ORIGINAL RESEARCH PAPER

Pathology

KEY WORDS: intraparotid schannoma, penile schwannoma, Fine needle aspiration cytology, neurofibroma tongue, histopathology

HISTOPATHOLOGICAL APPROACH TO THE DIAGNOSIS OF BENIGN PERIPHERAL NERVE SHEATH TUMORS AT UNCOMMON LOCATION

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ABSTRACT

Peripheral nerve sheath tumors are relatively common lesions that exhibit a wide morphological and biological spectrum. In the presence of classical morphological and immunohistochemical features, the histological diagnosis is usually straightforward, but they may represent diagnostic challenges. Schwannoma is a slow growing encapsulated tumor of neuroectodermal derivation that originates from the Schwann cells of the neural sheath. Most commonly presents as cerebellopontine angle mass but extracranial sites are known and needs to be considered in the differential diagnosis. Intraparotid and penile schwannomas are extremely rare. Their diagnosis could be missed on cytology due to cystic changes. Isolated plexiform neurofibroma of the tongue is again a rare tumor. Plexiform pattern recognition is important for the pathologist as these varients might show malignant transformation. Overall Fine needle aspiration cytology though inconclusive at times, help a lot initially to delineate between benign Vs malignant lesions. Moreover its minimally invasive so can be performed easily at the uncommon locations. Histopathology remains the gold standard. Clinicopathological and imaging correlation is must for definite diagnosis and treatment.

INTRODUCTION

Neoplastic lesions of peripheral nervous system represent a heterogenous group with a wide variety of morphological features and biological potential. They range from benign and curable (schwannoma and soft tissue perineurioma) to benign but potentially locally aggressive (plexiform neurofibroma) to the highly malignant (malignant peripheral nerve sheath tumors [MPNST]).[1] Diagnostic criteria and differential diagnosis for the major categories of nerve sheath tumors are well known, including neurofibroma, schwannoma, and perineurioma. Diagnostically challenging lesions including plexiform or cellular varients are highlighted to nail the correct diagnosis. In this paper we will discuss the common entities schwannoma and neurofibroma at uncommon location and how important it is for a pathologist to be aware of the classical histopathological features of these lesions and keep such possibilities in their differential diagnosis while routine reporting.

Schwannomas

Schwannomas are benign nerve sheath tumors arising from neoplastic Schwann cells. They develop at multiple body sites but intracranially they favor the vestibular branch of the VIII cranial nerve. On imaging, most commonly they present as cerebellopontine angle masses. Extracranial sites are uncommon but known. Nasal cavity and paranasal sinuses account for <4% of schwannoma of head and neck region, retroperitoneum 3%, breast 2.6% and oral cavity- ~1%. Intraparotid and penile schwannomas are few other uncommon locations of the lesion.[2]

Intraparotid Schawannoma

Most common differential diagnoses of parotid mass include sialadenitis, pleomorphic adenoma, Warthin tumor, and mucoepidermoid carcinoma. However, rare entities, such as intraparotid schwannoma could be considered with clinicopathological correlation. Overall, schwannomas account for 0.5% to 1.2% of all parotid gland tumors, of which 9% arise from the intraparotid portion of the facial nerve.[3] Fine needle aspiration cytology (FNAC) is a minimally invasive technique which guides a mesenchymal lesion to be of neural origin. **(Figure 1)** Imaging could add much to define the character of lesion however extent could be seen to plan surgical management. But histopathological examination remains the gold standard.

Gross And Microscopic Examination

Gross Findings:

Schwannomas appears as a round, encapsulated, pink to tan mass with pushing borders, usually less than 5 cm in diameter, which is in close association with nerve without invasion in surrounding tissue **(Figure 2).**

