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Neural Tumors of the Eyelids – A Literature Review

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Summary: Eyelid tumors in about 80–95% of cases belong to benign lesions. Because of the complex anatomy of the eyelids and the resulting diversity of potential sites of initiation of the neoplastic process, as well as because of the morphological similarity of the observed lesions, making a correct diagnosis at the initial stage of the diagnostic process is challenging. Neural tumors originating from peripheral nerves and neuroendocrine cells are rare neoplastic lesions of the eyelids. The most common initially benign neural tumors include plexiform neurofibromas, solitary neurofibromas, and schwannomas. In contrast, malignant peripheral nerve sheath tumors and neuroendocrine tumors originating from Merkel cells predominate among malignant lesions. Histopathological examination of the excised lesion is often necessary to make a definitive diagnosis and, if necessary, to implement adjunctive treatment. Complete excision of the lesion reduces the risk of local recurrence and, in the case of lesions showing the risk of malignant transformation, reduces the probability of its occurrence. This article summarizes the current state of knowledge regarding neural tumors of the eyelids – rare but potentially dangerous lesions – systematizing knowledge regarding their pathogenesis, diagnosis, and treatment.

Key words: neural tumors, neurofibroma, schwannoma, Merkel cell carcinoma, eyelid tumors.

1. Introduction

Approximately 80–95% of eyelid tumors are benign [1–3], with intradermal nevi being the most common. Among malignant tumors, basal cell carcinoma is the predominant type [4]. The complex anatomical structure of the eyelids, along with the numerous potential sites where the proliferative process can begin and the frequent similarity in clinical presentations, often makes accurate diagnosis challenging during the initial stages of treatment [1, 3]. Eyelid tumors of various origins may initially be misdiagnosed as chalazia or cysts. However, subsequent histopathological evaluation may reveal them to be sebaceous gland carcinoma, neuroma, Merkel cell carcinoma, or neurofibroma. Therefore, a definitive diagnosis is often possible only after histopathological examination of the excised lesion [1].

Neural tumors originating from peripheral nerves or neuroendocrine cells are uncommon lesions affecting the eyelids. The most common benign neural tumors include plexiform neurofibromas, solitary neurofibromas, and schwannomas. Among malignant lesions, malignant peripheral nerve sheath tumors and neuroendocrine tumors originating from Merkel cells are the most prevalent [5, 6].

This article provides an overview of the current understanding of rare yet potentially serious neural eyelid tumors, organizing key insights into their pathogenesis, diagnosis, and treatment.

2. Histopathological basis of eyelid tumors

The complex histological structure of the eyelids provides numerous potential sites for the initiation of the neoplastic process [1, 7]. The eyelids are composed of four primary layers: the conjunctiva, the tarsal plate, the orbicularis oculi muscle, and the subcutaneous tissue along with the skin and its appendages [5].

The skin of the eyelids is the thinnest in the entire body and uniquely lacks subcutaneous adipose tissue [2, 5]. Despite these subtle differences, it retains all other structural components typical of skin found in other body regions [5]. The outermost layer of the eyelid skin is the stratified squamous epithelium, which includes a basal layer containing melanocytes – highly differentiated cells derived from the neural crest [8]. In addition to playing a role in innate immune responses, melanocytes are responsible for producing melanin, a pigment that acts as a natural barrier against ultraviolet (UV) radiation [8, 9]. The dermis consists of fibrous connective tissue, along with blood and lymph vessels and peripheral nerve fibers [5]. The orbicularis oculi muscle comprises palpebral, preseptal, pretarsal, and ciliary (muscle of Riolan) portions. The orbicularis oculi muscle plays a key role in eyelid closure and functions as a tear pump ensuring the proper flow of tears produced by the lacrimal glands [2, 7]. The tarsus is the primary structural component of the eyelid, consisting of fibrous tissue with a cohesive, tightly interwoven structure. The primary function of the tarsus is to preserve the correct shape of the eyelids. It also houses the Meibomian glands and eyelash bulbs [2, 5]. The posterior surface of the eyelid is lined with the palpebral conjunctiva, composed of epithelium and subepithelial stroma – the substantia propria. The epithelium of the palpebral conjunctiva is primarily cuboidal and contains goblet cells, which produce mucus essential for maintaining proper ocular surface homeostasis [5].

