CASE REPORT

Hybrid Nerve Sheath Tumour, A Conglomerate of Separate Entities

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ABSTRACT

Hybrid nerve sheath tumours (HNSTs) are benign tumours showing combined features of more than one peripheral nerve sheath tumour (PNST) entities. Most literature highlight combination of two entities. Only few reported cases involve all three components of PNST. Herein, we report a case of 33-year-old Malay lady, with left proximal middle finger soft tissue swelling for three months. Microscopically, the tumour is well-circumscribed, containing all three components of PNST, with each displaying its typical morphology and immunohistochemical staining pattern. This case suggests that PNSTs may be more closely related than what was earlier believed. However, whether HNSTs are part of the PNSTs spectrum with tumour syndromes association or a distinct entity is still a continuous debate. We also highlight the possibilities of recurrence and risk of malignant transformation in HNSTs. The exact pathogenesis, potential for recurrence and malignant transformation criteria for HNSTs are still vague due to their extreme rarity.

Keywords: Hybrid nerve sheath tumour, NF1, NF2, schwannomatosis, PNST, MPNST

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INTRODUCTION

Hybrid nerve sheath tumours (HNSTs) are mixed peripheral nerve sheath tumours (PNSTs) with benign biological potential. This entity was recently included in the 4th and 5th edition of WHO Classification of Soft Tissue and Bone Tumours. It affects all age groups with peak incidence in young adults and shows equal sex distribution (1-2).

HNSTs show wide anatomical distribution within the somatic soft tissue (1-2), with hybrid schwannoma/reticular perineurioma mostly seen on fingers (1). However, HNSTs may rarely arise in non-somatic tissue such as the bone, visceral organ, lymph node, spinal nerve, and cranial nerve (2). They usually present as painless mass within the dermis or subcutaneous adipose tissue (1-2).

Macroscopically, HNSTs are well-circumscribed nodular lesions with a polypoid appearance (2). Cut sections usually show firm greyish surface (1-2). Most tumours measure between 1cm to 8cm in size (2).

Microscopically, most frequently seen combination is the hybrid schwannoma/perineurioma, which usually occurs sporadically. The second being hybrid neurofibroma/schwannoma, which is strongly associated with neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2) or schwannomatosis. The third is hybrid neurofibroma/perineurioma, which is rare and is usually associated with NF1 (1). The components show typical morphology and immunohistochemical staining pattern of each entity (2).

Our case highlights the existence of a HNST containing all three PNST entities. This is considered as a rare occurrence within a readily rare tumour (2).

CASE REPORT

Our case, a 33-year-old Malay lady, presented with left proximal middle finger lesion for 3 months. She had no prior known medical illness. No radiological imaging done as the lesion was clinically suspected to be a benign well-circumscribed dermal tumour.

A marginal excision was performed and grossly, the lesion was soft, lobulated, and circumscribed, measuring

35x23x23mm. Cut sections of the lesion showed greyish gelatinous surface.

Microscopically, the centremost of the lesion is composed of schwannoma-like component, intimately surrounded by alternating neurofibroma-like and perineurioma-like components and encased by a thin layer of perineurioma-like component (Figure 1).

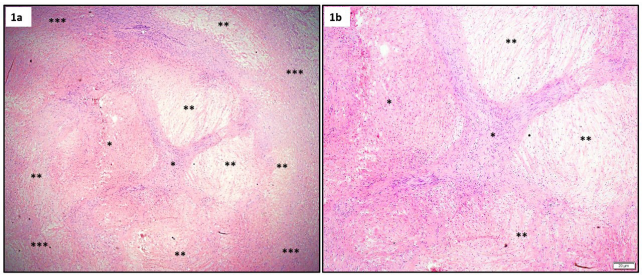

Figure 1: A cross section of the lesion; The centremost is composed of schwannoma-like component, intimately surrounded by alternating neurofibroma-like and perineurioma-like components and encased by a thin layer of perineurioma-like component. (Haematoxylin and Eosin stain, original magnification; Fig. 1a: x20 and Fig. 1b: x100; *Schwannoma-like area, **Perineurioma-like area, ***Neurofibroma-like area).

The schwannoma-like component is composed of Schwann cells with elongated, wavy, tapered ended hyperchromatic nuclei, pale eosinophilic cytoplasm, and indistinct cell borders. They are arranged in hypercellular Antoni A areas and hypocellular Antoni B areas. The hypercellular areas contained foci of Verocay bodies, which are composed of palisading Schwann cells. The hypocellular areas show presence of hyalinized blood vessels in a more collagenous stroma. Degenerative or ancient Schwann cells were not seen in our case (Figure 2).

The neurofibroma-like component is composed of admixture of smaller Schwann cells, occasional perineurial cells, fibroblasts, lymphocytes, and mast cells, in the background of myxoid stroma with shredded carrot-like collagen fibres. The Schwann cells typically show comma-shaped nuclei with scant cytoplasm. No plexiform architecture seen in our case (Figure 3).

