CASE REPORT

Plexiform neurofibromatosis involving face and oral cavity

Dorairaj Jayachandran, Selvaraj Sunantha[1], Hema Gopalaiah[2], Gajendra Veeraraghavan[3]
Department of Periodontics and [1]Depatment of Prosthodontia, Vinayaka Missions Sankarachariyar Dental College, Salem,
[2]Department of Oral Medicine and Radiology, Sree Mookambika Institute of Dental Sciences, Kanyakumari, Tamil Nadu,
[3]Department of Oral Medicine and Radiology, Vishnu Dental College, Bhimavaram, Andhra Pradesh, India

Address for correspondence:
Dr. Gajendra Veeraraghavan,
Third Cross Old Uco Bank Street,
Ramamurthy Nagar,
Bangalore - 560 016, Karnataka, India.
E-mail: drgajendrav@gmail.com

ABSTRACT

Plexiform neurofibromas (PNFs) are one of the most common and debilitating complications ofneurofibromatosis type I (NF-I). They account for substantial morbidity, disfigurement, functional impairment and are life threatening. PNFs can also be subjected to transformation into malignant peripheral nerve sheath tumor (MPNST). This complication is refractory to treat due to paucity of effective therapies for malignant soft tissue sarcomas in general and also the delay in diagnosis from a preexisting tumor. We report a case of PNF of face involving oral cavity with literature review.

Key words: Café- au- lait macules, facial plexiform neurofibromatosis, peripheral nerve sheath tumor, von Recklinghausen's disease

INTRODUCTION

A neurofibroma is a benign nerve sheath tumor in the peripheral nervous system. At least eight forms of neurofibromatosis are recognized, the most common form being neurofibromatosis type I (NF-I) or von Recklinghausen's disease. NF-I is an autosomal dominant genetically inherited disease, which can result in a range of symptoms from physical disfiguration, pain to cognitive disability. Neurofibromas arise from nonmyelinating-type schwann cells that exhibit biallelic inactivation of the NF-I gene that codes for the protein neurofibromin.[1] This protein is responsible for regulating the retrovirus associated DNA sequences (RAS) mediated cell growth signaling pathway. In contrast to schwannomas, another type of tumor arising from schwann cells, neurofibromas incorporate many additional types of cells and structural elements in addition to schwann cells, making it difficult to identify and understand all the mechanisms through which they originate and develop.[2] NF-I is estimated to occur in one in every 3000 births with no sex predilection.[3-7] Although, in principle, diagnosis of NF-I should be possible through genetic testing, only two-thirds of cases can be diagnosed and moreover, genetic testing cannot predict severity of the disease. The diagnosis of NF-I is still dependent on identification of the cardinal signs of the disease, two or more of which must be present to establish the diagnosis. Some researchers say that neurofibromas alone are pathognomonic of the disease. The condition can cause disfigurement by entwining important supportive structures.[8,9] Plexiform neurofibromas (PNFs) are uncommon and occur almost exclusively in about 5-15% patients with NF-I.[10] PNFs are benign tumors that originate from nerve sheath cells, subcutaneous or visceral peripheral nerves that can involve multiple fascicles.[1] PNF presents at birth and often progresses during early childhood at a growth rate and pattern that vary significantly and unpredictably.[3-7] Because of the involvement of multiple fascicles of nerves and tissues and the spread of PNF, there is high risk of neurological and functional destruction when surgical resection is carried out. Therefore surgical interventions are frequently postponed as long as possible from the early childhood. Most cases require repeated surgeries, as they are limited to debulking and PNFs often regrow later.[9]

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CASE REPORT

A 56-year-old female patient presented to the dental clinic, with a history of growth on the lip and tongue. Lesions are also noted on face, both sides of the chin and jaws [Figure 1]. The patient reported that the face-disfiguring growth started at birth and continuously increased in size since then. Patient complained of difficulty in speech, occasional pain and itching on the face. The patient came to hospital with these lesions for the first time and had not taken any prior treatment for the same. There was no known evidence of hereditary disease in the family and none of the other relatives had a known history of this disease. On physical examination, she was pale and face was disfigured with growth of completely overhanging skin folds typically termed as elephantiasis skin. The patient presented with macrocheilia and macroglossia. The

