CASE REPORT

Schwannoma of the Tongue: A Case Report with an Insight on its Variants and Pathogenesis

G. Deepthi, Keerthi Sai Surapaneni, Mary Oshin, D. Shyam Prasad Reddy
Department of Oral and Maxillofacial Pathology, Kamineni Institute of Dental Sciences, Sreepuram, Narketpally, Telangana, India

Email for correspondence: drdeepthireddy999@gmail.com

ABSTRACT

Neurilemmoma or schwannoma is a benign, slow growing, solitary, and encapsulated perineural tumor. Approximately 25–45% of all neurilemmomas occur in the head and neck region. Of these 1–12% occur intraorally, the most common site being tongue. Consideration of this lesion into the differential diagnosis of soft-tissue lesions was often not accounted. The definitive diagnosis can only be given by microscopic examination. Here, we present a case report of 27-year-old male patient with a solitary oval growth on the right dorsolateral margin of tongue, which was clinically diagnosed as traumatic fibroma. However, final diagnosis of neurilemmoma was made by histological examination. This article also focuses on giving an insight into the variants of neurilemmoma and a dig into its pathogenesis.

Key words: Neurilemmoma, Schwann cells, schwannoma, tongue

INTRODUCTION

Neurilemmoma, also called schwannoma, neurinoma, and perineural fibroblastoma, is a benign tumor of nerve sheath origin.[1] Neurilemmoma was first described by Verocay in 1910. He then named it as "Neurinoma". The term schwannoma was introduced by Masson in 1932.[2] Later, in 1935, Stout used the term, neurilemmoma, and further detailed its histopathology.[3] In 1940, Tarlov described the tumor to be of fibroblastic origin and coined the term perineural fibroblastoma.[4] The neoplasm can occur alone or as a part of genetically inherited diseases: Neurofibromatosis Type 1 (NF1) or Type 2 (NF2) and schwannomatosis. NF2 gene functions as a tumor suppressor and a regulator of Schwann cells.[5] Schwannomas can arise from any nerve covered with a Schwann cell sheath, which include the cranial nerves (except for the optic and olfactory), the spinal nerves, and the autonomic nervous system.[1]

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Approximately 25–45% of all schwannomas occur in the head-and-neck region.[6] Of these, approximately 1–12% occur intraorally with the tongue being the most common site followed by palate, floor of the mouth, buccal mucosa, lips, and jaws.[7] Schwannomas of the tongue most commonly occur between the second and fourth decades of life and display no gender predilection (52.8% female vs. 47.2% male) and often present as a painless mass (69.6%).[5] The present paper highlights a case report of neurilemmoma of tongue with an insight on its variants and pathogenesis.

CASE REPORT

A 27-year-old male patient presented to the Department of Oral Medicine and Radiology, Kamineni Institute of Dental Sciences with a chief complaint of growth on right dorsolateral margin of tongue which was small initially and gradually increased to the present size causing discomfort while chewing food, pain, and tenderness while eating hard foods [Figure 1]. On intraoral examination, on inspection, a solitary oval growth of approximately 1 × 2 cm^2 was seen on right dorsolateral margin of tongue, extending 1.5 cm away from tip of tongue and 1 cm over to the

dorsum from the lateral margins of the tongue. The growth was pale pink and surrounded by white periphery, indentations of tooth are also observed on its anterior most part. On palpation, the growth was solitary, sessile, roughly oval in shape, tender on palpation, and firm in consistency at the base and soft at apex. There is no evidence of discharge, blanching on pressure, fluctuations, and compressibility. Based on the above clinical findings, a provisional diagnosis of irritational fibroma on the right lateral border of the tongue was given. Excisional biopsy was done and sent to Department of Oral and Maxillofacial Pathology for the histopathological examination of the specimen.

A single bit of tissue measuring 1 × 1 cm^2, brownish-white in color, irregular in shape, and firm in consistency was received for histopathological examination [Figure 2]. The whole bit was taken for tissue processing. Hemotoxylin and eosin stained tissue section showed the presence of hyperplastic stratified squamous epithelium of variable thickness with underlying connective tissue stroma. In few areas of the stroma, there were fascicles of spindle shaped cells arranged in the palisading form resembling Antoni A areas. In between these areas, there were acellular eosinophilic materials resembling verocay bodies. The stroma also showed the presence of irregular arrangement of spindle-shaped cells resembling Antoni B areas [Figures 3 and 4]. The connective tissue stroma also showed mixed inflammatory cell infiltrate chiefly composed of neutrophils, eosinophils, and lymphocytes along with few hemorrhagic areas. Based on the histopathological findings, a final diagnosis of neurilemmoma was made.