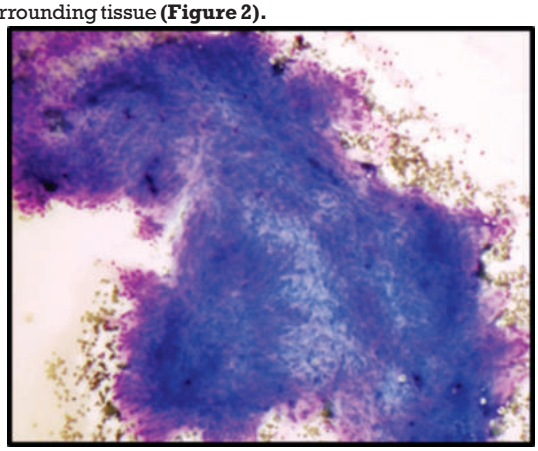

Figure 1 Cohesive Cluster Of Spindle Cells With Wavy Nucleus And Pointed Ends (Giemsa 40x)

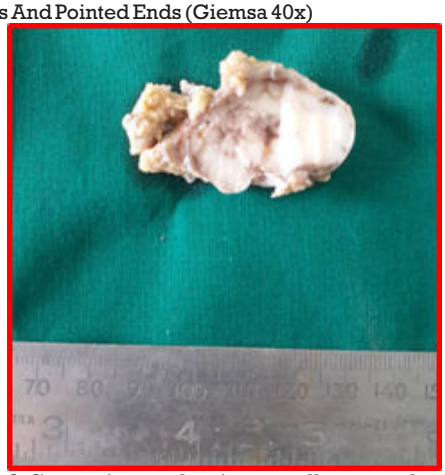

Figure 2 Gross picture showing a well encapsulated mass with central area of degeneration

Microscopic Findings:

Microscopic examination show presence of a biphasic tissue architecture composed of areas of relative hypocellularity with abundant acellular material punctuated by bland, cigar-shaped nuclei (Antoni B architecture), as well as areas of hypercellularity featuring numerous cigar-shaped nuclei and ill-defined cytoplasm with occasional nuclear palisading and Verocay body formation (Antoni A architecture) **(Figure 3)** Additional findings that may suggest the diagnosis of schwannoma include perivascular hemosiderin and hyaline change of vessels. Larger lesions may feature prominent cystic degeneration within areas of Antoni B architecture, and collections of abundant lipid-laden macrophages, or xanthoma cells. [4]Unguided FNAC might hit these cystic areas and often lead to inconclusive diagnosis on cytology. Mild degree of cellular atypia and few mitoses may be seen in a schwannoma, moderate to marked atypia or abnormal mitoses should raise a consideration of possible malignancy but clinical and imaging correlation must be done to exclude the possibility of ancient schwannoma. Hemorrhage may be seen in schwannoma, but necrosis is generally absent grossly or microscopically. Most of the times the classical morphology is enough for diagnosis but sometimes immunohistochemistry is required for definite diagnosis and furthermore the location is also uncommon.

Immunohistochemistry:

To rule out other diagnoses, S100, smooth muscle actin, CD68, and pancytokeratin immunohistochemical stains may be done. S100 staining is strongly positive, whereas the other stains yield a negative result **(Figure 4).** Since it's a benign lesion so Ki-67 proliferative index is expected to be less than 1%. A smooth muscle actin is done to rule out leiomyoma. CD68 may be used to rule out a histiocytic lesion, as abundant xanthomatous change within the schwannoma may introduce that possibility into the differential diagnosis. A pancytokeratin stain may be performed to rule out a spindle cell carcinoma or other tumor of epithelial origin in grey zone areas. [5] Other stains may potentially be of use, such as calretinin, which was found to be helpful in distinguishing schwannoma from neurofibroma, given that schwannoma will display diffuse staining, while neurofibroma will stain weakly or not at all.

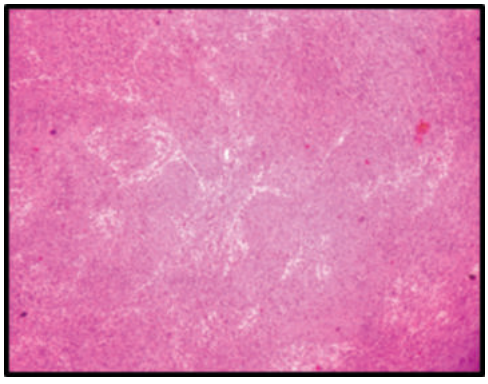

Figure 3: Section Shows Hypocellular And Hypercellular Areas Corresponding To Verocay Body Formation (H&E 40x)

