ANTICANCER RESEARCH *39*: 1971-1985 (2019)
doi:10.21873/anticanres.13308

Non-odontogenic Intraosseous Radiolucent Lesions of the Mandibular Body Are Rare Findings on Panoramic Views of Patients With Neurofibromatosis Type 1

REINHARD E. FRIEDRICH[1,2*] and HANNAH T. SCHEUER[1,2*]

[1]*Department of Oral and Craniomaxillofacial Surgery, Eppendorf University Hospital, University of Hamburg, Hamburg, Germany;*
[2]*Neurofibromatosis Laboratory Hamburg, Hamburg, Germany*

Abstract. *Background/Aim: The purpose of the study was to investigate whether non-odontogenic intraosseous translucent lesions of mandibular body are depicted on radiographs of patients with neurofibromatosis type 1 (NF1). Materials and Methods: The panoramic radiographs of 179 NF1 patients were analysed for translucent lesions of the mandibular body that were of intraosseous, non-odontogenic origin. The results were compared to findings obtained in panoramic radiographs of age- and sex-matched controls. Results: Only three patients showed intraosseous translucent lesions. These were always unilocular findings. There were no statistically significant differences between the groups (p=0.248). Conclusion: Intraosseous neurofibroma of the jaw is a very rare finding in NF1 patients compared to oral neurofibromas. Accurate and exact diagnosis should be made in the case of such findings because malignant tumours in the jaw area can arise in rare cases in NF1 patients. Plain radiology findings cannot clearly indicate the type and biology of the lesion.*

Neurofibromatosis type 1 (NF1) is an autosomal dominant hereditary disorder with almost complete penetrance and a very variable phenotype (1-3). The hallmark of NF1 is multiple tumours of peripheral nerve sheaths (neurofibroma). The tumours are frequent and particularly conspicuous in the integument (4). NF1 is also a disease of the skeletal system (5, 6). The clinical diagnosis of the disease requires the unequivocal identification of a defined number of characteristic findings (7, 8) which is sufficient for assessing affected individuals in the majority of cases (9). The molecular-genetic identification of the constitutional mutation on chromosome 17q11.2 (10) is principally possible in the vast majority of patients (11). NF1 is one of the most common tumour suppressor gene disease with a prevalence of about 1:2,500 to 1:3,000 live births (3). NF1 is considered the most common genetic disorder predisposing to cancer (3). Although soft tissue sarcomas (STS) very rarely develop in humans, they are particularly common in patients with NF1 and are a major cause of their lower life expectancy compared to the normal population (12). STS in NF1 is characteristically a malignant peripheral nerve tumour (MPNST) that may arise from pre-existing plexiform neurofibroma (PNF) or *de novo* (13).

The occasionally very noticeable phenotype of neurofibromatosis patients has long attracted medical attention (3). Disfigurements of the maxillofacial region have also been described (14-16). Soft tissue tumours, skeletal changes or both occur in this region (14-18). Previous reports on oral and maxillofacial pathology in NF1 have focused primarily on tumour biology (19-25), disfigurement (26-28), genuine skeletal alterations of the skull and skeletal changes in relation to peripheral nerve sheath tumours (29-45), dental anomalies (46-49), oral health care problems (50-56), radiological changes in the periapical area of teeth (57, 58) and giant cell granuloma (59-65). The majority of reports on neurofibromatosis-related osseous pathologies of the jaws combined with peripheral nerve sheath tumour describe experiences derived from a single or few cases (66-97).

NF1: Oral and jaw findings with special reference to skeletal findings and neurofibromas. The formal restriction of reports referring to experiences derived from individual cases or study groups of small size applies in particular to *intraosseous* neurofibromas of the jaws in NF1. However, reports on rare cases of intraosseous neurofibromas were

*Both Authors contributed equally to this study.

Correspondence to: Prof. Reinhard E. Friedrich, MD, DMD, PhD, FEBOMFS, Department of Oral and Craniomaxillofacial Surgery, Eppendorf University Hospital, University of Hamburg, Martinist. 52, D-20246-Hamburg, Germany. Tel: +49 40741053259, Fax: +49 40741055467, e-mail: rfriedrich@uke.de

Key Words: Neurofibromatosis type 1, panoramic view, jaw - lesion, neurofibroma – intraosseous, simple bone cavity, Stafne's bone cavity.

usually solitary findings unrelated to NF1 (98-137). Indeed, intraosseous neurofibromas are considered rare in this entity (30, 80, 110, 116, 120). More often, bone deformities arise in relation to soft tissue neurofibromas (117, 138). Some authors have compared their own cases with the results derived from the collection of previous case reports (30, 76, 80). These general reports indicate that intraosseous nerve sheath tumours are much less common in NF1 than in sporadic cases. However, the differentiation between (intra)osseous neurofibroma in patients with sporadic neurofibroma (98-137) and those in patients with neurofibromatosis (66-97) is not considered in every document concerning tumours affecting the jaws. So far, all reports on the relationship of intraosseous neurofibroma of the jaw and tumour suppressor gene disease are based on individual reports and the compilation of other case reports. Nonetheless, an intraosseous neurofibroma and neurogenic sarcoma is considered a rare finding in the whole skeleton in general (19) and in particular in the systematics of oral pathology (138-140). The very rare development of intraosseous neurofibromas may be one of the reasons why this differential diagnosis has not been recorded, even in recent textbooks on jaw pathology (141). However, many reports have been published in the meantime on this subject of oral and maxillofacial disease (66-137).

Indeed, the neurofibroma arises mainly in soft tissues. This preference also applies to the oral and maxillofacial regions. In reports of neurofibromas of the oral cavity in NF1, mucous membranes are obviously much more frequently affected than bone (18, 45). Neurofibromas developing directly next to the jaws are rarely invasive (138), and the differentiation to MPNST should be sought in these cases (19, 21, 138). However, bone invasion by adjacent neurofibromas may be difficult to assess if the jaw adjacent to the soft tissue tumour area is dysplastic. Blackwood and Lucas (101) have already pointed out that a distinction should be made between primary intraosseous nerve sheath tumours and those developed in the oral mucosa, with the latter being in contact with the bone over a wide area of infiltrated soft tissues and able to penetrate from the periosteum into the bones and the dental socket (138).

NF1: Jaw deformity and plexiform neurofibroma (PNF). In the jaws and adjacent bones, characteristic osseous changes occur which, as a rule, affect only one side of the body and particularly conspicuously influence the shape of the lower jaw (35, 39, 40, 44). These skeletal malformations are indicators of a plexiform neurofibroma (PNF) of the trigeminal nerve (44). PNFs occur almost exclusively in NF1 patients and can lead to significant disfigurement (45). In contrast to cutaneous neurofibroma, PNF is considered a congenitally manifestation of neoplasm (142) that is likely present even in the embryonic phase and is capable of affecting the development of adjacent bone (44). PNF-associated jaw deformities primarily alter the external shape of the distal parts of the jaws on the same side (35, 39, 43, 44), and are frequently associated with enlarged mandibular foramen (35) and disturbed tooth eruption of permanent teeth (47). On the other hand, there are also strictly intraosseous jaw lesions in NF1, *e.g.* intraosseous neurofibromas, which are not associated with teeth. It remains unknown whether oro-facial PNF is associated with intraosseous neurofibromas.

Non-odontogenic intraosseous osteolytic jaw lesions in NF1. No data from larger studies are available for assessment of the prevalence of intraosseous neurofibromas of the jaw in NF1 according to current diagnostic standards of this entity. The suspicion of such a finding is probably most likely based on an overview X-ray of the jaw. However, several diagnoses have to be considered in the case of radiologically-identified non-odontogenic osteolysis. Furthermore, no reports exist which address the frequency of definitely diagnosed non-odontogenic intraosseous lesions of the jaw in NF1. This study was intended to determine the frequency of such lesions on radiological images, which have been provided with a standard radiographic projection used in dental practice. The results of this study intended to specify the skeletal phenotype of the disease in the area of the jaws taking into account the types of nerve sheath tumours of this region.

Materials and Methods

Patients

Total cohort. Three hundred and fifty-eight panoramic views obtained from 358 patients were evaluated in this study (mean age=34.63 years; range=12.57-69.13 years). The characterisation of the patient groups has been described in detail elsewhere (44). In brief, panoramic views of 179 patients of Caucasian origin with NF1 were investigated (NF1 patient group: mean age=34.84 years; range=12.83-68.89 years; 44.13% male (n=79), 55.86% female (n=100). These patients had been radiologically examined as part of their physical examination in the neurofibromatosis outpatient clinic at the clinic for oral and maxillofacial surgery to assess dental and facial-skeletal pathologies. All patients fulfilled the updated diagnostic criteria for NF1 (1, 2, 7, 8) and were citizens of Germany.

Patient group. The patient group was differentiated with respect to the manifestation of trigeminal PNF considering our experience in evaluating skeletal findings in NF1 patients: alterations of the jaws are characteristically formed when a PNF of the 2nd or 3rd branch of the trigeminal nerve of the same side is present (44). For all cases of trigeminal PNF in this study, the jaw deformities manifested on the same side as the PNF and were unilateral. Panoramic views of 67 patients (37.43%) who showed histologically verified facial PNF (facial PNF group, right side: 33 patients, left side: 34 patients) were evaluated. The definition criterion for this group was that a patient had to have at least one facial PNF irrespective of whether further disseminated cutaneous neurofibroma (DNF) occurred in this region. The extent of visible infiltration of the PNF into the cutaneous territory of the nerve varied considerably. A further 112 patients (62.60%) showed DNF but no facial (trigeminal) PNF, as revealed

by physical inspection and complementary imaging [computed tomography (CT), magnetic resonance imaging (MRI) and B-scan ultrasound], if available, and also histology in the course of surgical treatment for neurogenic tumours by the senior author. These patients constituted the DNF group (44).

Reference group. The reference group consisted of 179 panoramic views of age- and sex-matched individuals that were selected from the archives of the Institute of Diagnostic Radiology in Dentistry of Hamburg University Dental Clinic. The age of these individuals was 12.57-69.13 years (mean=34 years). For this group, the same exclusion criteria of diagnosis were applied, as previously described (44).

Inclusion criteria. A non-odontogenic intraosseous radiolucent lesion was defined as a radiotranslucency within the mandibular body and limited by it, for which neither an anatomical structure of the bone was causal nor a connection with an odontogenic anatomical or pathological entity can be made.

Exclusion criteria

Dental status. The dental status was not further specified for a study dealing with radiological non-odontogenic findings. Lesions, such as apical translucency in deeply-eroded teeth (70) or periradicular radiopacity in root canal-treated teeth that may had odontogenic causes were left unconsidered. Similarly, intraosseous translucency was assessed as odontogenic if this finding occurred in the toothless area of the alveolar process and the shape of the osteolysis could be regarded as the residuum of a dental socket. Patients with a history of surgical skeletal procedure or trauma of the facial skeleton were excluded from evaluation. The radiological diagnosis of odontogenic disease on panoramic views in this group has already been described in detail elsewhere (56).

