Orbital peripheral nerve sheath tumors

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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.
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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, parangangioma, amputation neuroma, melanotic neuroectodermal tumor of infancy, and primary orbital neuroblastoma.

\section{Epidemiology}

PNSTs often involve the head and neck, but are uncommon in the orbit. Karciglu 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\%.\textsuperscript{52} Benign PNSTs most commonly affect adults aged between 20 and 60 years,\textsuperscript{59,112} with the exception of plexiform neurofibromas, in which 50\% of lesions are diagnosed between 1 and 5 years of age.\textsuperscript{42,43} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{40} This case suggests a second hit phenomenon, which may be applicable to other benign PNSTs as well.

Localized orbital neurofibromas have an 11\%–28\% association with systemic neurofibromatosis or a family history of neurofibromatosis.\textsuperscript{6,119} 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;\textsuperscript{41} 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.\textsuperscript{2} 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.\textsuperscript{37} Patients with neurofibromatosis are also at increased risk for other orbital tumors, including optic nerve glioma (10\%–15\%),\textsuperscript{37} optic nerve sheath meningioma (2\%–8\%),\textsuperscript{14} and less commonly, orbital schwannoma (1.5\%).\textsuperscript{117}

Solitary schwannomas affecting the orbit are rarely associated with systemic features of neurofibromatosis.\textsuperscript{119} 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.\textsuperscript{137} 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.\textsuperscript{110}

Rarely, benign neurofibromas and schwannomas may undergo malignant transformation.\textsuperscript{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.\textsuperscript{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.\textsuperscript{151} Radiotherapy for prior malignancy may be associated with increased risk of MPNSTs in patients with NF-1.\textsuperscript{34} To our knowledge, only 1 case has been reported of a primary orbital epithelial MPNST,\textsuperscript{108} a form of MPNST portending a dismal prognosis when found outside the orbit.\textsuperscript{56}

\section{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{40} 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.\textsuperscript{29} These tumors primarily arise from the V1,\textsuperscript{62} rarely from V2\textsuperscript{25} or the nerves innervating the extraocular muscles.\textsuperscript{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,\textsuperscript{25,111} the
cranial nerves in the orbit,\textsuperscript{118,125} and the nerves innervating the extraocular muscles\textsuperscript{20,75} have been reported. More rarely, schwannomas can affect the globe, with reported origins being the ciliary body,\textsuperscript{78,129} choroid,\textsuperscript{29,131,159} iris,\textsuperscript{111} and sclera\textsuperscript{89,95} with pathological demonstration of tumor origination from the posterior ciliary nerve.\textsuperscript{41,131} While Schwann cells are specific to peripheral nerves, optic nerve schwannomas occur,\textsuperscript{28,67,86,112,133} with the proposed mechanism stemming from autonomic perivascular nerves surrounding the optic nerve sheath.\textsuperscript{112}

MPNSTs generally arise de novo\textsuperscript{62} but may also originate from neurofibromas or schwannomas.\textsuperscript{3,62,149} An estimated 25\%–50\% of MPNSTs are found in patients with neurofibromatosis and a history of plexiform neurofibroma.\textsuperscript{3,62,149} The cell type origin of many MPNSTs often remains unknown given the diverse cellular proliferation; however, the Schwann cell is considered to be the typical, but not the only known, cell type of origin. Similar to benign PNSTs, MPNSTs have a predilection for the superior orbit, specifically V\textsubscript{1}.\textsuperscript{34,90} MPNSTs are known to metastasize to regional lymph nodes and lungs\textsuperscript{59,90}, with a higher risk of metastasis following postsurgical recurrence.\textsuperscript{62}

4. Clinical features

In the orbit, benign PNSTs commonly present with an insidious onset and are governed by the tumor location, their slow rate of growth, and their noninvasive nature. Localized neurofibromas and schwannomas present with lid swelling and proptosis in 50\%—with ptosis, decreased vision, and diplopia presenting features in 4\%–20\%.\textsuperscript{119} Late manifestations including visual obscuration and pain are potentially ominous manifestations of nerve root compression, globe indentation, or transformation to invasive tumor types such as MPNST. Approximately 1/3 of localized neurofibromas extend into the superior orbital fissure.\textsuperscript{112} Similarly, the rate of extension into the superior orbital fissure for schwannomas is 16\%–24\%.\textsuperscript{32,119,148}

Localized neurofibromas typically present with progressive unilateral proptosis of less than 1-year duration. Visual acuity is often preserved in the absence of optic nerve compression. Extraorbital localized neurofibromas may undergo an accelerated rate of growth during pregnancy and puberty.\textsuperscript{149} Localized neurofibromas affecting the orbit are not typically associated with NF-1; however, when this association is present, the orbital lesions are generally preceded by café au lait spots.\textsuperscript{149} Multiple localized neurofibromas in the same orbit in the absence of NF-1 are rare.\textsuperscript{76,132} PNSTs affecting the orbits bilaterally in the absence of NF-1 have been reported only in 2 patients: one with Charcot-Marie-Tooth disease (a disorder with a defect on the same gene locus as NF-1)\textsuperscript{88} and one with several features of multiple endocrine neoplasia type IIB.\textsuperscript{97}

Orbital plexiform neurofibroma will often present in childhood or adolescence with lid swelling in an S-shaped curvature of the upper eyelid highly characteristic of NF-1.\textsuperscript{142} The strong association of postseptal neurofibroma with preceding eyelid involvement has prompted some to consider orbital involvement a product of early posterior spread across the septum.\textsuperscript{149} Careful palpation of the ocular adnexa may demonstrate the classic “bag of worms” texture.\textsuperscript{149} Palpation may also reveal pulsatile proptosis or enophthalmos, indicating sphenoid wing dysplasia and herniation of orbital contents into the cranium—which may be specific for plexiform neurofibroma in the setting of a benign, slow-growing orbital tumor.

