Clinicopathological Profile, Management and Clinical Outcomes in Recurrent Cases of Ocular Surface Squamous Neoplasia at a Tertiary Care Centre: Original Article

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Abstract

Purpose

This study was taken up at this centre to look into the various causes of recurrence, clinicopathological profile and final outcomes in recurrent OSSN.

Methodology

A prospective cohort study was conducted and total 18 patients were recruited. All patients were subjected to detailed history, comprehensive eye examination and imaging studies. A treatment plan was formulated based on the size and extent of the lesion. Primary outcome measures were resolution/regression of tumor, recurrence of the lesion and incidence of complication associated with each treatment modality.

Results

The common cause of recurrence in our study was misdiagnosis of the lesion as in 15 cases it was diagnosed as pterygium and in 03 cases it was actinic keratosis. Excision Biopsy with adjunctive cryotherapy was the preferred treatment modality followed by topical interferon @ 2b drop in our study. We could achieve good outcomes in terms of complete regression of the tumor in 15 cases. The complication associated with this treatment was minimal in our study as few patient develop redness and irritation which got subsided after application of topical lubricants. There was no recurrence of the lesion even after 06 months of follow up in all 18 cases.

Conclusion

Recurrence can be mitigated in all cases of OSSN if they are diagnosed on time with institution of appropriate treatment modality. Regular follow- up is required to assess the response to treatment and change over to new treatment plan in cases with inadequate response to curb the incidence of recurrence in OSSN.

Introduction

Lee et al from Australia first coined the term ocular surface squamous neoplasia (OSSN) in 1995. OSSN comprises of benign, pre-malignant and malignant, slowly progressive epithelial lesions of the conjunctiva and cornea [1, 2]. The lesions may be papilliform, leukoplakic, gelatinous or nodular appearing mostly at the limbus [3, 4]. This is seen more often in elderly population and the common etiology is exposure to ultraviolet (UV) radiation, infection with HIV and human papilloma virus, immunosuppression [5, 6]. It is also very prevalent among smokers, in patients diagnosed with Xeroderma Pigmentosa, patients with history of exposure to chemicals and patients with Vitamin A deficiency features [7, 8]. Morbidity is low if it is localized but relatively high once it has spread to other part of the body and if there is recurrence of the lesion. When the lesion is small then excision with wide margins with adjunctive cryotherapy is the

treatment of choice.^[9] Immunoreduction in larger lesion with topical chemotherapeutic agents like 5FU, mitomycin and interferon is advocated followed by excision [10, 11]. The incidence of recurrence in excision ranges from 15–52% whereas recurrence rates in cases treated with chemotherapeutic drugs like 5 FU was 1–7.3%, in mitomycin it was 0–4.3% and with interferon alpha 2b 5 to 13.3% respectively [12, 13, 14, 15]. Recurrence is a problem with OSSN whatever is the treatment modality [16, 17, 18, 19, 20, 21, 22, 23, 24, 25]. The treatment of recurrent OSSN lesions is difficult and the therapeutic challenges posed by these recurrent lesions need to be unraveled. However, there is paucity of studies which have analyzed the clinical parameters, how these recurrent lesions are being treated and what was the final outcome in these cases. Our centre being a tertiary care centre received all referral cases of Ocular Oncology from northern and central part of India. Hence, this study was conducted to assess the clinicopathological profile and clinical outcomes in recurrent cases of OSSN. This study is the first of its kind from this geographical location which have analyzed the clinicopathological profile and ramifications in recurrent OSSN.