Giant cell granuloma. Also excluded from the study was one NF1 patient with intraosseous giant cell granulomas, a report on whom has already been published (64). Further cases of giant cell granuloma did not occur in the study population (65). Giant cell granuloma is a well-known and rare diagnosis in jaw lesions of NF1 patients (143).

Bone deformities. Similarly, apparent deformities of the jaws in NF1 patients that had only changed the outline of the jaw were not considered, because these changes occurred in association with a PNF adjacent to or surrounding the bone. Thus, it was likely that external effects on the bone had caused – at least in part – this change in shape (138). The bone changes were a valuable finding for the screening of PNF of the trigeminal nerve and thus for the subtyping of the NF1 patient group (43). Enlargement and deformation of the mandibular foramen is frequently observed in PNF-associated mandibular deformities and were addressed as cyst-like lesions in a previous investigation (39). The changes may appear as intraosseous lesions on panoramic views (39). Alterations of the mandibular foramen and other deformities of the mandibular ramus and their significant association with trigeminal PNF have been described in detail elsewhere (44).

Bone destruction by external causes. Cases who were showing radiographic findings revealing progressive mandibular destruction that apparently resulted from external resorption of parts of the bone, were excluded. This pathology resulted in loss of mandibular ramus (n=2) (16, 144). In both cases, the creeping destruction of the bone developed on the side of an extensive perimandibular PNF, which completely covered the mandible at this site. Deformations of the ramus and jaw angle were of the same type as previously described (44, 45). However, no intraosseous lesions occurred during phases of creeping destruction in these cases.

Disorders of tooth emergence associated with neurofibromas. External causes of mandibular malformation (resorption, growth inhibition) were also suspected for those cases in which tooth eruption had been prevented or was severely restricted by surrounding oral neurofibroma. This characterisation applies to patients with facial PNF and the typical but variable deformation of the mandible (44). In these cases, there is a frequent continuum between the outer tumour-infiltrated mucosa and the soft-tissue covering of the retained teeth (87, 138). Therefore, these skeletal findings were not considered to be primarily intraosseous lesions (but with potential influence on tooth development and eruption).

(Periapical) cemento-osseous dysplasia. So-called cemento-osseous dysplasia (COD) is a fibro-osseous lesion of the jaws of unknown aetiology and pathogenesis (144). The initial phase of COD is a translucent lesion that is conspicuous in the X-ray image (139) and develops very frequently at the root apices of vital teeth (145). This finding can be confused with a cystic or granulomatous bone lesion. It has been reported that COD is very common in women with NF1 and exclusively related to females (57). This association of a dental finding could not be confirmed in further investigations (40, 58). In this study, COD is not considered taking into account the possible odontogenic pathogenesis. Our results for the frequency and characteristics of COD in this study group have been reported in detail elsewhere (58).

Ethics. All patients gave informed consent to the scientific study of X-ray images and the evaluation of medical findings. This study was approved by the local University Clinic authority for one of the authors (HTS) as a preliminary to meeting the requirements for a thesis in dentistry.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Data were anonymised prior to analysis, and the investigators studying the radiographs were blinded to the diagnosis, the identity of individuals, and the assignment of the single case to a diagnostic group. The investigations of anonymised data were performed in accordance with Hamburgisches Gesundheitsdienstgesetz (Hamburg Health Service Act).

Equipment. Several panoramic X-ray devices were used in this Department during the recruitment period (48). Panoramic views from other institutions were also evaluated. The technical principles and the imaging characteristics were identical for all panoramic views. However, this X-ray imaging technique is sensitive to deviations of the object from the focal trough (146). Imaging quality limitations should be taken into account for the assessment of bone structures on panoramic views. However, there were no technical limitations for the assessment of the target structures in the study group. The parameters for the evaluation of the radiographs have been described elsewhere in detail (44).

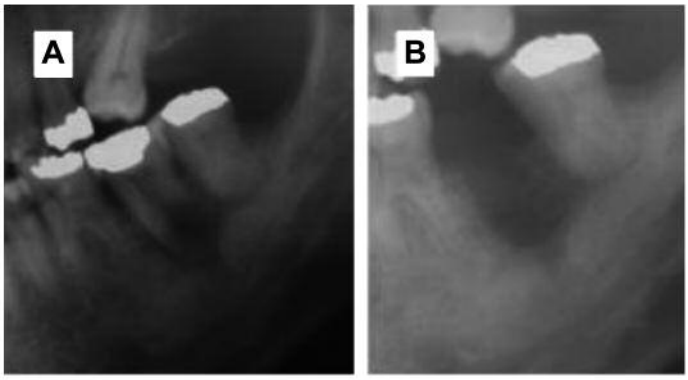

Figure 1. *Intraosseous neurofibroma in a 42-year old male with Neurofibromatosis type 1. A. Extensive bone destruction of alveolar bone in the region of mandibular left first molar. The roots of the tooth are partially dissolved (Panoramic view, cropped image). B. Bone defect after tooth extraction and excavation illustrating the extension of the lesion (Panoramic view, cropped image).*

Statistical analysis. All of the measurements were realised by both examiners. Data were registered in Excel 2015™ (Microsoft Corporation, Redmond, USA) and analysed in SPSS 24.0 (IBM, Armonk, USA). Fisher's exact test was used for statistical analysis. Statistical significance level was defined at $p<0.05$. Parametric data were expressed as mean and standard deviation (M [SD]).

Results

Three lesions located inside the mandible were found in the group of patients with NF1. All three lesions occurred in patients who were exclusively affected by cutaneous neurofibromas in the maxillofacial region. It was each a single entity in one patient. These or other non-odontogenic radiotranslucent lesions inside the mandibular body were not recorded in the control group.

Intraosseous neurofibroma. The 41-year-old male patient had presented to the outpatient Department for the treatment of multiple cutaneous neurofibromas. The patient was also examined orally. The mandibular left first molar showed noticeable mobility and was sensitive to percussion. There was no soft tissue tumour of the oral mucosa in this area. The radiograph showed a considerable destruction of the tooth roots and the alveolar process (Figure 1A). Upon extraction, the distal root was apically destroyed and the alveolus filled with a soft, solid tumour (Figure 1B). Wound healing proceeded without complications. The histological findings confirmed diagnosis of neurofibroma without malignant changes. The patient was lost to follow-up.

Simple bone cavity. A 24-year-old male patient was admitted to the outpatient clinic to assess oral health. On a panoramic view, a sharply limited osteolysis was seen in the area of the roots of the premolar and first molar of the left side of the mandible (Figure 2A). Teeth were firmly anchored in the bone and were sensitive to adequate stimuli. The diagnosis could not be made with certainty on the basis of these findings. The diagnosis of a simple bone cavity was considered but osseous neoplasm or cyst could not be excluded from the radiographic findings. Surgery revealed an empty cavity during exploration. Histological examination of the bone wall sample confirmed diagnosis of simple bone cavity. Bone healing after bleeding into the cavity was rapid (Figure 2B) and stable for many years (Figure 2C). In the meantime, the NF1 patient has developed a considerable number of internal tumours.

Stafne's bone cavity. A 34-year-old female patient with Stafne's bone cavity presented in the course of a general examination to assess her disease. The suspicion of Stafne's bone cavity was made on the basis of a routinely performed recent panoramic view (Figure 3B), which had recorded this incidental finding. The finding had unsettled the patient because she had initially suspected a neoplasm at this site causing a bone defect. On further questioning, the patient presented another panoramic view that had been taken 5 years before. The lesion was of identical size on this X-ray image (Figure 3A). At the time of the oral examination a whole-body MRI had already been performed in order to record the patient's internal tumour load. Here, the left submandibular gland could be identified on several cross-sectional images, from which a small, isointense area filled the cavity (Figure 3C and D). This finding was taken as confirmation of Stafne's bone cavity. No treatment of the condition was necessary.

Neither in the NF1 group nor in the control group did further radiological findings appear that were classified as non-odontogenic intraosseous lesions according to the definition criteria. There was no statistically significant difference between the findings of the NF1 group and the control group ($p=0.25$) and between both NF1 groups ($p=0.29$). The difference in the number of findings between the two groups also did not reach

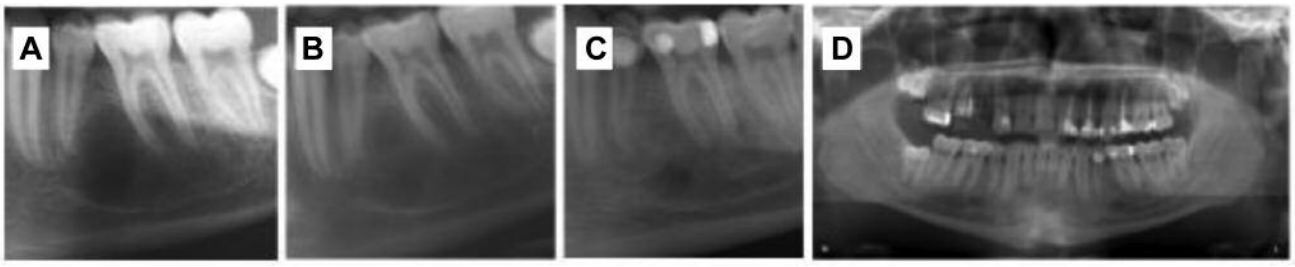

Figure 2. *A series of radiographs depicting the region of a simple bone cavity of a male patient with neurofibromatosis type 1. A-C: cropped radiographs of panoramic views, D: panoramic view. A. There is periradicular and interradicular osteolysis in the area of the first premolar and the first molar of the left side of the mandible in a 24-year old male. The second premolar is missing (on both sides, see Figure 1D). The outlines of the tooth roots included in the osteolysis are intact. On the radiograph, the upper border of the nerve canal is not defined and the mental foramen can only be seen in shadow. B. Five months after the opening of the cavity, ossification of this area is evident. C. Twelve years later, the area is completely ossified and indistinguishable from the surrounding bone. The mental foramen is skeletally defined. The upper border of the nerve canal is clearly visible in the former area of the cavity. D. As an incidental finding, there is periapical translucency of vital right lower second incisor in the 36-year old patient. The finding was not present on previous panoramic view 12 years ago and is compatible with the initial stage of periapical cemento-osseous dysplasia (57).*