Neurofibromatosis may have additional ophthalmic manifestations, notably iris melanocytic hamartomas (Lisch nodules) occurring in 92\% of patients \( \geq 6 \) years of age with NF-1.\textsuperscript{87} The second most common ophthalmic manifestation in NF-1 is choroidal hamartoma.\textsuperscript{7} The most common orbital tumor in patients with NF-1 is optic pathway glioma, which may arise in the orbit or intracranially in 15\%–20\% of patients with NF-1.\textsuperscript{87} Other ocular manifestations of NF-1 include retinal astrocytic hamartoma, choroidal melanoma, choroidal schwannoma, and retinal vascular occlusions.\textsuperscript{62} Ocular manifestations of NF-2 are less common, but include juvenile posterior subcapsular or peripheral cortical cataracts, episcleral membrane, retinal hamartomas, and ocular motor abnormalities, in that order of frequency.\textsuperscript{52,92,95}

Orbital schwannomas present similarly to neurofibromas with early manifestations of gradual nonpulsating proptosis and lid swelling. Late manifestations include diplopia, restriction in ocular motility, mild impairment in visual acuity, and symptoms of optic nerve compression including scotomas, dyschromatopsia, and decreased contrast sensitivity. When proptosis does occur, inferior displacement is most common, as the superior quadrant is the location of primary involvement in 40\%–60\%.\textsuperscript{19,135,148} Occasionally, orbital schwannomas may present with a deep, dull pain or with paresthesias in the distribution of the affected nerve. On occasion, a mass in the orbit may be palpated. Only 1 case is known with simultaneous bilateral orbital involvement.\textsuperscript{122}

As with neurofibromas, case reports describe rapid growth of orbital solitary schwannomas during pregnancy.\textsuperscript{13,21,142} In one case, progesterone receptors were diffusely found on immunohistochemistry of the tumor,\textsuperscript{32} and in another case, estrogen and progesterone receptors were absent with histology and serial imaging demonstrating intratumor hemorrhage as the likely etiology of rapid growth.\textsuperscript{143} This finding of intratumor hemorrhage has also been observed in the rare reports of rapid solitary schwannoma growth in nonpregnant patients.\textsuperscript{135}

MPNSTs affecting the orbit have increased incidences of pain, redness, and rapidly progressing ptosis\textsuperscript{59,90,119} differentiating them from their benign counterparts. Unfortunately, MPNSTs may have early metastasis with spread along peripheral nerves to the cranium leading to the presentation of neurological changes in addition to orbital complaints.\textsuperscript{29} Rapid recurrence of previously diagnosed benign PNSTs following partial excision should raise clinical suspicion for MPNSTs.\textsuperscript{59}

5. Differential diagnosis

The clinical differential diagnosis for PNSTs includes other slow-growing tumors such as meningioma, cavernous hemangioma, lymphangioma, fibrous histiocytoma, lymphoma, dermoid cyst, hemangiopericytoma, and pleomorphic adenoma of the lacrimal gland. These lesions are very
difficult or impossible to differentiate on clinical examination. Imaging techniques have become extremely useful to aid in the identification of orbital tumors; however, even with modern, high-resolution imaging, many tumor types remain difficult to distinguish. If consecutive imaging is performed, particular attention should be focused on the tumors evolution in size, location of spread, and specific imaging contrast techniques described in the following. An increase in the growth rate or new development of pain is atypical for benign PNST and should be concerning for high-grade neoplasm or malignancy.

### 6. Diagnostics

#### 6.1. Imaging

**6.1.1. Computed tomography/magnetic resonance imaging**

Radiographically, solitary lesions in the orbit include neurofibroma, schwannoma, MPNST, cavernous hemangioma, meningoima, lymphoma, solitary fibrous tumors, dermoid cysts, and others. Both computed tomography (CT) and magnetic resonance imaging (MRI) assist in narrowing the differential of orbital masses. In relationship to PNSTs, CT is best used for monitoring bony erosion and for surgical planning, while MRI may help to assist in characterizing the structure of the tumors and their involvement with adjacent soft-tissue structures.

##### 6.1.1.1. Neurofibroma

Localized neurofibromas on CT demonstrate homogenous density and may be smoothly margined, round, ovoid, or lobulated. The majority of these tumors will be isodense to extraocular muscles and will variably enhance, with some demonstrating peripheral ring enhancement. Adjacent bony opacification from tumor pressure may be seen, highlighting the tumors slow growth. Neurofibromas typically lack the secondary degenerative changes, including calcification, that may be seen on CT in schwannomas, meningiomas, or more rarely cavernous hemangiomas. Based on CT images, confusion between cavernous hemangioma and neurofibroma is common, as both demonstrate a well-outlined, enhancing lesion with similar homogeneity. Neurofibromas, however, may be more rounded and are more commonly extracranial on CT.

