Ocular surface squamous neoplasia with 360° limbal involvement: A comparative study of 130 patients

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Abstract

Purpose

To describe the risk factors, clinical features and management outcomes of ocular surface squamous neoplasia (OSSN) with 360° of limbal involvement (360-OSSN).

Methods

Retrospective comparative study.

Results

Of 1250 patients diagnosed with OSSN during the study period, 30 (2%) had 360-OSSN. A total of 100 patients of OSSN with segmental limbal involvement (SL-OSSN) were included for comparison. 360-OSSN patients more often had longer duration of symptoms (mean, 17 months vs 8 months; p, 0.003), prior misdiagnosis (17% vs 6%, p, 0.13) and prior intervention (47% vs 13%; p, 0.0002) than patients with SL-OSSN. 360-OSSN tumors were more extensive (mean diameter, 24mm vs 8 mm; $p < 0.0001$), had diffuse ocular surface involvement (63% vs 3%, $p < 0.0001$), scleral fixity (57% vs 16%; $p < 0.0001$), corneal/scleral melt (17% vs 0%; p, 0.0005), intraocular tumor extension (17% vs 0%; p, 0.003), orbital tumor extension (33% vs 1%; $p < 0.0001$), and advanced T stage at presentation (Tis: 37% vs 76%, T1: 0% vs 15%; T2: 7% vs 4%; T3: 27% vs 4%; T4: 30% vs 1%; $p < 0.001$). Over a mean follow-up of 15 months in patients with 360-OSSN and 13 months in those with SL-OSSN, lymph node metastasis (8% vs 0%; p, 0.05) and distant metastasis (4% vs 0%; p, 0.23) was more common in 360-OSSN group vs SL-OSSN group.

Conclusion

Risk factors of 360-OSSN include prolonged symptoms, prior misdiagnosis and prior intervention. It represents an advanced form of disease with larger, diffuse lesions, propensity for corneo-scleral melt and invasive disease which requires aggressive management.

Introduction

Ocular surface squamous neoplasia (OSSN) is the most common ocular surface malignancy, with limbal location being the commonest. The pathogenesis of OSSN has been attributed to several extrinsic factors such as exposure to UV light and chemicals, and intrinsic or host-related factors such as immune suppression and defective DNA repair mechanisms which promote tumorigenesis.[1] The cellular origin of OSSN is poorly understood with limbal stem cells playing a purported role of cancer stem cells.[1]

Though OSSN most often originates at the limbus,[1] few case reports (Table 1) have documented involvement of 360° of the limbus by the tumor (360-OSSN).[2–6] In addition, 360-OSSN poses a unique challenge in terms of management[7] with outcomes likely to be affected by the extent of disease as well as resultant damage to the limbal stem cells. The study of 360-OSSN, therefore, offers a unique opportunity in understanding the pattern of limbal involvement and hypothesize its potential course of progression. Herein, we describe the risk factors, clinical features, management and outcomes of patients with 360-OSSN in a relatively larger cohort of patients.

Table 1
Cases of ocular surface squamous neoplasia with involvement of 360° of limbus described in literature

Author	Age/Sex	Symptom	Duration (months)	Risk factors	Morphology	% of ocular surface involved	Configuration of lesion	Histo-pathology	Management	Fi ou (t
ZareiGhanavati[2] 2014	62/M	#	#	None	Papillary	30	Circumferential (2 patients)	CIN	IFNα2b	Fr tu
	60/M	#	#	None	Papillary	#		CIN	IFNα2b	Fr tu
	55/M	#	#	None	Placoid	#		CIN	IFNα2b	Fr tu
	51/M	#	#	None	Gelatinous	20		CIN	IFNα2b	Fr tu
	73/M	#	#	None	Papillary	#		CIN	IFNα2b	Fr tu
Kalamkar[3] 2016	16/M	Photophobia (OU)	#	Xeroderma Pigmentosum	OD Placoid OS nodular	OD 25 OS 100	OD circumferential OS diffuse	OS SCC	OD MMC OS Excision + MMC	O pe tu
Kumar[4] 2017	65/M	DOV	0.5	None	Papillary	30	Combined	SCC	Excision + MMC	Fr tu
Patel[5] 2018	80/M	Tearing, itching	#	None	Placoid	25	Combined	CIS	IFNα2b	Fr tu
	81/M	DOV	12	Basal Cell Carcinoma upper eyelid SCC cheek	Placoid	30	Circumferential	CIS	IFNα2b	Fr tu
Mohamed-Noriega[6] 2019	82/M	Mass	24	None	Placoid	30	Circumferential	Not Available	5 fluorouracil	Fr tu

M: male; #: details not available; OU: oculus universus; OD: oculus dexter; OS: oculus sinister; CIN: conjunctival intraepithelial neoplasia; SCC: squamous cell Interferon alpha 2B; diminution of vision; MMC: mitomycin C

Methods

This was a retrospective study conducted at the Operation Eyesight Universal Institute for Eye Cancer, L V Prasad Eye Institute, Hyderabad, India and an approval from the Institutional Ethics Committee was obtained. The study adhered to the tenets of the Declaration of Helsinki. Electronic database search was conducted with the term "OSSN" and all records were reviewed. Amongst patients with clinico-tomographic[8] and/or histopathological diagnosis[8] of OSSN, those who presented with OSSN involving 360° of the limbus i.e. 12 clock hours (360-OSSN group) between September 2012 and September 2020 were included. Every 10th patient with a segmental involvement of limbus during the same study period were also included as controls for comparison (SL-OSSN group). Suspicious lesions with uncertain diagnosis were excluded.