Methodology

A prospective cohort study was conducted from Aug 2019 to Dec 2020 which included follow-up period at a tertiary care centre located in northern part of India. 18 cases of recurrent OSSN were recruited for this study after obtaining informed consent from the patient. This study was approved by the institutional review board and adhered to the tenets of the declaration of Helsinki. In all cases detailed history was taken and patient underwent complete eye evaluation. Ocular examination included recording of vision, refraction, slit lamp and fundus examination. Slit lamp photographs and ASOCT images were captured in all cases (Figs. 1, 2 and 3). Patients who gave history of prior ocular surgery for OSSN lesion and recurrent cases were included in the study. Patients who have been diagnosed recently with OSSN and patients lost to follow-up were excluded from the study. Details about demographic characteristics and clinical history which included age of the patient, gender, laterality, home address, duration of symptoms, risk factors, history of prior systemic condition and details of previous treatment history were recorded during evaluation of the patient for the study. Clinical features of the tumor like size of the tumor and its extent (no of clock hours), location, appearance, tissue involvement, presence of surface keratin, feeder vessels and intrinsic vascularity were also recorded. Tumors were classified as small (< 5 mm in size and less than 3 clock hours involvement), medium (5–10 mm in diameter with 3 to 6 clock hours involvement), and large (> 10 mm in size with more than 6 clock hours involvement) as per Li et al in our study. All the tumors were graded based on the 8th edition of American Joint Committee for Cancer Classification. All tissues were sent for histopathological examination in cases where excision was performed. Systemic examination was done in all cases which included examination of regional lymph nodes. Patient with invasive disease underwent CT orbit to look for orbital invasion.

Treatment plan

In our centre we formulated our own treatment protocol depending upon the extent of the lesion and based on results of already published studies. Patients with small tumor of less than 5 mm basal

diameter or less than 03 clock hours were subjected to wide surgical excision with 4mm normal conjunctival tissue with cryotherapy to normal margin with alcohol epitheliectomy followed by covering the defect with amniotic membrane graft. In our study we advocated interferon alpha 2b dose 1 million unit four times in a day and perilesional interferon alpha 2b (3 million unit) once in a month in medium to large lesion (5 to 16 mm basal diameter) for immunoreduction. Maximum cases in which we started interferon alpha 2 b lesion subsided except two cases where excision was performed for residual lesion. One patient had orbital spread at the time of presentation at our centre so he was subjected to exenteration. All patients were examined on first post operative day, after one month, 03 months and 06 months. In each visit slit lamp photographs and ASOCT images were taken. The primary outcome measures evaluated were reduction in the size of the lesion, recurrence of the lesion and overall complications rates.

Statistical methods

The statistical analysis was done by using Epi Info version 3.4.3 and by entering the collected data in Microsoft excel 2007. Descriptive statistics such as percentages, mean and standard deviation were calculated.

Results

Total 18 patients were recruited in the current study based on inclusion criteria. All patients were from northern and western part of India. Two patients with recurrent OSSN had HIV and one patient was found to be HBsAg positive. Clinical profile of patients recruited in our study has been mentioned in (Table 1). The mean age group of the study population at the time of presentation in our institute was 64 ± 6.2 yrs (range was from 52 to 74 yrs) in our study group. They were 15 males and 03 females in our study group. Right eye was involved in 14 cases whereas left eye was involved in 04 cases. Most of the patients in the current study had visual acuity of 6/6 to 6/12 (12/18). The common clinical presentation was papilliform mass (6/18; 33.3%) and common symptom was redness. The risk factors which we found in our study was history of smoking (02/18, 11.1%), HIV (03/18, 16.6%), HbsAg infection (01/18, 5.5%), xeroderma pigmentosa (01/18, 5.5%)s history of renal transplantation (01/18, 5.5%). The common location of the tumor was nasal quadrant and the size of the tumor was 5 mm (09/18, 50%) in our study group. The common tissue which was found involved in the current study was conjunctiva and limbus (18/18; 100%). The mean time interval between initial intervention and tumor recurrence was 7.6 ± 1.85 months. The common cause of recurrence in our study was inaccurate diagnosis of the lesion as in 15 cases (83.33%), pterygium was diagnosed and in 03 (16.6%) cases, actinic keratosis was diagnosed. All patients gave history of prior treatment before enrolling for this study. Excision was performed in 15 cases (83.3%) and in 03 (16.6%) patients lubricants were prescribed somewhere else. Histopathological profile of patients recruited in current study is listed in (Table 2). Out of 18 patients as per AJCC staging, 11 (73.3%) patients had AJCC T1 grade, 6 (33.3%) patients had T2 grade and 01 (5.5%) patient had T4 grade. In the current study biopsy was done in 14 (77.77%) cases and histopathology report showed invasive carcinoma in 11 (61.11%) cases and squamous cell carcinoma in situ in 03 (16.6%) cases. HPE

report also demonstrated positive surgical margins in two biopsied tissues post excision in which adjuvant chemotherapy were advised for 03 months (topical interferon alpha 2b).

