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Evaluation of Pattern and Frequency of P53 Expression in Ocular Surface Squamous Neoplasia

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Abstract

Introduction: Ocular Surface Squamous Neoplasia (OSSN) is the most common tumor of ocular surface involving the limbus, cornea and conjunctiva and includes mild dysplasia to intraepithelial neoplasia and squamous cell carcinoma (SCC). The TP53, a tumor suppressor gene, mutation is an important prognostic marker in more than half of human tumors and is reported in ocular malignancies.

Aims and Objectives: To evaluate the frequency and pattern of expression of p53 in OSSN.

Methods: It is a cross sectional study done over a period of 6 months in a tertiary health center including 35 cases of histo-pathologically confirmed OSSN cases ranging from various grades of conjunctival intraepithelial neoplasia (CIN) to carcinoma in-situ and SCC. Representative sections of each lesion were subjected to immunohistochemical marker p53 staining and its expression was evaluated. The association between P53 expression and pathological parameters were assessed using MedCalc and SPSS statistical software.

Results: The age of the total 35 cases ranged from 18-77 years with the mean age of 47.9 years and female to male ratio of 1.05. Among 35 cases, 8 cases were seropositive for Human Immunodeficiency Virus (HIV). Majority of cases were grade III CIN (n=14) followed by SCC (n=10). The p53 expression was positive in 25 out of 35 cases. The mutant P53 expression showed significant association with higher grades of OSSN (p = 0.02), with mutant p53 expression in grade III of intraepithelial neoplasia (64.2%) and SCC (90%). There was no significant association between pattern and intensity of expression of p53 in different grades of OSSN.

Conclusion: The p53 gene mutation plays a major role in the pathogenesis of OSSN. The mutant p53 expression in OSSN are associated with bad prognosis and progression to higher grades.

Keywords: Ocular surface squamous neoplasia, TP53, Conjunctival Intraepithelial neoplasia (CIN)

Introduction

Ocular Surface Squamous Neoplasia (OSSN) is defined as the range of disease from mild dysplasia to carcinoma in situ and invasive squamous cell carcinoma. OSSN may be located on cornea, conjunctiva and limbus but is mostly found on inter palpebral fissure.[1] OSSN's regional occurrence varies. Previous epidemiological research found that the incidence of OSSN was 0.13 per lakh in Uganda and less than 0.20 per million each year in the UK. According to reports, Brisbane, Australia, had an incidence of 1.9/100000 people.[2]

Mutational inactivation of p53 has been reported in ocular malignancies including OSSN and is associated with poor prognosis.[3] Ultraviolet B (UVB) rays induced CC to TT dimer transition of the p53 tumor suppressor gene have been observed in OSSN lesion.[4]

The interest in p53 lies in its implication for the development of cancer therapies and its prognostic merit. Tumors with mutant p53 do not respond well to DNA damaging radiotherapy and chemotherapy. Hence in the present study we aim to evaluate the frequency and pattern of p53 expression in OSSN cases.

Methodology

It is a cross sectional study done over a period of 6 months from December 2023 to May 2024 in a tertiary health center including 35 cases of histo-pathologically confirmed OSSN cases ranging from various grades of conjunctival intraepithelial neoplasia (CIN) to carcinoma in-situ and SCC. The clinicopathological parameters were documented. Representative sections of each lesion were subjected to immunohistochemical marker p53 staining and its expression was evaluated.

Mutant p53 staining pattern is determined by either Null pattern - complete absence of p53 expression with internal control (positive) showing moderate to strong staining, variable staining or over expression pattern which is strong staining in more than 80% tumor cell nuclei much stronger compared with the internal control or by cytoplasmic staining which is determined by predominant cytoplasmic staining in the absence of strong nuclear staining in more than 80% of tumor cell nuclei.

The association between clinico-pathological parameters with p53 expression was assessed using MedCalc and SPSS statistical software. The quantitative variables were expressed in terms of mean, median, range and standard deviation. The categorical variables were expressed in terms of percentages. The association between the categorical variables were assessed using Chi Square test and p value of less than 0.05 was considered as significant.

Results

The study included a total of 35 histo-pathologically confirmed OSSN cases. Of which, 17 cases (48.6%) were males and 18 cases (51.4%) were females constituting 1.05:1 female to male ratio. The age of the cases ranged from 18-77 years with mean age of 47.9 years and standard deviation 15.1 years. (Table 1)

Among the spectrum of OSSNs, majority of the cases belonged to grade III intraepithelial neoplasia. Ten

cases were SCC, six cases were grade II intraepithelial neoplasia, two cases of carcinoma in-situ and remaining three cases were grade I intraepithelial neoplasia. (Table 2)

The p53 mutant expression was seen in 25/35 cases (71.4%). Of which, majority of the p53 mutant expression was noted in grade II intraepithelial neoplasia (6/6 cases, 100%), followed by SCC (9/10 cases, 90%) and grade III intraepithelial neoplasia (9/14 cases, 64.2%). (Table 2) There was no age and gender association with various grades of intraepithelial neoplasia, carcinoma in-situ, squamous cell carcinoma and p53 expression. (Table 1)

