



Original Research Article

Study of Treatment Modalities of Ocular Surface Squamous Neoplasia and Methods to Reduce Recurrence Rates

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ABSTRACT

Ocular surface squamous neoplasia refers to entire spectrum of dysplastic, preinvasive condition of conjunctiva and cornea or both coined by Lee and Hirst. Annual incidence across all age groups is around 17-20 cases per million per year, affecting older individuals of 6 or 7 decade of all sexes, and is more common in Caucasian men and also seen in tropical countries.

Methods: It was a retrospective study of 46 patients attending tertiary eye care hospital during January 2014 – December 2014. Excision biopsies of all lesions were sent to histopathological examination and confirmed the diagnosis. Marginal clearance was specifically looked for in all the biopsy sample by histopathology. Patients with margin involvement were resubjected for margin clearance. Cryotherapy is applied to the margins in all patients. Patients having more than 3 clock involvement were subjected to amniotic membrane graft. All patients were subjected to topical mitomycin 0.04% eyedrops as postoperative chemotherapy.

Results: Good tumor control was achieved using surgical excision with cryotherapy coupled with mitomycin C in all the patients. This also reduced the recurrences rate in patients with ocular surface squamous neoplasia. Xeroderma pigmentosa patients had bilateral involvement. Both xeroderma pigmentosa patients and human immunodeficiency virus positive patients presented at younger age groups.

Keywords: Ocular surface squamous neoplasia (OSSN), Mitomycin C, xeroderma pigmentosa, excision biopsy, cryotherapy.

INTRODUCTION

The term ocular surface squamous neoplasia was first described in 1995 by Lee and Hirst to denote a spectrum of neoplasms originating from squamous epithelium ranging from simple dysplasia to invasive squamous cell carcinoma, involving the conjunctiva, the limbus, and the cornea. [1]

Ocular surface squamous neoplasia is the condition affecting conjunctiva in old age with common risk factors being ultraviolet-B light and human papilloma virus, petroleum products, vitamin A deficiency, smoking, xeroderma pigmentosa. Usually asymptomatic, detected by chance. Few present with redness, foreign body

sensation, irritation in inter-palpebral area with elevated mass at or near the limbus.

Ocular surface squamous neoplasia encompasses spectrum of epithelial neoplasia of conjunctiva and / or cornea manifesting as dysplasia, carcinoma in situ and invasive squamous cell carcinoma. Worldwide prevalence of ocular surface squamous neoplasia ranges from 0.2 – 3.5 cases per 1,00,000. [2] The disease is predominantly unilateral but bilateral disease is reported in the patients having xeroderma pigmentosa, human immunodeficiency virus infection, long term immunosuppression and post organ transplantation.

Ocular surface squamous neoplasia has predilection for limbal area due to presence of stem cells and greatest mitotic activity in limbus and also it is the portion which is maximally exposed to sunlight. The role of limbal stem cells in development of OSSN is controversial. These cells are long-lived and have great potential to clonogenic division. OSSN may arise from dysfunctional limbal stem cells and from mutagenic agents such as UV radiation leading to mutations in the P53 tumor suppressor gene, also known as *TP53* gene. Conjunctival Ocular surface squamous neoplasia usually presents in three forms- gelatinous, leukoplakic or papilloform. Lesions can be of nodular or diffuse variety. Later can develop a feeder vessel. Corneal lesions are ground glass and have mottled appearance, usually avascular with characteristic fimbriated borders which may be smooth or ragged, well delineated with Rose Bengal or Lissamine green or Fluorescence, best seen with retro-illumination. Histopathology consists of spindle cells or mucoepidermoid cells may be interspersed with squamous cells. Electron microscopy in cases of OSSN reveals excessive mitochondria, tonofilaments and endoplasmic reticulum;

decreased desmosomes, alteration/ absence of basement membrane and deposition of fibrillogranular material between the basement membrane and bowman's layer.

Definitive treatment is always surgery with or without adjunctive cryotherapy, with or without postoperative chemotherapy. Surgical management include wide surgical excision biopsy with no touch technique avoiding direct manipulation by holding normal conjunctival borders to prevent tumor seeding into normal conjunctiva. Surgical excision with or without cryotherapy and with or with postoperative chemotherapy is used to prevent recurrences. [3] Postoperative chemotherapy treatment modalities available are Mitomycin C, 5Fluorouracil, Interferon alpha 2b. Exfoliative cytology using cytobrush, biopore impression cytology can be used to aid the diagnosis.

Recurrence rate following excision alone is very high. Surgical excision combined with cryotherapy decreases recurrence rate. Further reduction in recurrence rate is brought about by postoperative use of Mitomycin C 0.04%, 4 times a day for 4 cycles with interval of one week free each cycle.

MATERIALS AND METHODS

This study was retrospective study conducted at tertiary care eye hospital, department of ophthalmology in South India between January 2014 to December 2014 who were clinically diagnosed and confirmed histopathologically to have Ocular surface squamous neoplasia. The study included 49 eyes of 46 patients having Ocular surface squamous neoplasia. All patients demographic profile with systemic profile, factors like history of HIV, HPV infection, xeroderma pigmentosa and others were obtained. Best corrected visual acuity both distance and near were recorded. Slit-lamp examination, fundus examination,

gonioscopy and intraocular pressure were recorded. Serological workup for HIV using ELISA was done in all patients. Systemic examination was done to rule out any systemic pathology.

