Original Article

OSSN in South India: Clinical presentation, treatment outcomes, and histopathologic correlations

Tejaswi Prasad P V, Shanti Radha Krishnan[1], Naveen Radhakrishnan[2], Sahithya Bhaskaran[3], N Venkatesh Prajna

Purpose: This study aimed to analyze the clinical presentation, treatment outcomes, and histopathology features of ocular surface squamous neoplasia (OSSN) in a South Indian population and correlate the area of lesions to the histopathological grade/severity of carcinoma *in situ* (CIN) and squamous cell carcinoma (SqCC) invasive and noninvasive tumors. **Methods:** The study was a retrospective cross-sectional study. The study reviewed electronic medical records (EMRs) of 99 eyes of 99 South Indian patients who underwent en bloc excision and biopsy for tumors in the corneal and conjunctival epithelium with suspicion of OSSN over 1 year from January 2019 to December 2019. Postoperatively, patients were treated with three cycles of topical 0.04% mitomycin C eye drops. Sixty-three had requisite EMR data with a follow-up period of 1 year. **Results:** Patients had equal gender distribution with an age range of 28–83 years. The most common clinical variant was leukoplakic lesion, and the area of the lesion was the only predicting factor for SqCC and CIN. **Conclusion:** Bigger (T2) lesions should be strongly suspected for OSSN and promptly excised. Histopathologic analysis should be performed, and post-op topical mitomycin C or interferon alpha 2b is administered to avoid recurrence. In this study, by correlating the area of the lesion, we introduce a new variable that may aid in clinical prognostication alongside the AJCC classification.

Access this article online

Website: https://journals.lww.com/ijo

DOI: 10.4103/IJO.IJO_909_24

Quick Response Code:

Key words: Conjunctival carcinoma, conjunctival intraepithelial neoplasm, histopathology, ocular surface squamous neoplasia

Ocular surface squamous neoplasia (OSSN) refers to a range of precancerous and cancerous growths on the conjunctiva and cornea, including dysplasia, carcinoma *in situ* (CIN), and invasive squamous cell carcinoma (SqCC).[1,2] Squamous conjunctival carcinoma is the most common ocular malignancy that can cause both vision loss and life-threatening issues. Cancer can spread to nearby structures in the eye and even to other parts of the body, including the cornea, sclera, uvea, eyelids, orbit, sinuses, and brain.[3,4] Recently, there has been an increase in cases of OSSN in India.[5]

OSSN is usually unilateral and commonly associated with middle-aged or older patients, males, immunocompromised patients mainly with human immunodeficiency virus (HIV) infection and post-organ transplantation, and xeroderma pigmentosum. The conjunctival tumor may be the only apparent manifestation of HIV in patients presenting with OSSN; hence, every patient undergoing excision biopsy should be tested for HIV.[1,2,6,7] It typically manifests as a raised or flat, nodular, fleshy, gelatinous growth in the interpalpebral region. Vision is usually not impacted unless the lesion is situated close to the pupil. Common symptoms include swelling, redness, and discomfort. There may be noticeable dilated blood vessels in the vicinity of the lesion. Clinically, it is difficult to distinguish CIN from SqCC. Features like feeder vessels, intrinsic vascularity, and nodular lesion tend to suggest SqCC.[8,9]

All suspected OSSN patients undergo complete and gentle surgical excision using the "no-touch" technique as the treatment of choice. The steps include making a conjunctival incision 4 mm outside the tumor margin, dissecting in the episcleral plane including the conjunctiva and the tenon capsule to reach the limbus, removing thin layers of tumor-free sclera, applying alcohol to the cornea, scrolling off the corneal epithelium, removing the entire tumor in toto, and applying cryotherapy if needed. The conjunctiva is then closed directly or with an amniotic membrane graft.[9]

OSSN has a tendency for recurrence. CIN has the potential to invade the stroma of the conjunctiva and cornea, and in the case of SqCC, studies have shown intraocular and intraorbital recurrence rates of 2%–15% and 12%–16%, respectively.[10,11] Lee and Hirst[1] reported 17% recurrence after excision of conjunctival dysplasia, 40% recurrence after excision of CIN, and 30% recurrence for Squamous cell carcinoma (SqCC) of the conjunctiva. However, using a protocol-based technique, the recurrence rate can be reduced to less than 5%.[9,12,13] While the

