American Journal of Ophthalmology Case Reports 36 (2024) 102178

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Metastatic conjunctival squamous cell carcinoma presenting as infectious sclerokeratouveitis

Ogul E. Uner [a], Roma B. Pegany [a,b], Hillary C. Stiefel [a], Richard D. Stutzman [a], Travis K. Redd [a,*]

[a] Casey Eye Institute, Oregon Health & Science University, 515 SW Campus Dr, Portland, OR, USA
[b] Department of Ophthalmology, University of California, San Francisco, 490 Illinois St, San Francisco, CA, USA

ARTICLE INFO

Keywords:
Ocular surface squamous neoplasia
Conjunctival squamous cell carcinoma
Sclerokeratitis
Pyogenic granuloma
Exenteration

ABSTRACT

Purpose: We describe a case of metastatic conjunctival squamous cell carcinoma (SCC) presenting as an infectious sclerokeratouveitis in a patient with autoimmune disease.

Observations: A 63-year-old Caucasian female presented to the cornea service with a raised perilimbal scleral infiltrate, hypopyon, and corneal perforation concerning for infectious necrotizing sclerokeratoveitis. She had an ocular history of a recurrent "pyogenic granuloma" and her medical history was notable for well-controlled systemic lupus erythematosus and rheumatoid arthritis. Scleral debridement and repair with a corneal patch graft was performed. Bacterial cultures grew 4+ *Proteus mirabilis* sensitive to tobramycin. One month later, she developed bulky painless scleral lesions with leukoplakic features. A scleral biopsy revealed squamous cell carcinoma. Imaging suggested ciliary body and medial rectus infiltration without perineural invasion. Right anterior exenteration was performed as immunotherapy was felt to be unlikely to achieve success in light of her autoimmune conditions. Six months later, she developed a palpable right parotid mass with biopsy confirming metastatic squamous cell carcinoma. She underwent a right parotidectomy and is now undergoing consolidative radiotherapy.

Conclusions and Importance: Ocular surface neoplasia can present as a necrotizing sclerokeratouveitis, contributed by both the tumor and an atypical infectious process. Malignancy with superinfection should be in the differential diagnosis of recurrent ocular surface inflammation.

1. Introduction

Ocular surface squamous neoplasia (OSSN) is a diagnosis that encompasses conjunctival intraepithelial neoplasia, carcinoma in situ, and squamous cell carcinoma (SCC). Clinical presentation can be variable, but most cases present as a gelatinous mass with or without conjunctival feeder vessels or can have a velvety appearance, papilliform pattern, appear nodular or leukoplakic, or present as a diffuse lesion with or without pigmentary changes.[1–5] There have been reports of necrotizing scleritis or sclerokeratitis as presenting signs of conjunctival SCC, appearing as a nodulo-ulcerative mass that delays diagnosis.[6–8] Despite extensive intraocular and orbital involvement in some of these cases, no case had evidence of metastatic disease. Further, involvement of the anterior chamber at presentation in conjunctival SCC, especially with orbital invasion, has not been reported. Here, we present a case of invasive conjunctival SCC in a patient with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) that presented with a superimposed *Proteus mirabilis* infectious sclerokeratouveitis with corneal perforation. The tumor rapidly progressed, invaded the orbit, and metastasized to the parotid gland. We underscore the importance of considering superinfected neoplasms in the evaluation of anterior segment inflammation, especially when inflammation is recurrent.

2. Case report

A 63-year-old White female with a history of well-controlled type 2 diabetes mellitus, SLE on hydroxychloroquine, RA, and myocardial infarction status post coronary artery stent was referred to our cornea service with several weeks of worsening right eye pain and mucopurulent discharge. She had been managed with topical ofloxacin and prednisolone. She had a history of a pterygium along with a history of excision of a perilimbal pyogenic granuloma in this eye, but 8 months later, a nodular "recurrent pyogenic granuloma" had developed near the excision site. No pathology report was present.

