Clinicopathological Characteristics of Ocular Surface Squamous Neoplasia: A 10-Year Review from a Referral Tertiary Centre in Nigeria

Dauda Eneyamire Suleiman (✉ desuleiman@atbu.edu.ng)

Abubakar Tafawa Balewa University <https://orcid.org/0000-0003-1880-1298>

Almustapha Aliyu Liman

Ahmadu Bello University

Garba Dahiru Waziri

Ahmadu Bello University

Yawale Iliyasu

Kaduna State University

Saad Aliyu Ahmed

Ahmadu Bello University

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Abstract

Background: Ocular surface squamous neoplasia is a heterogeneous group of proliferative squamous lesions on the ocular surface with varying biologic behaviours. This study aims to report the clinical profile and pathologic characteristics of cases of OSSN seen at a tertiary referral centre in North West Nigeria

Methods: A retrospective review of all cases of OSSN diagnosed over a 10-year period was done

Results: OSSN accounted for 68 out of 91 ocular surface lesions affecting twice as many males as females and a peak incidence in the 30-39 years age group. They frequently presented as higher grade and higher stage lesions with invasive squamous cell carcinoma being the most frequently diagnosed OSSN. They also frequently show association with HIV infection and a relatively long duration of symptoms before presentation

Conclusion: OSSN occur in a relatively young age group in our environment. Certain clinical and epidemiological features appear to [predict the occurrence of higher grade lesions and this may help in the clinical prediction of likely pathologic grade and/or biologic behaviour of these lesions.

Introduction

The terminology 'Ocular surface squamous neoplasia' (OSSN) was first coined by Lee & Grant in 1995 as an umbrella term that encompasses a spectrum of dysplastic, pre-invasive and invasive squamous epithelial lesions of the conjunctiva and cornea.[1] OSSN was the term proposed to replace previous terminologies such as ocular surface epithelial dysplasia (OSD), Bowenoid epithelioma, precancerous epithelioma of the limbus, conjunctival intraepithelial neoplasia among others.[1,2] OSSN is not a single pathological entity but rather a heterogeneous group of lesions of the ocular surface with varying biologic behaviours. While the initial usage of OSSN also includes benign tumours like squamous papilloma, in current usage, the term OSSN refers to various grades of conjunctival and corneal squamous intraepithelial lesions, as well as *in situ* and invasive squamous cell carcinoma.[2,3]

Two clinico-epidemiological patterns of OSSN occurrence have been highlighted: the first pattern is seen in older, predominantly male patients in temperate climates and show no association with Human Immunodeficiency Virus (HIV) or human papilloma virus (HPV) infection. The second pattern occurs among younger men and women in tropical climates, and shows strong association with HIV and HPV.[3]

While it is difficult to attribute the pathogenesis of OSSN to a single aetiological factor, important risk factors that have been associated with OSSN includes ultraviolet (UV) radiation exposure, HIV and HPV infections and smoking.[3,4] UV light induces the formation of pyrimidine dimers and is mutagenic for the p53 gene.[2,4,5] The inability to repair UV-induced DNA damage explains the high incidence of OSSN lesion in patients with xeroderma pigmentosum.[4] In addition to causing DNA damage, UV radiation is

thought to alter the expression of Matrix Metallo-proteinases (MMP) particularly MMP-1 and MMP-3, and this is thought to play some role in the pathogenesis of OSSN.[4,6]

In addition to DNA damage and failed DNA repair, decreased immunity is also an important event in the development of OSSN.[7] It has been suggested that vitamin A deficiency impairs cell-mediated immunity and differentiation of stem cells; it also compromises epithelial integrity increasing the risk for HPV invasion and the associated consequences.[7,8] Temporal light that passes through the anterior chamber strikes the nasal limbal cells where there is less amount of melanin and these foci reflects the common site for OSSN, pterygium, eyelid malignancy and cataract.[8,9] Clinically, the presentation of OSSN lesions are diverse but usually appears as a unilateral sessile, fleshy, elevated lesion in the inter-palpebral region of the limbal area.[6] Various clinico-morphological types of OSSN have been described including placoid, nodular, diffuse and fungating types.[2,10] The placoid types may be further subdivided into those that are leukoplakic, gelatinous, velvety, or papilliform.[10]

This study aims to report the clinical profile and pathologic characteristics of cases of OSSN seen at a tertiary referral centre in North West Nigeria

