Oral Lesions in Neurofibromatosis Type I: Report of a Case and Clinical Implications

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Neurofibroma is a benign peripheral nerve sheath tumor and one of the most frequent tumors of neural origin. Its presence is one of the main clinical criteria for the diagnosis of neurofibromatosis Type I (NF-I). NF-I is a hereditary disorder inherited as an autosomal dominant trait and the patients present with skin lesions, i.e., café au lait spots and neurofibromas. Diagnosis is mainly based on a series of clinical criteria. NF-I may present with definite oral lesions, which mandate the dental surgeons with the responsibility of accurate diagnosis. The paper emphasizes the role of an oral diagnostician in the recognition of NF-I in a family.

Keywords: Mucocutaneous, Neurofibroma, Neurofibromatosis Type I, Oral manifestations

INTRODUCTION

The term neurofibromatosis (NF) designates a group of neurocutaneous genetic disorders that primarily affect the neural tissues cell growth. Among the eight different forms recognized, NF mostly encompasses NF-I and NF-II. NF-I, also known as Von Recklinghausen’s disease, is a neurodermal dysplasia, first described by the pathologists, Von Recklinghausen and Friedrich Daniel in 1882. It is the most common variant of NF with an incidence of 1:2200 to 3000 live births and accounts for 90% of all cases.¹ It is usually transmitted as an autosomal dominant trait with variable expressivity and complete penetrance, with mutations on the long arm of chromosome 17 (17q11.2) and sometimes with aberrations of the protein product of the NF-I gene. In the disease process, ectodermal and mesodermal derivatives are affected due to the defect in the embryonic neural crest cells.²

Manifestations of NF-I may vary widely among affected people ranging from mild lesions to several complications and functional impairment. Multiple neurofibromas that can occur anywhere in the body are the most common sign of NF-I. And another highly characteristic feature is the presence of café au lait pigmentation. Lisch nodules, translucent brown-pigmented spots on the iris, are found in nearly all affected individuals.³

Oral manifestations occur in 72-92% of all cases. Oral neurofibromas are present in about 25% of NF-I patients with commonly affected sites are tongue and buccal mucosa. Oral Radiographic findings include an enlarged mandibular canal, mandibular foramen, and mental foramen. Intraosseous neurofibromas have also been reported with well-demarcated unilocular, but occasionally multilocal, radiolucent lesions.⁴

A case of NF-I with oral manifestations on the hard palate is being reported here with a discussion of the oral manifestations of NF-I.

CASE REPORT

A 24-year-old female patient reported to the Department of Oral Medicine and Radiology with the chief complaint of swelling and pain in relation to the left upper back tooth region. The pain was of gradual in onset, intermittent in frequency, dull aching in nature, localized and relieved on taking medication. The patient had taken medication for the same, but the swelling did not subside. Family history revealed that her father and brother had multiple nodular swellings over the body and face. On general examination,
the patient was moderately built and nourished, and vital signs were within the normal limits.

Clinical examination revealed the presence of multiple nodule over the body, especially prominent on the face and flexor aspects of the forearms. The nodules were sessile and pedunculated; round to oval in the shape of size varying from a few millimeters to centimeters, with a smooth surface, the skin over the nodules was normal in color. On palpation, nodules were soft to firm and non-tender. Numerous brownish macules of varying diameter and smooth borders were also appreciated in the vicinity of these nodules over the face and forearms (Figures 1 and 2).

Intraoral examination revealed diffuse soft cystic swelling of size 4.5 cm × 3 cm noted in the left posterior hard palate in relation to 25, 26, 27, 28 region with a smooth surface and distinct margins. There was a grossly decayed 28 noted. A provisional diagnosis of neurofibroma of the left hard palate and an additional diagnosis of the acute periapical abscess was elucidated (Figure 3).

Panoramic radiographic examination showed caries exposed (28) and rested all other areas was within normal limits radiographically (Figure 4). Ultrasonographic examination of the left palate showed well-defined hypoechoic area with hyperechoic internal architecture. Similar findings obtained from the lesion over the left hand (Figure 5a and b).

Computed tomography showed oral lesion of 21 mm × 10 mm in the posterolateral hard palate on the left side. It showed small fluid density areas and shows enhancement 20-30 HU in the arterial phase and 20 HU noted in the venous phase. No periosteal reaction was observed (Figure 6).

