

Facial Diffuse Plexiform Neurofibroma-associated Mandibular Deformities: Surgical Interventions and Monitoring of Treatment Results in a Patient for Over 40 Years

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Abstract

Background/Aim: Neurofibromatosis type 1 (NF1) is an autosomal dominant hereditary tumor-predisposition syndrome and a genetic bone disease. The case report describes tumor-associated mandibular changes, their therapy and follow-up over several decades. The aim of the presentation is to highlight the tumorous and hamartomatous components of the facial skeleton and to examine the stability of surgical measures over the long term.

Case Report: A 13-year-old male patient had developed an extensive diffuse plexiform neurofibroma of the left cheek and neck region. Radiological examination showed a mandibular defect, which enlarged over time. Surgical treatment consisted of a corrective procedure for the asymmetrical bony chin and augmentation osteoplasty of mandibular defect. The transplant was an integral part of a functionally stable bone for decades.

Conclusion: Head and neck diffuse plexiform neurofibroma can be associated with craniofacial bone malformations. Distinction between deformity-related bone changes from an infiltrating and destructive tumor can be difficult, especially in cases of rapidly progressive local bone loss. Presumably, both tumor-associated functional lesions of the masticatory muscles and tumor-related effects on the bone influence the shape of the affected bone. Diagnosis of tumor-associated bone lesions can be challenging in NF1. Reconstructive bone surgery of the jaw provides options for functional and esthetic improvement of the affected individual. However, long-term follow-up checks are advisable to assess treatment results. An exact assessment of the tumor type and long-term monitoring of the findings are the basis of a viable surgical therapy.

Keywords: Neurofibromatosis type 1, mandible, osteoplasty, plexiform neurofibroma, bone dysplasia.

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Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant heritable tumor suppressor gene disease. With a frequency of approximately one in 2500 live births, NF1 is the most common hereditary disease, with a predisposition for the development of cancer. NF1 is characterized by tumors that originate in nerve sheath cells. Schwann cells or their precursors are considered tumor cells of origin in neurofibroma. The *NF1* gene product, neurofibromin, has important, however largely unknown, functions in the development of tissues and organs, including bone. The best-studied function of neurofibromin is its involvement in the functional control of the rat sarcoma (*RAS*) gene (1).

In the cranial region, characteristic but variable disorders of bone are frequently recorded, which in many cases are topographically associated with a type of neurofibroma almost exclusively developing in NF1, the diffuse plexiform neurofibroma (DPN) (2). These tumors can have a considerable impact on the physical appearance of the patient through invasive and destructive growth (2). DPN is considered a congenital tumor that can cause conspicuous changes to the face during prenatal development or shortly after birth. Facial DPN (FDPN) typically develops on one side of the face. Tumor-associated changes in the jaws are limited to the tumor side (3, 4). The DPN can be assigned to the terminal branches of the trigeminal nerve (5), usually defined by clinical assessment of the tumor's extension in the facial skin (6). If the tumor manifests in all three branches, a hemi-FDPN may develop, which alters the affected face in stark contrast to the unaffected half of the face. The bony changes can be distinct and may initially escape notice due to the voluminosity of soft-tissue tumor but significantly determine both physical expression and functional orofacial performance (7). Tumor-side hypoplasia of the jaws determines the skeletal phenotype, which is particularly noticeable in the lower jaw (3, 7). Local jaw hyperplasia in NF1 is rarely described (8, 9). The topographical association of jaw lesions with DPN has

been repeatedly documented (8, 9). Alterations of jaw size and shape are assessed to be largely stable in cases of FDPN in adults (10). In contrast to the assessment of stable bone shapes in adulthood, individual courses have demonstrated further deformation and degradation of bone in close contact with an invasive nerve sheath tumor over time in young patients (10). Indeed, extensive FDPN can occasionally cause the complete destruction of the ramus and jaw angle (11-13).

This report contributes to the knowledge on deforming and osteolytic facial skeletal pathology of patients with NF1, a disease which frequently develops in topographical association with a neurogenic neoplasm. This is suspected to be a preliminary stage of malignant disease of the peripheral nerves. We detail the course of the disease over more than 40 years using an example of FDPN-associated mandibular dysplasia and reveal the influence of surgical measures on bone shape, regeneration, and adaptation in a tumorous soft-tissue environment. The case is illustrated by the sequential presentation of radiological findings (Figure 1, Figure 2, and Figure 3) and the comparison of the external aspect over time (Figure 4).