Departments of Cornea, [1]Head, Ophthalmic Pathology Laboratory Services, [3]Pediatric Ophthalmology and Strabismus, Aravind Eye Hospital and Postgraduate Institute of Ophthalmology, Madurai, Tamil Nadu, [2]Department of Cornea, Aravind Eye Hospital, Pondicherry, India

Correspondence to: Dr. Tejaswi Prasad P V, Department of Cornea, Aravind Eye Hospital, No. 1, Anna Nagar, Madurai – 625 020, Tamil Nadu, India. E-mail: tejaswiprasadpv@gmail.com

Received: 17-Apr-2024 Revision: 30-Jul-2024
Accepted: 23-Aug-2024 Published: 25-Oct-2024

Cite this article as: Prasad PV, Krishnan SR, Radhakrishnan N, Bhaskaran S, Prajna NV. OSSN in South India: Clinical presentation, treatment outcomes, and histopathologic correlations. Indian J Ophthalmol 2025;73:586-9.

overall outlook is positive, utilizing treatment methods based on results from the histopathologic examination (HPE) can help reduce the likelihood of recurrence.[9] Therefore, it requires appropriate management and close postoperative monitoring.

In this study, we aim to analyze the clinical presentation, treatment outcomes, and histopathology features of OSSN with a protocol-based approach from a single institute in the South Indian population and correlate the area of lesions to the histopathologic grade/severity of CIN and SqCC invasive and noninvasive tumors, which may help in prognostication.

Methods

This is a retrospective study conducted at a tertiary care hospital in South India and approved by the Institutional Review Board. Electronic medical records (EMRs), anterior segment photographs, and pathology reports were reviewed of 99 eyes of South Indian patients who underwent en bloc excision and biopsy for tumors in the corneal and conjunctival epithelium with suspicion of OSSN over a period of 1 year from January 2019 to December 2019 were included in this study. Patients who were suspected of having OSSN, but had a different histopathology diagnosis, insufficient data, or had previously undergone ocular surface intervention were excluded.

Definition

CIN was defined as the presence of dysplastic tumor cells involving the entire thickness of the epithelium with no breach of the basement membrane. It was further classified as mild (CIN 1), moderate (CIN 2), or severe dysplasia (CIN 3), based on the extent of dysplastic lesions. Those involving the basal one-third of the conjunctiva were classified as CIN 1, lesions involving the inner two thirds were classified as CIN 2, and lesions involving the entire thickness with no breach of basement membrane were classified as CIN 3 [Fig. 1]. *In situ* SqCC was defined as a lesion made up of malignant-appearing squamous epithelial cells that are confined to the basement membrane. Invasive SqCC [Fig. 2] was defined as a lesion that involves the substantia propria, and locally invasive lesions involve the adjacent adnexa and orbit.[2,14] According to the American joint committee on cancer classification of SqCC of conjunctiva 8th edition, clinically lesions were classified as small (Tis and T1) and large (T2).

Routine preoperative evaluation was performed, including an enzyme-linked immunosorbent assay–tridot test to rule out HIV infection. Excision biopsy was considered the first-line treatment for the lesions included in the study, following the institute's protocol. Patients underwent a gentle wide surgical excision 4 mm outside the clinically determined tumor margin using a no-touch technique, followed by double freeze–thaw cryotherapy of the margin and base. Postoperatively, patients were advised to use topical antibiotic and steroid eye drops. If the HPE report did not document the extent of free margin clearance or if the tumor involved the surgical margin, patients with CIN 3 and SqCC were treated with three cycles of topical 0.04% mitomycin C eye drops, administered three times per day for 2 weeks, followed by a 2-week treatment-free interval for three cycles. Patients were followed up for 1 year to monitor for recurrence.

