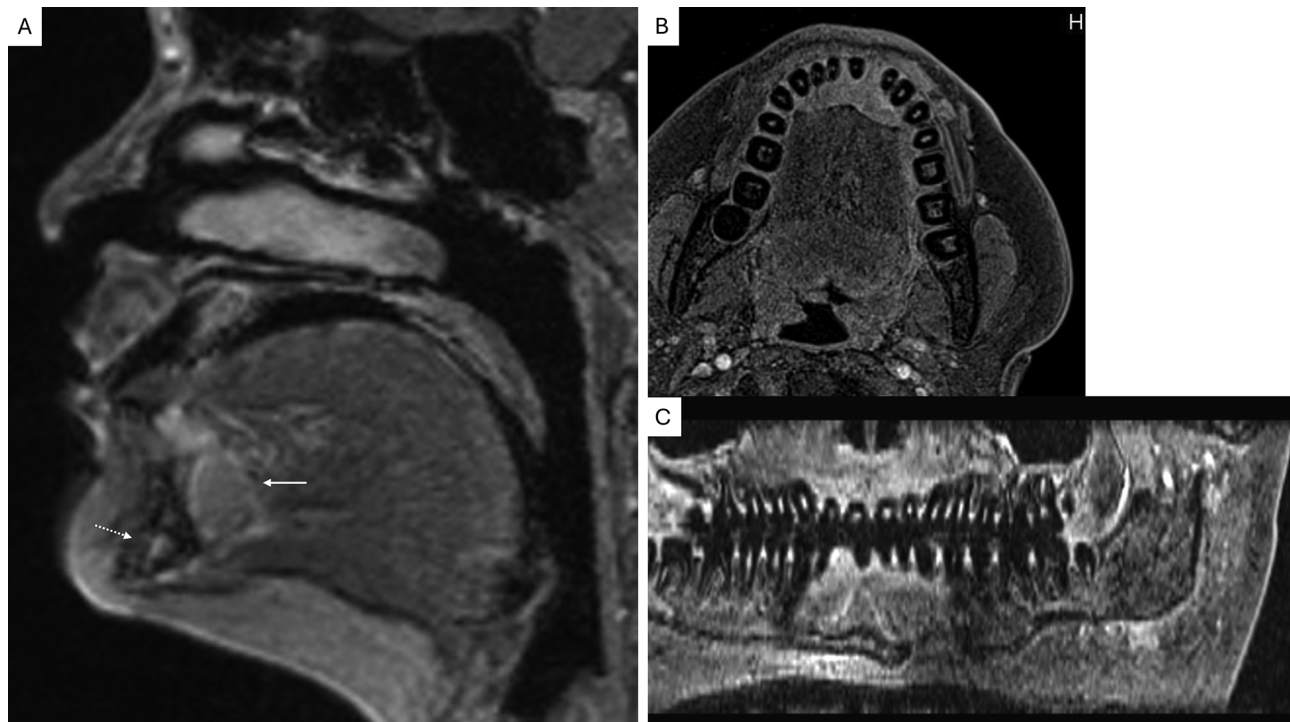


Figure 3. Magnetic resonance imaging of the oral cavity at the time of first treatment. (A) The lateral view shows the hyperintense tumor adjacent to the lingual aspect of the anterior mandible (arrow). There is a sharp boundary between the hypointense signal of the bone and the hyperintense, smoothly bounded mass. A tumorous infiltration of the mandible *per continuitatem* is not detectable on this projection. (B) Axial view of the tumor extension, which is located between the first premolars on both sides. The tumor grows on both sides around the mandibular left central incisor and reaches the vestibular mucosa on the left side. (C) Reconstructed panoramic view of the jaws. Slightly hyperintense interforaminal region of the mandible in the tumor area. The cord-like hyperintensity inside this region, angled craniocaudally, could correspond to the anterior mandibular basal signals in (A) (dotted arrow).

developed symmetrically to each other and showed no deviations in outline and internal structure from the expected radiologic anatomy of this region (Figure 2A).