Data captured included demographic details (age, gender and occupation), history of presenting symptoms, smoking, immune status, systemic illness, referral diagnosis and prior treatment. Clinical notes, images and ancillary investigations were reviewed to record presenting visual acuity, tumor morphology, location, epicenter, extent, dimensions of the lesion, presence of surface keratin, pigmentation, intrinsic vascularity, feeder vessels, scleral fixity and regional lymphadenopathy. Configuration of tumor was assessed as circumferential, radial or combined with respect to the orientation of the long axis of the tumor to the circumference of the limbus (Fig. 1). Tumors were classified according to the 8th edition of the American Joint Committee on Cancer (AJCC) classification.[9] Details of primary and secondary treatments [immunotherapy, chemotherapy, excisional biopsy, enucleation, exenteration, plaque brachytherapy (PBT) and external beam radiotherapy (EBRT)] rendered were recorded. Final outcomes in terms of resolution of tumor, globe salvage, vision salvage, status of ocular surface, complications, recurrence, any occurrence of locoregional or systemic metastasis or death were noted.

Data were entered in Microsoft Excel® for Mac (Version 16.41, Microsoft Corporation, Redmond, WA, USA). Descriptive data were expressed as mean, median, range and proportions. Recorded data was compared between the two groups (360-OSSN and SL-OSSN). Statistical analysis was performed using STATA v11.0 (StataCorp, College Station, TX, USA). The normality of continuous data distribution was assessed by Shapiro-Wilk test and the equality of variance by Levene test. Continuous data and categorical were compared between groups by Student t-test (parametric data with equal variance) or Mann-Whitney (non-parametric data and parametric data with unequal variance) and Chi-square or Fisher Exact tests respectively. A p-value of < 0.05 was considered statistically significant and Bonferroni correction was applied for multiple comparison testing.

Results

Of 1250 patients with OSSN during the study period, 30 patients (2%) had 360° of the limbus involved by the tumor. One hundred patients with a segmental involvement of limbus during the same study period were included for comparison by systematic sampling. The demographic features and risk factors for OSSN in both the groups are summarized in Table 2. Mean age of presentation was comparable (p = 0.09) in both 360-OSSN group (mean 57 years; median, 56 years; range, 20 to 87 years) and SL-OSSN group (mean 51 years; median, 51 years; range 5 to 86 years). Rate of prior misdiagnosis (17% vs 6%, p = 0.13) was comparable but prior intervention (47% vs 13%, p = 0.0002) was significantly higher in 360-OSSN group. Misdiagnoses of 360-OSSN tumors before referral to our center included microbial keratitis (n = 1), fungal keratitis (n = 1), herpes simplex keratitis (n = 1), episcleritis (n = 1) and phthisis bulbi (n = 1) (Fig. 1). Prior interventions included combinations of topical medications (n = 4; antibiotics, antivirals, medications with no traceable details), tarsorrhaphy (n = 1), imprint cytology (n = 1), incisional biopsy (n = 2), debulking (n = 1), excisional biopsy (n = 6), topical mitomycin C (MMC; n = 2), interferon alpha 2B (IFNα2B; n = 1) and evisceration (n = 1). Known risk factors of OSSN such as male gender, smoking, outdoor occupation, human immunodeficiency virus infection and xeroderma pigmentosum were comparable between the two groups (Table 2). Patients with 360-OSSN had a significantly longer duration of symptoms (mean of 17 months vs 8 months; p = 0.003) than patients with SL-OSSN.

Table 2
Clinical features at presentation in ocular surface squamous neoplasia with 360° and segmental involvement of limbus

