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Conjunctival Stromal Tumor

Martina C. Herwig, MD^{1,2}, Jill R. Wells, MD¹, and Hans E. Grossniklaus, MD, MBA¹

¹Department of Ophthalmology, Emory University, 1365 Clifton Road, BT 428, Atlanta, GA 30322

²Department of Ophthalmology, University of Bonn, Ernst-Abbe-Str. 2, 53127 Bonn, Germany

Abstract

Purpose—To describe the clinical, histopathologic, immunohistochemical, and ultrastructural features of a case series of benign stromal tumors in the bulbar conjunctiva.

Design—Observational case series.

Participants—Four patients with a conjunctival lesion that were classified histologically as low grade stromal tumors consisting of spindle-shaped cells with occasional pseudonuclear inclusion and multinucleated cells in a partly myxoid matrix.

Methods—Four cases of low grade conjunctival stromal tumors were retrospectively identified in an ophthalmic pathology laboratory database. Patients' records were analyzed for demographic data, clinical appearance and the post-operative course. Formalin-fixed paraffin-embedded specimens were routinely processed and stained with hematoxylin and eosin (H&E) and periodic acid Schiff (PAS). Immunohistochemical stains for vimentin, S100, CD34, SMA (smooth muscle actin), CD68, and factor XIIIa were performed. Transmission electron microscopy (TEM) was performed on three of the cases.

Main Outcome Measures—Histopathologic evaluation (including immunostains and TEM) and clinical correlation.

Results—All four tumors occurred in the bulbar conjunctiva of patients between 41 to 53 years of age. None of the patients developed recurrence after excisional biopsy. Histologically, all tumors exhibited spindle-shaped cells with pseudonuclear inclusions and occasional multinuclear cells. Mitotic figures were not observed. The stroma appeared myxoid to collagenous. Immunohistochemical stains were positive for CD34, vimentin, and focally for CD68, but were negative for S100 and SMA.

Conclusions—We propose to classify these benign lesions which share distinct histopathologic features as “conjunctival stromal tumor (COST)”. A reactive/inflammatory component needs to be considered in the pathogenesis of this lesion.

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Address for reprints: Hans E. Grossniklaus, MD, MBA, Emory Eye Center, L.F. Montgomery Laboratory, BT 428, 1365 Clifton Road, Atlanta, Georgia 30322, phone number: 404-778-4611, fax number: 404-778-4610, ophtheg@emory.edu.

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Introduction

Mesenchymal proliferations of the conjunctiva are rare. The differential diagnosis includes conjunctival (cellular) myxoma, neurothekeoma, subconjunctival herniated orbital fat, fat-free spindle cell lipoma, pseudotumor, neurofibroma, dendrocytoma, solitary fibrous tumor, fibrous histiocytoma, nodular fasciitis, hemangiopericytoma, giant cell angiofibroma, and rhabdomyosarcoma.^{1–13} Due to the location of the conjunctiva on the ocular surface and its role in antigen recognition, various factors and stimuli such as inflammation need to be considered as a contributor to the pathogenesis of conjunctival tumors. Classification of conjunctival tumors helps predict the clinical course and allows for recommendations regarding treatment and follow-up examination. Herein we describe four conjunctival lesions with mesenchymal derivation that were not able to be categorized within the above mentioned differential diagnoses. We introduce the term “conjunctival stromal tumor (COST)” to classify this unique group of lesions.

