Case Report

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NEUROFIBROMATOSIS: A NEUROCUTANEOUS DISORDER WITH ATYPICAL ORAL MANIFESTATION

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ABSTRACT:

Neurofibromatosis is the most common type of peripheral nerve neoplasm. It is an autosomal dominant disease which is the result of spectrum of mutations affecting the NF1 gene. Patients present with skin lesions (café au lait spots and neurofibromas) as well as bone malformations and central nervous system tumors. 4% - 7% of cases present with oral manifestations. So it is the role of the dentist to diagnose the lesion and intervene timely to overcome the functional and esthetic complications. Here a case of neurofibromatosis with oral manifestation in a patient with chronic periodontitis is presented.

Key words: Neurofibromatosis, Periodontitis, Oral manifestations, Osseous lesions

INTRODUCTION:

Neurofibromatosis (NF) refers to a group of genetic disorders that affect the cell growth of neural tissues. Neurofibromatosis was first described in 1882 by the German anatomopathologist von Recklinghausen.[1] It is considered to be the most common type of peripheral nerve neoplasm, arising from several cell types including Schwann cells, melanocytes, perineural and endoneurial fibroblasts resulting in altered skin pigmentation. Eight different clinical phenotypes of NF are identified. NF1 is also known as von Recklinghausens disease, and is the most common type of NF and accounts for almost 85% to 97% of all cases.[2] The prevalence is one in 3000 births and have no sex predilection.[3] NF1 is an autosomal dominant disease caused by a spectrum of mutations that affect the gene located at 17q11.2 chromosome, which is also known as NF1 gene.[4] Oral manifestations of NF1 include lesions on tongue, buccal mucosa, gingiva and lips. Association of neurofibromatosis with periodontitis have been reported by Pollack RP et al.[5] in 1990 and Powell et al in 2006.[6] This case report is unique in that multiple enlargement occurred in the oral cavity in relation to the lingual aspect of lower anteriors, retromolar region and tongue. This resulted in improper oral hygiene maintenance which further lead to chronic periodontitis.

CASE DETAIL:

A 35yr old male patient presented to Department of Periodontics with the chief complaint of mobility of lower front teeth and occasional mild pain which aggravates

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on biting since two months. Patient had noticed a small growth on the inner aspect of gums in relation to the lower front teeth 3years back which gradually increased in size. There was no associated pain or discharge from the growth. Patient gave a history of similar growths on tongue and other parts of mouth since childhood.

The general clinical examination revealed multiple cutaneous nodules on the body, including the face and neck (Figure 1a,b). He had undergone multiple surgeries on ear, tongue and gastrointestinal tract for similar growths in the past. The patient was diagnosed with plexiform neurofibromatosis. Cafe – au – lait pigmentation was present which has been included as one of the criteria for diagnosis (Figure 2a,b).

Patient gave a history of headache one month back for which a CT (Computed Tomography) brain was done which revealed asymmetric enlargement of left cavernous sinus and soft tissue mass in left parotid and post auricular regions. He had visual and auditory impairment on left side. Family history was noncontributory.

Periauricular soft tissue swelling extending to parotid region was observed on left side leading to facial asymmetry. Both external ears showed malformation (Figure 3 a,b)

Intraorally, soft tissue examination revealed a soft well circumscribed smooth non tender sessile growth on lingual aspect of lower anteriors involving the attached and marginal gingiva extending from 43 to 34 region with size 5x10cm (Figure 4a). This lesion was submucosal, non-ulcerated, nonpainful and presented with normal colour. A soft compressible nontender diffuse mass of tissue almost completely involving the left lateral aspect of tongue was observed with a tissue tag of approximately 1cm length from its anterior extension (Figure 4b). A similar lesion of 1x 3cm in dimension was noted on the retromolar area on left side extending from the distal aspect of 37 to the pterygomandibular raphae (Figure 4c).

A hard non tender rounded nodule was noted on attached gingiva 1cm short of marginal gingiva of 35. Buccal mucosa showed brownish gray pigmentation with intermingled atrophic areas. Mouth opening was apparently normal.

Intra orally (Figure:5 a,b,c) hard tissue examination revealed an end on occlusion with generalized severe attrition. A comprehensive periodontal examination was done which revealed heavy deposits of calculus on lingual surface of mandibular anteriors. The oral hygiene maintenance was compromised due to the overgrowth on lingual aspect of 43 to 34 interfering with proper plaque removal. Periodontal probing resulted in profuse bleeding. Class III gingival recession was noted in relation to both labial and lingual aspect of 31andGrade 2 mobility of 31 and 32. Deep pockets (>6mm) in relation to 18,17,24,26,31,to 47. Based on the comprehensive periodontal evaluation and radiographic findings a provisional diagnosis of generalized chronic periodontitis was made.