Patients' demographic information, such as age and gender, and presenting symptoms, including conjunctival growth, pain, photophobia, irritation, and redness, were obtained from the EMRs. Patients' medical history, including any history of cancer, HIV, hepatitis B, and xeroderma pigmentosum, was also retrieved. Clinical information, including the location, area, and appearance of lesions like leukoplakic [Fig. 3], nodular, diffuse, and papillomatous [Fig. 4], as well as the presence of feeder vessels and recurrences during 1-year follow-up period, was recorded. Histopathology results were also obtained and classified as conjunctival intraepithelial neoplasm 1, 2, 3 and squamous cell CIN and invasive.

Data were statistically analyzed using Statistical Package for the Social Sciences (SPSS) statistical software (ver. 12; SPSS, Inc., Chicago, IL, USA), and statistical significance was defined as a P value <0.05.

Results

Of the 99 eyes of 99 patients who underwent en bloc excision biopsy, 63 eyes with requisite EMRs and HPE data were included in the study. The mean age at presentation was 55.11 years (median 55 years; range 28–83 years). There were 35 males (55.56%) and 28 females (44.44%). The most common complaint among patients was conjunctival growth (57%), followed by irritation (36.5%), redness (28.5%), pain (22%), photophobia (9.5%), and incidental findings (9.5%).

The right eye was more commonly affected (57%) than the left eye (43%). Nasal and temporal OSSN were equally (49.21%)

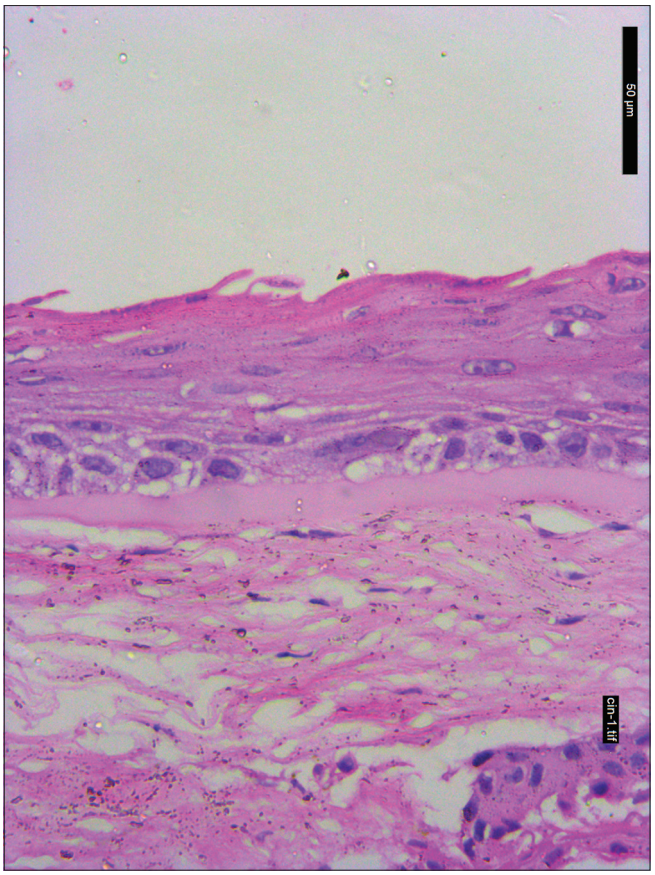

Figure 1: HPE microscopic picture of carcinoma *in situ* – 3. HPE = histopathologic examination

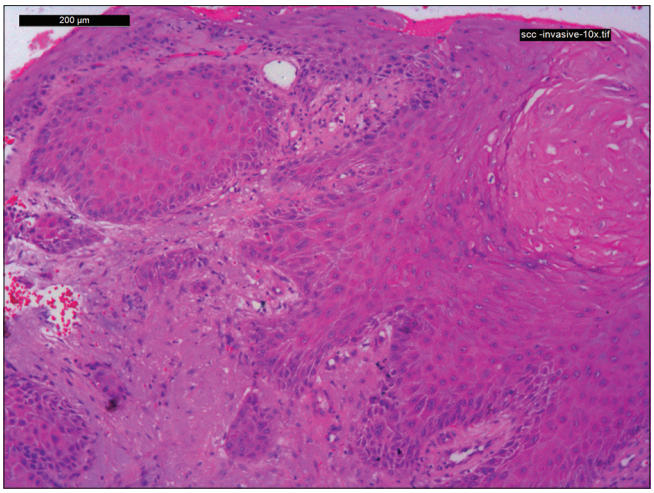

Figure 2: HPE microscopic picture of invasive squamous cell carcinoma. HPE = histopathologic examination

