Ocular Surface Fibroma: Clinical, Histopathological, and Immunohistochemical Features of 10 Cases

Hardeep Singh Mudhar^a Lindsay A. McGrath^b Andy K.K. Chung^c
Jeremy Bowyer^d Ian Rennie^b

^aDepartment of Histopathology, Royal Hallamshire Hospital, National Specialist Ophthalmic Pathology Service (NSOPS), Sheffield, UK; ^bSheffield Ocular Oncology Service, Royal Hallamshire Hospital, Sheffield, UK; ^cDepartment of Ophthalmology, Pinderfields Hospital, Wakefield, UK; ^dDepartment of Ophthalmology, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK

Keywords

Conjunctiva · Plica · Fibroblast · Fibroma · Tenon's capsule · CD34 · Factor XIIIa · Mast cells · Ocular surface · Ocular surface fibroma

Abstract

Aim: To describe the clinical, histological, and immunohistochemical (IHC) features of a series of 10 cases of ocular surface fibroma (OSF) and correlate the findings with other similar histological entities. **Method:** The patient demographics and features of the lesions were analysed from the clinical notes. All cases in the series had routine diagnostic excisional biopsies with standard histopathological and IHC evaluation. Each case was analysed by histology and immunohistochemistry with antibodies to: CD34, Factor XIIIa, desmin, smooth muscle actin, S100, Melan-A, β -catenin, neurofilament, and Ki67. **Results:** OSF occurred on the bulbar, tarsal, or forniceal conjunctiva, and typically presented as a white, pink, or yellow sheet-like or nodular lesion. The most common symptom was irritation or a foreign-body sensation. Lesions ranged in size from 4 to 13 mm. Only 1/10 cases showed a recurrence after an incomplete excision. Histologically, OSF comprised bland spindle cells in a collagen stroma. The

spindle cells were CD34-positive (in 10/10 cases) and a smaller subset was positive for Factor XIIIa (6/10 cases). Normal resident spindle cells in the conjunctival stroma, Tenon's capsule, and tarsal plate were positive for CD34 and Factor XIIIa, implicating these cells in the origin of OSF. **Conclusion:** OSF is a benign lesion of resident CD34- and Factor XIIIa-positive spindle cells in the conjunctiva and Tenon's capsule. We have called to attention another lesion to be included by clinicians in the differential diagnosis of benign ocular surface lesions composed of CD34- and Factor XIIIa-positive spindle cells.

© 2019 S. Karger AG, Basel

Introduction

Epibulbar or conjunctival fibromas were first described by Herschorn et al. [1]. There has been only one other bulbar conjunctival case [2] and one case arising in the tarsal conjunctiva [3] reported in the literature. It has been proposed that some of these fibromas are derived

Dr. Lindsay A. McGrath and Dr. Hardeep Singh Mudhar are joint first authors.

Table 1. A summary of patients' details and clinical features of ocular surface fibroma

Case	Age, years	Gender	Laterality	Location	Lesion size, mm	Clinical features	Duration of symptoms/lesion, months	Symptoms	Follow-up duration
1	39	M	R	UL tarsal conjunctiva near lid margin	4 × 4 × 3	pink vascular nodule	approx. 12	irritation, FB sensation	2 years: recurrence (full-thickness wedge excision = same diagnosis). 4 years: no further recurrence
2	82	M	L	plica	8 × 3 × 3	pink oval lesion	approx. 12	irritation	3 years: no recurrence
3	85	M	R	UL tarsal	7 × 7 × 4	oval sheet-like pink/white plaque	6	irritation	12 years: no recurrence
4	29	F	R	temporal limbus and bulbar conjunctiva	8 × 5 × <1	oval sheet-like yellowish translucent	5	pain, epiphora	6 years: no recurrence
5	83	F	R	UL fornix	4 × 3 × 3	pink papillary, oval	1	irritation	3 years: no recurrence
6	77	F	R	plica	13 × 5 × 3	sheet-like, pink	approx. 12	irritation, FB sensation	5 years: no recurrence
7	33	F	L	inferotemporal bulbar	6 × 4 × 3	white/yellow nodule-like dermoid	uncertain	asymptomatic	5 years: no recurrence
8	80	M	R	superotemporal bulbar	5 × 2 × 1	pink oval nodule	2	asymptomatic	3 years: no recurrence
9	59	M	L	inferobulbar	3 × 2 × 2	pink nodule	approx. 12	FB sensation	4 years: no recurrence
10	87	F	L	inferotemporal bulbar	4 × 2 × 1	white/yellow oval nodule	uncertain	asymptomatic	4 years: conjunctival inclusion cyst at site of surgery but no tumour recurrence.