CBCT. The right side of the jaw was slightly curved from the angle of the jaw to the chin region, whereas the arched shape of mandibular body was slightly flattened on the left side (Figure 2B). The right chin region was more caudally developed and slightly more prominent in the sagittal direction. The caudal view revealed the shorter sagittal projection of the left corpus compared to the prominent right side (Figure 4). The irregular pattern with a bony crest on the chin surface extending from the anterior mandible basal right to the left lateral incisor's alveolar crest possibly reflected the interface of differentially

stimulated osseous growth centers in this region. The unequal amount of bone on the mandibular sides was associated with a different position of the mental foramen. Both foramina were situated between the roots of the two premolars, but the vertical position differed significantly. The right mental foramen was positioned more caudally than the left. The right mental foramen lay below the root tips of the premolars, and the left between the antimers' lower part of roots. Overall, the left side of the mandible appeared somewhat less voluminous (Figure 4). The mandibular tooth sizes and shapes of both sides were symmetrical and corresponded to the expected anatomical range (33). Changes in the position of the teeth in the lateral comparison only affected the anterior mandible and the teeth in which the tumor had grown

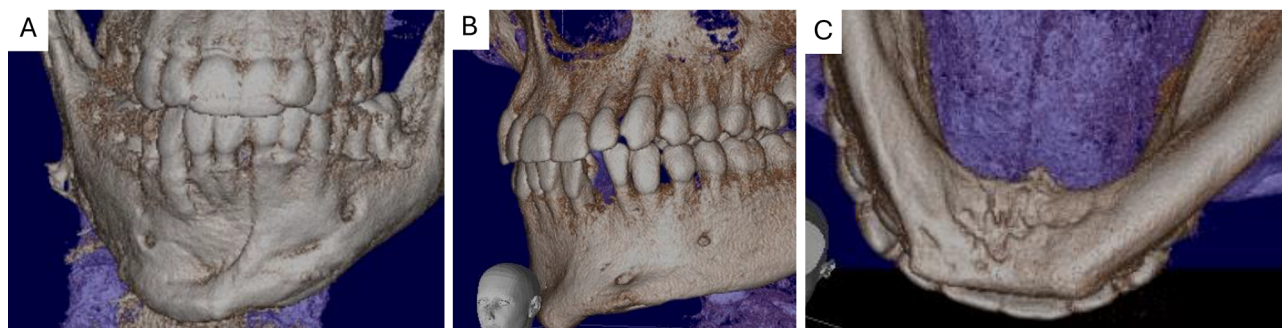


Figure 4. Three-dimensional surface reconstruction of the anterior mandible of the 20-year-old patient. (A) The anterior aspect shows the asymmetry of the chin, the different vertical position of the mental foramina, and the different shape of the mandibular base when compared side to side. (B) The projection conveys the tumorous bone loss around the tooth roots and the additional foramen beneath this lesion. (C) The caudal projection illustrates the irregular shape of the mandibular lingual bone surface in the tumor area (front teeth area).

through to the vestibule with a large volume between the teeth. In this area, the tooth no longer had any proximal contact, which meant that tooth 31 was stuck in the tumor without contact to the adjacent teeth (Figure 2).

A plexus of interconnecting canals with lingual and a vestibular foramen periradicular to tooth 31 was conspicuous. The canal system had connections to the periradicular osteolysis of the cold-sensitive tooth 31 (Figure 2B-D). However, the lumen-side bone boundaries of the canals were partially imaged as a radiopaque layer and thus appeared sclerosed.

MRI. MRI revealed a solid mass adjacent to the lingual side of the chin region with protrusion into the floor of the mouth (Figure 3). The homogeneous oral mass was hyperintense on T2-weighted images and showed no target sign (Figure 3A and B). In the reconstruction of the MRI as a panoramic view of the jaw, the homogeneous hyperintensity of the chin region was striking (Figure 3C). Further tumors in the facial-neck region were not visible on the sectional planes.