Case Report

The male patient first attended the Clinic for Oral and Craniomaxillofacial Surgery at the age of 13 years. At that time, a diagnosis of NF1 had already been established (Recklinghausen's neurofibromatosis). The child's examination was aimed at assessing the tumor on the left side of the head and neck region, which primarily affected the supraclavicular to the pinna region. Additional radiological imaging of the lower jaw revealed the rarefaction of the bone around the left jaw angle (Figure 1A). The radiograph depicted a deepened coronoid notch, an increased transparency of the ramus between the coronoid notch and above the mandibular foramen, giving the impression of an enlarged mandibular foramen, plus a roundish notch at the angle of the jaw with transition to the ramus. At that time, there was no indication for surgical intervention. The panoramic radiograph (PR)

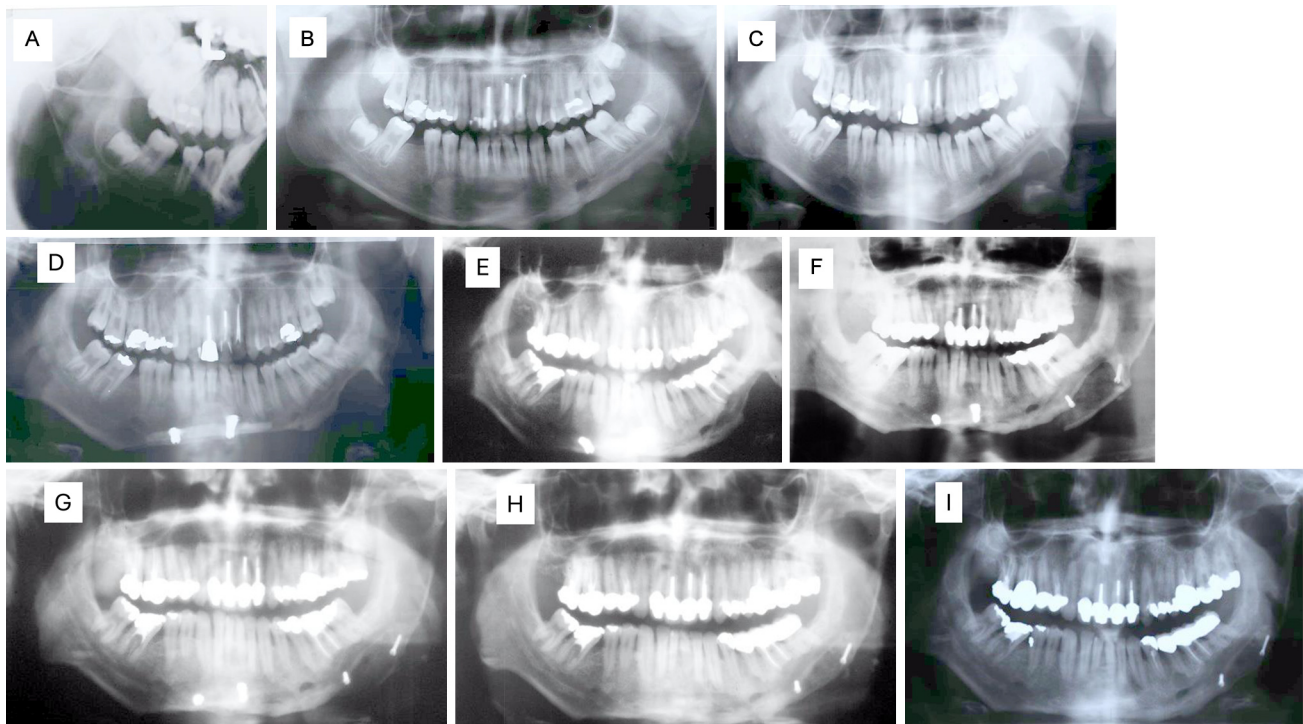


Figure 1. A series of radiographs of the jaws of the patient with left-sided plexiform neurofibroma of the cheek-chin-neck region. (A) Oblique mandibular radiograph of the left side taken at the age of 13 years. The antegonial notch was emphasized and the area of the mandibular foramen was more translucent. (B) The image taken 1 year later shows the hypoplasia of the mandibular angle with spicule-like dorsal bone outgrowths. (C) Another year later, the bone loss on the affected side had almost reached the lower limit of the nerve canal. A residual spur indicates the dorsal border of the ramus. Images (B) and (C) show the asymmetry of the chin region with a plus of caudally extending bone on the tumor side. (D) The figure shows the horizontal level after the chin osteotomy. The osteosynthesis screws of the region form an internal reference of the chin contour. In the left mandibular angle, the then triangular defect had enlarged into the ramus. (E) In the 31-year-old patient, a