Diffuse neurofibromas on CT typically demonstrate an irregular, poorly defined soft-tissue mass with variable contrast enhancement. Typically, these tumors are isodense with the extraocular muscles; however, there are cases of nonorbital neurofibromas and 1 orbital case where these tumors have appeared dark on CT imaging, similar to orbital dermoid cyst or lipoma.

Plexiform neurofibromas may be distinguished from solitary neurofibromas, schwannomas, and other solitary tumors by the degree of infiltration of adnexal structures seen on imaging. These tumors typically appear as a multilobular, oblong, diffuse mass. Absence of one or both wings of a sphenoid bone is a characteristic feature of NF-1, particularly in the presence of plexiform neurofibromas. Additionally, adolescents with NF-1 may have remodeling and expansion of the ipsilateral bony orbit.

On MRI, neurofibromas may appear similar to schwannomas in that they may be hypointense to orbital fat and iso-intense to gray matter on T1-weighted images and intermediate to hyperintense on T2-weighted images. Commonly, a peripheral ring of hyperintensity on T2-weighted images will create a “target sign,” further aiding in differentiating this tumor. MRI intensity and degree of heterogeneity represents the histological features of the tumors, with greater water content in myxoid regions of these tumors shown to represent hyperintensity regions on T2-weighted images and hypercellular and more collagenous regions demonstrating hypointensity on T2-weighted images. In MRI studies, enhancement is similarly variable for both schwannoma and neurofibroma.

**6.1.1.2. Schwannoma**

Orbital schwannomas tend to be less round and more oval or spindle-shaped compared to other PNSTs. Schwannomas are typically smooth, well-circumscribed tumors molding to the shape of the cavity with characteristic growth along the axis of the orbit. Schwannomas imaged on CT appear homogenously dense, typically isodense to extraocular muscles, with smooth round or elongated morphologies. Schwannomas often demonstrate enhancement with contrast on CT. Calcification within the tumor has been reported for solitary primary schwannomas. Schwannomas are more often extraconal, whereas meningiomas and hemangiomas are often intraconal. Extension through the superior orbital fissure is more indicative of schwannoma than meningioma aiding in differentiating these tumors. One proposal is that bone expansion without erosion of the fissures is characteristic of extraconal schwannomas, a finding demonstrated with lesser frequency in cases of neurofibromas.

Schwannomas affecting the orbit have various MRI features; however, these lesions typically produce a hypointense signal on T1-weighted images and a hyperintense signal on T2-weighted images. Orbital schwannomas may demonstrate homogenous or heterogeneous enhancement. Some MRI findings are a result of the underlying histology and macroscopic morphology of these tumors. Shen and colleagues demonstrated corresponding Antoni A regions to have intermediate signal intensities with postcontrast enhancement in both T1- and T2-weighted image, contrasting to Antoni B regions demonstrating hypointensity on T1-weighted images, hyperintensity in T2-weighted images, and no contrast enhancement. Cystic degeneration may be seen in as high as 41% of schwannomas, with these regions being found to have similar radiologic features to Antoni B regions. MRI may be useful in differentiating schwannoma from other lesions. On MRI, schwannomas and lymphomas may have similarly round shapes, however, lymphomas have intermediate T2 signal and will classically mold around structures, in contrast to schwannoma which may abut and distort anatomy of adnexal structures. Similarly, the shape of dermoid cysts may correspond to that of schwannomas and occur in similar locations; however, these round benign masses are hyperintense on T1-weighted images and lack gadolinium enhancement, differentiating them from...
Solitary fibrous tumors and schwannomas have similar T1- and T2-weighted image intensities and locations. To differentiate between these tumors, dynamic contrast-enhanced MRI may be of use. Studies using dynamic contrast-enhanced MRI comparing contrast washout proposed that tumors with high-cellularity stroma, such as solitary fibrous tumors, have a smoother washout curve than schwannomas, which have a persistent or plateau-shaped washout curve presumably from their nonuniform, loose cellular arrangement. Dynamic contrast-enhanced MRI has also been shown to assist in differentiating cavernous hemangiomas from schwannomas with cavernous hemangiomas demonstrating progressive enhancement in later images which is atypical for schwannoma.

6.1.1.3. MPNST. Imaging characteristics of MPNSTs are more variable than the other PNSTs. On CT, MPNSTs often appear as a well-defined, rounded, homogeneously enhancing mass commonly located in the superior orbit, indistinguishable from other solitary orbital tumors, including benign FNSTs. These tumors may be well-circumscribed and found to erode through adjacent bony structures. On MRI, orbital MPNSTs may have an isointense homogenous signal on T1-weighted images, hyperintense on T2-weighted images with diffuse enhancement to gadolinium with regions of intense enhancement. Lesions with an irregular shape and/or adjacent bone invasion should be highly concerning for malignancy in patients with NF-1.

