American Journal of Ophthalmology Case Reports 35 (2024) 102089

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Video

A rare case of acantholytic squamous cell carcinoma presenting on non-sun exposed palpebral conjunctiva

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ARTICLE INFO

Keywords:
Conjunctival lesions
Conjunctival neoplasia
Squamous cell carcinoma
Eyelid malignancies
Ocular histopathology

ABSTRACT

Purpose: This report describes the clinical and histological characteristics and management of a keratinized lesion of the palpebral conjunctiva in a 59-year-old male. The lesion was identified as a rare acantholytic variant of squamous cell carcinoma that atypically arose from a non-sun exposed region of palpebral conjunctiva. Management was complete excision via Mohs surgery.

Observations: A 59-year-old male presented with ocular irritation and chronic foreign body sensation in the right eye. Exam revealed a keratinized lesion in the right lower tarsal conjunctiva, and an initial shave biopsy was non-diagnostic. 12 months later, the patient presented with similar symptoms and a larger, more irregular lesion for which histopathology of a tarsal-involving excisional biopsy was consistent with acantholytic squamous cell carcinoma with involved margins. The patient subsequently underwent complete excision via Mohs surgery and a secondary reconstruction.

Conclusions and importance: Acantholytic variants of squamous cell carcinoma are rare and are described as arising from areas with routine sun exposure. This case reports such a lesion arising from non-sun exposed tarsal conjunctiva, as identified by histopathology of a full-thickness excisional biopsy. The lesion was successfully managed with complete excision via Mohs surgery and secondary reconstruction. Given that this histologic variant may be more aggressive and have higher rates of recurrence than other forms of squamous cell carcinoma, this case highlights the importance of complete excisional biopsy and accurate histopathology of concerning periocular lesions and offers a template for management of similar lesions. The unique presenting location should bring awareness to consideration of this type of malignancy developing on palpebral conjunctiva.

1. Introduction

Squamous cell carcinoma (SCC) is an epithelial malignancy characterized by full-thickness atypia and increased mitotic activity of squamous cells.[1] Keratin formation is generally seen in more well-differentiated lesions. Risk factors for SCC include chronic ultraviolet (UV) light exposure, human papillomavirus (HPV) infection, and immunosuppression; with periocular occurrence predominantly in sun exposed areas including the eyelids and the bulbar conjunctiva.[2,3] Treatment of SCC is wide surgical excision, with adjuvant chemotherapy (5-fluorouracil or mitomycin-C, following unavailability of interferon alfa-2b) commonly used in conjunctival ocular surface squamous neoplasia (OSSN).[4] It is essential to send biopsies to pathology to evaluate margins and rule out rare histologic variants. Patients should be followed closely for recurrence. We report a patient with a keratinized lesion of the palpebral conjunctiva for which an initial shave biopsy was non-diagnostic and subsequent full-thickness excisional biopsy identified acantholytic SCC, a rare histopathologic variant that typically presents only on sun-exposed epithelial surfaces.

2. Case report

A 59-year-old male presented with a two-month history of nonprogressive ocular irritation and chronic foreign body sensation in the right eye. He noted this worsened when looking down and to his left. He reported no significant ocular history, with no prior ocular infection, foreign body, or trauma. The patient had no history of skin cancers. He reported taking no systemic medications and had no immunosuppression but endorsed being a long-term smoker.

Anterior segment examination revealed a keratinized palpebral

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https://doi.org/10.1016/j.ajoc.2024.102089
Received 4 October 2023; Received in revised form 19 May 2024; Accepted 1 June 2024
Available online 8 June 2024

conjunctival lesion of the right lower eyelid, near the medial canthus. The lesion measured 2.0mm × 1.5mm, with ring-like keratinization around an area of central clearing (Fig. 1). He was placed on a month-long taper of neomycin/polymyxin/dexamethasone ointment prior to coming to ophthalmology, with no improvement in symptoms and no change in appearance of the lesion.

Given the presence of keratin on the mucosal surface of tarsal conjunctiva and concern for OSSN, a full-thickness tarsal-involving biopsy was recommended. At that time, the patient found the lesion mildly irritating only when the eye was in inferior adduction and strongly preferred to minimize any surgical eyelid disruption, so a shave biopsy was performed in-clinic as the first attempt to obtain a histologic diagnosis. This removed all surface keratin and some palpebral conjunctiva without incision into tarsus, and the specimen was sent in formalin to ocular pathology. H&E (Fig. 2) and PAS-stained sections revealed several fragments of stratified squamous epithelium without underlying stroma. The epithelium was hypercellular and atypical, with areas of intercellular bridging. Frequent apoptotic cells were observed. Focal areas of keratinization and parakeratosis were present. Mitotic figures were not identified. Foreign bodies were not identified under polarized light.

