Review Article

# Hybrid peripheral nerve sheath tumours – A Review

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**Abstract**

Hybrid peripheral nerve sheath tumours (PNSTs) are mainly benign, which represent combined areas of neurofibroma, schwannoma, and perineurioma in various combinations and pose challenges to the surgeon and the pathologist. They are relatively new in pathology and were first published in the fourth edition of World Health Organization Classification of Tumors of Soft tissue and Bone in 2013. They are mainly dermal or subcutaneous, and the most common variant of hybrid nerve sheath tumour is perineurioma-schwannoma. The combination of neurofibroma/schwannoma usually has an increased frequency with neurofibromatosis (NF) type 1 or 2 and schwannomatosis. In contrast, neurofibroma/perineurioma, mainly associated with NF1, are rare. Diagnosis is established by histopathology and immunohistochemistry. Hence, they embark diagnostic challenge and demand extreme vigilance and caution. However, the molecular pathogenesis, recurrence rates, and risk of malignant transformation of hybrid PNST remain poorly understood. A novel *CHD7-VGLL3* fusion gene in a hybrid schwannoma-perineurioma and recurrent *ERBB2* mutations in a subset of hybrid neurofibroma/schwannomas were identified. We have tried, via this article, to represent a brief update on hybrid nerve sheath tumours.

**Keywords:** Benign, hybrid nerve sheath tumour, neurofibroma, perineurioma, Schwannoma

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## INTRODUCTION

Peripheral nerve sheath tumours (PNSTs) are common neoplasms with major categories included, schwannoma, neurofibroma, and perineurioma, according to their histopathological features. Schwannomas are benign PNSTs purely made up of Schwann cells, and histologically, they have classic Antoni A (compact) and Antoni B (loose and haphazard) pattern. Neurofibroma is another benign PNST composed of Schwann cells along with fibroblasts, mast cells, and perineurial like cells. Sporadic neurofibroma is a common subtype; however, the multiple neurofibroma and plexiform type of neurofibroma is a key feature associated with NF type 1 patients. Perineuriomas are benign PNST composed of perineurial cells and are of two types: intraneural and soft tissue perineuriomas. A comparatively new chapter added in pathology, hybrid PNSTs (HPNSTs) are composite PNSTs having elements of schwannoma, perineurioma, and neurofibroma in various combinations.[1] They got recognition and published in the fourth edition of World Health Organization (WHO) classification of tumour of soft tissue and bone in 2013 and revised in 2016 as classification of the central nervous system.[2,3] They affect all age groups (mean age 38 years) with peak incidence in young adults and almost an equal male-to-female ratio.

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These tumours, with wide anatomic distribution, are usually located on upper and lower extremities, head and neck, and trunk and less commonly affect intraabdominal areas.[4-7] Intraoral cases are very rare, and till now, only one case has been diagnosed on the lower vestibule as hybrid neurofibroma and schwannoma.[8] Grossly, HPNSTs are well-circumscribed nodular lesions, usually measured between 1 and 8 cm in size (may reach more than 17 cm), with firm consistency and a greyish yellow cut surface.[6,8-11] Microscopically, these tumours demonstrate biphasic features of two components, which show either abrupt transition or closely intermixed cellular components. In the latter case, sometimes, it is not evident on H and E-stained slides and so, immunohistochemical staining is required for confirmation of dual cell lineage.[1,6,8-11] While the frequency of hybrid tumours reported is less, the routine use of immunohistochemistry (IHC) may increase their frequency and correct diagnosis.[12] They are mainly benign lesions and do not recur after adequate local excision and with rare incidence of metastasis or transformation to malignant PNST.[1,5,6]

