Solitary neurofibroma of the gingiva

Prakriti Dayal, BDS, *Junaid Ahmed,* MDS, BDS, *Ravikiran Ongole,* MDS, BDS, *Karen Boaz,* MDS, BDS.

ABSTRACT

الورم الليفي العصبي هو ورم عمدي عصبي طرفي حميد، يتواجد عادة مع مرض فون ريكلنغهاوزن في الجلد. يحدث النوع المنفرد عادة في منطقة الرأس والرقبة، مما يؤثر في الغالب على البالغين الشباب. ويتميز بأنه كتل بطيئة النمو وغالبا تكون عديمة المرض وتتواجد في اللسان وفي مخاطية الشدق. تسلط الأدبيات الحديثة الضوء على حالات مختلفة في مواقع أخرى. ونستعرض في هذا التقرير عن حالة ورم ليفي انفرادي لمريض يبلغ من العمر 72 عاماً و استمر معه المرض لمدة 15 عاماً. وكشف علم أمراض الأنسجة ستروما فايبرومسود مع الحزم العصبية المتعرجة في نواة ملتوية.

Neurofibroma is a benign peripheral nerve sheath tumor, usually found in association with Von Recklinghausen's disease of the skin. The solitary variant commonly occurs in the head and neck region, mostly affecting young adults. They are characteristically slow-growing masses, often asymptomatic and have been found most commonly in the tongue and buccal mucosa. A recent literature review highlighting incidences in various other locations has been tabulated here. We also report a case of a solitary neurofibroma of the gingiva in a 72-year-old male of 15 years duration. Histopathology revealed a fibromyxoid stroma with sinuous nerve bundles with buckled nuclei.

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From the Department of Oral Medicine and Radiology (Dayal, Ahmed, Ongole), and the Department of Oral Pathology (Boaz), Manipal College of Dental Sciences, Manipal University, Mangalore, India.

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Address correspondence and re-print request to: Dr. Ravikiran Ongole, Department of Oral Medicine and Radiology, Manipal College of Dental Sciences, Manipal University, Mangalore, India. Tel. +91 (944) 8430387. E-mail: oralcare@gmail.com

Neurofibromas are benign nerve sheath tumors in the peripheral nervous system presenting as either a localized lesion, a diffuse plexiform variant, or as part of the generalized syndrome of neurofibromatosis known as neurofibromatosis type-1 (NF-1). The NF-1 is inherited as an autosomal dominant trait with a high degree of penetrance but variable expressivity, affecting approximately one in every 3000 individuals worldwide, and has one of the highest mutation rates among genetic diseases. The solitary neurofibroma is similar to the disseminated form of the disease except the systemic manifestations and hereditary factors, which are absent in the former. The cause of solitary neurofibroma is yet unknown.[1] It is observed mainly in the third decade of life although the reported age of occurrence varies from 10 months to 70 years of age.[2] No specific predilection to race or gender has been reported. Neurofibromas may often occur in the cervico-facial region and intraoral neurofibromas unrelated to NF-1 are common. Oral manifestations may be seen in as many as 70% of patients with neurofibromatosis.[3] The solitary forms are most commonly seen on the tongue and buccal mucosa whereas overgrowths of gingival soft tissue are found more in association with neurofibromatosis. They are clinically characterized by slow growth, lack of pain, and a superficial location. The use of traditional histochemical stains, immunohistochemistry with a variety of biomarkers, and electron microscopy have demonstrated a mixed lineage of Schwann cells, perineural cells, and fibroblast differentiation in these tumors. We report a rare case of solitary neurofibroma of the gingiva in a 72-year-old man. Our objective in presenting this particular case is to highlight the importance of including neurofibroma as a differential diagnosis of solitary swellings affecting the oral mucosa, especially the gingiva.

