

Surgical Measures Improving Functional Limitations of the Masticatory System, Aesthetic Deficits, and Skeletal Malformations in Neurofibromatosis Type 1-associated Hemifacial Diffuse Plexiform Neurofibroma Complicated by Rapidly Growing Midfacial Peripheral Nerve Sheath Tumor

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Abstract

Background/Aim: Neurofibromatosis type 1 (NF1) is a genetic disorder characterized by the development of multiple tumors, including plexiform neurofibromas (PNFs), which often affect the craniofacial region and cause significant functional and aesthetic impairments. This report presents long-term surgical management of a patient with hemifacial diffuse PNF, complicated by the emergence of a rapidly enlarging midfacial tumor.

Case Report: The patient was treated for hemifacial invasive diffuse plexiform neurofibroma. During follow-up, the patient developed a rapidly growing tumor suggesting malignant transformation. Histological analysis revealed plexiform and diffuse neurofibroma with necrosis. Defect coverage after resection was complex and required tissue replacement with a microvascular graft. In the further course, new neurofibromas developed in the oral transplant.

Conclusion: Surgical measures enable functional and aesthetic improvements despite extensive facial destruction caused by the tumor. Rapid tumor growth is a finding that requires immediate diagnosis in patients with NF1. Even in tumor-free transplants at the time of tissue transfer, (nodular) neurofibromas can develop at the recipient site.

Keywords: Neurofibromatosis type 1, orbit, mandible, osteoplasty, plexiform neurofibroma, bone dysplasia, MPNST, microvascular grafts.

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The results were partially presented orally at the Annual Joint Symposium of the Working Group for Oral and Maxillofacial Surgery and the Working Group for Oral Pathology and Oral Medicine (Arbeitsgemeinschaft für Oral- und Kieferchirurgie und Arbeitskreis für Oralpathologie und Oralmedizin), German Dental Association (Deutsche Gesellschaft für Zahn-, Mund- und Kieferheilkunde), Bad Homburg v.d.H., 24.5.2025



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Received June 18, 2025 | Revised July 3, 2025 | Accepted July 4, 2025



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Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant hereditary tumor suppressor gene disease (gene locus 17q11.2) (1, 2). Patients with NF1 typically develop neoplasms derived from neural crest cells. The entity has therefore also been referred to as neurocristopathy (3). According to current knowledge, the *NF1* gene product, called neurofibromin, is involved in the control of the RAS-pathway (RAS: rat sarcoma) (4-8). Restricted neurofibromin function leads to increased RAS activity resulting in increased cell proliferation and cell division. However, only biallelic loss of the *NF1* gene function is associated with a substantial risk of tumor development in patients with NF1 (9). Tumors arising from peripheral nerve sheath cells are particularly common in NF1 (2). The characteristic tumor of patients with NF1 is the neurofibroma of the skin, which arises from Schwann cells or their precursors (10, 11). These benign tumors usually develop first during puberty and are not considered to have malignant potential (12, 13). However, patients with NF1 have an increased risk of developing malignant diseases, which is the main factor for their reduced life expectancy (14, 15). Among the malignant tumors arising in patients with NF1, the malignant peripheral nerve sheath tumor (MPNST) is of particular importance both in terms of frequency in NF1 and tumor-related mortality (15). Rapid tumor growth and functional impairment are the leading and often initial findings of malignant transformation in neurofibromas of patients with NF1 (16, 17). MPNST develop predominantly on the trunk and extremities, but in rare cases also in the maxillofacial region in both sporadic (18, 19) and NF1-associated (20) lesions. Neurofibromas may also develop within peripheral nerves clinically presenting as nodular lesions or thickening of the nerves. These so called plexiform neurofibromas (PNF) are pathognomonic for NF1 and often present as congenital lesions or develop in early childhood. PNF are regarded as pre-malignant tumors, predisposing to the development of MPNST (13). However, numerous second (somatic) mutations apparently occur

in the *NF1* gene of patients with NF1 in many body regions without resulting in neoplasm (21). In any case, MPNST development in patients with NF1 is a multi-step genetic process, for which several alterations of the tumor cells are necessary (22).

In addition to neoplasia, abnormalities in the physical and mental development are observed in patients with NF1, which are apparently related to *NF1* germline mutations (13). NF1 is therefore both a tumor predisposition syndrome (13) and a disease of disturbed histogenesis and general development (23). In this respect, it is an essential diagnostic task to differentiate between the causes and consequences of the disease in relation to aberrations of development and homeostasis or neoplastic dedifferentiation (23), which can be difficult to assess in individual cases, especially in long-term observation and considering the effects of interim therapeutic measures on the phenotype (20, 24-26). This case report intends to describe the complex findings and challenges in the long-term treatment of NF1 associated tumor disease in the cranial and orofacial region, the acute exacerbation of the neoplasm in this area, and conspicuous findings during surgical treatment.

Case Report

Medical history. This patient first presented at the age of 53 years (height: 153 cm, body weight: 75 kg). He suffered from extensive neurofibroma on the right side of his face. Facial asymmetry and tumor growth had been noticed since birth and multiple surgical interventions had been performed since childhood and adolescence. The vision of the right eye had been largely lost from the age of seven years. Orbital exenteration of the tumor-destroyed eye had been performed one year before the current consultation. Other medical events included a tibia fracture and some years later a traumatic spleen rupture in young adulthood. One of the patient's three children was also diagnosed having NF1.

The patient visited our outpatient clinic to receive surgical help for improving oral continence and retention

of the upper jaw prosthesis, and the aesthetically striking empty orbit.

The long-term treatment of the patient falls into different phases, the photographic documentation of which is summarized in Figure 1, Figure 2 and Figure 3. Figure 1 shows the clinical and radiological findings as well as the results of the surgical measures (facelift, dental implants) of the first treatment phase. Figure 2 shows the skeletal deformation of the skull, especially of the mandible, the insertion of the orbital implant and the osteoplasty of the maxilla in the tumor area. Figure 3 shows a rapidly growing cheek tumor in the third treatment phase, which gave rise to the suspicion of an MPNST, and the surgical measures required to cover the resection defect and improve chewing function.

Physical and radiological findings. External aspect. The patient had developed a tumor infiltrating the skin of the right side of the face that had partially destroyed many functions of the facial and masticatory muscles (Figure 1). The affected areas of the facial skin were non-homogeneously pigmented darker than the other parts of the skull (Figure 1H). The tumor-infiltrated skin extended cranially to the parieto-occipital region, posteriorly to behind the pinna, and caudally to the lower border of the mandible. The right eyebrow was missing and the hairline with alopecia was more advanced on the right tumor infiltrated side than on the left side. The tumor-infiltrated eyelids on the right side formed a flaccid, static curtain that covered the empty orbit. Despite multiple plastic surgery procedures, the nose was enlarged on the tumor side, with the right side of the nose positioned further caudal. The pinna was displaced caudally (Figure 1A, B, G, and H). Hearing was impaired on the right side due to the sunken pinna and the kinking of the external auditory canal (Figure 1A and G). The tips of the lips could be pursed, but when smiling, the sagging skin of the cheek was superimposed over the right corner of the mouth (Figure 1A). Oral continence for fluid intake was limited due to bulky tumor of the cheek and right side of upper lip. Multiple cutaneous neurofibromas were present over the body and the patient had axillary freckling.