3. Radiographic evaluation

IOPA (Intra Oral Periapical Radiography) revealed interdental bone loss in relation to

31,32,33,34 extending to apical one third. A well defined radioopacity 8x6mm was noted overlapping the root of 33 (Figure 6a). Occlusal view of the lower arch revealed thickening of cortical plate in relation to 33 to 35 area (Figure 6b). Panoramaic view revealed generalized interdental bone loss, thinned out condyle and coronoid with atrophic ramus and deepening of sigmoid notch on left side. Impacted 27, 28, 38 and a supernumerary behind 18 was present (Figure 6c).

4. Treatment

Initially nonsurgical periodontal therapy including scaling and root planning was performed. Excisional biopsy of the oral lesion extending from the marginal gingiva of 42-32 to the floor of the mouth was performed (Figure 7a,b,c,d). Suturing was done with 4-0 vicryl. The excised tissue was send for histopathological examination. Comprehensive periodontal flap surgery for the periodontally involved teeth was performed and the patient was planned to be kept under periodic follow up.

5. Histopathology

Histopathological examination of the excised tissue revealed parakeratinized stratified squamous epithelium and connective tissue with proliferation of neoplastic spindle cells with interspersed collagen fibres, prominent neurovascular bundles, diffuse inflammatory cells and mast cells.(Figure 8a,b,c,d)

DISCUSSION:

The diagnosis of NF1 and NF2 is still based on the clinical criteria despite the advances of the various molecular biologic techniques. In the case of NF1, the diagnostic criteria include the appearance of two or more of the following presentations: cafe-au-lait spots, two or more neurofibromata, freckling in the axillary and inguinal regions, optic pathway tumour, lisch nodules and distinctive osseous lesions.[7] In NF1, pigmented lesion is one of the most common manifestations, which may often present at birth or appear during the first year of life. The pigmented lesions appear as cafe-au-lait spots and freckles.[8] This patient reported multiple cafe-au-lait spots which appeared during childhood.

Neurofibromata are benign complex tumours arising from peripheral nerve sheaths, which constitute one of the main manifestations of NF1. Clinically they appear as either discrete or localized and plexiform neurofibromata.[4] A localized neurofibroma presents as a focal mass with well defined margins and can occur either superficially or may involve deeper peripheral nerves. It arises from a single site along a peripheral nerve. Neurofibromata, although most commonly seen on skin, but can involve many organs including stomach, intestines, kidney, bladder, larynx and heart. This patient revealed a history of multiple lesions in stomach, intestine, spine and undergone excision for the same. The most commonly affected sites in the head and neck region include the scalp, cheek, neck and the oral cavity.

A plexiform neurofibroma is a peripheral nerve sheath tumour that extends along the length of a nerve. The occurrence of the lesions can be either superficial or deep inside the body. This type of a lesion is a major source of morbidity mainly due to

their tendency to grow in larger sizes and cause considerable disfigurement. The cranial nerves mostly involved are the fifth, ninth and tenth nerves [3]. There is a low percentage of malignant neoplasias in these individuals. The most common malignancy seen is the malignant peripheral nerve sheath tumour.(MPNST).[4] The case presented here showed the presentation of plexiform neurofibromata.

Osseous alterations may be seen in more than half of the patients with neurofibromatosis.[9] Bone growth can also be stimulated by adjacent neural tumour leading to hyperplasia. These changes can be manifested as either cortical erosion or as medullary resorption from intraosseous lesions.[6] According to Geist et al bony defects may arise from mesodermal dysplasia unrelated to the proximity of the neural lesion.[10]

Radiographic findings of the lesions involving the mandible include enlargement of the mandibular foramen (34%), enlargement of mandibular canal (29%), or branching of the mandibular canal. (24%).[11]

Plexiform neurofibroma on the face can present with facial asymmetry. In this case considerable facial asymmetry was noted due to periauricular soft tissue swelling extending to parotid region on the left side of the face. Shapiro et al reported that exophthalmia can occur which is the result of sphenoid wing dysplasia.[12]

Based on the literature review, the frequency of intraoral manifestations of NF1 was estimated to occur in 4% to 7 % of all cases.[13] However studies by D'Ambrossio et al[11] and Shapiro S D et al [12] suggested that oral manifestations are much higher. According to Shapiro et al, oral manifestations were found in 72% of patients with NF1.

