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ORIGINAL ARTICLE

Oral soft tissue alterations in patients with neurofibromatosis

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Abstract Our aim was to characterize the type and frequency of oral soft tissue alterations in neurofibromatosis. A total of 103 patients with neurofibromatosis 1 (NF1) and three patients with neurofibromatosis 2 (NF2) were clinically evaluated for their oral soft tissue alterations. Disturbing growths were removed from nine patients with NF1 and from one patient with NF2. The specimens were analyzed using routine histological methods and with immunohistochemistry using antibodies to S100, type IV collagen, CD34, neurofilament, and neuron-specific tubulin (TUBB3). Alterations including oral tumors, overgrowths of gingival soft tissue, and enlarged papillae of the tongue were discovered in 74% of NF1 patients. The results showed that three tumors clinically classified as plexiform neurofibromas and five out of six discrete mucosal tumors displayed histology and immunohistology consistent with that of neurofibroma. The histology of one palatal lesion resembled that of a scar, and the lesion removed from the patient with NF2 was classified as an amyloid tumor. To conclude, oral soft tissue growths are common findings in NF1, but most lesions do not require treatment and the patients may even not be aware of these alterations. Collagen IV, S100, and CD34 are useful biomarkers in the analysis of NF1-related oral soft tissue tumors. The clinicians should recognize that oral soft tissue alterations are relatively common in NF1. Some of the growths are disturbing, and plexiform neurofibromas may bear a risk of malignant transformation.

Keywords Mouth · Schwann cell · Tumor syndrome · Dentistry

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Introduction

Neurofibromas are benign tumors with involvement of the elements of peripheral nerve, and they occur as sporadic lesions or multiple lesions associated with neurofibromatosis type 1 (NF1). NF1, also referred to as von Recklinghausen's disease, is one of the most common dominantly inherited diseases in man affecting about 1 in 3,000

individuals worldwide [1, 2]. NF1 is caused by a germline mutation in the *NF1* tumor suppressor gene located at 17q11.2 [3]. The diagnosis of NF1 is based on the presence of two or more of the findings presented in Table 1 [4]. Neurofibromatosis 2 (NF2) is caused by the mutation in *NF2* gene on chromosome 22, the hallmark of the disease being bilateral schwannomas of the eight cranial nerve [5]. The estimated incidence of NF2 is 1 in 25,000 [5].

Neurofibromas are most commonly lesions of the skin, and in general population, they rarely affect the oral cavity [6, 7]. However, their presence within the oral cavity is not uncommon in association with NF1 [8]. In previous reports with smaller study populations, oral soft tissue and radiographic manifestations of neurofibromatosis have been reported in 72–92% of affected persons including the intraoral tumors in ~25% of patients [8, 9]. The tongue, the buccal mucosa, the alveolar ridge, the gingiva, the lips, the palate, the floor of the mouth, and the pharyngomaxillary space have been reported to be affected with tumors in association with NF1, the tongue being the most common location [8–10]. Other reported findings concerning oral soft tissue in NF1 patients include macroglossia and enlarged papillae of the tongue.

Histologically, neurofibromas are mixed tumors consisting of cells with divergent differentiation. The use of traditional histological stains, immunohistochemistry with a variety of biomarkers, and electron microscopy has been taken as proof for Schwann cell, perineurial cell, and fibroblast differentiation [11–13]. In addition, cutaneous neurofibromas contain numerous mast cells and axonal processes, all embedded in an abundant collagenous extracellular matrix [12]. Neurofibromas are often classified into two broad categories: dermal and plexiform [14]. In more detail, the classification of neurofibromas into cutaneous, subcutaneous, nodular plexiform, and diffuse plexiform has proven useful. Mucosal neurofibromas refer to, e.g., oral, intestinal, and vaginal neurofibromas. Plexiform neurofibromas are congenital tumor masses involving nerve trunks and growing around more or less distorted nerve fascicles. A diffuse neurofibroma involving the skin and subcutaneous tissues is a common variant of neurofibroma which is often seen in head and neck region and may involve the oral cavity [15]. In the head and neck, plexiform neurofibromas most commonly involve the fifth cranial nerve, especially the first and second divisions [16].