As a key component of the eye's protective system, the eyelids are rich in glandular tissue. The eyelids contain three main types of glands: eccrine glands, including sweat glands and the accessory lacrimal glands of Wolfring and Krause; apocrine glands (glands of Moll); and sebaceous glands, including the Meibomian glands and the glands of Zeiss [7]. In addition to the structures mentioned above, the eyelids also contain nerve fiber endings, as well as blood and lymphatic vessels [10]. The classification of eyelid tumors based on the type of tissue from which the neoplastic process may originate is presented in Table I.

3. Neural tumors of the eyelids

3.1. Neurofibromas

Neurofibromas are common and typically benign tumors that most frequently occur in the head and neck region, as well as on the chest and back [11, 12]. These lesions are composed of a mixture of neuromesenchymal cells, Schwann cells, mast cells, fi-

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Epidermal tumors	Melanocytic tumors Non-melanocytic tumors
Tumors originating from skin appendages	Sebaceous gland tumors Sweat gland tumors Hair follicle tumors Cystic lesions
Stromal (mesenchymal) tumors	Fibrous tissue tumors Fibrohistiocytic tumors Lipomatous tumors Smooth muscle cell tumors Skeletal muscle cell tumors Vascular tumors Perivascular tumors Neural tumors Lymphoid, plasmacytic, and leukemic tumors Cartilage and bone tumors Hamartomas and choristomas Palpebral conjunctival tumors
Metastatic tumors **Inflammatory or post-infectious lesions that mimic neoplastic lesions**	

Were developed on the basis of Pe'er et al. [5]

Tab. I. Classification of eyelid tumors based on the initiation site of the proliferative process.

broblasts, and perineural cells [11]. Neurofibromas can present in a plexiform form (typically as multiple lesions) and are considered one of the symptoms of neurofibromatosis type 1 (NF1) – a condition first described in 1882 by von Recklinghausen [13]. The lesions can also take the form of solitary (single) neurofibromas, which may be linked to neurofibromatosis type 2 (NF2), but are typically not associated with a systemic disease [13–15].

3.1.1. Plexiform neurofibroma

Plexiform neurofibromas typically develop in the course of NF. Morphological features characteristic of this disease entity – including café-au-lait spots, Lisch nodules in the iris, axillary freckles (Crowe's sign), or bone defects – represent key diagnostic markers [1, 16]. Plexiform neurofibromas are estimated to occur in approximately 10–30% of patients with NF1 [1, 17]. Typically, they become apparent at birth or before the age of five, as the defective gene is already fully expressed during this period [15].

NF1 is the most common neurocutaneous syndrome and follows an autosomal dominant inheritance pattern. However, it is important to note that half of the diagnosed cases result from *de novo* mutations. The incidence of NF1 is estimated at 1: 2.500–4.000 cases, with no significant variation across races or genders [13]. Research into the etiopathogenesis of NF1 has shown that it results from an inactivating mutation in a gene located at *locus* 17q11.2 on chromosome 17, which is responsible for synthesizing the neurofibromin protein. This molecule functions as a suppressor of *RAS* gene activity, and its mutation leads to excessive cell growth stimulation, contributing to the formation of neurofibroma-like lesions, among other effects [14, 15]. NF1 may have an insidious course, which makes definitive diagnosis challenging, particularly in cases arising from *de novo* mutations [13]. Additionally, it has been observed that the disease can vary in severity within the same family, which may further complicate diagnosis [13]. NF 1 is diagnosed based on the clinical picture (Table II), while in doubtful cases genetic diagnostic methods are employed, though they are not used on a routine basis [13].