Methods

After review of the database between 1941 and 2011 of the L.F. Montgomery Ophthalmic Pathology Laboratory, Emory University, Atlanta, GA, four cases of unclassified low grade conjunctival stromal tumors revealing distinct histopathologic features such as spindle-shaped cells with occasional pseudonuclear inclusions, multinucleated cells, and a partly myxomatous matrix were identified. The medical records of the corresponding patients were retrospectively reviewed with regard to patient's history, age, gender, race, localization of the lesion, its clinical appearance, clinical diagnosis, treatment, and outcome. The specimens had been submitted in 10% formaldehyde and were grossly examined for size and color. They were routinely processed for light microscopic examination and stained with hematoxylin and eosin (H&E) and periodic acid-Schiff (PAS). The histological specimens were analyzed for size, cell type, cytologic features, and immunohistochemical findings. The excisional biopsies were independently reviewed by all authors. Immunohistochemical stains for CD34 (DAKO; 1:320), CD68 (DAKO; 1:2560), desmin (DAKO, Carpinteria, CA; 1:640), factor XIIIa (Calbiochem, La Jolla, CA; 1:400), Ki67 (DAKO; 1:160), myosin (DAKO; 1:400), SMA (DAKO; 1:160), S100 (DAKO; 1:3200), vimentin (DAKO; 1:320), as well as alcian blue (alcian blue stain pH 2.5 procedure; American Master Tech, Lodi, CA) and colloidal iron (American Master Tech) stains were performed. Formalin-fixed paraffin-embedded tissue from cases 1–3 was recovered and submitted for transmission electron microscopic processing. Institutional Review Board (IRB)/Ethics Committee approval was obtained for this study. The research adhered to the tenets of the Declaration of Helsinki

Results

Demographic data

This unique mesenchymal conjunctival tumor was observed in four patients (1 female, 3 males) aged from 41 to 53 years (mean value: 47 years) between 1941 and 2011 in the L.F. Montgomery Laboratory, Atlanta, GA. (Tab. 1). All lesions were soft and localized on the bulbar conjunctiva. The color varied from whitish to reddish. The specimens were analyzed histologically for cytologic features and extracellular matrix characteristics (Tab. 2) as well as immunohistochemical (Tab. 3) and transmission electron microscopy (TEM) findings.

Case 1—A 41-year-old Caucasian male presented with a cystic, tender conjunctival lesion (Fig. 1, Tab. 1) localized over the insertion of his right lateral rectus muscle for four years. The whitish-yellow mass was accompanied by overlying mild injection without any signs of malignancy. Local or systemic treatment was not utilized since the patient did not complain about pain or foreign body sensation. As the mass interfered with the patient's glasses, an

excisional biopsy was performed. Follow-up (15 years) was uneventful. Histologic examination showed a myxoid to collagenous fibrovascular tissue infiltrated by pleomorphic cells (Fig. 1, Tab. 2). Some cells were multinucleated and exhibited pseudonuclear inclusions. Occasionally, a floret-like configuration of cells could be observed. There were no mitotic figures in the mass. Some cells stained positive with alcian blue and colloidal iron, although the extracellular matrix was negative. Immunohistochemical stains were positive for CD34 and myosin in many cells, and negative for desmin, S100, and smooth muscle actin (SMA) (Fig. 1, Tab. 3). Factor XIIIa was expressed in occasional cells. Transmission electron microscopy showed spindle-shaped cells with mitochondria, rough endoplasmic reticulum (RER), and free ribosomes. Vacuolations were present within the nucleus. Collagen bundles could be observed. There were no intercellular junctions present nor did the cells produce basal lamina.

Case 2—A 47-year-old man, complaining about irritation and redness of his left eye, presented with a lesion involving the conjunctiva and cornea (Tab. 1). A lupus erythematosus-related posterior blepharitis has been treated with cyclosporine 0.05% bid in his left eye. His systemic medication was hydroxychloroquine sulfate 200mg bid. As the clinical differential diagnosis included dysplastic epithelium and intraepithelial neoplasia, an excisional biopsy of the lesion was performed. The patient was followed for seven years and underwent an amniotic membrane graft reconstruction due to stem cell deficiency in the left eye five years after the intervention. Histologically, the conjunctival tissue consisted of loosely arranged pleomorphic spindle cells in a myxoid extracellular matrix with wiry collagen fibers (Fig. 2, available at <http://aaojournal.org>; Tab. 2). Some of the cells contained pseudonuclear inclusions. There were also some multinucleated cells present. Mitotic figures were absent. Some cells and the extracellular matrix stained positive with alcian blue and colloidal iron. Immunohistochemical stains were positive for vimentin, CD34, and CD68, and negative for S100, SMA, myosin, and factor XIIIa (Fig. 2, available at <http://aaojournal.org>; Tab. 3). The corneal specimen displayed mild reactive changes in the basilar keratocytes.

Transmission electron microscopy showed spindle-shaped fibroblast-like cells with intracellular inclusions in a collagenous matrix (Fig. 2E, available at <http://aaojournal.org>). There were no intercellular junctions present nor did the cells produce basal lamina.