Although the histopathology of cutaneous and plexiform neurofibromas has been thoroughly investigated, studies on mucosal NF1-related tumors are rare. In the present study, a total of 103 NF1 patients in different age categories and three NF2 patients were clinically evaluated for their oral soft tissue alterations. Oral soft tissue alterations including tumors, enlarged papillae of the tongue, and overgrowths of gingival soft tissue were discovered in 74% of NF1 patients. A debilitating soft tissue growth was removed from nine patients with NF1 and one patient with NF2, and the specimens were analyzed using routine histological methods together with immunohistochemistry and a panel of selected biomarkers.

Patients and methods

A total of 103 Caucasian patients with NF1, 55 female patients aged 3–68 years and 48 male patients aged 8–73 years, and 3 patients with NF2 were included in this study [17, 18]. The patients were recruited to the study among the patients attending the NF1 clinic at the Department of Dermatology and Department of Oral Diseases, Turku University Hospital, as well as among members of the Finnish NF patient organization. All patients fulfilled the NIH diagnostic criteria for NF1 [4] or NF2 [5]. The study was approved by the Ethics Committee of Southwest Finland Hospital District, Turku, Finland, and the examination was performed with appropriate written consents. All patients were examined at the Department of Oral Diseases, Turku University Hospital by the same clinician between years 2005 and 2008.

Table 1 Diagnosis of neurofibromatosis type 1 (Stumpf et al. [4])

The NF1 patient should fulfill two or more of the following criteria	
1.	Six or more café-au-lait macules
	Diameter ≥5 mm in prepubertal individuals
	Diameter ≥15 mm in postpubertal individuals
2.	Two or more neurofibromas of any type or one plexiform neurofibroma
3.	Axillary or inguinal freckling
4.	Optic glioma
5.	One or more Lisch nodules of the iris
6.	A distinct osseous lesion, such as
	Sphenoid dysplasia
	Pseudarthrosis
7.	A first-degree relative with NF1 according to the preceding criteria