narrow bone bridge in the inner mandibular angle constitutes the continuity of the corpus and ramus mandibulae. The edges of the defect are slightly uneven in shape compared to the previous image. (F) The osteoplasty had filled the basal defect and completed the hypoplastic mandibular angle region. (G) Within 1.5 years, the graft had been resorbed in the sagittal plane to the level of the basal jaw margin. (H) With the incorporation of the graft into the bone, its resorption had stopped. (I) At the age of 36 years, graft and bone were indistinguishable. During the entire examination documentation of the dentate patient, the shape of the left articular process, which was somewhat narrower on the left side in the collum area, did not change. The coronoid notch also remained unchanged in size and vertical position.

taken 1 year later showed the notch at the angle of the jaw and the narrowing of the condylar process on the tumor side (Figure 1B). The antegonial notch had increased in size; in other words, the bone had lost substance in the antegonial notch region. In contrast, the outermost angle of the jaw adjacent to the dorsal notch was elongated like a hook. PRs showed the asymmetrical development of the bony chin (Figure 1B and C). At the age of 18 years, the patient decided to undergo genioplasty to make the chin appear less prominent and asymmetric. The healing

process following osteotomy was unremarkable. At that time, further angular osteolysis in the area of the antegonial notch was documented (Figure 1D).

The patient did not appear for a check-up until 13 years later. The now 31-year-old patient had an atrophic cheek on the tumor side, a caudally sunken ear, and skin covered by multiple cutaneous neurofibromas (Figure 4A). The facial aspect confirmed the extension of the DPN from the left infraorbital region to the clavicle. The chin was covered by a prominent palpable spongy soft-tissue