Treatment. The oral cavity lesions were removed under general anesthesia. The tumor extended to the periosteum and covered the entire anterior mandible around the alveolar processes (premolar to premolar region). To cover the wound, the mucosa of the floor of the mouth was

mobilized and fixed over the defect area (including the alveolar process gap) (Figure 1A-F). Wound healing was unremarkable.

Histology. Histological examination of the main tumor specimens revealed diffuse neurofibroma (DNF) (Figure 6). In separately taken biopsies from the peri-radicular osseous gap of tooth 31 the same neurogenic tumor was detected. Degenerative changes of nerve fascicles walled in the neurofibroma were identified.

Molecular genetics. A mutation of the NF1 gene was detected in the patient's blood (Exon 5 c.702G>A) (34).

Follow-up. Oral tumor. One year after oral surgery, the oral mucosa of the floor of the mouth and mandibular anterior alveolar process had an inconspicuous structure. The oral mucosa of the anterior lingual alveolar process was smooth and homogeneous against the bone. Further control examinations six and seven years after the removal of the oral tumor showed no clinical evidence of tumor recurrence and radiologically only a slight expansion of the circular osteolysis of the severely loosened tooth 31 (Figure 1G). At the age of 27 years, the patient appeared in the outpatient clinic again because he had noticed renewed tumor growth in the front area of the floor of the mouth. The oral examination revealed a solid tumor adhering to the

