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ORIGINAL ARTICLE

Manifestations of the tongue in Neurofibromatosis type 1

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OBJECTIVE: The aim of this study is to analyse alterations of the tongue and the correlation between these lesions and different types of tumor.

SUBJECTS AND METHODS: A total of 258 cases (131 females, 127 males) of neurofibromatosis type 1 were screened between 1994 and 2004 in our Dermatology Department. All patients included in this study have NF1, as defined by the NIH Consensus Conference. Three cases of neurofibromas of the tongue in patients with neurofibromatosis type were reported.

RESULTS: Our patients showed nodular lesions on the tongue, related to neurofibromas in two patients and plexiform neurofibroma in one patient, respectively. Clinical and hystopatological findings were useful in distinguishing between neurofibromas and other soft tissue tumors. An increased prevalence of malignancy has been documented in patients affected by neurofibromatosis type 1. Changes in the size of a pre-existing mass, compression, or infiltration of the adjacent structures indicate malignant degeneration. Histological and clinical evaluation should be performed in order to choose the most appropriate treatment strategy for these patients.

CONCLUSION: The oral manifestations of NF are well-documented but may not be at the forefront of the clinician's mind in the differential diagnosis of intra-oral swellings.

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Neurofibromatosis type 1 (NF1), also known as von Recklinghausen's neurofibromatosis, is an autosomal dominantly inherited disease affecting 1:3000 newborn. About 50% of NF1 patients have no family history of the disease. There is no prevalence for gender or race in NF1. Expressivity in NF1 is tremendously variable (Friedman and Riccardi 1999) but subtle phenotypic patterns may exist within subgroups of affected patients. The existence of such subgroups is supported by the observation of a relatively consistent phenotype among patients with deletions of the entire *NF1* gene (Leppig *et al*, 1997; Riva *et al*, 2000). The disorder has almost 100% penetrance but variable expression. Furthermore, 50% of cases are sporadic and arise from germ-cell mutations.

However, the expression of signs and symptoms is highly variable. The precise constellation of findings in any one individual is extremely variable, both within a family and between different families. NF1 is characterized by cafe' au lait spots, intertriginous freckling, Lisch nodules and multiple cutaneous neurofibromas. NF1 can be associated with optic gliomas, spinal and peripheral nerve neurofibromas, neurologic or cognitive impairment, scoliosis and abnormalities in the oral and maxillofacial region (Friedrich *et al* 2003), malignant tumors of the nerve sheath, pheochromocytoma, and vasculopathy (Friedman and Birch, 1997; Rasmussen *et al*, 2001; Obermoser *et al*, 2004).

A total of 258 cases (131 females, 127 males) of NF1 were screened between 1994 and 2004 in our Dermatology Department. All patients included in this study have NF1, as defined by the NIH Consensus Conference (Table 1) (NIH Consensus Development Conference, 1988; Gutmann *et al*, 1997).

We excluded cases described as segmental NF or 'other type of NF'.

In this report, we present three cases of neurofibroma of the tongue in patients with NF1.

The aim of this study is to analyse the alterations of the tongue and the correlation of these lesions with the type of tumor.

Patients and methods

The investigation was based on physical inspection and a histological diagnosis. The histological diagnosis of soft-tissue tumors was established for all patients. We are aware that a distinction between neurofibroma and plexiform neurofibroma is useful when evaluating the severity of the findings. This distinction simplifies histopathological subtypes of NF1 and is therefore adopted for this study

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Table 1 Diagnostic criteria for neurofibromatosis type NF1

At least two criteria are needed for diagnosis
Six or more 6 café-au-lait macules, > 5 mm diameter in prepubertal and > 15 mm diameter in postpubertal patients
Two or more neurofibromata of any type, or one plexiform neurofibroma
Axillary or groin freckling
Optic glioma
Two or more Lisch nodules: pigmented hamartomas, often bilateral, appearing as domed-shaped elevations on the surface of the iris upon slit lamp examination
A distinctive bony lesion, dysplasia of the sphenoid bone, dysplasia or thinning of long bone cortex
First-degree relative with NF1

The biopsy specimen was fixed in 10% neutral formalin solution and embedded in paraffin. Sections of 4 μm thick were obtained and stained with hematoxylin–eosin. We investigated three patients, one man and two women (Table 2).

