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Microdont Developing Outside the Alveolar Process and Within Oral Diffuse and Plexiform Neurofibroma in Neurofibromatosis Type 1

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Abstract. *Background/Aim: Numerical aberrations of permanent dentition and dystopic tooth eruption are part of the phenotype of the tumor predisposition syndrome neurofibromatosis type 1 (NF1). In these cases, surplus tooth germs usually develop in the alveolar processes of the jaw. This report attests to the dystopic development of a dysplastic supernumerary tooth in NF1 arising outside the jaw. Case Report: The 8-year-old male patient developed a microdont outside the bone and above the occlusal plane of the retained maxillary right second molar. The supernumerary tooth was completely embedded in oral soft tissue. Hyperplastic oral soft tissue in the molar region and microdont were excised. Specimen of the mucosa surrounding the teeth was interspersed with diffuse and plexiform neurofibroma. The retained upper right first molar emerged spontaneously within a few months after surgery. The upper right second molar did not change position. Conclusion: Odontogenesis can take place within tumorous oral mucosa in NF1. Surgical removal of the tumorous mucous membrane facilitates tooth eruption in some cases.*

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Numerical aberrations of the permanent dentition have been reported in patients with neurofibromatosis type 1 (NF1) (1). NF1-associated supernumerary teeth were found more frequently in the molar region than in other tooth types (2, 3). A topographic relationship between dental numerical aberrations and nerve sheath tumors typically arising in NF1 has been noticed in some cases (3). However, supernumerary teeth are regarded a constitutive finding in NF1 (3). This case report describes the diagnosis and treatment of a patient with NF1 who developed a supernumerary tooth of small size.

Case Report

The male patient was subjected to several surgical procedures in the Clinic for Oral and Craniomaxillofacial Surgery, Eppendorf University Hospital since early childhood because of an extensive facial plexiform neurofibroma (Figure 1A-G). In this patient, the congenital nerve sheath tumor extended from the right orbital region to the lower edge of the mandible on the same side (Figure 1E-G). The term hemifacial plexiform neurofibroma (PNF) was introduced for this expression of PNF in the facial area (1). Diagnosis of facial PNF very often is associated with several skull alterations (1). Initially, the focus of surgical treatment was corrective surgery of the eyelids and a reduction of the tumor mass of the right cheek. The surgical measures in the cheek area were operations through skin incision and clearly distant from the jaw and oral mucosa. At the age of 6 years, orthopantomography (OPT) of the jaw was performed because oral findings had given rise to the suspicion of non-erupting teeth or aplasia of teeth in the molar region on the affected body side (Figure 1B). The patient met the currently valid diagnostic criteria for NF1 (4).