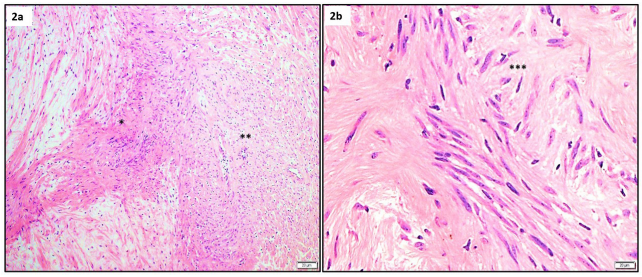

Figure 2: The centre of the lesion; shows schwannoma-like component with the typical Antoni A and Antoni B areas. Foci of Verocay body formations are also present. (Haematoxylin and Eosin stain, original magnification; Fig. 2a: x200 and Fig. 2b: x400; *Antoni A area, **Antoni B area, ***Schwann cells).

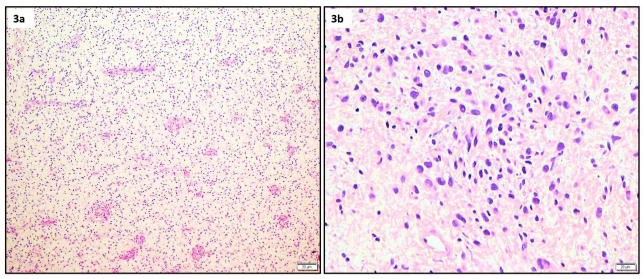

Figure 3: The Neurofibroma-like component; focal areas of the neurofibroma-like areas showed mild worrisome features (Haematoxylin and Eosin stain, original magnification x400; Fig. 3a: Area with mild increase in cellularity and Fig. 3b: Area with mild nuclear pleomorphism).

Additionally, our case showed focal worrisome features within the neurofibroma-like component, characterized by mild increase in cellularity in few areas and mild cellular pleomorphism in other separate areas. However, there is no mitoses, necrosis, or loss of the typical neurofibroma architecture.

The perineurioma-like component is composed of perineurial cells arranged in lamellar, reticular, and concentric architecture in loose to dense fibrous stroma. The perineurial cells show long slender nuclei with bipolar cytoplasmic processes. Storiform and whorling architecture were not present. Nerve bundles were seen adjacent and within the capsule, as well as within the lesion.

Immunohistochemistry using S100 (Ventana, antibody clone 4C4.9) and SOX10 (Cell Marque, antibody clone SP267) stains showed strong diffuse positive immunoreaction within the schwannoma-like component and weaker patchy positive immunoreaction within the neurofibroma-like component due to its mixed cellular composition. The perineurioma-like component showed positive immunoreaction toward Epithelial Membrane Antigen (Ventana, antibody clone E29) and Glucose Transporter 1 (Cell Marque, polyclonal antibody) stains, and negative immunoreaction toward S100 and SOX10 stain (Figure 4).

The case was concluded as hybrid nerve sheath tumour. Patient was well post excision and discharged after post-operative review at follow up clinic.

DISCUSSION

The existence of a single tumour exhibiting combination of two or more components of distinct PNST entities such as seen in our case may indicate the close relation between each entity. This can be supported by their common embryological origin (3). The peripheral somatic sensory and autonomic nerve systems, together with their supporting Schwann cells, and the adrenergic cells within adrenal gland have been found to originate from neural crest progenitor cells (3). This differs to the central nervous system (CNS) and the peripheral

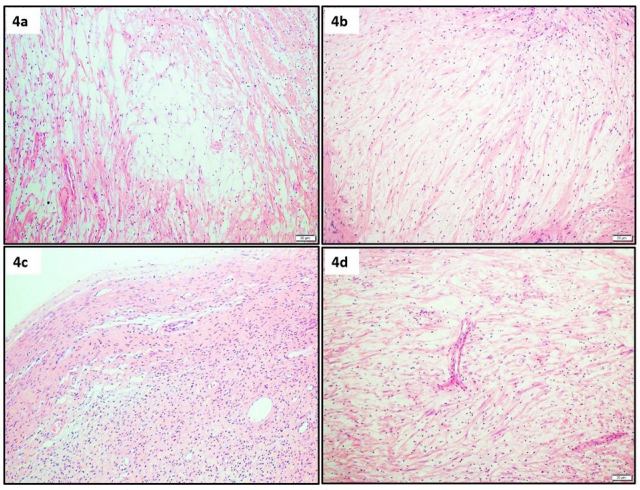

Figure 4: The Perineurioma-like component; shows slender bipolar perineurial cell proliferation in reticulated, lamellated and concentric pattern (Haematoxylin and Eosin stain, original magnification x400; Fig. 4a: Reticulated pattern, Fig. 4b: Lamellated pattern, Fig. 4c: Concentric pattern and Fig. 4d: Perineurial cells).

somatic motor nerve system which originate from the neuroectoderm progenitor cells (3). The perineurial cells, on the other hand, have conflicting conclusions on their origin, whether they also originate from neural crest progenitor cells or from CNS-glial cells (4).

