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DEMOGRAPHIC CLINICAL PRESENTATION AND TREATMENT OUTCOME OF OCULAR SURFACE SQUAMOUS NEOPLASIA

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ABSTRACT **Purpose:** The aim of the study is to analyze demographic, clinical profile and treatment outcome of ocular surface squamous neoplasia (OSSN). **Methods:** It was a retrospective study and analysis of 36 eyes (36 cases) diagnosed with OSSN, treated at teritiary eye care center over 3 years. **Results:** The median age of the treated patients was 53 years, patients with outdoor activity were 77.7% (28/36), while human immunodeficiency virus infection (2/36) with predisposing conditions had a younger median age of (32 years). Carcinoma insitu was found in half of the patients n=18 (50%) and treatment advised was wide local excision (4 mm margin clearance) with cryotherapy followed by topical treatment with mitomycin-c 0.04% . Overall, complete regression was achieved in all cases during a mean follow-up of 16.8 ± 3.65 months. No recurrence was seen. **Conclusion:** Although OSSN is associated with old age, earlier onset of OSSN is seen in patients with systemic predisposing conditions. Males and females are equally prone to OSSN. Most of the patients with OSSN belong to 41-60 years age group. In HIV positive patients, OSSN appeared at an early age and was more aggressive in nature. Nasal quadrant was most commonly involved and the tumor epicenter was limbus. Most common symptom was mass or growth followed by redness and diminution of vision. Sunlight exposure is a major risk factor. Carcinoma insitu was most common histopathological diagnosis followed by Dysplasia and Squamous cell carcinoma. Surgical excision and cryotherapy followed by topical Mitomycin-C weekly on and off for 3-4cycles is associated with best control of primary OSSN with no tumor recurrence.

KEYWORDS : mitomycin-c, epicenter, carcinoma in-situ, ocular surface squamous neoplasia,

Ocular surface squamous neoplasia (OSSN) refers to epithelial squamous malignancies, ranging from dysplasia to invasive squamous cell carcinoma. OSSN has worldwide incidence of 0.02–3.5 cases per 100,000 people.[1] The incidence was higher in tropical countries (countries closer to the equator).[2] Usually OSSN occurs in the sixth and seventh decades of life. But, in immunocompromised individuals, OSSN may occur at a younger age.[3,4]

Factors responsible for OSSN are exposure to ultraviolet radiation, human immunodeficiency virus (HIV) infection, human papillomavirus infection[5],heavy cigarette smoking[6,7] ,exposure to petroleum products, male sex and 6th-7th decade age.[5,6,7,8,14,19,2]

The standard practice for treatment of OSSN is wide surgical excision with "no-touch" technique [9] and adjunctive cryotherapy, followed by chemotherapeutic agents like 5-fluorouracil, Mitomycin-C (MMC) or interferon-a 2b (IFNα2b).[10] This is a report of our findings of current demographic and clinical profile, and the treatment outcome of patients presenting with OSSN at a tertiary eye care center in Visakhapatnam.

METHODS

Retrospective analysis of medical records of all patients admitted and clinically diagnosed with OSSN between January 2014 to December 2016 were reviewed. Institutional ethical committee approval was obtained for the study,(IEC Reg.No:IRB0000712 Institutional Research Board of Sankar Foundation Eye Hospital and Institute of Ophthalmology)

All the in-patient records of Ocular surface tumors were reviewed, the demographic and clinical history details of the patients include duration of symptoms, age at presentation, gender, laterality, occupation, duration of symptoms, risk factors (history of ocular trauma or surgery, sunlight exposure, any predisposing conditions, genetically predisposed state), and previous treatment history. Clinical and investigational data by slit lamp bio-microscopy, gonioscopy and laboratory investigations were recorded. Post-operative investigational data was collected from pathology laboratory. Follow-up data of Snellen's visual acuity charts, slit lamp bio-microscopy were also recorded for patients diagnosed in between January 2014 to December 2016. All clinically relevant data was extracted from clinical case records and entered in study proforma.

