Uncommon Oral Manifestations of Neurofibromatosis Type I: A Case Report

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Abstract
Neurofibromatosis type I is an autosomal dominant genetic disorder. It is related to a mutation in the long arm of chromosome 17; however, it shows variable penetrance and about half of the cases have no family history of the disease. These patients present skin lesions such as cafe-au-lait spots, multiple neurofibromas, bone malformations, and central nervous system tumors as well. Diagnosis of NF-I & NF-II is based on clinical criteria. It is progressive in nature and one of its unique characters is the diversity of clinical expression from one patient to another and even within a family. NF-I also presents with certain oral manifestations which confers to the dentists a major responsibility for accurate diagnosis and report of the disease. We, herein, report a case of 35 year old female patient who was diagnosed incidentally for NF–I with unusual oral manifestations such as large tongue mass and hypo-plastic ramus & body of the right side of mandible.

Keywords: Neurofibromatosis; Inferior alveolar canal; Antegonial notch

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Introduction

The term neurofibromatosis (NF) is used for a group of genetic conditions that primarily affect the cell growth of neural tissues. The heterogeneity of Neurofibromatosis (NF) has become well established in recent years [1]. Riccardi recognizes at least seven types of NF while Gortin et al. added two other forms of Neurofibromatosis; NF-VIII and NF-IX. However, generally neurofibromatosis is divided into two forms, a peripheral form known as NF-I, and a central form known as NF-II. NF-I is also known as Von Recklinghausen's disease [2]. It is the most common type of NF and accounts for about 90% of all cases. Prevalence of this genetic disorder is one case in 3,000 births, however, no sex or race predilection is reported. It is an autosomal dominant trait caused by a spectrum of mutations that affect the gene located at peri-centromeric proximal gene locus on chromosome 17, known as NF-I gene [3]. It has one of the highest spontaneous mutation rates among genetic diseases in human beings. Further, only one half of all cases of NF-I patients have positive family history of the disease while other 50% of the patients represent new mutations. The clinical expressivity of the disease is extremely variable, with manifestations ranging from mild lesions to several complications and functional impairment. The frequency of oral manifestations is controversial in the literature. Some authors report a frequency of 4-7% of cases, whereas others suggest that these manifestations are present in up to 72% of cases [4]. The present case report focuses on atypical oral manifestations of Neurofibromatosis type I in a 35 year old female patient and the role of oral diagnostician in accurate and early diagnosis which is central to timely treatment and ultimate well-being of the patients.

Case Report

A 35 year old female patient reported in our department with complaint of tooth pain in back region of right side of lower jaw. The history dates back to one week when patient felt pain in her tooth, and consulted to a local practitioner; got medicine, however, did not get relieved. Thereafter she consulted to our hospital for management of the same. Past medical and dental history was non-contributory. Extra-oral examination revealed asymmetrical face with reduced right posterior facial height, short ramus and prominent antegonial notch. (Fig. 1 & 2) On further examination, multiple nodules were seen not only over the face but also all over the body, especially prominent on the face, trunk, back, and extremities. (Fig. 3, 4 & 5) These were round to oval in shape, size varying from millimeters to centimeters, smooth surfaced with normal overlying skin. On palpation, these were sessile in nature, soft to firm in consistency and non-tender. In addition, multiple brown colored macules were present over neck, trunk and arms (café-au-lait spots). The ophthalmological examination revealed presence of well-defined yellowish-brown colored dome shaped elevations projecting from the surface of the iris; Lisch nodules. However, no cervical lymph node was palpable. Intraoral examination showed normal mouth opening, poor oral hygiene, and grossly carious & tender 47. Moreover, carious 28, 38, 37, 36 and 46 were also noted. Further, a multilobular mass was seen at the lateral border of right side of tongue which extended up to the ventral surface, and it was around 3.0 x 2.5 cm², normal mucosal colored, non-ulcerated, non-tender, and soft in consistency. Another swelling was noted lingually in relation to mandibular anterior teeth extending from attached gingiva to floor of mouth which was around 3.0 x 2.5 cm² in size, sessile in origin and hard in consistency. (Fig. 6 & 7) X-ray OPG view showed apical radiolucency with respect to 47. Additionally, it showed hypoplastic ramus and body of
right side of mandible with prominent antegonial notch. (Fig. 8 (left)) Moreover, widening of inferior alveolar canal and mental foramen were also present. On the basis of clinical and radiographic findings; provisional diagnosis of acute exacerbation of chronic periapical infection of grossly carious 47, and additional diagnosis of neurofibromatosis type-I were made. Patient’s consent was taken; 47 was extracted with curettage of socket under local anesthesia. Further, incisional biopsy (Fig. 9 (right)) was performed for histopathological examination which showed neurofibroma of tongue. (Fig. 10 & 11) As biopsy had also reduced the tongue mass, no additional intervention was done; nevertheless, the patient was kept on follow up so that any new lesion or any abrupt change, in the existing one could be noted timely and appropriate measures could be taken.
Fig. 6 & 7 Showing gingival growth lingually at anterior region of mandible and multilobular mass at the right side of tongue.

Fig. 8 (left) X-ray OPG showing short ramus height, prominent antegonial notch and wide inferior alveolar canal at right side of mandible. Fig. 9 (right) Intraoperative view.