* Corresponding author. Casey Eye Institute, Oregon Health & Science University, 515 SW Campus Drive, Marquam Hill, Portland, OR, 97239, USA.
E-mail address: redd@ohsu.edu (T.K. Redd).

https://doi.org/10.1016/j.ajoc.2024.102178
Received 30 April 2024; Received in revised form 5 September 2024; Accepted 25 September 2024
Available online 3 October 2024

On presentation, best-corrected visual acuity (BCVA) in the affected right eye was 20/100 and 20/25 in the left eye. Examination was notable for a 7.5mm × 6.5mm raised superonasal friable nodular scleral infiltrate bordering the limbus that could be easily peeled away at the slit lamp with jewelers forceps (Fig. 1A). There was underlying scleral necrosis with thinning, but no perforation. Adjacent corneal thinning with Descemet's membrane folds and a 2mm layered hypopyon were present. The remainder of the exam, including pupils, extraocular motility, intraocular pressures (IOP), and dilated fundus exam of both eyes was normal. Bacterial and fungal cultures were collected, and she was started on topical tobramycin and amphotericin, both 6 times daily, as well as oral levofloxacin 750mg. Topical prednisolone was rapidly tapered every 3 days. A scleritis workup was unremarkable for syphilis (RPR, FTA), tuberculosis (Quantiferon-GOLD), and granulomatosis with polyangiitis (ANCA). Of note, she was a 60-pack-year former smoker and had significant sun exposure growing up but denied drug use, history of sexually transmitted diseases, or recent travel. She also denied new systemic, joint, lung, abdominal or dermatological symptoms.

The patient was seen the next day and a perforation was noted at the site of sclerocorneal thinning prompting urgent repair via scleral debridement of the necrotic tissue and placement of a limbal halo patch graft. Intraoperative bacterial and fungal cultures were collected. Both preoperative and intraoperative bacterial cultures from the corneoscleral infiltrate grew 4+ *Proteus mirabilis* sensitive to tobramycin. The patient reported improvement in pain after scleral debridement. One month later, she developed 3 new painless 'cauliflower-like' scleral lesions with leukoplakic features around the limbal halo patch graft (Fig. 1B). BCVA was 20/80, the anterior chamber was quiet, and a dilated fundus exam was unremarkable. Repeat scleral debridement with biopsy revealed epithelial cell proliferation with areas of squamous differentiation and marked atypia (Fig. 2A and B). The lesion stained positive for cytokeratin (CKCT), negative for adipophilin, and did not show organisms on Brown & Hopps stain (Fig. 2C). Tumor mutational burden (TMB) was 33 Mut/Mb. A diagnosis of invasive conjunctival SCC was made. She was started on topical 5-fluorouracil (5-FU) four times daily, alternating with prednisolone 1 % weekly and referred to ocular, medical, and radiation oncology services.

Further imaging with ultrasound biomicroscopy showed iris and ciliary body thickening along the 3 o'clock meridian, findings concerning for early intraocular involvement. B-scan ultrasonography was normal. MRI brain and orbits with and without contrast showed a 14mm T2-hyperintense and contrast-enhancing lesion in the superonasal orbit, continuous with the insertion of the right medial rectus muscle without evidence of perineural spread, indicating American Joint Committee on Cancer (AJCC) stage T4a conjunctival SCC (Fig. 1C). Whole-body positron emission tomography (PET) scan was remarkable only for focal radiotracer uptake in the anterior right globe, consistent with the diagnosis.

After 1 month of 5-FU treatment, there was regrowth of bulky confluent nodular scleral lesions (Fig. 1D). BCVA was 20/40 and repeat ultrasound biomicroscopy confirmed the lesions to have grown from 3mm to 6.3mm in thickness. A tumor board was convened with medical and radiation oncology, ocular oncology, cornea, and oculoplastics services. There was a consensus recommendation to treat with anterior exenteration, which was performed by the oculoplastics service. There was no intraocular involvement in the sampled sections from the globe pathology specimen, which showed well-differentiated SCC with involvement of the medial rectus muscle (Fig. 3).

