Neurothekeoma of the Cornea

Mina M. Naguib^a Caroline Craven^a Alan Kozarsky^b Hans E. Grossniklaus^a

^aDepartment of Ophthalmology, Emory University School of Medicine, and ^bEye Consultants of Atlanta, Atlanta, Ga., USA

Key Words

Neurothekeoma · Nerve sheath myxoma · Corneal lesion · Corneal neoplasm

Abstract

Neurothekeomas (NTKs) are benign cutaneous neoplasms of fibrohistiocytic origin and most commonly occur in the head, neck, and upper extremities. Traditionally, NTK and nerve sheath myxoma (NSM) were classified as subtypes of a single neoplasm with a common histogenesis, but recently immunostaining has demonstrated that the lesions are most likely of distinct cellular origin. Rarely, NTKs have been reported to occur in the ocular adnexa, and the present case of a 39-year-old female is the first to describe a cellular NTK originating in the cornea and mimicking a Salzmann's nodular degeneration. This report describes the clinical and pathological findings of the patient, discusses the changes in the classification of these rare neoplasms in light of advances in immunohistochemistry, and reviews all cases of ocular NTK found in the literature.

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Introduction

The term neurothekeoma (NTK), first introduced by Gallager and Helwig [1] in 1980, has traditionally referred to a benign superficial cutaneous neoplasm of peripheral nerve sheath origin subclassified into histologic variants (cellular, myxoid, or mixed) depending on the degree of myxoid differentiation [2]. Nerve sheath myxoma (NSM), first described by Harkin and Reed [3] earlier in 1969, was classified as a subtype of NTK accounting for most of the neoplasms labeled as myxoid. This classification was later challenged due to inconsistent immunohistochemical similarities between NTK and NSM, and subsequently several retrospective case series demonstrated that the two entities were in fact separate based on consistent differences in their clinical, histologic, and immunohistochemical features [2, 4, 5]. In particular, lack of consistent S100 positivity among tumors labeled as cellular or myxoid NTK casts doubt upon whether the entity is of neural differentiation at all, with further staining indicating a possible 'fibrohistiocytic' origin [5]. NTKs commonly present in patients as solitary nodular growths usually occurring in the head, neck, and upper extremities. In general, the occurrence of ocular tumors of nerve sheath origin is very rare, with neurofibroma being most commonly reported. Ocular NTKs are even more rare, being

Table 1. Features of NTK and NSM

	NTK	NSM
M:F ratio	1:2	1:1
Mean age, years	21–25	36
DE, %	17	86
H/N, %	68	12
Recurrence rate, %	<8	50
Myxoid, %	10	100
Histology	Lobules poorly marginated and infiltrative	Lobules sharply demarcated
Cell of origin	Fibrohistiocytic	Peripheral nerve sheath
ImmunoHC	NKI-C3+, vimentin, MITF, CD10; S100–, desmin	S100+, GFAP

DE = Distal extremities; H/N = head/neck; HC = histochemistry.

described only 11 times with the present case included, which reports the first case of cellular NTK involving the cornea. Despite the rarity, NTKs are benign and have a low rate of recurrence with complete excision regardless of location [5].

Case Description

A 39-year-old Caucasian female presented to her optometrist with a white lesion on her left cornea. At that time, she was diagnosed with an infection and treated with Tobradex and Lotemax. On follow-up, the patient was found to have increased intraocular pressure secondary to the steroids and was treated with a course of Alphagan. Three months later, the patient presented to a corneal specialist with persistence of the lesion. She denied any pain, irritation, photosensitivity, or acute changes in vision. She previously wore contact lenses more than 10 years ago, otherwise her past ocular history was negative. The patient's past medical history was only significant for hypothyroidism treated with levothyroxine. She had no family history of ocular lesions, glaucoma, or macular degeneration and did not smoke cigarettes or drink alcohol. On exam, vision in the right eye was 20/20, and in the left eye, it was 20/50. Slit-lamp examination was within normal limits with the exception of a lesion on the left cornea. The lesion consisted of a white opaque and elevated pannus-like mass extending across the mid-periphery of the superior cornea from 10 to 2 o'clock. The superior margin was linear and fairly well defined, and the lesion did not extend to the limbus superiorly. The inferior margin was less opaque and scalloped, possibly encroaching on the visual axis. The lesion did not appear to cross the limbus temporally but seemed to extend to the nasal conjunctiva. The surrounding sclera and conjunctiva were clear, quiet, and noninjected.

Etiologies of corneal dystrophies and degenerations of the cornea were considered which included scarring from previous infection, limbal stem cell deficiency, band keratopathy, and stromal dystrophy. Given the quiet appearance of the eye, infectious and inflammatory etiologies of the lesion were lower on the differential diagnosis. Due to the clinical appearance, a preoperative diagnosis

of Salzmann's nodular degeneration was made. Treatment options were discussed, and the patient elected surgical excision and underwent lamellar keratectomy for excision of the lesion.

