IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 6 Ver. VI (June. 2016), PP 88-91
www.iosrjournals.org

Discrete Subcutaneous Neurofibroma of Skin Associated with Neurofibromatosis 1, Alongwith Solitary Neurofibroma Involving The Tongue --- An Unusual Case Report.

Dr. Mayur B. Chaudhary[1], Dr. Shweta D. Chaudhary[2], Dr. Anuraag Choudhary[3], Dr. Shailesh Kumbhare[4], Dr. Chaitanya Varangaonkar[5]

[1]*Associate Professor Department Of Oral Pathology And Microbiology Bharati Vidyapeeth Deemed University Dental College And Hospital Pune, Maharashtra-411043, India.*
[2]*Associate Professor Department Of Pedodontics And Preventive Dentistry Bharati Vidyapeeth Deemed University Dental College And Hospital Pune, Maharashtra-411043, India.*
[3]*Associate Professor Department Of Oral Medicine And Radiology Vidya Shikshan Prasarak Mandal's Dental College And Hospital Nagpur, Maharashtra-440001, India.*
[4] *Dental Surgeon,Nagpur, Maharashtra-440001,India.*
[5] *Dr. Chaitanya Varangaonkar, Assistant Professor, Department of Dentistry,Dr. Ulhas Patil Medical College and Hospital, Jalgaon, Maharashtra,India.*

Abstract: *Neurofibroma, constitutes a distinct clinical entity especially if its occurrence is seen in oral cavity. They have been divided into two broad categories viz; dermal and plexiform. Dermal lesions are further classified as discrete cutaneous neurofibromas, discrete subcutaneous neurofibromas and deep nodular neurofibromas. In oral cavity it may appear as a solitary or; multiple disseminated, associated with von Recklinghausen disease. Here we present a case report of discrete subcutaneous neurofibroma of skin associated with Neurofibromatosis 1, alongwith solitary neurofibroma involving the tongue, focusing on clinical features, histopathology and various treatment modalities.*

Key-words: *Oral neurofibroma, discrete subcutaneous neurofibroma, solitary neurofibroma of tongue*

I. Introduction

Neurofibroma, a benign nerve sheath tumor of the peripheral nervous system is usually found in individuals with neurofibromatosis type I (NF1), an autosomal dominant genetically-inherited disease.[1] Neurofibroma has been subdivided into two broad categories: dermal and plexiform. Dermal neurofibromas being associated with a single peripheral nerve, plexiform neurofibromas are associated with multiple nerve bundles. According to the World Health Organization classification system, dermal and plexiform neurofibromas are grade I tumors. Dermal neurofibomas are further classified as discrete cutaneous neurofibromas, discrete subcutaneous neurofibromas and deep nodular neurofibromas. Discrete cutaneous neurofibromas appear as sessile or pedunculated masses on the skin, which may be non-tender. Discrete subcutaneous neurofibromas appear as nodules on the skin, which may be tender. Deep nodular neurofibromas involve tissues and organs underneath the dermis. [2] Neurofibroma of oral cavity associated with dermal lesions is a clinically rare entity. Thus we report a case of discrete subcutaneous neurofibroma of skin associated with Neurofibromatosis 1, alongwith solitary neurofibroma involving the tongue and also focus on its clinical features, histopathology and various treatment modalities.

II. Case report

A 52 year old male reported to the department of Oral Pathology with chief complaint of multiple swellings (bumps) over the face and body since 20 years (Figure 1) and inability to move left hand since two months. According to the patient, few swellings on the face and chest appeared to be tender. He also complained of a single, small nodular swelling on dorsum of tongue since two months (Figure 2). The multiple swellings covered the face and whole of the body gradually (few of the swellings were tender) and later on he noticed a single, small nodular swelling on the tongue which was of a greater concern for him as it caused an undesirable, irritational feeling during mastication. On clinical examination, patient showed normal vital signs, normal built and gait and normal color of the skin except presence of multiple swellings on the face and body and inability to move left hand. Magnetic resonance Imaging of the lesion showed a 7.1x5.4x4.6 cms mass in supraclavicular region indenting and displacing left subclavian artery and the left internal jugular vein (Figure 3). No intraspinal extension was seen. Extra-oral examination of the patient revealed normal facial symmetry except presence of multiple swellings, bilaterally smooth and synchronous temperomandibular joint movements, competent lip seal and non-palpable and non-tender lymph nodes. Intra-oral examination revealed normal oral

hygiene status except a presence of single nodular swelling on the dorsum of tongue. A provisional clinical and radiographic (MRI) diagnosis of discrete subcutaneous neurofibroma of skin associated with Neurofibromatosis 1, alongwith solitary neurofibroma involving the tongue was given which was confirmed by histopathology report where the biopsied tissue in hematoxylin and eosin stained section showed interlacing bundles of spindle-shaped cells with wavy nuclei (Figure 4). These cells were associated with collagen bundles and myxoid matrix.