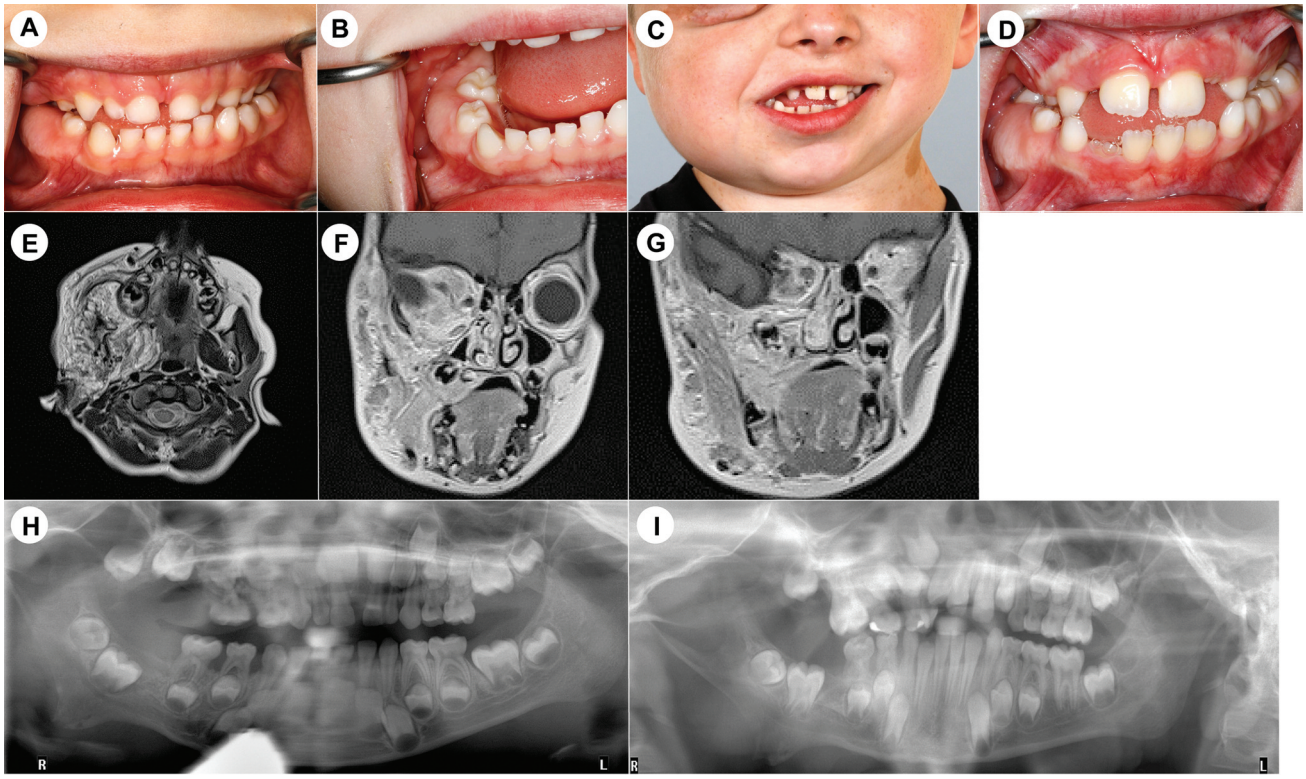

Figure 1. *Clinical findings (A-D), magnetic resonance images (E-G) and orthopantomograms (H-I) of a patient with right-sided plexiform neurofibroma (PNF) and maxillary microdont. (A) Photographs of oral inspection of the 6-year-old patient (A, B) reveal deciduous dentition, tumorous bulging of alveolar process due to oral PNF, and no emergence of mandibular right first permanent molar (B). Photographs en face [(C), cropped image] and oral view (D) reveal an extensive soft facial tissue tumor and physiological functioning of perioral muscles, vestibular bulging of right mandibular alveolar process and delayed emergence of mandibular right second incisor (C and D: 8-year-old patient). Magnetic resonance images show (E) the extension of the facial PNF of the right half of the face and skull base using the example of the plane showing the maxillary molars (axial plane). (F) Figure shows cranio-caudal extension of the tumor from the right skull base to the lower margin of the mandible. The half-sided delimitation of the tumorous lesions is also clearly visible in this plane. On the right side, the maxillary right first molar is completely encased by tumorous tissue in the crown area. The apical dimension of the tooth borders cranially on a thin layer of bone. A few sections further dorsal, the placement of the second right upper molar is shown (F and G: coronal plane; E-G: 7-year-old patient). (H) Orthopantomogram of the 6-year-old boy shows complete deciduous dentition and germs of all four first and second permanent molars. (I) Three years and two months later, the three first molars emerged into the oral cavity and gained occlusal contact. The root of the mandibular right first molar is developed (visible bifurcation of roots). However, root development is far behind compared to the mandibular left first molar. Positions and developmental stage of second molars did not change substantially during the observation period (H and I).*

Oral findings. On admission, the patient could open his mouth without restriction and had deciduous teeth (Figure 1A). Distal to the right second deciduous molars, no teeth had emerged (Figure 1B). The oral mucous membrane in the lower jaw had grown to the occlusal level of the deciduous molar. There was also a thickened oral mucosa in the upper jaw. However, maxillary soft tissue hyperplasia was not so prominent because the alveolar process had hardly developed in the right molar region. When opening the mouth, the mandible shifted to the right side. The misalignment of the jaws relative to one another was primarily caused by the mandibular corpus, which was shortened on the right side (Figure 1).

Imaging findings. Magnetic resonance imaging (MRI) (Figure 1E-G) showed extensive infiltration of the right half of the face by the PNF. The orbit was completely invaded by tumorous tissue. The chewing muscles were infiltrated by the tumor. The area of tumor spread corresponded to the distribution pattern of the trigeminal nerve on this side. Molars on the right were observed in both jaws in several images. In the upper jaw, the second molar formed tooth roots that adjoined the bones apically (Figure 1F). In the lower jaw, tooth crowns of incompletely developed molars were located in a trough-like bone defect of the distal alveolar process and the right angle of the jaw (Figure 1G, Figure 2A-E, Figure 3A-C).