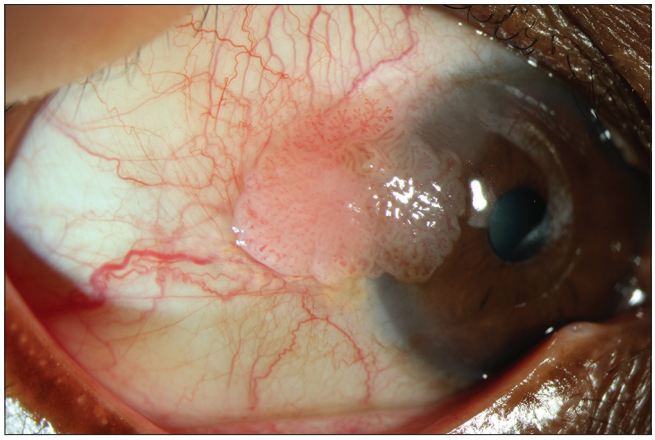

Figure 4: Clinical picture of papillomatous OSSN with feeder vessels and internal vasculature. OSSN = ocular surface squamous neoplasia

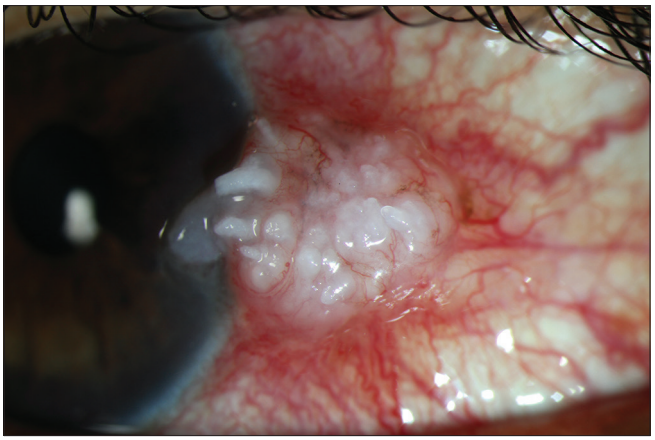

Figure 3: Clinical picture of leukoplakic OSSN with keratin and feeder vessels. OSSN = ocular surface squamous neoplasia

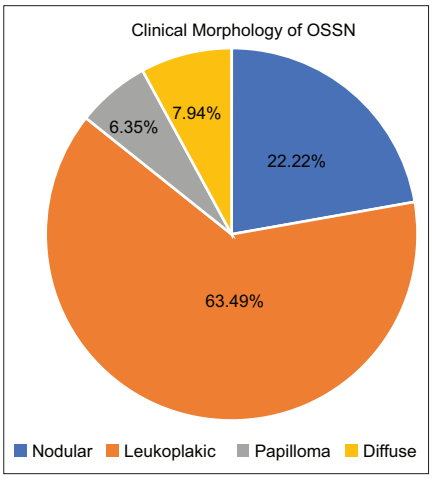

Figure 5: Pie chart showing the clinical morphology of OSSN. OSSN = ocular surface squamous neoplasia

reported, while one patient (1.59%) had corneal OSSN. The most common clinical appearances of the condition were leukoplakic (63%), nodular (22%), diffuse (8%), and papillomatous (7%) [Fig. 5].

The area of the lesion was significantly larger in SqCC (Interquartile Range (IQR) 16 mm^2, range 15–30 mm^2) compared to CIN [Fig. 1] (IQR 9 mm^2, range 4–5.5 mm^2), with a *P* value of 0.003 (Mann–Whitney test).