III. Discussion

Peripheral nerve tumors are either intraneural or extraneural tumors. Neurofibromas amongst them are intraneural, benign, spindle cell tumors, most of which are often associated with von Recklinghausen's disease. They arise from non-myelinating-type Schwann cells that exhibit biallelic inactivation of the NF1 gene that codes for the protein neurofibromin. [1] This protein is responsible for regulating the RAS-mediated cell growth signaling pathway. 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. [3]

Although the mutations in non-myelinating Schwann cells make them susceptible to the transformation into neurofibromas, it is still unclear why only the non-myelinating variety as compared to the myelinating ones gives rise to neurofibromas. [4]

Secondly, it has been hypothesized that the proliferating non-myelinating Schwann cells secrete chemoattractants such as the KIT ligand, and angiogenic factors such as the heparin-binding growth factor midkine that promote the migration of different kinds of cells(fibroblasts, perineurial cells, endothelial cells, and mast cells) that are heterozygous for the NF1 gene into the hyperplastic lesions created by these non-myelinating Schwann cells. Finally, the mast cells secrete mitogens or survival factors that alter the developing tumor microenvironment and result in neurofibroma formation.

The World Health Organization (WHO) has subdivided neurofibromas into 2 broad categories: dermal (arising from single peripheral nerve) and plexiform (arising from multiple nerve bundles). Other clinicopathologic subtypes include localized neurofibroma (sporadic neurofibroma), diffuse neurofibroma, plexiform neurofibroma, and epithelioid neurofibroma. Dermal neurofibromas are further subclassified as: [2] 1) Discrete cutaneous neurofibromas: Sessile or pedunculated masses on the skin, which are fleshy and non-tender, and can, vary in size. 2) Discrete subcutaneous neurofibromas: Lie below and look like bumps on the skin, which can sometimes be tender. 3) Deep nodular neurofibromas: Involving tissues and organs underneath the dermis, but otherwise resembling cutaneous and subcutaneous neurofibromas.

The dermal lesions of the present case appeared same as that of discrete subcutaneous neurofibromas. Clinically the lesions appear as brown, pink, or skin colored, soft or firm single or multiple nodules. Café-au-late spots (irregularly shaped, brown pigmented macules) may or may not be associated with the dermal lesions. Involvement of the oral cavity by a solitary and peripheral plexiform neurofibroma in patients with no other signs of neurofibromatosis is rare. Sporadic cases have been reported in the submandibular gland, tongue, and on the periosteum at the mental foramen. Several authors have suggested that these isolated neurofibromas may represent a hamartomatous growth. Localized or solitary neurofibroma is the most frequent manifestation and develops along a peripheral nerve as a focal mass with well-defined margins but not encapsulated. The lesions appear in late childhood or in young adults. Solitary neurofibromas are sporadic, but may be associated with the NF-1 syndrome. Most of these arise in the third to fourth decades of life.[5]

The lesions in the oral cavity usually appear as multiple or solitary, non-tender, pedunculated or sessile, usually painless discrete masses that range in size from a few millimeters to several centimeters. Pain or paresthesia is not a sign of neurofibroma, but may be seen due to nerve compression especially when trigeminal nerve is involved. The tongue, buccal mucosa, hard palate, gingiva and the vestibular areas are the most common sites of presentation. There may be enlarged fungiform papillae on the dorsum of the tongue and diffuse enlargement of the gingiva. When mandible is involved, enlargement of the inferior alveolar canal and a flaring of the inferior alveolar foramen can be observed. The oral lesion of the present case was a single, solitary, sessile and a discrete mass on the dorsum of tongue.