DISCUSSION

Schwannoma or neurilemmoma is a benign, slow growing, encapsulated, and neural tumor, thought to originate from Schwann cells around the nerve sheath which surround cranial, peripheral, and autonomic nerves. The Schwann cells proliferate and later compress and displace the affected nerve.[8] The rate of malignant transformation for head-and-neck schwannoma is reported to be 8–10%, with one case of malignant transformation reported in the tongue.[9]

Most cases of schwannoma are sporadic, but in some individuals, they are associated with

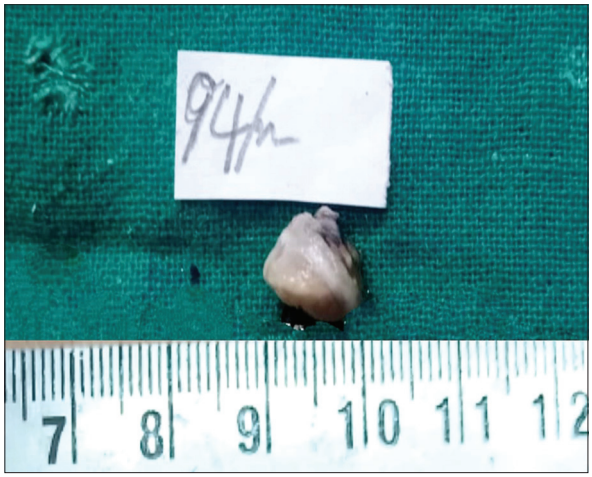

Figure 2: Specimen measuring 1 × 1 cm^2, brownish-white in color and firm in consistency was received for tissue processing

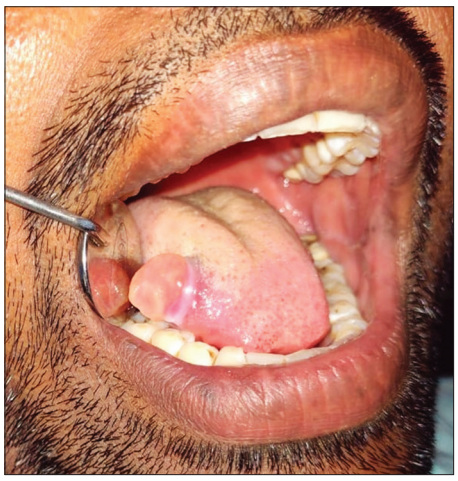

Figure 1: Clinical picture showing solitary oval growth of approximately 1 × 2 cm^2 I size on right dorsolateral margin of the tongue

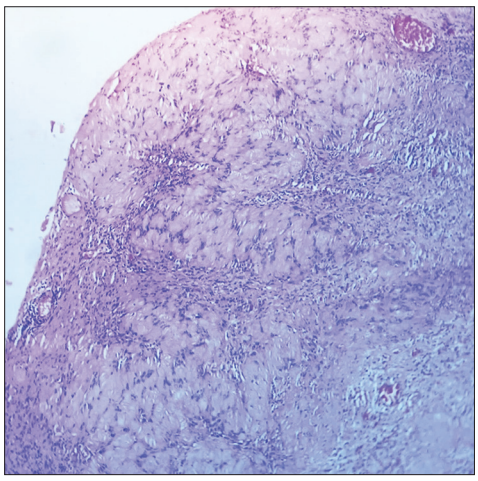

Figure 3: Hematoxylin and eosin stained section shows spindle shaped cells arranged in both Antoni A and Antoni B morphologies (× 10)