It is also interesting to note that, despite previously believed as mesenchymal in origin, a study by Furlan A., et al. in 2018 reviewed the plasticity of Schwann cells which has the ability to transform into other non-Schwann potentials such as melanocytes and endoneural fibroblast (5). This phenomenon may explain the occurrence of hybrid schwannoma/perineurioma in a congenital melanocytic nevus with neural differentiation reported by Wang et al. in 2013 in a 36-year-old male with a black tumour on his arm since birth (2). Requena L., et al. and Yamada S., et al. in 2013 also reported cases of hybrid perineurioma and cellular neurothekeoma (2). In 2015, Linos K., et al. reported a case of benign cutaneous biphasic hybrid tumour of perineurioma and cellular neurothekeoma (BCPHTPCN), a recently described entity within head and neck region which microscopically demonstrates a plexiform pattern (2). Neural crest progenitor cells, also show potential for epithelio-mesenchymal transformation (4).

The question whether HNSTs are part of the PNSTs spectrum arising from known tumour syndromes as a result of clonal germ-line genetic alteration or indeed another distinct entity arising from a localized sporadic somatic change in the genetic microenvironment of the neural crest progenitor cells have been a conundrum. The fact that our case highlights a sporadic occurrence in a patient that does not have any features of known tumour syndromes, does support that HNSTs can be a distinct entity. Lang SS., et al. in 2012 also reported a rare occurrence of multiple hybrid neurofibroma/schwannomas in a 28-year-old female with no clinical features of any tumour syndromes and showed negative NF1 genetic testing (2). Sporadic hybrid schwannoma/perineurioma has also been reported following radiation (2).

Few of the reported sporadic HNSTs had also shown ability to recur (2). Rekhi B., et al. in 2011 also reported the first case of malignant peripheral nerve sheath tumour (MPNST) transformation in a hybrid schwannoma/perineurioma in a young male (2). Our case also had shown focal areas of increased proliferation and presence of focal mild pleomorphism within the neurofibromatous area, without any other aggressive features such as invasion, necrosis, increase in mitoses or loss of the typical architecture. However, there are no definite malignant criteria present for HNSTs, particularly in cases where the malignant transformation arises from the perineurial elements (2).

There are also few reported cases of HNSTs in patients with tumour syndromes such as NF1, NF2 and schwannomatosis, supporting that HNSTs may still be part of the PNSTs spectrum (2). Those associated with tumour syndromes were often multiple and carries a higher risk of recurrence and malignant transformation (2). Kacerovska et al. in 2013 published a series of five cases of HNSTs occurring in the setting of NF1. Out of those cases, one showed malignant transformation in the neurofibromatous component, and interestingly, three of the patients were members of same family with variable malignant neoplasms (2).

The exact pathogenesis, rates of the recurrence and malignant transformation remains unknown due to the rarity of these tumours. Stahn et al. performed analysis of 22 hybrid neurofibroma/schwannoma using immunohistochemistry, quantitative RT-PCR, array comparative genomic hybridization and cultured Schwann cells, in which 44% showed monosomy of chromosome 22 and involvement of α-T-catenin/CTNNA3 in the molecular pathogenesis of HNSTs (2). In another precision oncology program via whole-exome sequencing, an activating mutation, p.Asp769Tyr in the catalytic domain of the ERBB2 receptor tyrosine kinase was identified in a patient with schwannomatosis-associated HNST, and targeted treatment with the small molecule ERBB inhibitor lapatinib led to prolonged clinical benefit and a lasting radiographic and metabolic response in that patient (2). Larger case series and genomic research may be required to recognise the exact aetiology and risks of these tumours.

CONCLUSION

We discussed the components of HNSTs and whether HNSTs are distinct entity or part of a closely related PNSTs spectrum. We also highlighted the presence of recurrence and malignant transformation in HNST. The exact pathogenesis, recurrence rates, risk of malignant

transformation, and specific malignant criterion need to be recognised for these tumours.

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REFERENCES

1. Fletcher C DM, Bridge JA, Hogendoorn P, Mertens F. WHO Classification Of Tumours Of Soft Tissue And Bone. Fifth Edition. WHO 2020; IARC WHO Classification Of Tumours. ISBN-13 9789283224341.
2. Ud Din N, Ahmad Z, Abdul-Ghafar J, Ahmed R. Hybrid Peripheral Nerve Sheath Tumors: Report Of Five Cases And Detailed Review Of Literature. BMC Cancer. 2017;17(1):349.
3. Catala M, Kubis N. Gross Anatomy And Development Of The Peripheral Nervous System. In: Elsevier; 2013:29-41.
4. Kucenas S. Perineurial Glia. Cold Spring Harb Perspect Biol. 2015;7(6):A020511. Published 2015 Mar 27. Doi:10.1101/Cshperspect.A020511.
5. Furlan A, Adameyko I. Schwann Cell Precursor A Neural Crest Cell In Disguise? Developmental Biology. 2018;444:S25-35.