Human Pathology Reports 35 (2024) 300728

Contents lists available at ScienceDirect

Human Pathology Reports

journal homepage: www.journals.elsevier.com/human-pathology-reports

Conjunctival stromal tumour: A case report

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ARTICLE INFO

Keywords:
Conjunctiva
Conjunctival stromal tumour
Myxoma
Carney complex

ABSTRACT

Conjunctival stromal tumour (COST) is a rare and newly described mesenchymal tumour of the conjunctiva. We present a case of a slow-growing conjunctival lesion in a 54-year-old female. Due to persistent irritant symptoms, the lesion was excised. Histopathological assessment showed a paucicellular tumour set in an oedematous and collagenous background within the lamina propria. Significant nuclear degenerative atypia was noted. Lesional cells were positive for CD34 immunohistochemistry. The features were consistent with COST. The condition is typically unilateral and arises in the bulbar conjunctiva, with both inflammatory and neoplastic origins considered. They are sporadic and occur most frequently in adults. COSTs are indolent and managed effectively with complete surgical excision. Conjunctival myxoma is the most important differential diagnosis due to its association with the Carney complex, a potentially life-threatening condition that requires close clinical follow-up. Accurate recognition of COST and myxoma is crucial to stratify care appropriately.

Introduction

Mesenchymal tumours of the conjunctiva are a rare and emerging group of lesions. They include vascular tumours, myofibroblastic lesions and smooth and skeletal muscle tumours. Although uncommon, mesenchymal tumours have potentially important clinical implications and accurate recognition is essential.

Herwig et al. [1] first described mesenchymal conjunctival stromal tumours (COSTs) in 2012 following a case study of 4 patients. These tumours represent fewer than 0.001 % of conjunctival lesions [2] and are uniformly benign. They must be distinguished from their closest mimicker, conjunctival myxoma, given the association of myxoma with the Carney complex, a rare genetic condition.

We present a case of a 54-year-old female with a slow-growing conjunctival mass. Approval for the case report was obtained from the institutional Health Sciences Research Ethics Committee (HSREC), reference number UFS-HSD2023/0543/2507. The patient provided written informed consent for the publication of the information.

Case report

The patient is a 54-year-old woman who visited an ophthalmologist due to a fleshy lesion in her right eye that had been present for several months. She reported that the eye was scratchy, red and tearful. The patient had no relevant medical history of allergies, chronic medical conditions, or previous ocular trauma or surgery. However, she had a smoking habit and wore glasses.

During clinical examination, a slightly elevated lesion was identified in the infratemporal region of the right eye. It measured approximately 3 mm in greatest dimension and appeared focally cystic (Fig. 1). An excision biopsy was performed under local anaesthetic. The tissue was submitted in formalin for histological analysis. Routine haematoxylin and eosin (H&E) stains were performed. Microscopic examination confirmed the presence of conjunctival epithelium with underlying stroma. A paucicellular spindle-cell tumour was identified within the stroma with focal nuclear pseudoinclusions. No mitoses were present. The background stroma appeared eosinophilic and collagenous (Fig. 2 A–D). Histochemical stains for mucin were negative and a Congo red stain for amyloid was negative.

Immunohistochemical stains were performed in the presence of

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https://doi.org/10.1016/j.hpr.2023.300728
Received 8 September 2023; Received in revised form 6 December 2023; Accepted 6 December 2023

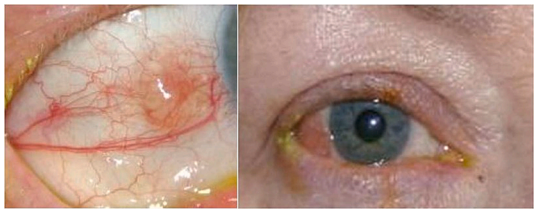

Fig. 1. A pale pink subconjunctival mass is noted on the temporal bulbar conjunctiva. The lesion is elevated with surrounding ectatic blood vessels. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

adequate controls. The spindle-cells were positive for CD34 but negative for SOX10, CD31, Desmin and D2-40 (Fig. 2 E and F). The morphological and immunohistochemical features were consistent with a conjunctival stromal tumour.