Clinical characteristics (Figure1) of the tumor were noted, which included location, extent, tissues involved presence laterality, epicenter, location growth pattern (nodular/sessile), clinical type (pappilliform, gelatinous, fungating, ulcerative), leukoplakic, pigmentation, localized or diffused, and lymph nodal or systemic metastasis.

INCLUSION CRITERIA:

(1) Cases diagnosed clinically and confirmed as ocular surface squamous neoplasia by histopathology. (2) Cases that were followed up for ≥ 1 year.

EXCLUSION CRITERIA:

(1) Non-consenting patient (2) Non-cooperative patient (3) Poor general condition (4) Single eye patient (5) Recurrent OSSN (6) Followed up for less than 1 year.

Data analysis:

The observations were recorded in spread sheets (Microsoft® Excel®2013). Tables and graphs were prepared and analysed by using spread sheets. Descriptive statistics (mean, standard deviation, median and range) were calculated for quantitative parameters.

RESULTS :

A total of 45 patients diagnosed with OSSN and 9patients were excluded from sudy, 36 patients were included in the study, 9cases were not included due to non consent-2, Single eye-1 lost to followup-6. The median age of presented patients was 53 years (range: 29–80 years). 14 patients-38.8% (14/36) were younger than 50 years at presentation. Females-56% out numbered males 44%. 89%(n = 32) of the patients belonged to lower middle class and lower class on assessment of socioeconomic status. 77.7% of the patients (28/36) were involved in outdoor occupation, Of 36 patients, 41.66%(17/36) had prolonged history of sun exposure. Histopathology reports of all patients were available and Carcinoma in-situ was found in half of the patients n=18 (50%), Dysplasia in n=11(31%) and Squamous cell carcinoma in n= 7 (19%) . HIV (n = 2) 5.5%, OSSN was the presenting feature in the HIV patient. The median age of the two HIV presented patients was 32 years.

Demographic and Clinical details: Table1,Mean duration of symptoms was 8.1 months. The presenting symptom was an ocular surface mass in n=19, 53% of cases and redness in n=8, 22% of cases. Out of the 36 cases studied, the left eye was involved in 22(61%)

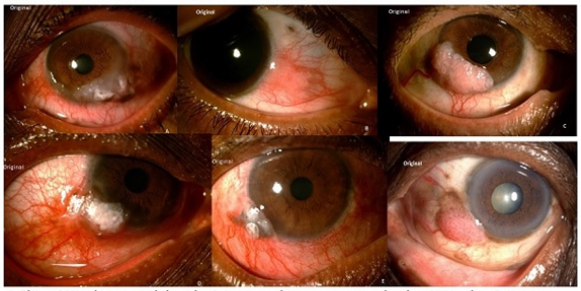
patients. Right eye was involved in 14 (39%). OSSN was most commonly noticed at nasal quadrant in 18 (50%) patients. Temporal and inferior quadrant was involved in 10(28%) and 2 (5%) respectively. We did not find any patient with superior quadrant involvement. 6 patients (17%) had diffused involvement. Tumor epicenter was located at limbus in 16(44%) followed by bulbar conjunctiva in 8 (22%), cornea in 6(17%) patients, while it was diffused in 6 (17%) patients. The most common site of involvement was the limbus. No lymph nodes and no intraocular involvement, no distant metastasis was noticed. Majority of tumors are gelatinous appearance n=26(72.2%) and with nodular growth pattern n=34(94.4%). According to *AJCC grading of tumor T_1 02(5.5%), T_2 04(11.1%), T_3 30(83.3%), T_4 0. Leukoplakia was seen in 16(44.5%), pigmentation in 24(66.6%) cases.

Table 1: Demographic Clinical characteristics of ocular surface squamous neoplasia (n=36)