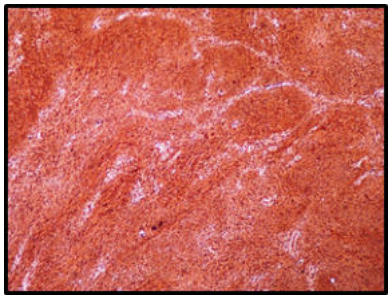

Figure 4 Strongly Positive S-100 Staining In The Neural Cells (IHC S-100 x40x)

Differential Diagnosis:

There are numerous differential diagnosis of a spindle cell lesion but since it is in close association with the facial nerve, the diagnostic possibilities are narrowed. The most important diagnosis to rule out in this case is that of a malignant peripheral nerve sheath tumor (MPNST), which would directly affect prognosis for the patient. MPNST is usually nonencapsulated with infiltrating borders, but can grossly appear well circumscribed. Histologically, a variety of patterns may be observed, including relatively monomorphic spindled nuclei arranged in a herringbone or storiform pattern, as well as more epithelioid differentiation or a schwannian appearance with nuclear palisading. In general, frequent mitoses and geographic necrosis are seen.

A second consideration in the differential diagnosis of intraparotid schwannoma is neurofibroma, which may also arise from peripheral nerves, although intraparotid neurofibroma is even rarer than intraparotid schwannoma. Neurofibromas are generally ill-defined, nonencapsulated masses with hypocellular architecture in a myxoid background featuring bland spindled cells with low mitotic activity and strands of thick, ropelike collagen. Additionally, mast cells may be present within the stroma. [6] Unlike schwannoma, which tends to push axons aside with growth, neurofibromas are closely associated with the nerve, and often, one can appreciate axons on histology. On immunohistochemistry, a calretinin stain may help distinguish schwannoma from neurofibroma, given that schwannoma will stain diffusely, while neurofibroma will stain focally and weakly.

Treatment And Prognosis:

The management of intraparotid schwannoma needs a multidisciplinary approach for management. Different school of thoughts advocate conservative over surgical management for patients with minimal to no facial nerve dysfunction or tumor localized to the parotid gland without intratemporal extension. This is a very important issue, as unnecessary surgery may lead to lifelong morbidity for the patient. Additionally, if the diagnosis of schwannoma is not in the differential diagnosis before and during surgery, the result may be inadvertent transection of the facial nerve, with permanent and potentially devastating loss of function.

If the mass cannot clearly be distinguished from the facial nerve by imaging and/or an exploratory surgery, most authors advise observation and follow-up, except in the case of severe facial nerve dysfunction. Several studies suggest incisional biopsy to confirm the diagnosis. If a clear surgical plane is available between the schwannoma and the facial nerve, prognosis is excellent; however, if isolation of the schwannoma is difficult or facial nerve sacrifice with nerve grafting is necessary, the patient may have residual and possibly permanent facial nerve dysfunction.

Penile Schwannoma

Penile schwannoma is extremely rare and mostly located at the penile shaft and the dorsum of the penis. Dyspareunia is the most complained symptom for sexual dysfunction. No evidence-based clinical guideline exists for diagnosis or treatment. It is important to consider schwannoma in differential diagnoses of benign soft tissue lesions of penis. [7] FNAC in such sensitive location is of great help as it is minimally invasive and can guide to different between benign Vs malignant lesion of neural origin **(Figure 5)**.