M, male; F, female; R, right; L, left; UL, upper lid; FB, foreign body.

from Tenon's capsule fibroblasts [1]. We report a series of 10 cases of ocular surface fibroma (OSF) from the conjunctiva and plica, and describe the clinical, histological, and immunohistochemical (IHC) findings. This series provides evidence that these lesions are derived from CD34-positive and Factor XIIIa-positive resident spindle cells in the tarsal plate, conjunctiva substantia propria, and Tenon's capsule.

Methods

This was a routine histopathological diagnostic descriptive case series study. Ten cases of conjunctival fibroma were identified from the database of the National Specialist Ophthalmic Pathology Service (NSOPS), Department of Histopathology, Royal Hallamshire Hospital, Sheffield, UK, between 2006 and 2018. These patients were analysed for age, gender, involved side, clinical features, symptoms, and follow-up. Patient demographics, clinical findings, and histopathology were reviewed for all cases. Statistical analyses were descriptive due to the small sample size.

All specimens were fixed in 10% buffered formalin and processed to wax. Sections (4-µm) were cut, stained with haematoxylin and eosin (H&E), and viewed with a light microscope. Sections were then stained with Toluidine Blue (mast cells) and Alcian Blue (to detect any suspected myxoid matrix). Each case was routinely exposed at the time of diagnosis to the following IHC panel, designed to detect the identity of spindle cells in soft-tissue lesions: CD34 (Agilent, ready-to-use antibody), Factor XIIIa (Cell Marque, 1:100 dilution), desmin (Dako, 1:75 dilution), smooth-muscle actin, S100, Melan-A, β-catenin (all Agilent, ready-to-use antibody), neurofilament (Agilent, 1:500 dilution), and Ki67 (Agilent, ready-to-use antibody).

Results

Table 1 shows patients' characteristics and details of the OSF presentations. There were 5 males and 5 females in this series. The median age was 78.5 (range 29–87) years. The right eye was affected in 6 cases and the left in 4 cases. Two patients had lesions involving the tarsal con-

Fig. 1. Clinical appearance of ocular surface fibroma (OSF) in patients 1–4. **a** Tarsal conjunctival OSF at lid margin. **b** Plical OSF. **c** Tarsal OSF. **d** Bulbar conjunctival OSF.

Table 2. Summary of the histological features of ocular surface fibroma

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Cell type	spindle + plump; some plump cells had intra-nuclear inclusions	spindle	spindle	spindle + plump	spindle + plump	spindle	spindle + plump	spindle	spindle	spindle
Stroma	ropey	wiry and ropey	keloid-like	keloid-like	ropey and keloid-like	ropey	ropey	ropey	keloid-like	keloid-like
Mast cells	present	present	present	–	present	present	present	present	absent	absent
Inflammation	absent	a band of sub-epithelial chronic inflammation	absent	absent	absent	a band of subepithelial chronic inflammation	absent	absent	absent	absent

junctiva, 5 had bulbar conjunctival involvement, 2 had plical involvement, and 1 had a lesion in the fornix (Fig. 1). The lesions tended to be white, yellow, or pink nodules but sheet-like plaques were also seen. Patients experienced symptoms from their lesions for a median of 9 (range 1–12) months prior to presentation. The follow-up period was 1–12 years. In 1 patient (Case 1), clinical recurrence was recorded after incomplete excision. None of the patients required additional therapy after surgery. There were no signs of globe displacement or motility restriction to suggest orbital involvement. On slit-lamp examination, all OSFs were well circumscribed and did not require further delineation with computerised tomography or magnetic resonance imaging.