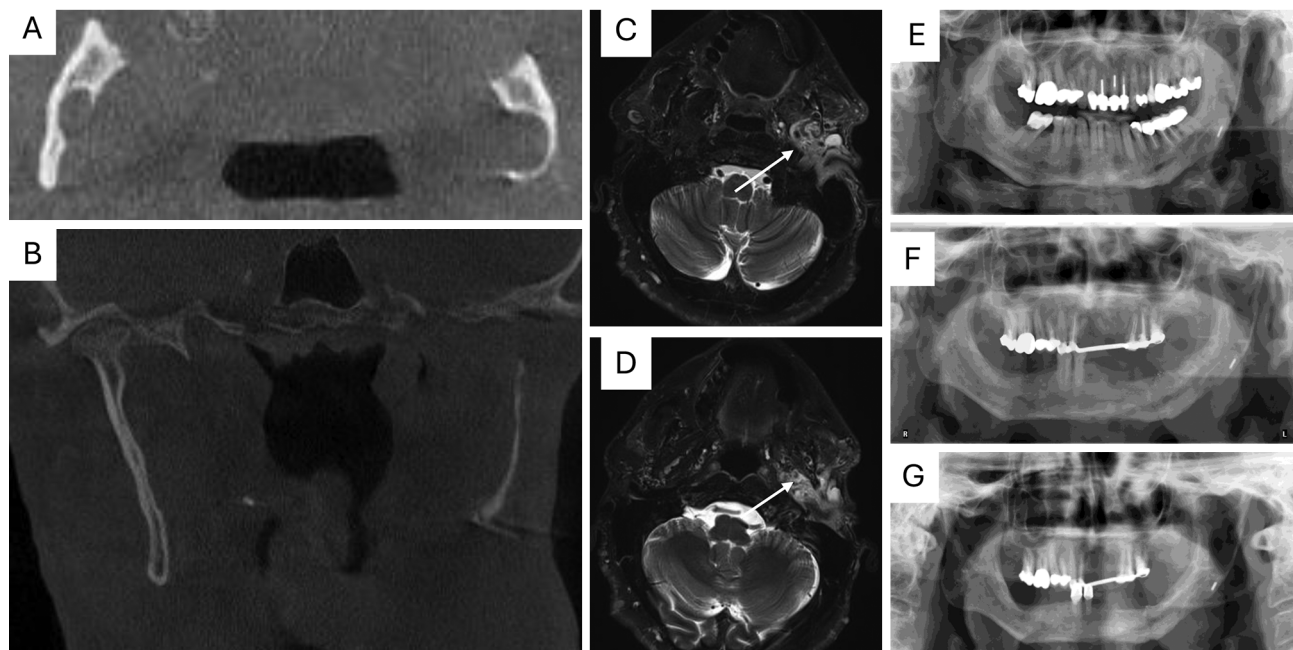


Figure 2. Changes of the ramus and the mandibular angle of the tumorous left side in a patient with facial plexiform neurofibroma. Illustration of the relationship between bone and soft tissue and the involution of the mandible after tooth loss. (A) Section of axial cone-beam computed tomography at the level of the mandibular foramen at age 60 years. The right ramus shows the typical anatomical figure of the cortical bone layers converging dorsally in a wedge shape. The foramen had a normal diameter with the formation of a lingula. On the left side, the region of the foramen formed a deep cavity extending to the dorsal end of the ramus. The foramen's diameter was larger both in the transverse and sagittal planes than on the unaffected side. A lingula was missing. (B) The coronal view of the same region shows that the thinning of the vertically shortened left ramus had affected the entire length of the bone segment. The hyperdense line artifacts at the lower end of the left ramus indicate the position of the osteosynthesis screw. The axial views (C, D) show diffuse hyperintensity of the left parotid region, which is analogous to fatty degeneration on magnetic resonance imaging. (C) The infiltration by the diffuse lesion led to the lack of an outline of the medial pterygoid muscle on the medial side of the ramus (arrow). (D) In contrast, the cord-like connection of the lateral pterygoid muscle to the articular process was identifiable (arrow). The next sequence of images shows the transformation of the patient's mandible with advancing age. (E) At age 46 years, the patient had advanced periodontitis, resulting in alveolar bone loss. However, the bony outline was unchanged. (F) After complete tooth loss on the left side of the lower jaw, involution of the alveolar process had begun. At the age of 55 years, the basal region of the mandible was not affected by the involution. (G) At age 59 years, the involution of the edentulous mandible had led to an approximation of the nerve canal to the upper border of the bone. The basal region of the mandible had not changed since the graft was adapted to the contour of the mandible about 7 months after surgery (see Figure 1).

tumor. The left, more voluminous, parts of the chin tumor were located at the side where the lower edge of the chin extended further caudally. The soft-tissue tumor continued with the left-sided cheek tumor, extended distally to the pinna and covered the skin above the clavicle caudally. The PR of the jaws showed the sharply marked and slightly enlarged, wedge-shaped destruction of the bone anterior to the left mandibular angle (Figure 1E). The facial asymmetry was obviously the combined result of facial muscle atrophy due to progressive tumor

infiltration, the effects of gravity in the tumor area on soft tissue (cheek, pinna), and bone deformity (Figure 2 and Figure 4). However, the corrected chin region was unchanged from the postoperatively documented contour, compared in transversal and sagittal planes (Figure 1 and Figure 2). On the other hand, the chin osteoplasty was no longer distinguishable from the rest of the bone on subsequent X-ray examinations (Figure 1E).