	All patients n = 130 n (%)	360-OSSN n = 30 n (%)	SL-OSSN n = 100 n (%)	p-value#
Age (years) Mean (median, range)	52 (52, 1 to 87)	57 (56, 20 to 87)	51 (51, 5 to 86)	0.10
Male gender, n (%)	85 (65)	21 (70)	64 (64)	0.70
Smoking, n (%)	13 (10)	3 (10)	10 (10)	1.00
Outdoor occupation, n (%)	54 (42)	9 (30)	45 (45)	0.21
Human immunodeficiency virus, n (%)	25/96 (26)	7/25 (28)	18/71 (25)	1.00
Xeroderma Pigmentosum, n (%)	5 (4)	2 (7)	3 (3)	0.59
Duration of symptoms Mean (median, range)	10 (4, 0.1 to 72)	17 (12, 1 to 72)	8 (3, 0.1 to 72)	0.003
Misdiagnosis	11 (8)	5 (17)	6 (6)	0.13
Prior intervention	27 (21)	14 (47)	13 (13)	0.0002
Symptoms, n (%)				
None	10 (8)	1 (3)	9 (9)	0.45
Watering	14 (11)	8 (27)	6 (6)	0.004
Foreign body sensation	11 (8)	2 (7)	9 (9)	1.00
Mass	100 (77)	23 (77)	77 (77)	0.84
h/o trauma	22 (17)	2 (7)	20 (20)	0.15
Tumor morphology, n (%)				
Papillary	34 (26)	10 (33)	24 (24)	0.10
Nodular	33 (25)	8 (27)	25 (25)	
Placoid	55 (42)	8 (27)	47 (47)	
Nodulo-ulcerative	8 (6)	4 (13)	4 (4)	
Quadrantic location, n (%)				
Nasal	42 (32)	2 (7)	40 (40)	< 0.001
Inferior	6 (5)	1 (3)	5 (5)	
Temporal	52 (40)	5 (17)	47 (47)	
Superior	8 (6)	3 (10)	5 (5)	
Diffuse	22 (17)	19 (63)	3 (3)	
Lesion configuration, n (%)				
Circumferential	49 (38)	15 (50)	34 (34)	0.28
Radial	24 (18)	4 (13)	20 (20)	
Combined	57 (44)	11 (37)	46 (46)	
Extent of ocular surface involvement				
% of ocular surface involved Mean (median, range)	26 (18, 2 to 100)	65 (75, 30 to 100)	14 (10, 2 to 70)	< 0.0001
Largest diameter Mean (median, range)	12 (8, 2 to 55)	24 (22, 9 to 55)	8 (6, 2 to 40)	< 0.0001

360-OSSN: Ocular surface squamous neoplasia with 360 degrees limbal involvement; SL-OSSN: Ocular surface squamous neoplasia with segmental limbal involvement; #On applying Bonferroni correction, a p-value of < 0.002 was considered statistically significant.

	All patients n = 130 n (%)	360-OSSN n = 30 n (%)	SL-OSSN n = 100 n (%)	p-value#
Thickness Mean (median, range)	4 (2, 1 to 35)	8 (4, 1 to 35)	2 (2, 1 to 10)	< 0.0001
Associated features n (%)				
Keratin	100 (77)	23 (77)	77 (77)	0.84
Intrinsic vessels	120 (92)	30 (100)	90 (90)	0.12
Feeder vessels	98 (75)	23 (77)	75 (75)	1.00
Scleral fixity	33 (25)	17 (57)	16 (16)	< 0.0001
Tumor pigment	64 (49)	10 (33)	54 (54)	0.08
% of pigmentation in tumors	38 (30, 5 to 100)	39 (30, 10 to 80)	38 (30, 5 to 100)	0.60
Corneal/scleral melt	5 (4)	5 (17)	0 (0)	0.0005
Intraocular extension	6 (5)	5 (17)	1 (1)	0.003
Orbital extension	11 (8)	10 (33)	1 (1)	< 0.0001
Lymph node metastasis	1 (0)	1 (3)	0 (0)	0.23
Distant metastasis	1 (0)	1 (3)	0 (0)	0.23
T stage (at presentation), n (%)				
Tis	87 (67)	11 (37)	76 (76)	< 0.001
T1	15 (12)	0 (0)	15 (15)	
T2	6 (5)	2 (7)	4 (4)	
T3	12 (9)	8 (27)	4 (4)	
T4	10 (8)	9 (30)	1 (1)	

360-OSSN: Ocular surface squamous neoplasia with 360 degrees limbal involvement; SL-OSSN: Ocular surface squamous neoplasia with segmental limbal involvement; #On applying Bonferroni correction, a p-value of < 0.002 was considered statistically significant.

Tumor morphology was comparable between the two groups (p = 0.10) but 360-OSSN tumors showed greater proportion of diffuse quandrantic involvement (63% vs 3%; p < 0.0001), greater proportion of ocular surface involvement (65% vs 14%; p < 0.0001), greater largest diameter (24 mm vs 8 mm; p < 0.0001) and greater thickness (8 mm vs 2 mm, p < 0.0001). In 50% (n = 15) of 360-OSSN tumors, circumferential configuration (Fig. 2) was noted which was also observed in 34% (n = 34) of SL-OSSN tumors (p = 0.28). Other tumor features such as presence of keratin, intrinsic vascularity, feeder vessels and tumor pigmentation were comparable between the groups. Fixation to sclera (57% vs 16%; p < 0.0001), corneal/scleral melt (17% vs 0%; p = 0.0005), intraocular tumor extension (17% vs 1%; p = 0.003), orbital tumor extension (33% vs 1%; p = 0.0001) and advanced T stage (p < 0.0001) were all higher in the 360-OSSN group (Table 2). Lymph node metastasis (8% vs 0%; p = 0.05), and distant metastasis (4% vs 0%; p = 0.23) were comparable.