Histology

All the lesions were well-defined (Fig. 2a) and comprised 2 principal components: spindle cells and a collagen-rich matrix. The spindle cells were slender and wavy with densely stained nuclear chromatin and slender, tapering, eosinophilic cytoplasm (Fig. 2b). In some cases, plumper, ovoid cells with more open nuclear chromatin were present (Fig. 2c). In 1/10 cases, the spindle cells showed intra-nuclear cytoplasmic inclusions (Fig. 2d). Generally, the spindle cells were evenly distributed in the collagen. There was no-to-minimal nuclear pleomorphism and no mitotic figures were identified. No multinucleate cells were identified. The collagen matrix varied

Fig. 2. **a** Scanning-power stained section of a tarsal conjunctival OSF showing its well-defined outline. **b** Typical spindle cells and collagen stroma of OSF. **c** Some plumper spindle cells in some cases of OSF at the same magnification as in **b**. **Inset** (top right) A higher-power representation of the plumper spindle cells. **d** 1/10 cases of OSF showed cells with intra-nuclear cytoplasmic protrusions, characterised by central nuclear clearing (at the centre). **a–d** H&E. **e** Purple-stained mast cells in OSF. Toluidine Blue.

from rope-like to keloid-like. No cases showed a myxoid stroma when tested with Alcian Blue stain. A notable feature was the presence of mast cells, sparse in number and distributed evenly throughout many of the lesions (Fig. 2e). In 2/10 cases, foci of chronic inflammation were identified at the edges of the lesion (not shown).

The case with recurrence (Case 1) was initially punch-biopsied and not excised. The histology of the punch biopsy was identical to in the recurrence, except for a slightly raised Ki67 fraction in the recurrence compared to the original biopsy.

These findings are summarised in Table 2.

IHC Findings

Immunohistochemistry showed that the spindle and plump cells were all positive for CD34 in all cases (Fig. 3a), corresponding to a fibroblastic phenotype. Factor XIIIa

stained a subset of these spindle cells that were similar in nature to dermal dendrocytes and appeared slightly larger and more dendritic than the CD34-positive fibroblasts (Fig. 3b). All cases were negative for Melan-A, smooth-muscle actin, desmin, β -catenin, and neurofilament (not shown). CD68 showed some macrophages amongst the chronic inflammation in the 2/10 cases alluded to above (not shown).

We also exposed normal Tenon's capsule, bulbar and tarsal conjunctiva, and tarsal plate control tissue to immunohistochemistry. This established that the native spindle cells in the conjunctival stroma (Fig. 3c, d), tarsal plate (Fig. 3e), and Tenon's capsule (Fig. 3f, g) were all positive for CD34. A smaller subset of spindle cells also expressed Factor XIIIa. The immunohistochemistry findings are summarised in Table 3.

Fig. 3. **a** The spindle cells of OSF are CD34-positive on immunohistochemistry (brown = positive staining). **b** A subset of the spindle cells in OSF is positive for Factor XIIIa. **c** Normal conjunctival substantia propria containing CD34 resident spindle cells corresponding to mature fibroblasts. **d** Normal conjunctival substantia propria containing far fewer Factor XIIIa resident spindle cells than CD34-positive cells. **e** Normal tarsal plate showing numerous CD34-positive fibroblasts between the sebaceous lobules. A smaller number of Factor XIIIa-positive cells were also present (not shown). **f** Normal Tenon's capsule containing numerous CD34-positive spindle-shaped fibroblasts. **g** Normal Tenon's capsule containing occasional Factor XIIIa-positive spindle cells.

Discussion

This case series described CD34-positive lesions comprising spindle cells in a collagenous matrix and mast cells affecting the bulbar, tarsal, forniceal, and plical conjunctiva. Some cases showed a subset of spindle cells to be focally Factor XIIIa-positive. We propose the phrase “ocular surface fibroma” (OSF) to describe such lesions. The clinical and morphological description of this series matches the original description of a case of epibulbar fibroma of the conjunctiva substantia propria [1] and is

very similar to an earlier study on epibulbar subconjunctival fibroma (thought to be derived from the Tenon's capsule) and a case of tarsal fibroma [2, 3]. However, none of these previous studies employed immunohistochemistry.