Materials And Methods

This retrospective descriptive study was based on all histologically confirmed cases of OSSN obtained from specimens submitted to the Pathology Department of the institution for histopathological examination in the period from 1st January 2005 to 31st December 2014. All cases from the histopathology diagnosis record book with a histological diagnosis of conjunctival/corneal intraepithelial neoplasia/dysplasia, carcinoma in situ or invasive squamous cell carcinoma over the study period were extracted. The requisition forms from the clinicians were also retrieved and relevant clinical and demographic data were extracted. Information retrieved included the age, sex, presenting symptoms, clinical characteristics of the lesions, HIV status, tumour site, and the American Joint Committee on Cancer (AJCC) 7th edition stage of the tumours.[11,12]

Data was analysed with the aid of the Statistical Package for Social Sciences version 21 software (SPSS Inc, Chicago IL., USA), and quantitative variables were summarized using descriptive statistics.

To evaluate which clinical and pathologic features were associated with increasing histologic grade, a chi-square analysis was performed for categorical variables using the linear-by-linear association P value output. A correlation coefficient was calculated for continuous variables and data was presented as frequency distribution tables. Ethical clearance was received from the institutional Hospital Research and Ethics Committee (HREC). [HREC Number: ABUTH/HREC/M32/2014; Date of approval: 30th December, 2014].

Results

Demographic characteristics

There were a total of 91 conjunctival/corneal lesions over the study period, out of which 68 were OSSN. The remainder included squamous papilloma, pterygium and vascular, melanocytic and soft tissue lesions. The 68 OSSN cases includes 46 males and 22 females (M:F, 2.1:1) with a peak age of occurrence in the 30-39 years age group (Table 1). A single case of OSSN was reported in the 0-9 years age group and this was in a 3 years old boy with conjunctival squamous cell carcinoma on a background of xeroderma pigmentosum.

Table 1 Age and sex distribution of 68 cases of OSSN			
Age group (years)	Male	Female	Total (%)
0-9	1	0	1 (1.5)
10-19	0	0	0 (0)
20-29	4	1	5 (7.4)
30-39	18	6	24 (35.3)
40-49	12	8	20 (29.4)
50-59	5	5	10 (14.7)
60-69	4	2	6 (8.8)
≥70	2	0	2 (2.9)
Total	46	22	68 (100.0)

Clinical history

The commonest presenting symptom was conjunctival/corneal growth/mass. Other presenting symptoms include foreign body sensation, eye redness, impaired vision and proptosis. The average duration of symptoms was 16 months (range: 4-24 months).

Clinical characteristics of OSSN lesions

Majority of the OSSN lesions occur either in the nasal limbus or orbit. Invasive squamous cell carcinomas were more likely to present as orbital masses ($p<0.05$) while carcinoma *in situ* and conjunctival intraepithelial neoplasia were most likely to occur in the nasal limbus ($p<0.05$).

All the cases seen were unilateral lesions, 24 of which presented as fungating ocular and/or orbital masses, 17 cases presented as papilliform lesions, 13 cases were leukoplakic, 7 cases presented as nodular conjunctival lesions while gelatinous lesions make up the remaining 7 cases. All the fungating masses were histologically diagnosed as invasive squamous cell carcinoma (Tables 2 and 3).

Table 2
Anatomic location of OSSN lesions

Diagnosis	Location				
	Nasal	Temporal	Inferior	Superior	Orbital
SCC (<i>n</i> =41)	12	4	1	0	24
CIS (<i>n</i> =16)	9	5	1	1	0
CIN (<i>n</i> =11)	6	3	2	0	0
Total (<i>n</i> =68)	27	12	4	1	24
Key: SCC- invasive squamous cell carcinoma; CIS= squamous cell carcinoma <i>in situ</i> ; CIN- conjunctival intraepithelial neoplasia					

Table 3
Clinical characteristics of OSSN cases

Histologic diagnosis	Clinical appearance				
	Fungating	Gelatinous	Leukoplakic	Nodular	Papilliform
SCC (<i>n</i> =41)	24	0	5	3	9
CIS (<i>n</i> =16)	0	3	5	3	5
CIN (<i>n</i> =11)	0	4	3	1	3
Total (<i>n</i> =68)	24	7	13	7	17
Key: SCC- invasive squamous cell carcinoma; CIS= squamous cell carcinoma <i>in situ</i> ; CIN- conjunctival intraepithelial neoplasia					

AJCC Tumour stage

The primary tumour (T) stage of majority (68.3%) of the invasive squamous cell carcinoma cases was T4 with the remainder being either T2 (9(.8%) or T3 (14.6%). The primary tumour could not be assessed (Tx) in 14 (20.6%) OSSN cases (Table 4). No nodal or distant metastasis was observed in all cases.