D'Ambrosio et al.[11]reported that 92% of their patients had some form of oral involvement. Enlargement of the fungiform papillae was found in 53% of cases, with intraoral neurofibromas reported in 26% cases.

Regezi and Sciubba reported intraoral neurofibromas in 25% of neurofibromatosis patients.[9] Among the oral mucosal sites tongue and buccal mucosa are the most common sites. Diffuse macroglossia can also be present.[14] This patient reported with diffuse involvement of tongue. Solitary neurofibromas are usually treated by surgical excision and have little chances of recurrence.

Shapiro et al stated that the involvement of the gingiva is 5%.[12] In this case enlargement of the gingiva in relation to the lingual aspect of 33 to 43 was observed which extends to the ventral aspect of the tongue. The enlargement resulted in plaque accumulation and subsequent development of periodontitis. The excision of the lesion was planned due to the interference created by the lesion for proper oral hygiene maintenance. NF1 commonly leads to tongue and gingival tissue overgrowth, which can progress to oral cancer.[15] The disease is caused by a variety of inactivating mutations of NF1 gene, which codes for neurofibromin. Neurofibromin is a tumour suppressor and negative regulator of RAS signalling.[16] RAS is an oncogene and a small G-protein which is

active when bound to GTP (Guanosine Tri Phosphate) and inactive when bound to GDP (Guanosine Di Phosphate). Active RAS results in stimulation of pathways leading to mesenchymal cell proliferation. Mutant forms of NF1 are inactive and result in overactive RAS signalling, increased epithelial to mesenchymal transition, proliferation and fibrosis.[17] Hence regular monitoring is essential to detect the occurrence of overgrowth in these patients.

CONCLUSION:

Neurofibromatosis is one of the most common genetic disorder and the oral manifestations accounts almost 72%. So dentists should be aware of the characteristics of the disease. The most fatal complication of the disease is the malignant transformation of the lesions. Hence periodic follow up is necessary and management should be carried out by the involvement of a comprehensive medical team to reduce the morbidity and mortality of the disease.

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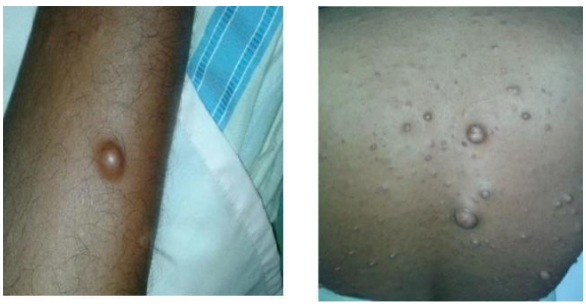
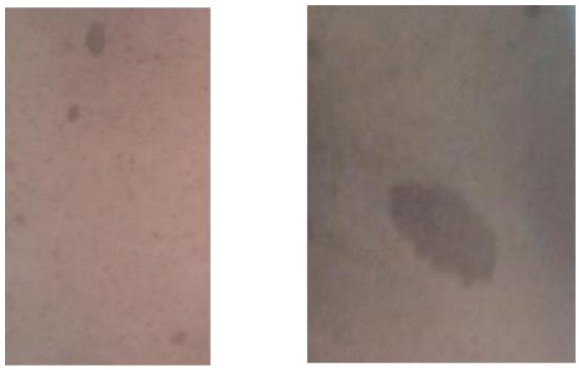
FIGURES:



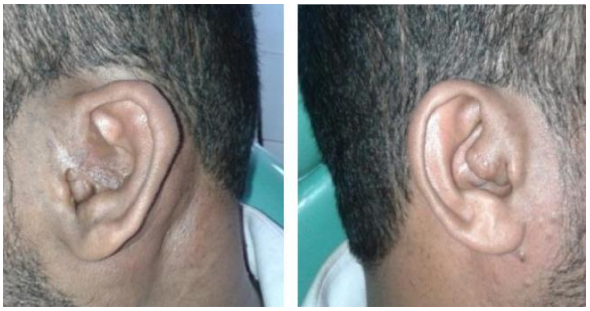
1(a) 1(b)