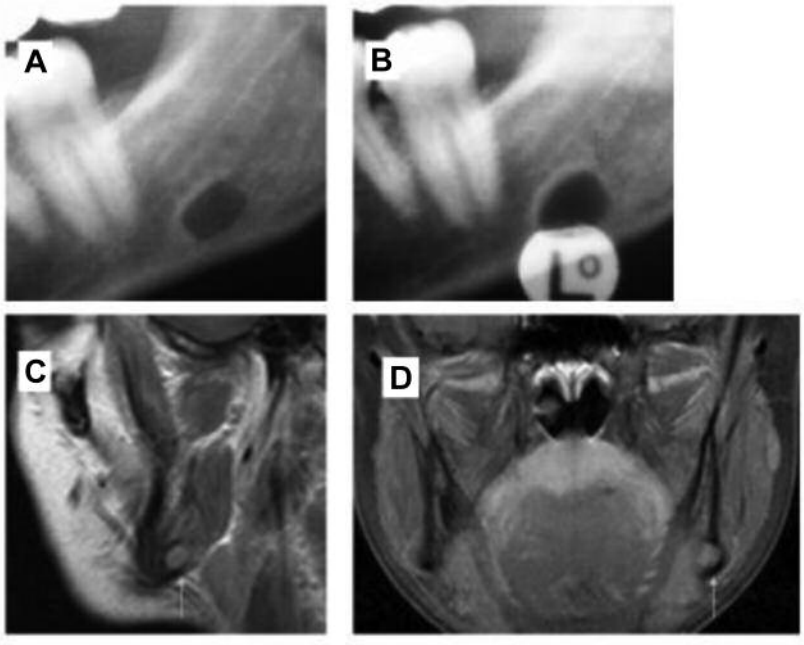

Figure 3. *Stafne's bone cavity in a female patient with neurofibromatosis type 1. A. Panoramic view at the age of 29 years (cropped image). B. Panoramic view (cropped image) at the age of 34 when the patient was examined. The oval translucent lesion is located below the nerve canal, completely circumscribed by bone, and has the largest diameter in the anterior-distal direction. The two X-ray images show no change in findings. C. Magnetic resonance image (sagittal plane) of the patient's head showing a hyperintense, well-defined lesion in the dorsal part of the left side of mandible (arrow). D. Coronal view of this region depicts the hyperintense intraosseous lesion (arrow) in continuity with adjacent salivary gland.*

any statistical significance when adding the patient with radiolucency due to giant cell granuloma of mandibular body in NF1 (64) to the number of translucent lesions of the mandibular body in the patient group (in total 4 cases) (p=0.13).

The characteristics of the patient findings are illustrated in Figures 1-3.

Discussion

The present study reveals that certain osseous lesions of mandibular body develop rarely in patients with NF1. Similar lesions were not registered in the control group. The individual findings of a simple bone cavity, a Stafne's bone

cavity, and an intraosseous neurofibroma reveal that such osseous lesions can occasionally develop in this patient population. There was no association between the lesions and a facial PNF.

Classification of intraosseous findings as non-odontogenic lesions. The distinction of simple bone cavity from odontogenic cyst and apical intraosseous neurofibroma from other osteolytic and root-dissolving lesions can only be made by exploration and histological examination (141, 147). This requirement was met by the surgical exploration of both lesions by the senior author. Stafne's bone cavity is characterised by loss and remodeling of the lingual corticalis of the lower jaw. The extent of the defect is variable. For larger defects, the lingual defect may be associated with a buccal protrusion of the corticalis. The cause of the loss of bone substance is unclear. So far, it has not been refuted that genuinely osteoclastic remodeling is at least a co-factor for the development of Stafne's bone cavity. Therefore, Stafne's bone cavity is considered an intraosseous skeletal lesion in this study. The requirement for surgical examination of the contents of the bone defect for a reliable (histological) diagnosis of Stafne's bone cavity also applies to the present case. However, the radiological pattern of the lesion is so characteristic that no diagnostic exploration or histological determination of the 'cyst' content is usually necessary for diagnosis (148, 149). Nevertheless, other lesions can mimic the radiographic signs of Stafne's bone cavity (150).

Frequency of neurofibroma in the oral cavity. Oral neurofibromas are rare findings. For example, in an institute-related analysis of oral and maxillofacial pathologies in patients with a maximum age of 16 years (n=4,406), neurofibromas were a rarity (20 cases, 0.45%). The authors did not explicitly describe the topography of the samples, but it can be assumed that the donor sites were soft tissue regions. The authors expressly pointed out that at the time of diagnosis, none of the patients had been diagnosed as neurofibromatosis patients (151).

The cutaneous manifestations of neurofibromatosis type 1 affect the entire body surface. However, previous studies have indicated a lower frequency of oral neurofibromas compared to skin lesions (139). Recent research has shown that the oral mucosa of NF1 patients develops large numbers of neurofibromas (18). Predilection sites of tumour development in oral soft tissues are registered (18, 32). The prevalence of intrabony neurofibromas of the mandible is unknown. The data in the literature can serve to describe the variable phenotype, but cannot be used to estimate the frequency of the diagnosis.

Intraosseous neurofibroma in NF1 and mandibular canal. The presented radiological results suggest that the internal structure of the jaw is rarely affected by neurofibroma in NF1. Nerve sheath tumours can develop within the mandibular nerve canal. This rare observation is more frequent in schwannomas than in neurofibromas (76). There was no intra-canalicular neurofibroma visible on radiographs of the present study group. The observation of enlarged mandibular nerve canal (45) in NF1 could be an anatomical adaptation to a neurofibroma (often symmetrically visible). However, there are no histological studies that prove this assumption. The finding of an enlarged mandibular canal suggests an anatomical adaptation rather than a lesion, because the boundary of the enlarged canal is preserved and the growth is proportional on panoramic views (45). In the case of an intraosseous neurofibroma, the radiological demarcation of the mandibular nerve canal can be resolved (85). However, the foramina of the canals can also be enlarged. It is believed that this change in shape is caused by an adjacent nerve sheath tumour (152). The suspicion is given especially with an asymmetric diameter of the foramen. However, reference values for the assessment of an enlarged nerve canal or mental foramen on panoramic views were not mentioned (45).

Intraosseous neurofibroma in NF1 and radiological studies. Ellis *et al*. presented 7 new cases and a literature review on intraosseous benign nerve sheath neoplasms (30). Intraosseous neurogenic tumours were predominantly diagnosed in the dorsal section of the mandible (both in patients and according to the reviewed literature). Ellis *et al*. (30) concluded that only 3 reports showed association of benign nerve sheath tumours with Recklinghausen's disease and none of their own was affected with neurofibromatosis. However, one of the cited papers (76) focused on schwannomas (neurilemmomas) and schwannoma-like parts (in Recklinghausen's disease) had also been diagnosed in the reported case of a neurofibroma. Schwannoma-like regions can occur in neurofibromas (153). However, the authors admitted that the intraosseous origin could not be proven for all tumours with certainty (76).

However, there is a very informative case report on multiple intraosseous neurofibromas in NF1 (82). This report meets current diagnostic criteria of NF1 (2, 3, 7, 8). Interestingly, the majority of histologically confirmed neurofibromas were localised close to but not in the mandibular canal. Destruction of tooth roots adjacent to neurofibroma was not reported for this case and the reproduced X-ray shows that the bone defects were clearly far from the roots or end just before the apices. In the well-documented report, the authors pointed out that the male patient showed multiple cutaneous neurofibromas and that both the father and several children had demonstrably visible stigmata of NF1. In the examined children, intrabony radiolucencies were ruled out. This single report supports the

assumption that the intraosseous development of neurofibromas in NF1 are among the rare manifestations of the disease and do not necessarily affect the nerve running in the mandibular canal.

In a radiological study, Shapiro *et al*. (32) identified intraosseous lesions in four out of 22 neurofibromatosis patients (18.2%). These lesions were all localised in the mandible. The authors gave no information on the diagnosis of the lesions. The representatively reproduced X-ray image (panoramic view, cropped image) shows osteolysis that resembles the intrabony neurofibroma of this study. However, no histological findings of these lesions were reported. The authors expressly pointed out that no cysts of marrow spaces have been registered by the mandible.

D'Ambrosio *et al*. (34) reported on jaw and skull changes identified on radiographs of 38 neurofibromatosis patients. The authors mentioned intraosseous lesions of the maxilla and mandible, illustrating this finding with a cropped image of a lateral cephalogram. The figure illustrated a roundish cyst-like translucency in the region of mandibular foramen. No further details were reported on intraosseous lesions in a study on neurofibromatosis that also reported about acoustic neuroma.

Polak *et al*. (120) presented a case of solitary intraosseous mandibular neurofibroma and a literature review on the subject of intrabony neurofibromas. The authors explicitly indicated that NF1 patients had no evidence of intrabony neurofibroma of the jaw. According to the renewed literature review, with focus on mandibular neurofibromas, only 3 out of 29 cases (10.3%) were affected by NF1 (120). The quoted sources were broadly in line with quotations presented by Ellis *et al*. (30).

Kaplan *et al*. (36) described radiological findings of the skull of four NF1 patients. In one case, the reproduced radiograph showed an intraosseous neurofibroma of the mandibular body that had been histologically verified.

Lee *et al*. (37) reported 3 cases of cyst-like translucencies in their radiologic study of 10 NF1 patients. This finding was not further specified in the publication.

Sigillo *et al*. (154) reported on diagnostic and surgical experiences with 6 children who had been diagnosed with NF1. The authors reported on two of the 6 children having intraosseous lesions. The report did not elaborate on the topography of these lesions. An X-ray image, presumably a cropped image of a panoramic view, probably shows an external osteolysis in the area of the left angle of the jaw.

Che *et al*. (25) reported four cases of intraosseous nerve sheath tumours and illustrated the expansive growth of these tumours in two patients with NF1. In one case, computed tomography allowed the visualisation of intraosseous osteolysis far beyond the mandible into the base of the skull. In these cases, the tumour was diagnosed histologically as a neurofibroma. A further, sporadic case with radiological evidence of root resorptions of adjacent teeth was a malignant peripheral nerve sheath tumour. The radiological aspect of this case was similar to the neurofibroma with root resorption in the case reported in the present study (Figure 1). In another case of an adult patient, the detection of an intrabony neurofibroma led to the diagnosis of previously unrecognised NF1.

Visnapuu *et al*. (40) reported in their study on 102 NF1 patients primarily the deformities of the jaw in the group of six patients who had developed a facial PNF. The osteolyses described were unilateral bone deformations that had occurred in the vast majority of cases on the side of the tumour. A case with a contralateral punch-shaped defect of the posterior margin of the ramus contralateral to the side of the PNF might indicate a small local PNF at this site. This special case was a marginal defect of bone resembling Stafne's bone cavity of mandibular ramus.