Six months after anterior exenteration, the patient developed a palpable right parotid mass. This prompted a fine-needle aspiration

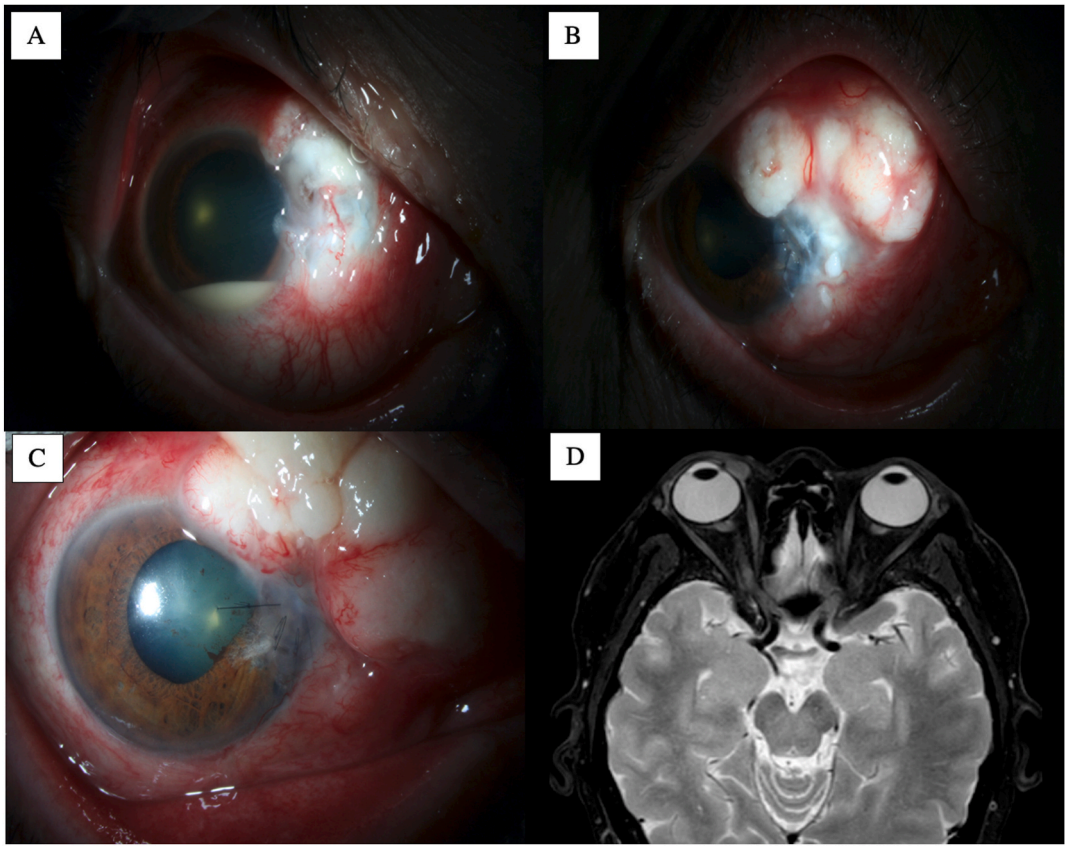

Fig. 1. Slit Lamp and Magnetic Resonance Imaging of Sclerokeratouveitis and Conjunctival Squamous Cell Carcinoma. (A) A scleral infiltrate with keratitis and hypopyon in the right eye on initial presentation. (B) Post-operative month one after repair of limbal perforation demonstrating new scleral nodules (C) that grew into confluent leukoplakic lesions. (D) T2-MRI demonstrates a superonasal conjunctival lesion that extends into the medial rectus muscle insertion site.