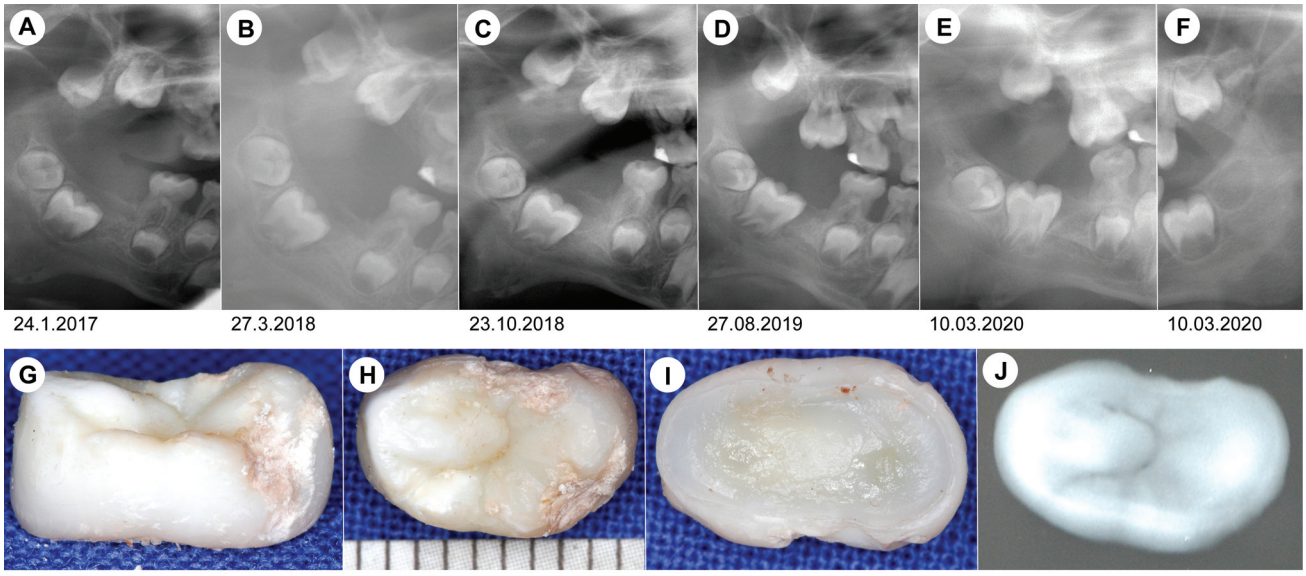

Figure 2. *Supernumerary microdont of permanent dentition in neurofibromatosis type 1. (A-F) Cropped images of orthopantomograms taken between the 6th and 9th year of age (A-E show right mandibular angle, F shows left mandibular angle). (A) Detail of figure 1H: Crowns of right upper molars surrounded by thin bony trough (6-year-old). (B) Initial calcification of supernumerary tooth superimposing the occlusal plane of the second molar. (C) Further growth of a small radiopaque lesion different to the second molar's crown. The distance between the first and second upper molar is increased, and first molar's root is further developed. (D) First molar is moving in mesial direction and caudally after removal of tumorous mucosa and microdont (9-year-old). (E) Eight months later, the maxillary right first molar developed occlusal contact with mandibular deciduous second molar. (F) On the left side, third molars are developing in both jaws at the same time. Lateral (G), occlusal (H) and apical (I) photographs of the microdont after excision. Note opposing enamel mineralization disorders of the tooth (maximum length about 10 mm). (J) Contact radiograph of microdont shows enamel defects and inhomogeneous radiopacity.*

Orthopantomogram of jaws (OPT) (Figures 1H-I, 2A-F) of the jaws showed bone deformity of the affected right body side. The teeth of the deciduous and permanent dentition had developed symmetrically at the time when first radiographs were taken at 6 years of age (Figure 1H). However, the positions of the permanent molars differed significantly between the two sides. The molars on the right side were located more distally and there was a gap between the molars and the premolars (Figure 1H). The jaw bones showed typical deformations on the affected side as described for NF1 patients with extensive congenital PNF (1), *i.e.*, deep coronoid notch, hypoplasia of the ramus with narrow processes, a smaller jaw angle, and a slightly arched indentation at the lower edge of the distal mandibular corpus (usure). Figure 1H and 1G show the initial and final positions of the teeth. Figures 2A-F are cropped images of OPTs taken between 6 and 9.5 years of age.

Cone beam computed tomography (CBCT) (Figure 3) showed no supernumerary tooth had yet been developed at 6 years of age (Figure 3A). The crown of the microdont had developed at 8 years of age (Figure 3B and C). The three-dimensional reconstruction of the jaw and teeth showed the positional relationship of the supernumerary tooth to the second molar. The extensive, tumorous circular bone defect of the permanent lower molars was evident on the selected planes.

Treatment. The hyperplastic oral soft tissue covering the retained maxillary right molars was removed under general anesthesia. The connective tissue was a fixed, firm layer above and around the teeth. The crowns of the upper molar teeth were exposed to the oral cavity by wide circular mucosa excision. The surplus microdont was removed from the margin of the second molar crown's distal surface (Figure 2G-J). The same procedure was carried out to expose the lower right first molar. The oral wounds were covered with a bandage fixed with individual sutures and granulated by secondary intention. The epithelialization of the wound was achieved without complications within 7 days. However, the soft tissue around the exposed teeth was regrown 7 days after the surgical procedure. Therefore, the tissue surrounding the tooth crowns was excised again. During further wound healing there was no connective tissue hyperplasia in the peri-coronal area. In the mandible, further observation showed a slow overgrowth of the tooth with oral mucosa. In the maxilla, the first molar's crown remained