Computerized tomography (CT scans) and Magnetic resonance imaging (MRI) are valuable in determining the involvement of bone (enlargement of nerve canals) and the compression of specific nerve by neurofibromas. Magnetic resonance Imaging of the lesion in present case showed a 7.1x5.4x4.6 cms mass in supraclavicular region indenting and displacing left subclavian artery and the left internal jugular vein. No intraspinal extension was seen.

Genetic evaluation can be carried to identify the defect either in NF1 or NF2 gene. In the present case, genetic evaluation could not be carried out due to non-compliance on part of the patient.

Macroscopically, neurofibromas appear to be soft to firm in consistency with a shiny, whitish surface. Histopathologically, neurofibromas contain spindle-shaped cells, with fusiform or wavy nuclei distributed within a delicate myxomatous connective tissue matrix. This matrix is rich in mucopolysaccharides. Mast cells

may be seen scattered within the connective tissue stroma. The histopathologic appearance of the cells in the present case showed interlacing bundles of spindle-shaped cells with wavy nuclei and associated with collagen bundles and myxoid matrix.

Plexiform neurofibroma shows spindle-shaped cells, with fusiform or wavy nuclei and tortuous aggregates of neural tissue distributed in a myxoid matrix. Foci of possible nuclear atypia may be seen.
Diffuse neurofibroma presents with the similar features of neurofibroma with an ill-defined infiltration of neoplastic neural tissue into underlying connective tissue with a spindle-shaped or fusiform or rounded Schwann cells.

A hematologic-biochemical examination for protein melanoma inhibitory activity may be used to detect the presence of neurofibromas. [6]

Immunohistochemical examination when used for confirmation of the diagnosis shows positivity of the lesional cells for S-100 protein, signifying that they originate from neural crest–derived tissue. The lesional cells in the present case showed positivity for S-100 protein. Antibodies to epithelial membrane antigen, CD57, and collagen IV are used only when histologic differentiation with other neural tumors is difficult.

Dermal neurofibromas are surgically removed only when they are painful or for esthetic purpose. CO_2 lasers are another treatment modality for removal of dermal neurofibromas.[7] On other hand plexiform neurofibromas due to their location, extensive spread and due to the possibility of malignant transformation are difficult to remove. Other treatment modalities for neurofibroma include gene therapy [8], stabilizing the axon-Schwann cell interactions and reducing mast cell infiltration. [9] and use of drugs like ACE inhibitors.[10] There are certain other drugs for treatment of neurofibromas (example: Imatinib, Pegylated Interferon, Sirolimus, Sorafenib, Tranilast etc.) but, since these are in clinical trial phases, their incorporation either oral or systemic in the host does not warrant their adverse outcomes. So in general, treatment modalities for neurofibroma are for cosmetic purpose and to treat its complications.

The complications of neurofibroma include recurrence of the lesion, scarring, numbness and malignant transformation. In the present case, the complication seen on the patient was his inability to move left hand.
Prognosis for solitary neurofibroma is good, but becomes poor when there is malignant transformation of the lesion. The average 5-year survival rate is 15-20%.

IV. Conclusion

Solitary neurofibroma involving the tongue associated with discrete subcutaneous neurofibroma of skin represent a distinct entity where there are very few case reports being reported of this lesion. Such lesions belong to a group of peripheral intraneural tumors where non-myelinated Schwann cells are mutated resulting in secretion of certain chemoattractants that promotes the migration of different kinds of cells. Here we have discussed a case of discrete subcutaneous neurofibroma of skin alongwith solitary neurofibroma involving the tongue and have tried to focus on its clinical features, histopathology and various treatment modalities.