Langford and Ruppin (87) reported on the incidental findings of bilateral intraosseous neurofibroma in close association with retained teeth. On panoramic radiograph, crowns of retained lower wisdom teeth were depicted to be associated with well circumscribed radiolucencies extending into the mandibular ramus. Radiographic findings of this young female with known neurofibromatosis were compatible with inflamed and/or hyperplastic dental follicles and dentigerous cysts, but the authors considered also the possibility of neurofibromata. In this case, pericoronal osteolysis may had been in contact with the oral mucosa, so that in retrospect an exclusively intraosseous lesion cannot be assumed with certainty. Similar findings were also available in the report of Lorson *et al*. (80).

Earlier research suggests that the proportion of NF1-associated intraosseous neurofibromas is about one in ten patients (30, 120). The compilation of case reports of sporadic and NF1-associated intraosseous neurofibromas of jaws presented here (66-137, 154) does not claim to be complete, not least because the diagnostic criteria have changed over a long period of time, the topography of the tumour and adjacent bone is not described exactly enough to categorise the lesion properly, and even in current publications the certainty of the diagnosis (sporadic, inherited) cannot always be recorded from the documents. Nevertheless, the list allows a rough calculation of the frequency of sporadic compared to NF1-associated mandibular neurofibromas (without applying strict definition of intraosseous neoplasm). Although it shows that the sporadic neurofibroma of the jaw clearly outweighs this, the reported neurofibromatosis-associated cases are significant, over 10% (30). It could also be important for this change in the relationship between sporadic and NF1 identified cases that the public relations work of neurofibromatosis lay groups has generated increasing recognition of the disease (155).

Frequency of mandibular pseudocysts. Frequency data on these cysts are very variable. For example, the difficulty in obtaining simple bone cavity data on prevalence, incidence, or frequency is due to the fact that some authors attribute this entity to the entire number of jaw cysts, while others omit these lesions for definitional reasons (148). Consequently, some authors refrain from such statements concerning simple bone cavities (148). On the other hand, calculations are reported on the Stafne's bone cavity, although this entity is also to be expected among the pseudocysts (range= 0.10% to 3.84%) (148). Despite these limitations in reporting, recent data on non-odontogenic, cyst-like lesions continue to be highly variable. In recent studies, for example, both simple bone cavities and Stafne's bone cavities are omitted in reviews on odontogenic and non-odontogenic cysts, probably because they are pseudocysts (156). Simple bone cavity represented 0.2% of all oral pathological findings from a catamnestic analysis of single institutional group of 20,469 cases. The proportion of simple bone cavity in all jaw bone pathologies was 11.86% (157). On the other hand, no Stafne's bone cavities were found in the analysis of incidental findings on cone beam computed tomograms (CBCT) of 999 individuals who were screened for non-dental incidental findings of jaws (158). The authors included Stafne's bone cavity in the registry, but not simple bone cavity (158). In another current study, CBCT revealed a much higher prevalence of Stafne's bone cavity (0.59%, n=1,684) (159) than can be expected in the panoramic view (149). This value corresponds to the prevalence of Stafne's bone cavity in this study (0.56%) but is about ten times higher than the value obtained in a large collective of panoramic views (0.064%) (149) and in a comparative study also on panoramic views (159).

Cyst-like lesions on radiographs of patients with NF1. Little has been reported on cysts or cyst-like lesions of the jaws in NF1 patients. Particular attention has been paid to giant cell granulomas in NF1, not least because these lesions are similar to tumours (61), but a cyst-like appearance of bone lesions is well known on skull radiographs for this entity (65). Lee *et al*. (37) noted 3 cases with cyst-like lesions of the jaws out of 10 reported cases (30%) with ascertained NF1 and referred to a further 5 cases in the literature. However, the localisation and characteristics of the findings were not further specified in this report. At least one of the referred case-reports identified a cyst-like lesion as an intraosseous neurofibroma of mandibular body (66).

The cyst-like lesions of a previous study on radiographic findings on panoramic views of NF1 patients were osteolysis of the mandibular ramus: The lesions are believed to be lingually localised, which are tumour-associated depression related to mandibular foramen and extensive ipsilateral PNF (39).

Simple bone cavity (synonymous: simple bone cyst, solitary bone cyst, traumatic bone cyst, idiopathic bone cyst, extravasation cyst). The simple bone cavity was described by Lucas and Blum (160) as a separate entity. The diagnostic criteria of the simple bone cavity are (161): uni-cameral lesion without epithelial lining surrounded by bone; the lesion is located above the nerve canal; inter-radicular, orally-directed growth may result in a scalloping outline of the lesion around the roots of vital teeth (162); the cavity is either empty at opening or contains clear or slightly bloody fluid; the biology of the lesion is benign, but growth of the lesions is observed; and the diagnosis is confirmed by surgical exploration of the lesion with biopsies of the bone wall (162). The tissue finding demonstrated normal bone covered by a very thin fibrous soft tissue layer. The pathogenesis of cavity formation is unknown. The simple bone cavity was classified in the group of bone-associated lesions (aneurysmal bone cyst, ossifying fibroma, fibrous dysplasia, bony dysplasia, central granular granuloma, and cherubism). The occurrence of a simple bone cavity with syndromes has been reported only sporadically (163).

Simple bone cavity usually occurs in adolescents or young adults (164). The mandible is predominantly affected and especially the central and tooth-bearing sections. Men develop simple bone cavity more often than women. The cavity is most frequently incidental finding on routine radiographs of the jaw. The teeth remain vital, even with significant growth of the lesion. Neither displacement of the teeth nor fractures occurred despite occasionally extensive growth (141).

Although simple bone cavities are rare findings in relation to the total number of oral pathologies, the proportion of this entity in the group of non-odontogenic cysts, however, was relatively high: 28.3% (151). This information is valuable because it is the analysis of oral histological findings from patients under the age of 16, who were surveyed over a 30-year interval. The case presented here was at the time of diagnosis slightly older than the patients of the reference group (151) and at this age was also slightly above the age at which the vast majority of diagnoses are made (148). On plain radiograph, an intraosseous mandibular neurofibroma can map in exactly the same way as the simple bone cavity shown here (101).

To the best of our knowledge, this entity has not yet been described in NF1. The healing process in this patient did not differ from that of other patients with the same diagnosis of a bone defect without this genetic background. Therefore, the coincidence of a simple bone cavity with a tumour suppressor gene disease is presumed. It is likely that this cavitation inside the bone is a developmental disorder that does not underlie any genetic defect.

Stafne's bone cavity. Stafne's bone cavity is a notch of the mandibular lingual cortical bone around the angle of the jaw

(165). The structure was originally described as a radiological incidental finding (165), which had no pathological significance in most cases (166). The alternatively proposed term 'mandibular posterior-lingual bone depression' describes the main site of this bone disorder (167). The depression or 'defect' is typically monocortical, occurs between the molar region and the mandibular foramen, and lies below the mandibular canal. Exceptions to this definition, such as bicortical extension, superposition of translucency on the nerve canal or even beyond it, as well as similar skeletal defects in other regions of the mandible have been described repeatedly (for review: 149). The cause of the phenotype is unclear. Local pressure on the bones by neighbouring organs was postulated as an explanation, especially transmitted by salivary gland tissue or arteries (148, 168-170). However, convincing reports were also published that could not prove the presence of any of the tissues or organs in the cavities (148, 171). For some of the findings, some authors attributed the faulty surgical dissection of the region, which shifted the contents out of the cavity, creating the false impression of an empty cavity (148). However, this assessment cannot be invoked for all findings that contradict the unifying theory of bone reduction due to salivary gland pressure (171). No congenital Stafne's bone cavities have been observed so far. The occurrence of the entity is presumably rare (Prevalence: 0.08% (149) and 0.10% to 0.48% (169)). Anatomical studies suggested that the radiological representation of early stages of this structure is not possible in panoramic radiographs (149). Therefore, the earliest radiographic detection of the cavity is not equal to the time of origin. On the other hand, studies have shown, in individual cases, that the cavity can arise in the intact bone of adults, thus revealing a secondary event and not a congenital osseous malformation. The finding was almost always unilateral (149, 165). The preference for the development of Stafne's bone cavity in males has been widely confirmed (149).

In the present case, the cavity is in a typical position. The development of the cavity in a woman is very likely to be coincidental. However, this finding is in contrast to our own investigation results in a large study group in which only men were affected (149). The historical comparison of the frequency of Stafne's bone cavity in NF1 patients and a numerically much larger study of unselected patients (149) showed no statistically significant differences (p=0.12, Fisher's exact test). Of note is the MRI finding, as it can be shown that there is continuity between the signal-intense submandibular gland and the contrast-enhancing cavity. The homogeneously hyperintense, similar to fat signal-giving, intracavitary roundish structure in the area was equal to the image of Stafne's bone cavity on the plain radiograph. A connection of the structure with other compartments is not recognisable, so MRI supports the assumption of an isolated soft tissue process, which has developed into the bone at the base of the mandible. The combination of both imaging techniques makes the diagnosis of Stafne's bone cavity very likely, although without exploration a different process such a neurofibroma cannot be ruled out completely. Indeed, the differential diagnosis of Stafne's bone cavity includes both soft-tissue and hard-tissue lesions and tumours (150). As far as we know, Stafne's bone cavity has not yet been reported in NF1.

Clinical significance of the examination results. Although each of the three entities is a single finding in different individuals, there are different implications for the clinical assessment of each intra-osseous lesion of the mandible in NF1 patients: 1) This study confirms earlier assumptions on rarity of intraosseous mandibular neurofibroma in NF1 (30). The often extensive facial PNFs may cause severe bone deformities, but are not associated with intraosseous mandibular neurofibroma on panoramic views of the jaws. The literature review suggests that intraosseous mandibular neurofibroma in NF1 is likely to be more frequent than previously thought. However, the literature is usually not precise enough in describing the topography of the tumour and adjacent osseous lesion, neither on sporadic nor NF1-associated neurofibromas involving the jaws. Therefore, it frequently cannot be distinguished whether the reports are about a true intraosseous tumour or a neoplasm localised in a jaw cavity but in topographical relationship to an oral diffuse plexiform neurofibroma of the trigeminal nerve. The rare occurrence of intraosseous neurofibromas in NF1 should prompt careful examination of the histological diagnosis in such cases because there are several reports of MPNST in the oral and maxillofacial regions (19-24, 172). 2) Simple bone cavity develops in NF1. Current data on the frequency of this lesion cannot be relied upon for a statement on the prevalence of this entity. There are several investigators who interpret local and general bone changes in NF1 patients as a consequence of haploinsufficiency of bone (173-175). In the present case, the simple bone cavity developed in the typical location and was diagnosed only some years after the expected decade where most cases are diagnosed (148). It is probably a chance finding that is unrelated to the underlying disease. The harmless osseous alteration requires histological diagnosis, because the radiograph does not allow a clear definition of the entity. 3) Stafne's bone cavity is a harmless anomaly of the mandible, which also develops in NF1. In this disorder, the differential diagnosis of the lesion should be considered (101, 125) because other neoplasms may mimic the radiographic pattern.

