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Major review

Orbital peripheral nerve sheath tumors

Adam R. Sweeney, MD[a,*], *Divakar Gupta, MD*[b], *C. Dirk Keene, MD, PhD*[c], *Patrick J. Cimino, MD, PhD*[c], *Christopher B. Chambers, MD*[a], *Shu-Hong Chang, MD*[a], *Eissa Hanna, MD*[a]

[a] *Department of Ophthalmology, University of Washington, Seattle, Washington, USA*
[b] *Department of Ophthalmology, Duke University, Durham, North Carolina, USA*
[c] *Department of Pathology, University of Washington, Seattle, Washington, USA*

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ABSTRACT

Peripheral nerve sheath tumors of the orbit and ocular adnexa are a rare group of neoplasms hallmarked by nonspecific clinical presentations, variable tumor locations, challenging therapeutic efforts, and occasional diagnostic dilemmas. We review these tumor types and provide an updated summary on their clinical, histopathologic, radiological, and emerging molecular features.

1. Background

In 1768, Akenside first described a patient with multiple tumors involving the peripheral nerves. Over a century later, von Recklinghausen reported on "neurofibromatosis" and demonstrated numerous neurofibromas as belonging to a single nerve. The neurinoma was differentiated from neurofibromas histologically by Verocay in 1910 and later named schwannoma after Masson confirmed that the cell of origin was the Schwann cell. The term neurilemmoma was introduced by Stout, leaving schwannoma and neurilemmoma synonymous through a great span of medical literature until the advent of electron microscopy.

* Corresponding author: Adam R. Sweeney, MD, Department of Ophthalmology, University of Washington, Box 359608, 325 Ninth Avenue, Seattle, WA 98104, USA.
E-mail address: asweeney@uw.edu (A.R. Sweeney).
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Peripheral nerve sheath tumors (PNSTs) are derived from the neuroectoderm and neural crest and may involve the nerve fascicles or branches of cranial nerves III–VII in the orbit.[117] The PNSTs more commonly involved with these nerves include the neurofibroma, schwannoma, and malignant PNST (MPNST).

MPNSTs have historically been referred to as neurogenic sarcoma, neurofibrosarcoma, malignant schwannoma, or malignant neurilemmoma. Schwann cell origin has not been demonstrated in all cases leaving MPNSTs as a distinct clinicopathologic entity.[43]

Tumor subtypes differentiate the localized solitary neurofibroma from the diffuse and plexiform neurofibromas. Schwannomas are classified as conventional (solitary) or by their distinguishing histologic features: melanotic, plexiform, and neuroblastoma-like schwannoma. MPNSTs may also have a histological variant referred to as the epithelioid subtype. PNSTs are associated with the neurofibromatoses; however, 90% of solitary orbital PNSTs occur in the absence of oculoneurocutaneous syndromes.[128,134]

Other exceptionally rare tumors affecting peripheral nerves have been described but are out of the scope of this review. These include traumatic neuroma, paraganglioma, amputation neuroma, melanotic neuroectodermal tumor of infancy, and primary orbital neuroblastoma.

2. Epidemiology

PNSTs often involve the head and neck, but are uncommon in the orbit. Karcioglu summarized 5 large studies of biopsy-proven orbital tumors and found the relative frequency of PNSTs to all orbital tumors to be neurofibroma (all types) 0.4%–3.0%; schwannoma (subtypes not specified) 0.7%–2.3%; and MPNST 0%–0.2%.[62] Benign PNSTs most commonly affect adults aged between 20 and 60 years,[19,119] with the exception of plexiform neurofibromas, in which 50% of lesions are diagnosed between 1 and 5 years of age,[42,43] initiating debate for this tumor type to be considered a congenital lesion.[37] Previously, MPNSTs were considered tumors of adulthood, with rare occurrences in children with neurofibromatosis type 1 (NF-1)[59]; however, more recent case reports demonstrate involvement in children with or without NF-1.[17,36,40] PNST involvement is approximately equal between genders with some reporting a slightly higher occurrence in women.[27,119,141] No racial predilection has been observed.