Incisional biopsy of the palatal lesion had performed, and histopathological examination showed a connective tissue stroma with abundant proliferating haphazardly arranged spindle to ovoid cells. Many cells showed wavy comma-
shaped nuclei. Neurites and mast cells were seen amidst the tumor cells. A grenz zone was seen separating the tumor from the overlying surface epithelium (Figure 7a and b).

On the basis of the history revealed by the patient and correlating with the clinical, radiographic features, the case was diagnosed as NF-I with palatal lesions and the diagnosis was confirmed by histopathological finding. The patient was put on a recall program every 3 months for evaluation of the oral lesions.

**DISCUSSION**

NF is a group of autosomal dominant genetic disorders characterized by multiple cutaneous lesions. It mainly encompasses two clinical forms: Peripheral - NF-I and central - NF-II, of which Von Recklinghausen’s disease (NF-I) is the most common type which accounts for about 90% of all cases. NF-II occurs less frequently than NF-I with an incidence of 1/25,000 individuals. In contrast to NF-I patients, tumors in NF-II patients are smaller in size, however, these tumors may compress associated nerves and can cause considerable pain, nerve dysfunction, and intracranial pressure. Moreover, patients with NF-II may develop nervous tissue tumors including meningiomas or gliomas.

The diagnosis of NF-I and NF-II are still based on clinical criteria regardless of the advances in molecular biology (Tables 1 and 2). The National Institute of Health Consensus Development Conference established the diagnostic criteria for NF-I in 1987 as reported. Two or more of the below criteria are required to designate the patient as NF-I individual, and the case reported here fulfilled 3 criteria, that is, (1) Numerous café au lait spots over face and the hands, (2) Multiple neurofibromas, and (3) First-degree relatives (patient’s father and brother) with NF-I.

Pigmented lesions such as café au lait spots and freckles are one of the most common manifestations of NF-I. These lesions often present at birth or may appear during the 1st year of life. The color of the café au lait spots may vary from yellowish to chocolate-brown and they are typically oval shaped with smooth, regular borders sometimes may be large, involving a significant body segment. Pigmented lesions are distributed randomly over the body except for a disproportionately few number on the face. Freckles in the axillary or inguinal areas referred to as Crowe’s sign are very frequent findings although at times they may occur diffusely over the trunk, extremities, upper eyelids, and base of the neck. The present case had numerous café au lait pigmentation over the face and the flexor aspect of hands.

Neurofibromas are benign complex tumors that arise from peripheral nerve sheaths which is one of the most important

<table>
<thead>
<tr>
<th>Table 1: Clinical criteria for the diagnosis of NF-I²</th>
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<td>At least two of these clinical criteria are needed to diagnose NF-I</td>
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<tr>
<td>Six or more café au lait spots, &gt;0.5 cm diameter in prepubertal age and &gt;15 mm diameter in postpubertal age</td>
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<td>Two or more neurofibromas of any kind or a plexiform neurofibroma</td>
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<td>Axillary or inguinal freckles - Crowe’s sign</td>
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<td>Optic glioma</td>
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<td>Two or more Lisch nodules: Pigmented bilateral hamartomas, that appear as copular elevations on iris surface</td>
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<tr>
<td>Distinctive bone lesion, sphenoidal dysplasia, dysplasia or thinning of long bones cortical</td>
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<tr>
<td>Relatives in first degree with NF-I</td>
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<td>NF-I: Neurofibromatosis Type I</td>
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<th>Table 2: Diagnostic criteria for NF-II¹</th>
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<td>The criteria are met by an individual who satisfies condition 1 or 2</td>
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<tr>
<td>Bilateral vestibular schwannomas (VS) or</td>
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<td>Family history of NF-II (first-degree family relative) plus</td>
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<td>1. Unilateral VS &lt;30 years or</td>
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<td>2. Any two of the following: Meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract</td>
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NF-II: Neurofibromatosis Type II
findings of NF-I. Multiple neurofibromas can be seen in persons with NF-I, and solitary neurofibroma can occur in an individual who may not have the disease. There are three types of neurofibromas that may differ widely in their natural history: “Discrete” or “localized” and “plexiform” neurofibroma.