Because the lower jaw had extremely thinned in the left angular region (Figure 1E) and a reactive, load-

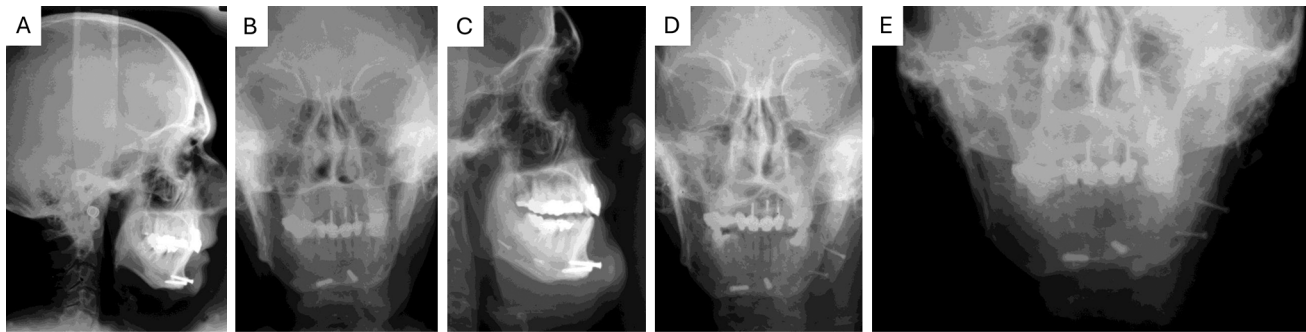


Figure 3. Changes in the contour of the mandible after mandibular surgery as seen in cephalograms (cropped images), age 31 years. (A) Chin reduction with osteosynthesis screws; furthermore, double contour of the antegonial notch. As a result of the loss of basal bone on the left side, this region of the bone appeared increasingly transparent on the lateral projection of the skull. (B) The postero-anterior projection taken at the same time shows the reduced mandibular arch of the affected side, and corresponding skeletal hypoplasia of the lower face. (C) At 5 weeks after the previous, preliminary images, the lateral projection shows the defect filling of the left side of the jaw with a bone graft. (D) The postero-anterior projection shows the transversal overcompensation of the bone deficit by the voluminous bone. (E) Seven months later, the bone located lateral to the mandible showed clear resorption.



Figure 4. Development of the patient's tumor region over time, after genioplasty at 30 years old (A) and at 53 years old after multiple chin reductions (soft tissue) (B). The left-sided tumor extended from the region of the ear anteriorly to the chin region and caudally to the clavicle. The musculature of the lips was unaffected. In the left mandibular angle region, the curvature of the mandible was flattened, the pinna was lower than on the opposite side and protruded from the skull. In the midline area, the irregularly distributed tumor, which was characterized by local, hyperpigmented bulges, had infiltrated the skin of the opposite side by a few centimeters. The slow progressive tumor growth was conspicuous in the chin area.

resistant reinforcement of the internal trabecular structure of the remaining bone to increase the bending strength could not be determined from the x-rays, augmenting osteoplasty was performed to seal the defect (iliac crest autograft) (Figure 1F; Figure 3C and D). Subsequently, the graft, which had grown into the bone

and was intrinsically modeled, remained dimensionally stable (Figure 1I). The healing process was unremarkable. Further follow-up checks documented the complete integration of the graft into the mandibular bone. However, there was considerable lateral resorption of the bone graft during the following years (Figure 1G and H;

Figure 3D and E). The resorption of the graft had caused the screw heads to protrude above the level of the vestibular bone surface and they were palpable during the follow-up. The discomfort of the protruding screws justified their removal at 5 years after transplantation (Figure 2E). The distal screw was firmly ingrown in the bone and could not be loosened without ablation of the surrounding bone and was therefore removed at the bone level (Figure 2E). Again, the healing process was unremarkable.

During the following years, surgical interventions to reduce the prominent soft-tissue masses were repeatedly performed. Further follow-up over 20 years showed the involution of the alveolar process after tooth loss and discrete resorption of the lower edge of the mandible on the left side, which transposed the external mandibular angle slightly cranially (Figure 2F and G). The bone graft fitted into the shape of the bone in all dimensions. The transplant merely followed the minor basal resorption of the bone (Figure 1I and Figure 2G). The articular process and coronoid notch had hardly changed when comparing the initial findings in adolescence (Figure 1A-D) with the x-ray findings of the elderly patient (Figure 2G). The hypoplasia of the ramus had remained largely unchanged since the examination at the time of bone augmentation, as had the contour of the surgically modeled chin.

Three-dimensional imaging of the bone on cone-beam computed tomograms showed that the enlargement of the mandibular foramen on the PR corresponded to a cup-like hollowing of the lingual side of the bone with deformation of the thin ramus (Figure 2A and B). On the PR taken during adolescence and early adulthood, the thinned, shell-like curved ramus may have been partially located outside the focal trough of the device due to the deformation, thus creating the impression of an enlarged foramen. The tomograms taken later show the shell-like thinning of the ramus, which appears on the PR as a tumor-associated enlargement of the mandibular foramen (Figure 1; Figure 2A, B, and E-G).