Plexiform neurofibromas are characterized by slow, painless growth and features of local invasion into adjacent tissues [15]. The most common site for these lesions is considered to be the craniosacral-maxillofacial region [17]. Studies have shown that the presence of plexiform neurofibromas is associated with a 2–16% risk of malignant transformation into malignant peripheral nerve sheath tumors (MPNST). This risk has been shown to be higher when lesions are located in deeper tissue layers [18]. Ocular symptoms in NF1 are common and may be associated with the involvement of multiple visual structures. The most commonly diagnosed lesions are Lisch nodules – nodular hamartoma-like lesions of the iris typically appearing between the ages of 5 and 10. Other frequently detected lesions include optic nerve gliomas, choroidal and retinal hamartomas, and orbital bone pathologies. Importantly, some authors have also suggested an increased risk of choroidal melanoma in these patients [13].

Treatment of plexiform neurofibromas involves surgical excision of the lesion; however, there is a nearly 20% chance of local recurrence, even after complete excision. For unresectable lesions, interferon- therapy is a viable option. The prognosis is challenging to determine due to the often unpredictable progression of the disease, which results from individual variation in defective gene expression [17].

Six or more café-au-lait spots greater than 5 mm in diameter before puberty, or greater than 15 mm in diameter after puberty
Two or more neurofibromas of any type, or a single plexiform neurofibroma
Freckles and/ or discolored patches in areas of the body not exposed to light (such as the armpits and mons pubis)
Optic nerve glioma
Two or more Lisch nodules in the iris
Characteristic skeletal findings (such as sphenoid bone dysplasia, cortical thinning of long bones, with or without pseudarthrosis)
A first-degree relative who meets the aforementioned criteria

Tab. II. Diagnostic criteria for neurofibromatosis type 1 according to the National Institutes of Health (NIH)*.
Were developed on the basis of Fitzpatrick i wsp. [16]

3.1.2. Solitary neurofibroma

Solitary neurofibroma (also referred to as single or isolated) is the most common cutaneous tumor arising from peripheral nerve sheaths [1]. As previously mentioned, the occurrence of this predominantly benign lesion is not linked to NF1 [1]. Solitary neurofibromas occur with equal frequency in both women and men, and no correlation has been found between their occurrence and ethnic origin. These lesions typically appear much later than plexiform neurofibromas, usually between the ages of 20 and 40 [1].

Initially, solitary neurofibromas – like many other neural eyelid tumors – may mimic other tumor-like lesions, such as chalazion [1]. The precise pathophysiological mechanism underlying the development of solitary neurofibromas remains incompletely understood [12]. Similar to plexiform neurofibromas, solitary neurofibromas most commonly occur in the head and neck region, though they can also appear in less typical locations, such as the skin of the hands and feet [11].

On histopathological examination, neurofibromas appear as uncapsulated tumors, well-demarcated from surrounding tissues and usually located within the dermis. Poonam et al. found no histopathological differences between solitary neurofibromas located in the eyelids and those occurring in the skin of other body regions [12]. Neurofibroma structure is characterized by a fine mesh of slender, spindle-shaped cells with an irregular arrangement [11]. Cytologically, these tumors are composed of Schwann cells, perineural-like cells, and endoneural fibroblasts [12]. Schwann cells stain positively for the S-100 protein, a marker specific to cells derived from nervous tissue, which is helpful in differential diagnosis [11]. Partial positive staining for the CD34 antigen is attributed to the presence of fibroblasts, while neurofibromas typically show negative staining for epithelial membrane antigen and keratin [12].

Given the benign nature of these lesions, they can typically be managed with observation in most cases. Complete excision reduces the risk of local recurrence, which may occur if the excision is incomplete [12]. The risk of malignant transformation in solitary neurofibromas is considered very low [12]. However, Krol et al. documented a case of malignant transformation in a recurrent solitary neurofibroma [19].

3.2. Schwannomas

Schwannomas, also known as neurilemmomas, result from the proliferation of Schwann cells within peripheral nerve endings [20]. Although schwannomas usually present as solitary lesions, it is important to note that multiple schwannomas may be associated with NF1 or NF2 [5, 20, 21]. Epidemiological studies have not identified any racial or gender predisposition to the development of these lesions [5]. Schwannomas are typically diagnosed in adults, though there have been reported cases in the pediatric population as well [21].