Oral cavity. In the oral cavity, a soft tissue tumor had developed on the right side of the palate, which was laterally in continuity with the cheek tumor and respected the midline of the palate as a basal growth boundary (Figure 1C). With residual dentition and lumpy mass of the palatal arch, the cover denture had no sufficient retention. On admission, the patient was fitted with a cover denture in the maxilla, the dental retention of which was only secured by the last remaining tooth (left upper canine) (Figure 1D). The prosthesis had no adhesion to tooth and gum because tumorous soft tissue had grown prominently and extensively on the tumor side, filling the vestibular fold and covering the palate. Inside the oral cavity, the maxillary transverse tumor spread ended at the midline of the palate. This means that the half-sided limitation of the tumor extension applied to the oral manifestation in the midface area as well as to the face. However, the tumor had created a convex, arch-like deviation of the median raphe to the non-affected side (Figure 1C and O) (27). The tongue showed a symmetrical structure, inconspicuous volume and no abnormalities of the specialized mucosa (28).

Orbit. The right globe and adnexa were missing. Also missing on the right side were the eyelashes. The orbit was filled with an inhomogeneous hyperintense mass on MRI (Figure 1M). The mass extended anteriorly into the right nasal region and spread laterally as a continuous soft tissue layer across the temporo-parietal region toward the occipital region. The tumor layer tapered distally. The calvarium was not eroded. Within the orbit, the tumor mass extended beyond the orbital borders to the temporal pole and as far as the distal borders of ethmoid. The medial portion of the anterior border of the temporal lobe appeared displaced by dysplastic bone and the orbital tumor (Figure 1M and P). Furthermore, the hypodense boundary layer between the parenchyma of the temporal lobe and the dorsolateral border of the tumor in the orbital funnel was significantly widened. Computed tomography confirmed the skeletal defect of the orbital funnel on the side of the tumor (Figure 1P), as

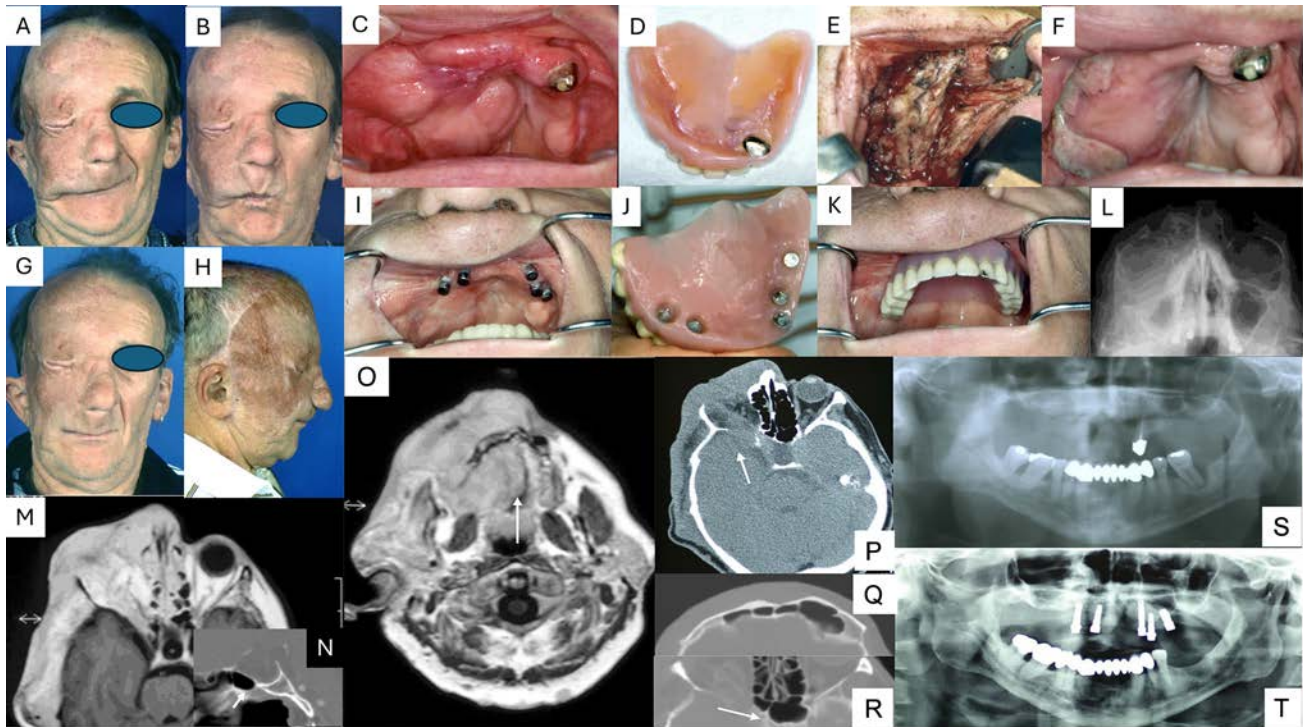


Figure 1. Illustration of the initial findings (A-D, L-S) and the first surgical measures and treatment results (E-K, T). Cross-sectional images show the sections of the entire image relevant for individual findings (M-R). (A and B) The plexiform neurofibroma (PNF) is localized on the right side and extends from the parietal region to the mandibular base. The oral manifestation of the tumor fills the right side of the palatal arch causing insufficient prosthetic retention (C, D). After removal of the oral tumor (E), the arch is secondarily epithelized (F). The right corner of the mouth is defined horizontally by repeated facial skin lifting procedures (G and H). After repeated tumor removal and insertion of dental implants (I) as well as magnetic anchoring in the prosthesis base (J), the prosthesis is firmly in place and functional (K). (L) The extended radiologic diagnosis shows the vertical straightening of the right orbit with caudal displacement of the infraorbital rim, the deformation of the lateral border of the right orbit and the hypoplastic right maxillary sinus. (M) The axial magnetic resonance image (MRI) shows the homogeneous tumor mass from the nose to the temporoparietal region. The right orbit, which is devoid of functional compartments, is filled by a solid mass that merges uniformly into the facial tumor. The tumor extended medially beyond the confines of the orbit, encroaching slightly into the adjacent cranial base. The brain's temporal pole recedes dorsally in front of the space-occupying tumor but is separated from the orbital content by a hypodense layer. (N) Insert to M: Sagittal section of a computed tomogram (CT) at the level of the dorsum sellae shows the enlarged sella turcica, the flattening of the planum sphenoidale and a hypoplastic sphenoid sinus [pre-sellar type (56)]. (O) A more caudal axial section of the MRI shown in (M) shows the conspicuous mass of the right palate (arrow), which, with a base ending strictly at the curved median raphe (Figure 1E), extends clearly across the midline to the left within the oral cavity (Figure 1C). The medial pterygoid muscle can be differentiated from the masticatory muscles on the right side. (P) Axial CT shows the defect of the sphenoid wing (arrow) and the deformation of the residual bone at the lateral border of the defect. The ethmoidal cells of the tumor side form a smaller total area than that of the healthy side. The thinning of the calvaria, which is conspicuous in lateral comparison, affects the lateral aspect of the skull further dorsally and beyond the sphenoid region to approximately the visible dorsal border of the extensive tumor. (Q) Axial section at the level of the frontal sinuses shows reduced aeration of the cavity on the tumor side and a slight flattening of the frontal convexity. (R) Sagittal section (CT) at the level of the sphenoid sinus shows reduced aeration of the sphenoid's right side [also indicated in (M) and (P)]. The antero-posterior line of the lateral border of the ethmoid to the right orbit remains unaffected by this hypoplasia because an ethmoid cell has already compensated for the lack of lateral expansion of the sphenoid sinus. (S) The orthopantomogram (OPG) shows a numerically reduced dentition with prosthetic and conservative treatment. The maxilla is edentulous except for the left canine. The alveolar ridge is more atrophic on the tumor side than on the left side (especially the tuberosity region) (38). The right mandibular collum is slightly bent medially. (T) General view (OPG) after implant insertion (maxilla). This image shows the kinking of the right mandibular nerve canal in front of the mandibular foramen and the slightly shortened vertical dimension of the ramus.