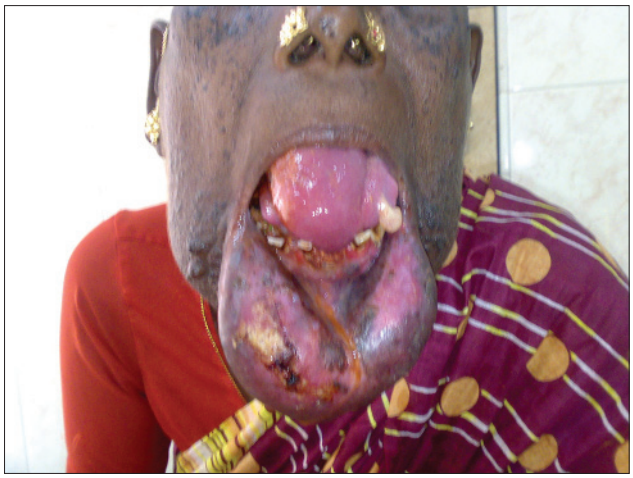

Figure 1: Clinical image showing diffuse swelling involving the tongue and lower lip

ca*fé-au-lait* macules (with some measuring over 5.5 mm) as well as several freckles were observed in the axilla, back and chest. Imaging modalities did not reveal any bone abnormality.

An incisional biopsy was taken from the lip lesion. Five-micrometer sections were made and stained with hematoxylin and eosin (H and E) and 3-μm sections were taken for S-100 immunohistochemical staining.

Histopathological features

The H and E stained section shows [Figure 2] cellular neoplasm composed of combined proliferation of schwann's cells, fibroblast, perineural cells and axon cells. Schwann cells are spindle cells with wavy nuclei arranged in bundles. The endoneurium showed myxoid changes. The interstitium showed thickened fibroblast bundles interspersed with scattered spindle cells and also shows plexiform features. Immunohistochemistry [Figure 3] showed S-100 positivity in the cytoplasm of tumor cells, which confirms their schwannian origin. On the basis of clinical and histopathological features, a clinical diagnosis of NF-I and PNF was made [Table1].

DISCUSSION

PNFs can grow from nerves in the skin or from more deeper nerve bundles. They can be very large. Internal PNFs are very difficult to remove completely because they are extended through multiple layers of tissue and the attempt would damage healthy tissue or organs. PNFs occur earlier in life and are thought to be congenital defects.

PNF is a rare type of generalized neurofibromatosis, which occurs due to overgrowth of neural tissue in the subcutaneous fat or deeper tissues in the body. It is usually considered to be a hamartoma rather than a typical tumor.[10] They originate from nerve sheath cells, subcutaneous or visceral peripheral nerves and can involve multiple fascicles. Malignant

Table 1: Histological feature of our case in comparison with the literature

Neurofibroma-I	Case study
HPE: cellular neoplasm composed of proliferation of Schwann's cells, fibroblast, perineural cells and axon cells. Endoneurium shows myxoid changes. Immunohistochemistry: CD34 and S-100 positive in all cases	Cellular tumor showing bundles of Schwann cells with wavy nuclei admixed with perineural cells and axon cells seen in myxomatous stroma. Also stroma shows bundles of fibroblast with round nucleus suggesting features of PNF. It shows floridly S-100 cytoplasm and tumor cells that is considered as schwannian-derived tumor.

PNF: Plexiform neurofibroma, CD: Cluster of differentiation

changes in 2.4-29% of patients with neurofibromatosis have been reported.[11] The condition is autosomally dominant, with variable penetration and presents as multiple nodules of various sizes, which are firm and non-tender, often associated with *café-au-lait* spots and spindle deformities. Two types of PNF that have been recognized are (i) diffuse type/elephantiasis neurofibromatosis and (ii) nodular neurofibromatosis.[8] PNF can occur anywhere along a nerve and may appear on the abdomen,[11,12] face,[10,13,14] orbit and globe,[15] legs,[10] scalp, neck, chest, pelvis or spinal cord and frequently involve the cranial and upper cervical nerves.[13] The fifth, ninth and tenth cranial nerves are most commonly involved.[16] The condition can be quite disfiguring, as in this case, presenting as hemifacial hypertrophy, occurring secondary to a plexiform tumor involvement.[17] Symptoms ranging from minor discomfort to extreme pain may occur.[8,16,18] Complications include bleeding from trauma, neurological deficits, limited limb and psychological disturbance because of abnormal anatomy.[10] There is evidence that only 50% of PNF patients have a positive family history of the disease and the remaining represent spontaneous mutation. Although most individuals who develop neurofibromatosis are not born with *café-au-lait* macules, these skin lesions develop during the first 3 years of life and were observed in our patient. Lisch nodules that are hamartomas of the iris, which appear dome-shaped and are found superficially around the eyes on slit lamp examination, helped us to confirm the disease. Axillary freckling (observed in our patient) and inguinal freckling often develop during puberty.[8] Various neurologic abnormalities, acoustic nerve involvement and deafness as well as gliomas of the optic nerve may occur.[10,16-18]

The patient in our case fulfilled many of the criteria; she had more than six *café-au-lait* macules, PNF and fleckles in the axilla, but there was no evidence of central nervous system (CNS) tumors, macrocephaly, mental deficiency, seizures, short stature or sclerosis.