The histopathology report described that the specimen was limited, superficial, and insufficient to make a definitive diagnosis. Based on features from the available tissue, a joint report from ocular pathology and dermatopathology provided a differential including OSSN and squamous cell carcinoma, which were noted to be less likely due to the lesion arising from an area without sun exposure. The reported differential also listed benign conditions that could lead to the identified features, including reactive atypia and metaplasia, medication toxicity, Sjögren's syndrome, mucous membrane pemphigoid, and prior radiation.

The patient was informed about the lack of a definitive diagnosis from the initial biopsy and educated about the benign and malignant conditions within the differential. Given the clinical concerns and presence of malignant squamous neoplasia on the histopathologic differential, we discussed options for adjuvant treatment with 5-fluorouracil and/or to proceed to the operating room to obtain a full-thickness, tarsal-involving excisional biopsy. At that time, the shave biopsy had removed all surface keratin and the visible lesion, and the patient reported complete resolution of all symptoms and a desire to hold off on further intervention unless we had definitive evidence of malignancy. After counseling about all options, he elected for close monitoring, and was doing well without return of symptoms or clinical recurrence of the lesion at 3-month and 7-month post-procedure examinations.

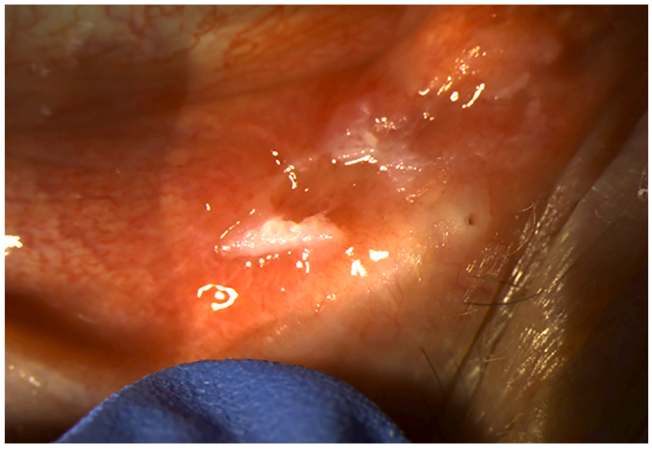

Fig. 1. Initial Clinical Appearance. Eversion of the right lower eyelid reveals a lesion of the palpebral conjunctiva measuring 2.0 × 1.5 mm, with ring-like keratinization around an area of central clearing just posterior to the medial eyelid margin.

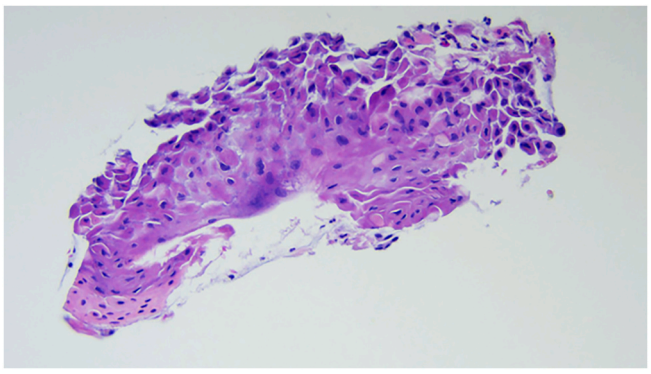

Fig. 2. Initial Biopsy Histopathology. H&E-stained sections of an initial shave biopsy show stratified squamous epithelium without underlying stroma. Epithelium was hypercellular and atypical, with areas of intercellular bridging. Frequent apoptotic cells were observed along with areas of keratinization. Mitotic figures were not identified. Specimen was insufficient to provide a histopathologic diagnosis.

One year after the initial biopsy, the patient presented again with similar symptoms. External exam remained normal, without lesions or disruption of eyelid architecture (Fig. 3). Examination with lower eyelid eversion revealed a 13.0mm × 6.4mm lesion of the palpebral conjunctiva inside the right lower eyelid with areas of mucosal thickening and a whitish, keratinized plaque extending around the punctum (Fig. 4).