The knowledge of these various benign bony pathologies may help tailor and adapt the patient's therapy to the individual's needs and avoid extensive resections (85).

Conclusion

The differential diagnosis of intrabony lesions of the mandible in patients with NF1 needs to be extended to

include the simple bone cavity and Stafne's bone cavity. These lesions are rare, as is the intraosseous development of a neurofibroma. In view of the rare occurrence of lesions and the significantly increased risk of the NF1 patients developing cancer, in particular STS (19, 176), intraosseous lesions should be carefully examined and histologically verified in certain cases.

Conflicts of Interest

The Authors report no conflicts of interest related to this study.

Author's Contributions

REF designed the study, acquired and interpreted the data, wrote and revised the manuscript. HTS contributed to the design of the study, acquired and interpreted the results, wrote and revised the manuscript. Both Authors have given final approval of the version to be submitted and any revised version.

References

1 Gutmann DH, Ferner RE, Listernick RH, Korf BR, Wolters PL and Johnson KJ: Neurofibromatosis type 1. Nat Rev Dis Primers *3*: 17004, 2017. PMID: 28230061. DOI: 10.1038/nrdp.2017.4

2 Ferner RE and Gutmann DH: Neurofibromatosis type 1 (NF1): Diagnosis and management. Handb Clin Neurol *115*: 939-955, 2013. PMID: 23931823, DOI: 10.1016/B978-0-444-52902-2.00053-9

3 Riccardi VM: Neurofibromatosis. Phenotype, natural history, and pathogenesis. 2nd edition. The Johns Hopkins University Press, Baltimore, pp. 1-8, 30-31, 66, 108-118, 224-250, 1992.

4 Recklinghausen FD: Über die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen. Hirschwald, Berlin, 1882.

5 Adrian C: Über Neurofibromatose und ihre Komplikationen. Beitr Klin Chir *31*: 1-98, 1901.

6 Elefteriou F, Kolanczyk M, Schindeler A, Viskochil DH, Hock JM, Schorry EK, Crawford AH, Friedman JM, Little D, Peltonen J, Carey JC, Feldman D, Yu X, Armstrong L, Birch P, Kendler DL, Mundlos S, Yang FC, Agiostratidou G, Hunter-Schaedle K and Stevenson DA: Skeletal abnormalities in neurofibromatosis type 1: approaches to therapeutic options. Am J Med Genet A *149A*: 2327-2338, 2009. PMID: 19764036. DOI: 10.1002/ajmg.a.33045

7 Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. Arch Neurol *45(5)*: 575-578, 1988. PMID: 3128965. DOI: 10.1001/archneur.1988.00520290115023

8 Gutmann DH, Aylsworth A, Carey JC, Korf B, Marks J, Pyeritz RE, Rubenstein A and Viskochil D: The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA *278(1)*: 51-57, 1997. PMID: 9207339. DOI: 10.1001/jama.1997.03550010065042

9 Burkitt Wright EM, Sach E, Sharif S, Quarrell O, Carroll T, Whitehouse RW, Upadhyaya M, Huson SM and Evans DG: Can the diagnosis of NF1 be excluded clinically? A lack of pigmentary findings in families with spinal neurofibromatosis demonstrates a limitation of clinical diagnosis. J Med Genet *50(9)*: 606-613, 2013. PMID: 23812910. DOI: 10.1136/jmedgenet-2013-101648

10 Fountain JW, Wallace MR, Bruce MA, Seizinger BR, Menon AG, Gusella JF, Michels VV, Schmidt MA, Dewald GW and Collins FS: Physical mapping of a translocation breakpoint in neurofibromatosis. Science *244(4908)*: 1085-1087, 1989. PMID: 2543076. DOI: 10.1126/science.2543076

11 Upadhyaya M: Neurofibromatosis type 1: diagnosis and recent advances. Expert Opin Med Diagn *4(4)*: 307-322, 2010. PMID: 23496147. DOI: 10.1517/17530059.2010.494660

12 Rasmussen SA, Yang Q and Friedman JM: Mortality in neurofibromatosis 1: An analysis using U.S. death certificates. Am J Hum Genet *68(5)*: 1110-1118, 2001. PMID: 11283797. DOI: 10.1086/320121

13 Scheithauer BW, Woodruff JM and Erlandson RA: Atlas of Tumor Pathology. Third Series. Fascicle 24. Tumors of the Peripheral Nervous System. Armed Forces Institute of Pathology, Washington, pp. 385-405, 1999.

14 Heine J: Über ungewöhnliche Missbildungen bei Neurofibromatose. Beitr Path Anat *78*: 122-159, 1927.

15 Cohen MM Jr: Perspectives on craniofacial asymmetry. VI. The hamartoses. Int J Oral Maxillofac Surg *24(3)*: 195-200, 1995. PMID: 7594750.

16 Friedrich RE: Maxillofaziale und Orale Neurofibromatose Typ 1. Shaker, Aachen, p. 117, 2010.

17 Friedrich RE, Schmelzle R, Giese M and Mautner VF: Zur Häufigkeit intraoraler Raumforderungen bei Neurofibromatose Typ 1. Dtsch Z Mund Kiefer GesichtsChir *18*: 207-209, 1994.

18 Jouhilahti EM, Visnapuu V, Soukka T, Aho H, Peltonen S, Happonen RP and Peltonen J: Oral soft tissue alterations in patients with neurofibromatosis. Clin Oral Investig *16(2)*: 551-558, 2012. PMID: 21301902. DOI: 10.1007/s00784-011-0519-x

19 Ducatman BS, Scheithauer BW and Dahlin DC: Malignant bone tumors associated with neurofibromatosis. Mayo Clin Proc *58(9)*: 578-582, 1983. PMID: 6310276.

20 Tiede D: Neurofibroma – neurofibromatosis – neurofibrosarcoma. Stomatol DDR *27(4)*: 242-50, 1977.

21 Neville BW, Hann J, Narang R and Garen P: Oral neurofibrosarcoma associated with neurofibromatosis type I. Oral Surg Oral Med Oral Pathol *72(4)*: 456-461, 1991. PMID: 1923446.

22 Pape K: Tumors of the peripheral nervous system in the region of jaw and face. Dtsch Stomatol *41(4)*: 136-139, 1991.

23 de Oliveira MG, Pozatti Moure S, Sérgio Batista P, Moraes Chaves AC, Rados PV and Sant'Ana Filho M: NF1 diagnosis criteria and associated sarcomatous tumor review of the literature and case report. Oral Maxillofac Surg *12(4)*: 231-235, 2008. PMID: 18815819. DOI: 10.1007/s10006-008-0137-1

24 Krause HR, Hemmer J and Kraft K: The behaviour of neurogenic tumours of the maxillofacial region. J Craniomaxillofac Surg *21(6)*: 258-261, 1993. PMID: 8227375.

25 Che Z, Nam W, Park WS, Kim HJ, Cha IH, Kim HS, Yook JI, Kim J and Lee SH: Intraosseous nerve sheath tumors in the jaws. Yonsei Med J *47(2)*: 264-270, 2006. PMID: 16642559. DOI: 10.3349/ymj.2006.47.2.264

26 Mautner VF, Hartmann M, Kluwe L, Friedrich RE and Fünsterer C: MRI growth patterns of plexiform neurofibromas in patients with neurofibromatosis type 1. Neuroradiology *48(3)*: 160-165, 2006. PMID: 16432718. DOI: 10.1007/s00234-005-0033-4

27 Avery RA, Katowitz JA, Fisher MJ, Heidary G, Dombi E, Packer RJ and Widemann BC/ OPPN Working Group: Orbital/periorbital plexiform neurofibromas in children with neurofibromatosis type 1: multidisciplinary recommendations for care. Ophthalmol *124(1)*: 123-132, 2017. PMID: 27817916. DOI: 10.1016/j.ophtha.2016.09.020

28 Wolkenstein P, Durand-Zaleski I, Moreno JC, Zeller J, Hemery F and Revuz J: Cost evaluation of the medical management of neurofibromatosis 1: a prospective study on 201 patients. Br J Dermatol *142(6)*: 1166-1170, 2000. PMID: 10848741.

29 Holt JF and Wright EM: The radiologic features of neurofibromatosis. Radiology *51(5)*: 647-664, 1948. PMID: 18891292. DOI: 10.1148/51.5.647

30 Ellis GL, Abrams AM and Melrose RJ: Intraosseous benign neural sheath neoplasms of the jaws. Report of seven new cases and review of the literature. Oral Surg Oral Med Oral Pathol *44(5)*: 731-743, 1977. PMID: 270070.

31 Gupta SK, Nema HV, Bhatia PL, Sasibabu K and Kesharwani R: The radiological features of craniofacial neurofibromatosis. Clin Radiol *30(5)*: 553-557, 1979. PMID: 111891.

32 Shapiro SD, Abramovitch K, Van Dis ML, Skoczylas LJ, Langlais RP, Jorgenson RJ, Young RS and Riccardi VM: Neurofibromatosis: oral and radiographic manifestations. Oral Surg Oral Med Oral Pathol *58(4)*: 493-498, 1984. PMID: 6436765.

33 Maceri DR and Saxon KG: Neurofibromatosis of the head and neck. Head Neck Surg *6(4)*: 842-850, 1984. PMID: 6423572.

34 D'Ambrosio JA, Langlais RP and Young RS: Jaw and skull changes in neurofibromatosis. Oral Surg Oral Med Oral Pathol *66(3)*: 391-396, 1988. PMID: 3140162.

35 Sailer HF, Künzler A and Makek MS: Neurofibro-hemangiomatous soft tissue changes with pathognomonic mandibular deformity. Fortschr Kiefer Gesichtschir *33*: 84-86, 1988. PMID: 3044956.

36 Kaplan I, Calderon S and Kaffe I: Radiological findings in jaws and skull of neurofibromatosis type 1 patients. Dentomaxillofac Radiol *23(4)*: 216-220, 1994. PMID: 7835527.

37 Lee L, Yan YH and Pharoah MJ: Radiographic features of the mandible in neurofibromatosis: a report of 10 cases and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod *81(3)*: 361-367, 1996. PMID: 8653472. DOI: 10.1016/S1079-2104(96)80338-6

38 Hall RK: Neurofibromatosis type 1 (NF 1) - cranio-maxillofacial and oral features. Ann R Australas Coll Dent Surg *16*: 139-140, 2002. PMID: 14507160.