Discussion

The nomenclature for myxoid conjunctival lesions has evolved in recent years. In the past, all conjunctival myxoid tumours were diagnosed as myxomas, but in 2012, Herwig et al. [1] revised the nomenclature to include a distinct group called "conjunctival stromal tumour" (COST). This change aimed to differentiate myxomas, which have potential life-threatening associations, from reactive mesenchymal proliferations. By using COST as a separate term, the classification of myxoid lesions in the conjunctiva has become more accurate and specific.

Conjunctival stromal tumours arise almost exclusively from the bulbar conjunctiva, with- or without involvement of the limbus [2]. They are invariably unilateral. Corneal involvement is rare [3]. They are described as slow-growing, plaque-like or cystic lesions that are pale yellow to pink in colour. Surrounding conjunctival induration is common. Rare cases of exotropia have been reported in large tumours. However, most tumours measure between 3 mm^2 and 14 mm^2 [2]. Lesions have negligible effects on visual acuity. A single case of tumour extension into the medial and inferior recti muscles has been documented [4].

Although these lesions most frequently occur in patients between 30 and 70 years of age [2,5,6], rare cases in childhood have been reported, such as an 11-year-old boy described by Haw-Haedrich et al. [3]. Although their exact pathogenesis is unknown, several factors point to both reactive and neoplastic aetiologies [2]. Their location on the bulbar