Upon recurrence of the lesion, the patient acquiesced to a definitive surgical biopsy, and a 10mm × 7mm full-thickness excisional biopsy of palpebral conjunctiva and tarsus was performed, sparing the punctum and canaliculus. The specimen was sent in formalin, with sections reviewed by both ocular pathology and dermatopathology. The H&E (Fig. 5) and PAS-stained sections revealed nonkeratinizing stratified squamous epithelium with goblet cells adjacent to markedly atypical regions of keratinizing squamous epithelium. There was marked dyskeratosis with individual cell keratinization, and resulting acantholysis with desquamation of the cells both onto the surface and into centers of tumor lobules. The malignant cells showed marked nuclear pleomorphism, prominent nucleoli, mitotic figures, and intercellular bridging. A chronic, non-granulomatous inflammatory reaction was present. The histopathologic diagnosis was reported as acantholytic squamous cell carcinoma (ASCC), characterized by full-thickness atypia with extension of tumor cells into the underlying stroma. Biopsy margins were involved. Distinguishing features of the acantholytic variant included discohesive (acantholytic) squamous cells with a pseudoglandular pattern.

The patient was scheduled to see a Mohs surgeon and underwent complete excision of the malignant acantholytic squamous cell carcinoma with negative margins five weeks later. A secondary reconstruction was performed by oculoplastics. The post-Mohs defect measured 20mm posteriorly x 14mm horizontally, with complete loss of the right lower punctum and canaliculus, partial loss of the eyelid margin, and loss of tarsus and posterior conjunctiva 20 mm into the inferior fornix, without involvement of bulbar conjunctiva. The medial canthal tendon remained intact, with notable horizontal laxity. Silicone intubation and stenting was performed through the superior punctum to preserve some nasolacrimal system patency. Medial canthopexy was performed to tighten the lid medially towards the globe and prevent medial retraction/ectropion. Reconstruction of the 14 mm defect of the eyelid margin was performed with a layered margin closure, and the posterior tarsal defect was left to heal by secondary intention.

The patient was evaluated by dermatology and oncology, who recommended no further imaging or lymph node evaluations. Given complete excision of the lesion via Mohs procedure, no adjuvant radiation or topical chemotherapy was advised. Evaluations alternating every 6

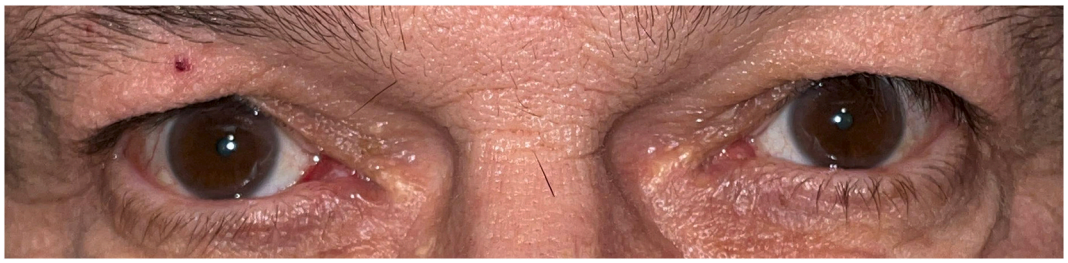

Fig. 3. External Appearance at Time of Lesion Recurrence. External view demonstrates no eyelid lesions and no disruptions to eyelid architecture.

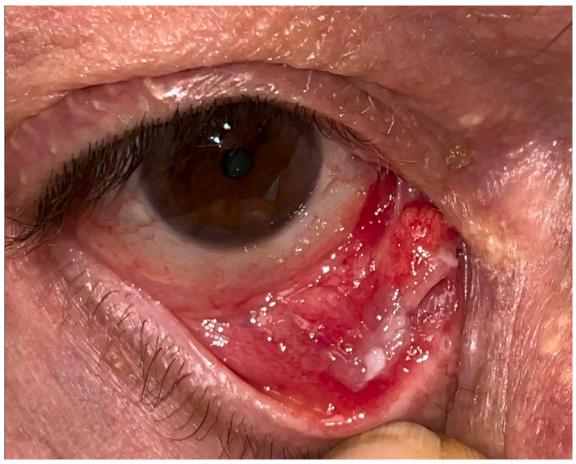

Fig. 4. Clinical Appearance of Recurrent Lesion. Eversion of the right lower eyelid reveals a recurrent lesion of the medial palpebral conjunctiva measuring 13.0 × 6.4 mm, with areas of mucosal thickening and a whitish, keratinized plaque extending around the punctum.