The specimen was sent for pathologic examination. It consisted of a cellular proliferation (fig. 1a) composed of lobules and nests of epithelioid cells arranged in sheets (fig. 1b). These cells contained round to oval vesiculated nuclei, prominent nucleoli, and a moderate amount of eosinophilic cytoplasm (fig. 1c). Immunohistochemical stains were positive for microphthalmia transcription factor (MITF) (fig. 1d), CD68 (fig. 1e), CD10, NSE, SMA, and HAM56, and negative for S100 (fig. 1f), Melan A, HMB45, desmin, CK7, CK20, EMA, CD34, and CD1a. All above-mentioned pathologic features were diagnostic for cellular NTK.

The patient underwent the procedure without complications and was postoperatively treated with Vigamox q.i.d., prednisolone q.i.d., and oxycodone as needed. At the 1-week follow-up, vision in her left eye had improved to 20/25. After 3 months of follow-up, the lesion has not recurred, and the patient continues to maintain the improvement in visual acuity achieved postoperatively.

Discussion

Despite an original classification as subtypes of a single entity, large series separately analyzing NTK and NSM have found clear differences in epidemiological, histological, immunohistochemical, and clinical features of the lesions [4–6] summarized in table 1. NTKs present as solitary, slow-growing dome-shaped papules involving the skin and superficial adipose layer [5]. These lesions show a 2:1 female-to-male predominance, occur in individuals with a mean age of 21–25 years, are found in the upper limb or head/neck in 68% of cases and in the distal extremities only in 17% of cases. Immunohistochemistry shows that NTKs tend to have positivity for NKI-C3, MITF, vimentin, and CD10 and are essentially universally negative for S100, GFAP, and desmin. Histological-

(For legend see next page.)

Table 2. Differential diagnosis of NTK

Lesion	Histology	Immunohistochemistry
NTK	epithelioid, spindle cells with abundant eosinophilic cytoplasm; whorled growth	NKI-C3+, vimentin, MITF, CD10; S100–, HMB45, desmin, CD34
NSM	myxoid, multilobular masses with fibrous border; spindled, stellate-shaped epithelioid Schwann cells; organized into cords	S100+, GFAP
Cutaneous myxoma	pleomorphic, single/multinucleated, stellate, and spindled tumor cells; cytoplasmic nuclear invaginations; scattered inflammatory cells throughout the myxoid matrix	CD34+, actin; – or weakly reactive to S100
Melanocytic tumors	epithelioid, spindle cells arranged in nests with focal whorling	S100+, HMB-45, Melan A, tyrosinase; – ???
Dermatofibroma	elongated nuclei, scant cytoplasm; proliferation of fibrohistiocytic cells within the dermis; peripheral entrapment of collagen	CD34–
Reticulohistiocytoma	epithelioid cells; rare tendency for whorled growth; cytoplasmic retraction with filopod extensions	CD163+, CD68, vimentin, focal + S100; CD3–, CD20, CD30, HMB45, keratins
PFT	defined, elongated cell fascicles with spindled, myofibroblastic cells, abundant, densely eosinophilic cytoplasm; rare nuclear atypia; low mitotic activity	CD68+, vimentin

ly, NTKs show myxoid features in 10% of cases, and the lobules of NTKs are typically poorly margined and tend to infiltrate the surrounding dermal collagen or subcutaneous adipose tissue. Of clinical importance, the local recurrence rate for NTK is quite low (<8%) and was associated with incomplete excision in all cases. The cellular derivation of NTK is not clear, since histologic and immunohistochemical findings are neither specific nor conclusive. Fetsch et al. [5] have suggested a derivation from fibroblastic cells which can produce myxoid matrix and differentiate into myofibroblasts. Additionally, these authors indicate that NTK may have phagocytic properties that enable cells to recruit inflammatory or ‘histiocytic’ cell types. This may explain the positivity for the histiocytic markers CD68 and HAM56 as demonstrated in the present case. Therefore, Fetsch et al. [5] concluded that the term ‘neurothekeoma’ meaning ‘nerve sheath tumor’ would be inappropriate and suggest the more descriptive-

ly accurate term ‘superficial micronodular (myxo/myo) fibroblastoma’.

Despite differences in epidemiological and diagnostic features, NSM should be included in the differential diagnosis of NTK, as the two lesions present with a similar clinical appearance. NSMs occur equally in males and females with a mean age of 36 years, are found in the upper limb or head/neck in only 12% of cases, and in the distal extremities in 86% of cases [4–6]. All these epidemiological parameters differ from NTK. On immunohistochemistry, NSMs show positivity for peripheral nerve sheath markers such as S100 and GFAP. Histologically, NSMs have a predominantly myxoid architecture in mostly 100% of cases and lobules that are usually sharply demarcated. Clinically, nearly 50% of NSM cases locally recur, with several cases recurring multiple times, which stands in contrast to the relatively low recurrence rate of NTK. The cellular derivation of NSM is established as peripheral nerve sheath based on consistent positivity with neural specific antigens such as S100 and GFAP.