Case no. 1 is a 74 year old woman with no family history of neurofibromatosis. The patient showed a skin involvement with patches of cutaneous pigmentation and multiple cutaneous tumors. The neurofibromas are soft, flesh-colored, and not painful tumors that range in size from several millimeters to many centimeters in diameter. A large number of both cutaneous and subcutaneous neurofibromas are scattered over the entire patient's skin.

The lesions in the oral cavity are located on the right side of the tongue with nodular mass, without defined borders and covered by mucosa. The lesions are firm and not fluctuant. Discomfort is a common complaint (Figure 1).

The histopathological specimen contains interlacing bundles of elongated cells with dark staining nuclei. The cells are associated with strands of collagen, and small to moderate amounts of mucoid material separate the cells and collagen. Occasional mast cell and lymphocytes are present in the stroma. The diagnosis is neurofibroma (Figure 2).

Case no. 2 is a 35 year old woman. She has a family history of neurofibromatosis. Random café au lait spots occur all over the body. The cafe'-au-lait macules vary in number and are flat, brown-pigmented and range from a few millimeters to several centimeters in size. Discrete cutaneous neurofibromas are present. Non-ulcerated, non-painful, nodular lesions of different sizes (3–10 mm), without defined borders and covered by a reddish mucosa are present on the left side of the tongue (Figure 3). The patient complains of discomfort.

An excisional biopsy of an oral lesion is performed. Histopathological and immunohistochemical analysis confirm the clinical hypothesis of plexiform neurofibroma. The lesion has a diffuse dermal and submucosa component. A proliferation of isolated Schwann cells is interspersed with thick wavy collagen bundles (Figure 4a). A focal tactile differentiation with spherical, aggregated pseudo-Meissnerian corpuscles is present (Figure 4b). The mucoid matrix is abundant.

Case no. 3 is a 40-year-old men. He has no family history of neurofibromatosis. Café au lait spots occur randomly, distributed all over the body. The cafe'-au-lait macules are flat, brown-pigmented that range from a few millimeters to several centimeters in size and vary in number.

Intertriginous freckling and discrete subcutaneous neurofibromas are present. The lesion is located in the left posterior side of the tongue. Intra-oral examination revealed two painless firm, exophytic, nodular masses, without defined borders and covered by a reddish mucosa of approximately 1.0 cm (Figure 5). The patient complained of discomfort.

The histopathological analysis of one lesion confirmed the diagnosis of neurofibroma.

Discussion

NF1 is an autosomal dominantly inherited genetic disorder. It is associated with deletions, insertions or mutations of the NF1 gene. This gene is a tumor-suppressor gene located in the pericentromeric region of chromosome 17 (Nussbaum *et al* 2001). This protein demonstrates significant homology to proteins that activate the GTPase activity of the RAS oncogene product.

NF1 is usually diagnosable clinically by its cutaneous manifestations and family history.

NF1 is diagnosed in an individual with two or more of the following signs: café au lait macules, two or more neurofibromas of any type or a single plexiform neurofibroma, freckling in the axillary or inguinal region, optic glioma, two or more Lisch nodules and a distinctive first degree osseous lesion. Scheletal abnormalities occur in almost 40% of patients with this disease (Weiss and Goldblum 2001).