- Figure :1 (a),(b) multiple cutaneous nodules on the body



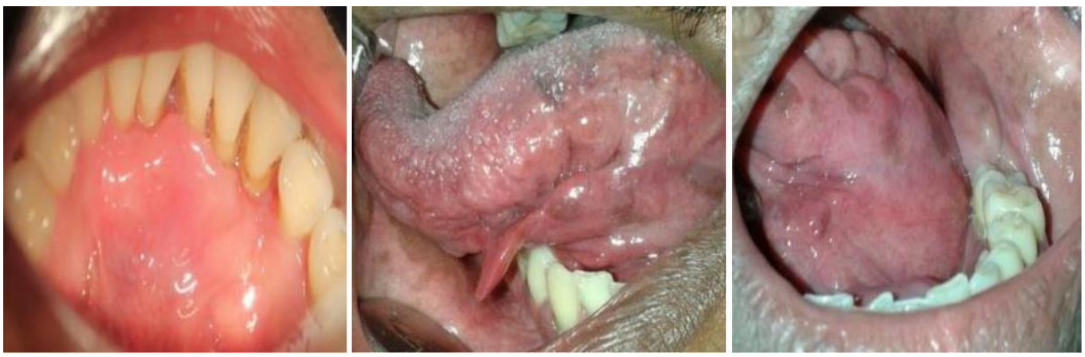
2(a) 2(b)

- Figure : 2 (a),(b) Cafe – au – lait pigmentation



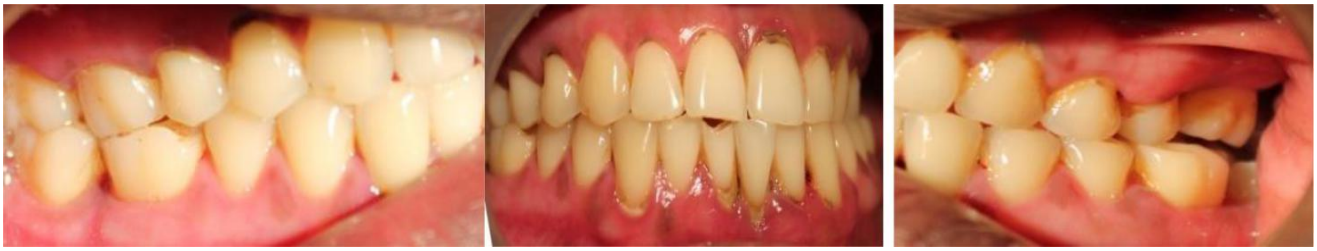
3(a) 3(b)

- Figure: 3 (a),(b) External ears showing malformation



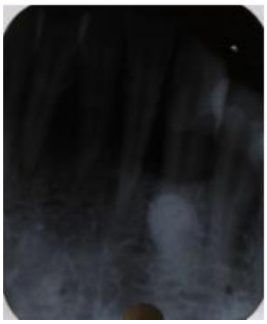
4(a) 4(b) 4(c)

- Figure :4 Intra oral manifestations (a) Growth on lingual aspect of lower anteriors (b) Diffuse mass on the left lateral aspect of tongue (c) Lesion on left mandibular retromolar area

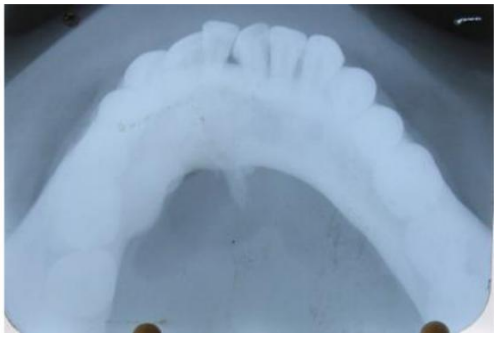


5(a) 5(b) 5(c)

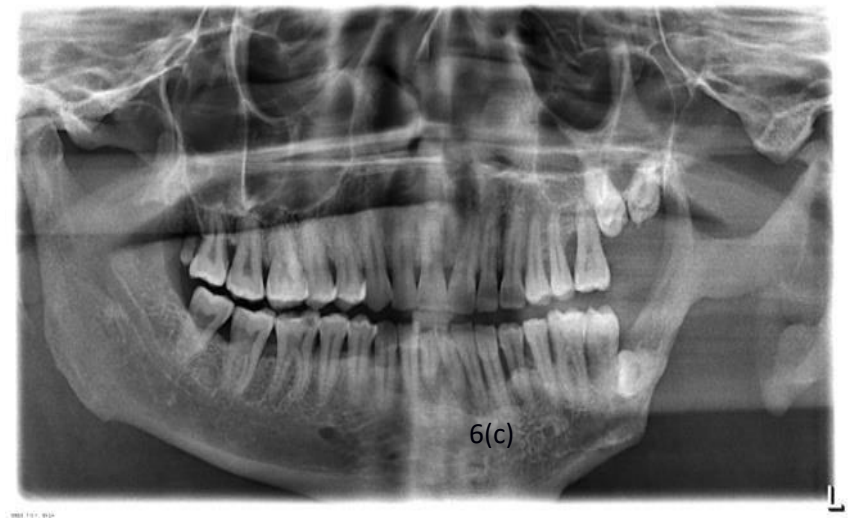
- Figure 5a,b,c Intra oral soft & hard tissue changes