We did not find metastasis in our study group at the time of presentation. There was involvement of anterior part of the orbit on presentation in one case at our centre. Treatment profile of all enrolled patients is depicted in (Table 3). In 11 patients as lesion was localized and small (5 mm in size), wide surgical excision with cryotherapy and placement of amniotic graft over bare area was done. In 06 patients topical interferon alpha 2 b (1 million unit) was started four times in a day and perilesional interferon alpha 2b (3 million unit) once in a month as lesions were medium to large in size. In 04 patients complete resolution could be achieved with 06 cycles of topical and 03 cycles of perilesional interferon whereas in two patients size of the lesion reduced but lesion did not disappear completely after 06 cycles of immunotherapy. Another 03 cycles of topical interferon were continued after complete resolution of tumor in 04 cases. Wide excision with cryotherapy to margin was done in cases in which complete resolution could not be achieved with interferon .Patient with orbital spread at the time of presentation underwent exenteration. Follow- up period was of one year. The outcomes in the current study are enumerated in Table 4.

Discussion

Ocular surface squamous neoplasia is a common neoplasm of ocular surface with significant morbidity [26]. It is a great masquerader and can masquerade as conjunctivitis, inflamed pterygium or an abnormal growth at limbal area, superior limbic conjunctivitis, necrotising scleritis and sclerokeratitis [27, 28, 29, 30]. Hence, it is often misdiagnosed and not treated appropriately resulting in recurrence of the lesion. The traditional treatment in localized OSSN is excision with no- touch technique combined with adjuvant therapies to mitigate recurrence rate. However, the recurrence rate is about 5% and regional metastasis is about 2% even with the modern techniques due to the microscopic extension of disease beyond the edge of the surgical margin at the time of presentation because of late diagnosis of this clinical masquerade. [12,14,15] The other causes of recurrence are the tumor size, positive surgical excision margins, location of tumor, histopathological grade, lack of adjuvant treatment in addition to surgical excision and length of follow-up [17, 20].

In our study the mean interval between initial treatment and recurrence was 07 months. In the current study recurrence was found more common in the sixth decade with a male preponderance. This is in concordance with the study which was undertaken by Li et al, Kirre et al, Cevantes et al, Kim et al, Meel et al and Mckelvie et al as they also reported higher incidence of this disease in sixth decade and in males [15, 26, 29, 31, 32, 34]. However, all these studies reported similar finding in recently diagnosed cases of

OSSN. Risk factors which we found in our study like smoking, HIV infection, Xeroderma Pigmentosa and immunosuppression were similar to studies conducted by Li et al, Kim et al and Meel et al.