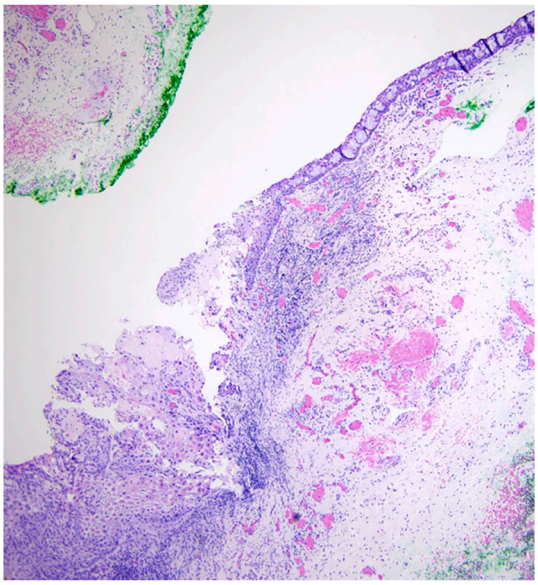

Fig. 5. Histopathology of Full-Thickness Biopsy of Palpebral Conjunctiva. H&E-stained sections from a full-thickness biopsy of the recurrent lesion demonstrate nonkeratinizing stratified squamous epithelium with goblet cells adjacent to markedly atypical regions of keratinizing squamous epithelium. There was marked dyskeratosis with individual cell keratinization and resulting acantholysis with desquamation of the cells both onto the surface and into centers of tumor lobules. The malignant cells showed marked nuclear pleomorphism, prominent nucleoli, mitotic figures, and intercellular bridging.

months with ophthalmology and dermatology have revealed no recurrences to date, with new baseline photography performed at 6-months post-reconstruction (Fig. 6).

3. Discussion

Squamous cell carcinoma (SCC) is an epithelial malignancy characterized by full thickness atypia with increased mitotic activity of the squamous cells.[1] Acantholytic squamous cell carcinoma (ASCC), also called adenoid SCC, is a rare histologic variant of SCC that develops from the loss of desmosome adhesion proteins.[5] ASCC was first described by Lever in 1947 as an adenoacanthoma of the sweat glands.[6] Since then, ASCC has been associated with sun-exposed areas of the head and neck and represents 2–4% of cutaneous SCC cases.[7,8] Rare cases have also been reported as arising on breasts,[9] oral cavity,[10] esophagus,[11] and penis.[12] ASCC uncommonly develops from the conjunctiva and has previously only been reported to arise from sun-exposed intrapalpebral bulbar conjunctiva.

ASCC is rarely seen around the eyes. One study investigating cutaneous SCC reported that of 1569 SCC cases, only 1.5 % were on the eyelid, and 0 of 82 ASCC variant cases presented on the eyelid.[2] In the largest case series of conjunctival ASCC, Mauriello et al. performed a 12-year review of all ocular SCC cases accessioned at the Armed Forces Institute of Pathology, and identified only 14 cases of conjunctival ASCC.[13] Of these 14 lesions, all were from sun-exposed locations. Seven arose from the corneoscleral limbus, while the others developed elsewhere on the intrapalpebral bulbar conjunctiva. This is consistent with the literature that these rare ocular lesions typically occur in areas of sun and ultraviolet exposure, such as the limbus of the interpalpebral conjunctiva.[3] After conducting a literature review on 2/19/2024 utilizing PubMed and Google Scholar using the key words "squamous cell carcinoma", "acantholytic squamous cell carcinoma", "adenoid squamous carcinoma", "palpebral conjunctiva", "periocular", "and "eyelid", we were unable to identify any prior reports of an acantholytic squamous cell

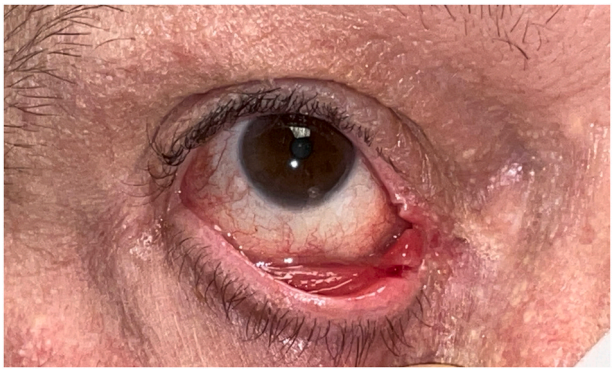

Fig. 6. External Photograph of Eyelids 6 Months After Mohs/Reconstruction. External view with medial lower eyelid everted demonstrates a healed medial tarsal defect of the inferior eyelid with post-granulation changes in mucosa of the inferior fornix. No recurrent squamous neoplasia or keratin is identified.

carcinoma arising from non-sun exposed palpebral/tarsal conjunctiva.