Variables such as HIV status, laterality, and presence of feeder vessels were not found to be statistically significant. HPE revealed that 30% of cases were SqCC [Fig. 2] and 70% were CIN. Among 44 CIN patients, CIN 1 was 19.04% (range 2–14 mm^2), CIN 2 was 25.4% (1–35 mm^2), and CIN 3 was 25.4% (5–42 mm^2). Among 19 SqCC patients, 26.66% had *in situ* SqCC (10.5–21 mm^2) and 73.33% had invasive SqCC (4–120 mm^2) [Tables 1 and 2].

Three eyes (4.76%) developed recurrences within 1 year of follow-up and required further management. Three patients (4.76%) who were diagnosed with HIV underwent excision biopsy, with two having CIN 2 and one patient undergoing exenteration for invasive SqCC.

Discussion

OSSN reporting is increasing globally and in India as well with the increase of HIV.[7,15] In the West, the average age at diagnosis is 63–69 years, with a male predominance.[16,17] In India, the average age at diagnosis has been around 45–49 years, with a male predominance.[5,18] In our study, the average age was 55.11 years, with a slight male predominance. In contrast, many African studies report much lower mean ages at diagnosis ranging from 33 to 39 years, with a female predominance attributed to a strong association with HIV prevalence.[19,20] Gichuhi *et al*.[15] concluded in their review article that Africa has the highest incidence in the world, and that African women are at a higher risk of developing OSSN due to a higher prevalence of HIV and Human Papilloma Virus (HPV).

There is no previous literature associating the area of the lesion with the risk of SqCC or CIN. This study establishes that a larger lesion increases the risk of it being OSSN significantly. In contrast, SqCC cannot be ruled out in smaller lesions. We found that the smallest area for invasive SqCC is 4 mm^2. Other variables such as feeder vessels, laterality, and location (nasal/temporal) were not significant in determining the nature of the lesion.

Hence, any suspected OSSN lesion should be promptly treated with standard management, that is, wide excision biopsy with no-touch technique and cryotherapy of the

Table 1: Lesion area in CIN and SqCC

HPE	Mean (mm²)	Range (mm²)	Percentage (*n*)
CIN 1	8.33	2–14	19.04% (12)
CIN 2	12.00	1–35	25.40% (16)
CIN 3	16.00	5–42	25.40% (16)
SqCC	26.50	4–120	30.16% (19)

CIN=carcinoma *in situ*, HPE=histopathologic examination, SqCC=squamous cell carcinoma

Table 2: Lesion area in SqCC

HPE	Mean (mm²)	Range (mm²)	Percentage (*n*)
In situ	15.37	10.5–21	26.66% (4)
Invasive	29.46	4–120	73.33% (15)

HPE=histopathologic examination, SqCC=squamous cell carcinoma

margin and base. Depending upon the HPE report, patients should be treated with topical chemotherapy with Mitomycin C (MMC) or interferon alpha 2b. With such a standardized treatment protocol, our study has shown a low recurrence rate of 4.76%. Since larger lesions have a significantly higher risk of being invasive OSSN, they should be treated early with regular follow-ups, and immunocompromised patients should be followed up more frequently.

The study has several strengths, including a large cohort of OSSN patients without prior treatment and a standardized treatment protocol from a single institute, allowing precise outcome assessment. However, the retrospective design, short 1-year follow-up period, and lack of preoperative Anterior segment optical coherence tomography and ultrasound biomicroscopy (AS-OCT and UBM) scans are limitations. A prospective study comparing the outcomes of medical management alone versus surgical management for less-severe cases, along with AS-OCT and UBM-based comparison, is suggested for future research.

Conclusion

To sum up, in our study, the leukoplakic lesion is the most common morphologic variant. The only variable that could predict SqCC/CIN was the area of the lesion. Smaller lesions (Tis/T1), however, do not exclude SqCC**.** Larger lesions should be strongly suspected for OSSN and promptly excised and sent for histopathologic analysis. In this study, by correlating the area of the lesion, we introduce a new variable that may aid in clinical prognostication alongside the AJCC classification. Depending on the histopathology reports, post-op chemotherapy with topical mitomycin c or interferon alpha 2b avoids recurrence.