PNF can cause pain, disfigurement, neurological and other clinical deficits. PNFs have the potential to cause severe clinical complications if they occur in certain areas.[19] About

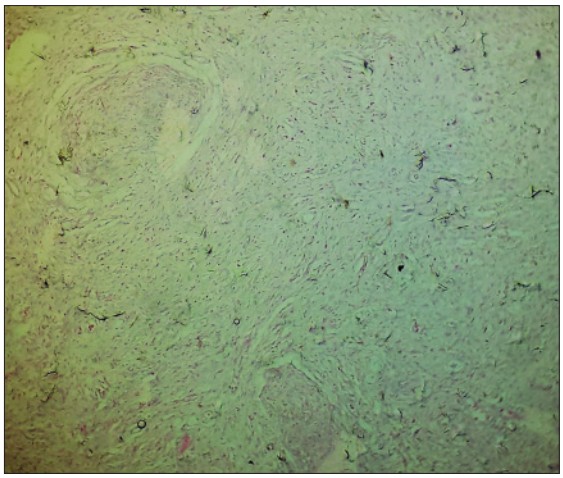

Figure 2: The photomicrograph of the sections shows bundles of Schwann cells in myxomatous stroma (H&E stain, ×100)

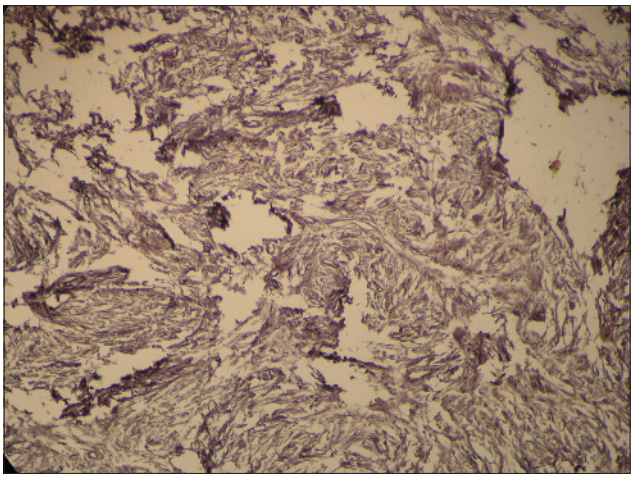

Figure 3: The photomicrograph showing tumor cells positive for S-100 protein (IHC stain, ×100)

10% of PNFs undergo transformation into a malignant peripheral nerve sheath tumor (MPNST).[20] The formation of malignant tumor from neurofibroma is associated with the loss of expression of the cyclin-dependent kinase inhibitor 2A (CDKN2A) or TP53 gene in nonmyelinating schwann cells that also exhibit biallelic inactivation of the NF-I gene.[21]

The primary treatment option for PNF was surgery.[21] Removal of PNF is difficult because they can be large and cross tissue boundaries. However, besides pain, PNFs are sometimes removed due to the possibility of malignant transformation. Once a PNF has undergone malignant transformation, radiation and chemotherapy can be used as treatment. However, radiation is generally not used as a treatment for PNFs because of concerns that this could actually promote malignant transformation.[22]

Angiotensin-converting enzyme (ACE) inhibitors have been proposed as a novel treatment of neurofibromas. ACE inhibitors are currently used to treat hypertension and congestive heart failure; to help remodeling and avert reinfarction after myocardial infarction; to ameliorate diabetic nephropathy and other renal diseases. ACE inhibitors work by indirectly downregulating transforming growth factor-beta (TGF-β), which is a growth factor that has been shown to influence the development of tumors.[23]

Gene therapy for the neurofibromin 1 gene represents the ultimate solution to prevent the cluster of maladies that are enabled by the mutation.[24,25]

The strategy adopted for our patient with neurofibromatous lesion presenting on lip and tongue was surgical excision because of the dimension of the lesion, interference with the function and esthetics of the patient. The patient underwent surgery and 6 months postoperative follow up without registering any complaints or apparent signs of recurrence of the lesion. It was decided to keep the patient under observation and review her once every 6 months for as long as possible.

CONCLUSION

The disfiguring nature of facial PNF can be psychologically traumatic for most patients and requires good counseling. PNF is conclusive evidence for arriving at a diagnosis of NF-I. A few but not all cardinal signs may be seen in patients with NF-I. Patients with PNF should be periodically recalled to rule out recurrence or malignant conversion.

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