6.1.2. Ultrasound

Ultrasonography has a limited role in the evaluation of PNSTs; however, it may still be used for expedited evaluation, routine follow-up, or to monitor for progression. On B-scan, neurofibromas are generally diffuse and irregular, with internal vascularity sometimes appreciated. The characteristics of schwannomas on B-scan have been more thoroughly described. These tumors may appear as round, well-defined, solid lesions with a highly reflective surface or sometimes as a heterogeneous or cystic mass with several tissue interfaces that attenuate the signal intensity. Additionally, acoustic hollows have been suggested in schwannomas to correlate with hemorrhage within the tumor. MPNSTs have similar sonographic findings as schwannomas.

6.2. Histological features

6.2.1. Neurofibroma

On gross pathology, solitary neurofibromas appear as a poorly vascularized, firm, rubbery, well-circumscribed gray mass. On low power, neurofibromas can be distinguished from schwannomas by the lack of a true capsule and lower cellular density. Cytologically, there is variability in cell type density; however, classically neurofibromas demonstrate an overall low cellularity, with a loose myxoid background composed of mucopolysaccharide matrix punctuated by circumscribed proliferations of interlacing bundles of elongated, wavy, spindle-shaped cells. This pattern is a result of the
endoneurial growth pattern of neurofibromas in which the nerve is expanded radially entrapping and separating cells. Characteristic wavy collagen bundles will be present, often abundantly, throughout the tissue (Fig. 3A) and may be best appreciated with a trichrome stain. With neurofilament immunostaining, neurofibromas can usually be shown to contain scattered axons arranged individually or in small clusters, a pattern that is typically absent in schwannomas (Fig. 3B). In neurofibromas, spindle cells with darkly stained nuclei resemble cells of endoneurial fibroblast origin, whereas other spindle cells with comma shaped nuclei resemble those of Schwann cell origin. Mast cells are often present throughout the tumor (Fig. 3C).

Diffuse neurofibromas are morphologically appreciated grossly or on low power as spreading diffusely, surrounding structures of the ocular adnexa. These neoplasms have increased vasculature compared to localized neurofibromas. Histologically, diffuse neurofibromas have similar cell types as localized neurofibromas; however, they may be distinguished from localized neurofibroma by a greater degree of cellular density and by extensive infiltration to surround structures of the ocular adnexa, corresponding to the gross appearance. The mode of spread is via connective tissue septa and intracellular spaces along the adnexa. Collections of Schwann cell processes may make up ovoid bodies in this subtype.

Plexiform neurofibromas may identify themselves on imaging or intraoperatively by their nodular, tortuous, “bag of worms” appearance, owing to irregular hyperplasia that is often referred to as “spilling out” into surrounding tissue. Similarly to the diffuse subtype, plexiform neurofibromas may contain greater vascularity than solitary neurofibromas (Fig. 3D). Cytologically, this PNST contains the same cell types as solitary and diffuse neurofibromas; however, plexiform neurofibromas demonstrate different cell type densities with a higher degree of endoneurium and perineurium hyperplasia spacing out axons. Perineurial sheathing is characteristic. Increased nuclear atypia and cellularity seen histologically coincides with a greater risk of malignant transformation.

All neurofibroma subtypes will stain positively for S-100; however, neurofibromas generally only have a subset of positively staining cells, grossly staining intermittently and less intensely than schwannomas, demonstrating the greater degree of mixed cell types in neurofibroma. The matrix of a neurofibroma will stain positive for Alcian blue, whereas the schwannoma will be negative.

The cellular composition of neurofibroma includes neoplastic Schwann cells, fibroblasts, mast cells, and vasculature. Both the neoplastic and microenvironment cellular components host different molecular elements to neurofibroma tumorigenesis. Within the neoplastic cells, biallelic inactivating mutations in the tumor suppressor NF-1, which codes for the protein neurofibromin, are commonly associated with neurofibromas. The loss of NF-1 leads to over-activation of Ras, which signals through 2 major effector pathways, including PI3K/Akt/mTOR and Raf/MEK/ERK. Recurrent gene mutations in NF-1 associated or sporadic cases of neurofibromas outside of NF-1 have not been described. In a case of an individual with NF-1, whole-exome sequencing demonstrated a low variant allele frequency missense mutation in MYB within a plexiform neurofibroma. On malignant transformation to MPNST, as well as

Fig. 3 – Neurofibroma. A: Loose spindle cells interspersed with wavy collagen; B: longitudinal section of single, large, myelinated axon in neurofibroma; and C: loose myxoid tissue with occasional mast cell and axon; and D: plexiform neurofibroma demonstrating increased vascularity and sheet-like architecture.
metastasis, the MYB variant allele frequency increases, indicating more of the neoplastic cells harbored the mutation. The importance of MYB gene mutation in the setting of neurofibromas is yet to be determined. Recurrent copy number alterations of whole or partial chromosomes (outside of the 17q region encoding NF-1) are not present in neurofibromas. Similar to their unique genetic signatures, recent epigenetic profiling has shown that methylation profiles of neurofibroma differ from that of MPNST and schwannoma. Furthermore, methylation classification can discriminate between dermal, localized intraneural, and plexiform subtypes. Methylation classification has the potential for clinical diagnostic utility when there is a diagnostic dilemma of plexiform neurofibroma, which may imply a possible association with NF-1. In concert with the neoplastic component, the microenvironment is important for neurofibroma tumorigenesis, mainly contributed by hematopoetic-derived mast cells. The contribution by mast cells to neurofibroma development and maintenance includes molecular effectors such as TGF-beta and c-Kit.