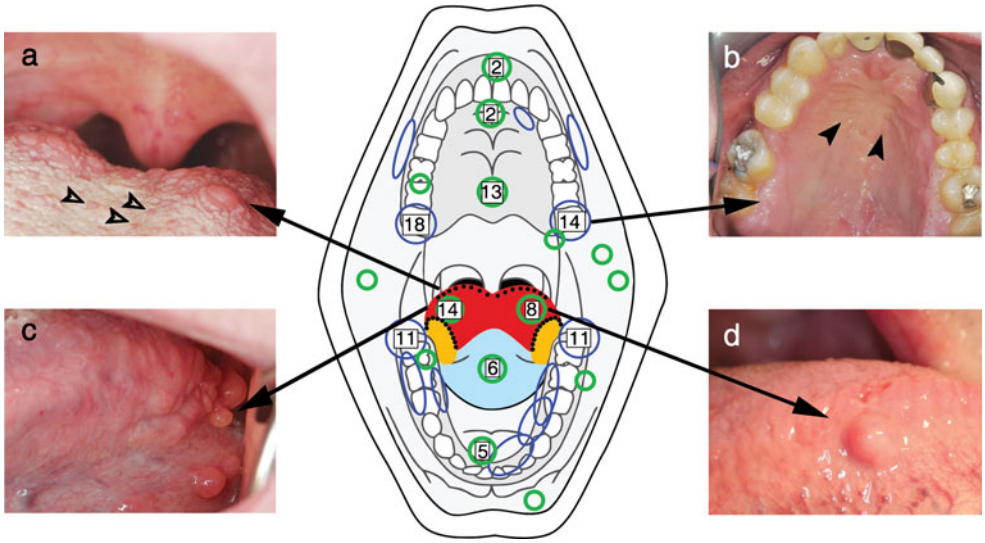


Fig. 1 Overview of soft tissue alterations in patients with NF1. **a** Enlarged vallate papillae (*arrow*), open arrowheads point to the fungiform papillae. **b** Overgrowth of gingival soft tissue (*arrow*), arrowheads point to palatal rugae. **c** Typical view of the lateral aspect of the tongue shows small mucosal tumors and enlarged lingual papillae (*arrow*). **d** Mucosal neurofibroma on dorsal tongue (*arrow*). The distribution of alterations is shown in the diagram in the *center*: the locations of prominent lingual papillae (*black dots*), overgrowths of gingival soft tissue (*blue linings*), mucosal tumors (*green circles*) are shown; the *numbers inside the circles* refer to the total number of alterations in all NF1 patients studied. Dorsal aspect of tongue (*red*), lateral aspect (*yellow*), and ventral aspect (*light blue*). The patients with plexiform neurofibromas are not included. Diagram modified from Rautava et al. [27]

The patients were categorized into three groups according to age: children (up to 12 years), adolescent (13–18 years), and adult (19 or older). Surgical removal of disturbing tumor was recommended to 15 patients. Subsequently, a soft tissue alteration was removed from nine patients with NF1 and one patient with NF2. Healing in all cases was uneventful.

The tissue samples were fixed in 10% neutral formalin and embedded in paraffin. Sections, 5 μm thick, were cut and stained with hematoxylin–eosin, periodic acid Shiff, Van Gieson, Masson's trichrome, toluidine blue, and Congo red. In addition, a panel of selected biomarkers was used for immunocytochemistry in which the avidin–biotin method was used as described [19]. CD34 was stained with Ventana Benchmark XT immunostainer (Ventana Medical Systems, Tucson, AZ) by using a multimer detection system. Diaminobenzidine was used as a chromogen in all immunohistochemical stainings.

Antibodies

The following primary antibodies were used: mouse monoclonal antibody to human type IV collagen (Sigma-Aldrich Inc., Saint Louis, MO), mouse monoclonal antibody to human neurofilament (ab8970; Abcam Ltd, Cambridge, UK), mouse monoclonal antibody, Tuj-1, to rat class III β-tubulin, (MMS-435P; Covance, Princeton, NJ), CD34 clone QBEnd/10 (Ventana Medical Systems), and rabbit polyclonal antibody to cow S100 protein (18-0046; Chemicon International Inc., Temecula, CA). The antibody to S100 protein recognizes both A and B subtypes of the protein.

Microscopy

The sections were imaged with Olympus BX 51 virtual microscope equipped with Olympus U-CMAD3 camera

Table 2 Oral soft tissue findings in NF1

Age	0–12 years	13–18 years	≥19 years	All cases
Number of patients	25	14	64	103
Oral tumors	2 (8%)	4 (29%)	32 (50%)	38 (37%)
Overgrowth of gingival soft tissue	2 (8%)	2 (14%)	25 (39%)	29 (28%)
Prominent lingual papillae[a]	7 (28%)	5 (36%)	29 (45%)	41 (40%)

The figures refer to the number of patients with oral tumors, overgrowth of gingival soft tissue, and prominent lingual papillae

[a] The foliate, fungiform, and vallate papillae are not listed separately

Table 3 Location, clinical presentation, and histological diagnosis of lesions removed from nine NF1 patients

Case	Age	Sex	Tumor location	Clinical presentation	Histological diagnosis
1	17	M	Buccal mucosa	Plexiform	Neurofibroma
2	56	F	Left retromolar area	Plexiform	Neurofibroma
3	31	F	Lower surface of tongue	Plexiform	Neurofibroma
4	65	M	Right border of tongue	Discrete mucosal	Neurofibroma
5	31	M	Right border of tongue	Discrete mucosal	Neurofibroma
6	31	F	Right border of tongue	Discrete mucosal	Plexiform neurofibroma
7	42	M	Maxillary tuberosity	Discrete mucosal	Neurofibroma
8	24	F	Palate	Discrete mucosal	Neurofibroma
9	64	F	Palate	Discrete mucosal	Scar/fibroma

and dotSlide1.2 software. High magnification images were taken with Zeiss AxioImager M1 microscope equipped with AxioCam ICc3 camera and AxioVision Release 4.8 software. Amyloid tissue was identified by apple-green birefringence when stained with Congo red and seen under polarized light.