Primary management options in 360-OSSN tumors included immunotherapy with topical and subconjunctival IFNα2B in 23% (n = 7), enucleation in 13% (n = 4) and exenteration in 50% (n = 15). Four patients who refused primary treatment were not included for assessment of outcomes. Of the remaining 26 patients, at a mean follow-up of 16 months (median, 6 months; range 1 to 94 months), tumor-free survival was achieved in 85% (n = 22) and 12% (n = 3) were alive with residual disease in the form of microscopic residual disease post exenteration (n = 1), lymph node metastasis (n = 2) and residual ocular disease (n = 1). Disease-related death from intracranial extension was seen in 4% (n = 1), who also had lymph node metastasis.

Of 7 patients who received IFNα2B, six showed complete resolution with IFNα2B, of which 2 patients had tumor recurrence. One was managed by topical mitomycin (MMC, 0.04%) and the latter underwent excisional biopsy and developed a second recurrence which warranted exenteration. One patient with diffuse papillary OSSN who was lost follow-up after initiation of IFNα2B therapy, resumed treatment and was on IFNα2B therapy at the time of compilation of data. Thus, globe salvage was feasible in 5 patients amongst whom 2 had limbal stem cell deficiency (LSCD) and poor ocular surface accounting with resultant vision salvage in 3 patients (Fig. 3). One patient had LSCD that was not severe enough to cause visual compromise (Fig. 3). No recurrences were seen after enucleation and orbital exenteration.

SL-OSSN tumors were primarily managed by immunotherapy with topical and subconjunctival IFNα2B in 26% (n = 26), topical chemotherapy with MMC in 1 (n = 1), excisional biopsy in 61% (n = 61), enucleation in 2% (n = 2,) and orbital exenteration in 1% (n = 1).

Eleven patients with SL-OSSN refused any form of treatment and were not included for assessment of outcomes. Tumor-free survival was achieved in 96% of cases at a mean follow-up period of 13 months (median, 6 months; range 1 to 108 months). Residual disease was present in 4% in the form microscopic involvement of surgical margins (n = 4).

Recurrences were seen in 8% (n = 7) of SL-OSSN group [s/p excisional biopsy (n = 6); s/p topical MMC (n = 1)] which were managed by IFNα2B (n = 2), alcohol keratoepitheliectomy (n = 2), enucleation (n = 1), orbital exenteration (n = 1) and one patient was lost follow-up. Thus, globe salvage was achieved in 83% of cases and vision salvaged in 81%. Visual compromise in 2% was attributed to pre-existing cerebral visual impairment and chronic retinal detachment in one patient each. Four patients had focal LSCD that did not affect visual acuity. No recurrences were seen after IFNα2B, enucleation and orbital exenteration.

Histopathological features were assessed in patients (94/130) who underwent incisional biopsy, excisional biopsy, enucleation or exenteration. The 360-OSSN tumors showed greater proportion of invasive squamous cell carcinoma (83% vs 27%, p < 0.0001) than SL-OSSN tumors (Table 3). Well-differentiated squamous cell carcinoma was less common in 360-OSSN than SL-OSSN group but the difference did not reach a statistical significance (Table 3).

Table 3
Management, histopathological features and outcomes of ocular surface squamous neoplasia with 360° and segmental involvement of limbus

Management	**All**	**360-OSSN**	**SL-OSSN**	**p-value#**
	N = 130	**N = 30**	**N = 100**	
	N (%)	**N (%)**	**N (%)**	
Primary management				
Interferon alpha 2B	31 (24)	7 (23)	24 (24)	1.00
Mitomycin C	1 (1)	0 (0)	1 (1)	1.00
Excision biopsy	61 (47)	0 (0)	61 (61)	< 0.0001
Enucleation	6 (5)	4 (13)	2 (2)	0.03
Exenteration	16 (12)	15 (50)	1 (1)	< 0.0001
Refusal to treatment	12 (10)	4 (13)	11 (11)	0.75
Histopathological features	NA in 36	NA in 7	NA in 29	
Conjunctival Intraepithelial Neoplasia	56 (60)	4 (17)	52 (73)	< 0.0001
Squamous Cell Carcinoma	38 (40)	19 (83)	19 (27)	
Differentiation				
Well differentiated	19 (53)	6 (38)	13 (65)	0.16
Moderately differentiated	12 (33)	8 (50)	4 (20)	
Poorly differentiated	5 (14)	2 (12)	3 (15)	
Treatment outcomes	All	360-OSSN	SL-OSSN	
	N = 115	N = 26	N = 89	
	N (%)	N (%)	N (%)	
Mean follow up, months [mean (median, range)	14 (6, 1-108)	15 (6, 1–93)	13 (6, 1-108)	0.40
Tumor free survival	107 (93)	22 (85)	85 (96)	0.08
Lymph node metastasis (new)	2 (2)	2 (8)	0 (0)	0.05
Distant metastasis and death	1 (1)	1 (4)	0 (0)	0.23
Tumor recurrence	9 (8)	2 (8)	7 (8)	1.00
Globe salvage	79 (69)	5 (19)	74 (83)	< 0.0001
Vision salvage	75 (65)	3 (12)	72 (81)	< 0.0001
Limbal stem cell deficiency	7 (6)	3 (12)	4 (5)	0.35

360-OSSN: Ocular surface squamous neoplasia with 360 degrees limbal involvement; SL-OSSN: Ocular surface squamous neoplasia with segmental limbal involvement;

On applying Bonferroni correction, a p value of < 0.003 was considered statistically significant.