This study confirms the close association between tongue neurofibromas and NF1. Lesions in the oral soft tissues have been noted, with a reported prevalence of less than 10% (Baden *et al* 1984), 26% (D'Ambrosio *et al* 1988) and up to 72% of patients, respectively, in a review that documented all mucosal abnormalities (Shapiro *et al* 1984). The considerable difference of oral manifestations can be attributed to the heterogeneity of patients examined in specialized hospitals, and the

Table 2 Manifestations of the tongue in NF1 patients

Case number	*Age*	*Sex*	*Family history*	*Histopathology of neurofibromas of oral mucosa*	*Axillary freckling*	*Café au lait spots*	*Cutaneous neurofibromas*
1	74	F	No	Neurofibroma	Yes	Yes	Yes
2	35	F	Yes	Plexiform neurofibromas	Yes	Yes	Yes
3	40	M	No	Neurofibroma	No	Yes	Yes

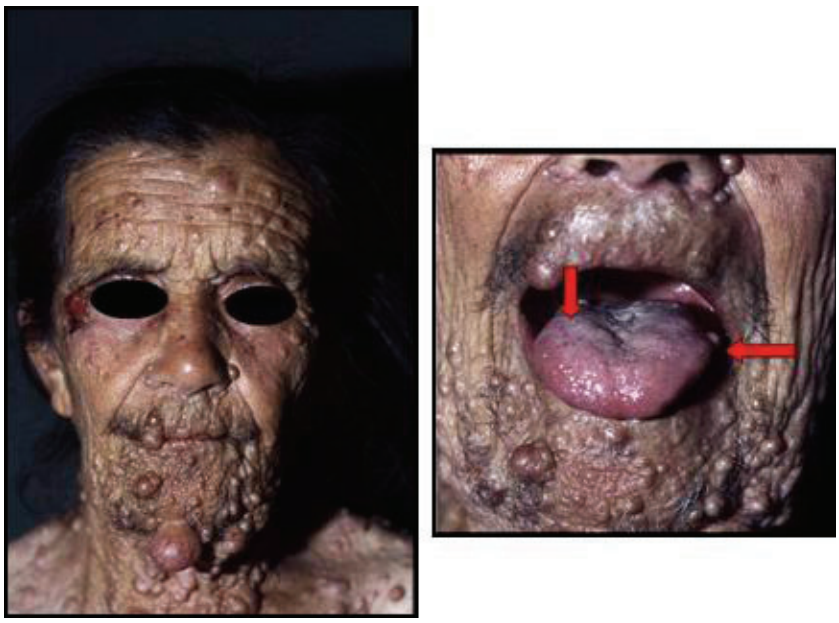

Figure 1 Case 1. A large number of both cutaneous and subcutaneous neurofibromas were scattered over the face. In the tongue nodular mass, without defined borders and covered by mucosa

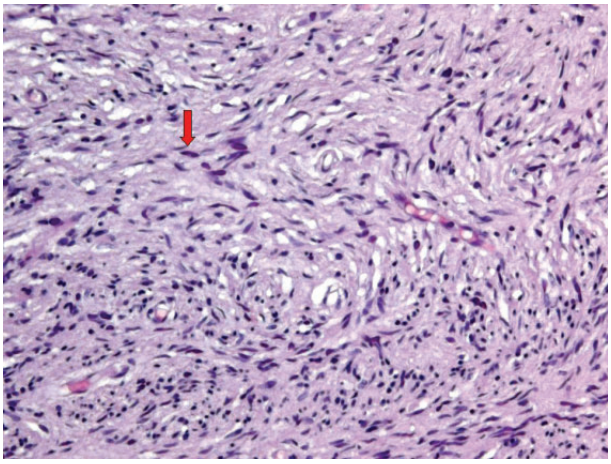

Figure 2 Interlacing bundles of elongated cells with dark staining nuclei (hematoxylin–eosin, ×250)

differences in symptoms investigated and the methods of investigation applied.

The early diagnosis of asymptomatic neurofibromas of the tongue requires a high index of clinical suspicion. Early oral lesions may not be identified due to the clinicians' failure to focus attention on possible intraoral anatomical changes. Symptomatic lesions are more readily diagnosed when a patient complains of mass, or other discomfort, which will direct the clinician to the primary lesion.