## PATHOGENESIS

Schwann cells, perineurial cells, and fibroblasts are the main cells which form the normal connective tissue of peripheral nerve sheath. Schwannomas and perineuriomas are composed of nearly pure population of Schwann cells and perineurial cells, respectively. Neurofibromas are complex mixture of cells, consisting of Schwann cells, perineurial cells, fibroblasts, and mast cells [Figure 1]. The molecular pathogenesis of hybrid tumours is complex and poorly understood. Mutations in *NF1 (*17q11.2) and *NF2 (*22q12.2) gene, either somatic or germline biallelic gene mutations, characterise the majority of neurofibromas and schwannomas, respectively. *NF1* gene (17q11.2) encodes neurofibromin, and *NF2* gene is located at the 22q12.2 chromosomal locus and encodes Merlin.[1] However, intraneural perineuriomas harbour TRAF7 mutations and their soft tissue counterparts have been shown to have mutations in either *NF1* or *NF2* gene.[1,13] Tumours with histologic features of more than one peripheral nerve sheath are known as hybrid nerve sheath tumours. Hybrid PNSTs are important to acknowledge because of their association with neurofibromatosis type 1 and 2 (NF1, NF2) and schwannomatosis. The most frequently seen hybrid tumour, schwannoma/perineurioma, is usually a sporadic lesion.[1] Another one is neurofibroma/schwannoma, which mainly occurs in association with NF1, NF2 or schwannomatosis.[1,11,14] Neurofibroma/perineurioma is rare and appears to be associated with NF1.[1] HPNST, containing all three PNSTs (schwannoma, neurofibroma, and perineuriomas), is considered very rare.[15,16]

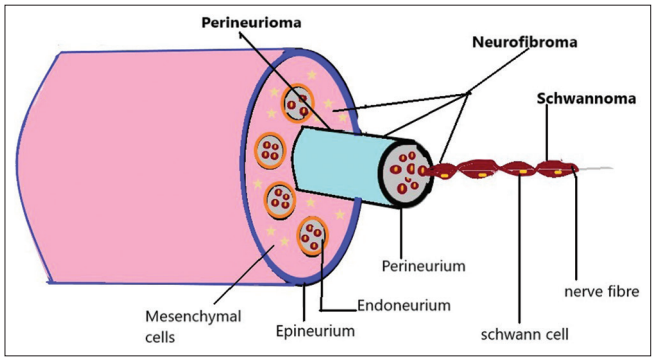


**Figure 1:** Schematic diagram of peripheral nerve and the tumour

## DIAGNOSIS

IHC is essential for correct diagnosis of hybrid PNST to demonstrate the dual cell components, along with routine histological stains. S100 and SOX10 protein are specific markers for Schwann cells. Neurofibromas exhibit an admixture of cells, S100 and SOX10 stain Schwann cells, CD34 stains fibroblastic stromal cells, and neurofilament protein (NFP) typically outlines numerous entrapped axons. Epithelial membrane antigen (EMA)/Claudin-1/Glut-1 are antibodies for perineurial differentiation, which are considered quite specific in relation to HPNST. To differentiate between a schwannoma and neurofibroma component is difficult because both are S100 protein-positive; however, it is also sometimes useful to note that the Schwann cells of schwannomas are large with plump nuclei compared to those of neurofibromas in which nuclei are wavy and more curved. Schwann cells are positive for S100 and SOX10, but they are diffusely positive in schwannoma (100% of tumour cells) while limited expression in neurofibroma (approximately 50% of tumour cells). CD34 positivity demonstrates a fibroblastic population in neurofibromas, but it also highlights the perineurial cells of perineuriomas. Thus, meticulous attention has to be paid to see the morphology of the stained cells. Fibroblasts have a bland round to oval nuclei in neurofibromas, and the perineurial cells show thin spindle cells with elongated and undulating nuclei with a long bipolar process. Diagnosis of hybrid PNST demands extreme vigilance and caution.[1,5,6,12,17]

## SCHWANNOMA/PERINEURIOMAS

Hybrid schwannoma/perineurioma tumours have two populations of cells that can be presented in a segregated

manner or closely intermingled mixture. The largest series of hybrid schwannomas, perineuriomas (42 cases), was published by Hornick *et al.*,[6] which showed wide anatomic distribution of these tumours without any association of NF1. They are circumscribed but usually unencapsulated and composed of an intimate admixture. On lower magnification, they mainly look like perineuriomas due to storiform, fascicular, reticular, and whorled growth patterns. However, on higher magnification, schwannoma like cytomorphology was very prominent showing numerous spindle cells with plump, tapering nuclei and pale eosinophilic cytoplasm along with a slender elongated perineurial component. The histological hallmark of schwannoma like Antoni A (Verocay bodies) and B regions and hyalinized vessels was not evident.[5,18,19] Sometimes, degenerative nuclear atypia like scattered pleomorphic cells containing hyperchromatic nuclei with variably smudged chromatin is present.[6] All these findings were also confirmed by several authors.[1,5,18]