At the age of 61 years, the patient developed a left-sided submandibular swelling in the anterior part of the FDPN

within a short period of time. The ultrasound examination showed an oval-shaped, low-echoic mass that was compressible. This finding was difficult to distinguish sonographically from a diffuse neurofibroma or rapidly growing tumor. However, the swelling showed no functional limitations or complaints. The suspicion of subcutaneous hemorrhage originating from diffuse neurofibroma was confirmed in the follow-up, during which the mass resorbed after 4 weeks. In addition, magnetic resonance imaging (MRI) of the head and neck region was performed. The imaging revealed a significantly enlarged left internal jugular vein in a tumor mass that included the parotid gland and the musculature around the mandibular processes and coronoid notch. The extensive dissolution of the barely visible masticatory muscles of the affected side was striking, as illustrated by the comparison with the unaffected opposite side (Figure 2C and D).

The following findings of the aged patient are conspicuous from the summary of the radiological diagnostics during the follow-up (Figure 2): the left mandibular foramen was now located further caudally than the right one on PR (hollowing of the lingual ramus side). However, the left outer jaw angle was slightly displaced cranially because of bone resorption. The left mental foramen had a larger diameter than the right one. This finding had no correlation to the terminal extent of the nerve canal on each side: On PR, the mandibular *canalis incisivus* could be traced on both sides up to the lateral incisors and had the same diameter and mesial spread on both sides (Figure 1, Figure 2, and Figure 3). The mandibular left collum with articular process was narrowed, yet the coronoid notch was not deepened (Figure 1). However, the vertical loss of ramus height and the significant thinning of the ramus were constant findings into old age (Figure 1, Figure 2, and Figure 3). The left glenoid fossa had flattened. The antegonial notch (attachment region for the masseter muscle) was missing on the left side and the augmented bone showed no resorption resembling the bone loss of youth (which is interpreted as a defect aligned perpendicular to the basal bone line of the body). The basal cortical of the mandible

was poorly defined on the tumor side. The atrophy of the alveolar process of the left side after tooth loss appeared symmetrical in lateral comparison of the mandible (Figure 2F). The chin was symmetrical in shape and showed no increase in vertical dimension almost 40 years after genioplasty (Figure 2G). Assessing facial bones and soft tissues beyond the jaws, the orbital region was symmetrically developed, and the soft-tissue auditory canal of the left side was bent more caudally in accordance with the caudal displacement of the pinna. Figure 4 illustrates the external clinical findings of the adult over time.

Histology. The intra-operative aspect of the primary tumor at the age of 31 years was that of a diffuse plexiform neurofibroma. However, histology identified only a diffusely infiltrating neurofibroma in the most recent operation at the age of 53 years (World Health Organization grade I).

Discussion

This report indicates that both ablative and augmentative skeletal procedures of the mandible can remain stable for decades, with adaptive changes in the affected bone occurring in alignment with the contour of the organ.

Progression of disease-characteristic findings in NF1. NF1 is a chronic progressive disease. The progression of the disease is easily recognizable by the very frequent increase in number and size of cutaneous neurofibromas as a function of age (Figure 4). Cutaneous neurofibromas typically appear during or after puberty, are limited in diameter to a maximum of a few centimeters and can develop in very variable numbers and skin regions throughout life. According to current estimates, these tumors only develop at the time of puberty and do not grow infiltratively in muscle or bone (1, 5). These tumors are not expected to change the shape of the jaw.

Disease-characteristic skeletal changes can show an aggravation of the findings over time, for example kyphosis of the spine or non-union of long bones. However, in these distortions of the axial skeleton, the

association with a DPN is frequently noted, but not an obligatory finding (14, 15). On the other hand, jaw malformation in patients with NF1 usually indicates adjacent DPN (3, 11-13). The bone changes can have a predilection for a progressive course, particular during the early phases of life (16-18).