In our study limbus was involved in all cases and most of the lesion were small (5 mm in size). This is in conformity with Li et al, Meel et al which also showed the similar finding [15, 33]. However, Meel et al and Mirzayev et al reported higher frequency of medium to larger tumors in their study [33, 35]. The common clinical presentation in our study was papilliform mass which was similar to study conducted by Kim et al [32]. But current studies finding were in discordance with Li et al which reported maximum patient had leukoplakic lesion (16/43), whereas Meel et al found majority of tumors had a gelatinous appearance (35/57, 61.4%) [15, 33]. The main cause of recurrence in our study was found to be incorrect diagnosis hence not treated appropriately. The other reason of recurrence of the lesion in this study as patients were not followed-up at their initial centre where they were treated. Hence, awareness among general population about the entity is important so that these lesions are diagnosed early and treated on time with appropriate treatment modalities. Galor et al reported tarsal involvement and positive pathologic margins were the strongest predictors of clinical recurrence.^[12] Yousef and finger et al reported that tumor size more than 5 mm is associated with a higher risk of recurrence [4]. All patients with recurrent OSSN had unilateral presentation. This is in accordance with Kiire et al, Kim et al and Meel et al which also reported the similar findings [26, 32, 33]. Most of the patients had already undergone excision somewhere else before reporting at our centre. The common pathological grade which was found in current study was invasive squamous cell carcinoma. This is in conformity with Mirzayev et al which also reported invasive SCC in most of the lesion (46.4%) [35]. However, these findings are in discordance with Li et al and Kao et al as they found more number of squamous cell carcinoma in situ during histological examination of biopsied tissues [15, 36]. The treatment with different treatment modalities achieved good clinical outcomes in all cases of recurrent OSSN in the current study with no recurrence of the lesion over a period of 12 months. This is similar to study conducted by Sturges et al and Palamer et al as they also reported nil recurrence in their study population during a follow-up period of 35 months [20, 37]. But current study finding differed from Li et al and Nanji et al which, as in their studies recurrence rate was 7% and 6% respectively after a mean follow-up period of 24 months [15, 38]. In 16 patients complete regression of the tumor was noted whereas in one patient there was reduction in the size of the tumor but lesion did not disappear completely. In patients who underwent wide excision with amniotic membrane graft transplantation, AMG was found displaced after one week. The AMG was placed again over bare area and secured with fibrin glue. Two patients in whom we started interferon, they complained of pain, irritation which subsided after administration of lubricants. The patient who underwent exenteration complaining of oozing from the operated site, which subsided after pressure bandage of few days. Other than this we did not encounter any major complications in our study. In a study conducted by Kirre et al, corneal scarring was found in 09 patients, symplepharon in 01 patient and allergic reaction in 01 patient [26]. Mirzayev et al reported dry eye symptoms in 14 (12.5%) patients after topical chemotherapy and mild stem cell deficiency in 5 (4.5%) cases [35]. Overall, these studies also reported minimal complication rates in their studies like our study.

The present study is unique in many ways. In all published data regarding OSSN, whatever may be the mode of treatment, recurrence was seen in few percentage of cases. But in the current study we did not find any sign of recurrence after 12 months of follow-up period. Our institutional devised treatment protocol yielded good results in the study population, hence this treatment protocol may be considered for managing recurrent cases of OSSN. Second, to the best of our knowledge, our study addressed the outcome in recurrent OSSN among our clientele for the first time as there are very few published studies which have analysed the outcome in recurrent OSSN worldwide and in India till date. Third, the common cause of recurrence in the current study was found to be misdiagnosis of the lesion and not following patients on time whereas in other studies reported larger size of the lesion, immunosuppression, positive pathological margins, multifocal lesion, nodular morphology and incomplete excision as the common cause of recurrence in their study population. Fourth, the current study found majority of the tumors were small when treated initially somewhere else, so size of the lesion plays no role in increased rate of recurrence. Whatever is the size of the lesion, if not treated properly it will definitely escalate the incidence of recurrence in the affected population.

The limitation of study is small sample size and short follow-up. The outcomes of the study may not be the true representative of the entire population. Recurrence of the disease has been reported upto 12 years after surgical excision in some published studies.^[10] Hence, longer follow-up and study from larger population need to be carried out to validate the outcome result in recurrent OSSN.

Conclusion

Ocular surface squamous neoplasia is a common malignant ocular surface tumor. It has the potential to cause surface destruction, orbital invasion and rarely metastasis. Recurrence is a frequent challenge in the management of OSSN. If the disease is diagnosed on time and treated meticulously, the recurrence rate in OSSN can be mitigated. Even in recurrent OSSN the risk of recurrence is high if various factors of recurrence are not taken care of during management. The reason for nil recurrence in our study are multifactorial. One of the main reason was selection of appropriate treatment modality in each case and starting of adjuvant therapy based on histopathological report where it was indicated. Second, all patients were closely monitored to look for any sign of recurrence of the disease. Hence, timely diagnosis of OSSN and adopting appropriate treatment strategy depending upon the extent of the lesion is of paramount importance to alleviate the recurrence rate in this disease entity.