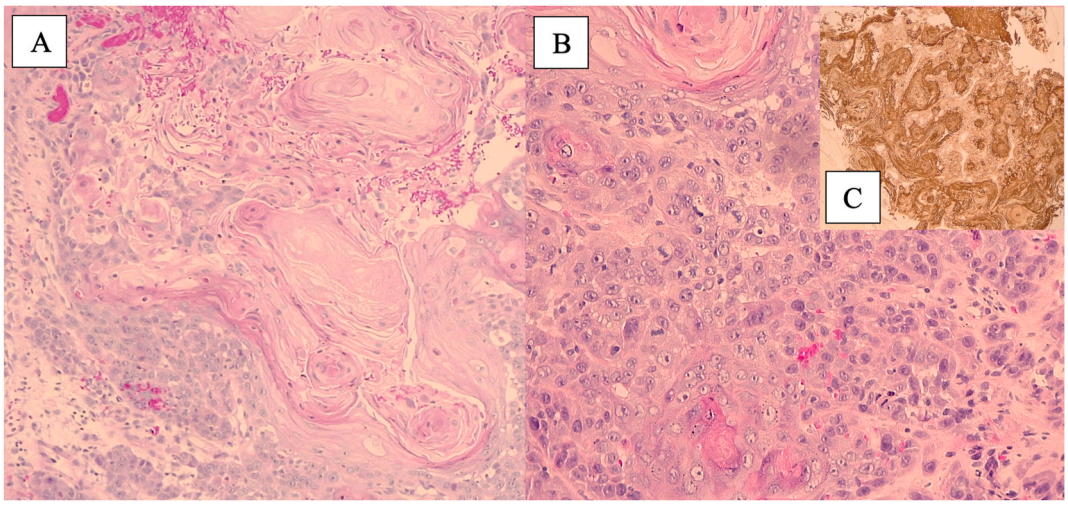

Fig. 2. Histopathology images of scleral biopsy. Hematoxylin and eosin (H&E) stain of the specimen. (A) Squamous cell proliferation with abundant keratin pearls at 10x magnification. (B) Marked cellular atypia at 20x magnification. (C) The specimen shows positive staining with cytokeratin cocktail (CKCT), confirming epithelial origin.

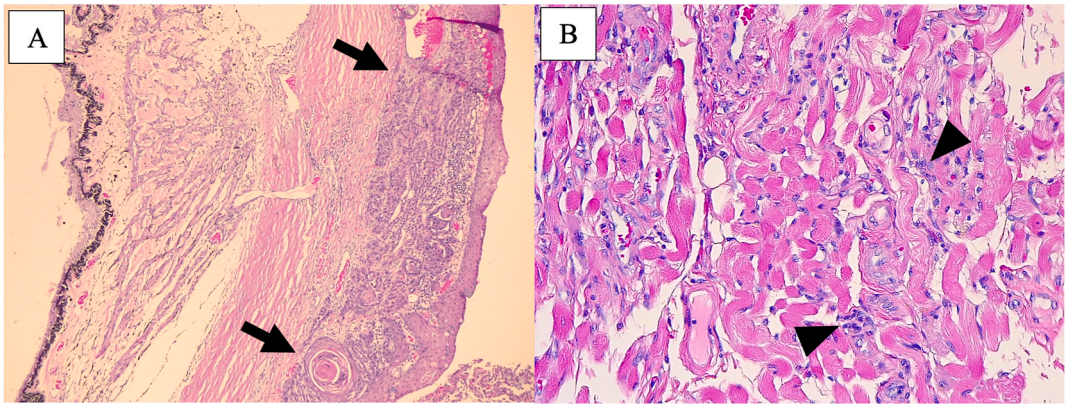

Fig. 3. Histopathology images of globe specimen after anterior exenteration. Hematoxylin and eosin (H&E) stain of the specimen shows well-differentiated squamous cell carcinoma invading the sclera (arrows, A). The tumor was in close proximity to the medial rectus muscle, with atypical squamous cells noted between muscle fibers (arrowheads, B).