Gross And Microscopic Findings

Gross Findings:

They are usually solitary, and the cut surfaces display a light-tan appearance surrounded by a fibrous capsule. A yellow color is frequent because of lipid content or lipid-laden macrophages. Variably sized cysts and hemorrhagic changes may be present. **(Figure 6)**

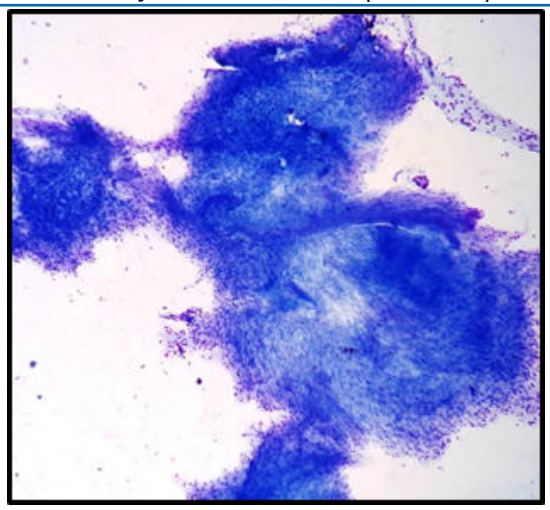

Figure 5 Spindle Cell Lesion With Kinky Nucleus And Pointed Ends Of Neural Origin (Giemsa 40x)

Figure 6 Gross Picture Showing A Well Encapsulated Yellow Mass Covered By Penile Skin

Microscopic Findings:

Histologically, in their classic form, schwannomas contain compact patterns (Antoni A), alternating with loose patterns (Antoni B). The Antoni A zones are characterized by increased cellularity and spindle nuclei. These zones are studded with clumps of cellular aggregates, where palisading patterns called Verocay bodies may be encountered, which are almost diagnostic at the histologic level. The Antoni B zones are disorganized arrangements that are hypocellular and feature a variable macrophage infiltrate**. (Figure 7)** The surrounding capsule is formed by multiple layers of collagen fibers. Other common histologic findings in schwannomas include hyalinized vessels with perivascular hemosiderin deposition, cystic spaces, and degenerative atypia ("ancient change"). Malignant transformation in schwannomas is exquisitely rare but usually takes the form of epithelioid malignant peripheral nerve sheath tumor (MPNST), a round cell malignancy or angiosarcoma. [8] Immunohitochemistry helps to nail the diagnosis in such uncommon location.

Immunohistochemistry:

Schwannomas are diffusely positive for mature Schwann cell markers, including S100 **(Figure 8)** and SOX10 proteinprotein. Collagen IV and reticulin special stains are positive around individual cells. Epithelial membrane antigen (EMA) outlines perineurial cells peripherally but is negative in neoplastic cells. Neurofilament protein (NFP) highlights rare entrapped axons, but these are usually encountered in the periphery. Neoplastic cells in schwannoma also express vascular endothelial growth factor and antiangiogenic therapy with bevacizumab is often used for progressive vestibular schwannomas in NF2 patients.

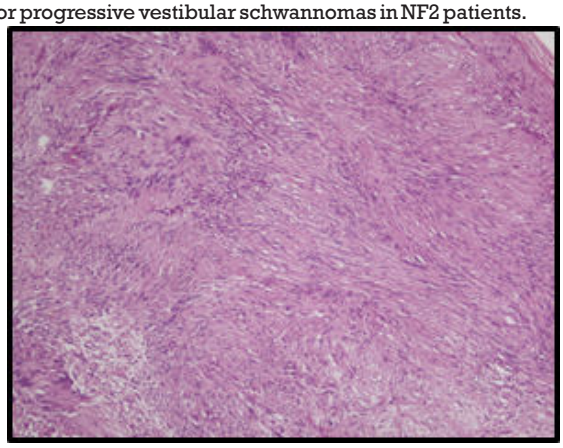

Figure 7 Section shows alternating compact pattern (Antony A) with loose areas (Antony B) (H&E 40x)

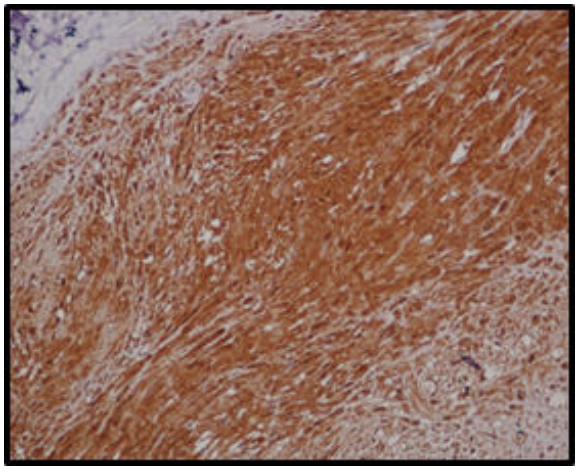

Figure 8 Strongly positive S-100 staining in the neural cells (IHC S-100 x40x)

Treatment

Penile-preserving excision is usually planned as it is a well-encapsulated tumor. Careful dissection is performed free from the penile shaft.