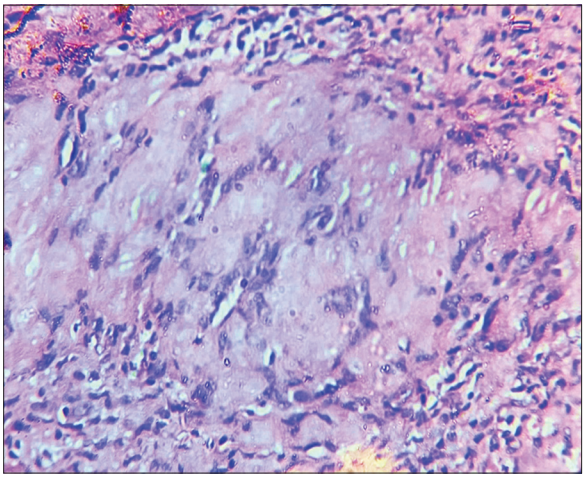

Figure 4: Hematoxylin and eosin stained section showing Antoni A areas with palisading nuclei and Verocay bodies (× 40)

neurofibromatosis Type II (schwannomatosis).[10] A review of the literature done by Lee *et al.* over the past 61 years showed 84 cases of schwannoma of tongue. Lingual schwannoma may arise at any age between 7 and 77 and shows no sex predilection. Despite the fact that it originates from nerve tissue, lingual schwannoma is usually painless.[11] It has been reported that pain is generally identified in subjects with schwannomatosis rather than sporadic cases, and nerve edema and myxoid alterations have been associated with this condition. In a case report and systematic review study by Sitenga *et al.*, it has been reported that about 70% of tongue schwannomas are painless.[12] In the present case, the patient had a history of discomfort, pain, and tenderness on the dorsolateral surface of the tongue.

Histologically, most of the schwannomas are encapsulated with two main patterns: Antoni A area and Antoni B area. The Antoni A areas are cellular and composed of spindle cells with wavy nuclei. Highly differentiated areas show "nuclear palisading" and Verocay bodies (eosinophilic cell bodies encircled by rows of nuclei). The Antoni B areas are hypocellular and the cells lack orientation. They are loosely arranged in a myxoid matrix accompanied by thin strands of collagen. Occasional mast cells may be identified in the Antoni B areas.[13] In addition to these characteristic patterns, diagnosis is aided by immunohistochemical markers like S-100 and Leu 7, which support the Schwann cell nature of these tumors. Capsular epithelial membrane antigen (EMA) and CD34 positivity were also observed in Antoni A areas of schwannoma.[14]

Verocay Bodies

These bodies were first described by Verocay in 1910; hence, they were eponymicaly called as Verocay bodies and were considered diagnostic of neurilemmoma.[15] The pathogenesis of the formation of verocay bodies is explained by the overexpression of lamininsin the schwann cells. Lamininspromotecell-celladhesionandarenormally foundinthebasementmembranesofseveraltypesofcells includingSchwanncellsandalsoitfacilitatesmyelination of axons and repair of nerve injury.[1,16]

Inschwannomas,thereispossiblyanoverexpression of laminins which causes the alignment of nuclei of cells into a tight pattern of rows separated by acellular material in between. It has been hypothesized that such an arrangement of nuclei may be an adaptive response to maintain cell-cell interaction which may otherwise be disrupted due to increased matrix deposition of laminin and phospholipids like lysophosphatidic acid (LPA) which *in vitro* has been found to induce cluster formation in Schwann cells.[16,17]

Antoni Areas

In 1920, Nils Ragnar Eugene Antoni described 2 distinct patterns of cellular architecture in peripheral nerve sheath tumors.[17] Antoni A areas ultrastructurally shows long interdigitating cell processes surrounded by a nearly continuous well-formed lamina separated by intercellular basement membranes which are rich in laminin. Immunohistochemical demonstration of laminin in the tumor serves to reliably differentiate Schwannomas from other histologically similar looking lesions such as histiocytomas and leiomyomas and their malignant counterpart's fibrosarcomas and leiomyosarcomas.[17]

Antoni B areas are less cellular, with a myxomatous background. Cells within the Antoni B regions are often thin and wispy and are separated from other cells by microcystic spaces filled with basophilic mucin. Microcysts may coalesce and form larger cystic spaces.[18]

Variants of Schwannoma

Several histologic subtypes of schwannoma have been described i.e., ancient schwannoma, cellular schwannoma, plexiform schwannoma, epitheloid schwannoma, melanotic schwannoma etc.