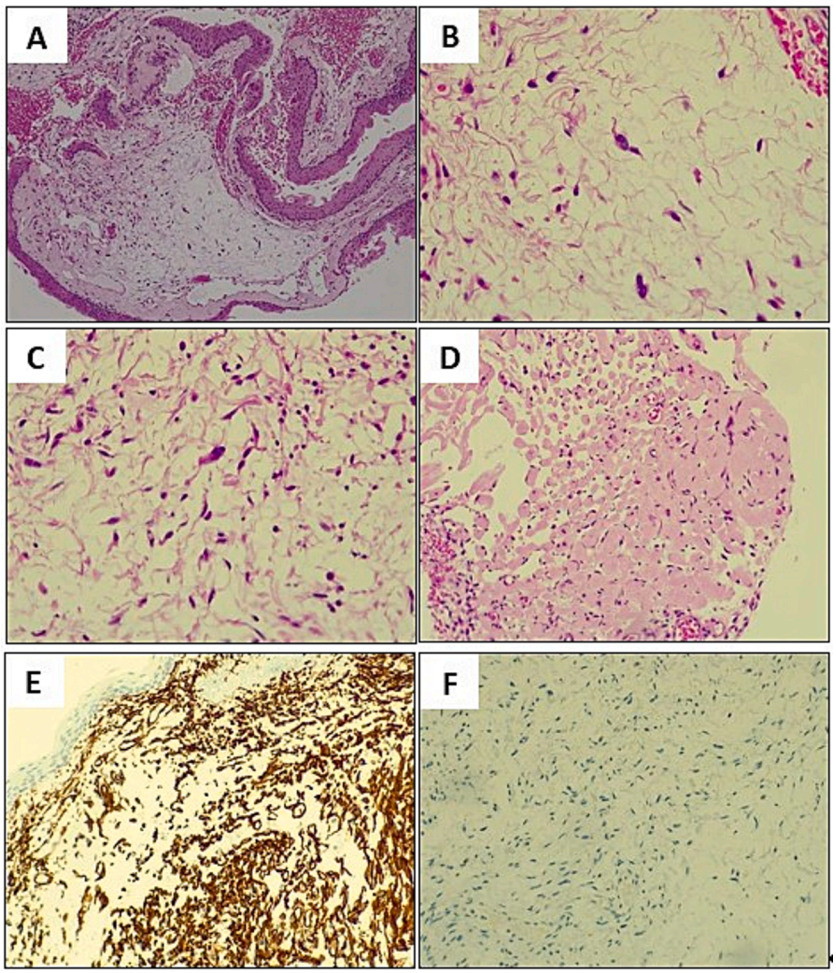

Fig. 2. Conjunctival stromal tumour immunohistochemistry findings. [A] Haematoxylin and eosin (H&E) stain of the conjunctival lesion (100X magnification). Microscopy shows a fragment of squamous epithelium with scattered goblet cells. Squamous metaplasia is evident, although no dysplasia is noted. The underlying lamina propria shows a paucicellular tumour set in an oedematous background. [B and C] H&E stain (400X magnification). High power view shows stellate and spindled cells. The nuclei show degenerative changes, including nuclear pseudoinclusions, hyperchromasia and irregular nuclear outlines. Scant cytoplasm is noted and an inflammatory infiltrate is absent. [D] H&E stain (400X magnification). Collagenous matrix is focally present. This is material is negative for Congo red staining. [E] CD34 immunohistochemistry demonstrating positive membrane staining (400X magnification). [F] Desmin immunohistochemical stain confirming a negative finding (400X magnification). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

conjunctiva of older adults, which serves as a protective barrier against external irritants, suggests a reactive origin [2]. This theory is further strengthened by scattered macrophages and factor XIIIa-positive dendritic cells within their stroma [1]. However, the typical pattern of unilateral growth with slow but steady enlargement points to a neoplastic cause.

Microscopy

Conjunctival stromal tumours appear lobulated and unencapsulated and subepithelial lesions displace the substantia propria [7]. These paucicellular tumours comprise singly dispersed spindle cells with elongated hyperchromatic nuclei and scant cytoplasm [1]. Focal large cells with abundant eosinophilic cytoplasm and multinucleate cells, described as having a floret-like nuclear arrangement [1,2], may be noted.

Mild degenerative nuclear features can be seen, including nuclear pseudoinclusions, enlarged hyperchromatic nuclei, multiple nucleoli [5] and irregular nuclear borders. Scattered mast and dendritic cells may be noted; however, a prominent inflammatory infiltrate is uncommon. Necrosis and mitotic activity do not occur [2].

These tumours are set in a variably collagenous or myxoid background [1,3,7], although some may appear very oedematous [4]. Blood vessels appear slightly dilated and delicate to thick, ropey collagen may be noted in the matrix [2,8]. The overlying epithelium may show squamous metaplasia but not dysplasia [2].

Stains

Vimentin positivity is common in mesenchymal tumours of the conjunctiva [8,9]. However, the diagnostic value of vimentin immunohistochemistry is limited as positivity is also seen in several epithelial, melanocytic and lymphoid tumours [10]. Strong and diffuse CD34 and BCL-2 positivity is common4 [7], and RB1 staining is retained [2]. The following are negative: SOX10, S100, SMA, desmin and STAT6 [2]. These tumours demonstrate a low proliferation rate and Ki67 is less than 5 % in most cases [5]. Rare positivity for myosin has been demonstrated in one case [1]. Histochemical stains may be positive for acid mucopolysaccharides [2]. Focal positivity with CD117 has been described [1].

Differential diagnosis

Conjunctival myxomas are considered the most important differential diagnosis for COSTs1 [3,11], due to their association with Carney syndrome. Clinical parameters are similar between these lesions regarding age, gender, tumour size, symptoms and a history of ocular trauma [8] On clinical examination, COSTS appear more solid and fibrovascular, whereas myxomas are usually cystic and gelatinous. COSTs are also localised to the bulbar conjunctiva, while myxomas may be juxtalimbal, orbital or present in the tarsal conjunctiva [8].

Microscopically, both lesions may show myxoid stroma. However, COSTs are usually less myxoid with more prominent ropey collagen. They are more cellular than myxomas, with more conspicuous multinucleate cells [1,3]. Additionally, spindle cell morphology is more common in COSTs, with stellate cells predominating in myxomas. Scattered inflammatory infiltrates with CD68 and factor XIIIa positivity are more common in COSTs [8]. There are conflicting data on the helpfulness of CD34 positivity to differentiate between these entities [2,3,8], and immunohistochemical investigation is not sufficient to differentiate between the entities [11].