Case 3—A 53-year-old Caucasian male developed a 1.25×1.5 mm elevated, non-tender conjunctival nodular lesion with accompanied redness one week after cataract surgery (Fig. 3, Tab. 1). Ocular history revealed blepharitis and regular use of soft contact lenses. Local steroid application (prednisolone acetate 1%, qid) - in addition to gatifloxacin 0.3% and ketorolac tromethamine 0.5% that were prescribed after cataract surgery - resulted in a diminished reddish appearance but the size of the lesion itself did not regress. Possible clinical diagnoses of this primarily unclassified conjunctival lesion included foreign body reaction versus lymphatic obstruction. Excisional biopsy was performed followed by intense topical steroid treatment to treat inflammation that resulted in a non-ulcerated conjunctival scar. No recurrence was observed with 5 years of follow-up. Histologic examination revealed a proliferation of pleomorphic spindle cells in a myxoid to collagenous matrix (Fig. 3, Tab. 2). The spindle cells had round to oval nuclei with inconspicuous nucleoli and did not exhibit mitotic figures. Pseudonuclear inclusions and occasional multinucleated cells could be observed. Scattered aggregates of lymphocytes and histiocytes were present. The extracellular matrix and sparse cells stained positive with alcian blue and colloidal iron. Immunohistochemical stains were positive for vimentin, CD34, and CD68 in scattered macrophages, but were negative for S100, SMA and myosin. A few cells expressed factor XIIIa (Fig. 3, Tab. 3). Transmission electron microscopy showed findings similar to case 2

(Fig. 3G). However, some cells displayed reactive findings with a plump shape, a higher amount of rough endoplasmic reticulum, and a more prominent nucleolus.

Case 4—A 45-year-old woman presented with a slowly enlarging whitish bulbar conjunctival cyst (Tab. 1). During surgery, a gelatinous, mucoid consistency was noted and the lesion could not be completely excised because of posterior extension. Histologic examination of the specimen showed fibrovascular, myxoid to collagenous tissue containing scattered cells with spindle shaped to stellate to fusiform nuclei with bland nucleoli (Fig. 4, available at <http://aaojournal.org>; Tab. 2). Many of these nuclei exhibited pseudonuclear inclusions. There were scattered multinucleated cells as well as clusters of cells arranged in florets present within the lesion. Occasional inflammatory cells and histiocytes were noted. An alcian blue and colloidal iron stain were positive for the extracellular matrix and some cells. Immunohistochemical stains were positive for vimentin, CD34, and CD68, and negative for S100, SMA, and myosin. Occasional cells were positive for factor XIIIa (Fig. 4, available at <http://aaojournal.org>; Tab. 3). Ki67 was expressed only in a few cells indicating to a proliferation rate of less than 5%.

Discussion

The lesions in our case series occurred in middle-aged patients and exhibited a spectrum of clinical appearances. The two patients without a remarkable ocular history (case 1 and 4) revealed whitish to yellow lesions. Reddish lesions were present in the two patients with blepharitis (case 2 and 3) in accordance with an additional inflammatory stimulus. All tumors were located in the bulbar conjunctiva. This location predisposes to exposure to several factors in the tear film and other environmental factors that may contribute to the development of these lesions. Blepharitis (case 2 and 3) as an additional inflammatory stimulus may also account for the pathogenesis of these conjunctival lesions. In addition, CD68 positive macrophages and factor XIIIa positive dendritic cells were present to some extent (with the fewest amount of macrophages in the biopsy of patient 3 who was pretreated with topical corticosteroids). With respect to the etiology of these lesions, an inflammatory pathogenesis or a reactive process is possible.