The incidence of schwannomas is estimated at 5 cases per 100.000 per year in adults, with a peak occurrence during the 5th and 6th decades of life, compared to 0.4 cases per 100.000 in children [5]. It has been hypothesized that schwannomas may arise as a result of impaired tissue healing and regeneration following trauma to the nerve endings [21]. Schwannomas, similarly to neurofibromas, are located mainly in the head and neck region; their occurrence in the eyelid region is rare [5, 21] – they constitute only 0.1–0.7% of all tumors [20]. Clinically, they present as solitary lesions characterized by slow growth and clear demarcation from surrounding tissues [5, 20]. In some cases, ptosis is the first symptom [20].

Electron microscopy imaging of schwannomas has revealed the presence of irregular polygonal cells surrounded by a basement membrane [22]. The evaluation of ultrastructure, along with characteristic immunohistochemical properties, allows for the differentiation of schwannomas from other tumors with a significantly worse prognosis, such as metastatic tumors and melanoma [22]. Histopathological examination reveals characteristic Antoni A (compact, densely packed spindle-shaped cells) and Antoni B (loosely arranged round cells) patterns [5]. In immunohistochemical examination, schwannomas exhibit strong positivity for the S-100 marker, the CD56 surface receptor, vimentin, and calretinin [12]. Staining for neurofilament is negative [18]. Furthermore, the absence of reactivity to HMB45 helps exclude a melanocytic lesion [23]. Due to their nonspecific clinical presentation, schwannomas require a broad differential diagnosis, which should include conditions such as hidrocystoma, epidermal inclusion cyst, amelanotic nevus, molluscum contagiosum, and basal cell carcinoma of the skin [21, 24].

The presence of spindle-shaped cells containing melanin granules and epithelial cells on histopathological examination is associated with unfavorable prognosis [20]. No cases of malignant transformation of eyelid schwannomas have been reported to date [20]. Among ocular structures, schwannomas most commonly occur within the orbit, followed by the conjunctiva, choroid, and sclera [23]. Notably, schwannomas can coexist with other neoplasms – both benign and malignant – within a single lesion. Two interesting cases of schwannomas coexisting with other neoplasms within a single eyelid tumor were described by Brown-Joel et al. The first case involved a 71-year-old female patient with a slowly growing tumor on the lower eyelid margin, present for five years. Clinically, the lesion appeared as an 11 mm x 4 mm nodule with central ulceration, accompanied by madarosis (eyelash loss within the affected area) and telangiectasias. Histopathological examination of a specimen from excisional biopsy revealed features consistent with both schwannoma and basal cell carcinoma. The second case involved a slowly growing lesion on the left lower eyelid margin over a period of three years. At the time of presentation, the lesion measured approximately 4.3 mm and was accompanied by a slight disruption in eyelash growth. Histopathological examination confirmed the coexistence of tissue features characteristic of both schwannoma and intradermal nevus [21].

Superficial schwannomas are typically treated with extensive excision, but deeper lesions are more likely to undergo malignant transformation. In such cases, adjuvant therapy should be considered alongside excision to prevent recurrence [22]. Malignant transformation of a single schwannoma is highly unlikely; however, the risk of neoplastic transformation increases with the presence of multiple lesions in the course of NF [23]. Complete excision of the lesion with clear margins is the preferred procedure to prevent recurrence and reduce the risk of potential malignant transformation. There have been documented cases of tumors exhibiting malignant features recurring after incomplete removal of initially benign lesions [20, 21].

3.3. Merkel cell carcinoma

Merkel cell carcinoma is a rare malignant neuroendocrine tumor of the skin [25]. It is estimated that approximately 1.500 cases of this cancer are diagnosed annually [26]. The tumor is characterized by poorly differentiated cells with a high mitotic index [27]. Merkel cells are neuroendocrine cells present in various body systems and organs, including the digestive system, lungs, and skin, where they function as appetite modulators, respiratory chemoreceptors, and tactile receptors, respectively [27]. A significant increase in incidence is observed in the 6th decade of life, with peak incidence in the 7th decade. According to the current study, men are slightly more at risk. Notably, more than 95% of cases occur in individuals of white race [26].