Case Report. A 72-year-old male patient presented with a swelling in the right mandibular gingiva. He had been aware of the lesion for 15 years and gave a history of gradual increase in the size of the swelling. He complained of mild pain on exerting pressure in the region for the past few months. Intraoral examination

revealed a solitary, pedunculated, erythematous, lobulated swelling of approximately 2.5 cm in diameter arising from the marginal gingiva of teeth 46, 47 (**Figure 1**). It was firm in consistency and non-tender on palpation. Grade III mobility of 47 was noticed. A panoramic radiograph revealed no evident radiolucency/radiopacity in the right mandibular region except for a generalized interdental bone loss. A provisional diagnosis of irritational fibroma was made. The differential diagnoses considered were that of pyogenic granuloma and peripheral giant cell granuloma.

The lesion was surgically excised, and microscopic evaluation revealed a fibromyxoid stroma, which was highly cellular exhibiting numerous interlacing sinuous nerve bundles with buckled nuclei, mast cells, and focal areas of calcifications. Areas showing chronic inflammatory cell infiltrates comprising plasma cells and lymphocytes were evident (**Figures 2 & 3**). The sample showed a mild S-100 positivity in immunohistochemical analysis, thus supporting the histopathological diagnosis of neurofibroma of the gingiva (**Figure 4**). A detailed questioning and re-examination of the patient was carried out, which revealed no relevant family history, and no evidence of café-au-lait spots, similar neurofibromas in any other part of the body, or any other stigmata associated with Von Recklinghausen disease. A 10-month follow-up showed no recurrence.

Discussion. Neurofibromas are benign tumors of the peripheral nerve sheath, described first by Smith

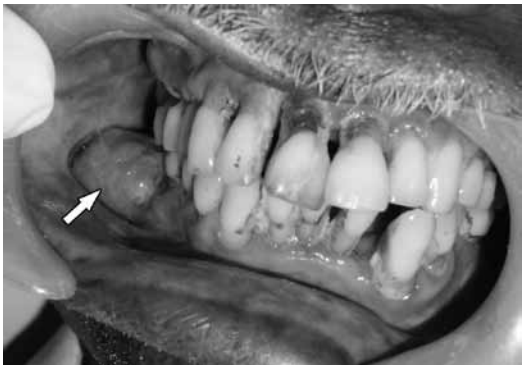

Figure 1 - Solitary pedunculated erythematous swelling in the right mandibular gingiva in relation to the marginal gingiva of teeth 46, 47.

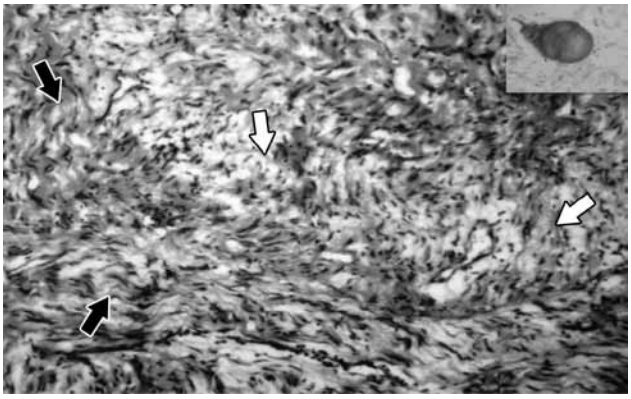

Figure 3 - Photomicrograph shows cellular stroma with interlacing bundles of nerve fibres (black arrows) and interspersed myxoid areas (white arrows). Foci of calcification seen (inset).