Discussion

Limbus (Latin, edge border) of the eye, refers to the zone of transition between the cornea and sclera with the latter being externally lined by the conjunctiva.[1] In addition to the well-known function of maintenance of corneal clarity, limbal stem cells have a presumed role in neoplastic processes.[1] This is supported by frequent occurrence of OSSN in the nasal quadrant which harbors stem cells in abundance that are triggered by ultraviolet (UV) exposure.[1] Concept of cancer stem cells may also explain the tendency of OSSN to spread in a circumferential fashion along the limbus[1] sometimes involving entire 12 clock hours or 360° of the limbus.[2–6] The present series attempts to describe the clinico-demographic profile and outcomes of patients with 360-OSSN and compare them with SL-OSSN in order to identify cues for early diagnosis and appropriate management.

In this study, patients with 360-OSSN were symptomatic for a longer duration than those with SL-OSSN (17 months vs 8 months; p = 0.003) which may have a role to play in advanced presentation of disease. While this lag time in receiving appropriate treatment may be due to multiple factors such as treatment seeking behaviour and logistics, erroneous diagnosis at first point of contact and sub-optimal prior interventions were identified as possible contributing factors. It was observed in this study that, 360-OSSN tumors were under-diagnosed or missed in 17% (5/30) of the cases of which were mistaken for microbial keratitis, fungal keratitis, viral keratitis, episcleritis or phthisis bulbi. OSSN has been shown to co-exist with corneal dellen and microbial keratitis.[10] Mass effect from the tumor lesion and limbal stem loss could predispose to corneal dellen formation, thinning and melt. Since limbal stem cells play a crucial role in corneal epithelial integrity, the authors propose that extensive involvement of limbus by 360-OSSN is likely to disturb the epithelial equilibrium to a significant extent even in relatively flat lesions. The red flag sign to identify the subtle tumor in such cases and in cases with extensive corneal melt is the presence of keratin. Keratin deposit is to be carefully looked for and an incisional may be performed to confirm the same if deemed necessary.

Prior intervention was identified as another important risk factor for 360-OSSN (p = 0.0002) in this study. Sub-optimal prior intervention for 360-OSSN was rendered either with an erroneous diagnosis or with a suspicion/clinical diagnosis of OSSN. In either case, this resulted in a delay of definitive therapeutic intervention which is likely to have facilitated tumor progression in due course of time. While prior intervention lacking therapeutic effect (in cases of erroneous diagnosis or those managed with topical MMC and IFNα2B) may have contributed to the lag time alone, invasive procedures such as multiple biopsies or debulking, may have resulted in microscopic seeding and spread of tumor accounting for extensive involvement of the limbus and ocular surface.

Gichuhi et al described the propensity of OSSN to spread along the limbus[1] and this configuration was seen in 50% of 360-OSSN as well as 34% of SL-OSSN. Few cases of 360-OSSN in published literature also show a similar pattern.[2,3,5,6] This finding supports the plausible role of limbal stem cell niche in origin and progression of OSSN. This wreath-like configuration, however, can be subtle with lesions reaching a height of as less as 1 mm. A high index of suspicion should therefore be kept for placoid lesions straddling the limbus in a circumferential fashion. On the other hand, involvement of entire limbus can also be seen with tumors with diffuse ocular surface involvement and large lesions[3–5] which was observed in 50% of the 360-OSSN tumors in this study (Fig. 2). Other clinical features such as larger tumor diameter, propensity for diffuse involvement of ocular surface, fixation to sclera, corneal/scleral melt, intraocular extension, orbital extension and advanced T stage at presentation signify that 360-OSSN is an advanced form of disease. Intraocular extension of tumor was seen in 17% of 360-OSSN, all of which had corneal/scleral melt. Corneal melt from aforementioned factors[10] is likely to have facilitated intraocular spread of tumor.

Management protocols of 360-OSSN, in this study, adhered to the general principles of management of OSSN.[7] Interventions described for 360-OSSN in literature include topical IFNα2B, MMC, 5-fluorouracil and combination of excisional biopsy with MMC.[2–6] The authors recommend against excisional biopsy for these lesions due to concerns of LSCD and its sequalae. Topical therapy with IFNα2B, MMC or 5-FU may be the first line of management in non-invasive disease but response should be closely monitored and excisional biopsy performed only for residual tumors with simple limbal epithelial transplant.[11] In advanced tumors, presence of intraocular invasion warrants enucleation and orbital exenteration be reserved for tumors with orbital extension or diffuse lesions which do not respond/progress despite any form topical immuno/chemotherapy.

This is the largest series of OSSN with 360-limbal involvement reported in literature. While pre-existing literature focussed on successful management of individual cases, this study elucidates the risk factors, the pattern of tumor spread, management and outcomes in a larger cohort of patients.