6.2.2. Schwannoma

Histologically, most schwannomas have features that justify designation of “conventional” schwannoma; however, 4 additional histological variants have been described: cellular schwannomas, melanotic schwannomas, plexiform schwannomas, and neuroblastoma-like schwannomas. In the orbit, cellular schwannomas are much less common than conventional schwannomas. Melanotic, plexiform, and neuroblastoma-like variants are exceptionally rare tumors in the orbit.

Macroscopically, conventional and cellular schwannomas demonstrate a true fibrous smooth capsule formed from the perineurium of the nerve of origin. Melanotic schwannomas may have a thin fibrous membrane at most, whereas a capsule may be less evident and lobulated in plexiform variant. In cases where the neoplasm is small, the parent nerve may be clearly identified with the tumor growing eccentrically from it. This eccentric growth pattern may help to distinguish the solitary schwannoma, especially from a neurofibroma, as the latter tend to grow within the nerve expanding it radially. Larger schwannomas can overgrow the nerve, but diffuse infiltration of the nerve, as seen in neurofibroma, is not a typical feature of schwannomas.

On low-power light microscopy, schwannomas distinguish themselves by the strikingly greater concentration of Schwann cells than seen in other tumor types. The characteristic identifying feature is the distinct biphasic morphological pattern owing to variable, patchy amounts of Antoni A and Antoni B tissue patterns. Antoni A areas are hypercellular and composed of bundles and fascicles of compact spindle cells with indistinct cytoplasmic borders arranged in parallel along their long axis. A common feature of Antoni A areas are Verocay bodies, which are strips or regions of nuclear areas bounded by clusters of elongated spindle cell nuclei arranged in palisades (Fig. 4A). In highly differentiated areas, whorled patterns of cells can mimic morphology seen in meningioma. A periodic acid Schiff stain will be strongly positive in schwannoma, as will immunoperoxidase assay for Laminin, reflecting the fact that each cell is producing a true basement membrane. At higher

Fig. 4 — Schwannoma. A: Verocay bodies classic for Antoni type A; B: Antoni type B with loose myxoid tissues; C: cellular schwannomas with poorly formed Verocay bodies focally; and D: cystic schwannoma with degenerative features.
magnification, mitotic activity may be seen but should not be brisk.

Antoni B tissue pattern is less cellular and less organized. The widely separated bland round often vacuolated cells arranged in sheets in a myxoid or microcystic appearing matrix. Scattered throughout this tissue pattern are irregularly spaced small, thick-walled, hyalinized vessels and occasional clusters of lipid rich (foamy) histiocytes, inflammatory cells surrounding vessels, and delicate collagen fibers (Fig. 4B).

These tissue patterns are each represented to a variable degree within a given schwannoma, and occasionally one pattern may predominate over the other or even be absent. Schwannomas with less cellular density and neurofibromas with greater density and a higher degree of organization can appear remarkably similar. Distinguishing features described previously, including infiltration of peripheral nerve, presence of a capsule, and S-100 immunopositivity, should be considered. In most cases, however, the alternating pattern of Antoni A and Antoni B regions, classic for schwannomas, will not be present in neurofibromas.43

The cellular schwannoma subtype is distinguished on low-power light microscopy by the paucity, or absence, of the Antoni B tissue pattern. The cells typically take a storiform appearance and are packed tightly together, arranged in fascicles. Occasionally, they hint of nuclear palisades; however, unlike the Antoni A tissue pattern of conventional counter-type, cellular schwannomas typically lack well-formed Verocay bodies (Fig. 4C). Cytologic atypia may be increased in cellular schwannomas, and mitotic activity may also be increased, which often raise consideration for malignancy in the differential diagnosis.124 Also in the histologic differential diagnosis of cellular schwannomas are benign smooth muscle neoplasms (leiomyomas), which can be distinguished by immunostaining for smooth muscle actin.

The plexiform schwannoma shares features with conventional schwannoma, including a true capsule and cell type population,149 but takes its origin from a nerve plexus or tional schwannoma, including a true capsule and cell type neoplasms (leiomyomas), which can be distinguished by immunostaining with anti-desmin and anti- actin. Schwannomas commonly show immunopositive collagen staining highlights pericellular collagen deposition.57,106 Schwannomas commonly show immunopositive collagen staining highlights pericellular collagen deposition.151 Melanotic schwannomas may have clinical utility in cases where there is question of melanoma in a schwannoma. Schwannomas closely resemble melanocytic lesions including malignant melanoma and negative for synaptophysin CD99 and neuron-specific enolase that permits relatively straightforward differentiation of these tumors from neurofibromas.46

The term “cystic schwannoma” has also been used in ophthalmology to describe a conventional schwannoma where degenerative microcystic and myxoid areas have coalesced to form a macrocystic form appreciated on low-power light microscopy (Fig. 4D).81,141 Plump Schwann cells may line microcystic spaces and produce a round or epithelioid appearance that may be confused with true epithelial differentiation.149