References

[1]. Muir D, Neubauer D, Lim IT, Yachnis AT, Wallace MR. "Tumorigenic properties of neurofibromin-deficient neurofibroma Schwann cells.". Am J Pathol 2003; 158 (2): 501–13.
[2]. "Case Based Pediatrics for Medical Students and Residents: Chapter XVIII.11. Neurofibromatosis", by Vince K. Yamashiroya, MD. August, 2002. Department of Pediatrics, University of Hawaii John A. Burns School of Medicine.
[3]. Miller RT. "Immunohistochemistry in the differential diagnosis of schwannoma and neurofibroma" (PDF). Propath October 2004.
[4]. Zheng H, Chang L, Patel N, Yang J, Lowe L, Burns DK, Zhu Y. "Induction of Abnormal Proliferation by Nonmyelinating Schwann Cells Triggers Neurofibroma Formation". Cancer Cell 2008; 13 (2): 117–28.
[5]. Johann AC, Caldeira PC, Souto GR, Freitas JB, Mesquita RA. Extra-osseous solitary hard palate neurofibroma. Braz J Otorhinolaryngol Mar-Apr 2008; 74(2):317.
[6]. Kolanczyk M, Mautner V, Kossler N, et al. "MIA is a potential biomarker for tumour load in neurofibromatosis type 1". BMC Med 2011; 9: 82.
[7]. Ostertag JU, Theunissen CC, Neumann HA. "Hypertrophic scars after therapy with CO_2 laser for treatment of multiple cutaneous neurofibromas". Clinical Orthopaedics and Related Research 2002; 28 (3): 296–8.
[8]. Wetmore DZ, Garner CC. "Emerging pharmacotherapies for neurodevelopmental disorders". J Dev Behav Pediatr September 2010; 31 (7): 564–81.
[9]. Zheng H, Chang L, Patel N, Yang J, Lowe L, Burns DK, Zhu Y. "Induction of Abnormal Proliferation by Nonmyelinating Schwann Cells Triggers Neurofibroma Formation". Cancer Cell 2008; 13 (2): 117–28.
[10]. Namazi H. "ACE inhibitors: a novel treatment for neurofibroma". Clinical Orthopaedics and Related Research 2008; 15 (5): 1538–9.

Legends:

Figure 1: Multiple solitary nodules on neck, chest and abdomen

Figure 2: Single solitary nodule on the dorsum of tongue

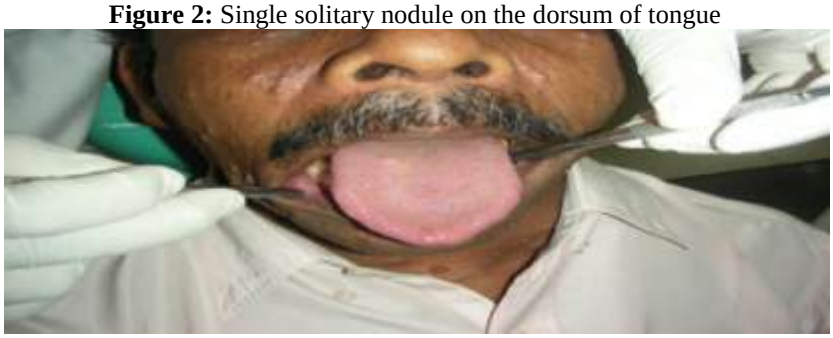

Figure 3: Magnetic resonance Imaging of the lesion showing a 7.1x5.4x4.6 cms mass in supraclavicular region indenting and displacing left subclavian artery (S) and the left internal jugular vein (I) and displacement of these vessels (yellow arrows)

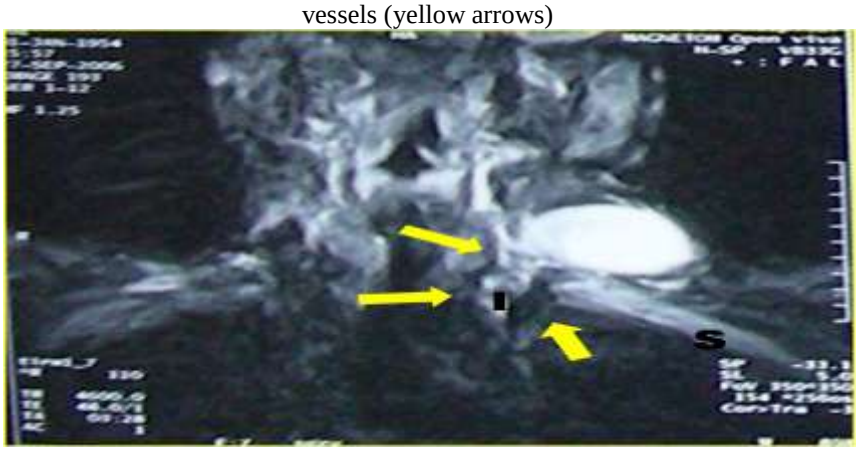

Figure 4: Microphotograph of the biopsied lesional tissue showing interlacing bundles of spindle-shaped cells with wavy nuclei and the associated collagen bundles and myxoid matrix (H&E x 10). Few blood vessels are also evident.