A significant correlation is also found between delay in diagnosis and the location of a lesion in the oral cavity. Soreness of the tongue is the most common complaint. The presence of discomfort is reported by the majority of patients with lesions of the tongue. The presence of a mass or lump is noted primarily in lesions of the tongue. Symptoms were more commonly reported in the presence of lesions of the tongue. When symptoms

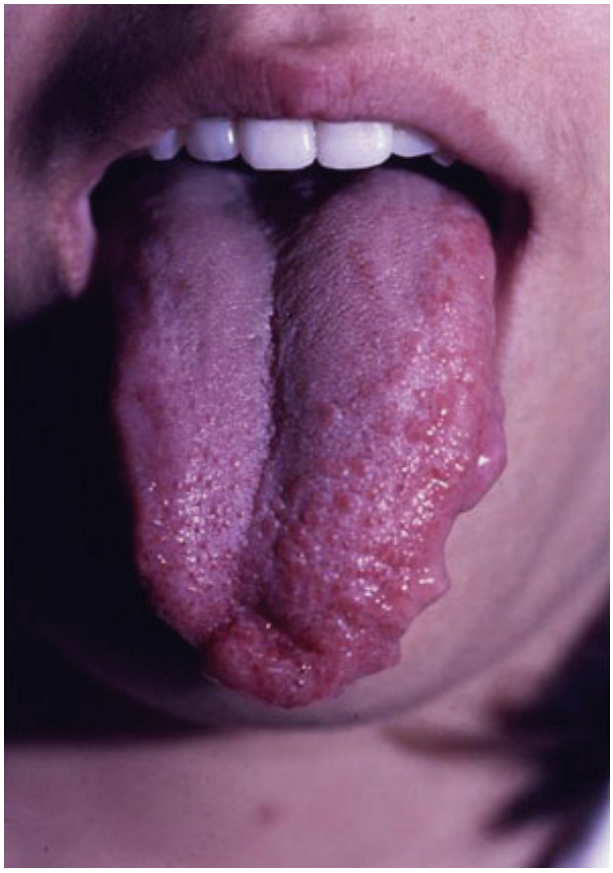

Figure 3 Case 2. Discrete cutaneous neurofibromas are present. Nodular lesions of different sizes (3–10 mm), without defined borders and covered by a reddish mucosa are present on the left side of the tongue

associated with lesions of the base of the tongue are reported, a neck mass, odynophagia, dysphagia, voice changes and ear pain can be noted.

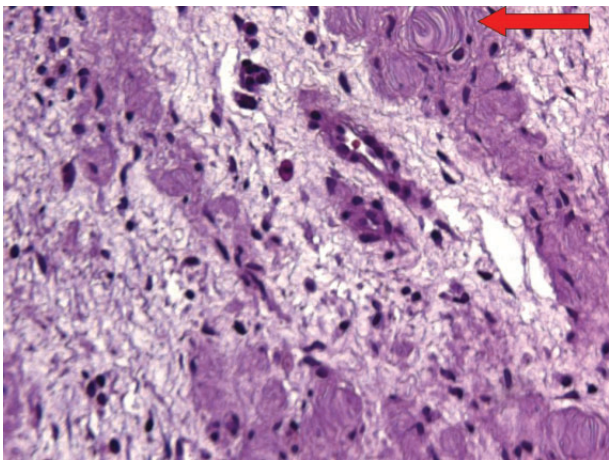

Figure 4 A focal tactile differentiation with spherical, aggregated pseudo-Meissnerian corpuscles is present (hematoxylin–eosin, ×320)

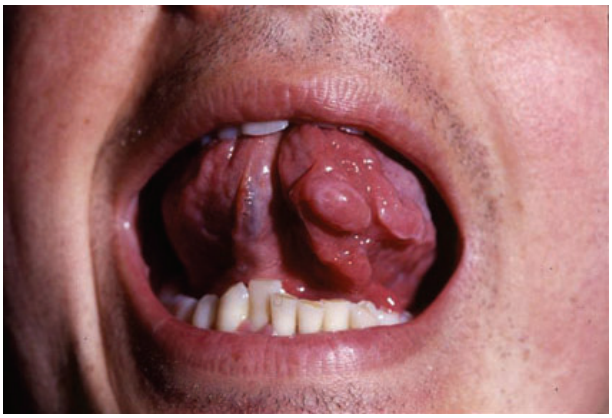

Figure 5 Two painless firm, exophytic, nodular masses, without defined borders and covered by a reddish mucosa