The ophthalmologic literature has used the term “ancient schwannoma” to describe longstanding tumors of the conventional and cellular variants that have undergone degenerative changes over time, which may include microcystic changes, hemorrhage, and focal calcification.66,98,122 Cytologically, ancient schwannomas can be a challenge owing to frank cytologic atypia and nuclear pleomorphism, and may be misconstrued as sarcomas. Indeed, so called “ancient change” may be seen in individual cells in most schwannomas, but the absence of mitotic figures, presence of Antoni A and B regions, and positive S-100 staining should guide diagnosis in these cases.66

All schwannoma variants stain strongly and diffusely positive for S-100 with less-intense staining in Antoni B areas as the Schwann cell population is less dense.149 Type-IV collagen staining highlights pericellular collagen deposition.37,106 Schwannomas commonly show immunopositive reactivity for SOX10, p16, and neurofibromin, while being completely negative for epidermal growth factor receptor, and the combination of these markers may aid in distinguishing cellular schwannoma from MPNST.106

Schwannomas may arise in the context of a clinical syndrome related to germline mutations, including NF-2 and schwannomatosis.28 NF-2 results from mutations in the NF2 gene located on chromosome 22q, and encodes for the protein merlin which signals through the Hippo/YAP pathway.133 NF2, LZTR1, and possibly yet undiscovered genes on chromosome 22.16,58,107,137 In sporadic cases of schwannoma, recurrent genetic mutations present often include the tumor suppressor NF2, and to a lesser extent, INI1/SMARC B1,11,51,121 Mutations in the genes LAT51 and LAT52, which encode for proteins that signal downstream from merlin, are found infrequently in schwannomas.104 Loss of chromosome 22q is the only frequently recurrent cytogenetic alteration found in schwannoma.116 Like neurofibromas, methylation classification can help distinguish schwannomas from other PNSTs and may have clinical utility in cases where there is question of morphologic and immunohistochemical characteristics.116
6.2.3. MPNST
On gross examination, MPNSTs are characterized as a fusiform, nodular mass with increased vascularity and perineural extension. Invasion or envelopment of the ocular adnexal structures is commonly seen.\cite{3,90} The absence of a capsule surrounding MPNSTs is typical and will assist differentiation of an early MPNST from a schwannoma.

The cell of origin of MPNSTs is difficult to surmise, as they consist of spindle-shaped cells with heterochromatic nuclei with various nuclei arrangements including oval shaped, comma shaped, and vesicular (Fig. 5A).\cite{3,146} Schwannomas and MPNSTs similarly contain nuclear palisading regions; however, in MPNSTs these regions are less organized and more sparse, only present focally, or entirely absent.\cite{3,149} Findings that may be somewhat concerning for early malignant changes in schwannoma are collections of positively staining S-100 epithelioid cells, eosinophilic cytoplasm, vesicular chromatin, and prominent nucleoli.\cite{96}

A common challenge is distinguishing a low-grade MPNST from a neurofibroma with atypical features. Histologically, these lesions may demonstrate a continuum of cellular and morphological changes with an admixture of neurofibroma or schwannoma appearance as it recapitulates nerve sheath cells in a disorganized manner.\cite{149} MPNSTs, however, will classically demonstrate malignant features such as brisk mitotic activity, increased cellularity, and a high degree of pleomorphism with packed cellular fascicles, nodular aggregates, and myoid zones (Fig. 5B).

Differentiation between a neurofibroma and an MPNST is typically based purely on histomorphological features, but the use of immunohistochemical techniques to evaluate PNST suspicious for MPNST is growing. Myelin basic protein, Leu-7, and PGP 9.5 are reportedly expressed in MPNST; p53 is suspicious for MPNST is growing. Myelin basic protein, Leu-7, and vesicular (Fig. 5A).\cite{3,146} Schwannomas and MPNSTs similarly contain nuclear palisading regions; however, in MPNSTs these regions are less organized and more sparse, only present focally, or entirely absent.\cite{3,149} Findings that may be somewhat concerning for early malignant changes in schwannoma are collections of positively staining S-100 epithelioid cells, eosinophilic cytoplasm, vesicular chromatin, and prominent nucleoli.\cite{96}

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Epithelioid MPNSTs are a histologic variant of MPNSTs accounting for 5% of extraorbital MPNSTs. Only 1 case has been reported as a primary tumor of the orbit.\cite{106} This subtype has a weaker association with NF-1 than the conventional MPNST. Histologically, this subtype shares the malignant features of conventional MPNST but may be distinguished by a mixed morphology with rounded, polygon-shaped cells in nest or chords. The appearance may resemble carcinoma or malignant melanoma, however, will be negative for HMB 45 and cytokeratin, which are associated with melanoma and carcinoma, respectively.\cite{102} Most epithelioid MPNSTs stain positive for S-100, epithelial membrane antigen, and neuron-specific enolase.\cite{92}