Results

The present study includes results of clinical oral soft tissue examination of 103 patients with neurofibromatosis type 1 and 3 patients with neurofibromatosis type 2. Based on this evaluation, the tumors were classified as plexiform growths if they appear as diffuse asymmetrical masses or rows of nodules. Tumor that appears as a single nodule and not in apparent connection with distinct nerve is in the present study called as discrete oral mucosal neurofibroma. Six patients with NF1 had plexiform neurofibroma involving the fifth cranial nerve. The histological and immunohistological data is based on the nine disturbing growths, including three plexiform neurofibromas, removed from patients with NF1 and one growth from a patient with NF2.

Oral soft tissue alterations were discovered in 76 patients representing 74% of all NF1 patients studied, and the findings were equally common in both sexes. The most common findings were mucosal tumors, overgrowths of gingival soft tissue, and prominent lingual papillae (Fig. 1; Table 2).

Oral mucosal tumors were discovered in 37% (38 patients) of all patients studied, and the most frequent location of NF1-related oral tumors in the current study was the tongue (Fig. 1). Removal of disturbing growth was recommended to 15 patients, and the tumors were categorized as plexiform or discrete mucosal tumors according to clinical inspection (Table 3).

Plexiform neurofibromas affecting the oral cavity

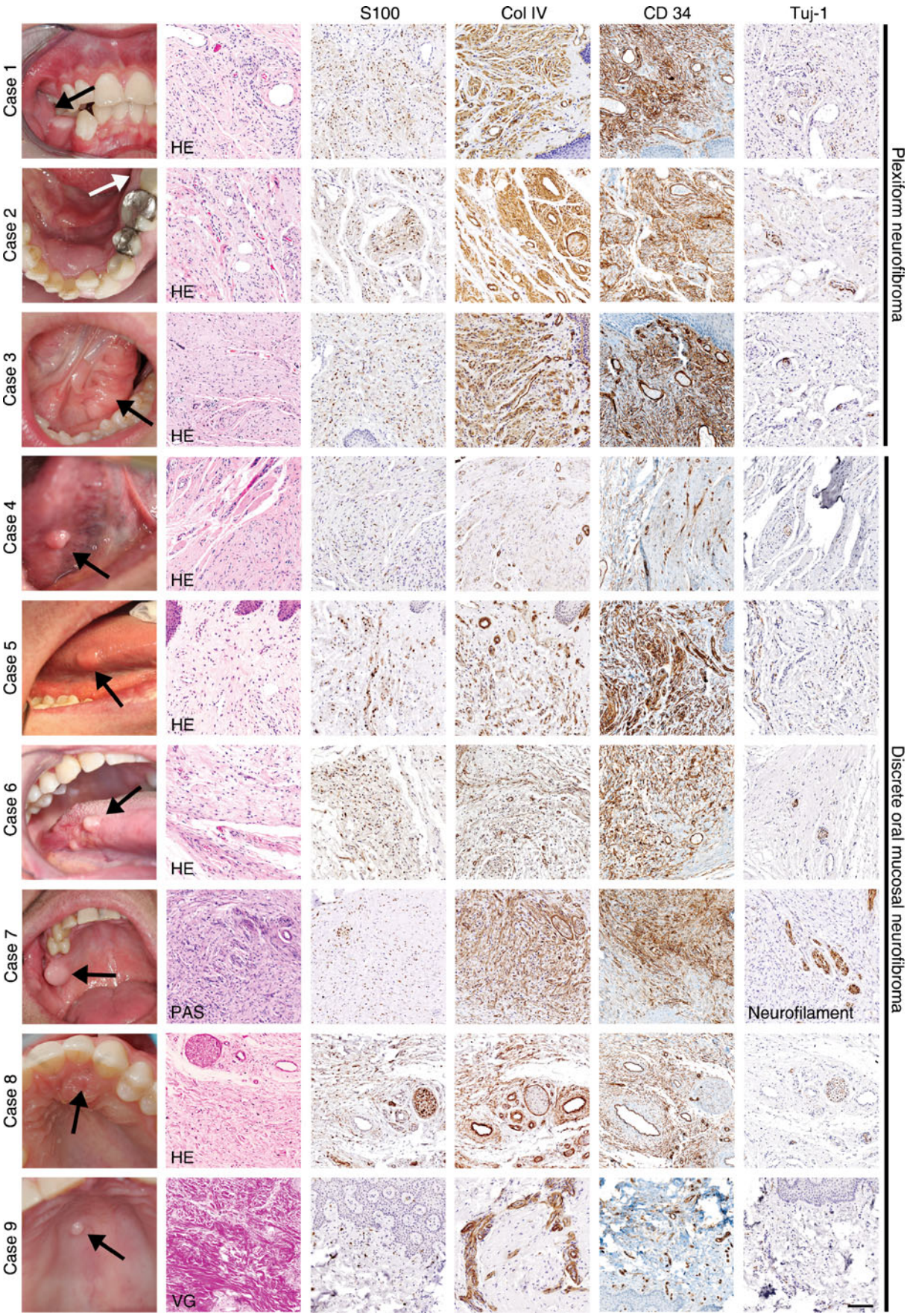
The three plexiform manifestations biopsied in the current study were located on the buccal mucosa, in the left retromolar area, and in lower surface of the tongue (Fig. 2). Not unexpectedly, the tumors clinically classified as plexiform NF1-related neurofibromas displayed histology and immunohistology consistent with that of neurofibroma [12]. Specifically, routine histopathological studies revealed the presence of neural elements within an abundant collagenous matrix. The neuronal components were visualized by immunofluorescence with neurofilament antibody and Tuj-1 antibody for neuron-specific tubulin [19], which indicated that in addition to organized nerve fascicles, few solitary axons traversed the diffuse tumor tissue.