6(a)

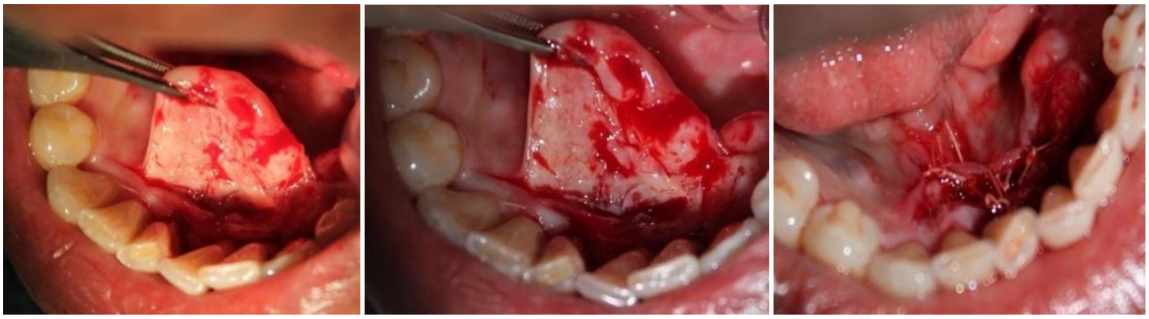


6(b)

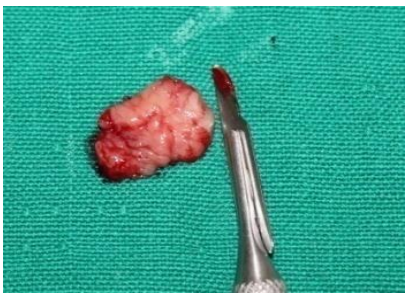


6(c)

- Figure: 6 Radiographic presentation (a) interdental bone loss in relation to 31,32,33,34 with radioopacity on root of 33 (b) Thickening of cortical plate in relation to 33 to 35 (c) OPG reveals generalized interdental bone loss, thinned out of condyle and coronoid with atrophic ramus and deepening of sigmoid notch on left side.

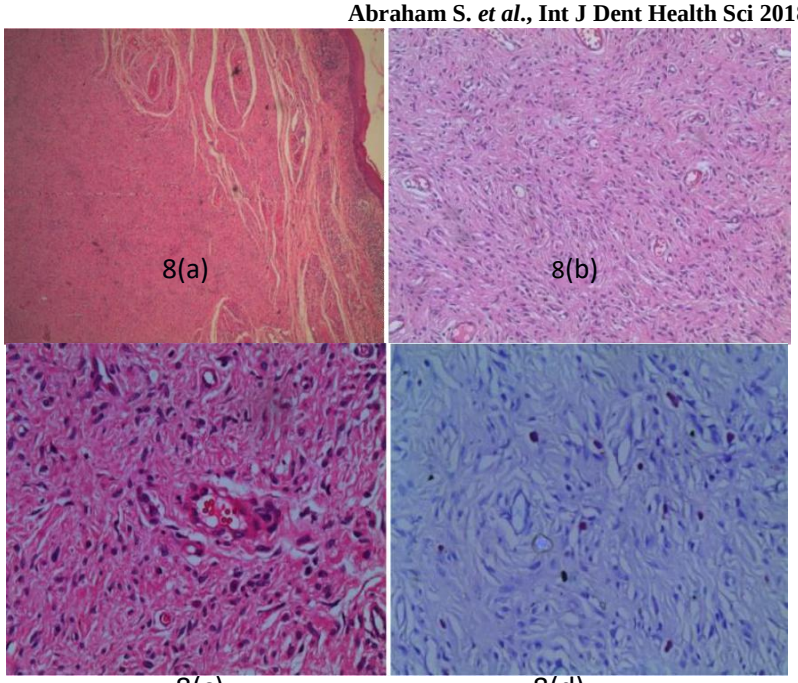


7(a) 7(b) 7(c)



7(d)

- Figure 7(a),(b),(c) Excision of oral lesion extending from the marginal gingiva of 42-32 to the floor of the mouth (d) excised tissue.



- Figure : 8 Histopathological view of the excised tissue (a) parakeratinized stratified squamous epithelium and connective tissue with proliferation of neoplastic spindle cells, collagen fibres and neurovascular bundles, 4x magnification. (b) connective tissue with inflammatory cell infiltrate 10x magnification (c)40x magnification (d) Toludiene blue staining 40x magnification