Similar to their benign neurofibroma counterpart, biallelic inactivation of NF-1 is well established to occur in the majority of NF-1 associated and sporadic MPNST cases.\cite{15,113,115,145} There are specific mutations that occur as neurofibromas transform into high-grade MPNST. CDKN2A, which encodes for the cell cycle tumor suppressor proteins p14\textsuperscript{ARF}, p15\textsuperscript{INK4B}, and p16\textsuperscript{INK4a}, is frequently lost in MPNST and not lost in neurofibroma.\cite{12,75,93,102} Loss of CDKN2A is independently associated with a significant decrease, up to an 83.3%, in 5-year overall survival rate.\cite{35} Loss of polycomb repressive complex 2 components (EED or SUZ12) is frequent in NF-1 associated (70%) and sporadic (92%) cases of MPNST.\cite{85} Polycomb repressive complex 2 loss commonly cooccurs with loss with NF-1 and CDKN2A loss.\cite{85} TP53 mutations are not commonly found in MPNST.\cite{146} Genetic studies of 2 individual cases of NF-1 associated MPNST arising from a neurofibroma showed that transformation of neurofibroma to high-grade MPNST in each individual involved loss of TP53.\cite{55,138} In a series of 62 MPNST, the BRAF-V600E mutation was identified in 1 of 37 (2.7%) NF-1 associated and 5 of 25 (20.0%) sporadic cases of MPNST.\cite{56} The prognostic and therapeutic relevance of BRAF-V600E mutation in MPNST has yet to be determined. As mentioned in previous sections, 450-k methylation profiling can help distinguish MPNST from other PNSTs.\cite{116} High-grade MPNST can be further divided into 2 methylation classifications, one of which that corresponds to loss of histone H3K27

Fig. 5 – Malignant peripheral nerve sheath tumor. A: High-power field of dense spindle-shaped cells with pleomorphic, irregular hyperchromatic nuclei and B: low-power field demonstrating increased cellularity, myoid zone, and mitotic activity.
trimethylation (H3K27me3). Loss of histone H3K27 trimethylation (H3K27me3) is found in a subset (34%–69%) of NF-1 associated and sporadic MPNST and is not present in neurofibroma, which can help in the differential diagnosis of these entities. Furthermore, within MPNST, loss of H3K27me3 is an independent predictor of a significantly worse overall survival, with hazard ratio of 2.6 (confidence interval 1.2–5.7, \( P = 0.0017 \)).

7. Management

7.1. Surgical excision

Complete excision of benign neurofibromas and schwannomas with full effort to maintain the capsular integrity is the mainstay of treatment. Numerous surgical approaches have been described to maximize access. Because most PNSTs are in the superior orbit, the most common approach is anterior orbitotomy through an eyelid crease incision. Lateral orbitotomy is commonly used for superolateral tumor locations. An inferior transconjunctival incision may offer adequate access for inferior or medial tumors. Medial access may be best obtained via a transcaruncular incision; however, recently an endoscopic endonasal approach for medial wall tumors may be as high as 62%. Therefore, if the child is in the critical stage of development, regular assessment for early development of amblyopia is needed including testing for stereopsis, color vision and visual acuity. Recently, 3D MRI has been used to measure the volume of plexiform neurofibromas of the orbit, associating a tumor volume of 10 cc to the development of amblyopia, with a majority of cases arising from anisometropia or ptosis. In children at risk of amblyopia, debulking procedures may be performed to maintain the tumor size, improve cosmesis for facial hypertrophy, and treat ptosis. Orbitotemporal plexiform neurofibroma should be surgically treated through a multidisciplinary approach and may include tumor reduction, tumor resection, grafting the sphenoid wing to correct bony defects, eyelid surgery to correct ptosis, or in the setting of a painful, proptotic eye with decreased visual acuity, enucleation.

MPNSTs often present aggressively and with local, regional, or even distant metastasis. Unfortunately, given the aggressive nature of the tumor, excision with tumor-free boarders is often impossible with aggressive recurrence or metastasis with extension via the nerve sheath often through bony fissures and into the intracranial vault. For cases involving a well-circumscribed malignant lobe attached to circumscribed lobe of benign tumor, outcomes may be better with a simple intact removal as these tumors will likely be found to harbor lower grade malignancy. In more advanced cases with boney invasion, exenteration with adjacent bone removal is recommended. Unfortunately, MPNSTs have poor sensitivity to chemotherapy. Palliative measures may include surgical debulking; however, the patient should be warned before surgical debulking of likely rapid, aggressive recurrence.

7.2. Radiation therapy

The role of radiation therapy in PNSTs is evolving. Early documentation of radiation therapy for orbital tumors reported high incidences of optic neuropathy attributed to direct injury or neurovascular damage. Retrospective studies have suggested a perceivable increased risk of optic neuropathy with radiation doses above 8–12 Gray. Fractionated radiotherapy has been used to reduce individual doses of radiation; however, despite advances in this modality, the optic nerve is often exposed to dosages equal to that treating the tumor—dosages previously demonstrated to cause optic neuropathy—which has limited the use of this modality. Despite the known radiosensitivity of the optic apparatus, however, the difficulty in surgically managing apical tumors often strongly adherent to nearby structures in a compact area with critical neurovascular structures has warranted ongoing nonsurgical alternative therapies including targeted radiation applications. Stereotactic radiotherapy using gamma knife surgery in orbital tumors has been increasingly reported, with encouraging outcomes in treating benign schwannomas and neurofibromas. One large study demonstrated tumor size reduction or stability in 16/23 patients with schwannomas and 3/3 with neurofibromas at a median follow-up of 34.5 months. Single-session gamma knife surgery in the treatment of orbital tumors near the apex has been deemed unsafe owing to frequently associated posttreatment optic neuropathy
manifesting as visual field deficits and vision acuity deterioration. Multisession gamma knife surgery for orbital tumors offers decreased morbidity from radiation exposure with preliminary outcomes demonstrating tumor control, with vision improved or unchanged in 46/49 patients. Multisession gamma knife surgery has been used in orbital schwannomas, with 1 study reporting tumor control (reduced or unchanged gamma knife surgery has been used in orbital schwannomas, limited efficacy and possible visual harm. Best be used as a palliative measure with full disclosure of limited efficacy and possible visual harm.