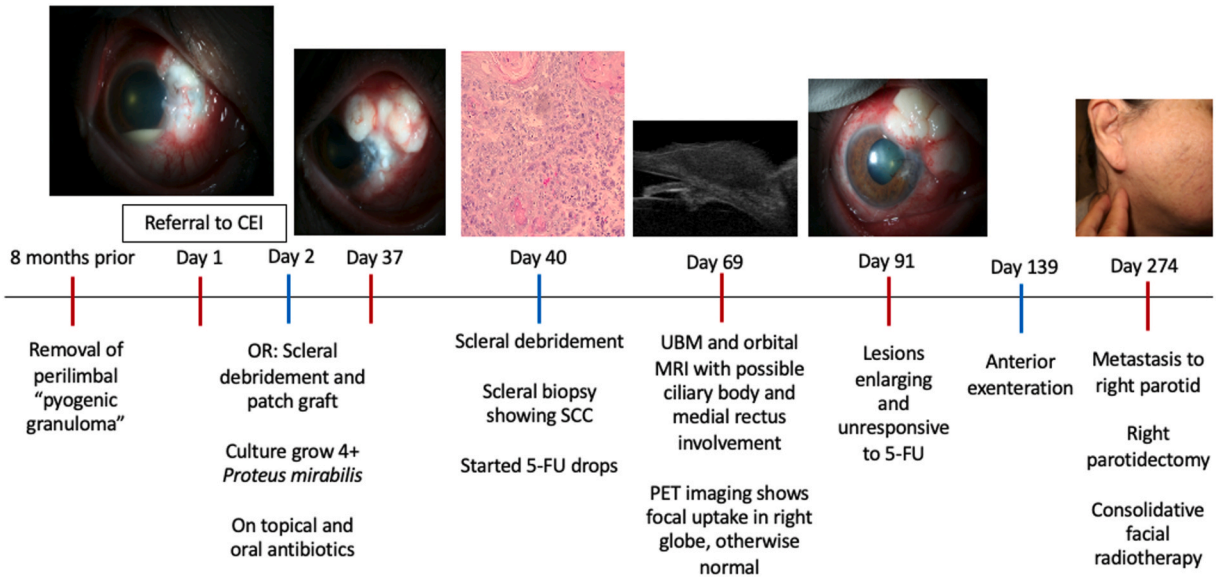

Fig. 4. Patient timeline from initial presentation to diagnosis of metastatic disease. CEI: Casey Eye Institute. 5-FU: Five-fluorouracil.

biopsy that confirmed metastatic SCC. Fine-needle aspiration biopsy of the left parotid gland also showed atypical squamous cells. A repeat whole-body PET scan noted increased radiotracer uptake in several head and neck lymph nodes, in addition to the right parotid gland. The patient underwent right parotidectomy and 24-lymph node neck dissection with the otolaryngology service. Pathology of the right parotid showed moderately differentiated SCC with lymphoid tissue focally investing the tumor without distinct perineural or vascular invasion. There was no clear evidence of SCC in the dissected lymph nodes. The patient continues to receive consolidative facial radiotherapy for metastatic conjunctival SCC (Fig. 4).

3. Discussion

We report a case of invasive, metastatic conjunctival squamous cell carcinoma presenting with superimposed infectious sclerokeratouveitis. Our case is rare in that there was a concurrent atypical *P. mirabilis* sclerokeratouveitis superimposed on a squamous cell malignancy that rapidly invaded the orbit and demonstrated metastases. Diagnosis was delayed due to the atypical presentation and lack of prior pathology from the presumed "pyogenic granuloma." The initial differential diagnosis included infectious and autoimmune etiologies. It is likely that the "pyogenic granuloma" was the beginning of a SCC nodule. A literature search revealed only 2 cases of *P. mirabilis* scleritis, one presenting as a spontaneous scleral abscess in an immunocompetent patient and the other after strabismus surgery.[9,10] The atypical pathogen and the recurrence of leukoplakic nodules were highly suspicious of underlying malignancy. Other features of nodulo-ulcerative conjunctival SCC include ulceration and necrosis of the conjunctiva and sclera, conjunctival thickening, associated feeder vessels, and prominent keratin.[6] Due to significant inflammation, they tend to result in scleral and corneal thinning similar to our case. A high index of suspicion for nodulo-ulcerative SCC in any case of unexplained corneoscleral thinning or perforation is warranted for prompt diagnosis and treatment.[11]