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

References

1. Lee GA, Hirst LW. Ocular surface squamous neoplasia. Surv Ophthalmol 1995;39:429–50.
2. Shields C, Shields J. Tumors of the conjunctiva and cornea. Indian J Ophthalmol 2019;67:1930.
3. Berenbom A, Milman T, Finger PT. FIT biopsy for conjunctival squamous cell carcinoma with extensive intraocular invasion. Graefes Arch Clin Exp Ophthalmol 2008;246:467–9.
4. Walsh-Conway N, Conway RM. Plaque brachytherapy for the management of ocular surface malignancies with corneoscleral invasion. Clin Exp Ophthalmol 2009;37:577–83.
5. Dandala PP, Malladi P, Kavitha. Ocular surface squamous neoplasia (OSSN): A retrospective study. J Clin Diagn Res. 2015;9:NC10-3.
6. Rathi SG, Ganguly Kapoor A, Kaliki S. Ocular surface squamous neoplasia in HIV-infected patients: Current perspectives. HIV AIDS (Auckl) 2018;10:33-45.
7. Pradeep TG, Gangasagara SB, Subbaramaiah GB, Suresh MB, Gangashettappa N, Durgappa R. Prevalence of undiagnosed HIV infection in patients with ocular surface squamous neoplasia in a tertiary center in Karnataka, South India. Cornea 2012;31:1282–4.
8. Farah S, Baum TD, Conton MR. Principles and practice of ophthalmology. In: Albert DM, Jakobiec FA, editors. Tumours of Cornea and Conjunctiva. 2nd ed. Philadelphia: WB Saunders; 2000. p. 1002-19.
9. Honavar S, Manjandavida F. Tumors of the ocular surface: A review. Indian J Ophthalmol 2015;63:187-203.
10. Othman IS. Ocular surface tumors. Oman J Ophthalmol 2009;2:3-14.
11. Tunc M, Char DH, Crawford B, Miller T. Intraepithelial and invasive squamous cell carcinoma of the conjunctiva: Analysis of 60 cases. Br J Ophthalmol 1999;83:98–103.
12. Cervantes G, Rodríguez AA, Gómez Leal A. Squamous cell carcinoma of the conjunctiva: Clinicopathological features in 287 cases. Can J Ophthalmol 2002;37:14–20.
13. Shields CL. Conjunctival nevi: Clinical features and natural course in 410 consecutive patients. Arch Ophthalmol 2004;122:167-75.
14. Pe'er J, Frenkel S, Singh AD. Conjunctival and corneal tumors: Ocular surface squamous neoplasia. In: Pe'er J, Singh AD, Damato BE, editors. Clinical Ophthalmic Oncology. Cham: Springer International Publishing; 2019. p. 159–84. Available from: http://link.springer.com/10.1007/978-3-030-06046-6_15. [Last accessed on 2024 Jan 09].
15. Gichuhi S, Sagoo MS, Weiss HA, Burton MJ. Epidemiology of ocular surface squamous neoplasia in A Africa. Trop Med Int Health 2013;18:1424–43.
16. Darwich R, Ghazawi FM, Le M, Rahme E, Alghazawi N, Zubarev A, *et al*. Epidemiology of invasive ocular surface squamous neoplasia in Canada during 1992–2010. Br J Ophthalmol 2020;104:1368–72.
17. Kao AA, Galor A, Karp CL, Abdelaziz A, Feuer WJ, Dubovy SR. Clinicopathologic correlation of ocular surface squamous neoplasms at Bascom palmer eye institute: 2001 to 2010. Ophthalmology 2012;119:1773–6.
18. Kaliki S, Vempuluru VS, Ghose N, Gunda S, Vithalani NM, Sultana S, *et al*. Ocular surface squamous neoplasia in India: A study of 438 patients. Int Ophthalmol 2022;42:1915–26.
19. Yousef YA, Finger PT. Squamous carcinoma and dysplasia of the conjunctiva and cornea. Ophthalmology 2012;119:233–40.
20. Makupa II, Swai B, Makupa WU, White VA, Lewallen S. Clinical factors associated with malignancy and HIV status in patients with ocular surface squamous neoplasia at Kilimanjaro Christian Medical Centre, Tanzania. Br J Ophthalmol 2012;96:482–4.