Fig. 10 & 11 Histopathological pictures showing neurofibroma.
Discussion

NF is a gradually progressive genetic disorder affecting skin and nervous system which is an autosomal dominant disease caused by an alteration in long arm of chromosome 17. Seven types of NF were described by Riccardi in 1982 while Gorlin et al. later added two further categories of type VIII “gastrointestinal” and type IX “neurofibromatosis/Noonan” forms. Further, Viskochil and Carey in 1992 proposed an alternative classification on the basis of clinical and molecular knowledge, and classified NF into two broad categories namely; Alternate form and Related form [2, 4].

NF-I is the most common type of the neurofibromatosis with prevalence rate of about 1 in 2500-3000 births. NF-I gene is highly complex; expressed in almost all the tissues, and amply in the brain, spinal cord and peripheral nervous system. Genetic linkage analysis was done in 1987, identified NF-I locus close to the centromere on the long arm of chromosome 17 whereas in 1990, the NF-I gene was identified by positional cloning, and it was found located at 17q 11.2 [5]. Neurofibromin is the protein product of NF-I gene which is a large peptide (220 KD) with 2,818 amino acids, and most abundantly present in the cells of nervous system like neurons, Oligodendrocytes and Schwann cells. Furthermore, it is also expressed in a variety of other cell types in adults, such as keratinocytes, adrenal medulla and white blood cells. Neurofibromin is ubiquitously expressed during embryonic development, and the adult pattern of tissue expression is established after the first week of postnatal life. It acts as a tumor suppressor, accelerating the conversion of the oncogene ‘Ras’ to its inactive form. Therefore, its absence could lead to higher Ras activity in Schwann cells, resulting in uncontrolled growth through a cascade of events not yet elucidated.

Further, Cafe au lait spots and axillary freckling are the distinct features of the disorder [5, 6]. It has been reported that these features could be present at birth or appear in the early years of life; multiple café au lait spots and axial freckling were noted in our case. Cutaneous neurofibroma and Lisch nodules are also pathognomonic to the disorder; nevertheless, in most people lesions do not develop until puberty. Additionally, features of NF-I include macrocephaly, short stature, scoliosis etc. It has also been reported that 30 to 60% of the patients may exhibit brain lesions that can be found in thalamus and present low IQ, memory and attention disturbances, deficits in the fine motor area and reduced oral skills; however, these findings were not seen in this case. Moreover, precocious puberty is a frequent manifestation of NF-I and occurs mainly in association with optic pathway tumors [7, 8].

Wide range of oral manifestations is also seen in NF-I. Neurofibromas present in NF-I could be simple (disseminated, cutaneous) neurofibromas and plexiform neurofibroma both of which can occur in oral mucosa [9, 10]. Gupta et al reported 44.8% of benign nerve sheath tumors to be located in head and neck region in a series of 303 cases, however, only 9% of them occurred intraorally. Moreover, macroglossia, enlarged fungiform papillae, bony deformities, wide inferior alveolar canal and enlarged mandibular foramen (blunderbuss foramen) [10] are other oral manifestations of the disease. Occasionally, cases of neurofibroma located centrally within the jaw have been reported which may exhibit large sizes with a considerable expansion potential [11]. Despite extensive oral symptoms, the dental status in NF-I patients has not been fully investigated yet. Our case showed oral manifestations; lobulated sessile mass at the right lateral border of tongue, enlargement of attached lingual gingiva in mandibular incisor region. Sailor et al in 1988 reported changes such as deformity or hypoplasia of the ascending ramus with perforation defects and inferiorly displaced external ear whereas Muller and
Slootweg stated that the skeletal lesions may be pathognomonic. Likewise, Jaffe stated that skeletal abnormalities seen in NF patients represent direct destruction from NF tissue proliferation and aberrations of skeletal development and growth either localized or systemic, indicating that NF is a disorder deeply rooted in germ-plasm. However, this case showed unusually short ramal height of mandible with marked antegonial notch of right side which is not reported previously in the literature.

Diagnosis of NF is done based on clinical criteria. According to National Institute of Health (NIH) Consensus Development Conference, the diagnostic criteria of pediatric NF-I include presence of two or more of the following criteria [5]:

- Six or more café au lait spots greater than 5 mm in prepubertal patients and greater than 15 mm in post-pubertal patients.
- Two or more neurofibromas of any kind or one plexiform neurofibroma.
- Crowe sign (freckles in the inguinal or axillary area), optic pathway tumors.
- Two or more Lisch nodules.
- A distinctive bone lesion designated as dysplasia of wing of sphenoid bone or thin cortex in long bones with or without pseudo-arthritis.
- Direct relatives (parents, siblings, offspring) with established diagnosis of NF-I.

Investigations such as radiographs, CT scans, MRI, [11, 12] biopsy and immunohistochemical detection of S-100 protein which is specific for cells of neural crest origin, are invariably helpful in diagnosis of NF-I. Although most individuals in childhood are mildly affected, prompt diagnosis of NF-I is of utmost importance since 3 to 30% of NF-I cases develop complications, such as neurofibrosarcoma, pheochromocytoma, leukemia, rhabdomyosarcoma, Wilm’s tumor, CNS tumors, optic gliomas and GI tumors [13-15].

As the disease has variable clinical presentation that can occur along with age and show wide range of severity, periodic lifelong evaluation of the patient is important to check for new disease manifestations and to prevent severe disease complications. Treatment requires multidisciplinary approach.

**Conclusion**

A good understanding of the molecular bases of NFI will not only help to understand the disease properly but also will aid in therapeutic applications and prevent unforeseen complications.

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