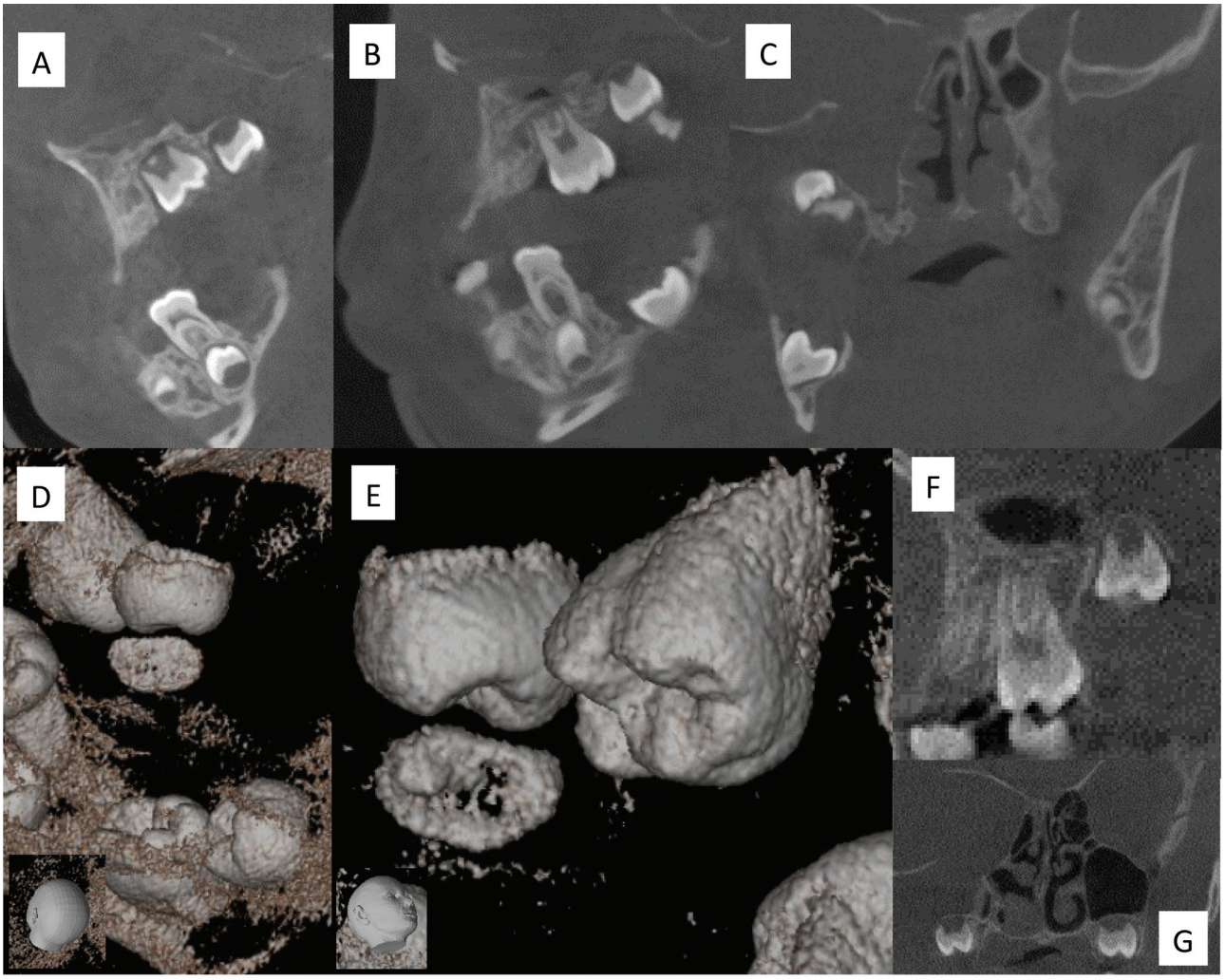

Figure 3. *Cone beam computed tomograms of supernumerary microdont in NF1 (cropped images). (A) Shows two upper molars of the right side developing in close contact to the bone. No microdont is visible. The shell-like depression in the mandibular alveolar process distal to the deciduous molar corresponds to the extent of the oral plexiform neurofibroma in this area (sagittal plane). (B) A year and a half later, the microdont had largely developed as a tooth crown (sagittal plane). The root growth of the first molar is advanced. The distance between the first and second molar on the right side of the upper jaw had increased. In the lower jaw, the crown of the right first permanent molar can be seen within the bone defect. Figures (D) and (E) show the surface reconstruction of the two right maxillary molars and the microdont from different perspectives (insert: the viewer's perspective of the skull). (F) Sectional view of the occluding molar with the apices still open (sagittal plane, 10-year-old). (G) Detail of a coronal section of the skull. Dysmorphism of the right orbit with defect of the right sphenoid bone. The right maxillary sinus is hypoplastic. The radiological development stage of the maxillary second molars is identical. Both teeth are parallel to the horizontal plane (10-year-old patient).*

permanently exposed to the oral cavity. The first molar was elongated after 18 months of observation and reached the occlusal plane without further measures (Figure 3D-E).

The removal of the mucosa and the subsequent rapid onset of mesial movement of the first molar through the alveolar process so far have had no influence on the position and development of the maxillary right second molar. The distance between the first and second molar had increased due to the migration of the first molar to the most distal deciduous tooth. In contrast, the exposure of the lower first molar had no effect on the position of teeth 46 and 47 in the mesio-distal plane. There was some growth of the mandibular right first molar's root but was well behind the root growth stage of the tooth 36.

X-rays revealed the germinal centers of the wisdom teeth on the left side in the 9.5-year-old patient (Figure 2F). On the other hand, no wisdom tooth anlage was visible on the tumorous right side.