Gender distribution	**N=36**
Male	16(44%)
Female	20(56%)
Age Distribution	**N=36**
21-40	7(20%)
41-60	21(58%)
61-80	8(22%)
Laterality	**N=36**
Right eye	**14(39%)**
Left eye	**22(61%)**
Quadrant involved	**N=36**
Nasal	18(50%)
Temporal	10(28%)
Inferior	2(5%)
diffuse	6(17%)
Clinical appearance	N=36
Gelatinous	26(72.2%)
Papilliform	10(27.8%)
Growth pattern	N=36
Nodular	34(94.4%)
Sessile	2(5.5%)
Feeder vessels	N=36
Present	36(100%)
Absent	0
Pigmentation	N=36
Present	24(66.6%)
Absent	12(33.3%)
Leukoplakia	N=36
Present	16(44.5%)
Absent	20(55.5%)
Epicenter	**N=36**
Limbus	16(44.4%)
Conjunciva	8(22.2%)
Cornea	6(16.6%)
Diffuse	6(16.6%)
AJCC* staging	**N=36**
T1	02(5.5%)
T2	04(11.1%)
T3	30(83.3%)
Symptoms	**N=36**
Mass	19(53%)
Redness	8(22%)
Diminution of vision	7(19.5%)
Nonspecific	2(5.5%)
Duration of symptoms	N=36
<6months	11(31%)
6-12 months	16(44%)
>12months	9(25%)
Outdoor activity	N=36
<2hrs	2(5%)
2-4hrs	6(17%)
4-6hrs	11(31%)
>6hrs	17(47%)

***AJCC- American joint committee on cancer**

Figure1:Clinical photographs showingthe clinical presentation of various types of OSSN



A. Diffuse OSSN with leukoplakia involving 6 clock hours, limbus, cornea and conjunctiva of HIV patient, B. Nodular gelatinous Dysplasia. C. Papilliform Squamous cell carcinoma involving limbus and cornea. D. Nodular gelainous Carcinoma in-situ with leokoplakia, E. Pigmented Nodular Carcinoma in-situ. F. Papilliform conjuntival Carcinoma in-situ.

Treatment and follow-up:Table2

Excision with no touch technique and Cryotherapy were the standard treatments. The defect created by excision was closed by Amniotic membrane graft in 19 (53%) patients, while it was closed with Conjunctivo limbal autograft in 5(14%) patients. Excision and Cryotherapy alone with no placement of graft, was done in 9 (25%) patients. Excision, Cryotherapy and Corneal patch graft placement was done in 3 (8%) patients, followed by topical Mitomycin-c 0.04% 4imes [Out of 36 patients, 20(56%) patients received 3 cycles and 16(44%) patients received 4 cycles]. Mean follow-up ranged from 12 to 26 months with a mean and standard deviation of 16.86 and 3.65 months, respectively. **Figure 2**,The main outcome measures checked were tumor recurrence and medication related toxicity. None of the patients in our study reported any serious side effects due to MMC. Few patients complained of mild to moderate eye redness and irritation that was controlled with lubricants and corticosteroid eye drops. On each follow up visit, Rose Bengal staining was done to look for any recurrence. We found no recurrence in our study patients during the follow up period.

Table2: Treatment and Hisopathological diagnosis of OSSN

Surgical procedure	N=36
Excision +cryotherapy	9(25%)
Excision +cryotherapy+AMG	24(67%)
Excision +cryotherapy+corneal patch graft	3(8%)
Histopathological diagnosis	N=36
Dysplasia	11(31%)
CIS	18(50%)
SCC	7(19%)
Treatment with MMC 0.04%	N=36
3cycles	20(56%)
4cycles	16(44%)

Figure 2 Before and after treatment of OSSN in HIV Patient.

A. Diffuse and gelatinous Carcinoma in-situ involving 6clock hrs of limbus, cornea and conjunctiva wih Leukoplakia- before treament, B. After treatment.

DISCUSSION

Ocular surface sqamous neoplasia has worldwide incidence of 0.02–3.5 cases per 100,000 people.[1] The incidence was higher in tropical countries.[2] Usually OSSN occurs in the sixth and seventh decades of life. But, in immunocompromised and HIV individuals, OSSN may occur at a younger age.[3,4] Factors responsible for OSSN are exposure to ultraviolet radiation, human immunodeficiency virus (HIV) infection, human papilloma virus infection[5],heavy cigarette smoking[6,7], exposure to petroleum products and 6th and7th decades of age.[5,6,7,8,14,19,20]