39 Friedrich RE, Giese M, Schmelzle R, Mautner VF and Scheuer HA: Jaw malformations plus displacement and numerical aberrations of teeth in neurofibromatosis type 1: a descriptive analysis of 48 patients based on panoramic radiographs and oral findings. J Craniomaxillofac Surg *31(1)*: 1-9, 2003. PMID: 12553919. DOI: 10.1016/S1010-5182(02)00160-9

40 Visnapuu V, Peltonen S, Tammisalo T, Peltonen J and Happonen RP: Radiographic findings in the jaws of patients with neurofibromatosis 1. J Oral Maxillofac Surg *70(6)*: 1351-1357, 2012. PMID: 21856061. DOI: 10.1016/j.joms.2011.06.204

41 Heervä E, Peltonen S, Pirttiniemi P, Happonen RP, Visnapuu V and Peltonen J: Short mandible, maxilla and cranial base are common in patients with neurofibromatosis 1. Eur J Oral Sci *119(2)*: 121-127, 2011. PMID: 21410551. DOI: 10.1111/j.1600-0722.2011.00811.x

42 Cung W, Freedman LA, Khan NE, Romberg E, Gardner PJ, Bassim CW, Baldwin AM, Widemann BC and Stewart DR: Cephalometry in adults and children with neurofibromatosis type 1: Implications for the pathogenesis of sphenoid wing dysplasia and the "NF1 facies". Eur J Med Genet *58(11)*: 584-590, 2015. PMID: 26360873. DOI: 10.1016/j.ejmg. 2015.09.001

43 Friedrich RE, Lehmann JM, Rother J, Christ G, Zu Eulenburg C, Scheuer HT and Scheuer HA: A lateral cephalometry study of patients with neurofibromatosis type 1. J Craniomaxillofac Surg *45(6)*: 809-820, 2017. PMID: 28365079. DOI: 10.1016/j.jcms.2017.02.011

44 Friedrich RE and Reul A: A combination of skeletal deformations of the dorsal mandible and temporomandibular region detected in orthopantomograms of patients with neurofibromatosis type 1 indicates an associated ipsilateral plexiform neurofibroma. J Craniomaxillofac Surg *46(7)*: 1091-1104, 2018. PMID: 29764701. DOI: 10.1016/j.jcms.2018.04.018

45 Visnapuu V, Peltonen S, Alivuotila L, Happonen RP and Peltonen J: Craniofacial and oral alterations in patients with Neurofibromatosis 1. Orphanet J Rare Dis *13(1)*: 131, 2018. PMID: 30092804. DOI: 10.1186/s13023-018-0881-8

46 Lammert M, Friedrich RE, Friedman JM, Mautner VF and Tucker T: Early primary tooth eruption in neurofibromatosis 1 individuals. Eur J Oral Sci *115(5)*: 425-426, 2007. PMID: 17850432. DOI: 10.1111/j.1600-0722.2007.00474.x

47 Friedrich RE, Giese M, Stelljes C, Froeder C and Scheuer HA: Size of tooth crowns and position of teeth concerning the extension of facial plexiform neurofibroma in patients with neurofibromatosis type 1. Anticancer Res *32*: 2207-2214, 2012. PMID: 22593511.

48 Friedrich RE and Reul A: Supernumerary molars and wisdom tooth shape alterations in patients with neurofibromatosis type 1. J Oral Maxillofac Res *8(4)*: e5, 2017. PMID: 29435207. DOI: 10.5037/jomr.2017.8405

49 Kobayashi R, Matsune K and Ohashi H: Fused teeth, macrodontia and increased caries are characteristic features of neurofibromatosis type 1 patients with NF1 gene microdeletion. J Pediatr Genet *1(1)*: 25-31, 2012. PMID: 27625798. DOI: 10.3233/PGE-2012-006

50 Arnaudow M: Neurofibromatose und Zahnersatz. Zahnärztliche Praxis (München) *14*: 49-50, 1963.

51 Ey-Chmielewska H, Sobolewska E and Fraczak B: Description of prosthetic treatment in case of neurofibromatosis in the course of Recklinghausen disease. Case course. Ann Acad Med Stetin *53(2)*: 83-86, 2007. PMID: 18557381.

52 Tucker T, Birch P, Savoy DM and Friedman JM: Increased dental caries in people with neurofibromatosis 1. Clin Genet *72(6)*: 524-527, 2007. PMID: 18001351. DOI: 10.1111/j.1399-0004.2007.00886.x

53 Tsang ES, Birch P, Friedman JM, Johnston D, Tucker T and Armstrong L: Prevalence of dental caries in children with neurofibromatosis 1. Clin Oral Investig *14(4)*: 479-480, 2010. PMID: 20049496. DOI: 10.1007/s00784-009-0361-6

54 Bardellini E, Amadori F, Flocchini P, Conti G, Piana G and Majorana A: Oral findings in 50 children with neurofibromatosis type 1. A case control study. Eur J Paediatr Dent *12(4)*: 256-260, 2011. PMID: 22185252.

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

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

57 Visnapuu V, Peltonen S, Ellilä T, Kerosuo E, Väänänen K, Happonen RP and Peltonen J: Periapical cemental dysplasia is common in women with NF1. Eur J Med Genet *50(4)*: 274-280, 2007. PMID: 17532280. DOI: 10.1016/j.ejmg.2007.04.001

58 Friedrich RE and Reul A: Periapical cemento-osseous dysplasia is rarely diagnosed on orthopantomograms of patients with neurofibromatosis type 1 and is not a gender-specific feature of the disease. Anticancer Res *38(4)*: 2277-2284, 2018. PMID: 29599350. DOI: 10.21873/anticanres.12472

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

60 van Damme PA and Mooren RE: Differentiation of multiple giant cell lesions, Noonan-like syndrome, and (occult) hyperparathyroidism. Case report and review of the literature. Int J Oral Maxillofac Surg *23(1)*: 32-36, 1994. PMID: 8163857.

61 Ruggieri M, Pavone V, Polizzi A, Albanese S, Magro G, Merino M and Duray PH: Unusual form of recurrent giant cell granuloma of the mandible and lower extremities in a patient with neurofibromatosis type 1. Oral Surg Oral Med Oral Pathol Oral Radiol Endod *87(1)*: 67-72, 1999. PMID: 9927083. DOI: 10.1016/S1079-2104(99)70297-0

62 De Lange J and Van den Akker HP: Clinical and radiological features of central giant-cell lesions of the jaw. Oral Surg Oral Med Oral Pathol Oral Radiol Endod *99(4)*: 464-470, 2005. PMID: 15772595. DOI: 10.1016/j.tripleo.2004.11.015

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

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

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

66 Uhlmann E and Grossman A: von Recklinghausen's neurofibromatosis with bone manifestations. Ann Intern Med *14*: 225-241, 1940.

67 Rushton MA: Neurofibroma affecting the jaws. Am J Orthodont Oral Surg *30*: 790-792, 1944.

68 Jacobs MH: Oral manifestation in Von Recklinghausen's disease (neurofibromatosis); with a case report. Am J Orthodont Oral Surg *32*: 28-33, 1946. PMID: 21011778.

69 Ullik R: Recklinghausen's neurofibromatosis of the maxillary region. Osterr Z Stomatol *47(10)*: 435-440, 1950. PMID: 14785902.

70 Toto PD: Neurofibromatosis and lipogranuloma of the mouth. Oral Surg Oral Med Oral Pathol *7(4)*: 423-426, 1954. PMID: 13154905.

71 Winters SE, Husser HF, Simard EE and Shebl JJ: Neurofibromatosis (von Recklinghausen's disease) with involvement of the mandible. Report of a case. Oral Surg Oral Med Oral Pathol *13*: 76-79, 1960. PMID: 13845344.

72 Baden E and Fischer RJ: Multiple neurofibromatosis and neurofibroma of the palate. Report of a case. Oral Surg Oral Med Oral Pathol *16*: 1356-1364, 1963. PMID: 14082311.

73 O'Driscoll PM: The oral manifestations of multiple neurofibromatosis. Br J Oral Surg *3(1)*: 22-31, 1965. PMID: 4958015.

74 Freeman MJ and Standish SM: Facial and oral manifestations of familial disseminated neurofibromatosis. Report of a case. Oral Surg Oral Med Oral Pathol *19*: 52-59, 1965. PMID: 14233399.

75 Mugnier A, Laufer J, Psaume J and Delarue F: A case of neurofibromatosis. Rev Stomatol Chir Maxillofac *68(3)*: 244-251, 1967. PMID: 4964638.

76 Fawcett KJ and Dahlin DC: Neurilemmoma of bone. Am J Clin Pathol *47(6)*: 759-766, 1967. PMID: 602507777.

77 Rittersma J, ten Kate LP and Westerink P: Neurofibromatosis with mandibular deformities. Oral Surg Oral Med Oral Pathol *33(5)*: 718-727, 1972. PMID: 4622799.

78 Baumann M and Kundert M: A case of multiple jaw lesions in generalized neurofibromatosis Recklinghausen. SSO Schweiz Monatsschr Zahnheilkd *83(11)*: 1280-1285, 1973. PMID: 4202172.

79 James PL and Treggiden R: Multiple neurofibromatosis associated with facial asymmetry. J Oral Surg *33(6)*: 439-442, 1975. PMID: 805219.

80 Lorson EL, DeLong PE, Osbon DB and Dolan KD: Neurofibromatosis with central neurofibroma of the mandible: review of the literature and report of case. J Oral Surg *35(9)*: 733-738, 1977. PMID: 407340.

81 Westphal D and Koblin I: Dental and jaw findings in neurofibromatosis in the maxillofacial region. Dtsch Zahnarztl Z *32(5)*: 418-420, 1977. PMID: 405193.

82 Vincent SD and Williams TP: Mandibular abnormalities in neurofibromatosis. Case report and literature review. Oral Surg Oral Med Oral Pathol *55(3)*: 253-258, 1983. PMID: 6403900.

83 Epstein JB, Schubert MM and Hatcher DC: Multiple neurofibromatosis. Report of a case. Oral Surg Oral Med Oral Pathol *56(5)*: 560-562, 1983. PMID: 6417581.

84 Pedersen S and Holst E: A case of neurofibromatosis with oral involvement. Tandlaegebladet *87(1)*: 23-26, 1983. PMID: 6403999.

85 Arendt DM, Schaberg SJ and Meadows JT: Multiple radiolucent areas of the jaw. J Am Dent Assoc *115(4)*: 597-599, 1987. PMID: 3116063.

86 Tsiklakis K and Nikopoulou-Karayianni A: Multiple neurofibromatosis associated with mandibular growth and facial asymmetry. Ann Dent *49(1)*: 14-17, 1990. PMID: 2111974.

87 Langford RJ and Rippin JW: Bilateral intra-osseous neurofibromata of the mandible. Br J Oral Maxillofac Surg *28(5)*: 344-346, 1990. PMID: 2123398.