Under local anaesthesia using 2% lignocaine and adrenaline injection, excision biopsy was done. Excised biopsy specimen was sent to histopathological examination. Patients reported to have margin involvement were resubjected for biopsy till margins were free, intraoperative nitrous oxide cryotherapy applied with 2.5 tip probe to the edges of resected conjunctiva and limbus with double freeze and slow thaw technique, repeated two or three times, applied for three seconds in all the patients. Patients having more than 3 clock involvement were subjected to amniotic membrane graft. All patients were subjected to postoperative topical mitomycin C 0.04% eyedrops four times a day, with one week on and one week off mitomycin C for 4 cycles after conjunctival epithelium heals.

RESULTS

The study included 49 eyes of 46 patients with age group ranging from 12-70 years. In this study as shown in table 1, 26(56.5%) patients are males and 20(43.5%) patients are females. Right eye was involved in 27(58.7%) patients, left eye was involved in 25(54.3%) patients. Unilateral involvement was seen in 43(93.5%) patients and both eyes were involved in 3 (6.5%) patients. The size of the lesion varied from 2mm to 15 mm in diameter, the average being 4mm -5mm in size.

Table 1: Sex Distribution And Laterality

Number of	Right eye	Left eye	TOTAL
Males	13	14	27
Females	13	9	22
Total	26	23	49

Among 46 patients, 3 patients had bilateral involvement.

As shown in table 2, OSSN is seen in 3 patients with xeroderma pigmentosa and 3

patients with immunocompromised state. Of the above 3 patients in each group 2 were male patients and 1 was female patient respectively.

Table 2: ossn and associations.

	Xeroderma pigmentosa	Immunocompromised (HIV)	Total
MALE	2	2	4
FEMALE	1	1	2
TOTAL	3	3	6

Among 3 patients who had bilateral involvement, 2 patients had xeroderma pigmentosa and 1 patient had immunocompromised state.

Surgical excision was done in all patients with marginal clearance of 4 mm around the lesion with intraoperative cryotherapy for 3seconds- double freeze and slow thawing for 2 -3 times depending on the lesion. The excised tumor was sent for histopathological examination and proved to have ocular surface squamous neoplasia. 3 patients had tumor cells in the margin for which repeat margin clearance was done and sent for histopathology. Mitomycin C 0.04% eyedrops was used 4 times a day with one week on and one week off regimen after epithelial defect healing as postoperative chemotherapy in all the patients, to prevent recurrence. Amniotic membrane graft was used in 2 eyes with large lesions (more than three clock hours). 3 patients with both eyes involved had Xeroderma Pigmentosa. 1 (3.33%) patient had recurrence within 6 months, in a patient with Xeroderma Pigmentosa. 3 patients had immunocompromised status - Human immunodeficiency virus positive patients.

DISCUSSION

The mean average being 58 years with male preponderance. The age group and sex distribution in this study is in consistence with other studies. [4] Among three patients who had both eyes involved, two patients had xeroderma pigmentosa and one patient had HIV. It is observed that the

immunocompromised patients as well as those who have xeroderma pigmentosa develop the ocular surface squamous neoplasia at a much younger age (6-22 years) as compared to others, and also they have propensity to have bilateral lesions and bigger lesions. [5,6]

Recurrence rate showed in our study is 3.33% but recurrence rate is reported to be 15-52% in earlier studies done by Gupta S et al. The recurrence rate is very high in tumors managed by surgical excision alone. This difference in the recurrence rate between our study and older studies is due to excision biopsy followed by cryotherapy which is then followed by postoperative mitomycin eye drops usage in all patients in our study. [7-9] One patient who had recurrence was a patient with xeroderma pigmentosa, who also harboured to have squamous cell carcinoma of the skin in our study. The recurrent tumor was surgically excised combined with cryotherapy and adjunctive chemotherapy.

It has been proposed that the presence or absence of positive surgical margins has no predictive ability with respect to the likelihood of developing recurrent tumors in the absence of adjunctive therapy. This suggests that equal concern is required for postoperative management of tumors that have been histopathologically been reported having clear margin resection and those having tumor infiltration in the resection margins. The demonstration that adjunctive therapy with mitomycin C greatly reduces the recurrence rate in eyes with positive surgical margins and significantly reduces the recurrence rate in those with negative margins suggests that such treatment should be provided in all histopathologically confirmed cases of intraepithelial neoplasia. [10]

Both the excision biopsy and cryotherapy of the involved quadrant of the

limbus leads to limbal stem cell deficiency, the manifestations are yet to be seen. None of the patients had manifested with signs of limbal stem cell deficiency during the study period.

In our study HIV positive patients had earlier onset of the disease. One patient with HIV had both eyes corneal involvement and a big lesion, where corneal keratectomy and amniotic membrane graft was done in addition to the above said procedures. [11] None of our patients had intraorbital or intraocular spread of the disease. The weakness of our study was that the other adjunctive postoperative chemotherapy like 5-fluorouracil, Interferon alpha 2b and pegylated interferon alpha 2b were not used and compared.

CONCLUSION

Surgical excision with intraoperative surgical adequate margins clearance with adjunctive cryotherapy and usage of postoperative Mitomycin C eye drops in all patients results in good tumor control rates and prevent recurrence rates without complications. In patients with xeroderma pigmentosa and immunocompromised status, should look for bilateral involvement and to be treated aggressively due to possibility of recurrence.

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Declaration of interest

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