Biphasic proliferation in a segregated manner is also evident in a few cases. Hyper- and hypocellular areas were present resembling Antoni A and Antoni B and were appreciable along with slender spindle cells having scant eosinophilic cytoplasm with a long bipolar process.[7,20]

All tumours showed staining for S100 (60%–70% cells) and EMA (30% to 40% cells) on IHC. GFAP, CD34, and claudin 1 were also positive in most lesions. CD34 was positive in most cases, but this feature is not interpreted as fibroblastic staining rather than a feature that may occur in more than 50% of perineuriomas[1,6] [Figure 2].

Hybrid schwannoma-perineurioma is frequently recognised by recurrent fusion events, including VGLL3 rearrangement. Dickson B. C *et al.*[13] studied a total of 18 cases; hybrid schwannoma-perineurioma is frequently identified by VGLL3 rearrangement in 14 cases by RNA sequencing, with the partner genes CHD7 in ten cases, CHD9 in two cases, and MAMLD1 in two cases.

## NEUROFIBROMA – SCHWANNOMA

Hybrid neurofibroma and schwannoma are characterised by schwannoma-like nodules within a neurofibroma-like tumour. They can occur sporadically or in association with underlying tumour predisposition syndrome like schwannomatosis, neurofibromatosis type 1 (NF1), and neurofibromatosis type 2 (NF2).[1,11] The co-existence of schwannoma and neurofibroma was first explored by Feany *et al.*[21] in a series of nine cases; among those, only one was associated with NF1. NF1 is the least frequently

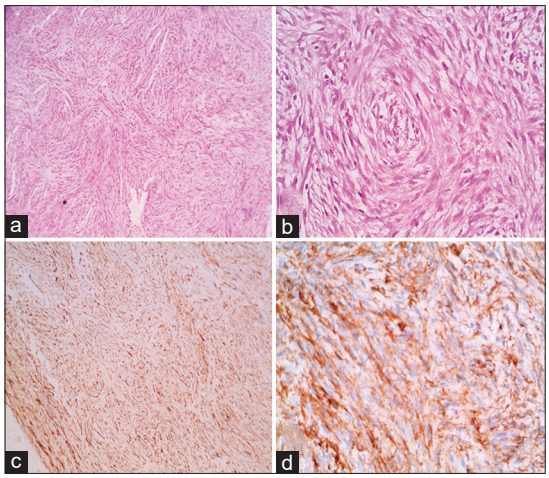


**Figure 2:** Hybrid schwannoma-perineurioma (a) Tumor showing a lamellar and storiform pattern (b) Tumor dominated by spindle cells with plump nucleus surrounded by slender elongated perineurial cells (c) IHC shows diffuse positivity for S-100 protein (d) EMA positivity in perineurial cells

encountered among the three inheritable genetic syndromes causing the development of PNST, namely, NF1, NF2, and schwannomatosis.[11]

More than 60% cases of hybrid neurofibroma and schwannoma are associated with these syndromes, and 9%, 17%, and 26% of patients are affected with NF1, schwannomatosis, and NF2, respectively.[11]

Classic schwannomas have alternating hyper- (Antoni A) and hypocellular (Antoni B) areas. Antoni A areas are arranged in short, whorling patterns with nuclear palisading (Verocay bodies). Antoni B areas are arranged in haphazard patterns. Neurofibromas have abundant myxo-edematous stroma along with thick collagen fibres arranged in haphazard patterns.[19] So, hybrid neurofibroma and schwannoma exhibit two components having Antoni A-like regions of schwannomas with high cellularity and palisading nuclei surrounded by neurofibroma-like areas having spindle cells with abundant collagen and myxoid change. These tumours are also known as neurofibromas with Schwann cell nodules. Typical features of schwannomas like hyalinized vessels are often present in Antoni A areas, whereas such vessels are not found in surrounding neurofibromatous regions.[1] Occasionally, Antoni B regions may be seen in larger nodules. Focal degenerative atypia with hyperchromasia, necrosis, and mitotic activity in schwannomatous component is rare.[1,11,21] 30% neurofibroma associated with HPNST was of plexiform type, which is pathognomonic for NF.[1] Harder A *et al.*[11] discussed that 71% (10 out of 14) of patients with schwannomatosis developed at least one hybrid neurofibroma/schwannoma, and 21% of

schwannomatosis patients (3 out of 14) showed multiple hybrid neurofibromas/schwannomas.