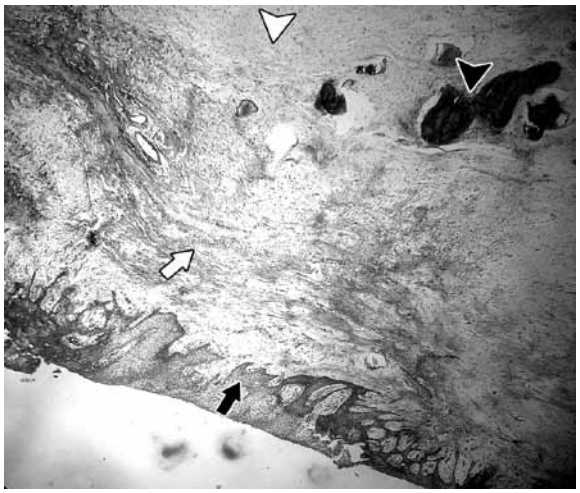

Figure 2 - Photomicrograph reveals gingival epithelium (black arrow) overlying proliferating neural tissue (white arrow) interspersed with myxoid areas (white arrow head) and discrete foci of calcification (black arrow head) (Hematoxylin and eosin stain; 4x).

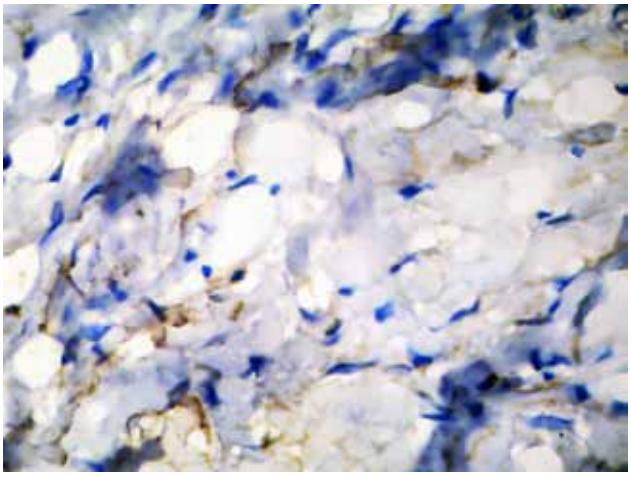

Figure 4 - Immuno-histochemical staining shows mild positivity to S-100 protein by Schwann cells (40x).

in 1849 and later by Von Recklinghausen in 1882.[4] They are believed to arise from perineural fibroblasts, which are neuroectodermal in origin. They are usually present in the first year of life after café-au-lait spots have appeared, and may show accelerated growth spurts during puberty and pregnancy. Neurofibromas show a tendency to occur in the trunk and head region. Lee et al[5] investigated patterns of occurrence of solitary neurofibromas in sites other than the above mentioned locations, and found no specific site predilection. Newer analytical techniques have helped increase the incidence reporting of this condition in literature from a previously reported 4-72%.[6] Clinically, neurofibromas are generally asymptomatic and may present variably as part of the generalized syndromes of NF-1 and NF-2, a plexiform variant, or a solitary or localized form.

The NF-1 is a neurocutaneous disorder inherited as an autosomal dominant trait with variable penetrance. It is believed to be caused by somatic mutations at the NF-1 gene, a tumor suppressor gene located in the pericentromeric region of chromosome 17.[7] Approximately 50% of cases show no family history. Described by Von Recklinghausen in 1882, the diagnostic criterion for the recognition of NF-1 include 2 or more of the following general features:[1,7] 1) Presence of 6 or more café-au-lait macules over 5 mm in greatest diameter in pre-pubertal people and over 15 mm in greatest diameter in post-pubertal people. The macules are smooth edged, yellowish tan to dark brown in appearance; 2) Two or more neurofibromas of any type in the body or one plexiform type of neurofibroma; 3) Freckling in the axillary (Crowe's sign) or inguinal region; 4) Two or more Lisch nodules in the eye, also called as iris hamartomas. They appear as translucent brown pigmented spots on the iris; 5) Distinctive osseous lesions such a sphenoid dysplasia or thinning of the long bone cortex with or without pseudoarthrosis; 6) A first-degree relative with NF-1.

Neurofibromatosis type II (NF-2) is the central form of the disease, caused by gene mutations of the tumor suppressor gene coding for schwannomin on chromosome 22 (q12.1). Bilateral acoustic neuromas are the hallmark of this disease. Ependymomas and subcapsular opacities of the eye are also commonly seen. Cutaneous stigmata are only occasionally observed.