To conclude, OSSN tumors tend to spread along the limbus in a circumferential fashion and uncommonly involve the entire limbus. When subtle or associated with co-existent corneal or scleral thinning, these lesions can be misdiagnosed, resulting in advanced presentation and delay in appropriate management. Raising awareness among practising ophthalmologists can aid in early detection of the disease. Globe and vision salvage can be achieved in early forms of disease but aggressive management is warranted for advanced tumors for life salvage.

Declarations

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Author Contribution: Swathi Kaliki contributed to the study conception and design. Material preparation, data collection and analysis were performed by Vijitha S Vempuluru, Neha Ghose, Monalisha Pattnaik, and Ashik Mohamed. The first draft of the manuscript was written by Vijitha S Vempuluru and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript

Ethics Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of LV Prasad Eye Institute

Consent to participate: Informed consent was obtained from all individual participants included in the study

Consent to Publish: The authors affirm that human research participants provided informed consent for publication of the images in Figures 1, 2, and 3

References

1. Gichuhi S, Macharia E, Kabiru J, et al. Clinical Presentation of Ocular Surface Squamous Neoplasia in Kenya. JAMA Ophthalmol 2015;133(11):1305–1313.
2. Zarei-Ghanavati S, Alizadeh R, Deng SX. Topical interferon alpha-2b for treatment of noninvasive ocular surface squamous neoplasia with 360° limbal involvement. J Ophthalmic Vis Res 2014;9(4):423–6.
3. Kalamkar C, Radke N, Mukherjee A, Radke S. Xeroderma pigmentosum with bilateral ocular surface squamous neoplasia and review of the literature. BMJ Case Rep. 2016 May 10;2016:bcr2016215364.
4. Kumar DA, Agarwal A. Giant Ocular Surface Squamous Neoplasia Wrapping Whole Cornea. Eye Contact Lens 2018;44:S358-S360.
5. Patel H, Jeang LJ, Shah A, Espana EM, Margo CE. Widespread Ocular Surface Squamous Neoplasia Treated with Topical Interferon Alpha-2b. Ocul Oncol Pathol 2018;4(5):298–303.
6. Mohamed-Noriega K, Treviño-Herrera AB, Olvera-Barrios A, Morales-Wong F, Mohamed-Hamsho J. Resolution of giant ocular surface squamous neoplasia with topical 5-fuorouracil 1. SAGE Open Med Case Rep. 2019 Apr 17;7:2050313X19843392.
7. Cicinelli MV, Marchese A, Bandello F, Modorati G. Clinical Management of Ocular Surface Squamous Neoplasia: A Review of the Current Evidence. Ophthalmol Ther 2018;7(2):247–262.
8. Nanji AA, Sayyad FE, Galor A, et al. High-resolution optical coherence tomography as an adjunctive tool in the diagnosis of corneal and conjunctival pathology. Ocul Surf 2015;13:226–235.
9. Conway RM, Graue GF, Pelayes DE, et al. Conjunctival Carcinoma. American Joint Committee on Cancer (AJCC). AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer; 2017.
10. Kapoor AG, Vempuluru VS, Laghimshetty S, et al. Ocular Surface Squamous Neoplasia With Coexistent Microbial Keratitis: Incidence, Risk Factors, Clinical Features, Microbiological Profile, and Treatment Outcome. Cornea. 2021 Jul 22. doi: 10.1097/ICO.0000000000002809. Epub ahead of print.
11. Kaliki S, Mohammad FA, Tahiliani P, Sangwan VS. Concomitant Simple Limbal Epithelial Transplantation After Surgical Excision of Ocular Surface Squamous Neoplasia. Am J Ophthalmol. 2017 Feb;174:68–75.