In peripheral nerves, Schwann cells and neurons express S100 protein. However, in oral mucosa, Langerhans cells are also positive for S100. In all three plexiform tumors studied here, ~60–80% of the cells were S100 positive. In this context, they were considered as Schwann cells. This finding was also supported by the fact that most of the cells were type IV collagen positive, a finding consistent with Schwann cell but not with Langerhans cell differentiation. Also consistent with the histology of neurofibroma, the tumors contained numerous mast cells as visualized by toluidine blue staining (Fig. 3a). The presence of voluminous extracellular matrix and the positivity of the tumors for CD34 served as differential diagnostic features present in neurofibromas but not in schwannomas [20].

Discrete oral mucosal neurofibromas

Only one, or few, discrete oral mucosal neurofibromas were found per patient, as opposed to the typical clinical presentation of numerous cutaneous neurofibromas. Figure 2 shows

Fig. 2 Clinical presentation and histological/immunohistological analysis of NF1-related oral tumors. Clinical cases 1–3 represent plexiform neurofibromas and cases 4–8 represent discrete oral mucosal neurofibromas. The plexiform and discrete neurofibromas are characterized by S100, collagen IV, and CD34 positive cells within an abundant collagenous extracellular matrix. Tuj-1 or neurofilament positivity reveals neuronal involvement. All these properties are consistent with histology of a neurofibroma. Case 9 resembles a scar. *Bar* **100 μm**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Plexiform neurofibroma
Discrete oral mucosal neurofibroma