ASCC as a histologic variant may be more aggressive in nature than other forms of SCC. In a large study of 155 cases with ASCC, although only five metastasized, all five patients died as a direct result of the tumors.[7] Another study reported a 19 % mortality rate from 35 cases of ASCC of the skin.[13] In a 2016 retrospective study of patients with ASCC of the conjunctiva, 5 of the 14 cases had recurrent tumors post excision, and three had more than one re-occurrence.[14] In a recent case report of a large ocular surface ASCC arising from the intrapalpebral bulbar conjunctiva, the patient was treated with enucleation, while the eyelids and palpebral conjunctiva remained uninvolved.[15]

Given the aggressive nature of these lesions, it is necessary to distinguish histologically between ASCC and other forms of SCC to determine prognosis and treatment. Treatment of SCC of the conjunctiva has been well-defined as surgical excision and adjuvant therapy including cryotherapy, chemotherapy (5-FU and Mitomycin C), and radiotherapy.[4] Current European guidelines recommend surgical excision with at least 10 mm margins as the ideal treatment for high-risk SCC such as ASCC.[16] An in-depth literature review reveals no standard of care in the treatment of conjunctival ASCC.

This case presents a rare conjunctival ASCC lesion developing in an atypical location, arising from the tarsal conjunctiva of a healthy patient without ectropion, where there is no sun exposure. The course of management and diagnosis is also instructive. Since palpebral/tarsal conjunctiva is adherent to tarsus and cannot be easily mobilized for biopsy, an initial shave biopsy was performed in accordance with the patient's desire to limit disruption of eyelid architecture. This biopsy was superficial and insufficient to provide a definitive histopathologic diagnosis, but resolved all symptoms, prompting the patient to initially delay further treatment. Although SCC was included in the shave biopsy differential along with other benign conditions, the lesion developing in an area without sun exposure prompted less concern for an aggressive malignant etiology, and close monitoring was permitted per patient preference. Upon lesion recurrence, a full-thickness biopsy involving tarsus confirmed a diagnosis of ASCC, and the patient was referred for Mohs surgery for complete surgical excision, with secondary reconstruction. This course highlights the importance of early full-thickness biopsy and illustrates the need to consider aggressive lesions like ASCC even for a lesion of the palpebral conjunctiva, where such a diagnosis would be unexpected. Since there are no prior descriptions in the literature of management for palpebral/tarsal ASSC, this case also provides a framework for management strategies of similar cases in the future.

4. Conclusions

This case demonstrates an atypical location and presentation of a rare acantholytic squamous cell carcinoma, which developed in an area of the palpebral conjunctiva without sun exposure. Aside from smoking, the patient had no significant risk factors for ASCC, with no other skin cancers or evidence of chronic UV exposure, no known HPV infection, and no immunosuppression, xeroderma pigmentosum, or HIV.[17,18] This case highlights the importance of obtaining a full-thickness biopsy to accurately diagnose periocular tumors and ensuring a deep enough section of tissue to rule out invasive carcinoma. Given that ASCC may be more aggressive and have an increased rate of recurrence compared to other variants of SCC, histologic subtyping is vital for guiding clinical management. Based on this report, ASCC should be considered even for concerning conjunctival lesions developing outside the sun-exposed area of the intrapalpebral fissure.

Claims of Priority

After conducting a literature review on 9/22/2023 utilizing PubMed and Google Scholar using the key words "squamous cell carcinoma", "acantholytic squamous cell carcinoma", "adenoid squamous carcinoma", "palpebral conjunctiva", "periocular", "and "eyelid", we did not find any prior reports of an acantholytic squamous cell carcinoma of the palpebral conjunctiva.

Patient consent

The patient provided written consent to publish this case including the use of images.