88 Geist JR, Gander DL and Stefanac SJ: Oral manifestations of neurofibromatosis types I and II. Oral Surg Oral Med Oral Pathol *73(3)*: 376-382, 1992. PMID: 1545973.

89 Holtzman L: Radiographic manifestation and treatment considerations in a case of multiple neurofibromatosis. J Endod *24(6)*: 442-443, 1998. PMID: 9693592.

90 Terezhalmy GT, Riley CK and Moore WS: Clinical images in oral medicine and maxillofacial radiology. Neurofibromatosis. Quintessence Int *32(2)*: 174-175, 2001. PMID: 12066679.

91 Cunha KS, Rozza-de-Menezes RE, Andrade RM, Almeida L, Janini M and Geller M: Oral manifestations of neurofibromatosis type 1 in children with facial plexiform neurofibroma: report of three cases. J Clin Pediatr Dent *39(2)*: 168-171, 2015. PMID: 25823487.

92 Cunha KS, Barboza EP, Dias EP and Oliveira FM: Neurofibromatosis type I with periodontal manifestation. A case report and literature review. Br Dent J *196(8)*: 457-460, 2004. PMID: 15105854. DOI: 10.1038/sj.bdj.4811175

93 Hisatomi M, Asaumi J, Konouchi H, Yanagi Y and Kishi K: Bone deformity showing a deep coronoid notch of the mandible in a patient with neurofibromatosis type 1. Dentomaxillofac Radiol *34(6)*: 380-383, 2005. PMID: 16227483.

94 Rawal YB, Rosebush MS, Rawal SY and Anderson KM: Mandibular abnormalities in a patient with neurofibromatosis type 1. J Tenn Dent Assoc *92(1)*: 29-31, 2012. PMID: 22870550.

95 Asgary S and Aminzadeh N: Unilateral gingival enlargement in patient with neurofibromatosis type I. N Y State Dent J *78(6)*: 50-53, 2012. PMID: 23488326.

96 Kopczyński P, Flieger R and Matthews-Brzozowska T: Changes in the masticatory organ in patients with Recklinghausen's disease - a case report. Contemp Oncol (Pozn) *16(5)*: 453-455, 2012. PMID: 23788929. DOI: 10.5114/wo.2012.31780

97 Rath R, Kaur S, Baig SA, Pati P and Sahoo S: Multifocal head and neck neurofibromas with osseous abnormalities and muscular hypoplasia in a child with neurofibromatosis: Type I. Case Rep Radiol *2016*: 3980270, 2016. PMID: 27382495. DOI: 10.1155/2016/3980270

98 Zilkens K: Über ein Neurinom am Unterkiefer. Ztschr Stomatol *35*: 461-467, 1937.

99 Goldman HM: Case reports from the files of the registry of dental and oral pathology: neurofibroma. Am J Orthodont *30*: 289-95, 1944.

100 Thornell WC and Germain WM: Solitary neurofibroma of the submaxillary region. Arch Otolaryngol *47(3)*: 333-335, 1948. PMID: 18870700.

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

102 Funcia Cornell C: Neurofibroma of the mandible. Bol Liga Contra Cancer Havana *29(3)*: 99-109, 1954. PMID: 13189954.

103 Bruce KW: Solitary neurofibroma (neurilemmoma, schwannoma) of the oral cavity. Oral Surg Oral Med Oral Pathol *7*: 1150-1159, 1954. PMID: 13214714.

104 Cornell CF and Vargas HA: Intraosseous neurofibroma of the mandible. Oral Surg Oral Med Oral Pathol *8(1)*: 34-39, 1955. PMID: 13224184.

105 Gartner F and Preis H: Neurofibromatosis and its isolated appearance in the maxillary and facial region. Zentralbl Allg Pathol *96(5-6)*: 296-300, 1957. PMID: 13457006.

106 Caldwell JB, Hughes KW and Cox RS Jr.: Neurofibroma of the mandible: report of case. J Oral Surg Anesth Hosp Dent Serv *19*: 166-167, 1961. PMID: 13689926.

107 Villa VG, Laico JE and Banez LO: Central neurofibroma in the mandible associated with occasional spontaneous hemorrhage. Report of a case. Oral Surg Oral Med Oral Pathol *15*: 836-842, 1962. PMID: 13925981.

108 Gutman D, Griffel B, Munk J and Shohat S: Solitary neurofibroma of the mandible. Oral Surg Oral Med Oral Pathol *17*: 1-9, 1964. PMID: 14113279.

109 Giamminola E, Fabri N and Merlini C: Neurofibroma of the mandible. Riv Ital Stomatol *20*: 318-333, 1965. PMID: 14315405.

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

111 Andersen AG: Et tilfaelde af solitaert, intraossöst neurofibroma I underkaeben. [A case of mandibular solitary, intraosseous neurofibroma]. Tandlaegebladet *75(5)*: 397-403, 1971.

112 Kuffer R and Brochériou C: Hemifacial myelinic neuromatosis. Rev Stomatol Chir Maxillofac *72(3)*: 403-414, 1971. PMID: 4998947.

113 Cundy RL and Matukas VJ: Solitary intraosseous neurofibroma of the mandible. Arch Otolaryngol *96(1)*: 81-83, 1972. PMID: 5032061.

114 Schneider HR: Various rare benign tumors in the oral cavity and jaw region. SSO Schweiz Monatsschr Zahnheilkd *83(11)*: 1247-1252, 1973. PMID: 4357048.

115 Singer CF Jr., Gienger GL and Kullbom TL: Solitary intraosseous neurofibroma involving the mandibular canal: report of case. J Oral Surg *31(2)*: 127-129, 1973. PMID: 4509702.

116 Larsson A, Praetorius F and Hjörting-Hansen E: Intraosseous neurofibroma of the jaws. Int J Oral Surg *7(5)*: 494-499, 1978. PMID: 102607.

117 Badger GR: Solitary neurofibromatosis in the maxilla: report of oral findings. J Am Dent Assoc *100(2)*: 213-314, 1980. PMID: 6928152.

118 Fitz CR and Noyek AM: Contemporary radiology in congenital craniofacial disorders. Otolaryngol Clin North Am *14(1)*: 65-81, 1981. PMID: 6789284.

119 Skouteris CA and Sotereanos GC: Solitary neurofibroma of the maxilla: Report of a case. J Oral Maxillofac Surg *46*: 701-705, 1988. PMID: 3294358. DOI: 10.1016/0278-2391(88)90117-6

120 Polak M, Polak G, Brocheriou C and Vigneul J: Solitary neurofibroma of the mandible: case report and review of the literature. J Oral Maxillofac Surg *47(1)*: 65-68, 1989. PMID: 2642961. DOI: 10.1016/0278-2391(89)90127-4

121 Pollack RP: Neurofibroma of the palatal mucosa. A case report. J Periodontol *61(7)*: 456-458, 1990. Erratum in: J Periodontol *61(10)*: NP, 1990. PMID: 2388143. DOI: 10.1902/ jop.1990. 61.7.456

122 Mori H, Kakuta S, Yamaguchi A and Nagumo M: Solitary intraosseous neurofibroma of the maxilla: Report of a case. J Oral Maxillofac Surg 51: 688-690, 1993. PMID: 8492209. DOI: 10.1016/S0278-2391(10)80271-X

123 Ueda M, Suzuki H and Kaneda T: Solitary intraosseous neurofibroma of the mandible: Report of a case. Nagoya J Med Sci *55(1-4)*: 97-101, 1993. PMID: 8247113.

124 Poupard RJ and Mintz S: Solitary intrabony neurofibroma of the maxilla. J Oral Maxillofac Surg *55*: 768-772, 1997. PMID: 9216514. DOI: 10.1016/S0278-2391(97)90596-6

125 Apostolidis C, Anterriotis D, Rapidis AD and Angelopoulos AP: Solitary intraosseous neurofibroma of the inferior alveolar nerve: Report of a case. J Oral Maxillofac Surg *59*: 232-235, 2001. PMID: 11213999. DOI: 10.1053/joms.2001.20508

126 Sinha R, Paul R, Sen I and Sikdar B: A solitary huge neurofibroma of the soft palate. J Laryngol Otol *116(8)*: 637-638, 2002. PMID: 12389695. DOI: 10.1258/00222150260 171669

127 Vivek N, Manikandhan R, James PC and Rajeev R: Solitary intraosseous neurofibroma of mandible. Indian J Dent Res *17(3)*: 135-138, 2006. PMID: 17176831.

128 Sharma P, Narwal A, Rana AS and Kumar S: Intraosseous neurofibroma of maxilla in a child. J Indian Soc Pedod Prev Dent *27*: 62-64, 2009. PMID: 19414978. DOI: 10.4103/0970-4388.50822

129 Tao Q, Wang Y and Zheng C: Neurofibroma in the left mandible: a case report. Kaohsiung J Med Sci *26(4):* 217-221, 2010. PMID: 20434104. DOI: 10.1016/S1607-551X(10)70032-2

130 Deichler J, Martínez R, Niklander S, Seguel H, Marshall M and Esguep A: Solitary intraosseous neurofibroma of the mandible. Apropos of a case. Med Oral Patol Oral Cir Bucal *16*: e704-e707, 2011. PMID: 21217615. DOI:10.4317/medoral.16853

131 Patel S, Pathak J, Dekate K and Mohanty N: Malignant peripheral nerve sheath tumour (MPNST) of mandible: solving the perplexity. BMJ Case Rep 2015 Mar 11, 2015. PMID: 25762575. DOI: 10.1136/bcr-2014-207790

132 Iqbal A, Tamgadge S, Tamgadge A and Chande M: Intraosseous neurofibroma in a 13-year-old male patient: A case report with review of literature. J Cancer Res Ther *14(3)*: 712-715, 2018. PMID: 29893349. DOI: 10.4103/0973-1482.176173

133 Depprich R, Singh DD, Reinecke P, Kübler NR and Handschel J: Solitary submucous neurofibroma of the mandible: Review of the literature and report of a rare case. Head Face Med *5*: 24, 2009. PMID: 19912641. DOI: 10.1186/1746-160X-5-24

134 Zwane NP, Noffke CE and Raubenheimer EJ: Solitary oral plexiform neurofibroma: Review of literature and report of a case. Oral Oncol *47(6)*: 449-451, 2011. PMID: 21571578. DOI: 10.1016/j.oraloncology.2011.04.005

135 Dalili Z and Adham G: Intraosseous neurofibroma and concurrent involvement of the mandible, maxilla and orbit: report of a case. Iran J Radiol *9(1)*: 45-49, 2012. PMID: 23329961. DOI: 10.5812/iranjradiol.6684

136 da Rosa MR, Ribeiro AL, de Menezes SA, Pinheiro JJ and Alves-Junior SM: Solitary giant neurofibroma of the mental nerve: a trauma-related lesion? J Craniofac Surg *24(3)*: e247-e251, 2013. PMID: 23714979. DOI: 10.1097/SCS.0b013e3182869f03

137 Pukara MM, Pukara SM and Boroleb BS: Huge solitary neurofibroma of the oral cavity – A case report. J Oral Maxillofac Surg Med Pathol *26(1)*: 96-97, 2014. DOI: 10.1016/j.ajoms.2012.08.004

138 Batsakis JG: Tumors of the Head and Neck, 2nd edition, Williams and Wilkins, Baltimore/London, pp. 325-326, 1979.

139 Shafer WG, Hine MK and Levy BM: A textbook of oral pathology. Saunders, Philadelphia, pp. 206-208, 1983.

140 Neville DW, Damm DD, Allen CM and Bouquot JE: Oral and Maxillofacial Pathology. 3rd ed., W.B. Saunders, Philadelphia, pp. 528-529, 2009.