Plexiform neurofibromas are congenital tumor masses involving nerve trunks and growing around nerve fascicles. They result in unilateral diffuse tortuous enlargement of the peripheral nerves. They are pathognomonic of the disease. A diffuse neurofibroma involving the skin and subcutaneous tissues is a common variant of neurofibroma often seen in the head and neck region and may involve the oral cavity. When in the head and neck region, plexiform neurofibromas most commonly involve the fifth cranial nerve (especially the first and second divisions), leading to mild to severe hemifacial disfigurement.

Localized neurofibroma or solitary forms of the disease are sporadic lesions seen in patients without NF-1. It is most common in young adults, and no gender predilection has been observed. It does not differ much from the disseminated form or multiple form of the disease except that the systemic and hereditary factors are absent. The first description of solitary neurofibroma of the oral cavity was given by Bruce in 1954[8] and since then only a few cases have been reported in the literature.[2] Papadopoulos et al[9] speculated that intraoral neurofibromas may originate from the branches of the fifth or seventh cranial nerve. In our case, the patient presented with a solitary lesion with neither taste nor sensory disturbances, so the cranial nerve branches from which the tumor may have originated remain unclear. Clinical findings specific to the solitary variant include oral lesions that appear as pedunculated or sessile nodules, with a slow growth rate and same color as normal mucosa. They can also present as submucosal discrete masses ranging from a few millimeters to several centimeters. They are usually unilateral and painless, but may compress surrounding vital structures (usually the trigeminal nerve) resulting in pain or paresthesia. The most frequent location observed is the tongue although they may occur at any site, especially on the palate, gingiva, cheek mucosa, and floor of the mouth. An intraosseous location in the mandible has been described in literature. In our review of the literature of the last 5 years, we found 11 published cases with the following intra-oral distribution: mandible (2); maxilla (2); palate (1); gingiva (3); lip (1); paranasal sinuses (1); salivary gland (1) (**Table 1**). This differs from the general view that neurofibromas are more commonly found in the tongue and buccal mucosa. All patients showed a negative family history except in 2 cases. Excision of the lesion was carried out in all the cases, with no recurrences noted.

Lesions in the base of the tongue may present with odynophagia, dysphagia, change in voice, and ear pain.[6] These tumors are nearly always nodular, but cases of diffuse macroglossia have been reported.[10] Gingival overgrowth has been found to be more in adults as compared with children and adolescents. Lesions affecting the gingivo-dento-alveolar complex can cause displacement and mobility of the erupted teeth. Absence, impactions, and mal-positioning of the teeth can be found in the primary dentition.[11]

Radiographic features are seen when neurofibromas arise centrally within the bone. These changes may manifest as a cortical erosion from the adjacent soft tissue tumors or as medullary resorption from intraosseous lesions.[12] If it occurs in the mandible, it causes enlargement and branching of the mandibular canal, increased bone density, concavity in the medial surface of the ramus and increased dimension of the coronoid notch.

Histopathologically, the solitary variant is well circumscribed but not encapsulated. Tumors arising outside the perineurium may blend with adjacent connective tissue. Interlacing bundles of spindle-shaped cells that often exhibit wavy nuclei with a serpentine configuration is commonly seen. The cells are closely associated with wire-like strands of collagen that resemble "shredded carrots" in appearance. These cells are associated with delicate collagen bundles and variable myxoid matrix. The stroma of the tumor is interspersed with occasional mast cells, lymphocytes, and rarely xanthoma cells. Some cases may show prominent Meissner bodies, which are sensitive, tactile receptors concentrated in the dermal papillae of the digital tips, palms, and soles,[3] and also in the gingival connective tissue. Mucinous changes may be prominent and result in a mistaken diagnosis of myxoma or myxoid liposarcoma. In certain respects, these cellular neurofibromas resemble Antoni A areas of schwannoma. Unlike schwannoma, they are not encapsulated and lack a clear partition into 2 zones.