The aim of this study is to evaluate demographic patterns, clinical presentations and surgical outcome of OSSN. Like most studies, even in our study most of the patients belonged to the 41-60 year age group. Lee and Hirst et al[11] , in their study found that the average age of OSSN patients is 56 years. In our study, mean age of patients was 53.25 years and the median age of the patients was 53.50 years. A majority of the

cases presented during the fifth to sixth decade with a marked male preponderance have been reported in other studies.[11,12,13,14,23] we found that the age of onset in HIV patients n=2(5.5%) is a mean of 32 years with less than six months of symptomatic duration.[8,15,16] Younger age of presentation in HIV-positive individuals has been reported from other developing countries.[17,18,24,25] our findings also support the same. Studies from Africa, OSSN occurred at earlier age and female preponderance in HIV infected patients and was often more aggressive than in immuno-competent patients. According to previous studies, prevalence of OSSN is higher among men than in women.[19,20,23] In our study, we did not find any statistically significant sex preponderance, female patients outnumbered the male patients (56% vs 44%). There is very less literature available regarding laterality and location of OSSN. One case control study done by Saurabh kamal et al[19] shows no statistically significant laterality involvement. In our study too, we did not find any statistically significant relation, the left eye was involved more than the right eye. In a study done by Sheetal Chauhan et al.[20] left eye was involved in 64% of patients. In the same study, Nasal quadrant was most commonly involved. In our study also 50% of the patients had nasal quadrant involvement. According to most of the studies, tumor epicenter commonly involved was limbus[13,18,28]. In our study also, in 44% patients tumor epicenter was located at limbus, 22% at conjunctiva. Most common presenting complaint in our study was mass growth followed by redness and diminution of vision. Duration of symptoms showed nearly 70% patients presented beyond six months. Various studies done in the past support the same.

In our sudy sunlight exposure is an established major risk factor for development of OSSN. In our study too, 78% patients had daily exposure of sunlight more than four hours. Majority of tumors are gelatinous appearance n=26(72.2%) and wih nodular growth pattern n=34(94.4%). Chauhan *et al*.[13] Dandala *et al*.18 and *Meel R, Dhiman R* et al.[28] also reported nodular pattern is the most common growth pattern. Based on the clinical characteristics, the AJCC grading of majority of the tumors were in stageT_3 n=30(83.3%) at clinical presentation, as the limbus is the most common site of origin for OSSN, tumor size more than 5mm size involved adjacent cornea and conjunctiva, our findings are supporting with Shields et al.[21] and Shah et al.[22] 63% and 86%respectively. Leukoplakia was seen in 16(44.5%), pigmentation in 24(66.6%) cases.

Excision biopsy and cryotherapy was performed in all the patients we studied. Histopathologically, Carcinoma insiu was most common followed by Dysplasia and Squamous cell carcinoma. In our study 50% patients had CIS. Both CIS and Dysplasia patients were included in single group of Conjuntival corneal intraepithelial neoplasia (CCIN). In our study CCIN accounts for almost 80% of the patients. Study done by Shields et al[14]. found that CCIN accounts for 39% of all premalignant and malignant lesion of conjunctiva. Saurabh Kamal et al[19] also found that CIN was more common than SCC in controls while SCC was more common in HIV patients. In some other studies, they found SCC was more common than CIN.

All the patients in our study, after histopathological confirmation of OSSN were given topical MMC (0.04%) eye drops. Surgical margins negative cases were given three cycles of MMC while margins positive and HIV positive cases given one extra cycle of MMC treatment. The minimum follow up period in our study was 12 months while maximum was 26 month. The mean follow up period was 16.86 month. In this period we did not find any patient with recurrence of OSSN which is in also noiced by Chen et al.[26], A. Gupta et al.[27] Shields et al.[29]also found no tumour recurrence. Shashikala Puttaswamy et al.[30] found recurrence in one patient with success rate of almost 92% in 40-49 months of follow up period. In our study there is no intraocular invasion or distant metastasis noiced, where as Meel R, Dhiman R et al[28] reported 12% (7/57) of T3 tumors in this study had intraocular extension. Metastasis is rare in OSSN with a reported incidence of 0%–16% in cases of squamous cell carcinoma.[31] In the present study, over all (36/36) 100% patients were disease free at a mean follow-up of 16.8 ± 3.65 months.