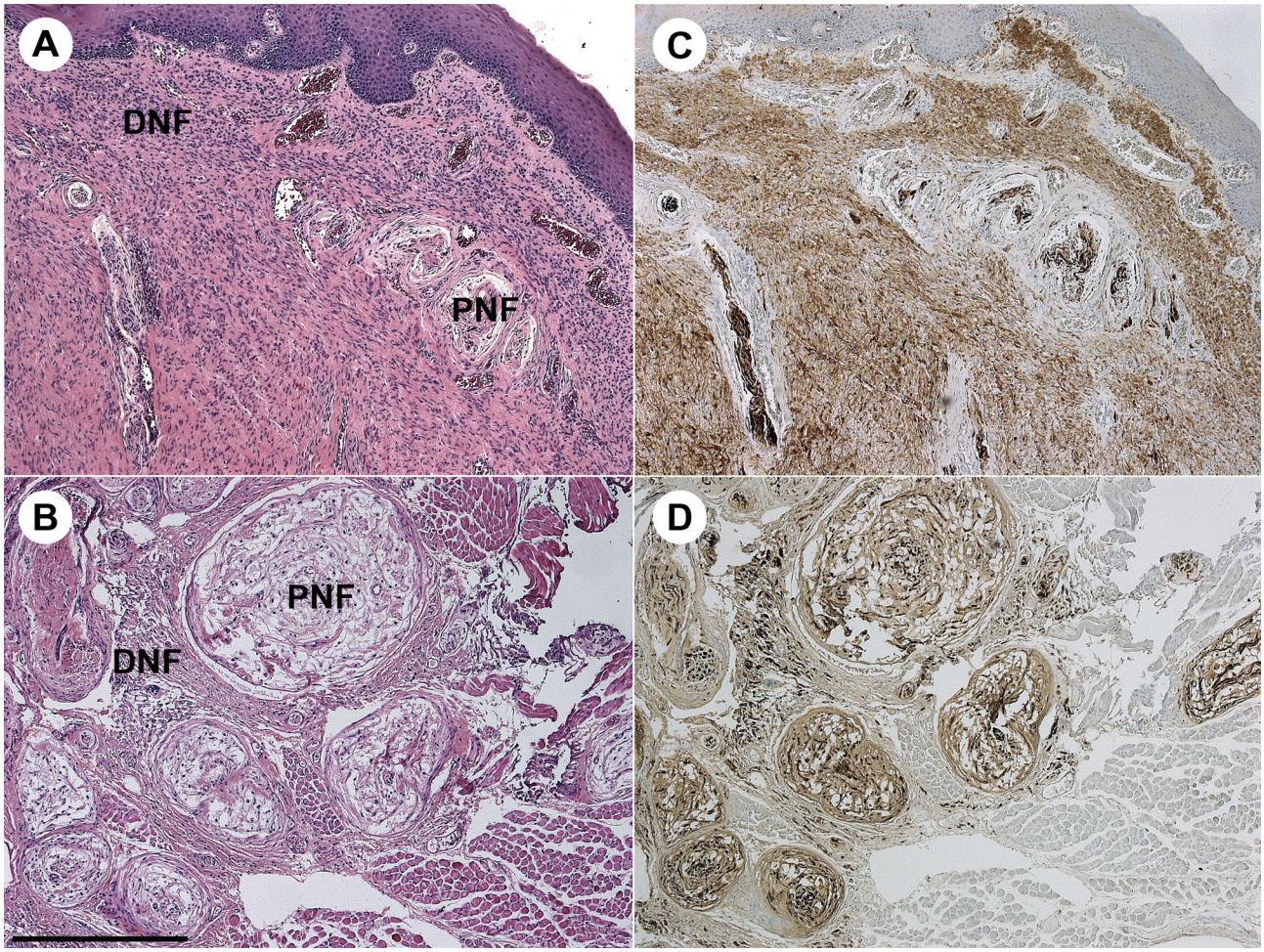

Figure 4. *Histology of oral plexiform neurofibroma in neurofibromatosis type 1. (A) mucosal skin with subepidermal diffuse neurofibroma (DNF) of medium cell density. Note the intraneural plexiform neurofibroma (PNF) of low cellularity within the DNF; (B) skeletal muscle and connective tissue with multiple intraneural plexiform neurofibromas (PNF) with loose myxoid matrix and low cell density. Note the increased cell density in the connective tissue indicating diffuse neurofibroma (DNF); (C) and (D), S100 protein immunohistochemistry depicting S100 protein positive neurofibroma cells of DNF and PNF. (A) and (B): H&E stain; scale bar=500 μm, applicable for all photomicrographs.*

Histology

Soft tissues. Facial and oral tumor samples showed the uniform pattern of a benign peripheral nerve sheath tumor (Figure 4). Tissue samples of the facial PNF, for example the lid and the orbit, already had revealed diffuse and plexiform neurofibroma of the face. The oral mucosa over the completely covered first molar was examined histologically. A diffuse neurofibroma had developed in both jaws. In addition, plexiform differentiated neural sheath tumor within the diffuse neurofibroma was found in the maxilla (Figure 4). When the oral dressing was removed one week after the first procedure, the hyperplastic marginal tissue around the exposed teeth was excised. The tissue samples of the hyperplastic regenerated soft tissue showed non-keratinizing squamous epithelium with florid granulocytic infiltrations and subepidermal vascularized granulation tissue, typical of a fibroma, but no neurofibroma (not shown).

