

Case Report

## Report of a rare gingival neurofibroma in neurofibromatosis type 1 patient

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**Abstract** Neurofibromatosis designates a group of neurocutaneous disorder that essentially affect the neural tissues cell growth. Neurofibromatosis type 1 (NF1), the most common amongst the variants accounts for about 90% of all cases. The expressivity of the disease is extremely variable, with oral involvement noted in 3.4 - 92% adults and 40% children. The diagnosis of the disease is principally based on clinical criteria. Treatment for neurofibromas is surgical excision. A rare case of gingival neurofibroma in NF1 patient is accounted in this case report.

**Keywords:** Gingiva, neurofibroma, neurofibromatosis type 1, NF1, oral neurofibroma.

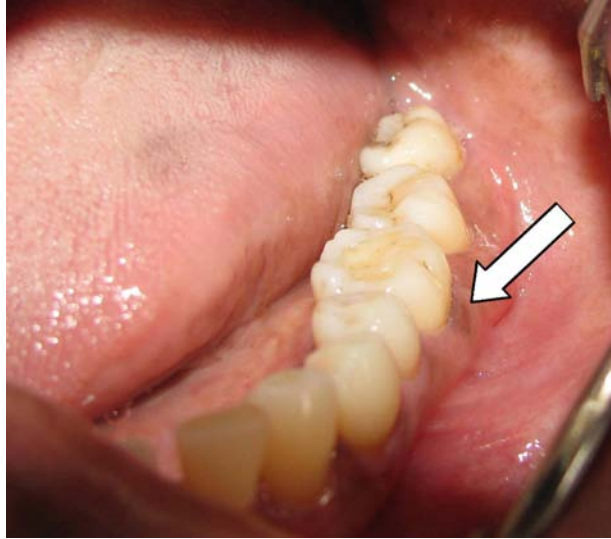
### Introduction

Neurofibromatosis designates a group of neurocutaneous disorder that essentially affects the neural tissues cell growth (Cunha *et al.*, 2004; Ferner, 2007). Although, evidence of people with supposed neurofibromatosis has been noted in literature as early as 1000 A.D., it was only in 1793 that Tilesius gave the initial description of multiple neurofibromatosis and then in 1882 von Recklinghausen extensively described the entity (Van Damme *et al.*, 1996; Ferner *et al.*, 2007). Neurofibromatosis (NF) mainly encompasses neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2), with more than 8 forms had been recognized (Neville *et al.*, 1991). NF1 or von Recklinghausen's disease is the most common variant which accounts for about 90% of all cases, with a birth incidence of one in 2500-3000 (Curtin and McCarthy, 1997; Ferner, 2007). The expressivity of the disease is extremely variable, with manifestations ranging from mild lesions to several complications and functional impairment (Cunha *et al.*, 2004). Oral involvement is noted in 3.4-92% adults and 40% children with NF1 (Visnapuu *et al.*, 2011).

### Case history

A 40 year old female patient reported with pain of fifteen days duration in the carious mandibular left third molar. She also desired evaluation of a small growth of six months duration in the adjacent buccal gingiva. Intraoral clinical and radiological examination showed endodontically and periodontally compromised 38, which was indicated for extraction. The interdental buccal attached gingiva of 36 and 37 displayed a circular, submucosal, sessile, homogeneous mass of 1.2 cm in diameter, with intact and normal appearing surface mucosa (Fig. 1). The lesion was firm and nontender. No other intra-oral lesions or abnormalities were noted. Intraoral periapical radiograph and panoramic radiography, skull views did not reveal any alteration. Also noted were multiple, discrete, sessile cutaneous putty-like masses, which had started appearing in childhood and multiple randomly distributed cafe au lait spots, with the largest (6 x 5 cm) on the left elbow region (Fig. 2). Axillary freckling was also noted.