Table 4
Summary of the 7th edition AJCC T staging of OSSN lesions

Primary Tumour(T)	Description	Number (%)
Tx	Cannot assess the tumour	14 (20.6)
T0	No evidence of tumour	0 (0.0)
Tis	Carcinoma in situ	16 (23.5)
T1	Tumour (≤ 5 mm in greatest dimension) invades through the basement membrane without invasion of adjacent structures	0 (0.0)
T2	Tumour (> 5 mm in greatest dimension) invades through the basement membrane without invasion of adjacent structures	4 (5.9)
T3	Tumour invades adjacent structures excluding the orbit	6 (8.8)
T4	Tumour invades orbit with or without further extension	
T4a	Tumour invades orbital soft tissues without bone invasion	12 (17.6)
T4b	Tumour invades bone	16 (23.6)
T4c	Tumour invades adjacent paranasal sinuses	0 (0.0)
T4d	Tumour invades brain	0 (0.0)

Histopathologic characteristics

Out of the 68 specimens received in the histopathology laboratory, 16 were ocular exenteration specimens while the remainder were small incisional or excisional biopsies. Following histopathological analysis of OSSN lesions, 41 were invasive squamous cell carcinomas of the conjunctiva/cornea, 16 were squamous cell carcinoma *in situ*, while the remainder (11) were conjunctival squamous intraepithelial neoplasia (conjunctival squamous dysplasia). Seven out of the 11 cases of conjunctival squamous intraepithelial neoplasia were reported as moderate dysplasia, 3 were severe dysplasia while only a single case of mild dysplasia was reported. Fig. 1 and Fig. 2 **show** micrographs of invasive squamous cell carcinoma and severe dysplasia respectively.

Association of OSSN with HIV infection

HIV status was available only in 38 out of the 68 OSSN cases. Of these, a total of 26 (68.4%) OSSN cases were HIV positive. HIV positive frequency was 78.3% of invasive SCC, 60% for carcinoma *in situ*, and 40% for conjunctival intraepithelial neoplasia (Table 5).

Table 5
Distribution of HIV status of OSSN cases

OSSN	HIV Positive (%)	HIV Negative (%)	Total
SCC	18 (78.3)	5 (21.7)	23
CIS	6 (60.0)	4 (40.0)	10
CIN	2 (40.0)	3 (60.0)	5
Total	26 (68.4)	12 (31.6)	38

Clinical and Pathological factors associated with high grade OSSN lesions

Predictive factors of higher grade OSSN lesions (severe dysplasia, carcinoma in situ and invasive squamous cell carcinoma) on univariate analysis were male gender, HIV positivity, temporal, as well as fungating and papillomatous clinical appearance. (Table 6)

Table 6
Summary of P values of Factors predictive of Higher grade OSSN

Predictive factors	P value
Male	0.02
HIV Positive	0.01
Temporal location	0.01
Fungating appearance	0.002
Papilliform appearance	0.03

Discussion

This retrospective study described the clinical and histopathological features of patients diagnosed with various forms of OSSN at a tertiary centre in Nigeria.

The peak age group of patients affected by OSSN was 30-39 years, slightly younger than the general average age of OSSN that have been reported in Nigeria and across sub-Saharan Africa which is usually in the 40-49 years age group.[13–15] However, in keeping with previous reports, the condition occurs in a much younger age group in our patients as compared to studies in Caucasian populations and this has been attributed to the higher association of OSSN cases in the tropics with HIV/AIDS.[2,3,16,17] This study reveals a predominant affectation of males in disagreement with early observations across sub-Saharan Africa where an equal sex prevalence was generally reported.[3,18,19] However, some recent studies have revealed a male predominance for OSSN in sub-Saharan Africa.[13,14] These variations in

sex prevalence are probably related to differences in study design as most of the single institution-based studies show a male predominance whereas the larger scale studies show an equal sex distribution. A female predominance has also been reported in occasional studies,[20] again highlighting the selection bias inherent in single institution-based studies. The commonest presenting symptom in this study was a conjunctival growth/mass in keeping

with most available literature.[6,20,21] There was relatively long average duration of symptoms before presentation (16 months) as observed in previous studies within the country.[14,20,22] This may be related to poor health seeking behaviours as well as cost of treatment due to poor health insurance cover. This may also account for the common presentation of fungating ocular and/or orbital masses in our series.