Figures

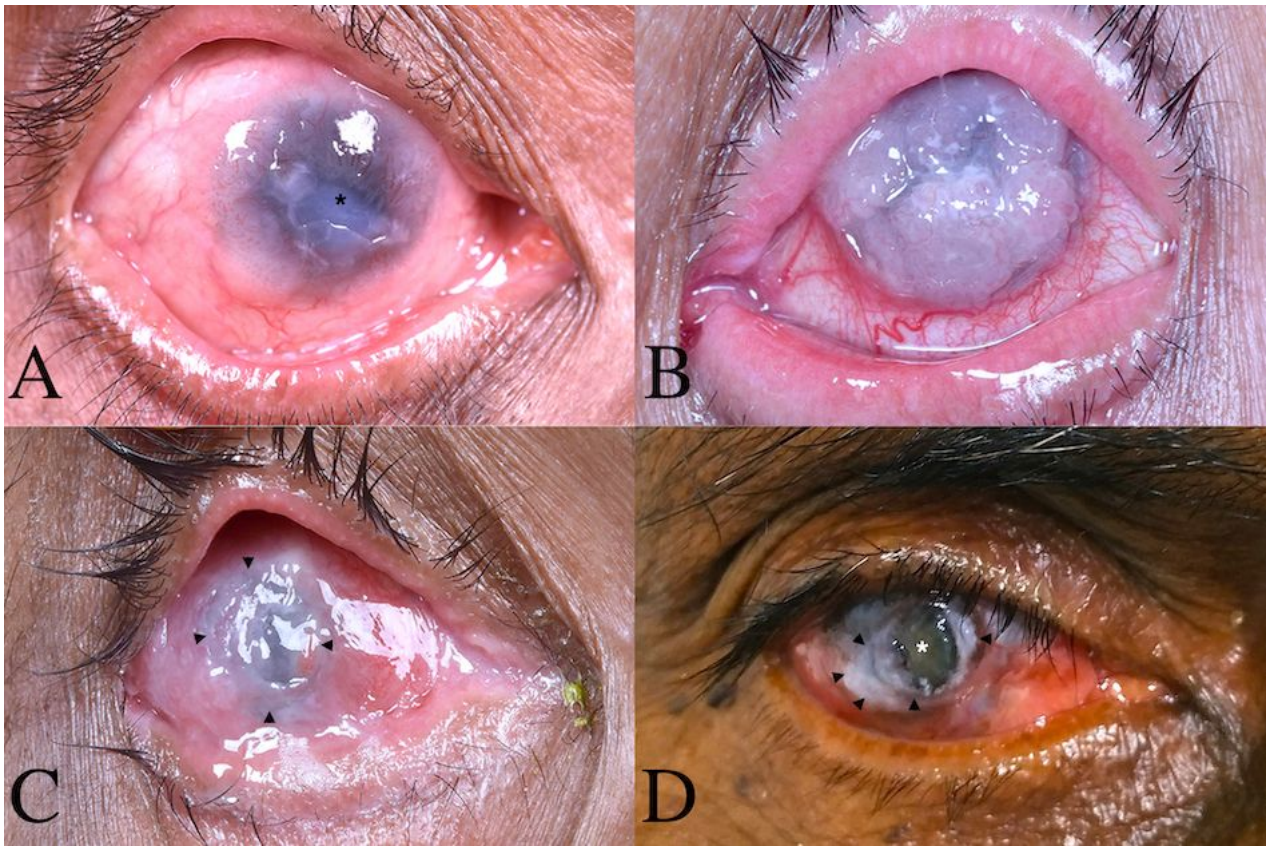

Figure 1

Clinical photographs of ocular surface squamous neoplasia (OSSN) involving 360 degrees of limbus in which the diagnosis was missed or delayed

(A) A 73-year-old gentleman with a papillary tumor straddling the entire circumference of the limbus and central dellen formation (asterix), primarily managed as a corneal ulcer

(B) An 83-year-old lady was treated as herpetic keratitis till tumor progressive increased in thickness and involved the entire cornea and limbus

(C) A 55-year-old lady was referred as phthisis bulbi. The clinical photograph shows placoid lesion involving the entire ocular surface with wreath like configuration (arrow heads) of keratinization encircling the cornea

(D) A 72-year-old gentleman was treated as fungal keratitis underwent evisceration for blind eye with corneal perforation. Retrospective review of clinical images shows central corneal melt (asterix) surrounded by a placoid keratinized lesion (arrow heads) surrounding the corneal perforation

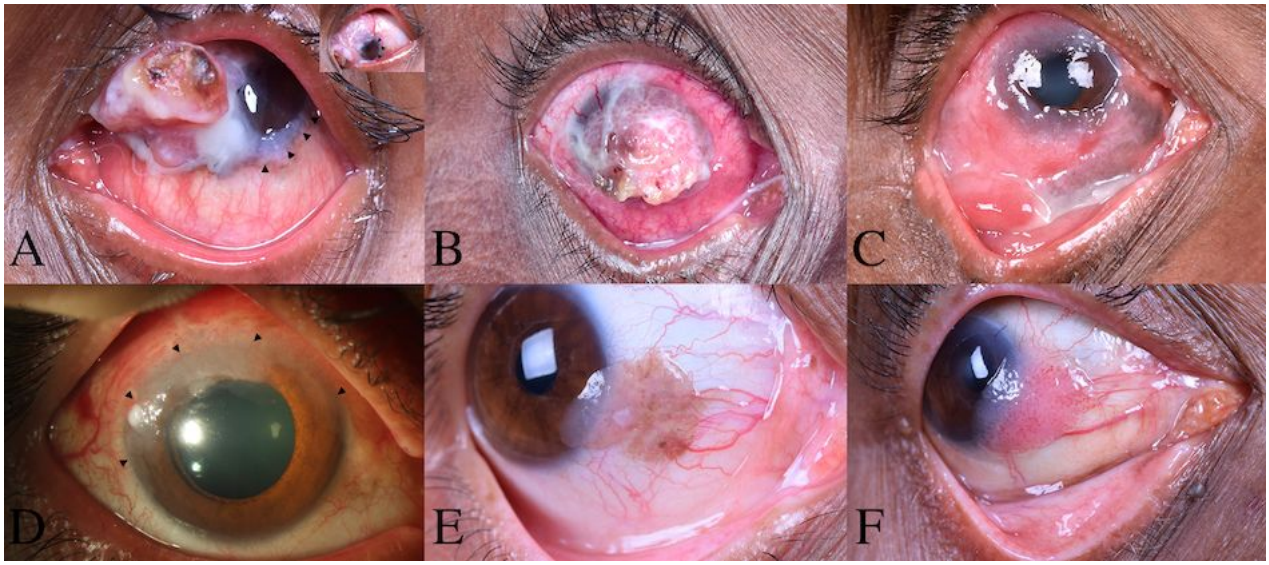

Figure 2

Clinical photographs illustrating the patterns of tumor spread in OSSN with 360 degrees limbal involvement (360-OSSN) and segmental limbal involvement (SL-OSSN)