Ancient Schwannoma

These are schwannomas with degenerative change with marked nuclear atypia. They are usually large tumors of long duration, and a

significant number are located in deep structures such as the retroperitoneum. Histologically shows degenerative changes such as cyst formation, calcification, and hyalinization with inflammatory cell infiltration by histiocytes and siderophages. The Schwann cell nuclei are large, hyperchromatic, and often multilobed but lack mitotic figures.[19,20]

Cellular Schwannoma

It is a well-recognized variant of the schwannoma; because of its cellularity, mitotic activity, and may be locally erosive but are benign tumors without metastatic potential. They occur more commonly in spinal and paraspinal regions, but about 10% occur intracranially. The tumors are composed predominantly of cellular Antoni A-type tissue, but without well-formed Verocay bodies and occasionally containing small foci of necrosis. Most tumors have fewer than four mitoses per 10 high power fields, but in some cases, the mitotic rate may be higher. Capsular and perivascular lymphocytic infiltrates may be a prominent feature.[19,20]

Plexiform Schwannoma

About 5% of schwannomas grow in a plexiform or multinodular pattern. Plexiform schwannomas usually occur in the skin and infrequently in deep sites. They show typical histological features of schwannomas, with predominantly Antoni A-type tissue and sometimes Verocay body formation. A minority of cases are associated with NF1 and 2 or schwannomatosis.[19,20]

Epithelioid Schwannoma

Kindblom *et al.* described these schwannomas consisting predominantly or exclusively of epithelioid Schwann cells. Like conventional schwannoma, they develop as a circumscribed or encapsulated mass in the superficial soft tissues. The tumor cells are small rounded schwann cells arranged singly, in small aggregates or in cords within a collagenous or partially myxoid stroma. The epithelioid schwann cells are small and rounded with sharp cytoplasmic borders and occasionally intranuclear cytoplasmic (pseudo) inclusions. The cells may be associated with dense collagen cores forming irregular collagen rosettes. Virtually all cells strongly express S-100 protein.[19,20]

Melanotic Schwannoma

These are uncommon pigmented Schwann cell tumors, which have a spindle cell and epithelioid cell morphology, often with intranuclear cytoplasmic pseudoinclusions, and usually lacking Verocay bodies. They are usually deep seated and commonly involve the spinal nerves, cranial nerves, and sympathetic chain, but may occasionally involve the gastrointestinal tract, soft tissues, skin, liver, and heart. A psammomatous subtype with calcospherites and often associated with cytoplasmic vacuolation of the tumor cells, sometimes resembling adipose tissue.[20]

NF2

NF2 is a dominantly inherited syndrome, characterized by the formation of multiple schwannomas. Individuals with NF2 may have a number of tumors in addition to schwannomas, including meningioma in 50–60% and ependymoma in about 6%, together with non-neoplastic features. Most individuals present with hearing loss and tinnitus because of the development of bilateral vestibular schwannomas; however, unilateral vestibular schwannomas with a number of other features may be sufficient for diagnosis. Peripheral schwannomas occur in about 70% of NF2 patients.[20]

Schwannomatosis

The entity of multiple schwannomas, or "schwannomatosis," has been variously considered an attenuated form of NF2 or a completely different disease, diagnostic criteria for schwannomatosis:

Molecular diagnosis:

1. Two or more schwannomas or meningiomas and genetic studies of at least two tumors showing loss of heterozygosity at chromosome 22 and NF2 mutations. The presence of a common SMARCB1 mutation defines SMARCB1-associated schwannomatosis.
2. One schwannoma or meningioma and a germline pathogenic SMARCB1 mutation.

Clinical diagnosis:

1. Two or more non-intradermal schwannomas (one with pathological confirmation) and the absence of vestibular schwannoma on thin-sliced MRI
2. One schwannoma or meningioma and affected first-degree relative
3. Possible diagnosis if two or more non-intradermal schwannomas (without pathological confirmation) and chronic pain associated with tumors.[20]

Pathogenesis

Schwannomas are usually solitary sporadic lesions. In a population-based study of schwannomas,

about 90% were sporadic, 3% occurred in patients with NF2, 2% in those with schwannomatosis, and 5% in association with multiple meningiomas in patients with or without NF2. Most schwannomas, whether sporadic or inherited, display inactivation mutations of the NF2 gene.[19]

Schwannomas are derived from tumorigenic Schwann cells, caused by loss-of-function mutations of the Nf2 tumor suppressor gene. Apart from tumorigenic Schwann cells and axonal processes of nerve cells, there are different types of cells like macrophages, T and B cells, and endothelial cells, which influence each other through a variety of paracrine and juxtracrine mechanisms.[21]