Neurofibromas are the hallmark of the NF1 and usually appear during childhood or adolescence after the emergence of café au lait spots. They form tumors on the tongue (Bekisz *et al* 2000) the gingiva (Friedrich *et al* 1994), the palate, cheeks, lips, the floor of the mouth or the pharynx. Besides tooth loss, impaction and malpositioning of the teeth are frequently found.

Neurofibromas of the tongue are nearly always nodular, but cases of diffuse macroglossia have been reported. Like other cephalic lesions, they are most often unilateral. Lesions in the oral mucosa in NF1 are correlated to the type of neurofibroma. It is important to specify whether a patient has a neurofibroma or a plexiform neurofibroma of the oral mucosa and maxillofacial region.

Severe hemifacial disfigurement is almost always caused by a plexiform neurofibroma of the trigeminal nerve (Friedrich *et al*, 1994; Keutel *et al*, 1997). The frequency of plexiform neurofibroma is not known. The tumors are normally visible during the first year of life. The total number of plexiform neurofibromata is thought to be about 21% of NF1 patients (Baden *et al*, 1984; Shapiro *et al*, 1984; D'Ambrosio *et al*, 1988; NIH Consensus Development Conference, 1988; Friedrich *et al*, 1994; Huson, 1994; Friedman and Birch, 1997; Gutmann *et al*, 1997; Keutel *et al*, 1997; Bekisz *et al*, 2000; Nussbaum *et al*, 2001; Rasmussen *et al*, 2001; Weiss and Goldblum, 2001; Obermoser *et al*, 2004). The hypothesis is that plexiform neurofibroma is embryonic in origin. These tumors are frequently found at birth or during childhood. However, plexiform neurofibroma can develop *de novo* at any stage during childhood (Waggoner *et al* 2000).

Our patients showed nodular lesions on the tongue related to neurofibromas in two patients and plexiform neurofimoma in one patient, respectively. The lesions evolve slowly and are painless, but tumor development can accelerate with growth, puberty and pregnancy, and clinical and hystopatological findings in this patients help distinguish neurofibromas from other soft tissue tumors.

Differential diagnosis of enlarging tongue masses includes lipoma, angiolipoma, chondroid lipoma, myolipoma, hamartomatous lesions, schwannoma, lymphangioma, granular cell tumor, fibroma, leiomyoma, rhabdomyosarcoma, hemangioma, neurofibroma, plexiform neurofibromas.

An increased prevalence of malignancy has been documented in patients affected by NF1, although the malignant transformation of the neurofibromatous elements have been a well-recognized phenomenon for decades (Poyhonen *et al*, 1997; Zoller *et al*, 1997). Malignant, peripheral nerve sheath tumors (MPNSTs) may develop within or associated with a plexiform neurofibroma. Malignant degeneration may occur in 1–29% of cases and is the foremost cause of cancer-related death in NF1 patients. A change in size of a pre-existing mass, compression, or infiltration of the adjacent structures indicate malignant degeneration.

Thus, histological and clinical evaluation should be performed in order to choose the most appropriate treatment strategy for these patients (Poyhonen *et al*, 1997; Zoller *et al*, 1997). The partial or total surgical removal of tumors can be performed to solve aesthetic and functional problems, but it is preferable to wait for the end of growth to reduce the risk of re-occurrence. There is no indication to date that surgery favors malignant degeneration.

Occasionally, oral manifestations and oral tissue specimens may provide the opportunity to diagnose NF. The oral manifestations of NF are well-documented but may not be at the forefront of the clinician's mind in the differential diagnosis of intra-oral swelling.

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