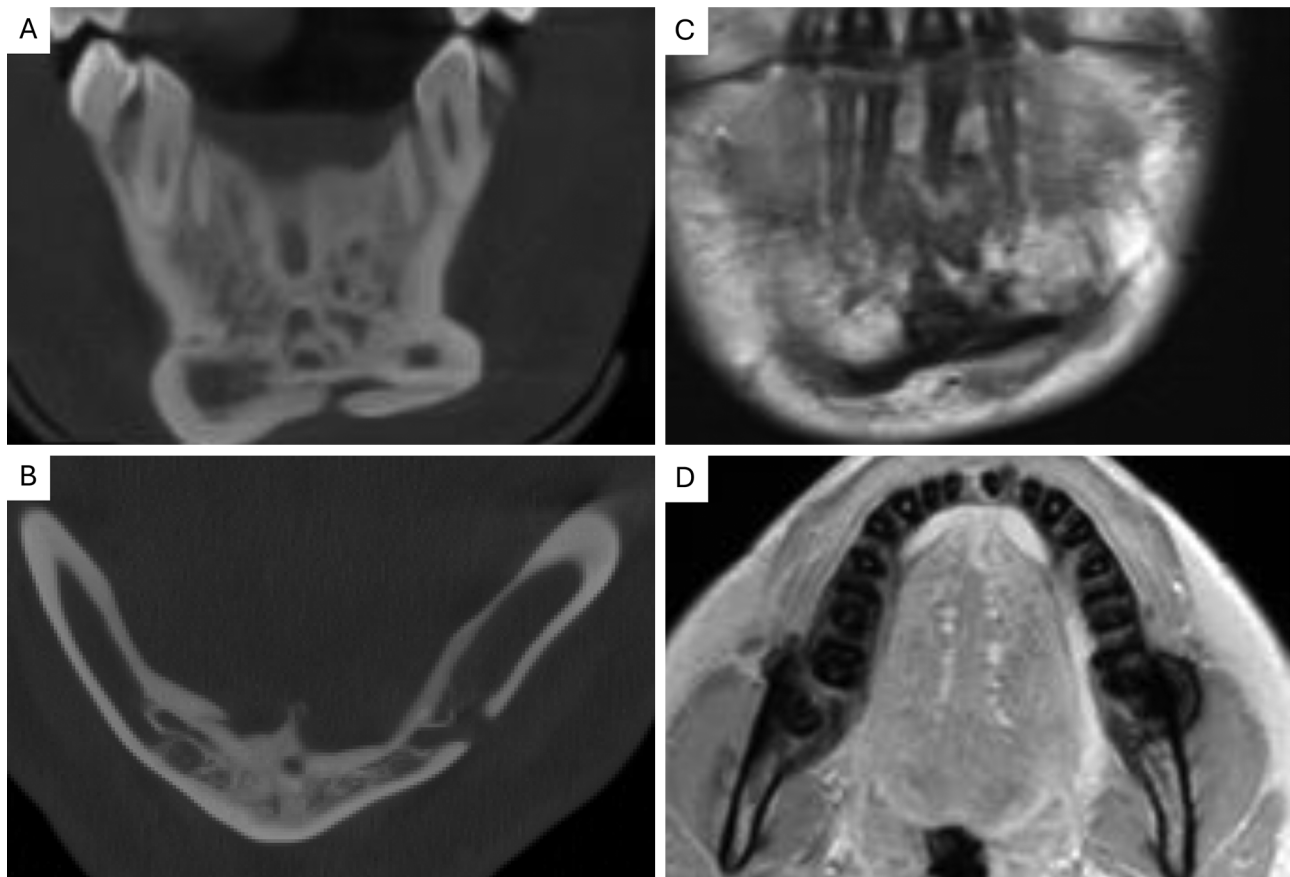


Figure 5. Radiological representation of the tumor recurrence [A, B: cone beam computed tomograms (CBCT); C, D: magnetic resonance images (MRI). Coronal view: A and C, axial view: B and D]. (A) The coronal CBCT section of the chin region shows the periapical osteolysis of the central incisor, which continues cranially into the oral soft tissues, as well as a system of connecting canals. The edges of the cavities are focally hyperdense (sclerosed). On the left side, the transition of the additional foramen into a canal is visible. (B) Noticeably wide mandibular incisive canals on both sides, which branch off from the foramen. The chin area is hyperdense. A central canal is located anterior to the spine. (C) The MRI shows a hyperintense marginal bone region adjacent to tooth 31 and extending laterally to the neighboring teeth at the level of the alveolar limbus. To the caudally adjacent, comparatively slightly hypointense layer, there is a dark hypointense demarcation line of approximately the same signal density of the referential hard tissues. (D) The axial slice shows the small, hyperintense, cushion-like soft tissue masses that lie adjacent to the lingual side of anterior alveolar process.

mandibular anterior lingual alveolar process, growing a little more to the left side. The lesion was smaller in dimensions than the previous tumor. However, the shape and consistency of the tumor on inspection and palpation were the same as 13 years previously. Recurrent nerve sheath tumor was suspected. The tumors of the lingual incisors' regions were excised in general anesthesia (Figure 1H). The mucosal defect was primarily closed by means of sliding flap plastic surgery. Removal of the solid masses was complicated by increased bleeding into the floor of the mouth, resulting

in a pronounced hematoma extending to the floor of the mouth and submandibular region. The further course with slow resorption of the hematoma proceeded without permanent restrictions on swallowing and speaking. A few weeks after the procedure, the oral mucosa of the anterior floor of the mouth and alveolar process was completely regenerated (Figure 1I). The sensitivity test of the tooth 31, which was surrounded by soft tissue and loosened, carried out repeatedly after the second procedure, always showed an adequate reaction to cold stimuli.