suspected by the MRI (Figure 1M). Furthermore, the CT scan showed that although the osseous defect was based on typical sphenoid dysplasia, the skeletal deformity

affected far more than just the sphenoid bone. The lateral border of the orbit was displaced laterally and inferiorly, and the lateral border of the ethmoid also appeared

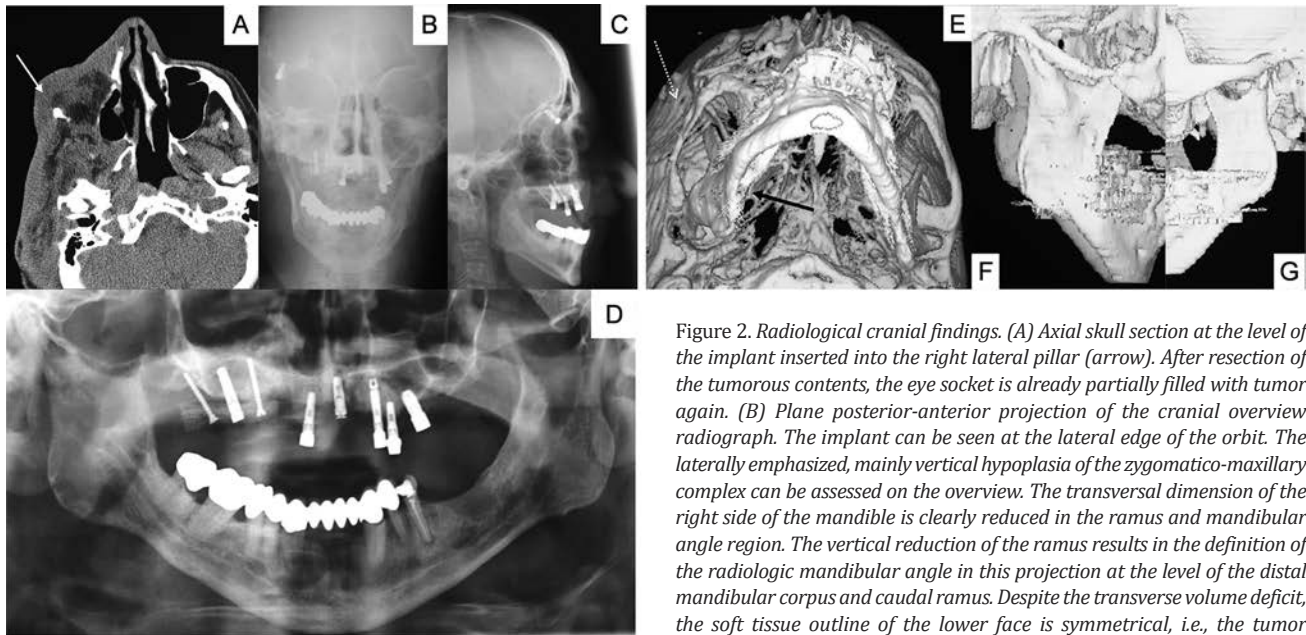


Figure 2. Radiological cranial findings. (A) Axial skull section at the level of the implant inserted into the right lateral pillar (arrow). After resection of the tumorous contents, the eye socket is already partially filled with tumor again. (B) Plane posterior-anterior projection of the cranial overview radiograph. The implant can be seen at the lateral edge of the orbit. The laterally emphasized, mainly vertical hypoplasia of the zygomatico-maxillary complex can be assessed on the overview. The transversal dimension of the right side of the mandible is clearly reduced in the ramus and mandibular angle region. The vertical reduction of the ramus results in the definition of the radiologic mandibular angle in this projection at the level of the distal mandibular corpus and caudal ramus. Despite the transverse volume deficit, the soft tissue outline of the lower face is symmetrical, i.e., the tumor compensates for the bone deficit in this projection (32). (C) The lateral

projection of the skull overview illustrates the position of the maxillary bone augmentation, the superimposed and contourally divergent mandibular angles and the dysplastic sella turcica (57). (D) Orthopantomography after jaw augmentation. Beginning of resorption of the graft. From the midline to the right side, three implants are inserted in the tumor area. The differences of the vertical positions of the implants in the bone illustrate the intermediate resorption. (E) Three-dimensional reconstruction of the skull from a computer tomogram (CT) in the caudal view. The projection illustrates the compression and medial rotation of the ramus/jaw angle (black arrow). The dotted arrow indicates the narrowed zygomatic arch. The muscle process visible underneath the arch appears somewhat misshapen and thickened. (F) Three-dimensional lateral reconstruction of the right jaw/temporomandibular joint (TMJ) region. The kinking and lengthening of the muscle process, the wide condylar notch, the caudally bent, narrowed zygomatic arch and the enlarged glenoid fossa are obvious. (G) Three-dimensional lateral reconstruction of the left jaw/TMJ region shows an inconspicuous ramus/TMJ complex on the non-affected side.

somewhat depressed. As a result of the deformation, the area of the ethmoid labyrinth (Figure 1P) and sphenoid sinus (Figure 1R) on the tumor side appeared smaller than that on the opposite side in the axial section. Consistent with the updated diagnostic criterion "sphenoid dysplasia" in clinical NF1 diagnosis only applicable in the absence of orbital PNF (29), the sphenoid wing was thinned in lateral, tumor-covered parts that constitute the calvaria (Figure 1P). However, calvaria thinning extended beyond the sphenoid wing to adjacent temporal bone (Figure 1P). Nevertheless, the plain radiography of the orbital midface region already showed that the skeletal malformation of this skull area affected not only the sphenoid but also the maxilla (caudal position of the orbital floor, "compression" of the lateral maxillary sinus wall, hypoplastic maxillary sinus), the

zygomatic bone (caudally displaced lateral pillar, dysplastic temporal process), and the temporal bone (zygomatic process, deformed glenoid fossa) (Figure 1L, S, and T, Figure 2B-D).