Schwannomatous (both Antoni A and B) regions are strongly and diffusely positive for S100 protein with often increased Ki-67 proliferation index, which ranged between 0.8% and 18.5%.[1,11] The neurofibromatous parts show virtually no mitoses and stain strongly with CD34 antibody, but the expression of S100 is variable or not as diffuse when compared to the schwannomatous area[1,11,21,22] [Figure 3].

These tumours should always be separated from malignant PNSTs as schwannomatous areas could be mistaken as foci of malignant degeneration in a neurofibroma.[1]

It is poorly understood that two lesions developed from a clonal genetic alteration or localised microenvironmental change.[21] Stahn *et al.*[23] exhibited that monosomy of chromosome 22 was frequent in these tumours. The subset of hybrid neurofibroma and schwannoma harbour ERBB2 kinase domain mutations, mainly associated with schwannomatosis, which may be helpful to develop future diagnostic algorithms and targeted therapeutic strategy.[24]

## NEUROFIBROMA – PERINEURIOMA

It is difficult to diagnose hybrid perineurioma-neurofibroma because neurofibromas already contain perineurial cells. EMA-positive perineurial cells, sparse but diffuse, are present in seven cases among 99 cases of neurofibromas.[25] Neurofibromas have haphazard arrangement of spindle cells and sometimes have shredded carrot patterns, and perineuriomas have arrangement of fibroblast-like looking cells into storiform, fascicular, whorled, or Pacinian (lamellar) growth patterns.[19] So, these tumours differ variably on H and E slides; a few show biphasic patterns or distinct patterns, and some showed merged or intermingled patterns of two components. Atypia, mitosis, and pleomorphism are not found. They show even admixture of the two cell types because 50% of the cells showed positivity for S-100 protein, whereas the other 50% showed clear positivity for EMA along with scattered intralesional axons. Hybrid schwannoma/perineuriomas showed sharp circumscription, more whorled appearance, and perivascular hyalinisation in schwannomatous areas which lacked in these cases. The overall architecture and appearance along with IHC should be considered to reach the final diagnosis of hybrid neurofibroma and perineuriomas.[12]

Kazakov *et al.*[20] presented two cases of neurofibroma and perineurioma. The first case was biphasic having retiform perineurioma-like features which merged into ordinary neurofibroma-like areas. IHC showed diffuse S-100 and CD34 positivity and EMA negativity in the neurofibromatous areas. Conversely, antibodies to EMA and claudin-1 were strongly positive in perineuriomatous areas along with CD34-negative and scarce S-100 protein positive