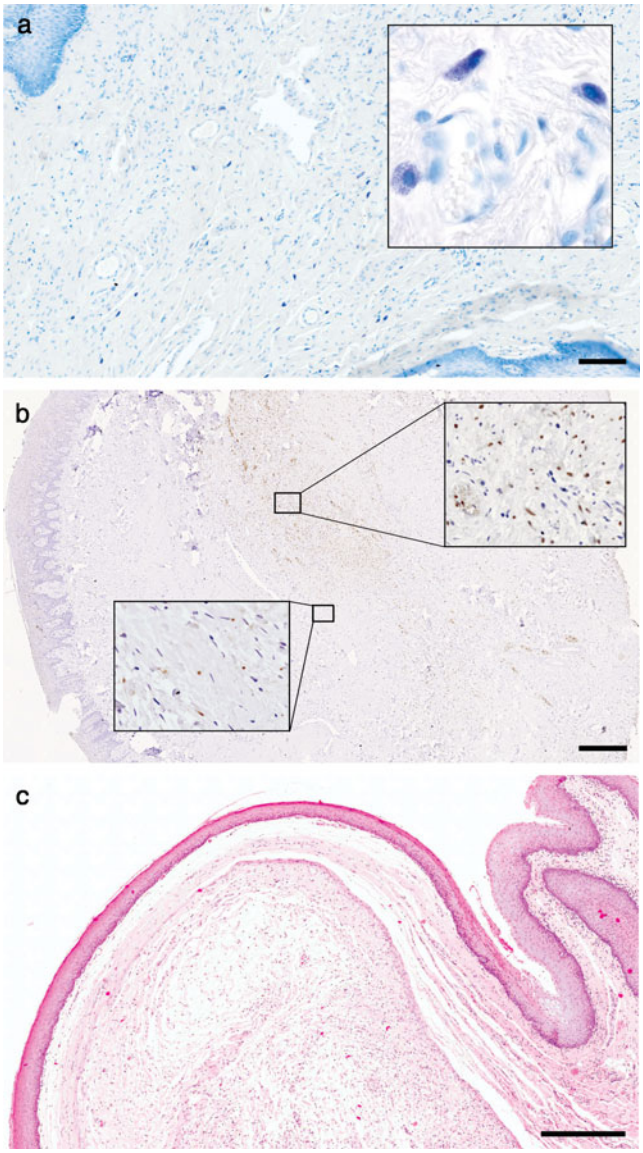

Fig. 3 **a** Toluidine blue staining for the visualization of mast cells (case 3). **b** S100 immunolabeling illustrates the heterogeneity of a discrete gingival neurofibroma (case 7). **c** Case 6 was clinically classified as discrete nodule, the histological characteristics suggested that the specimen represented a part of a plexiform neurofibroma with a capsule. *Bars* 100 μm for **a**, 500 μm for **b** and **c**

the location of discrete mucosal tumors subjected to histological and immunohistochemical analyses. Five out of six cases displayed S100 positive Schwann cells within collagenous matrix and were thus classified as neurofibromas. However, when compared to the three plexiform neurofibromas described above, and to cutaneous neurofibromas described previously [12, 21], the discrete mucosal neurofibromas were more heterogeneous containing areas with only few S100 positive Schwann cells (Fig. 3b). In analogy, the number of mast cells was highly variable within a single tumor and between different discrete oral neurofibromas as exemplified by the fact that some visual fields with ×20 lens displayed up to 4–6 mast cells, while some had none. Even though case 6 was clinically classified as discrete nodule, the histological characteristics suggested that the specimen represented a part of a plexiform neurofibroma (Fig. 3c).

One out of six discrete NF1-related mucosal tumors (case 9) did not contain neural elements. Instead, the histology of this highly collagenous lesion resembled that of a scar.

A discrete mucosal tumor was excised from a patient with NF2. This lesion was classified as amyloid tumor based on Congo red staining and polarized microscopy (Fig. 4).

Overgrowth of gingival soft tissue

Gingival overgrowth was clearly more common in adults (≥19 years; 39%; 25/64 patients) compared to children (0–12 years; 8%; 2/25 patients) and adolescent (13–18 years; 14%; 2/14 patients). The most common anatomical location affected was maxillary tuberosity (Fig. 1).

Lingual papillae

Different types of papillae, fungiform, vallate, and foliate were involved and are not listed separately. Prominent lingual papillae were somewhat more frequent in adolescent (36%; 5/14 patients) and adults (45%; 29/64 patients) than in children (28%; 7/25 patients). Thus, enlarged lingual papillae are a relatively early finding in NF1.