Maxilla. On oral inspection, the upper jaw was dominated by a soft tissue tumor, which covered the right side of the palate. The tumor layer above the anterior alveolar ridge was significantly flatter than in the palatal arch. The solid, soft tumor was covered by inconspicuous, intact mucosa. Orthopantomography (OPG) showed the typical hypoplasia of the maxillary tuberosity on the side of the tumor in the case of a diffuse PNF affecting the 2nd trigeminal branch and extending to the oral cavity (Figure 1S and T) (27, 30-33). However, neither OPG nor sectional imaging disclosed substantial osseous deficits of the palate.

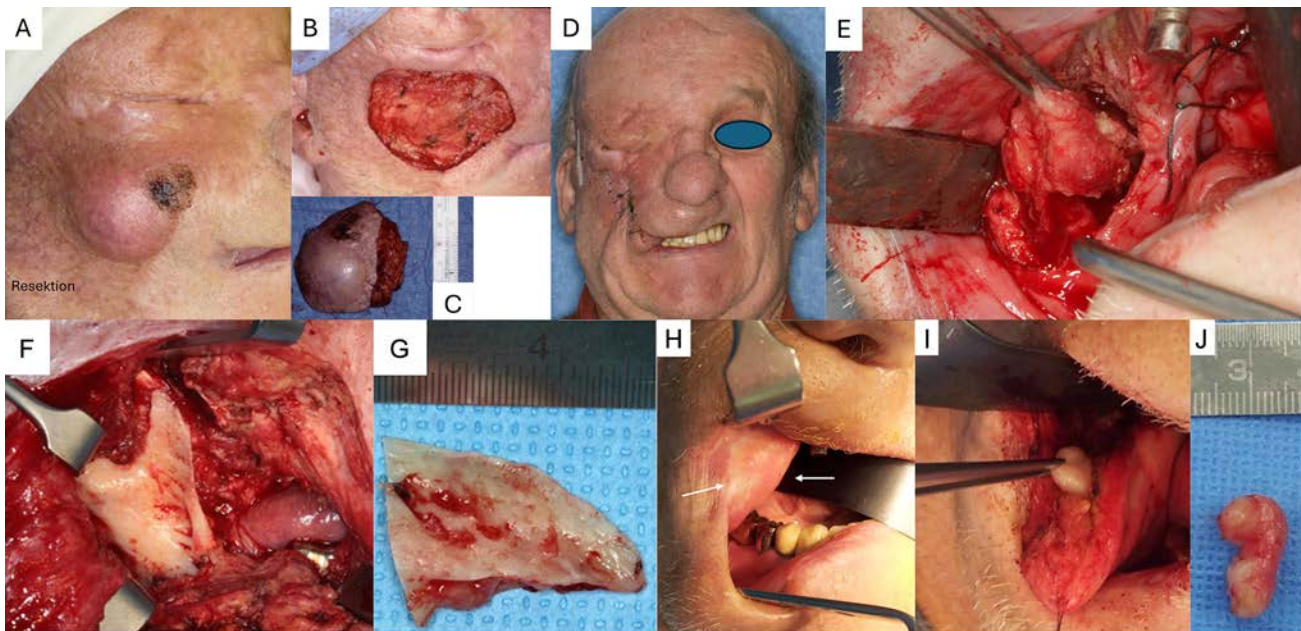


Figure 3. Documentation of surgical treatment for suspected malignant cheek tumor and subsequent defect coverage. (A) Findings of the rapidly growing cheek tumor with ulceration of the skin because of trophic disorders. (B) Resection area and (C) soft tissue specimen. (D) En face view of the wound after treatment with local sliding plasty. (E) Transoral resection of a rough tumor/scar complex from the maxillary sinus and cheek on the right (recurrent tumor). (F) Exposure of the right ramus and muscle process. The detached tissue is interspersed with diffuse neurofibroma. (G) Detached muscle process with irregular surface. (H-J) Clinical aspect of the right oral site three years after tumor resection and subsequent microvascular defect coverage of the oral side of the right cheek. (H) Oral aspect of the musculofascial graft extending to the right corner of the mouth (between both arrows). (I) Incision at the anterior border of the graft and detachment of the nodular tumor from its connective tissue. (J) Excised nodular neurofibroma of the graft.

Mandible. The outline of the lower face showed no conspicuous asymmetry in the assessment en face (Figure 1A). However, the radiologic examination revealed a vertically slightly shortened right ramus with an elongated collum (Figure 1S and T, Figure 2D, F and G). The compression of the ramus towards the midsagittal axis is clearly visible on the anteroposterior skull radiograph (Figure 2B). Both cephalometric projections indicate that the mandibular angle of the right side is formed by more distal/cranial parts of the mandibular angle than on the unaffected side (Figure 2B and C). The basis of the right condylar process deviated slightly anteriorly (Figure 1S, T, Figure 2C and D). The collum had a length of 33 mm on the right and 22 mm on the left (OPG; ratio: 0.67). The angle of the posterior ramus was determined by connecting the most posterior points of the articular process (P) and the external mandibular angle (G). A

second line connected the lowest points of the basal mandibular border (external mandibular angle and anterior corpus). The dorsally extended line formed an intersection with the ramus line (PG). This intersection with both lines defined the external mandibular angle. The angle was 148° on the right and 168° on the left. The bending of the collum from the posterior ramus line was 20° greater on the right side than on the left side. The lines iso-intense to cortical bone on the radiograph demarcated the superior and inferior borders of the right inferior nerve canal. These lines also bended slightly into the horizontal just before entering the right mandibular foramen. The angle between the line of the right basal nerve canal boundary of the ramus and the more proximal, bent segment formed an angle of about 145° , i.e., the kink of the mandibular canal is in the range and direction of the kink of the right collum. A corresponding

kink in the nerve canal was missing on the left side (Figure 1S and T, Figure 2D).

On the right side, the masseter and temporal muscles could not be differentiated on MRI. In contrast, the pterygoid muscles were identified on both sides. Both right-sided pterygoid muscles were surrounded by soft tissue isointense to fat in axial and coronal sections (Figure 1O). On OPG, the nerve canal's cranial and caudal border was clearly visible on both sides. The mandible appeared homogeneously translucent with defined small marginal cortical bone. The continuous cranial and caudal borders of the nerve canal were identified on both sides beyond the premolar region in mesial direction and terminated in the frontal teeth region. The distance between the two vertical boundaries on both sides was striking and indicated an unusually large incisive channel in these two dimensions (Figure 1S and T, Figure 2D).

There was a slightly deformed right coronoid process compared to the normally developed opposite side (Figure 2D-F). The temporomandibular joint's articular eminence was flatter on the tumor side (Figure 1P and Q, Figure 2D). The shortening of the ramus in relation to the *collum mandibulae* and the reduced distance of the mandible from the midsagittal plane were evident in the posterior-anterior and lateral cephalograms (Figure 2B and C), OPG (Figure 1P and Q, Figure 2D), and the three-dimensional reconstruction of the facial skeleton (Figure 2E and F). However, the vertical shortening was not very noticeable and the total length of the posterior side of the ramus was not significantly shorter than that of the healthy side due to the condylar bending. Regarding the outline of the lower face, the transverse deficit due to skeletal hypoplasia was compensated for by the neurofibroma (32). In this surgically treated case, the facial asymmetry was less obvious from the external aspect (Figure 1A, B, and G, Figure 2B).