A combination of bland spindle cells in a collagen matrix invokes the following histological differential diagnosis: conjunctiva stromal tumour (COST), spindle-cell lipoma (fat-free), schwannoma, neurofibroma, solitary fibrous tumour, fibrous histiocytoma/dermatofibroma, desmoplastic fibroblastoma/collagenous fibroma, and

Table 3. Immunohistochemical profiles for ocular surface fibroma

Case number	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
CD34	pos	pos	pos	pos	pos	pos	pos	pos	pos	pos
Factor XIIIa	neg	some spindle cells pos	some spindle cells pos	neg	some spindle cells pos	some spindle cells pos	some spindle cells pos	neg	neg	some spindle cells pos
Desmin	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
Smooth-muscle actin	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
Neurofilament	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
β -Catenin	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
S100	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
Melan-A	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
CD68	neg	occasionally scattered macrophages pos	neg	neg	neg	occasionally scattered macrophages pos	neg	neg	neg	neg
Ki67 proliferation fraction	up to 3%	neg	neg	neg	<1%	<1%	<1%	neg	neg	neg

pos, positive; neg, negative.

elastofibroma. COST mainly occurs on the bulbar conjunctiva and is characterised by spindle cells with intranuclear inclusions and multi-nucleate cells within a myxoid-rich collagenous matrix [4]. Mast cells are not observed.

In a later publication [5], the same study group described 3 more cases, 1 of which (Case 2), had a purely fibrous stroma (identical to in our series) and no intranuclear cytoplasmic inclusions within the spindle cells. The authors argued that a COST could also have a purely fibrous stroma, although this case lacked the defining features in the original case series [4]. This was backed up by a further case report by Greenberg et al. [6] who reported a COST with a purely fibrous stroma. In our series, the lesions occurred in all regions of the ocular surface (plica, caruncle, and tarsal and bulbar conjunctiva), intranuclear inclusions were seen in only 1/10 cases, and no myxoid matrix was observed on H&E or Alcian Blue staining. We are of the opinion that these cases in Auw-Haendrich et al. [5] and Greenberg et al. [6] were not typical COSTs but were in fact OSFs.

Regarding further histological differential diagnoses, fat-free spindle-cell lipoma is characterised by CD34-positive spindle cells with scattered mast cells, but it has a distinctive ropey collagen and the spindle cells show

vague nuclear palisading. There were no neurofilament-positive fibres within or to one side of the main lesion and transmission electron microscopy from one of these cases confirmed a fibroblastic phenotype with no ultrastructural features of Schwann cells. Furthermore, Melan-A staining was negative in all cases. Solitary fibrous tumour/giant-cell angiofibroma are more cellular than the cases in our series and show a distinctive collagen pattern whereby individual cells are invested in collagen. A haemangiopericytoma-like vascular pattern is often observed and these lesions are positive for STAT6. One of the cases in our series was negative for STAT6 upon staining. Fibrous histiocytoma/dermatofibroma tends to be strongly positive for Factor XIIIa throughout, rather than focally. Desmoplastic fibroblastoma/collagenous fibroma is composed of cells similar to those in our series but tends to be CD34-negative. Elastofibroma shows a distinctive pattern of elastin staining not seen in our cases.

We found that normal conjunctival substantia propria from the bulbar and tarsal sites, the Tenon's capsule, and the tarsal plate all contained resident spindle-cell fibroblasts positive for CD34 and, focally, also contained Factor XIIIa-positive spindle cells judged to be equivalent to dermal dendrocytes. It is therefore highly likely that the OSFs arose from these resident cells, and, when coupled

with the presence of inflammatory activity in some cases, this would argue in favour of a reactive, post-inflammatory scarring process rather than representing a benign neoplasm. However, no antecedent history of trauma or surgery was elicited in our cases. Previously, speculation had it that these lesions represent the scarred remnants of an earlier inflammatory process and it was thought that they arise from the Tenon's capsule [1–3]. We think that the clinically recurrent lesion could be attributed to biopsy trauma that stimulated residual lesional cells to proliferate, thus leading to a recurrence.