X-ray. In the adult patient, on the panoramic view of the jaw, the mandibular right articular process appeared somewhat clumsier and vertically shortened compared to the left side. The shape of the jaw (ramus, corpus) appeared symmetrical in the overview photograph, except for the chin region, which corresponded in outline to that of the radiograph of the adolescent. The measurement of the ramus length and the distance of the articular process from the coronoid notch confirmed a small plus on the right side. However, no relevant side difference was measured on the adult patient's radiograph for ramus height (posterior ramus length right: 111 mm and left: 93 mm). The diameters of the mandibular foramen showed no significant differences [right: 12.9 mm (sagittal) and 5.13 mm (transversal), left: 10.2 mm (sagittal) and 5.8 mm (transversal)] as well as the distances of the mandibular processus from the semilunar incisura (distance from the highest point of the condylar process to the lowest point of the semilunar incisure: right 47.7 mm, left: 41.8 mm; distance from the highest point of the muscular process to the lowest point of the semilunar incisure: right 23.6 mm, left 25.6 mm). There was also no evidence of an enlarged cranio-caudal diameter of the mandibular canal (vertical distance of the cortical boundaries of the mandibular canal. The distance was measured at a spatial distance of 10 mm from the distal end of the funnel-shaped mandibular foramen (right: 5.9 mm, left 6.5 mm). The mental foramina slightly differed in diameter [right; 4.9 mm (horizontal) and 5.6 mm (vertical), left: 3.2 mm (horizontal) and 2.16 mm (vertical)]. We used the lateral comparison of the crown diameters at the cemento-enamel junction of the second mandibular molars in the antero-posterior direction as an internal reference for the plausibility of measurements of radiographs without metric calibration (panoramic view) (right: 13.7 mm, left 13.6 mm). In summary, the examination results provided no evidence for a constellation of findings indicating PNF of the proximal portions of the mandible (20) nor for the repeatedly reported enlargement of the mandibular canal in NF1 (20, 21).

CBCT. A cone beam computed tomography of the jaw was performed prior to surgery (Figure 5A and B). The surface

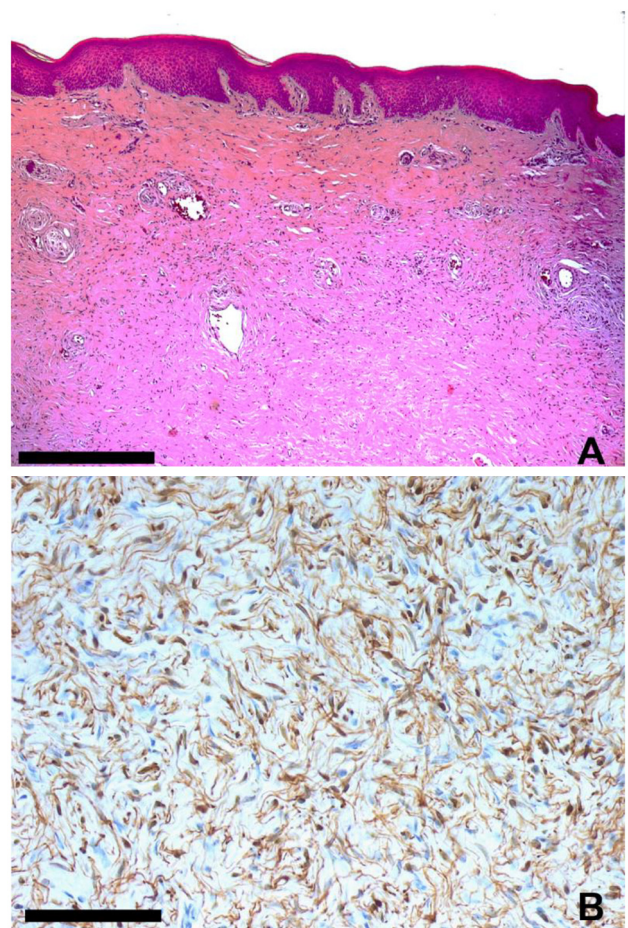


Figure 6. Oral cavity tumor: diffuse neurofibroma: (A) nonkeratinized epithelium with subepidermal infiltration of a diffusely grown spindle cell tumor of low to medium cell density, scale: 400 μ m. (B) Immunohistochemical labeling of tumor cells with S100-protein antibodies, scale: 100 μ m.