On the tumor side, the hypodense zone above the right mandibular foramen on the OPG showed an enlarged osseous opening for the nerve on OPG (Figure 1Q). However, the tomographic images and the three-dimensional reconstruction of the skull showed that the right ramus was

deformed like a bowl (Figure 2E) and therefore the hypodense right mandibular foramen area of the OPG was probably caused by the higher translucency of the bone layer that was thinned here and only partially captured in the focal trough of this imaging technique (25, 26).

Treatment. The palatal neurofibroma was removed first. Secondary wound healing of the ablated gum was without complications (Figure 1E, F and I). Following tumor removal and re-epithelialization of the palatal arch, no prosthetically relevant recurrence of the tumor was observed at this site over the course of 15 years. However, several tumor recurrences developed on the right side of the upper jaw's vestibule, which impeded the retention of the prosthesis and required repeated surgical revisions. Presumably, the adherence of the tumorous connective tissue to the vertically oriented lateral maxillary surface is more difficult to maintain and tends to cause the connective tissue to sag into the vestibule, while the cicatricial adhesion of the connective tissue to the palate is more stable - for unknown biological reasons (This observation has also been made in other NF1 patients with this tumor extension).

Oral cavity. The patient was fitted with implants to improve maxillary prosthesis retention. Although the prosthesis extended by several magnetic abutments improved the prosthesis retention, it could be relatively easily detached from the abutments on the tumor side. The maxillary bone atrophy on the tumor side in dorsal parts of the bone, which was considerably more advanced than on the non-tumor side, impaired sufficient retention for an additional implant. Therefore, an autogenous bone augmentation was used (iliac crest), which was fixed with screws and a threaded implant (Figure 2D). Although the bone graft was tightly covered by the local mucosa, bone resorption shortly after insertion was noticed and the transplant had to be removed. Despite the loss of bone retention, the implant inserted in the bone of tumor-affected area could be used for sufficient prosthetic retention for several years. However, neurofibroma recurred around the implant.

Orbit. As a prerequisite for an ocular epithesis, the tumor largely filling the cavity was excised. This procedure was necessary to be performed repeatedly because the tumor recurred rapidly. Although scarring or fibrosis was detectable in the resected areas, the specimens were always diagnosed as neurofibroma. In order to create retention for the planned ocular epithesis, an implant was inserted into the upper edge of the right orbit (Figure 2A-C). Healing was without complications, but the neurofibroma completely overgrew the insertion site, so that the tissue was removed several times. After the insertion of an eye prosthesis, the tumor recurrence led to proptosis and the hold of the magnet-secured epithesis was quickly lost. After a short period of use, the patient gave up using the epithesis.

Facial tumor. At the age of 64 years, the patient presented again because within a few weeks a swelling of the cheek below the orbit had developed on the side of the tumor. The patient feared a malignant tumor arising in his face and within the facial PNF. On admission, the cheek was prominently swollen and the skin covering the tumor was partially ulcerated (Figure 3A). In contrast to the surrounding diffuse neurofibroma, the tumor was coarse and not displaceable on the underlying surface. Sonography of the findings showed an inhomogeneous solid tumor with sparse vascularization. Under suspicion of malignant degeneration of the PNF, the tumor, which was 8 cm wide horizontally and 5 cm long vertically, was excised with a safety margin of 1 cm and initially covered temporarily with dressing materials (Figure 3B and C). After the tissue examination, the cheek defect was primarily closed by rotational flap. The parchment-thin skin adhering to the tumor connective tissue tore already under slight tension, so that the adaptation of the wound edges left a central dehiscence that healed secondarily without irritation. Four weeks later, complete wound closure was achieved by revision of the granulating defects and mobilization of the rotation flap. In this procedure, the oral extension of the midfacial tumor, which had once again prolapsed marginally around the

alveolar ridge, was removed through an oral procedure. The implants were firmly integrated into the bone. However, the bone showed significant resorption up to the screw threads of the implants.

Thirteen months later, the patient returned for follow-up treatment because scarring on his right cheek was impeding opening of his mouth (Figure 3D). The scars on the inner cheek were loosened, and exposed portions of the bone graft on the right side of the upper jaw were removed (Figure 3E). At that time, the implants were firmly inserted into the bone. Further prosthetic treatment was initially postponed due to the recent bone graft loss and the obstructed mouth opening following ablative surgery and reconstruction with local flaps. Six months later, again vestibuloplasty was performed on the right side of the upper jaw, and the implant in region 016 was exposed. Two weeks after the oral wounds had healed, the oral dressing was removed, and an impression cast was taken for a prosthesis. The patient received prosthetic treatment. However, in the further course a significant oral stricture developed again in the tumor region, obstructing opening of his mouth. Therefore, the 65.5-year-old patient underwent further surgery. Using a combined intra-extraoral approach, the mandibular ramus was exposed, and the scarred soft tissues of the zygomatic region adhering to the coronoid process were removed, including resection of the coronoid process (Figure 3F and G). The scarred oral layer of the cheek was replaced with a microvascular anastomosed forearm skin graft. The donor area showed no abnormalities. Explicitly, the donor area had not developed any visible skin tumors (cutaneous neurofibromas) or PNF. The temporary osteotomy of the mandible was bridged by osteosynthesis plates. Wound healing was unremarkable. Twelve months later, the voluminous graft was revised to contour the inner cheek and vestibular region. The surface of the forearm skin transplanted to cover the oral cavity appeared unremarkable, and no tumor was noticeable in the fascio-cutaneous graft (Figure 3H). However, after skin flap incision to prepare volume reduction of the graft, nodular tumor protruded (Figure 3I). These tumors could be

clearly identified in the subcutaneous graft layer by inspection. The neurogenic lesions showed the typical outline and solidity of nodular neurofibroma (Figure 3J). The tumors connected firmly to the forearm skin and distinguished from the diffusely infiltrative neurofibroma of the right side of the face that had always been predominant in previous procedures for many years.

Ear. The collapsed right external auditory canal was stabilized with a tube made of polymethyl methacrylate, thus improving sound conduction.

Histology. The tissue findings are presented by location.

1. Right orbit: The recurrent orbital tumors after clearance of the cavity in preparation for the placement of an orbital prosthesis repeatedly showed diffuse plexiform neurofibroma mixed with scar tissue.
2. Oral cavity: The palatal tumor was a diffuse neurofibroma. The samples around the implant posts revealed diffuse plexiform neurofibroma. In a sample from the implant post in region 25, tumor components were also detected on the non-tumorous side. Later samples from the maxillary implant posts failed to reveal any nerve sheath tumor.
3. Right side of the nose: The resected specimens revealed cartilage components in direct contact with diffuse neurofibroma.
4. Right cheek tumor: Diffuse neurofibroma with necrosis, but no increased tumor cell proliferation rate was observed (Figure 4).
5. Transplant at the oral site: Biopsies of the donor and recipient vessels supplying the transplant showed no infiltration by a neurofibroma at the time of covering the oral defect. The later diagnosed transplant's tumor was a nodular neurofibroma (Figure 5).