The NF2 gene is a tumor suppressor gene also called as "merlin" or "schwannomin," is located on chromosome 22, which encodes for moesinezrine-radixin cytoskeleton-associated protein, which localizes the motile portions of the cell. Most cases of NF2 are associated with inactivating mutations of the allele, resulting in absence of the gene product merlin in the tumors. A significant number of cases of NF2 and sporadic schwannomas have either no NF2 inactivation or inactivation of only one allele. It has been suggested that they have undetectable mutations or alternative pathways of merlin inactivation.[19]

In a resting non-injured nerve, most of the schwann cells will remain quiescent, but undergo dedifferentiation and proliferation following a nerve injury. Once a nerve has been damaged, the nerve part distal to the injury site begins to degenerate by inducing a Schwann cell de-differentiation program, with subsequent upregulation of inflammatory mediators such as cytokines, lipids, and other molecules. These substances recruit immune cells like macrophages, neutrophils, and T cells to the injury site. This is accompanied by the breakdown and fragmentation of myelin, which is initially cleared by Schwann cells and later, to a more substantial degree, by macrophages.[22]

In NF-2 deficient mouse models, it has been reported that there is a defect in nerve regeneration. One main reason for this severely impaired regeneration seems to be the incapacity of Schwann cells to re-differentiate. In their study, Schulz *et al.* showed that mice with heterozygous nf2 gene mutation in both the neuronal and the Schwann cell compartment develop schwannomas after a single nerve crush injury.[22] One of the reasons proposed for the development of schwannomas in this mouse model is a failure of Schwann cell re-differentiation into myelinating cells, due to absent signals from nf2-deficient neurons. Subsequently, Schwann cells upregulate proliferative signaling pathways, leading to the formation of schwannomas in these mice.[23]

Merlin gene or NF2 gene controls the crosstalk between Schwann cells and adjacent axons via the Neuregulin-ErbB2 signaling pathway. In the peripheral nervous system (PNS), axon-derived Neuregulin 1 is a critical regulator of myelin thickness during development. While Neuregulin 1 becomes dispensable for the maintenance of myelin sheaths after development, it regains importance during nerve repair processes and especially for re-myelination following nerve injury.[24]

Antoni A tissue may transform into Antoni Type B tissue during tumor progression. Evidence for this hypothesis is provided by the observation of a "transition zone" at the borders between Antoni A and B tissue. Macrophages are known to show high proliferation rates following activation and are, together with Schwann cells, mainly responsible for the clearance of debris during PNS degeneration. It is therefore reasonable to assume that macrophages contribute to the proliferative activity seen in the transition zone of schwannomas.[22]

Electron microscopic and immunohistochemical analysis by the lysosomal marker protein CD68 showed Schwann cells and inflammatory cells containing a high number of lysosomes and myelin figures, both indicative of active phagocytosis of myelin sheaths by tumorigenic Schwann cells. Macrophage infiltration in Antoni B tissue, in addition to T lymphocytes, further supports the theory of Antoni B areas resembling degenerated Antoni A areas with a tissue degeneration-like process taking place.[21]

Germ-line mutations in SMARCB1 have been reported in a number of patients with schwannomatosis. SMARCB1 protein is important in central nervous system development and has tumor suppressor functions including induction of cell cycle arrest, associated with downregulation of cyclin D1 and upregulation of p16. In addition to SMARCB1 mutations, somatic mutations of the NF2 gene or loss of heterozygosity of 22q have been described in schwannomas associated with schwannomatosis, giving rise to a four-hit hypothesis. Lately, few cases of schwannomatosis also showed germ-line loss of function mutations in LZTR1 gene, who do not

have SMARCB1 mutations, but tumors from these patients also show deletions of 22q and somatic mutations of the remaining NF2 allele.[20]

CONCLUSION

A differential diagnosis of neurilemmoma or Schwannoma should be kept in mind when dealing with an intraoral, well-circumscribed, soft-tissue lesion as it is clinically indistinguishable from other benign soft-tissue tumors. The definitive diagnosis can be made by the histopathological findings with supportive immunohistochemistry using S100, Leu 7, Capsular EMA, and CD34 markers.

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