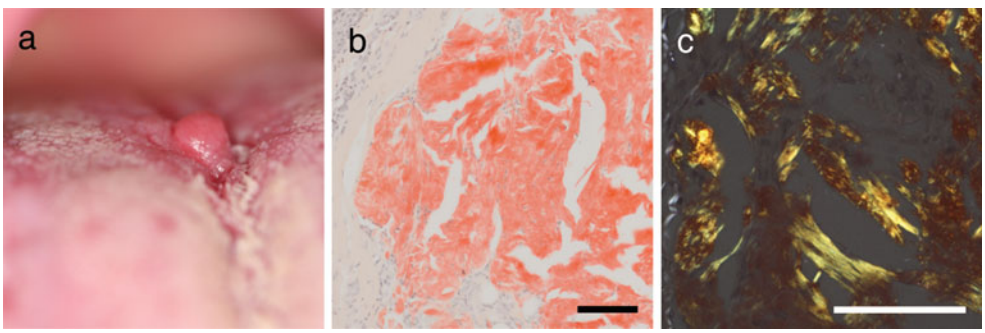

Fig. 4 Amyloid tumor in the center of the tongue of the patient with NF2 (**a**). Congo red staining (**b**) and apple-green birefringence (**c**) when stained with Congo red and seen under polarized light. *Bars* 100 μm

Discussion

Oral manifestations in neurofibromatosis 1 have been reported in a limited number of full-length papers [8, 9, 22, 23], including a review of literature between 1849 and 1981 [22]. The merits of the current communication include the fact that the study reports the highest number of NF1 patients systematically subjected to the clinical oral investigation to date, and histopathological and immunohistochemical analysis of nine oral tumors. In addition, we characterized one oral tumor which was removed from the tongue of a patient with NF2. The most common findings of the present study were prominent lingual papillae, overgrowth of gingival soft tissue, and mucosal tumors. These results are in agreement with those covered in the reports referenced above.

Tumors were detected in about one third of the patients studied and in about half of the adult patients. Collectively, we call these soft tissue growths as oral mucosal tumors. Typically, discrete oral mucosal neurofibromas started to grow during puberty which is in accordance with the manifestation of cutaneous neurofibromas. Although oral mucosal neurofibromas were frequent in NF1 patients, they were not numerous, and thus differed from typical multiple cutaneous neurofibromas, the number of which per anatomical area may be much higher. In general, the histological structure of mucosal neurofibromas was more heterogeneous, and the histopathological diagnosis may be verified only by immunohistochemistry.

The plexiform neurofibromas apparently affecting the second branch of the fifth cranial nerve were detectable on the buccal mucosa, the soft tissue on the mandible and the tongue. The histology and immunohistology of the oral plexiform neurofibromas were indistinguishable from those described in literature and affecting other anatomical locations.

Previous and the current results show that the clinical inspection and palpation are not sufficient for the diagnosis of neurofibroma even if the patient had NF1. Immunohistochemistry proved to be highly useful in the analyses of discrete oral mucosal tumors. This is particularly true since routine histology alone was not sufficient for definite diagnosis. Specifically, a panel of immunoreactions including S100, type IV collagen, CD34, and neurofilament or neuron-specific tubulin (TUBB3) demonstrated the presence of neural involvement in the fibromatous tumors. Toluidine blue staining visualized mast cells within the oral mucosal neurofibromas, which is in analogy to findings on cutaneous neurofibromas.

The cases classified as gingival overgrowths in the current study were more frequent than those reported in the literature. However, some of these changes may in fact represent neurofibromas in analogy to those described by Cunha et al. [24] and García de Marcos et al. [25].

To conclude, oral soft tissue tumors are seen frequently in NF1 patients. These may affect speech [26] and may cause discomfort for which reason the clinical oral examination of these patients is recommended. Troubling discrete intraoral tumors can be excised, but the treatment of plexiform neurofibromas is more complicated. A thorough histopathological analysis supported by immunohistochemistry is essential for the correct diagnosis of these oral soft tissue growths. We recommend S100, collagen IV, and CD34 as useful biomarkers in the analysis of oral NF1-related tumors.

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Conflict of interest The authors declare that they have no conflict of interest.

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