(A) 360-OSSN arising from the nasal quadrant with a placoid growth extension that involves the entire limbus in a circumferential fashion

(B) 360-OSSN arising from the nasal quadrant with long axis of the tumor perpendicular to the nasal limbus depictive of radial pattern of tumor spread

(C) 360-OSSN showing both circumferential spread around the limbus as well involvement of the bulbar, forniceal and tarsal conjunctiva suggestive of combined pattern of tumor spread

(D) SL-OSSN showing a plaocid lesion with scanty keratin and vascularity extending from 7:00 to 2:00 clock hours with long axis of the tumor extending circumferentially (arrow heads) along the limbus

(E) A pigmented placoid lesion with spread perpendicular to limbus greater than along the limbus, depicting radial pattern of tumor spread in SL-OSSN

(F) Papillary SL-OSSN which extends equally along the limbus and perpendicular to it suggestive of combined pattern of tumor spread

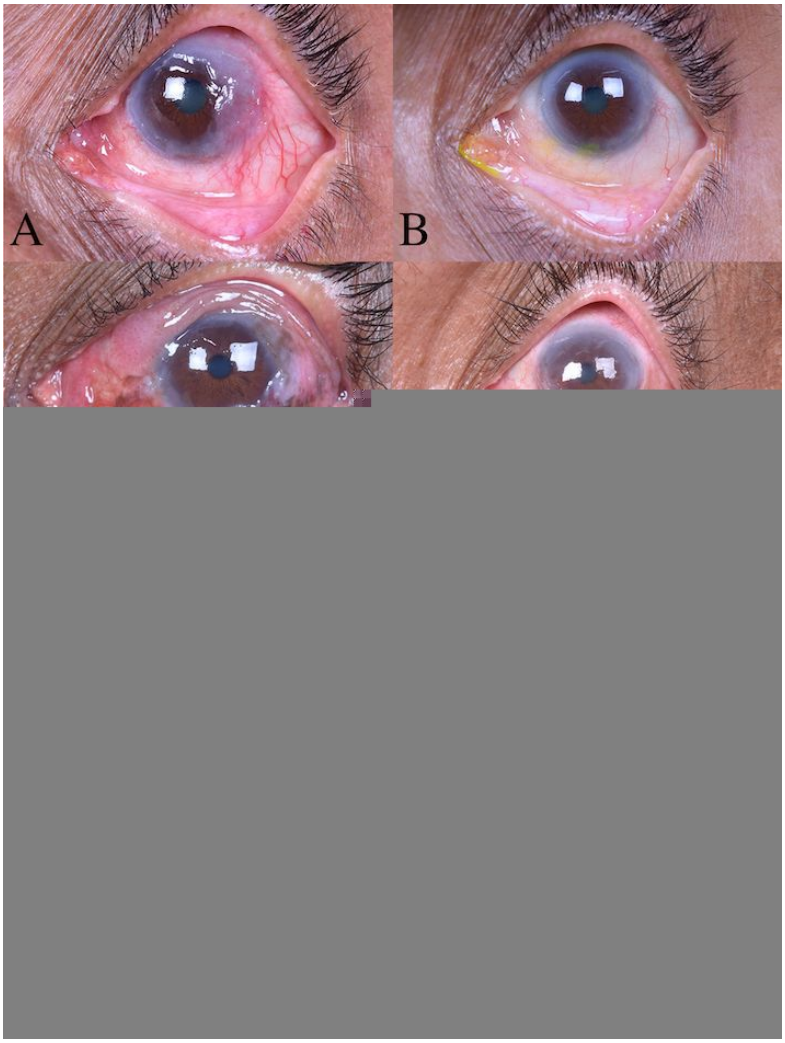

Figure 3

Clinical photographs depicting treatment outcomes in OSSN with 360 degrees limbal involvement (360-OSSN)

(A) 360-OSSN where the placoid tumor (B) completely resolved with a combination of topical and subconjunctival interferon alpha-2B therapy. The ocular surface remained healthy with a clear cornea.

(C) 360-OSSN managed with a combination of topical and subconjunctival interferon alpha-2B therapy that resulted in (D) complete tumor regression. However, limbal stem cell deficiency resulted with conjunctivalization and superficial corneal haze.

(E) 360-OSSN with scleral fixity managed by (F) enucleation

(G) 360-OSSN with extensive ocular surface and orbital involvement managed by (H) orbital exenteration