Inherent limitations

Despite all efforts, our study has some limitations: Single centre study, Small sample size, so may not be truly representative of all OSSN patients and involvement of only primary OSSN patients as study participants, so clinical profile of recurrent OSSN was not studied.

CONCLUSION

Our study is a retrospective, single centered, observational study. It included 36 patients who have been histopathologically diagnosed as Dysplasia, carcinoma in-situ and Ocular Surface Squamous Neoplasia after excision biopsy. Demographics and clinical presentations of OSSN were studied along with frequency of different histological presentations and their treatment outcome.

The following conclusions are drawn from the present study:

Males and females are equally prone to OSSN. Most of the patients with OSSN belong to the 41-60 years age group. In HIV positive patients, OSSN appears at an early age and is more aggressive in nature. Nasal quadrant is most commonly involved. According to AJCC grading of the tumors were in stageT_3at clinical presentation, as the limbus is the most common site of origin, Most common presenting complaint is mass or growth followed by redness and diminution of vision, sunlight exposure is a major risk factor. Carcinoma in situ is the most common histopathological diagnosis followed by Dysplasia and Squamous cell carcinoma. Surgical excision and cryotherapy followed by topical Mitomycin-C in weekly on and off cycles is associated with best control of primary OSSN with no tumor recurrence.

ABBREVIATIONS

OSSN	Ocular Surface Squamous Neoplasia
CCIN	Conjunctival Corneal Intraepithelial Neoplasia
CIN	Conjunctival Intraepithelial Neoplasia
CIS	Carcinoma in Situ
SCC	Squamous Cell Carcinoma
HIV	Human Immunodeficiency Virus