The dominant clinical appearance of OSSN was either as fungating, papilliform or leukoplakic lesions with nodular and gelatinous lesions comprising a minority of cases. This finding generally agrees with most other studies from within Africa but is in contrast to a study from Asia where gelatinous appearance was more predominant. [13,21,23] This finding suggests a possible racial/ethnic variation in clinical appearance of OSSN but this will need to be validated by more large scale, comparative studies.

Invasive squamous cell carcinoma accounts for the majority of OSSN cases in this study. While this may partly be explained by delayed presentation to the hospital, it raises the question as to whether our cases have a more inherent ability to progress rapidly along the continuum of OSSN from mild dysplasia to invasive squamous cell carcinoma.

Using the AJCC 7th edition staging system, majority (approx. 40%) of our cases were stage T4 at diagnosis, again reflecting the late presentation of our patients to the hospital. However, no nodal or distant metastasis was observed in keeping with most studies.[14,20,23–25] The histopathological spectrum of different diseases lumped under the rubric of OSSN serves to highlight the fact that OSSN is far from being a single biologic entity but rather a heterogeneous group of diseases that encompasses both premalignant and malignant diseases.

Therefore, the use of the term 'OSSN' as a 'bottom line' histological diagnosis is highly discouraged to avoid the perils of clinical misinterpretation inherent in such an approach. As Margo and White accurately asserted, the term OSSN, while conceptually appropriate may be rather misleading and perilous clinically. [26]

In keeping with the epidemiological association between OSSN and HIV in Africa, majority of our cases were HIV positive with invasive squamous cell carcinoma having the highest proportion of HIV positive individuals. This is corroborated by various studies in Nigeria and around Africa.[3,14,16,27]

Certain clinico-epidemiological and lesional factors were found to be predictive of higher grade OSSN. This includes male sex, HIV positive status, temporal location, and fungating and papilliform appearance of the lesions. Even though male gender was associated with the occurrence of higher-grade lesions of

OSSN, age was not found to be predictive of higher-grade lesions. It has been suggested that men have a more cumulative exposure to ultraviolet (UV) light as a result of their more common engagement in outdoor activities or occupations.[28] In the absence of definitive data on the rate or intensity of UV-B exposures, this remains a postulation that requires validation by other studies.

The association of fungating appearing lesions with higher grade lesions is not surprising as the size and extent of these lesions signifies a higher mitotic rate that is characteristic of more aggressive lesions. Similar explanations have been made for nodular lesions in other studies but this was not predictive of higher grade lesions in our series.[28] Even though OSSN lesions are generally more common in the nasal limbus, this study revealed that temporal lesions are more likely to be associated with higher grade disease. This may be related to the intensity of UV exposure, variations in HPV persistence in these areas or other factors yet to be determined.

Conclusion

As a single-institution study, our findings may be limited by the usual biases inherent in such studies. However, this study has revealed that majority of cases of OSSN in this environment are invasive squamous cell carcinomas with frequent orbital involvement, higher AJCC T stage and frequent association with positive HIV status. The clinician, in suspected cases, may employ the use of devices such as Optical Coherent Tomography (OCT) and high resolution ultrasound to determine the extent of invasiveness to facilitate early diagnosis and treatment. This study also demonstrates that certain patient and lesional characteristics are predictive of higher-grade lesions. Further studies are required to evaluate treatment outcomes and prognosis of OSSN as well as the relationship between HPV and OSSN in our environment.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Dauda Eneyamire Suleiman, Almustapha Aliyu Liman and Garba Dahiru Waziri. The first draft of the manuscript was written by Dauda Eneyamire Suleiman and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript

Ethics approval

Ethical clearance was received from the institutional Hospital Research and Ethics Committee (HREC). [HREC Number: ABUTH/HREC/M32/2014; Date of approval: 30th December, 2014].

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Figures

Figure 1

Micrograph showing a well differentiated invasive squamous cell carcinoma of the conjunctiva [H&E, x200]

Figure 2

Low power and high power of severe dysplasia of squamous epithelium of the conjunctiva. [H&E; x40 (left); x400 (right)]