Intraocular invasion of nodulo-ulcerative conjunctival SCC with uveal prolapse and infiltration has been reported.[6,7] Though sclerocorneal perforation occurred in our case, there was no evidence of intraocular involvement on pathological analysis of the exenterated globe specimen. An anterior chamber paracentesis and anterior segment optical coherence tomography (AS-OCT) were not pursued in the initial workup since the clinical appearance was less consistent with a neoplastic process and there was strong bacterial growth from cultures obtained from the ocular surface. AS-OCT in our case may have shown diffuse hyper-reflectivity and bands of hypo-reflective areas corresponding to scleral necrosis and edema, in contrast to the well-demarcated epithelial hyper-reflectivity in SCC.[12]

Our case highlights the rare metastatic potential of invasive conjunctival SCC, which can occur via lymphatic or hematogenous spread. Though there was no clear involvement in the dissected head and neck lymph nodes, the pathology report of the right parotid gland indicated lymphoid tissue within and surrounding the tumor without perineural spread. Primary SCC of the parotid is much rarer than metastatic SCC of the parotid, accounting for less than 3 % of all parotid carcinomas.[13] Squamous metastasis to the parotid is most commonly from cutaneous SCC, which has risk factors similar to conjunctival SCC.[14] Genomic profiling studies have shown that almost all parotid SCC analyzed to date have ultraviolet-induced mutational signature types typical of metastatic cutaneous SCC, questioning primary parotid SCC as a separate entity and making it a diagnosis of exclusion after a thorough metastatic work-up.[14] Although the mutational signature of the parotid specimen was not analyzed in our case, the interval changes in FDG uptake on whole-body PET scan and pathologic features of the parotid specimen support the diagnosis of metastatic conjunctival SCC, presumably from lymphatic spread of atypical squamous cells that may not have been observed in the dissected lymph nodes.

There is no standard of care for treatment of invasive conjunctival SCC, a rare cancer. Though topical treatment was attempted in our case, the patient ultimately required anterior exenteration for local control. Neoadjuvant chemotherapy prior to surgery was considered but not pursued due to patient comorbidities, as well as concern for both intraocular and extraocular muscle involvement that would not have changed the surgical plan. Orbital radiotherapy as primary treatment was also not pursued, as it would have required high doses, be associated with significant ocular and periocular toxicity, and not likely be vision-sparing. However, later, when the patient developed metastatic disease, the oncology services pursued consolidative radiotherapy to the parotid gland without systemic chemotherapy.

Immunotherapy with checkpoint inhibition has been shown to be promising in SCC treatment as the majority of ocular surface SCC expresses programmed death ligand-1 (PD-L1), with expression more prevalent in those with AJCC T3 or higher (79 %) conjunctival SCC than stage 2 or lower (31 %).[15] A case series of 5 patients with AJCC stage T4 tumors and tumor mutation burden >60 Mut/Mb showed treatment with cemiplimab or pembrolizumab achieved complete response in 3 and 1 patients, respectively.[16] Immunotherapy was not pursued for our patient, as there was concern that hydroxychloroquine would counteract treatment efficacy and could cause a lupus or rheumatologic flare. The tumor mutational burden in our case was also significantly lower than those with complete response in the case series, and it is well-documented that a high tumor mutational burden is associated with better immunotherapy response in SCC.[17]

4. Conclusions

Invasive conjunctival nodulo-ulcerative SCC can present with infectious sclerokeratouveitis, invade the orbit, and metastasize if not promptly diagnosed. The differential diagnosis of anterior segment inflammation should include neoplastic etiologies, especially in the setting of risk factors such as autoimmune disease, smoking, and chronic sun exposure. History of recurrent ocular surface lesions should also increase suspicion and surgical samples should always be submitted for pathological analysis.

Patient consent

The patient consented to publication of the case in writing and orally.

Funding

All authors are supported by the National Eye Institute (P30 EY010572, K23 EY032639), Research to Prevent Blindness (Tom Wertheimer Career Development Award in Data Science and unrestricted departmental funding), Collins Medical Trust, and the Malcolm M. Marquis, MD Endowed Fund for Innovation.