Myxomas are important to recognise because of their association with the Carney complex (or syndrome), an autosomal dominant condition caused by germline mutations in the *PRKAR1A* gene. Associated extra-ophthalmic tumours include cardiac and mucocutaneous myxomas, psammomatoid melanotic schwannomas, endocrine hyperactivity [6] and cellular blue nevus [2]. Conjunctival lesions often precede cardiac myxomas; thus, the accurate recognition of conjunctival myxomas can improve patient outcomes with early referral to cardiology [6,12]. Because myxomas will show *PRKAR1A* abnormalities, genetic studies may aid in diagnosing myxomas [8].

Conjunctival myxoid tumours are also associated with Zollinger-Ellison syndrome (ZES) [6] and multiple endocrine neoplasia (MEN) syndromes [13]. Benign conjunctival cysts tend to transilluminate on clinical examination. Squamous neoplasia, sarcoma and lymphoma may be ruled out on microscopic examination [2]. Giant cell angiofibromas are comprised of giant cells in a spindled background. These are vascular tumours with numerous capillary-type blood vessels [1].

Conjunctival rhabdomyosarcoma is a rare tumour with a high proliferation index and positivity for myosin, desmin, myoglobin, myogenin and MyoD1 [1,14]. Although COSTs can be focally myosin-positive, they have low proliferation indices and are negative for MyoD1 and myogenin. Confirmatory genetic testing can be performed for the characteristic translocation seen in alveolar rhabdomyosarcoma (FOXO1-PAX3 and FOXO1-PAX7) [14]. Lockhern-type cells and CD34-positive multinucleate cells may be noted in both pleomorphic lipomas and COSTs. However, pleomorphic lipomas show less myxoid background and at least a focal adipocytic component [3].

Solitary fibrous tumours share positivity for CD34. These tumours have variable cellularity and are described as having a “patternless growth pattern”. They exhibit variable degrees of thick collagen bands, keloid-like hyalinisation and staghorn “pericytic” vessels [15,16]. STAT6 is an effective immunohistochemical stain that is a reliable marker for the classic NAB2-STAT6 fusion in most solitary fibrous tumours [2]. Melanomas are often cyst-like conjunctival growths. These are relatively easily distinguished from COSTs based on their cellularity and pleomorphism. Immunohistochemistry for SOX-10, Melan-A and HMB-45 is confirmatory of melanoma [2].

Several mesenchymal tumours, such as neurofibroma, nodular fasciitis and fibrous histiocytoma, can present with a myxoid background. These tumours are infrequent in the conjunctiva and exhibit distinct histopathological characteristics that aid their differentiation [2].

Outcome

COSTs are effectively managed with complete local excision. In the case of incomplete removal, there is a low recurrence risk. Residual tumour margins can be further managed with the cytotoxic agent mitomycin C 0.02 % and double-freeze thaw cryotherapy [2]. No cases of malignant transformation at 30 months of follow-up has been reported [13].

Conclusion

The difficulty in diagnosing mesenchymal lesions is not specific to the conjunctiva and presents a challenge in various contexts. Accurate diagnosis of COST is crucial to prevent over- and under-treatment in patients with conjunctival mesenchymal lesions. Due to their association with Carney complex, the differential diagnosis for conjunctival mesenchymal lesions should always include conjunctival myxoid tumours. COST is a favoured term for lesions that do not fulfil the criteria for myxoma and contributes to the prevention of an unnecessary workup for Carney complex.

Ethics statement

Approval for the case report was obtained from the institutional Health Sciences Research Ethics Committee (HSREC), reference number UFS-HSD2023/0543/2507. The patient provided written informed consent for the publication of the information.

CRediT authorship contribution statement

Jane E. Buys: . **Christiaan H. Gouws:** Conceptualization, Writing – review & editing. **Stefanus W.D. van der Walt:** Conceptualization, Writing – review & editing. **Jacqueline Goedhals:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Dr. Daleen Struwig, medical writer/editor, Faculty of Health Sciences, University of the Free State, for technical and editorial preparation of the article.

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