Latency and progression of craniofacial bone findings in NF1. For the skull, enlargement of defects, growing of a tumor, and aggravations of the local findings, especially exophthalmos, have also been described using the example of diagnostically groundbreaking dysplasia of the sphenoid bone (19). The revised classification of the diagnostic criteria of NF1 corrects the finding of sphenoid dysplasia as usually being dependent on an orbital DPN. The skeletal diagnostic criterion is now only included in the diagnosis if the finding has been confirmed without evidence of topographically associated DPN (20). The analogy to the jaw findings in NF1 is obvious. In most cases, the bone findings, especially in the regions of the mandible close to the joint, are associated with a DPN. The skeletal changes may be indicative of DPN, although the tumor may escape advanced imaging and only be detected by surgical exploration (21).

Dysmorphia of the lower jaw is considered a comparatively stable finding in adult patients with NF1 (10). One-sidedness of the findings is a frequently noted feature of the mandibular dysplasia. The association with a DPN on the same side has been widely documented (3, 4, 6, 7, 13). However, some reports documenting extensive loss of parts of the mandible indicate that these patients do not necessarily have to have a stable skeletal condition (13). The walling of the resorbed ramus and distal mandibular angle by the DPN has been described in detail clinically and on MRI in these cases (13). However, complete mandibular resorption in FDPN cases with large tumor mass surrounding the mandible is not an inevitable fate of the affected bone segment. In most patients with extensive FDPN, follow-up examination of the severely dysmorphic mandibular side reveals a stable bone shape or only minor progress of dysplasia beyond childhood

(10). It can therefore only be assumed that additional factors cause the dissolution of the bone, for example tumor-associated destruction of the masticatory muscles at the site adhering to the ramus due to loss of shear stress on the bone, disorders of the bone's vasculature causing malnutrition, or the pathogenetically largely undefined stimulation of osteoclasts in NF1 (14-18).

In the case reported here, the osteotomy of the chin region remained stable for decades. Likewise, the diffuse neurofibroma of the chin remained largely stable and only showed very slow, visible increase in volume, which accentuated the chin region asymmetrically and justified minor surgical interventions (Figure 2 and Figure 4). The increases in tumor volume may be due to both a discrete increase in the number of tumor cells and the extracellular matrix, as well as to the effects of gravity on the tumor-infiltrated soft tissue of chin, which lacks normal, shape-maintaining connective tissue (22, 23).

Pathogenesis of bone deformity associated with muscle disease. The bone defect of the jaw angle was adjacent to the insertion of some masticatory muscles. It remains speculative whether the sharply defined resorption of the basal bone part had a correlation with a dystrophic muscle part, *e.g.*, the masseter muscle. MRI of the jaws taken at the same time showed infiltration of the pterygoid muscles and masseter.

However, the destruction of the skeletal muscles in the perimandibular area did not affect the muscles in the same way. While an at least partially dimensionally stable *lateral* pterygoid muscle was present on the tumor-side articular process for decades, the signal intensity of which corresponded to the same muscle on the opposite side, neither the shape nor signal of the medial pterygoid muscle was detectable in the lingual insertion area (Figure 2). While the articular process had largely developed normally, hypoplasia of the ramus with a shell-like defect had formed around the mandibular foramen. It is likely that the altered masticatory muscles in the tumor region had an influence on the bone shape. This effect of a degenerated musculature on the mandible, in particular

the ramus and articular process, is apparently particularly notable in childhood and adolescence. In the case presented, the somewhat thinner articular process remained unchanged during the examination interval, *i.e.*, it was already detectable during puberty. In contrast, although the defect of the mandibular angle was detectable at the same time, the conspicuous triangular defect did not develop until several years later. It is possible that degeneration of the masticatory muscles is associated with bone remodeling and that the early phase of life is particularly susceptible to this metamorphosis. Similarly, the metachronous course of bone remodeling (early narrowing of the articular process, larger defect of the mandibular angle a few years later) gives rise to the assumption that muscle degeneration also begins at different times and can be self-limiting. However, the correlation of retention or loss of bone shape of the process and ramus area depending on the detection of the skeletal muscles in imaging cannot explain why the bone graft of the antegonial notch was not completely resorbed. Surrounded by a tumorous environment, the avascular transplant underwent noticeable resorption. However, bone loss only affected the parts that protruded laterally beyond the contour of the bone. The bone embedded in the triangular defect was preserved over the following three decades, staying permanently in close contact with the tumor-infiltrated soft-tissue layer.