The most common type of neurofibromas are localized ones which arise from a single site along a peripheral nerve, and they are manifested as a focal mass with well-defined margins. They are seldom present at birth and frequently appear at the sight in late childhood or early adolescence. The number of localized neurofibromas may tend to increase with age, and varies broadly from person to person. Neurofibromas are found predominantly on the skin, but other organs involvement such as stomach, intestines, kidney, bladder, larynx, and heart is also reported.

Several soft tissue lesions compatible with neurofibroma could be seen all over the body of patient reported here. Plexiform neurofibromas are peripheral nerve sheath tumor which extends along the length of a nerve. This lesion may occur superficially or deeper inside the body. Plexiform neurofibromas are the main source of morbidity associated with NF-I since, their tendency to grow to large sizes and cause disfigurement. Multiple nerve involvement is also reported in some cases. Most commonly involved cranial nerves in plexiform neurofibromas are fifth, ninth, and tenth nerve.

Oral manifestations were reported in 72% of patients with NF-I. Oral manifestations of NF-I include discrete, non-ulcerated nodules, varying from normal mucosal color to red or even yellow. Common sites of the oral solitary neurofibromas include tongue (26%), buccal mucosa (8%), alveolar ridge (2%), labial mucosa (8%), palate (8%), gingiva (2%), nasopharynx, paranasal sinuses, larynx, floor of the mouth, and salivary gland at times, these tumors may also arise within the bone. The most common oral finding of NF-I reported in the literature is enlargement of the fungiform papillae of the tongue which occurs in about 50% of cases. Another common oral finding is the presence of single or multiple neurofibromas. Both hard and soft oral tissues have been reported to be affected with NF-I. Oral localized neurofibromas present as discrete nodules of normal color and they are usually asymptomatic; however, the majority of oral neurofibromas occur on the tongue. In the present case, we noted a localized neurofibroma on the hard palate, which is an uncommon location.

Oral radiographic findings characteristic to NF comprise lengthening, narrowing, and rarefaction of the coronoid and articular process, an enlarged mandibular canal, mandibular foramen, and mental foramen deepening of the sigmoid notch. Some of the other findings such as shortening of the ramus, notching of the inferior border of the mandible were also reported in some cases. Neurofibroma can also develop intraosseously which causes well-demarcated unilocular, sometimes multilocular, radiolucent lesions. The presence of impacted, displaced, or missing teeth, particularly in the mandibular arch, is also a recognized oral manifestation. However, radiographic changes were not observed in the reported case.

Accurate diagnosis of NF-I is mandatory as 3-30% of cases have been reported to develop complications such as neurofibrosarcoma, leukemia, pheochromocytoma, rhabdomyosarcoma, Wilms’ tumor, central nervous system tumors, and optic gliomas.

Since there is no cure for NF-I, multidisciplinary team supervision with the aim of preventing and controlling the complications is recommended. Although the rate of malignant transformation of neurofibroma of NF-I is less (3-5%), this neoplasia can cause other clinical problems including esthetic and functional compromise. Surgical treatment is not always satisfactory, as the total removal of large and multiple lesions, is not practical. Surgical intervention is mainly indicated when the patient’s function is compromised. Radiotherapy or chemotherapy is not recommended.

A long-term review of patients and genetic counseling is recommended owing to the likelihood of vertical transmission (50%) of the mutation. Because of the high frequency of oral manifestations dentists should be well aware of the oral manifestations of this disorder and patient must be kept on the regular follow-up because of the known risk for malignant transformation.

**CONCLUSION**

It is obvious from the above case that NF-I can present with significant oral manifestations. Even though NF-I cases are well documented in the literature, it never comes foremost into the clinicians mind when considering the differential diagnosis of intraoral swellings or enlargements. Hence, oral health care providers should be well versed with the clinical oral manifestations of NF, which will help in timely diagnosis and prompt treatment of this disorder. Even if there are no direct correlations between the severity of oral manifestations and oral health status, the psychological effects of a multisystem disorder like NF-I, coupled with oral and dental abnormalities will cause a significant oral health compromise in almost all patients. Thus, the significance of patient education for oral hygiene maintenance and regular dental check-ups must be highlighted in patients with NF-I to improve the oral health status.
REFERENCES


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