Merkel cell carcinoma is a rapidly growing tumor; however, due to its initially ambiguous macroscopic appearance, it can be

misdiagnosed as a chalazion, cutaneous keratosis, or basal cell carcinoma, leading to delays in the initiation of appropriate treatment [25]. Risk factors for the development of Merkel cell carcinoma include sun exposure, polyomavirus infection, and immunosuppression [25].

Histologically, Merkel cell carcinoma is characterized by clusters of oval cells with scant cytoplasm, a high proliferation index, and positive staining for cytokeratin 20, neuron-specific enolase (NSE), chromogranin A, and epithelial membrane antigen. The treatment of Merkel cell carcinoma involves surgical excision with a wide margin (5 mm), typically followed by adjuvant radiotherapy or chemotherapy. Additionally, research is currently ongoing into therapies that target key cellular pathways involved in tumor growth [27, 28].

Merkel cell carcinoma of the eyelid typically occurs on the upper eyelid and is frequently associated with madarosis [25]. This tumor is characterized by a poor prognosis due to its tendency for local recurrence and metastasis to regional lymph nodes [27]. Within 1.5 years of diagnosis, local metastases – most commonly involving the parotid and submandibular lymph nodes – develop in 66% of patients, while distant metastases are observed in up to 33–38% of cases [25, 26]. In Merkel cell carcinoma of the eyelid, the estimated cumulative metastasis rate is 10–30%, with regional lymph node metastases occurring in 20% of cases and distant metastases in 5% [26]. Interestingly, over 20 cases of spontaneous regression of Merkel cell carcinoma have been reported, including instances with local metastases. Current evidence suggests that this phenomenon may be mediated by T cells [26].

3.4. Malignant peripheral nerve sheath tumors (MPNST)

Malignant peripheral nerve sheath tumors are locally aggressive soft tissue neoplasms with a high potential for metastasis [29]. The incidence of MPNST in the general population is approximately 0.001% [30]. These tumors are most commonly diagnosed in adults between the 3rd and 6th decades of life, with no significant difference in frequency between men and women. Interestingly, studies have shown that MPNSTs tend to appear several years earlier in men than in women [30, 31]. It is estimated that approximately 80–90% of these lesions occur in individuals over the age of 20. Importantly, MPNSTs (similar to plexiform neurofibromas and schwannomas) have been linked to NF1 comorbidity, with an incidence approximately 100 times higher than in the general population. In addition, in patients with NF1, these changes typically manifest much earlier than in the general population: between the 2nd and 4th decades of life. It is estimated that nearly 50% of MPNSTs are linked to a neurofibromin defect when the lesion arises from a primary plexiform neurofibroma [30]. Local recurrences occur in approximately 40–65% of cases, while metastases are detected in 40–68% of patients [30]. Nearly 50% of MPNSTs are found on the trunk skin, 30% on the limbs (usually in the proximal regions), and around 20% on the skin of the head and neck [30, 31].

The diagnosis of MPNST, like most other neural tumors of the eyelids, is challenging due to their similarity to other nodular eyelid lesions [31]. These lesions are typically painful and may also be associated with local numbness or tingling sensation [31]. Risk factors for MPNST include prior radiotherapy, the presence of plexiform neurofibromas, and mutations in the *NF1* gene and adjacent genes [30].

The treatment of MPNST involves surgical excision with clear margins. For tumors larger than 5 cm or those causing significant compression of adjacent nerves, neoadjuvant chemotherapy or radiotherapy is typically recommended **[30].**

4. Conclusions

Neural tumors of the eyelid are an uncommon type of neoplasm, yet their unique origin presents significant diagnostic and therapeutic challenges. In this group of neoplasms, benign tumors are more prevalent; however, all the lesions described in this review carry a potential risk of malignant transformation. Due to the often non-specific clinical presentation, histopathological examination of the excised lesion may be required for a definitive diagnosis and to determine if adjuvant treatment is necessary. Complete excision of the lesion lowers the risk of local recurrence and, in cases where there is a potential for malignant transformation, reduces the likelihood of its occurrence.

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