Tooth and bone. The tissue sample contained bony and odontogenic hard tissue. The cortical bone had an irregular, marginal defect zone with moderately deep absorption lacunae, covered with multinucleated osteoclastic giant cells containing up to five isomorphic cell nuclei. The central bone parts had a regular, lamellar basic structure with occasionally demonstrable enlarged vascular canals showing osteoclastic resorption. The surface of the cortical bone showed focal, fibrous new bone formation. In these regions of new bone formation, there were also moderately deep absorption

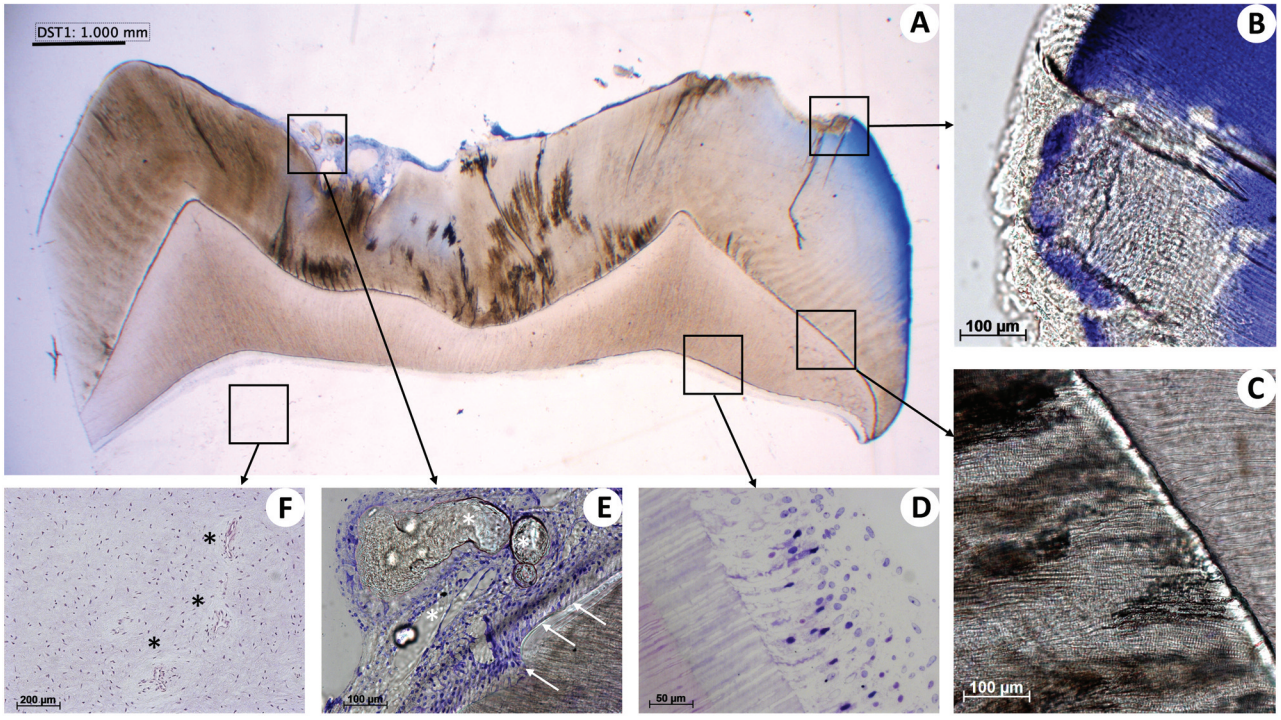

Figure 5. *Morphology of microdont in neurofibromatosis type 1. (A) Panoramic image of the whole dental crown. (B) Focal abnormal and hypomineralized enamel (left) in contrast to regular mineralized lamellar architecture (right). (C) Border between enamel (left) and dentin (right). (D) Basal dentin layer (left) and tall columnar odontoblasts with oval nuclei (right). (E) Irregular fragments of enamel (*) surrounded by ameloblasts and ameloblasts lining the surface (→) of the regular enamel matrix. (F) Loosely arranged fibroblasts of dental pulp with delicate vessels (*). The empty box in (A) is placed where the pulp was placed in situ. (A-E): Toluidine blue stain, (F): H&E stain.*

lacunae and isolated giant cells. There were multilayered squamous epithelia covering the periodontal fibroblastic stroma adjacent to the tooth. Here a focal, moderately cell-dense inflammatory granulation tissue, analogous to chronic, active periodontitis was visible. In this area, there were also small bone fragments, mostly cancellous bone with reactive structures, but no osteonecrosis. The sparse tooth structures had irregular surface and shape with slight dysmorphic dentin. Superficially, pre-dentin or odontoblastic proliferation without cell atypia had developed in several places. Proliferating odontogenic epithelia were absent. Histologically, the findings resembled a compound-type odontoma (Figure 5).