Neurofibroma

Neurofibroma is another benign tumor composed of neoplastic Schwann cells, but unlike schwannoma, it also contains additional non-neoplastic components, including fibroblasts, mast cells, perineurial-like cells, and residual axons. Neurofibromatosis is classified into cutaneous, subcutaneous, and plexiform subtypes. Sporadic cutaneous neurofibroma is the most common subtype. However, multiple neurofibromas are a key feature of NF1, in which there may be involvement of multiple cutaneous sites, peripheral nerves, and spinal roots. [9]

Plexiform Neurofibroma

Plexiform neurofibroma is the term applied to a diffuse neurofibromatosis of nerve trunks, which is often associated with an overgrowth of the skin and subcutaneous tissues. It is a distinct type of neurofibroma that expands a nerve into a large tortuous mass of fibers that has a "bag of worms" appearance. Solitary plexiform neurofibromas arising outside the context of NF I is very rare. There are two types of plexiform neurofibromas, nodular and diffuse. Diffuse plexiform

neurofibroma, is also known as *elephantiasis neurofibromatosa*, which shows overgrowth of epidermal and subcutaneous tissue along with a wrinkled and pendulous appearance. It is extremely rare in tongue. In the literature, there are only few reports of macroglossia caused by plexiform neurofibroma, and the cases are almost always associated with neurofibromatosis.[10]

Gross And Microscopic Examination

Gross Findings:

It's a well circumscribed mass with external irregular surface of tongue. Cut section is solid grey white with no necrotic or hemorrhagic areas. No cystic degeneration identified.

Figure 9 Clinical Examination Show An Enlarged Protruded Tongue

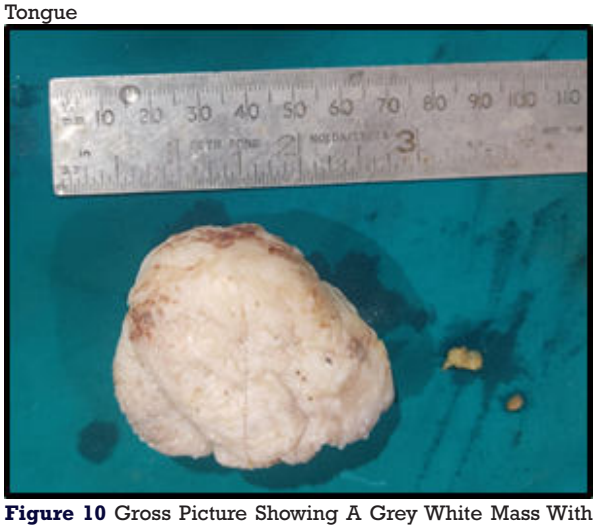

Figure 10 Gross Picture Showing A Grey White Mass With Irregular Surface

Microscopic Findings:

Sections reveal a well circumscribed lesions composed of serpentine nerve-like structures with abundant myxoid odematous stroma containing thick haphazardly arranged collagen fibers (shredded carrots appearance). Individual cells are elongated spindle wavy cells arranged against a myxoid background. No atypia or increase in mitosis is identified. Sometimes, the neoplastic proliferation may extend beyond the nerve-like structures into the surrounding tissues with a morphology closely resembling diffuse-type neurofibroma and obscuring the underlying plexiform architecture. The importance of a correct diagnosis of plexiform neurofibroma relies not only on its association with NF1 but also 5% cases might show malignant transformation.[11]