Other lesions on the differential diagnosis of NTK include cutaneous myxoma/angiomyxoma, melanocytic lesions (melanoma and benign nevus), dermatofibroma, reticulohistiocytoma, and plexiform fibrohistiocytic tumor (PFT). The histological and immunohistochemical findings [5] of these lesions are summarized in table 2.

Fig. 1. a Corneal biopsy showing cellular proliferation in the collagenous matrix. H&E. $\times 10$. **b** Cellular proliferation consisting of lobules, nests, and sheets of cells surrounded by collagen. H&E. $\times 25$. **c** Cells containing round to oval vesiculated nuclei, prominent nucleoli, and a moderate amount of eosinophilic cytoplasm. H&E. $\times 100$. Immunohistochemical staining showing weak MITF positivity (**d**). CD68 positivity (**e**) and S100 negativity are shown (**f**). Peroxidase anti-peroxidase technique. $\times 100$.

Table 3. Cases of ocular NTK

Case	First author, year	Age/sex	Type	Location	Preoperative diagnosis
1	Naguib, 2015 ^a	39/F	CN	Cornea	SND
2	Lefebvre [18], 2014	50/F	CN	Internal palpebrae	Chalazion
3	Galec [17], 2011	6/M	CN	Orbit	n.a.
4	Papalas [15], 2010	13/F	CN	Upper lid	Chalazion
5	Papalas [15], 2010	4/F	CN	Upper lid	Chalazion
6	Mathew [14], 2008	66/M	CN	Lower lid	n.a.
7	Hornick [6], 2007	29/F	CN	n.a.	Fibroma
8	Hornick [6], 2007	38/F	CN	n.a.	n.a.
9	Hornick [6], 2007	30/F	CN	n.a.	n.a.
10	Misra [12], 2004	24/F	CN	Upper lid	EIC
11	You [1], 1999	76/F	CN	Upper lid	EIC

CN = Cellular NTK; SND = Salzmann's nodular dystrophy; n.a. = not available; EIC = epidermal inclusion cyst.

^a This study.

Cutaneous angiomyxoma can be differentiated from NTK by CD34 positivity and a much higher reported recurrence rate (30–40 vs. <8%) [5]. Melanocytic lesions, most commonly Spitz nevus but also malignant melanoma, carry similar histological and epidemiological features as NTK. Additionally, there is overlap in immunohistochemical features, with both lesions demonstrating positivity for MITF and NKI-C3. MITF and NKI-C3 (also known as CD63) show reactivity in cells undergoing melanogenesis. Unexpected MITF and NKI-C3 positivity in NTK has been postulated by Fetsch et al. [5] as being a 'false positive' result due to unexplained cross-reactivity. Despite this immunohistochemical overlap, melanocytic tumors can be differentiated from NTK mainly by consistent S100 positivity. Furthermore, NTK are consistently negative for other 'melanocytic' markers such as HMB45, Melan A, and tyrosinase.

Dermatofibromas differ from NTK mainly in morphology, as these lesions demonstrate elongated nuclei and scant cytoplasm [7]. Reticulohistiocytomas (solitary epithelioid histiocytes) differ from NTK in that they rarely show whorled growth and cytoplasmic retractions with filopod extensions, and rarely demonstrate nuclear atypia. Additionally, they show strong positivity for CD163 and CD68 and, in some cases, focal positivity for S100 [8].

PFT may be difficult to differentiate from NTK based on epidemiological features and immunohistochemistry [9]. Distinction relies on morphology, as PFTs will often spare the upper dermis and have more subcutaneous invasion than NTK. Tumor cells in PFT will be better de-

fined and demarcated and lack the nuclear variability often seen in NTK. This distinction is important, as PFTs have been reported to rarely metastasize.

Ocular NTK are extremely rare neoplasms (table 3) having only been reported 11 times and usually occurring in the eyelid, with the exception of 1 case which occurred within the orbit and the present case with a corneal NTK [6, 10–18]. The mean age among the 11 cases is 33.5 years, which is higher than in nonocular NTK (21–24 years). Preoperative diagnoses were chalazion, fibroma, or epidermal inclusion cyst for the eyelid lesions and Salzmann's nodular dystrophy for the present corneal case. Complete excision of these lesions is needed as recurrence and re-excision was reported in 2 of the cases [7, 12]. Despite their rarity, NTK should remain on the differential diagnosis of any solitary, nodular mass of the eyelid or orbit. Additionally, with appropriate history and presentation (noninfectious/inflammatory), these lesions can be included in the differential of a corneal lesion or neoplasm.

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Statement of Ethics

This is a single case report and our university's IRB does not require approval for single case reports (i.e. it has IRB exempt status). No animals were used in our study.

Disclosure Statement

The authors declare that there are no conflicts of interest.

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