Funding sources

This work was supported in part by an Unrestricted Grant from Research to Prevent Blindness, Inc. to the UW-Madison Department of Ophthalmology and Visual Sciences. The authors did not receive any funding in relation to this manuscript, and funding organizations had no role in the design or creation of the manuscript.

Authorship

All authors attest that they meet the ICMJE criteria for authorship.

CRediT authorship contribution statement

Asha S. Jain: Writing – original draft. **Nicole B. Duncan:** Data curation. **Heather D. Potter:** Investigation, Data curation. **Cat N. Burkat:** Investigation, Data curation, Conceptualization. **Evan J. Warner:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization.

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

None.

References

1. Donaldson MJ, Sullivan TJ, Whitehead KJ, Williamson RM. Squamous cell carcinoma of the eyelids. *Br J Ophthalmol*. 2002;86(10):1161–1165.
2. Pyne JH, Myint E, Barr EM, Clark SP, David M, Na R. Acantholytic invasive squamous cell carcinoma: tumor diameter, invasion depth, grade of differentiation, surgical margins, perineural invasion, recurrence and death rate. *J Cutan Pathol*. 2017 Apr;44(4):320–327.
3. Kiire CA, Srinivasan S, Karp CL. Ocular surface squamous neoplasia. Int Ophthalmol Clin. 2010 Summer;50(3):35-46.
4. Gichuhi S, Irlam JH. Interventions for squamous cell carcinoma of the conjunctiva in HIV-infected individuals. *Cochrane Database Syst Rev*. 2013 Feb 28;2013(2), CD005643.
5. Ozer EE, Soydemir GP. Acantholytic squamous cell carcinoma of uncommon sites. Adv Can Res & Clinical Imag. 1(4): 2019. ACRCI.MS.ID.000516.
6. Lever WF. Adenoacanthoma of sweat Glands: carcinoma of sweat Glands with Glandular and Epidermal Elements; report of Four cases. *Arch Dermatol Syphilol*. 1947;56(2):157–171.
7. Johnson WC, Helwig EB. Adenoid squamous cell carcinoma (adenoacanthoma). A clinicopathologic study of 155 patients. *Cancer*. 1966; Nov;19(11):1639–1650.
8. Sajin M, Hodorogea Prisăcaru A, Luchian MC, et al. Acantholytic squamous cell carcinoma: pathological study of nine cases with review of literature. *Rom J Morphol Embryol*. 2014;55(2):279–283.
9. Parramore B, Hanly M, Yeh KA, McNeely T. Acantholytic variant of squamous cell carcinoma of the breast: a case report. *Am Surg*. 1999; May;65(5):467–469.
10. Shetty D, Suresh A, Acharya S, Desai A, Anehosur V, Kumar N. Acantholytic variant of squamous cell carcinoma in the mandible: a rare entity and a brief review. *Stomatol*. 2022;24(1):26–32.
11. Lee D. Acantholytic squamous cell carcinoma of the oesophagus with prevalent single isolated tumour cells including signet ring cells and many osteoclast-like giant cells. *Pathology*. 2016;48(3):281–283.
12. Cunha IW, Guimaraes GC, Soares F, et al. Pseudoglandular (adenoid, acantholytic) penile squamous cell carcinoma: a clinicopathologic and outcome study of 7 patients. *Am J Surg Pathol*. 2009;33(4):551–555.

13. Mauriello JA Jr, Abdelsalam A, McLean IW. Adenoid squamous carcinoma of the conjunctiva–a clinicopathological study of 14 cases. *Br J Ophthalmol*. 1997;81(11):1001–1005.
14. Nappi O, Pettinato G, Wick MR. Adenoid (acantholytic) squamous cell carcinoma of the skin. *J Cutan Pathol*. 1989;16(3):114–121.
15. Sharma A, Daigavane S, Bhake A. Invasive acantholytic ocular surface squamous neoplasia: a rare case. *Cureus*. 2023 May 19;15(5), e39219.
16. Stratigos A, Garbe C, Lebbe C, et al. Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. *Eur J Cancer*. 2015;51(14):1989–2007.
17. Wladis EJ, Wrzesinski SH, Rothschild MI, Adam AP. Emerging therapeutic options for periorbital and orbital cutaneous basal and squamous cell carcinomas. *Orbit*. 2023;42(2):117–123.
18. Gichuhi S, Ohnuma S, Sagoo MS, Burton MJ. Pathophysiology of ocular surface squamous neoplasia. *Exp Eye Res*. 2014;129:172–182.