Localized orbital neurofibromas have an 11%–28% association with systemic neurofibromatosis or a family history of neurofibromatosis.[76,119] This contrasts to extraorbital neurofibromas, which are characteristic of NF-1 and infrequently found outside of neurofibromatosis. An extraorbital neurofibroma fulfills 1 of 2 diagnostic criteria for NF-1. The plexiform neurofibroma subtype is described by some as pathognomonic for NF-1[3]; however, one group recently reported 3 individuals with plexiform neurofibroma without other systemic features meeting the diagnostic criteria of NF-1, and two of these individuals lacked the NF-1 mutation on peripheral blood DNA analysis.[9] This highlights that no single finding is diagnostic of NF-1.

Patients with NF-1 have a 2%–18% likelihood of developing orbital solitary or diffuse neurofibromas and a 5% likelihood of developing orbital plexiform neurofibroma.[37] Patients with neurofibromatosis are also at increased risk for other orbital tumors, including optic nerve glioma (10%–15%),[37] optic nerve sheath meningioma (2%–8%),[14] and less commonly, orbital schwannoma (1.5%).[117]

Solitary schwannomas affecting the orbit are rarely associated with systemic features of neurofibromatosis.[118] Plexiform schwannomas have a much weaker association with the neurofibromatoses, with only a few extraorbital cases associated with NF-1 or neurofibromatosis type 2 (NF-2) reported in the literature.[149] Multiple schwannomas affecting the orbit in the absence of vestibular schwannomas or other systemic features of NF-2 may be classified into a different category termed neurofibromatosis type 3, also referred to as schwannomatosis.[110]

Rarely, benign neurofibromas and schwannomas may undergo malignant transformation.[32,47,50,117,123,139] Solitary neurofibromas in the absence of NF-1 undergo malignant transformation to MPNSTs exceedingly rarely with only one reported.[22] While only a few case series discuss the epidemiology of orbital MPNSTs, more is known about extraorbital MPNSTs, which have a prevalence of 4% in patients with NF-1 and 0.0001% in the general population.[151] Radiotherapy for prior malignancy may be associated with increased risk of MPNSTs in patients with NF-1.[34] To our knowledge, only 1 case has been reported of a primary orbital epithelial MPNST,[108] a form of MPNST portending a dismal prognosis when found outside the orbit.[96]

3. Etiology

The molecular etiology of PNSTs is only partially understood. In patients with NF-1, neurofibromas are formed after biallelic loss of the tumor suppressor gene NF-1 (17q11.2) in Schwann cells. MPNSTs have been found to occur following both the loss of NF-1 and overexpression of RAS coinciding with inactivation of cell cycle regulators, such as p53.[39] The NF-2 gene (22q11.2) is also considered a tumor suppressor gene. Loss of NF-2 or the gene's encoded protein (merlin) in Schwann cells results in Schwann cell hyperplasia and schwannomas.[38] Less is known about the molecular etiology of sporadic PNSTs. One patient with sporadic plexiform neurofibroma without other features of NF-1 was shown to have a biallelic loss of the NF-1 gene with a mosaic Schwann cell population—some cells demonstrating a chromosomal rearrangement mutation in one allele and a deletion in the other allele.[10] This case suggests a second hit phenomenon, which may be applicable to other benign PNSTs as well.

Neurofibromas arise from nonmyelinated, neoplastic Schwann cells and differentiate themselves from schwannomas by their neoplastic incorporation of various other cell types.[29] These tumors primarily arise from the V1,[62] rarely from V2[43] or the nerves innervating the extraocular muscles.[1]

Schwannomas originate from myelin-producing Schwann cells and principally grow via hyperplasia of this cell of origin. Most orbital schwannomas arise from sensory nerves, particularly, branches of V1; however, tumors of V2,[25,118] the