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Tables

Table 1: Clinicodemographic features of recurrent cases of ocular surface squamous neoplasia

Features	N	Percentage(%)
Age	64 ±6.2 yrs	
Gender		
Male	15	83.3
Female	3	20
Laterality		
Unilateral	18	100
Bilateral	0	
Affected Eye		
Right Eye	14	77
Left Eye	4	22
Site		
Nasal	11	61
Temporal	07	38
Superior	0	0
Inferior	0	0
Size		
Small	11	50
Medium	04	44
Large	03	5
Involvement of tissue		
Limbus	18	100
Conjunctiva	18	100
Cornea	1	5
Whole tissue	1	5
Appearance		

Papilliform mass	06	33
Nodular	05	27
Leukoplakic	03	16
Gelatinous	04	22
Vision		
6/6 to 6/12	12	66
6/12 to 6/18	05	27.7
Less than 3/60	01	5.5
Risk factors		
Smoking	02	11
HIV	03	16.6
HbsAg	01	5.5
Xeroderma pigmentosa	01	5.5
H/O Kidney Transplantation	01	5.5

Table 2: Histopathological profile of patients who underwent Excision Biopsy

Grades	N	Percentage
AJCC		
T1	11	61.1
T2	06	33.3
T3	0	
T4	01	5.5
Histological		
Mild Dysplasia	None	
Moderate Dysplasia	None	
Severe Dysplasia	None	
Squamous cell carcinoma in situ	03	16.6
Squamous cell carcinoma, invasive	11	61.1
Positive margins	02	11.1

Table 3: Various treatment modalities in the current study

Treatment Group (Intervention)	N	Percentage
Excision Biopsy with adjunctive cryotherapy	11	61.1
Interferon @ 2b	06	33.3
Exenteration	01	5.5

Table 4: Clinical outcomes in our study

Outcome Parameters	Excision Biopsy	Interferon @2b	Exenteration
Resolution	Complete	Complete-03 Incomplete-01	Complete
Recurrence	Nil	Nil	Nil
Pain & irritation		02	
Redness		01	
Displaced AMG	01		
Limbal stem cell deficiency			
Symblepharon			
Diplopia			
Oozing of blood			Present

Figures

Figure 1

(a): Slit lamp photograph showing OSSN involving less than 6 clock hours of limbus,cornea and conjunctiva (b): Clinical photograph showing amniotic membrane graft in place post wide local excision with no sign of recurrence after one month (c): Clinical photograph showing no sign of recurrence post

excision after 06 months (d): AS-OCT image of OSSN showing the thickened hyperreflective epithelial tissue (red arrow) with an abrupt transition from normal to abnormal epithelium (black arrow) (e): Histopathology images (4x) of excised conjunctival growth showing hyperplastic conjunctival lining with full thickness dysplasia(black arrow) (f) : Histopathology images (20x) showing an invasive tumor arranged in form of small island and clusters (black arrow)

Figure 2

(a): Slit lamp photograph showing diffuse OSSN of the left eye (b): AS-OCT image of OSSN showing the thickened hyperreflective epithelial tissue(black arrow) before starting interferon drops (c): Slit lamp photograph showing complete regression of the tumor with 03 months of topical interferon @ 2b (d): Slit lamp photograph showing no sign of recurrence after 06 months

Figure 3

(a): Slit lamp photograph showing diffuse ocular surface squamous neoplasia with extensive involvement of conjunctiva, cornea and fornices (b) : CT orbit showing involvement of anterior part of the orbit due to ocular surface squamous neoplasia (c) : Histopathology images showing hyperplastic stratified squamous epithelium with full thickness dysplasia with invasion into the sub- epithelium (black arrow) (d) : Clinical photograph showing post-operative exenterated socket