REFERENCES

1. Yang J, Foster CS. Squamous cell carcinoma of the conjunctiva. Int Ophthalmol Clin 1997;37:73-85.
2. Gichuhi S, Sagoo MS, Weiss HA, Burton MJ. Epidemiology of ocular surface squamous neoplasia in Africa. Trop Med Int Health 2013;18:1424-43.
3. Porges Y, Groisman GM. Prevalence of HIV with conjunctival squamous cell neoplasia in an African provincial hospital. Cornea 2003;22:1-4.
4. Balint GA. Situation analysis of HIV/AIDS epidemic in sub-saharan Africa. East Afr Med J 1998;75:684-
5. Gichuhi S, Ohnuma S, Sagoo MS, Burton MJ. Pathophysiology of ocular surface squamous neoplasia. Exp Eye Res 2014;129:172-82.
6. Napora C, Cohen EJ, Genvert GI, Presson AC, Arentsen JJ, Eagle RC, et al. Factors associated with conjunctival intraepithelial neoplasia: A case control study. Ophthalmic Surg 1990;21:27-30.
7. Lee GA, Hirst LW. Retrospective study of ocular surface squamous neoplasia. Aust N Z J Ophthalmol 1997;25:269-76.
8. Gichuhi S, Macharia E, Kabiru J, Zindamoyen AM, Rono H, Ollando E, et al. Clinical presentation of ocular surface squamous neoplasia in kenya. JAMA Ophthalmol 2015;133:1305-13.
9. Shields JA, Shields CL, De Potter P. Surgical management of conjunctival tumors. The 1994 Lynn B. McMahan Lecture. Arch Ophthalmolo 1997;115:808-15.
10. Nanji AA, Moon CS, Galor A, Sein J, Oellers P, Karp CL, et al. Surgical versus medical treatment of ocular surface squamous neoplasia: A comparison of recurrences and complications. Ophthalmology 2014;121:994-1000.
11. Lee GA, Hirst LW. Ocular surface squamous Neoplasia Surv Ophthalmol 1995,39: 429-50.
12. Kim BH, Kim MK, Wee WR, Oh JY. Clinical and pathological characteristics of ocular surface squamous neoplasia in an Asian population. Graefes Arch Clin Exp Ophthalmol 2013;251:2569-73.
13. Chauhan S, Sen S, Sharma A, Tandon R, Kashyap S, Pushker N, et al. American joint committee on cancer staging and clinicopathological high-risk predictors of ocular surface squamous neoplasia: A study from a tertiary eye center in India. Arch Pathol Lab Med 2014;138:1488-94.
14. Shields CL, Demirci H, Karatza E, Shields JA. Clinical survey of 1643 melanocytic and nonmelanocytic conjunctival tumors. Ophthalmology 2004;111:1747-54.
15. Spitzer MS, Batumba NH, Chirambo T, Bartz-Schmidt KU, Kayange P, Kalua K, et al. Ocular surface squamous neoplasia as the first apparent manifestation of HIV infection in malawi. Clin Exp Ophthalmol 2008;36:422-5
16. Ateenyi-Agaba C. Conjunctival squamous-cell carcinoma associated with HIV infection in Kampala, Uganda. Lancet 1995;345:695-6..
17. Kaliki S, Kamal S, Fatima S. Ocular surface squamous neoplasia as the initial presenting sign of human immunodeficiency virus infection in 60 Asian Indian patients. Int Ophthalmol 2016
18. Dandala PP, Malladi P, Kavitha. Ocular Surface Squamous Neoplasia (OSSN): A retrospective study. J Clin Diagn Res 2015;9:NC10-3.
19. Saurabh Kamal, Swathi Kaliki, Dilip K. Mishra, Jyoti Batra, Milind N. Naik. Ocular Surface Squamous Neoplasia in 200 Patients, Ophthalmology 2015;122:1688-1694.
20. Sheetal Chauhan, Seema Sen, Anjana Sharma, Lalit Dar, Seema Kashyap, Pankaj Kumar, Mandeep Singh Bajaj, Radhika Tandon. Human papillomavirus: a predictor of better survival in ocular surface squamous neoplasia patients. Br J Ophthalmol, 2012;96:1517–1521
21. Shields CL, Kaliki S, Kim HJ, et al. Interferon for ocularsurface squamous neoplasia in 81 cases: outcomes based on the American Joint Committee on Cancer classification. Cornea 2013;32:248–56
22. Shah SU, Kaliki S, Kim HJ, et al. Topical interferon alpha-2b for management of ocular surface squamous neoplasia in 23 cases: outcomes based on American Joint Committee on Cancer classification. Arch Ophthalmol. 2012;130:159–164.
23. Kao AA, Galor A, Karp CL, Abdelaziz A, Feuer WJ, Dubovy SR, et al. Clinicopathologic correlation of ocular surface squamous neoplasms at Bascom Palmer Eye Institute: 2001 to 2010. Ophthalmology 2012;119:1773-6.
24. Kamal S, Kaliki S, Mishra DK, Batra J, Naik MN. Ocular surface squamous neoplasia in 200patients: A case-control study of immunosuppression resulting from human immunodeficiency virus versus immunocompetency. Ophthalmology 2015;122:1688-94.
25. Pradeep TG, Gangasagara SB, Subbaramaiah GB, Suresh MB, Gangashettappa N Durgappa R, et al. 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.
26. Chen, C.; Louis, D.; Dodd, T. & Muecke, J. Mitomycin C as an adjunct in the treatment of localised ocular surface squamous neoplasia.Br J Ophthalmol, 2004;88:17-8.
27. Gupta, A. & Muecke, J. Treatment of ocular surface squamous neoplasia with Mitomyci C, Br J Ophthalmol,2010;94:555-8
28. Meel R, Dhiman R, Vanathi M, Pusker N, Tandon R, Devi S. clinicodemographic profile andt reament oucome in patients of ocularsurface squamous neoplasia. Indian Ophthalmol2017;65:936-41.
29. Shields CL, Naseripour M, Shields JA. Topical mitomycin C for extensive, recurrent conjunctival-corneal squamous cell carcinoma. Am J Ophthalmol 2002;133:601-6.
30. Puttaswamy S, Mala B, Nagaraju G, Raviprakash D, Prakash KH. Mitomycin C: An effective adjuvant in the management of ocular surface squamous neoplasia. Clin Cancer Investig J 2013;2:298-301.
31. McKelvie PA, Daniell M, McNab A, Loughnan M, Santamaria JD. Squamous cell carcinoma of the conjunctiva: A series of 26 cases.Br J Ophthalmol 2002;86:168-73.