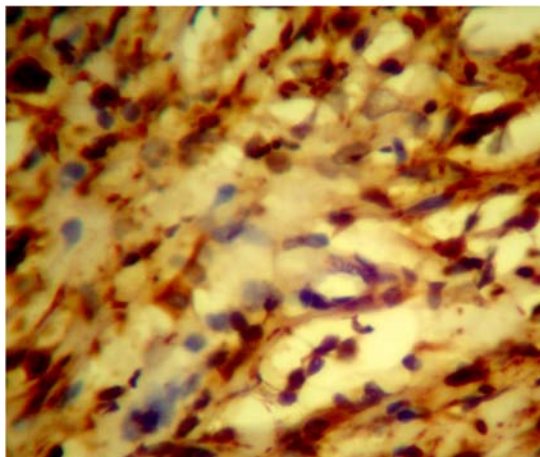
The patient was of short stature and cognitively competent. Patient had



**Fig. 1** Intraoral appearance of the lesion (arrow) on the left mandibular interdental buccal gingiva.



**Fig. 2** Café a lait spot with multiple tiny neurofibromas on the left arm.



**Fig 3** Photomicrograph of immunohistochemical analysis using S-100 stain under 40 x magnification showing diffuse positivity of the spindle cells of the tumour.

undergone excision of a giant right gluteal region mass 3 years ago, which was histopathologically diagnosed as neurofibroma. Therefore, gingival neurofibroma in NF1 was considered as the provisional diagnosis. Familial history and other diagnostic criterion for NF1 were negative. Excisional biopsy of the gingival lesion under routine hematoxylin-eosin stain revealed spindle cells with elongated wavy nuclei and fibrillar cytoplasm. S-100 marker was diffusely positive in tumor cells with clear delineation of serpentine nuclei, which substantiated the clinical diagnosis (Fig. 3). The patient is currently under follow up with no new intraoral lesions.

## Discussion

Neurofibromatosis type 1 (NF1), an autosomal dominant inherited genetic disorder, is one of the most common single gene disorders affecting the nervous system, owing to deletions, insertions or mutations affecting the NF1 gene that is located at 17q11.2 chromosome (Cunha *et al.*, 2004). Also designated as the peripheral type, this multifaceted, progressive, polysystemic neurocutaneous skeletal human disease demonstrates one of the highest spontaneous mutation rates amongst genetic diseases, with about 50% of the cases being sporadic attributable to spontaneous mutations (Curtin and McCarthy, 1997; Cunha *et al.*, 2004; García de Marcos *et al.*, 2007). The manifestations are boundless varying from cutaneous to bony lesions, physical deformity like short stature, scoliosis and macrocephaly, vasculopathy, impaired neurological functions and cognitive impairment, and abnormalities in the oral and maxillofacial region and, malignancy including peripheral nerve sheath tumours, and central nervous system gliomas and cutaneous angiomas (Curtin and McCarthy, 1997; Cunha *et al.*, 2004; Bongiorno *et al.*, 2006; Ferner 2007; Ferner *et al.*, 2007). There is no gender or race predilection (Cunha *et al.*, 2004).

Notwithstanding the headway in molecular biology, till date the diagnoses of NF1 are based predominantly on the clinical criteria of cutaneous manifestations and familial history (Munhoz *et al.*, 2010).

Diagnostic criteria National Institutes of Health (NIH) Consensus Development Conference 1987 for NF1 demands that two or more of the below criteria are required to designate the patient as NF1 individual and our case satisfied the first three criterion (NIH, 1987; Cunha *et al.*, 2004; Ferner *et al.*, 2007). The criterion encompasses: presence of 6 or more Cafe-au-lait spots (>5 mm in children or > 15 mm in adults), 2 or more cutaneous or subcutaneous neurofibromas or one plexiform neurofibroma, freckles in the axilla or groin, optic glioma, 2 or more lisch nodules (pigmented hamartomas of the iris), bony lesion with sphenoid wing dysplasia or bowing of the long bones with or without pseudoarthrosis, and/or first-degree relative with NF1.

Neurofibromas which characterize NF1, are benign and usually painless, slow growing peripheral nerve sheath tumours, but can get accelerated during puberty or pregnancy (Curtin and McCarthy, 1997; García de Marcos *et al.*, 2007). Cutaneous neurofibromata usually arise in the late teens or early twenties, manifest as multiple sessile, smooth tumors, or huge masses called elephantiasis neuromatosa (García de Marcos *et al.*, 2007).

Cafe au lait spots as observed in the present case can become obvious anywhere on the skin, but rarely on face. They are attributable to zones of focal epidermal melanosis that develop as an effect of the cutaneous nerve endings proliferation. With the hyperpigmented café au lait spots, hypopigmented macules may also be seen in some patients. (Bekisz *et al.*, 2000; Ferner *et al.*, 2007; García de Marcos *et al.*, 2007).