The role of radiotherapy and chemotherapy in MPNSTs is controversial. Some authors describe tumor radioresistance, and others have reported improvement in local control of extraorbital MPNSTs with adjuvant external beam radiation treatment with doses of 60 Gy. This dose is clearly associated with optic neuropathy in the eye and may best be used as a palliative measure with full disclosure of limited efficacy and possible visual harm.

7.3. Decompression

In patients with documented serial imaging suggesting a solitary neurofibroma or schwannoma affecting the apex or where resection is not feasible, orbital decompression alone may be beneficial. Two groups have demonstrated orbital decompression efficacy in alleviation of optic nerve compression symptoms, while avoiding risks of excision in well-documented, slow-growing tumors affecting the apex. Clearly, this strategy is most appropriate for cases with a high degree of suspicion for benign, slow-growing tumors. Additional criteria for the consideration of decompression may include intact vision, rapidly developing clinical decline, no history of systemic malignancy, advanced patient age, and patient agreement to serial imaging following decompression. Orbital decompression is not without adverse effects, notably diplopia, with hypoglobus, enophthalmos, and cerebrospinal fluid leak more rare adverse events.

8. Prognosis

Rose and colleagues described postoperative results for patients with benign neurofibroma and benign schwannoma and reported nonworsened visual acuity in 19/22 and 22/25, respectively, with approximately 45% in both groups demonstrating restricted eye movement postoperatively that improved considerably with time. Chronic ptosis and fixed mydriasis were found to be postoperative complications in a minority of patients. Rose and colleagues also reported incomplete excision in 13/25 cases of solitary neurofibroma, secondary to difficult to reach tumors, with no patients found to have recurrence at a mean time of 6.8 years following excision. On the contrary, diffuse and plexiform neurofibromas associated with NF-1 have high recurrence rates following incomplete excision, and incomplete excision should be considered a palliative treatment in these scenarios. When complete excision is achieved, there is a good prognosis for solitary benign schwannomas. Few cases of schwannoma recurrence have been described in the absence of systemic neurofibromatosis after complete excision. Kron and colleagues reported on 2 such occurrences with 1 man developing 2 distinct tumors 6 years after complete excision, and 1 child with multiple plexiform schwannoma recurrences following incomplete excision. Given the 2 simultaneous tumors, the former patient was considered to have schwannomatosis.

Long-term follow-up is needed to monitor for recurrence and malignant transformation. This is rare in isolated tumors, but may be higher in isolated neurofibroma than isolated schwannomas, particularly in patients with NF-1. MPNSTs have been shown to recur, particularly with increased odds of metastasis at recurrence. While it is prudent to consider syndromic association with any PNST recurrence, it is particularly relevant to recurrence of MPNSTs, given the increased risk of NF-1 with MPNSTs. Unfortunately, in the largest reported case series of orbital MPNSTs, 9/13 patients died within 5 years of diagnosis.

9. Conclusion

PNSTs are a rare group of neoplasms to affect the orbit with substantial variability in tumor activity predicated on histological, genetic or syndromic, and positional factors. Consideration of these tumor types in the differential diagnosis for orbital lesions will assist in early detection and appropriate counseling. Advances in CT and MRI imaging may offer improved ability to diagnose these lesions and guide treatment. Surgical excision remains the gold standard for definitive therapy; however, new modalities including radiation therapy demonstrate promise. Further studies to assist in noninvasive diagnostics are needed, as are randomized controlled trials comparing modern treatment modalities.

10. Method of literature search

This review was prepared using Medline with PubMed from 1900 until August 2015 using the following Medline subject headings: orbit, orbital disease, or orbital neoplasms in combination with neurilemmoma, neurofibroma, neurofibromatosis, neurofibromatosis 1, or neurofibromatosis 2. The search included non-English language articles. Abstracts were
reviewed for relevance and excluded for the following criteria: invasion or extension of PNSTs from other locations, orbital symptoms or diseases from PNSTs located outside the orbit, mention of PNSTs as 1 case in a group of cases studying a different disease, report on unrelated diseases with a patient history of PNSTs elsewhere, ocular PNSTs, surgical procedures unless specifically related to PNSTs removal, PubMed search results without abstracts, articles not pertaining to humans. Additionally, selected articles cited in the reference list of other articles were reviewed.

11. Disclosures

The authors have no financial interests and nothing to disclose.

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