Discussion

NF1 and dentition. NF1 is a syndromic disorder affecting multiple organs. Multiple neurofibroma of the skin is a hallmark of the disease (4). However, hard tissues are also affected in NF1 patients (4). Disorders of the dentition in NF1 concern, on the one hand, the occlusion of teeth rows, which can be caused by developmental disorders of the jaws and positional anomalies of teeth. On the other hand, the number of additional teeth in NF1 patients is also significantly higher than the calculated rates of sporadic numerical aberrations of permanent dentition in the general population (4). So far it can be hypothesized that the tooth shape of NF1 patients corresponds to that of normal populations (5). Kinking or twisted tooth roots on radiographs of deformed jaws are frequently recorded in patients with PNF, found on the same side as the facial PNF, and are interpreted as local adaptations of the growing root to the pathologically deformed bone (1, 3, 6). The findings presented here are unusual and noteworthy for several reasons. The development of the microdont takes place within a very short time, as far as can be determined by X-ray diagnostics. Furthermore, the tooth arises outside the bone and in a tumor-altered tissue. Third, this tooth is unusually small and looks like a micro-morph image of a molar with a reduced occlusal relief. The extracted tooth shows clear mineralization defects in the enamel. The eruption of the first molar was made possible by the surgical measure and the tooth spontaneously reached the occlusal surface within a relatively short observation interval. We

have already used the oral surgical measure repeatedly in the past and the success of the operation has also been reported by other working groups (7).

NF1 and neurofibroma. This study shows the ectopic development of a tooth within a hyperplastic oral mucosa covering multiple retained teeth. The oral mucosa at this site was densely infiltrated by a PNF. PNF in NF1 are regarded as tumors and especially as precancerous, which in some cases can transform into malignant peripheral nerve sheath tumors (8). However, facial PNF are rarely affected by malignancy (9, 10) and therefore only rarely contribute to the reduced life expectancy of NF1 patients (11). Rather, the facial PNF has a considerable negative impact on the quality of life of the affected individual. In the case presented here, the deformation of the face due to the tumor on the right side was noticeable, a typical finding of hemifacial PNF (1). The frequently slow growth of tumors and the tumor-associated changes in hard and soft tissues are an argument for the hypothesis that some findings in NF1 should be addressed as hamartoma (1). The directional development of a small tooth can be seen from the series of x-ray images. The tooth crown had an occlusal relief with marginal ridges. At the time the tooth germ was removed, the development of the crown was largely complete. Several foci of incomplete mineralization of the tooth enamel were noticeable under the microscope (Figure 2G-J, Figure 5). The differentiation disorders of the enamel were superficial, *i.e*. facing the tumorous connective tissue. The partially developed tooth and its localization are indicative of postnatal development of hamartoma.

In the case of ectopic tooth developments in the skull, the tooth germs are usually localized in the bone or at least have a close topographical relationship with the bone. However, the potential of oral soft tissue for extraosseous odontogenesis is well known (12-19). What is unusual about this case is the evidence of oral odontogenesis outside the bone in combination with a tumor.

Imaging of ectopic teeth on radiographs. OPT of the jaw is the preferred radiological method for surveying the dentition. Small excess teeth may not be shown on OPT (20). Limited visualization of tooth germs or even teeth on radiographs especially apply to OPT in cases with mixed dentition (20). Statements on the incidence of a supernumerary microdont are therefore estimates. The information on the frequency of one or more microdont or conical tooth varies between 0.1-4.3% of ethnically different populations (21). A microdont does not have to have completely developed roots to meet the definition (21). No further supernumerary teeth were shown on OPTs or on tomograms. CBCT confirmed a solitary, solid hard tissue formation. Evidence of solitary, homogenous hard tissue of tooth-like outline was assessed as an essential radiological feature distinguishing microdont from developing odontoma. Reports on the presentation of developing odontoma usually show small multiple odontogenic hard tissues appearing as multiple punctiform radiopacities (22).

The MRI was performed one year prior to first evidence of the microdont on OPT. MRI is suitable for displaying ectopic teeth (23). No microdont could be detected on the MRI produced at that time. This finding is in line with sequential OPTs of the patient. The MRI sections showed the first molar with root formation and the second molar located distal and cranially. Both teeth were encased in a solid, hyperintense mass that continuously merged into the extensive facial neurofibroma. In contrast to the partially inhomogeneous internal structure of the facial PNF, the oral tumor resting on the jaw and teeth showed a largely homogeneous signaling. The representation of the tumor expanding in the head and neck region in continuity to the oral cavity by means of MRI supported the clinical assessment that oral soft tissue hyperplasia is a PNF.

Histology. Histological findings contribute significantly to the differential diagnosis of odontogenic hard tissue developmental disorders (21, 24). The morphology of the malformation can be very variable, and it may be difficult to distinguish between odontogenic entities when transitional forms occur. Cyst-like structures can develop with retained and dysmorphic surplus teeth and thus indicate a normal tooth developmental stage (follicle) (25, 26), a developmental disorder (27, 28), or true neoplasm (29). In the case presented, the tooth had developed within the neurofibroma. No other odontogenic structure (*e.g*., follicle) was detected in the removed mucosa either during surgical intervention or in histological analysis. However, it cannot be completely ruled out that very small pieces of tissue were lost during the oral surgical procedure. The soft tissue examination confirmed the local manifestation of a benign nerve sheath tumor. The tissue findings of the hard tissue identified regularly differentiated parts of a tooth associated with focal resorptions of the adjacent bone.