In peripheral nerves, Schwann cells and neurons express S-100 protein under immunohistochemistry. However, in the oral mucosa, Langerhans cells are also positive for S-100. In the plexiform variant, Schwann cells exhibit S-100 positivity in around 60-80% of the cases. Discrete oral neurofibromas have been found to be more heterogeneous containing areas with only few S-100 positive Schwann cells.The mild positivity to

Table 1 - Tabulated literature review of the various neurofibromas in the head and neck region reported in the years 2008 - 2012.

Author	Variant	Location	Age/Gender	Features
Johann et al (2008)[13]	Solitary	Extraosseous hard palate near right alveolar border	39y/ F	Asymptomatic, sessile, fibrous pink, and smooth nodule
Sharma et al (2009)[14]	Solitary	Intraosseous right maxilla	0.5y/ M	Well-circumscribed, firm, and non-tender
Depprich et al (2009)[2]	Solitary	Submucosal mass in lingual aspect of left mandible	64y/ M	Painless pedunculated exophytic tumor
Lopez-Jornet et al (2010)[1]	Solitary	Upper lip	14y/ F	Well-defined exophytic lesion
Ohno et al (2010)[3]	Solitary	Gingiva	32y/ F	Pedunculated swelling
Thammaiah et al (2011)[15]	Plexiform	Right maxillary alveolar ridge	2.5y/ F	Well-defined, non-tender, non-fluctuant swelling, hard in consistency Radiographically, thinning of coronoid process, haziness of right maxillary sinus Cutaneous: Café-au-lait spots, Lisch nodules
Cegarra-Navarro MF et al (2011)[16]	Solitary	Left maxillary sinus	70y/ F	CT showed heterogeneous lesion eroding the lateral wall of sinus, no signs of tissue infiltration
Bisher et al (2011)[17]	Plexiform	Left submandibular gland	17y/ M	Firm consistency, not attached to skin Cutaneous: Café-au-lait spots, cutaneous neurofibromas
Shetty et al (2011)[11]	Generalized	Palatal gingiva	40y/ M	Limited mouth opening Well-defined swelling, firm in consistency. Generalized pockets and generalized tooth mobility Cutaneous: Multiple faint round densities in the skin
Komerik et al (2011)[18]	Generalized	Mandible	5y/ F	Asymptomatic submucosal diffuse enlargement of the alveolar ridge. Rubbery texture in retromolar region, rigid on tooth bearing area. Hypomineralization of teeth Panoramic radiograph showed enlargement of inferior alveolar canal and notching of the angulus Cutaneous: Café-au-lait spots, freckling on the neck and axillary region, short stature and mild scoliosis, mild learning disability
Asgary et al (2012)[19]	Generalized	Mandibular gingiva	32y/ F	Generalized painless fibromatosis Cutaneous: Multiple fibromas, Café-au-lait spots on the upper lip, and wrist

S-100 protein found in our biopsy specimen resonates with the above finding.

The treatment of choice is surgical excision of the solitary lesions, trying to conserve the nerve from which the tumor originates. Multiple lesions in the oral cavity can be treated with carbon dioxide laser. If present within the skin, a procedure known as dermabrasion is carried out. Usually, the prognosis for solitary neurofibroma is extremely good, with only rare instances of recurrence after resection.

Malignant transformation of neurofibromas into neurogenic sarcomas and neurofibrosarcomas is seen in 5-15% of patients with NF-1. Although these malignancies most commonly occur on the trunk and extremities, head and neck involvement has been reported.[10] The prognosis of malignant tumors associated with neurofibromatosis is poor. Other complications observed include bleeding from trauma, neurological deficits, and psychological disturbances because of abnormal anatomy. Surgery might be helpful in each of the above.

In conclusion, neurofibroma as a solitary variant rarely occur in the gingiva. However, this report highlights the need to consider it in the differential diagnosis of solitary swellings occurring on the gingiva or elsewhere in the oral cavity.

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