Histologically, our four conjunctival neoplasms consisted of spindle-shaped cells with pseudonuclear inclusions and multinucleated cells in a collagenous-to-myxoid stroma. Immunohistochemical stains were positive for vimentin, CD34, acid mucopolysaccharides, and focally for CD68 (and factor XIIIa), but were negative for S100 and SMA. The differential diagnoses comprised of conjunctival (cellular) myxoma,⁵ neurothekeoma,³ subconjunctival herniated orbital fat,⁷ fat-free spindle cell lipoma,² pseudotumor, neurofibroma,⁸ dendrocytoma,¹³ nevus with neuronal degeneration,¹⁴ solitary fibrous tumor,¹¹ fibrous histiocytoma,^{1, 6, 9} nodular fasciitis,¹⁴ hemangiopericytoma,⁴ giant cell angiofibroma,¹⁰ and rhabdomyosarcoma.¹² Our benign conjunctival lesions were differentiated from these entities by cytologic and immunohistochemical features. *Conjunctival myxoma* that is important to rule out because of a well-known possible association with the Carney complex comprising life-threatening conditions such as an atrial myxoma¹⁵, is the main differential diagnosis because our conjunctival stromal tumors revealed a partial myxomatous matrix. However, the lesions in our patients were more cellular than myxomas.⁵ Multinucleated cells are rarely found in myxomas.¹⁶ Pseudonuclear inclusions have been described in conjunctival myxomas.^{17, 18} Hence, the two conjunctival myxomas published by Herwig et al⁵ were subsequently stained for CD34 in order to differentiate them from our four cases. Both lesions were negative for CD34. However, further investigations of conjunctival myxomas for CD34 are recommended to entirely exclude that COST may be a variant of myxomas. *Solitary fibrous tumor, hemangiopericytoma, giant cell angiofibroma, fibrous histiocytoma, and nodular fasciitis*

consist of spindle shaped cells in a collagenous matrix that are except for reactive nodular fasciitis positive to different degrees for CD34.¹⁹ However, these neoplasms can be distinguished from our lesions by their morphologic growth patterns and cytologic features. In particular, giant cell angiofibroma can occur in the orbit^{10, 20, 21} and is composed of spindle cells with pseudonuclear inclusions and giant cells with occasional florets. However, these tumors are usually more cellular and exhibit a high vascular density with vascular-like spaces that allows for a distinction from the described lesions herein. *Conjunctival rhabdomyosarcoma* is a rare malignant lesion that can also occur in adults and represents conjunctival involvement of an orbital rhabdomyosarcoma.¹² Although one of our tumors showed a strong positivity for myosin (case 1), our tumors exhibited a very low proliferation rate in general, did not show mitotic figures, and exhibited a benign histologic appearance.

We interpreted the four mesenchymal proliferations as benign proliferation of spindle cells of the conjunctival stroma that share only some histopathological and immunohistochemical characteristics with previously described entities of the conjunctiva. We propose to categorize these CD34, vimentin and partly CD68 positive benign mesenchymal proliferations with pseudonuclear inclusions and multinucleated giant cells (that partly exhibit a floret-like configuration) as “conjunctival stromal tumor (COST)”. Although these lesions are benign, complete excisional biopsy of this lesion is recommended if possible, as we cannot exclude the possibility of local recurrence if incompletely excised. Ophthalmologic follow-up examination is also recommended. Identifying conjunctival lesions as COST may prevent overdiagnosis and consecutive overtreatment. Thus, this entity should be included in the differential diagnoses of benign lesions of the bulbar conjunctiva in patients usually in their 5th to 6th decade.

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Figure 1.

Case 1. Clinical appearance showing a whitish to yellow lesion of the temporal bulbar conjunctiva (A). Histologic examination revealed a fibrocellular tumor with polymorphous nuclei (B; H&E, 10 $\times$). Pseudonuclear inclusions (C, arrow; H&E, 40 $\times$) and multinucleated cells (D, arrow; H&E stain, 40 $\times$) were frequently observed. The spindle-shaped cells stained positive with myosin (E; myosin, 4 $\times$) and CD34 (F; CD34, 4 $\times$; insert: 40 $\times$).

Figure 2.

Case 2. The tumor is composed of loosely arranged collagen fibers and some large cells with inclusions (A, arrow; H&E, 40×). The extracellular matrix contained spindle-shaped cells with inclusions (arrow) and was positive for acid mucopolysaccharides (B; alcian blue, 40×). Immunohistochemical stains were positive for CD34 (C; CD34, 20×) in many areas and CD68 (D; CD68, 20×) in scattered macrophages. Transmission electron microscopy (TEM) revealed a spindle-shaped cell with branching processes and intracellular inclusions (E; TEM, 4655×). The cytoplasm contained rough endoplasmic reticulum and a few small mitochondria but Golgi apparatus were not identified, the nuclear chromatin was equally dispersed.