view of the mandible showed an asymmetrical chin with a more caudally formed bony protrusion on the right paramedian side. There was partial loss of the alveolar process between the left lower incisors. The mental foramina were localized on both sides around the premolars. The left foramen was slightly smaller than the right one (vide supra). A cup-shaped defect of the vestibular aspect of the mandible caudal to the left central incisor was conspicuous, reminiscent of an additional foramen. The tomographic image showed that a narrow duct connected the defect to the lingual side of the

mandible (Figure 5A). On the lingual side of the anterior mandible, an uneven cortical surface layer was formed, which extended from the basal border of the mandible to the alveolar process. The interconnecting bony canals of the chin were still present. However, the mandibular chin region appeared sclerosed compared to the cancellous posterior bone of the corpus. The root of the severely loosened tooth 31 was surrounded by extensive osteolysis. CBCT confirmed an inconspicuous bone outline and internal structure in the largely symmetrically developed proximal parts of the mandible (Figure 4, Figure 5A and B). In summary, compared to the panoramic view of the jaws, the CBCT showed further details of the altered bone surface in the tumor area, peri-dental bone destruction and a dense canal system extending from the oral lesion to the base of the jaw.

MRI. A whole-body MRI of tumor screening was carried out in the almost 23 years old patient. In retrospect, the images on T1-weighted axial sections of the skull showed bilateral soft-tissue masses of the lingual alveolar process with cushion-like expansion and homogeneous hyperintensity in relation to the muscles of the floor of the mouth (Figure 5C and D). The images raised the assumption that the tumor recurrence had already existed approximately 5 years previously and had only become subjectively conspicuous in the further course. The masticatory muscles on both sides were symmetrically developed and showed no structural changes (35, 36).

Histology. The recurrent oral tumor was diagnosed as DNF.

General condition. At the time of treatment for oral tumor recurrence, the patient was in good general health condition. His height was 188 cm and body weight 80 kg. Lisch nodules were recorded bilaterally. The examination revealed moderate dysphonia/dysarthria and a slightly clumsy and dystactic gait pattern. Repeated whole body MRIs showed multiple nodular PNF in the gluteal-inguinal region and in the lower extremities. These tumors showed a slow increase in number and size during the study

period. The tumors of the trunk and extremities had occasionally become symptomatic under local physical pressure. However, no diffuse or nodular PNF tumors were recorded in the head and neck regions. The MRIs of the head and neck region so far have shown no evidence of optic glioma recurrence. The last epileptic seizure dated one year before the current examination (permanent medication: valproate). The patient's hypothyroidism is treated with L-thyroxine and the vitamin D deficiency is substituted with oral administration of vitamin D₃. The synopsis of the findings allows the conclusion that the recurrent oral nerve sheath tumor was the only NF1-associated neoplastic manifestation of the head and neck in this patient on long-term antiepileptic medication.

Discussion

The report describes the diagnosis and treatment of a recurrent and invasively growing oral DNF. Clinical and radiological analysis showed that the nerve sheath tumor caused displacement of adjacent teeth and progressively invaded the bone. Bone invasion is unusual for this tumor in this location. Alterations of bony structures are much more commonly noted in PNF and/or DPN, which are associated with dysmorphic mandibles, presenting as changes of the outline and sagittal projection of the affected side of the jaw (35). Periodontal infiltrations of a neurofibroma are observed in oral PNF in connection with eruption disorders of permanent teeth and here primarily pericoronally (36). The impression of an invasive tumor growth can arise on overview photographs of the jaw, particularly around the mandibular foramen. However, these radiolucencies are PNF-associated thinning of the ramus, which on survey images appear as radiolucencies around the foramen and suggest infiltrative tumor growth and enlargement of the mandibular foramen (35). Reports of PNF growing in the bones usually show the typical deformation of the dysplastic mandible due to the congenital tumor, but no osseous origin of lesion (36). The PNF-associated deformations of the jaw often create bizarre outlines of the affected jaw region (36), but may