The significance of the presence of mast cells in OSF is uncertain, with some evidence that it correlates positively with the amount of collagenous stromal tissue in soft-tissue tumours [7]. The role of mast cells in fibrosis is also controversial, with some reports suggesting that their presence promotes fibrosis whereas some suggest their presence provides protection against fibrosis [8].

Since the initial description of COST, there has been a recent paper defining a lesion called a “conjunctival mucinous stromal tumour” (CMST) [9]. CMST has an almost identical cytological mix and IHC profile to COST, except for the very prominent Alcian Blue-stained positive stroma. In our series, whilst the spindle cells were similar, there were some intra-nuclear inclusions in only 1 case, but no multi-nucleate cells were identified, no myxoid matrix was present, and the stroma was fibrous. Unlike COST and CMST which are restricted to the bulbar conjunctiva, the lesions in our series occurred at the plica, fornix, tarsal conjunctiva, and lid margin. Whilst OSFs appear to have some distinct clinical and histological features, the expression of CD34 that they share with COST and CMST suggest that all these CD34-positive spindle-cell lesions lie on a spectrum, likely representing a reparative response to trauma/inflammation. It may be that CMST and OSF are at opposite ends of the histolog-

ical spectrum, i.e., ranging from an immature, myxoid, proteoglycan matrix of CMST through to the mature, collagenised matrix of OSF. It is also highly probable that they are derived from resident CD34-positive fibroblasts in the conjunctival substantia propria, Tenon's capsule, and tarsal plate.

In summary, we have described 10 cases of so-called ocular surface fibroma (OSF), a benign lesion of resident CD34 and FactorXIIIa-positive spindle cells in the conjunctiva and Tenon's capsule. We have brought another lesion to the attention of clinicians, one that they should include in the differential diagnosis of benign conjunctival lesions.

Statement of Ethics

The study was performed ethically in accordance with the World Medical Association Declaration of Helsinki. The subjects gave their informed consent to publish clinical photos of their ocular surface and the study protocol was approved by the institute's clinical research office.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not funded by any grant.

Author Contributions

H.S.M. wrote the text and contributed histology figures. L.A.M. wrote the text and collated clinical figures. A.K.K.C., J.B., and I.R. contributed data and edited the text.

References

- Herschorn BJ, Jakobiec FA, Hornblass A, Iwamoto T, Harrison WG. Epibulbar subconjunctival fibroma. A tumor possibly arising from Tenon's capsule. *Ophthalmology*. 1983 Dec;90(12):1490–4.
- Jakobiec FA, Sacks E, Lisman RL, Krebs W. Epibulbar fibroma of the conjunctival substantia propria. *Arch Ophthalmol*. 1988 May; 106(5):661–4.
- Clinch TJ, Kostick DA, Menke DM. Tarsal fibroma. *Am J Ophthalmol*. 2000 May;129(5): 691–3.
- Herwig MC, Wells JR, Grossniklaus HE. Conjunctival stromal tumor: report of 4 cases. *Ophthalmology*. 2012 Apr;119(4):682–7.
- Auw-Haedrich C, Danielewicz KD, Mendoza PR, Reinhard T, Grossniklaus HE. Conjunctival stromal tumor: expansion of findings in a newly described entity. *Ophthalmology*. 2016 May;123(5):1166–7.
- Greenberg EL, Espana EM, Margo CE. Conjunctival Stromal Tumor. *Ophthalmology*. 2018 Jan;125(1):88.
- Donhuijsen K, Sastry M, Völker B, Leder LD. Mast cell frequency in soft tissue tumors. Relation to type and grade of malignancy. *Pathol Res Pract*. 1992 Feb;188(1-2):61–6.
- Bradding P, Pejler G. The controversial role of mast cells in fibrosis. *Immunol Rev*. 2018 Mar;282(1):198–231.
- Qin XY, Jin ZH, Wang YP, Zhang ZD. Conjunctival myxoid stromal tumour: a distinctive clinicopathological and immunohistochemical study. *Br J Ophthalmol*. 2019 Sep; 103(9):1259–65.