Oral soft tissues and intrabony manifestations varies in adults (3.4-92%) and children (40%) (Curtin and McCarthy, 1997; García de Marcos *et al.*, 2007; Visnapuu *et al.*, 2011; Jouhilahti *et al.*, 2012). The most common reported oral finding of NF1 is on the tongue with enlargement of the fungiform papillae. Macroglossia due to plexiform neurofibromatosis may also occur (Curtin and McCarthy, 1997; Jouhilahti *et al.*, 2012). Additionally single or multiple

localized neurofibromata may be noted on buccal mucosa, alveolar ridge, gingiva, lips, palate, floor of the mouth, and pharyngomaxillary space, as localized, discrete asymptomatic nodules of normal colour. The rare (5%) gingival localization may cause dental malposition or impaction. On association with a cranial nerve these neurofibromas may affect the motor and sensory function (Curtin and McCarthy, 1997; García de Marcos *et al.*, 2007; Jouhilahti *et al.*, 2012). Owing to its diffuse appearance and soft consistency, peripheral neurofibroma is akin to lipoma, vascular malformation, lymphangioma or rhabdomyoma (García de Marcos *et al.*, 2007).

NF1 patients may also show facial disfigurement secondary to hypo or hyperplasia of maxilla and malar bone. The other expressions include neurofibroma of III, V, VII and VIII cranial nerves, enlargement of I, V, VIII cranial nerve foramina and inferior alveolar canal, widened mandibular foramen and mental foramen, various bony craniofacial anomalies like absence of sphenoid bone, coronoid notch morphology alteration and decrease in the mandibular angle. Dysplasia of the sphenoid major wing may result in exophthalmos. Hypoplasia of the mandibular ramus with radiolucency in the sigmoid notch and hypoplasia of the temporal and mandibular components of the temporomandibular joint have also been reported (Lee *et al.*, 1996; Van Damme *et al.*, 1996; Bekisz *et al.*, 2000; Ferner, 2007; García de Marcos *et al.*, 2007; Visnapuu *et al.*, 2011).

Radiographically, intraosseous variant is usually seen as a well demarcated unilocular radiolucency but can occasionally be multilocular (Curtin and McCarthy, 1997; García de Marcos *et al.*, 2007). On the CT scans, neurofibromas mostly show low attenuation, although some of them may show soft tissue density. Low density lesions encompass variable quantity of Schwann cells, which are rich in lipids, cystic degeneration and xanthomatous alterations. High density areas are believed to symbolize collagen rich or cellular areas. In the MRI scanned images, low signal in T1 and high signal in

T2, with a variable highlighting with the contrast is demonstrated. The bull's eye sign, a low central signal with a high peripheral signal in T2 weighted images is a distinctive for neurofibromas. An analogous sign can be picturized in CT as well, but, with a central high signal (García de Marcos *et al.*, 2007).

Biopsy of the lesions should be conducted for histopathological evaluation (Curtin and McCarthy, 1997). Histologically, neurofibromas are uncapsulated mixed tumors consisting of Schwann cells (36 to 80%), perineural cells (0.7% and 31%), and endoneural fibroblast (García de Marcos *et al.*, 2007). Collagen IV, S100, and CD34 are constructive biomarkers in the investigation of NF1-related oral soft tissue tumors (Jouhilahti *et al.*, 2012).

Individuals with NF1 demonstrate an increased incidence of both benign and malignant tumors, with the risk of malignant transformation being 3 to 5 % (Curtin and McCarthy, 1997; García de Marcos *et al.*, 2007). Malignant peripheral nerve sheath tumors may develop in 2–5% of NF1 patients, within or associated with a plexiform neurofibroma. Size variation in the existing mass, pain, compression, or infiltration to adjacent structures is denotive of malignant degeneration and this necessitates prompt clinical care (Bongiorno *et al.*, 2006).

Total resection with 1 cm margins whenever feasible is the treatment of choice for accessible and small tumors. It is appropriate to defer resection till cessation of growth phase to reduce the risk of recurrence. Radiotherapy or chemotherapy is not recommended (García de Marcos *et al.*, 2007).

Since NF1 is not curable, multidisciplinary team supervision with the aim of preventing and controlling the complications is recommended (Curtin and McCarthy, 1997). Long term review of patients and genetic counseling is recommended owing to the likelihood (50%) of vertical transmission (Ferner *et al.*, 2007). Dentists should be sentient of oral manifestations of neurofibromatosis and also educate the patients about abnormal symptoms, indicative of malignant degeneration.

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