rarely also be subtle, becoming apparent only when compared to the unaffected side (37). However, typically these PNF-associated mandibular lesions are accompanied by extensive soft tissue tumors that are already externally visible (13, 38). The probably congenital mandibular changes often affect the area of the temporomandibular joint process, mandibular foramen and ramus as well as distal parts of the mandibular corpus (20), *i.e.*, proximal parts of the bone. In fact, diffuse PNF were considered congenital tumors (39), although in some cases the clinical diagnosis is only made some time later (13). Riccardi's statement that congenital DPNs are not pure nerve sheath tumors but can have a field effect on the affected body region applies to these lesions (40). In contrast, oral nerve sheath tumors in NF1 may arise later in life and are located adjacent to the mandible or are adhering to the bone [localized neurofibroma (13)]. These lesions are usually characterized as soft tissue masses that either have no effect on the bone and teeth due to localization, size and completed tooth eruption (14, 16, 18, 19) or only cause circumscribed (periodontal) changes (6-9, 11, 17). The lesions that appear later in life are rarely reported in NF1 (40). However, a systematic study concluded that 'localized' lesions can be detected in almost 28% of cases, although the lesions were not reported to have an impact on the adjacent jaw (21). The solitary lesions were usually noticeably smaller than congenital lesions. Interestingly, the circumscribed oral lesions with a suspected clinical diagnosis of PNF were rarely diagnosed as such in the histological assessment. The alterations corresponded to 'discrete mucosal lesions' (21). It is therefore debatable whether congenital orofacial nerve sheath tumors with jaw changes are predominantly DPNs (39), while oral tumors arising in later phases of life are more likely to present as neurofibroma (6) or discrete mucosal neurofibroma (21).

Another characteristic of the presented case is the bone invasion of the lesion. According to the literature, intraosseous alterations in NF1 primarily comprise the enlarged mandibular canal. Several authors have suggested that the uniform enlargement of the mandibular canal

without caliber jumps is caused by neurofibroma (20, 41). However, morphological evidence of this osseous anomaly has not yet been provided (41). Interestingly, this finding may indeed be noticed on the side of a mandibular PNF but is obviously not obligatory associated with a diffuse/diffuse plexiform neurofibroma (20, 41). Clearly intraosseous neurofibromas of the mandible are considered a very rare finding in NF1 (27). However, degeneration of an oral peripheral nerve sheath tumor into a malignant peripheral nerve sheath tumor has been described (42). In rare cases the MPNST was very likely arising inside the bone (43, 44).

In the case presented here, a continuum between the oral tumor, the periodontal osteolysis and the network of intraosseous canals was found on histological examination. On the tomograms, the border of the intraosseous canals was characterized by a sclerotic margin, possibly an indication of slow, displacing growth that had come to a standstill. The osseous canals showed hardly any changes over time. In contrast, the periodontal defect increased considerably. Periodontal alveolar bone loss caused a change in tooth position and significant tooth loosening. The periodontal neurofibroma had wide contact with the lingual tumor. While the stable finding of the canal system is reminiscent of the enlarged and dimensionally stable mandibular canals observed in NF1, the periodontal defect resembles an inflammatory osteolysis.

The nerve sheath tumor presented here shows a combination of findings that are typically registered in (diffuse) PNF (changes in the shape of the mandible, but in an unusual place) or as DNF that do not cause any bone changes and only affect the jaw superficially and are locally limited. The question therefore arises as to whether there is evidence of a connection between location of the lesion, dentition, histological type of peripheral nerve sheath tumor and shape of mandible in NF1 patients.