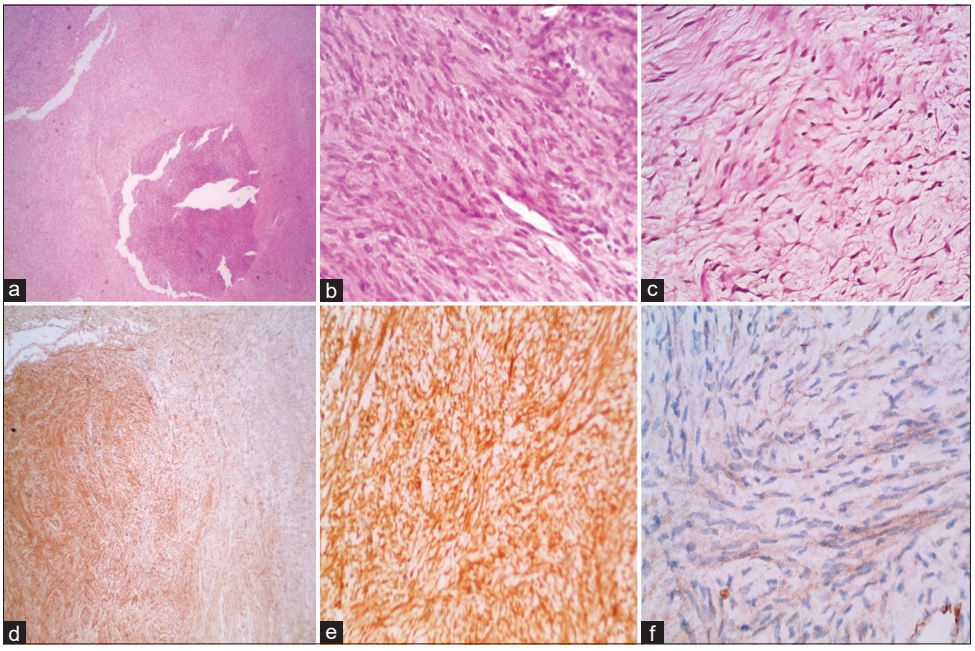


**Figure 3:** Hybrid Schwannoma-Neurofibroma (a) Tumor shows schwannomatous nodule surrounded by neurofibromatous component (b) Hypercellular schwannomatous area with mild focal atypia and hyperchromatism (c) Less dense and myxoid neurofibromatous component with spindle shape cells with wavy nuclei. (d) Diffuse S100 staining, intense in schwannoma and variable in neurofibroma areas (e) Diffuse CD34 staining in both schwannoma and neurofibroma areas (f) Negative epithelial membrane antigen staining in tumour areas

wavy cells. The second case showed closely intermingled patterns having spindled cells with wavy nuclei similar to neurofibroma along with spindled cells with bipolar or stellate nuclei identical to perineurial cells. Spindled cells with wavy nuclei exhibited S-100 protein-positive/EMA-negative/claudin-1-negative surrounded by EMA-positive/claudin-1-positive/S-100-protein negative stellate cells. CD34 was diffusely positive within the lesion.

Histologically normal-looking nerve fibres showed prominent reticular networks of EMA/claudin-1/GLUT-1-positive perineurial cells in cases hybrid neurofibroma – perineuriomas associated with NF-1 patients.[26,27]

Deletions in *NF2* and *NF1* genes in mutual exclusive fashion are reported in soft tissue perineuriomas.[25] Hybrid neurofibroma perineuriomas are usually not associated with neurofibromatosis or schwannomatosis but may contain mutation in *NF2* gene as highlighted by Kazakov *et al*.[19] A few hybrid PNSTs may be associated with underlying NF1 patients having intraneural perineurial cell proliferations.[27]

## SCHWANNOMA – NEUROFIBROMA – PERINEURIOMA

As we have discussed, most literature on hybrid PNST focussed on a combination of two entities, very few reported cases are classified as a hybrid tumour containing all three components of PNST (schwannoma, neurofibroma, and perineurioma), and it is extremely difficult to categorise these tumours.[15,16] These tumours are made up of schwannoma component (diffusely positive for S-100/SOX 10 but negative for EMA/GLUT 1), neurofibroma component (positive for S-100/CD34), and perineuiomatous part (positive for EMA/GLUT 1 and negative for S-100/SOX 10). It is difficult to recognise neurofibromatous and schwannomatous components on immunohistochemical slides because of the equal volume of S-100 and CD34-positive cells in the tumour. The perineuriomatous component accounts for 30% of the total tumour area, which is positive for EMA, Glut-1, or Claudin-1.[15] However, currently, no such quantitative criteria exist to classify these tumours.[1]

## CONCLUSION

Being a distinct entity, HPNSTs are diagnosed by both hybrid morphology and IHC. Hybrid neurofibromas–schwannomas are commonly associated with NF2 and schwannomatosis and, to a lesser extent, with NF1. Precision is required in diagnosis so that these tumours should not be mistaken for malignancy in neurofibroma. NF1 association with neurofibromas–perineuriomas may provide the genetic background. Meticulous interpretation of the non-perineuriomatous part of these tumours is essential and not to mistake them for schwannoma s–perineuriomas, which seem to be sporadic or non-syndromic tumours. Accurate diagnosis may be extremely confusing, when all three components can coexist in one tumour. Accurate molecular events occurring in these tumours remain largely an enigma and hence demand advanced molecular research and genetic studies to reveal their association with specific syndromes to help patient management and determining patient prognosis and also screening of the whole family. The risk for recurrence is very low, and transformation to malignancy is extremely rare in these cases.

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## Conflicts of interest

There are no conflicts of interest.

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