The soft-tissue layer (cheek) appeared hypoplastic when compared from side to side. Considering the photographic documentation of the patient's face at the time of jaw augmentation (Figure 4A), it is evident that the cheek hypoplasia already existed at this time and remained largely stable during the observation period (Figure 4B). In many cases, a strong increase in the volume of the FDPN is noticeable and the tumor side appears significantly larger than the unaffected side (7).

Frequency of mandibular deformity in NF1. These are rare findings in NF1 and analyses of jaw changes in a larger number of patients are biased by the referral characteristics of specialized clinics (3), so that generalizations about the

frequency of jaw deformities can only be drawn from a few reports to date. However, the methodological tools used in the studies rarely focus on comprehensive craniofacial diagnostics.

In Crowe *et al.*'s evaluation of clinical findings from 75 patients (25) [which come from the radiological case collection of Holt and Wright (25)] who had bony malformations, the authors described five children (6.7%) with asymmetry and facial neurofibroma, as well as three individuals (4%) with overgrowth of the mandible and maxilla, but without further description of the findings. In other craniofacial studies on patients with NF1, hypoplasia of the mandible was recorded far more frequently than hyperplasia (3, 7, 26). However, in single cases, unilateral hyperplasia of children with NF1 can reach extraordinary dimensions (8, 9) and this makes the diagnosis of coincidence with idiopathic mandibular hyperplasia impossible in retrospective evaluation.

Visnapuu *et al.* described changes in the jaws of 29 out of 102 patients with NF1 (28.4%) (10). This frequency of jaw changes is in the upper range of the registration of spinal changes (scoliosis) in this patient group (1). However, the jaw changes were generally described as relatively mild. Only six patients (5.8%) were found to have facial plexiform neurofibroma obviously in topographic relation to the unilaterally recorded jaw malformations. In these cases, typical alterations of mandibular size and shape were identified ipsilateral to the plexiform neurofibroma. The report describes the barely noticeable mandibular alteration in a 10-year-old, which only became clearly noticeable several years later. The time interval of the conspicuous bone change in that report corresponds to the phase of conspicuous defect formation in the present case. That study was based on the analysis of panoramic views of the jaws; the local tumor burden to be estimated beyond physical inspection remains unknown for most patients.

Malignant peripheral nerve sheath tumor. Malignant peripheral nerve sheath tumors of the craniofacial region are rare (27-34). Sporadic tumors predominate and only

rarely are clinical and genetic data available that clarify the syndromic association of the malignancy, presented as case reports (32, 33) or reviews (34).

Increase in bone defects associated with DPN are mainly observed in children and adolescents and require clarification (19, 33). The bony deformities of the facial skull are often already manifest congenitally or in early childhood. This early manifestation of skeletal changes in the vicinity of a DPN makes it difficult to analyze which changes are intrinsic malformations of the bone and which are the result of the influence of the neurogenic tumor on bone during development or later in life (33). However, the shape of the jaws of patients with NF1 without FDPN were not found to differ from that of a control group (2, 3). An integrated care concept using currently available imaging should be used for diagnosis in these cases (35), which can be supplemented by surgical exploration and advanced tissue analysis (36).

Conclusion

NF1 is a skeletal disease with a highly variable phenotype, including changes in the jaws. The differentiation of a dysplastic defect from tumor erosion and the suspicion of an invasive tumor can be difficult. Surgical measures can remain stable after a long observation period, including augmentation of the mandible after a rapidly occurring bony defect in a mechanically highly stressed area. The occurrence of bone deformities with destruction of the masticatory muscles in this region is striking. It can be assumed that these soft-tissue changes are related to tumorous alteration of the mandibular nerve. Individual variations in skeletal dysplasia in this phenotype may be related to the extent of tumorous changes in the branches of this nerve. The spectrum of histological diagnosis of nerve sheath tumors is large and can reveal different entities and different biological characteristics. Recommendations for a standardized diagnosis of patients with NF1 offer improvements for the appropriate diagnosis and treatment of these patients, whose phenotype often defies simple categorization (37).

Conflicts of Interest

None to declare.

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, writing – review and editing.

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