Follow-up. After the revision of the oral transplant, oral functions significantly improved. However, the patient stopped attending the outpatient clinic after approximately 15 years of repeated consultation. Years later, we were informed by relatives that the patient had gone blind because of glaucoma.

Discussion

This report describes reconstructive measures for orofacial functional and aesthetic improvement of a severely disfigured patient with NF1. The patient developed a rapidly growing tumor within the facial PNF during treatment. Clinical findings of solid tumor gave rise to the suspicion of a malignant change within the extensive tumor region justifying wide excision. PNFs are considered precancerous lesions (13). MPNSTs can arise within a PNF (18, 34) but rarely in the oral and maxillofacial regions (20). Histological examination revealed necrosis within the tumor but did not provide evidence for diagnosing MPNST (Figure 4). The findings showed no evidence of hemorrhage into the neurofibroma as the cause of the local swelling (25).

The ablative tumor treatment required further facial reconstructive measures including autologous tissue transfer to the resection side. Microvascular tissue transfer for the treatment of specific lesions of NF1 is a successfully established reconstructive surgical tool (35). In this case, the contracting scars were released after partial resection of the tumor-infiltrated fibrous tissues. The measures allowed improved mouth opening. An unusual feature of this case is the development of nodular neurofibromas in the thin layer of the transplanted tissue after unremarkable healing of the inconspicuous skin transplant in the recipient site. No nodular neurofibromas were visible on the forearm at the time of graft elevation and not in the oral recipient site. A generalized increase in size and number of neurofibromas was not observed during the interval between the time of the organ transfer and the surgical revision, neither in the skin nor in the oral site. The tumors likely developed or grew to a detectable size within a short period following flap transfer to the oral cavity. It is arguable that both the tissue injury (harvesting of flap, transfer) and adaptation to the recipient site (unphysiological mechanical and biochemical environment) were triggers for tumor formation. However, the development of the neurofibroma in the micro-vascularized, denervated fascio-cutaneous graft is noteworthy, suggesting local stimuli as trigger of tumor growth. The graft-related growth pattern of the

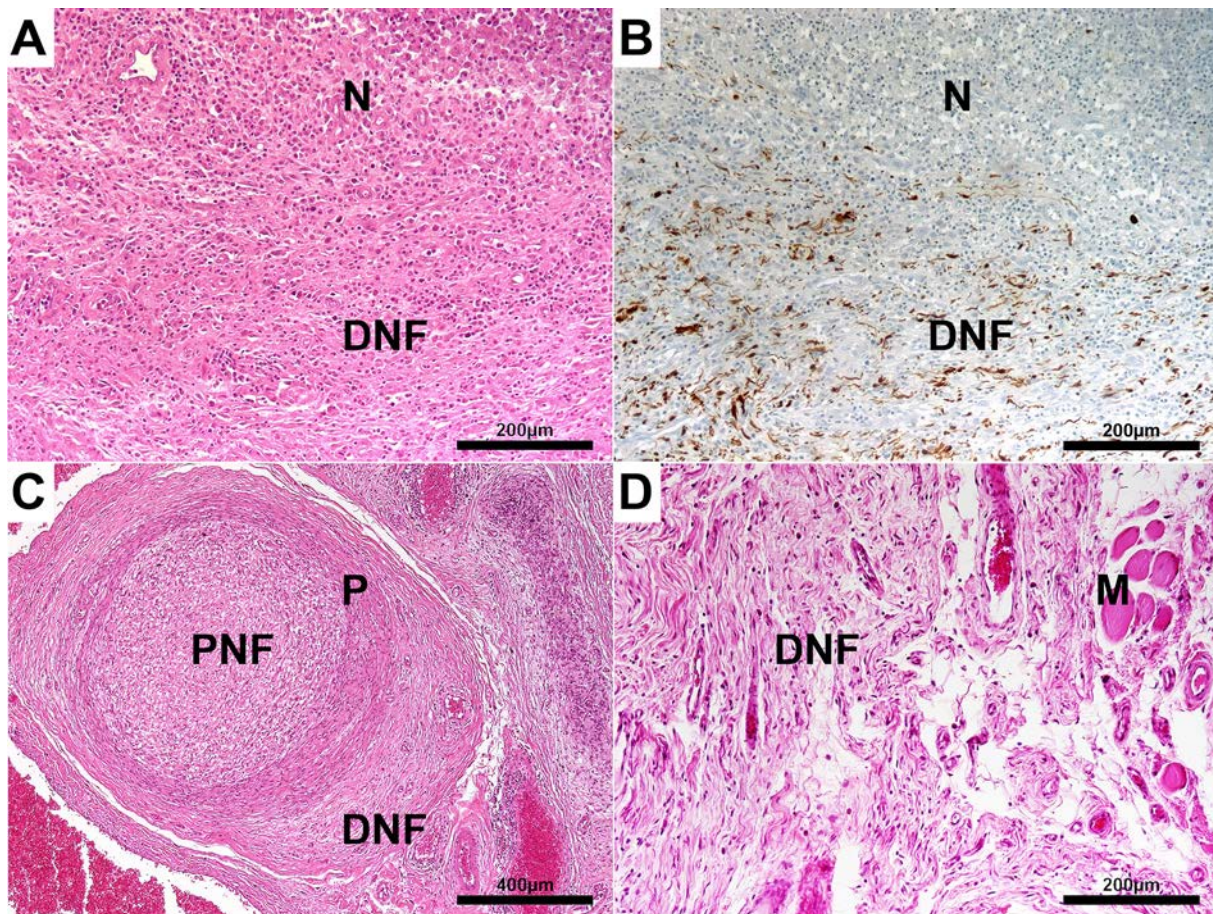


Figure 4. Histological findings in the suspected malignant cheek tumor (see also Figure 3A). (A) Diffuse neurofibroma (DNF) with extensive necrosis (N), hematoxylin & eosin stain. (B) S100-immunohistochemistry of the same tumor section as in A depicting S100-positive tumor cells in the vital tumor tissue (brown staining, chromogen diaminobenzidine). (C) Same tumor specimen as in A showing a small plexiform neurofibroma (PNF) ensheathed by perineurium (P). (D) Entrapped degenerated muscle fibers (M) within the DNF.

neurofibromas differed from the histological differentiation of the local tumor known from previous surgical interventions. The patient's neurofibroma, which had been registered over the entire right side of the face since early childhood, was a soft, poorly defined, infiltrative diffuse-plexiform neurofibroma assessed by physical inspection and histological investigation (7, 31). The tumor type was always diagnosed during the repeatedly necessary surgical oro-facial procedures. The development of a nodular neurofibroma within a diffuse invasive neurofibroma, especially in elephantiasis-like manifestations, is an occasionally reported phenomenon in follow-up of patients

with NF1 (36). It was assumed that nodular neurofibromas can change into a diffuse plexiform growth pattern when the original PNF infiltrates its surrounding perineurium and then diffusely invades the adjacent tissue (5, 6).

The finding of tumor development after surgical intervention in the transferred tissue is a clinical indication of the discussed impact of local tissue irritation on neurofibroma growth (37).