Diffuse PNF has been repeatedly demonstrated for congenital peripheral nerve sheath tumors in NF1 with deformation of the mandible adjacent to the tumor. The growth and differentiation disorder of neighboring tissue is recorded for this tumor (39). Indicators of embryonic tumor effects in mandibular development besides bone

deformation are the often-observable misalignments of the permanent teeth, which, for example, do not move mesially far enough to close the dental arch in contact with neighboring teeth or even remain retained in the bone (20). However, in this neurocristopathy, the odontogenesis of the individual tooth is apparently not disturbed if the dental anlage is present. The genetic influence of the underlying disease apparently does not affect the shape of the tooth but rather the ability of the permanent tooth to migrate in the bone. The well-known observation of completely impacted teeth (often permanent molars) and a diffuse PNF covering the alveolar process suggests that this complex malformation (deformed mandibular segment and retained teeth) has both mechanical causes (massive connective tissue tumor layer) and intrinsic causes of the bone (*e.g.*, misregulation of osteoblasts/osteoclasts in tooth movement). These are clear spatiotemporal effects of diffuse PNF on bone and teeth illustrating early onset of the hard and soft tissue pathology. Difficult eruption of permanent teeth can be a sign of an oral neurofibroma (6, 15). There are many factors that can prevent teeth from erupting, *e.g.*, positional anomalies or supernumerary teeth. Numerical aberrations of permanent dentition have been reported in oral PNF but are independent of tumor (45). In fact, studies show that tooth development (as a single organ) and tooth change (as a spatiotemporal process) of patients with NF1 do not differ from that of the normal population (46), except for the local effects of neurofibromas (*vide supra*). In contrast to congenital PNF with mandibular involvement, oral tumors that occur later in life, these lesions occasionally arise from the alveolar process and near teeth of mandible. Changes in the row of teeth then develop through displacing or, as in this case, infiltrative growth without having an influence on a larger section of the dental arch. In these cases, at the time of obvious oral tumor growth, the permanent teeth are already set into the dental arch (11, 14, 19). Similarly, osseous neurofibromas that develop later in life are conspicuous as osteolysis, which can resorb tooth roots, for example, depending on their location. The lesions typically do not lead to any change

in the shape of the jaws beyond the local osteolysis, although the displacing growth may represent radiological equivalents. Local changes in the position of the affected teeth may occur. In case of osteolysis with rapid tumor growth the differential diagnosis of malignant degeneration is paramount (28).

From these observations it can be concluded that in the case of complex tooth position disorders with evidence of nerve sheath tumors, it is worth carrying out a radiological examination of the jaw to determine whether and, if so, to what extent the jaw has changed. The findings of skeletal radiology should be supplemented with an examination technique that differentiates between soft tissues. Diffuse PNF arising in proximal parts of the trigeminal nerve's third branch has characteristic radiologic changes preferentially of the proximal mandible and the adjacent skull base, which can often be identified in children (47). DNF usually is a postnatal and localized lesion affecting mandibular mucosa and sometimes adjacent bone. Careful oral examination of the patient with NF1 should be included in general recommendations for the care of this patient group (25, 48).

Conclusion

Oral diffuse neurofibromas can spread inside the bone. An interconnecting canal system may develop in conjunction with the osseous tumor infiltrate. The neurofibroma growing into the bone may enlarge the bone defect over a prolonged time interval and provide the radiologic evidence of a bone-invasive tumor. Distinguishing between tumorous bone changes and skeletal dysplasia can be difficult or even impossible, both with adequate imaging and surgical exploration. Complete surgical removal of the diffuse neurofibroma can be challenging. Consistently ablative measures may lead to tooth and bone loss. Incomplete removal of lesion can lead to recurrence of the nerve sheath tumor. To the best of the authors' knowledge, the interconnecting mandibular duct system shown here in topographic relation to a diffuse neurofibroma has not been described before.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding the publication.

Authors' Contributions

R. E. Friedrich: Treatment of the patient, conceptualization, draft and corrections of the manuscript. F. K. Kohlrusch: Literature research, draft and correction of the manuscript. C. Hagel: histologic diagnosis, draft and corrections of manuscript. All Authors have agreed to the release of the manuscript for publication.

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