Review Article

Taiwan J Ophthalmol 2020;10:181-183

Access this article online

Quick Response Code:

Website:
www.e-tjo.org

DOI:
10.4103/tjo.tjo_28_20

Orbital hybrid peripheral nerve sheath tumors

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Abstract:

Hybrid peripheral nerve sheath tumors (HPNST) are recently classified tumors from the World Health Organization Classification of soft tissue tumors that display combined features of more than one peripheral nerve sheath tumor. Acknowledgment is important because of its association with the development of neurofibromatosis type 1, type 2, and schwannomatosis. Orbital involvement is rare and only six cases of HPNST have been documented on literature. This article serves to review the pathophysiology, clinical manifestation, diagnosis, treatment, and prognosis of this infrequent but important orbital tumor.

Keywords:

Hybrid peripheral nerve sheath tumor; neurofibroma-schwannoma; neurofibroma-perineurioma; orbital; orbital tumor

Introduction

Hybrid peripheral nerve sheath tumor (HPNST) is a unique pathological entity that contained mixed components of neurofibroma, perineurioma, and schwannoma. Three subtypes of HPNST have been identified: neurofibroma-schwannoma, schwannoma-perineurioma and neurofibroma-perineurioma in decreasing level of incidence. Significance of hybrid tumor is important because of its potential risk of associated neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and schwannomatosis.[1] Orbital involvement of HPNST is rare, but reports are growing with five new cases described in between 2017 and 2019.[2-6] Clinical manifestation and prognosis within the orbit remained largely unknown due to its paucity. This article reviews the pathophysiology, clinical manifestation, diagnosis, treatment, and prognosis of this infrequent but important orbital tumor.

Pathophysiology

HPNST are rare tumors categorized under the World Health Organization Classification of soft tissue tumors that display features of more than one peripheral nerve sheath tumor.[7] The development of neurocutaneous tumors (NF1, NF2, and schwannomatosis) and HPNST are highly linked to somatic and biallelic mutations of *NF1* gene (17q11.2) and *NF2* gene (22q12.2). Specifically, functional loss of neurofibromin protein in *NF1* gene mutation causes neurofibroma and subsequent NF1, where loss of *NF2* gene function contributed to development perineurioma and NF2.[8-10] Similarly, biallelic inactivation *NF2* gene mutation related merlin loss is associated with schwannoma and schwannomatosis development, which also includ mutations of the switch-sucrose nonfermentable chromatin remodeling subunit SMARCB1/INI1 (22q11.23).[11,12]

In hybrid neurofibroma-schwannoma, the plexiform type of neurofibroma is most commonly seen and is pathognomonic for NF1.[13] Surprisingly, hybrid neurofibroma-schwannoma has been

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Submission: 10-02-2020
Accepted: 28-04-2020
Published: 27-07-2020

How to cite this article: Leung KC, Ko TC. Orbital hybrid peripheral nerve sheath tumors. Taiwan J Ophthalmol 2020;10:181-3.

observed to be associated with the development of NF2, schwannomatosis, and NF1 in decreasing frequency.[11,14] A further study on this HPNST has also discovered that 44% of tested tumors harbor monosomy of chromosome 22 and linked to the development of NF2.[12] The reason why NF1 are less encountered remained unexplained. Preliminary studies have reported a possible precursor role for perineurial proliferation in NF1 in hybrid neurofibroma-perineurioma.[1,15] Little is known about the connection between hybrid schwannoma-perineurioma and neurocutaneous syndromes, which development appeared sporadic.

Clinical Manifestation

HPNST chiefly occurs in subcutaneous and subdermal areas, infrequently involving the orbit, facial nerve, and nasopharynx.[16,17] Literature review has reported six cases of HPNST that arose from within the orbit.[2-6,18] Orbital HPNST appears to occur in young adults without any gender (three males, three females) and laterality predilection. The most frequently occurring orbital HPNST subtype is neurofibroma-schwannoma (five cases) followed by neurofibroma-perineurioma (one case). The tumor tends to present unilaterally over the superior aspect of the orbit, which may involve the distribution of supraorbital and supratrochlear nerves. Extraconal orbital HPNST appears to present more often than intraconal involvement, which was speculated by the presence of a greater number of nerves in extraconal space relative to the intraconal area.[3]

Clinically, orbital HPNST manifest as a space-occupying lesion that causes local displacement over the course of the nerve. The onset is slow, and vision is not affected unless there is intraconal involvement. Orbital tenderness, diplopia, and hyperesthesia are infrequently described. Localized mass effect gives rise to clinical signs such as nonaxial proptosis, ptosis, and hypoglobus. All but one case was asymptomatic and was discovered as an incidental finding.