Localization of tooth germ and deviations from the expected tooth position. Teeth develop in genetically controlled, sequential patterns within the jaw. Tooth development disorders can cause numerical aberration of dentition, dysmorphism of single or multiple teeth, hamartoma, or even true neoplasm. In principle, tooth development can take place outside the jaw (19). Numerous reports testify to the development of teeth or tooth-like structures in many organs or tissues (15). These are usually sporadic cases, and the developmental disorder is rare. The situation is different within the jaw, where tooth development disorders occur more frequently, especially in the anterior upper jaw (mesiodens) and in the development of the wisdom teeth.

Anomalies in molar teeth position are particularly variable for wisdom teeth. However, development of the wisdom tooth outside the bone is rare. Consequently, a current classification of ectopic mandibular third molars does not consider any extraosseous development of wisdom tooth (30). In the maxilla, molar germs can be displaced into the surrounding area, especially in the maxillary sinus. Ectopic maxillary wisdom tooth situated outside the row of teeth can prevent eruption of second molar (14).

Allocation of the microdont to the development stage of the dentition. Human molars belong to the permanent dentition. However, they have no precursors. The second molar was already present at the time the microdont developed. The microdont developed on the distal edge of the occlusal surface of the second molar. It could be hypothesized the microdont is a matter of scattered particles of the tooth ridge from which a small wisdom tooth has emerged. In this case, the microdont would be a dysmorphic wisdom tooth, a relatively common finding that has been already registered for patients with NF1 (2). This hypothesis is unlikely because complete enamel formation of the second molar of the upper jaw is expected at the age of 7 to 8 years (21). The patient was in this age range at the time of radiological identification of the microdont's crown. On the other hand, complete crown development of the upper wisdom tooth does not take place until the age of 12 to 16 years (21). Deviations from this dentition scheme must often and generally be considered. In the case presented, the radiological evidence of wisdom tooth anlage on the non-affected side was provided for both jaws a few years later, at the age of nine. Both wisdom teeth on the left side developed distal to the second molars and had initial enamel formations of the crown. Radiological evidence of the incipient calcification of the left-sided wisdom teeth is to be expected between the 7^{th} and 10^{th} year of age and the patient's tooth germs appear in this interval on the left side in both jaws at the same time. Wisdom tooth germs on the right side could not be detected in any radiological projection during follow-up.

Microdont or developing odontoma. The distinction between odontoma and (dysmorphic) tooth is difficult in individual cases. Though evidence of odontogenic tissue and hard tissue formation in the lesion is an indication of an odontoma. However, clinical, and morphological findings frequently reveal significant hard tissue disorganizations in the odontogenic lesion that justify the diagnosis of an odontoma (22, 31, 32). Indeed, the shape and appearance of the odontoma may be reminiscent of a tooth, but the sum of the findings misses the individual characteristics of a functional tooth (22, 33, 34). The term *micromorph* tooth or microdont (21) is used if a tooth has developed all the components of the organ in an orderly manner, but overall, it does not have the required size of the tooth of the assigned tooth group. In the present case, a tooth root was not (yet) developed. The incomplete development of the small tooth could be interpreted as a developing odontoma. However, the miniaturized crown had a regular macro- and microscopic structure. Therefore, in this case the term (developing or incomplete) microdont is preferred. In a review of peripheral developing odontoma, Ide *et al*. (35) indicated that the peripheral developing odontoma was localized preferentially in the frontal areas of the jaw. However, the total number of developing odontoma in this overview was low and the authors noted the features of the samples varied considerably depending on lesioned tooth' developmental stage (35).
Nevertheless, there are convincing arguments to classify odontomas and supernumerary teeth as phenotypes of a variable differentiation capacity of odontogenic hard tissue, whose individual presentation, taking spatiotemporal criteria into account, turns out to be malformative or hamartomatous (36). Recurrences of odontomas are rare and likely caused by residual odontogenic epithelium after surgical removal of the lesion (37). In localized and solitary microdontia, recurrences after tooth removal are not yet known.

Conclusion

This report describes a finding relatively common in dental practice, *i.e*., a local differentiation disorder of odontogenic tissue, in this case a supernumerary microdont. What is unusual about the case is the evidence of a supernumerary tooth completely embedded in a nerve sheath tumor, tumor-associated retention of permanent teeth in topographical relation to the numerical aberration of dentition, and the successful spontaneous emergence of a permanent tooth that was freed from the covering tumorous oral soft tissue, finally attaching to the row of teeth. In some NF1 patients, retained teeth covered with oral PNF can be successfully treated by oral surgery.

Conflicts of Interest

The Authors have no conflicts of interest regarding the work presented.

Authors' Contributions

REF treated the patient. REF, HTS and HAS searched the literature and drafted the article. CH, AML and JZ performed morphological studies on the tissue specimen. All Authors approved the final article for publication.

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