CRediT authorship contribution statement

Ogul E. Uner: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization. **Roma B. Pegany:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Hillary C. Stiefel:** Writing – review & editing, Visualization, Investigation, Data curation. **Richard D. Stutzman:** Writing – review & editing, Visualization. **Travis K. Redd:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, 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.

Acknowledgments and Disclosures

RBP is a consultant for Beyeonics. The following authors have no financial disclosures: OEU, HCS, RDS, TKR. All authors attest that they meet the current ICMJE criteria for Authorship.

References

1. Blodi FC. Squamous cell carcinoma of the conjunctiva. *Doc Ophthalmol*. 1973;34(1):93–108.
2. Pe'er J. Ocular surface squamous neoplasia. *Ophthalmol Clin North Am*. 2005;18(1):1–13. vii.
3. Mehta M, Fay A. Squamous cell carcinoma of the eyelid and conjunctiva. *Int Ophthalmol Clin*. 2009;49(1):111–121.
4. Erie JC, Campbell RJ, Liesegang TJ. Conjunctival and corneal intraepithelial and invasive neoplasia. *Ophthalmology*. 1986;93(2):176–183.
5. Lee GA, Hirst LW. Ocular surface squamous neoplasia. *Surv Ophthalmol*. 1995;39(6):429–450.
6. Kaliki S, Freitag SK, Chodosh J. Nodulo-ulcerative ocular surface squamous neoplasia in 6 patients: a rare presentation. *Cornea*. 2017;36(3):322–326.
7. Lindenmuth KA, Sugar A, Kincaid MC, et al. Invasive squamous cell carcinoma of the conjunctiva presenting as necrotizing scleritis with scleral perforation and uveal prolapse. *Surv Ophthalmol*. 1988;33(1):50–54.
8. Mahmood MA, Al-Rajhi A, Riley F, Karcioglu ZA. Sclerokeratitis: an unusual presentation of squamous cell carcinoma of the conjunctiva. *Ophthalmology*. 2001;108(3):553–558.
9. Das N, Das J. Infective scleral abscess by Proteus mirabilis in an immunocompetent patient. *J Clin Ophthalmol Res*. 2018;6(3):113–116.
10. Hemady R, Sainz de la Maza M, Raizman MB, Foster CS. Six cases of scleritis associated with systemic infection. *Am J Ophthalmol*. 1992;114(1):55–62.
11. Kaliki S, Jajapuram SD, Maniar A, et al. Ocular surface squamous neoplasia with intraocular tumour extension: a study of 23 patients. *Eye (Lond)*. 2020;34(2):319–326.
12. Preetam Peraka R, Murthy SI. Role of anterior segment optical coherence tomography in scleral diseases: a review. *Semin Ophthalmol*. 2023;38(3):238–247.
13. Horáková Z, Stárek I, Kalfert D, et al. Primary squamous cell carcinoma of the parotid gland: study and review of the literature. *In vivo*. 2024;38(1):358–364.
14. Bradley PJ, Stenman G, Thompson LDR, et al. Metastatic cutaneous squamous cell carcinoma accounts for nearly all squamous cell carcinomas of the parotid gland. *Virchows Arch*. 2024;485(1):3–11.
15. Nagarajan P, El-Hadad C, Gruschkus SK, et al. PD-L1/PD1 expression, composition of tumor-associated immune infiltrate, and HPV status in conjunctival squamous cell carcinoma. *Invest Ophthalmol Vis Sci*. 2019;60(6):2388–2398.
16. Demirci H, Elner VM, Demirci FY, et al. Immunotherapy for conjunctival squamous cell carcinoma with orbital extension. *Ophthalmology*. 2021;128(5):801–804.
17. Goodman AM, Kato S, Bazhenova L, et al. Tumor mutational burden as an independent predictor of response to immunotherapy in diverse cancers. *Mol Cancer Ther*. 2017;16(11):2598–2608.