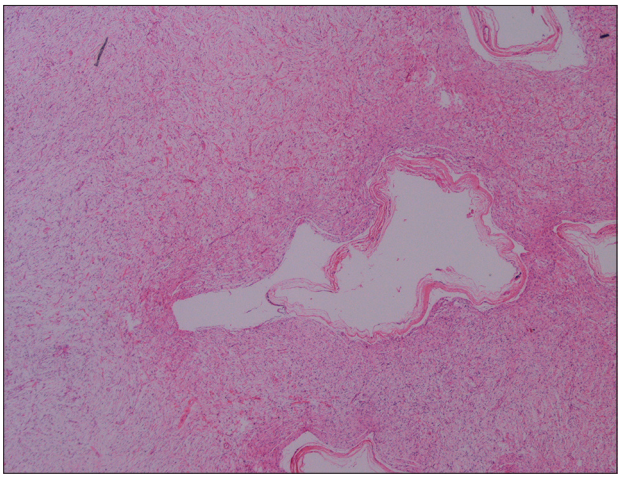

Figure 1: Example of a hybrid neurofibroma-perineurioma that displayed retiform arrangement merging into the background neurofibroma on haematoxylin and eosin stain. Low power view

Diagnosis

On histological analysis, orbital HPNST demonstrates a biphasic pattern, such as a clear transition of the different cell types or intermingling. Specifically, neurofibroma-schwannoma exhibits islands of schwannoma in a background of neurofibroma.[14] Schwannoma lobules classically display Antoni A and B areas, where Antoni A represents highly cellular spindle cells arranged in fascicles with nuclear palisading and Verocay bodies and Antoni B areas have reduced cellularity with myxoid regions. Neurofibroma demonstrates the proliferation of Schwann cells, perineural cells in a background of mucin, fibroplasia, and collagen, which nuclei showed wavy serpentine and pointed ends. Neurofibroma-perineurioma hybrid has a unique retiform appearance that has a mosaic arrangement of spindle cells that merge with background neurofibroma [Figure 1].[1]

Immunohistochemistry facilitates diagnosis with neurofibroma manifesting S-100 protein and immunostain positivity; schwannoma showing strong S-100 positivity; and perineurioma showing epithelial membrane antigen, glucose transporter protein 1 and claudin-1 positivity [Figure 2a-d].[19] The study of staining patterns of S-100 helps in differentiating schwannoma from neurofibroma. Expression of S-100 protein is more diffusely stained involving all of schwannoma tumor

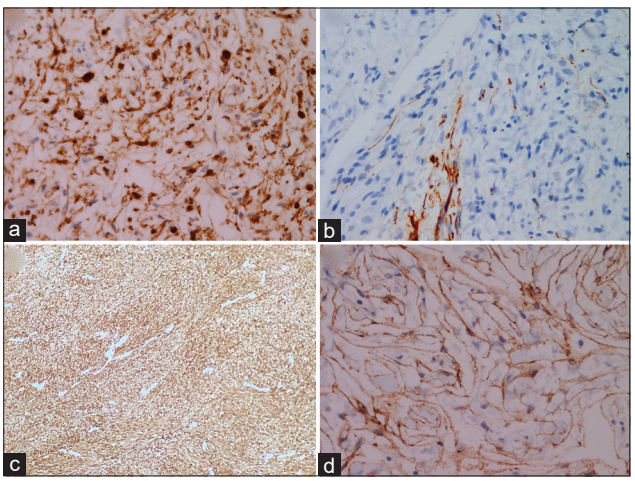

Figure 2: (a) Immunohistochemistry of neurofibroma staining positive with the S-100 protein × 200. (b) Immunohistochemistry of neurofibroma staining positive with immunostain × 200. (c) Immunohistochemistry of schwannoma staining positive with S-100 protein × 100. The staining pattern of schwannoma is characteristically much more diffuse and involves almost all tumor cells compared with neurofibroma. (d) Immunohistochemistry of perineurioma staining positive with epithelial membrane antigen × 200

cells, contrasting to neurofibroma, where staining is only limited to about 50% of cells.[1] Nonetheless, a biopsy of normal-looking nerve fibers may aid diagnosis in ambivalent cases.

Treatment and Prognosis

Surgical excision through anterior orbitotomy remains the mainstay of treatment for orbital HPNST, given its common superior extraconal presentation. For intraconal tumors excision through frontotemporal craniotomy and transconjunctival approach were reported for better surgical access. Tumors are commonly yellowish-gray, firm, well-demarcated, circumscribed, and devoid of vascularity, making *in vivo* identification and retrieval of tumor possible. The postoperative course is generally satisfactory with resolution of proptosis. Reports of dysesthesia over the course of supraorbital and supratrochlear nerve were regularly described after surgical exploration (three cases). Visual acuity and diplopia improved in cases of intraconal tumors, with mild residual abducens cranial nerve palsy after craniotomy.

No cases of malignant transformation were observed after total excision despite reports in extra-orbital neurofibroma-perineurioma hybrid tumors.[1,2] No associated cases of neurocutaneous syndromes were reported. To date, no recurrence of orbital HPNST were described after excision on 1-year follow-up, although long-term reviews are necessary to acertain the true recurrence rate given the slow and insidious nature with this tumor.

Summary

HPNST is increasingly being reported to occur within the orbit. Acknowledgment is important because of its association with the development of NF1, NF2, and schwannomatosis, with possible malignant transformation. Variable clinical presentations occur and relate to extraconal and intraconal involvement. Diagnosis is achieved through detailed histological and immunopathological examinations. The mainstay of treatment involved surgical excision, which yielded acceptable outcomes. Active screening for development into neurocutaneous syndromes, malignant transformation and recurrence postoperatively is essential for this infrequent and unique group of tumors.

Financial support and sponsorship
Nil.

Conflicts of interest
The authors declare that there are no conflicts of interests of this paper.

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