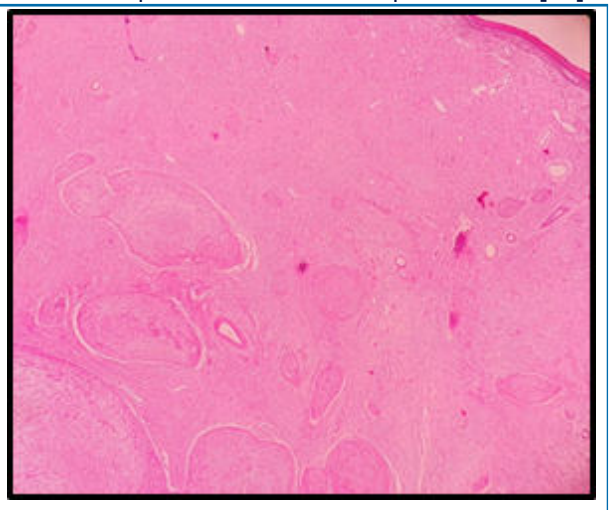

Figure 11 Section Shows Circumscribed Lesion With Numerous Bundles Of Nerve Fibers (H&E 40x)

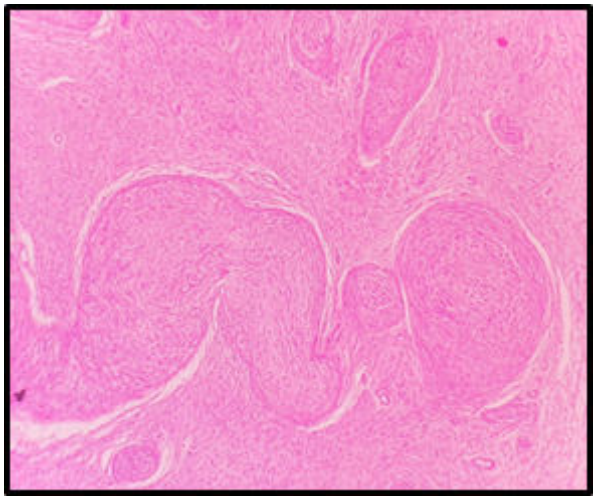

Figure 12 Section Shows Serpentine Nerve Bundles (H&E 40x)

How To Differentiate Neurofibromas From Schwannomas ?

Neurofibromas of the large nerves, which appear clinically as soft, drooping, and doughy masses, are benign neoplasms composed of neurites, Schwann's cells and fibroblasts within a collagenous or myxoid matrix. In contrast to schwannomas, they are nonencapsulated and engulf the nerve of origin. Plexiform neurofibromas, forming tortuous cords along the segments and branches of a nerve with a tendency to grow centripetally, are poorly circumscribed tumors. It needs to be differentiated from schwannoma which is encapsulated, while plexiform neurofibroma is noncapsulated; moreover, in schwannoma there are antony A and antony B along with prescence of verocay bodies on microscopic examination. Since neurofibromas are usually multiple lesions, the whole body must be examined and investigated. In patient with oral neurofibroma, larynx and trachea must also be examined as in such a case lesions in the upper airway may cause respiratory obstruction.[12]

Differential diagnosis of such a tongue mass include neurofibroma, schwannoma (neurilemoma), lymphangioma, hemangioma, hamartoma, teratoma, pyogenic granuloma, nerve sheath

Treatment :

The standard treatment for neurofibromas has been surgical excision and the diagnosis can only be confirmed by histological examination. Neurofibromas have extensive

vascularity and tend to bleed during surgery. Therefore, excessive bleeding should be kept in mind while attempting surgical removal. Early diagnosis in such a patient is very important and these patients need regular follow-up.

CONCLUSION

The spectrum of neoplasms that may involve the peripheral nervous system is wide, but most primary tumors have a Schwann cell phenotype. They range from the most benign to the most malignant tumors in surgical pathology. Minimally invasion technique like FNAC is very helpful to differentiate benign Vs malignant lesions however biopsy remains the gold standard. This paper describes the various unusual locations of peripheral nerve sheath tumors and enlightens pathologists to be aware of such differential diagnosis while reporting. Capsule should be well examined during grossing followed by identification of various patterns and degenerative changes as that makes a difference in prognosis.

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