Moderate staining intensity of p53 IHC marker was observed in 18/35 cases (56.2%). High intensity was seen in 15/35 cases (42.8%). Two cases showed null expression. Out of 25 mutant p53 expression, 21 cases showed nuclear staining (84%) and remaining 4 cases showed cytoplasmic staining (16%). (Table 3)

Of 35 cases, eight of them were seropositive for HIV infection. But it didn't show any significant association with various grades of OSSN and p53 expression. (Table 1)

Discussion

Ocular surface squamous neoplasia (OSSN) term encompasses pre-cancerous and cancerous epithelial lesions of the conjunctiva and cornea. It incorporates wide range of pathological changes from Dysplasia, Carcinoma in-situ (CIS) to Invasive SCC.[5] It is the most common non-pigmented malignancy of the ocular surface is OSSN with an incidence ranging from 0.03 – 1.9 per 1,00,000/ year in the Caucasian population to 3-3.4 per 1,00,000/year in African ethnicity populations.[6,7]

The common predisposing risk factors for the development of OSSN include exposure to sun light, HIV-AIDS infection and HPV type 16 infection. Other factors include exposure to cigarette smoke, deficiency of vitamin A, injury to ocular surface, chronic ocular inflammation, exposure to petroleum chemicals, chronic viral infections such as Hepatitis B, C and immunodeficient states.[8]

The mean age of presentation is 56 years with an age range of 4 - 96 years. In the present study, the age of the patients ranged from 18 – 77 years with the mean age of 47.9±15.1 years. Males and females were equally affected by OSSN. In the study done by Carrilho et al, the age of the 75 patients ranged from 21-67 years with the mean age of 39.8 years.[9]

The tumor suppressor gene, p53, found on short arm of chromosome 17 (17p13.1), its mutation is thought to be the most common genetic abnormalities seen in most of the human malignancies. The primary function of p53 protein encoded by TP53 gene is cell cycle arrest at G1-S checkpoint and aid in DNA repair. In the cells where the damage is irreparable, p53 facilitates programmed cell death (apoptosis). Mutation of p53 leads to genomic instability and accentuates the risk of cancer which is supported by the evidence of increased risk of developing OSSN in Xeroderma Pigmentosa patients, where there is defect in DNA repair mechanisms due to UVB rays induced p53 gene mutations. Various other studies have also reported increased nuclear p53 in individuals with OSSN.[10] In the present study, the mutant p53 expression was seen in 25 cases (71.4%) out of 35 cases of OSSN. In the similar study done by Mohamed A et al, 22 cases (55%) out of 40 cases were positive for mutant p53 expression. [1]

Several studies have indicated that HIV infection increases the risk of OSSN. [11,12] In the present study, eight cases (22.8%) were seropositive for HIV infection which did not show significant association with different grades of OSSN and p53 expression. Similar findings were seen in the study done by Mohammed A et al., where the p53 expression was not affected by HIV status of the patient.[1]

There are very few studies in the literature regrading the clinicopathological correlation with p53 expression in OSSN. Our study being one among the other few studies adds to the rarity of the research conducted exclusively on p53 expression in OSSN.

Conclusion

Mutation of p53 gene play a major role in the pathogenesis of OSSN. P 53 expression came positive more in higher grades such as grade III and SCC with statistical significance.P53 mutation in higher grades proves bad prognosis in p53 mutant cases of OSSN. The pattern and intensity of mutant p53 expression was not associated with different grades of OSSN except for percentage of p53 expression. Further studies with greater sample size and prospective evaluation for prognosis of the disease and its association with p53 expression are required for more conclusive and elaborate on the findings.

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Legend Tables & Figures:

Table 1: Demographic details of cases

Parameter	**No. Of Cases**	**Association With Mutant P53 Expression**
1.AGE (In years)		**P = 0.16 (Not significant)**
11-20	1	
21-30	4	
31-40	7	
41-50	9	
51-60	7	
61-70	5	
71-80	2	
2. Gender		**P = 0.52 (Not significant)**
Males	17	
Females	18	
3. HIV Infection Status		**P = 0.79 (Not significant)**
Present	8	
Absent	27	

Table 2: Association of histopathological grades of OSSN with p53 expression

P53 expression	**Grade I**	**Grade II**	**Grade III**	**Carcinoma in-situ**	**SCC**	**Total**
Mutant	1	6	9	0	9	25
Wild-Type	2	0	5	2	1	10
Total	3	6	14	2	10	35
Chi-square test	P = 0.02	Significant				

Table 3: Pattern and intensity of p53 expressi0n

Pattern Of P53 Expression	**Grade I**	**Grade II**	**Grade III**	**Carcinoma In-Situ**	**SCC**	**Total**
Nuclear	3	5	11	1	9	29
Cytoplasmic	0	1	2	0	1	4
No Expression	0	0	1	1	0	2
Total	3	6	14	2	10	35

Chi-square test	P =0.31	Not significant				
Intensity Of P53 Expression	**Grade I**	**Grade II**	**Grade III**	**Carcinoma In-Situ**	**SCC**	**Total**
Moderate	3	3	**8**	**1**	**3**	**18**
High	0	3	**5**	**0**	**7**	**15**
No Expression	0	0	**1**	**1**	**0**	**2**
Chi-square test	P = 0.07	Not significant				