MRI. MRI is the examination technique of choice for the differentiation of NF1-associated nerve sheath tumors (31) and provides valuable information for differentiating

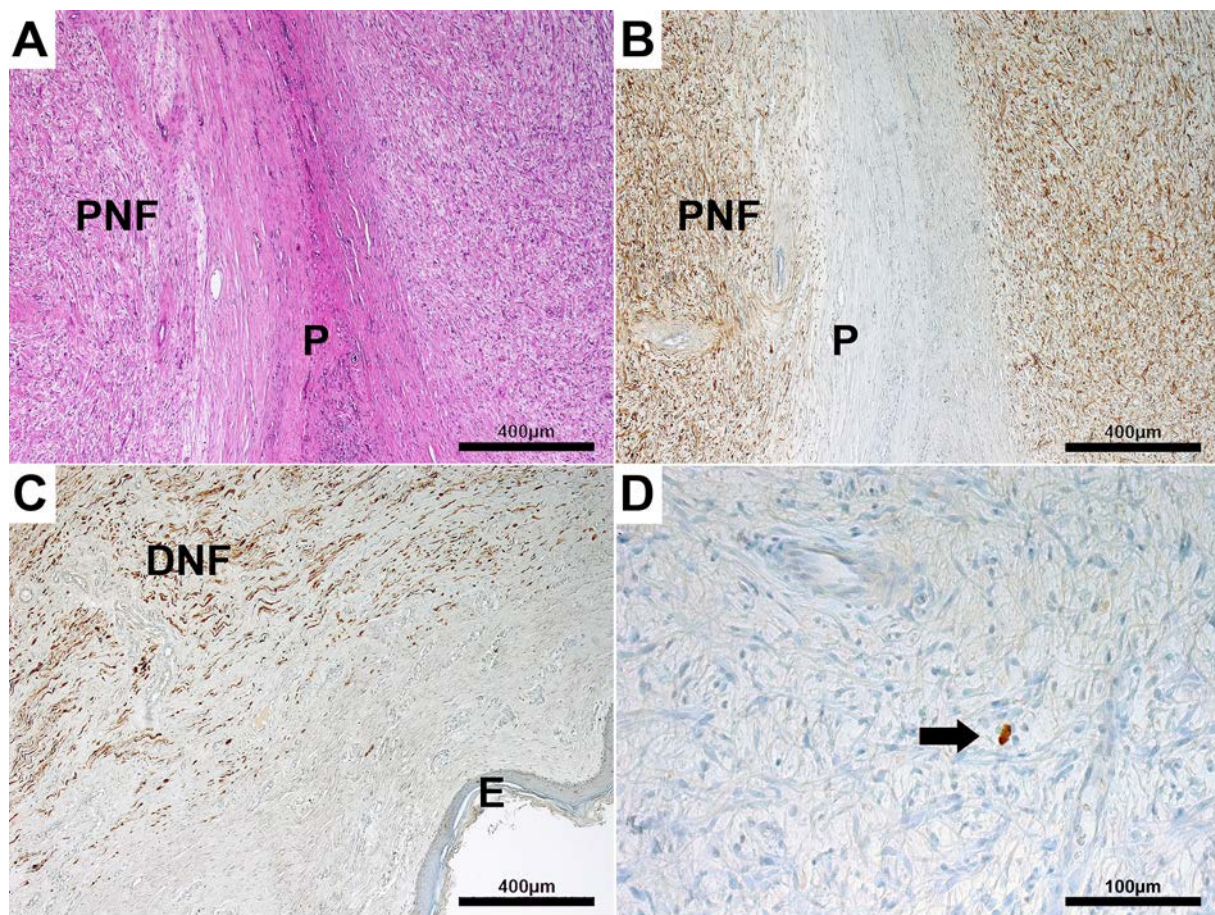


Figure 5. Histological findings in the nodular neurofibroma that had developed in the oral microvascular graft from the forearm skin (see also Figure 3H-J). (A) Two fascicles of a PNF separated by perineurium (P), hematoxylin & eosin stain. (B) S100-immunohistochemistry of the same tumor section as in A demonstrating S100-positive tumor cells (brown staining, chromogen diaminobenzidine). (C) Demonstration of a diffuse tumor invasion of the dermis (DNF) by S100-immunohistochemistry (E: keratinized squamous epithelium). (D) Detection of a sole proliferating nucleus by immunohistochemical labelling with proliferation marker Ki-67 (arrow).

malignant from benign lesions of nerve sheath tumors in this syndromic complex (34). In the situation of suspected facial MPNST, an MRI was not performed because previous examinations of the patient using this examination technique had shown that the maxillary and orbital implants interfered with the magnetic fields and that the region to be examined would not have been imaged adequately under these conditions.

CT. Cranial CT showed the skeletal deformities of the skull and served as a planning tool for the navigated insertion

of the orbital implant. In addition, the CT showed the asymmetrical sizes of mandibular rami (Figure 2E and F). Although the right pterygoid muscle was identifiable in the same axial plane as the contralateral muscle on MRI (Figure 10), CT revealed extensive tumor invasion from the facial subcutaneous layer to the right entire skull base (2A). It is debatable whether the mandibular deformity frequently described for NF1 patients with facial PNF on the tumor side (38, 39), for which an association with hypoplastic masticatory muscles has been described (30), should be noted as more than merely coincidental also in

this case. In the case presented, the relatively slight deformation of the anteriorly elongated and displaced articular process could be skeletal adaptation to tumor-associated ramus dysplasia (missing lateral masticatory muscles, reduced vertical growth, bowing of bone) based on largely intact neuromuscular activity of the lateral pterygoid muscle. Assuming a neuromuscular interaction that determines the altered shape of the mandible in NF1 patients with the trigeminal nerve's third branch PNF, the underdeveloped vertical ramus dimension could be caused by the severely affected lateral masticatory muscles, at least in part. The masseter muscle cannot be differentiated in the MRI from the diffuse neurofibroma mass. This feature was radiologically interpreted as a tumorous dissolution of the muscle. The assumption is also supported by the intraoperative findings (Figure 3F and G), the histological assessment of soft tissue masses adjacent to ramus and coronoid process, and the skeletal deformities of the bones on the tumor side where this muscle attaches and inserts (reinforced antegonial notch, dysplastic zygomatic arch) (Figure 1S and T, Figure 2B-F). The tumor-side temporal region is of normal external outline (after multiple tumor debulking interventions) (Figure 1A, B, G, and H). However, the soft tissue tumor filled the temporal fossa (Figure 1M). The deformation of the coronoid process may also be the result of functional interaction with the dysplastic temporal muscle. The muscle cannot be differentiated from tumor tissue on MRIs (Figure 1M). However, the impact of previous surgical procedures cannot be considered in assessing the muscle's atrophy in this case (Figure 3F).