Figure 3.

Case 3. Clinical appearance showing a nodular lesion of the bulbar conjunctiva (A) surrounded by a vascular injection (B, higher magnification). Histology revealed polymorphous spindle-shaped cells (C; H&E, 20×) with nuclear inclusions and an alcian blue positive extracellular matrix (D; alcian blue, 40×). Immunohistochemical stains were positive for vimentin (E; vimentin, 10×), CD34 (not shown), and CD68 in scattered macrophages (F; CD68, 10×). Transmission electron microscopy (TEM) showed a fusiform cell with branching processes as well as intracytoplasmic and intranuclear inclusions surrounded by plumper cells (G; TEM, 7018×). The cytoplasm contained rough endoplasmic reticulum. Mitochondriae and Golgi apparatus were not observed. The nuclear chromatin was equally dispersed and the nucleus showed infolding of its membrane.

Figure 4.

Case 4. Spindle-shaped cells within a myxoid and collagenous matrix (A; H&E, 20 $\times$). Nuclear inclusions (arrow) and floret-like multinucleated cells (bold arrow & insert) are present (B; H&E, 40 $\times$). The stroma and some nuclei were alcian blue positive (C; alcian blue, 40 $\times$).

Table 1

Demographic and clinical data of four patients with conjunctival stromal tumor.

	Age	Gender	Race	Localization	Clinical Picture	Tissue characteristics	Color	Size [mm]	Topical Steroid Application
Case 1	41 yrs	male	Caucasian	temporal bulbar conjunctiva	cystoid lesion	soft, affixed to underlying episclera	whitish-yellow	4×5×4	NO
Case 2	47 yrs	male	N/A	superior next to the limbus (also involving the cornea)		N/A	reddish	3×1×1	NO - but cyclosporine
Case 3	53 yrs	male	Caucasian	temporal bulbar conjunctiva	nodular lesion with overlying capillary bed	non-tender conjunctival mass	hemorrhagic lesion	3×3×1	YES (prednisolone)
Case 4	45 yrs	female	N/A	bulbar conjunctiva	conjunctival cyst	gelatinous, mucoid consistency	whitish	N/A	NO

N/A: not applicable; yrs: years

Table 2

Histological Findings and Differential Diagnoses.

	Case 1	Case 2	Case 3	Case 4
Cytologic Features				
spindle-shaped cells	60–80%	70–80%	80%	70–80%
cellularity	high	low - medium	medium	medium - high
pleomorphism	+	+	+	+
pseudonuclear inclusions	+	+	+	+
multinucleated cells	+	+	(+)	+
floret-like cells	+	–	–	+
mitotic figures	–	–	–	–
Extracellular Matrix				
stroma (myxoid/collagenous)	collagenous /myxoid	myxoid /collagenous	myxoid /collagenous	myxoid /collagenous
wiry to ropey collagen	+	+	+	+
focal areas of palisading	+	–	(+)	–
pseudovascular spaces	+	+	+	+
perivascular hyalinization	+	–	+	–
chickenwire pattern	–	–	–	–
Diagnosis (dx)				
original histological dx	undifferentiated spindle cell tumor	mesenchymal proliferation	spindle cell proliferation	spindle cell proliferation
differential dx	undifferentiated neoplasm, nevus, neurofibroma	reactive changes, benign fibrohistiocytic proliferation	benign fibrocytic/vascular proliferation, reactive process	reactive process, subconjunctival hemiated orbital fat, neurofibroma

Table 3

Immunohistochemical findings and stains for acid mucopolysaccharides.

	Case 1	Case 2	Case 3	Case 4
CD34	+	+	+	+
CD68	N/A	+	(+)	+
Factor XIIIa	(+)	-	(+)	-
Vimentin	N/A	+	+	+
Desmin	-	N/A	N/A	N/A
S100	-	-	-	-
SMA	-	N/A	-	-
Myosin	+	-	-	N/A
Ki67	< 5%			
Alcian Blue / Colloidal Iron	some positive nuclei, stroma negative	some positive nuclei, stroma positive	some positive nuclei, stroma positive	some positive nuclei, stroma positive

N/A: not applicable