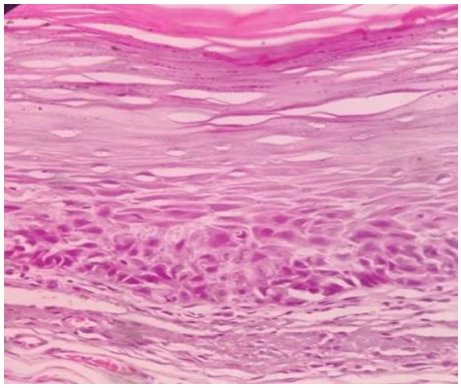

Figure 1: Grade I-II OSSN

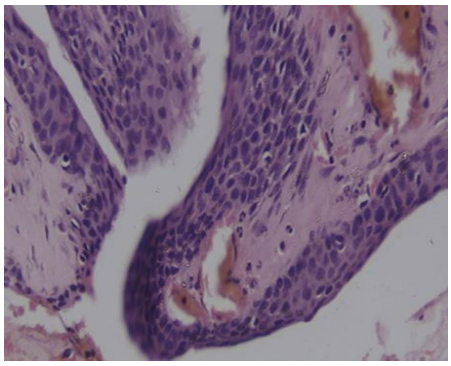

Figure 2: Grade III OSSN

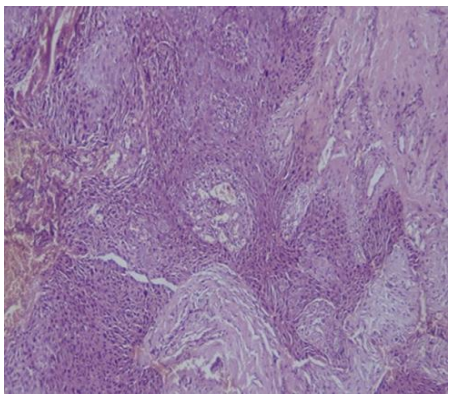

Figure 3: SCC

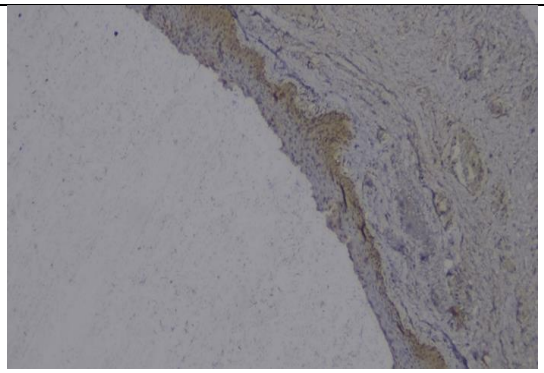

Figure 4: p53 Mutant with Grade I OSSN

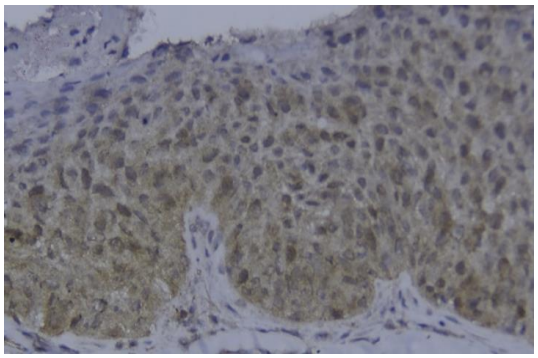

Figure 5: P53 Mutant with Grade II OSSN

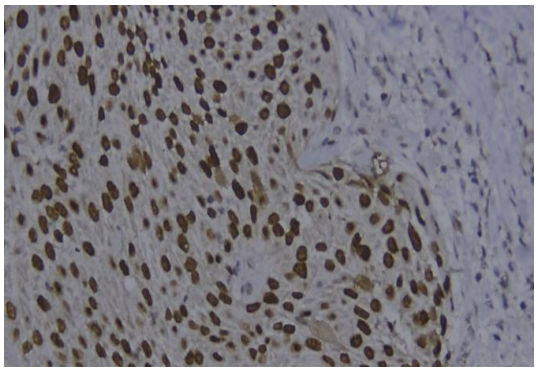

Figure 6: P53 Mutant with Grade III OSSN

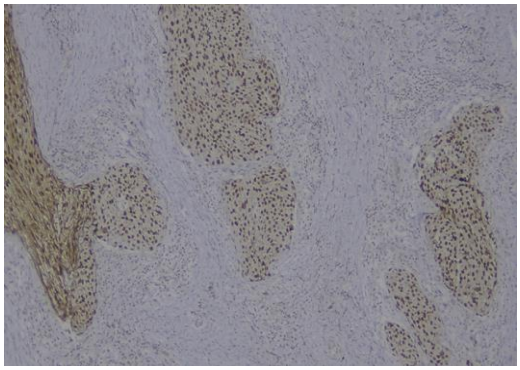

Figure 7: P53 Mutant with SCC