Reports in the literature suggest that PNF-associated dysplasia of the mandible is not necessarily a congenital finding but may develop early in life. The assessment of a dystrophic bone developing mainly in early childhood corresponds to the clinical experience with pseudarthrosis of the long bone in these patients (13, 23). The growth disorders and deformities, especially in the lower jaw, are associated with nerve sheath tumor (27, 38). However, tumor detection can be difficult because fatty tissue can form a greater part of the tumor mass, thereby influencing

the preferred imaging (MRI) in the presentation of the tumor. In this situation, even careful and targeted surgical exploration obtained biopsies may yield inconsistent tissue findings in individual cases (39). The extent of mandibular alterations on the side of facial plexiform neurofibroma (PNF) involving the third branch of the trigeminal nerve exhibits a broad spectrum of phenotypic manifestations (38, 40). Based on our clinical observations, there appears to be a correlation between the proximity of the PNF to the nerve's origin and the severity of mandibular changes – the more proximally the tumor arises along the nerve, the more pronounced the skeletal deformities tend to be. This phenotype frequently presents as a marked and often bizarre deformation of the mandibular ramus and angle region (24, 38). In contrast, when the manifestation is restricted to the buccal skin, representing tumors localized distally within the peripheral distribution of the nerve, mandibular alterations are either confined to regions adjacent to the tumor or may be entirely absent.

Some patients with facial PNF develop unilateral mandibular deformity in childhood (33, 38). However, anecdotal reports describe tumor-associated deformities of the mandible on the PNF-affected side of the face, particularly in the ramus and temporomandibular joint, that were not present in early childhood and must have had developed in adolescence (40). It follows that in addition to the aforementioned topographical influences of tumor development, the temporal framework must also be taken into account in order to classify the bone changes of the facial skull. Most changes are registered during the growth phase (24, 38, 40).

Comparison of jaw and tooth development over time using panoramic views of the jaws in patients with facial PNF can reveal deformities of the jaws and disturbances of tooth movement that indicate adjacent PNF (24, 38) and associated involutions of the soft tissues (for example, adipose tissue equivalent transformation of masticatory muscles on MRI (39).

Histology. Diffuse PNF may grow invasively and destructively (31, 34). MPNSTs can arise from PNFs (31).

Facial MPNSTs are rare in NF1 (20). Sporadic facial MPNSTs predominate in reports and usually arise without the precursor PNF (13, 19, 20). Imaging can support the assessment of tumor biology (31, 34), but current non-invasive imaging diagnostics remain erroneous with uncertainty regarding tumor characteristics. Histological assessment can also yield ambiguous results if only part of a large PNF is malignant and the imaging diagnostic tools cannot be used to precisely differentiate between benign and malignant components. The difficulty in assessing the differentiation of a neurofibroma can arise particularly in large diffuse PNFs, which have been collectively referred to as *elephantiasis neuromatosa* (41).

Orbit. The orbit and periorbital region can be severely affected by PNF, although the phenotype is highly variable. The term orbital/periorbital neurofibroma (OPPN) has been proposed as an umbrella term for the large number of findings in this region (42). However, the differentiated pathology of the entity designated by the term OPPN is limited to sphenoid dysplasia with regard to the skeletal component, despite the two-fold mention of the anatomical unit "orbit" in the proposed name (42). In the surgical assessment of treatment, it has been argued that an eye embedded in a tumor mass, functionless and often aesthetically disfiguring, constitutes the indication for enucleation/exenteration and rehabilitation should inaugurate epithetic replacement (43).

In a case report with an overview of a further 14 published cases, the histological and clinical findings of enucleated eyes of patients with NF1 were analyzed (44). Eleven patients had developed a neurofibroma of the orbit and variable PNF-associated ocular changes. The frequent correlation between an extensive tumor mass and a non-functional eye can be deduced from the documentation in the compilation of the findings for the decision to enucleate in many cases. In two cases an optic glioma of the non-PNF side was registered and, in another case, a not further described enlarged canalis opticus of the tumor side was recorded. Orbital bone defects were documented in two patients and were localized on the

tumor side. The evaluation of the literature focuses on the pathological findings. Reconstructive measures are only referred to in individual cases (44).

The defect of the orbit, primarily registered as sphenoid bone defect, has a wide spectrum in patients with NF1 and encompasses small defects with subsequent enlargement of the superior orbital fissure without esthetic or functional consequences to extensive herniation of the temporal lobe due to the insufficient osseous demarcation of the orbit (45, 46). Many cases with NF1-associated sphenoid dysplasia were apparently asymptomatic and did not require surgical correction (47).

The prevalence of sphenoid dysplasia in NF1 is estimated to be around 10%. It can be assumed that the rate is somewhat higher because small defects of the large wing escape diagnosis or findings are not listed (47). For example, the sphenoid dysplasia shown in the patient's CT scan was not included in the original radiological assessment, probably considering the extensive tumor of a half sided affected face as the relevant finding.

Nose. The PNF has also retained the half-sided tumor extension in the nose. The surgical measures in this organ focused on reducing the enlarged side of the nose and preserving it. Repeated interventions were necessary for effective tumor reduction.

Mandible. The deformation of the mandibular right side affected especially the dorsal sections, *i.e.*, the mandibular angle and ramus. The association of the bone deformities with tumor-altered or destroyed masticatory muscles was also evident in this case (25, 26). On the ground of previous observations, we had already suspected that the masticatory muscle functions can be disturbed in diffuse invasive PNF (48-51). Infiltrating and displacing tumor and fatty degeneration of muscles may inhibit adequate functional stimuli to the bone during the development and growth of the mandible (38, 39). The type of bone deformation could indicate the time and topography of functional impairment of the masticatory musculature by PNF, possibly in individual cases as early as congenital.

However, other reports show that the typical mandibular deformities can also become manifest later and with the child's osseous development (40). In addition, the bone-destroying effect of the tumor in mandibular PNF has been described in detail as a process that takes many years and has been documented into adulthood (51). In this respect, the distinction between causes and consequences is also essential for assessing the phenotype of the skeletal alterations of the face of the patient with NF1 (23). The descriptions to date suggest that the early development of facial PNF adjacent to the mandible is associated with bone deformation and alterations of the masticatory muscles. Rarely, the growing tumor makes it difficult or impossible to preserve the tumor-enclosed bone (51). However, PNF-associated mandibular dysplasia is a characteristic of childhood and adolescence and apparently has the greatest potential to change the bone during this phase of life. With a few exceptions (51), the mandibular deformities are largely stable in adulthood (25). However, reliable epidemiological data on the frequency, severity and progression of jaw changes in NF1 are scarce and have not been investigated in larger studies on the classification of this disease (13, 29, 52-55).

Conclusion

The hemifacially PNF of patients with NF1 often requires various and repeated measures for functional and esthetic rehabilitation. The extent of the tumorous destruction of the functional units determines the surgical treatment concept. Rapidly growing tumor within a PNF is an important characteristic of malignant dedifferentiation. These tumors should be removed and expertly analyzed. Reconstruction with vascularized transplants expands the reconstructive tools for patient care. New neurofibromas may develop in these grafts.

Conflicts of Interest

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

Authors' Contributions

Reinhard E. Friedrich: Treatment of patient, project administration, conceptualization, investigation, methodology, writing – original draft, writing – review and editing. Felix K. Kohlrusch: Conceptualization, methodology, writing – review and editing. Christian Hagel: Histology, investigation, writing – review and editing.

Acknowledgements

The Authors thank the patient for consenting to the publication of this case report in anonymized form.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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