141 Jundt G: Kiefertumoren. *In*: Freyschmidt J, Ostertag H, Jundt G (eds) "Knochentumoren". Springer, Berlin Heidelberg, pp. 945-1055, 2010.

142 Heard G: Nerve sheath tumours and von Recklinghausen's disease of the nervous system. Ann R Coll Surg Engl *31*: 229-248, 1962. PMID: 13963661.

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

144 Friedrich RE and Scheuer HA: Unilateral creeping destruction of deformed mandibular ramus and angle associated with extensive facial plexiform neurofibroma in neurofibromatosis type 1: A case report with analysis of the literature for diagnosing osteolytic events of the mandible in tumor-suppressor gene syndrome. Anticancer Res *38(7)*: 4083-4091, 2018. PMID: 29970534. DOI: 10.21873/anticanres.12698.

145 MacDonald D: Oral and maxillofacial radiology: A diagnostic approach. Wiley-Blackwell, Hoboken, 2011.

146 Riecke B, Friedrich RE, Schulze D, Loos C, Blessmann M, Heiland M and Wikner J: Impact of malpositioning on panoramic radiography in implant dentistry. Clin Oral Investig *19*: 781-90, 2015. PMID: 25074723. DOI: 10.1007/s00784-014-1295-1

147 Suga K, Ogane S, Muramatsu K, Ohata H, Uchiyama T, Takano N, Shibahara T, Eguchi J, Murakami S and Matsuzaka K: Intraosseous schwannoma originating in inferior alveolar nerve: a case report. Bull Tokyo Dent Coll *54(1)*: 19-25, 2013. PMID: 23614949. DOI: 10.2209/tdcpublication.54.19

148 Reichart PA and Philipsen HP: Odontogenic Tumors and Allied Lesions. Quintessence, London, pp. 343-349 (Simple Bone Cavity (Simple Bone Cyst)), pp. 351-358 (Lingual Mandibular Bone Depression (Stafne's Cavity)), 2004.

149 Assaf AT, Solaty M, Zrnc TA, Fuhrmann AW, Scheuer H, Heiland M and Friedrich RE: Prevalence of Stafne's bone cavity – retrospective analysis of 14,005 panoramic views. In Vivo *28(6)*: 1159-1164, 2014. PMID: 25398816.

150 Parvizi F and Rout PG: An ossifying fibroma presenting as Stafne's idiopathic bone cavity. Dentomaxillofac Radiol 26(6): 361-363, 1997. PMID: 9482014. DOI: 10.1038/sj.dmfr.4600294

151 Jones AV and Franklin CD: An analysis of oral and maxillofacial pathology found in children over a 30-year period. Int J Paediatr Dent *16(1)*: 19-30, 2006. PMID: 16827841. DOI: 10.1111/j.1600-0714.2006.00451.x

152 Imaizumi A, Kodama S, Sakamoto J, Sasaki Y, Otonari-Yamamoto M, Kuribayashi A, Kurabayashi T and Sano T: Imaging findings of benign peripheral nerve sheath tumor in jaw. Oral Surg Oral Med Oral Pathol Oral Radiol *116(3)*: 369-376, 2013. PMID: 23953423. DOI: 10.1016/j.oooo.2013.06.010

153 Naber U, Friedrich RE, Glatzel M, Mautner VF and Hagel C: Podoplanin and CD34 in peripheral nerve sheath tumours: focus on neurofibromatosis 1-associated atypical neurofibroma. J Neurooncol *103(2)*: 239-245, 2011. PMID: 20821344. DOI: 10.1007/s11060-010-0385-4

154 Sigillo R, Rivera H, Nikitakis NG and Sauk JJ: Neurofibromatosis type 1: a clinicopathological study of the orofacial manifestations in 6 pediatric patients. Pediatr Dent *24(6)*: 575-580, 2002. PMID: 12528952.

155 Mautner VF and Friedrich RE: Von Recklinghausen Gesellschaft: the German lay organization for patients with neurofibromatosis. Anticancer Res *23(2A)*: 1163-1164, 2003. PMID: 12820366.

156 Tekkesin MS, Olgac V, Aksakalli N and Alatli C: Odontogenic and nonodontogenic cysts in Istanbul: analysis of 5088 cases. Head Neck *34(6)*: 852-855, 2012. PMID: 21850702. DOI: 10.1002/hed.21820

157 Flores IL, Hamilton ME, Zanchin-Baldissera E, Uchoa-Vasconcelos AC, Chaves-Tarquinio SB and Neutzling-Gomes

AP: Simple and aneurysmal bone cyst: Aspects of jaw pseudocysts based on an experience of Brazilian pathology service during 53 years. Med Oral Patol Oral Cir Bucal *22(1)*: e64-e69, 2017. PMID: 27918745. DOI: 10.4317/medoral.21551

158 Togan B, Gander T, Lanzer M, Martin R and Lübbers HT: Incidence and frequency of nondental incidental findings on cone-beam computed tomography. J Craniomaxillofac Surg *44(9)*: 1373-1380, 2016. PMID: 27460918. DOI: 10.1016/j.jcms.2016.06.026

159 Mourão CF, Miranda ÁM, Santos EJ and Pires FR: Lingual cortical mandibular bone depression: frequency and clinical-radiological features in a Brazilian population. Braz Dent J *24(2)*: 157-62, 2013. PMID: 23780355. DOI: 10.1590/0103-6440201302091

160 Lucas C and Blum T: Do all cysts in the jaw originate from the dental system? J Am Dent Assoc *16*: 647-661, 1929.

161 Rushton MA: Solitary bone cysts in the mandible. Br Dent J *81(2)*: 37-49, 1946. PMID: 20992458.

162 Wangerin K: Cysts, bone lesions, odontogenic tumors. *In*: Lambrecht JT (ed) Oral and Implant Surgery. Quintessence, New Malden, pp. 153-156, 2009. DOI: 10.1038/sj.bdj.2010.97

163 Nagori SA, Jose A, Agarwal B, Bhatt K, Bhutia O and Roychoudhury A: Traumatic bone cyst of the mandible in Langer-Giedion syndrome: a case report. J Med Case Rep *8*: 387, 2014. PMID: 25421062. DOI: 10.1186/1752-1947-8-387

164 Jaffe HL: Giant-cell reparative granuloma, traumatic bone cyst, and fibrous (fibro-osseous) dysplasia of the jawbones. Oral Surg Oral Med Oral Pathol *6(1)*: 159-175, 1953. PMID: 13026160.

165 Stafne EC: Bone cavities situated near the angle of the mandible. J Am Dent Assoc *29*: 1969-1972, 1942.

166 Prechtl C, Stockmann P, Neukam FW and Schlegel KA: Enlargement of a Stafne cyst as an indication for surgical treatment - a case report. J Craniomaxillofac Surg *41(3)*: 270-273, 2013. PMID: 23218505. DOI: 10.1016/j.jcms.2012.10.013

167 Liu L, Kang BC, Yoon SJ, Lee JS and Hwang SA: Radiographic features of lingual mandibular bone depression using dental cone beam computed tomography. Dentomaxillofac Radiol *47(6)*: 20170383, 2018. PMID: 29589968. DOI: 10.1259/dmfr.20170383.

168 Richard EL and Ziskind J: Aberrant salivary gland tissue in mandible. Oral Surg Oral Med Oral Pathol *10(10)*: 1086-1090, 1957. PMID: 13465121.

169 Samson J, Carlino P, Di Felice R and Fiore-Donno G: Inclusioni intramandibolari di tessuto ghiandolare salivare [Intramandibular inclusions of salivary gland tissue]. Minerva Stomatol *39(7)*: 573-585, 1990.

170 Philipsen HP, Takata T, Reichart PA, Sato S and Suei Y: Lingual and buccal mandibular bone depressions: a review based on 583 cases from a world-wide literature survey, including 69 new cases from Japan. Dentomaxillofac Radiol *31(5)*: 281-290, 2002. PMID: 12203126. DOI: 10.1038/sj.dmfr.4600718

171 Friedrich RE, Zustin J, Scheuer HA, Assaf AT and Gröbe A: An unilateral basal bone defect of the mandible occupied by fatty tissue: Stafne's cavity. In Vivo *26(6)*: 1045-1048, 2012. PMID: 23160691.

172 Colmenero C, Rivers T, Patron M, Sierra I and Gamallo C: Maxillofacial malignant peripheral nerve sheath tumours. J Craniomaxillofac Surg *19(1)*: 40-46, 1991. PMID: 2019658. DOI: 10.1016/S1010-5182(05)80270-7

173 Yu X, Chen S, Potter OL, Murthy SM, Li J, Pulcini JM, Ohashi N, Winata T, Everett ET, Ingram D, Clapp WD and Hock JM: Neurofibromin and its inactivation of Ras are prerequisites for osteoblast functioning. Bone *36(5)*: 793-802, 2005. PMID: 15804420. DOI: 10.1016/j.bone.2005.01.022

174 Schindeler A and Little DG: Recent insights into bone development, homeostasis, and repair in type 1 neurofibromatosis (NF1). Bone *42(4)*: 616-622, 2008. PMID: 18248783. DOI: 10.1016/j.bone.2007.11.006.

175 Yang FC, Staser K and Clapp DW: The plexiform neurofibroma microenvironment. Cancer Microenviron *5(3)*: 307-310, 2012. PMID: 22821631. DOI: 10.1007/s12307-012-0115-x.

176 Ferner RE and Gutmann DH: International consensus statement on malignant peripheral nerve sheath tumors in neurofibromatosis. Cancer Res *62(5)*: 1573-1577, 2002. PMID: 11894862.

Received January 26, 2019
Revised March 23, 2019
Accepted March 23, 2019