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Evaluation of Serum β2-Microglobulin in Oral Potentially Malignant Lesions and Oral Squamous Cell Carcinoma

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A B S T R A C T

Background: Several biomarkers are known to have a crucial role in the progression of oral malignancy. One such marker is β2-Microglobulin (β2-M). This study was done to identify its significant role in the early detection of oral Malignancy.

Aim: This study aims to compare the level of serum beta-2 microglobulin (β2-M) in healthy individuals and patient with oral potentially malignant lesions disorder (PMLD) and oral squamous cell carcinoma (OSCC).

Methodology: Total samples studied were 384. 4 groups were studied with 96 samples in each group. Group A consisted of healthy control individuals who did not have any clinical conditions or diseases. Group B involved subjects who had a history of tobacco/areca nut chewing and smoking habit. Group C consisted of potentially malignant lesion patients (PML) such as erythroplakia, leukoplakia, oral submucous fibrosis (OSMF) and lichen planus and Group D included freshly diagnosed Oral Squamous cell carcinoma patients (OSCC).

Results: There was a significant increase in serum β2-M levels in OSCC patients and PMLD patients as compared to healthy controls.

Conclusion: The evaluation of these markers would be useful in assessing early detection and diagnosis, malignant change and also in assessing the spread and invasiveness of the malignancy.

INTRODUCTION

Oral cancer and oropharyngeal cancer are on the rise, with 177,757 and 48,143 deaths worldwide each year, and 377,713 and 98,412 new cases, respectively. (GLOBOCAN 2021, IARC, WHO) [1] Oral cancer is a serious type of cancer that is causing an increasing concern around the world.[2]

Oropharyngeal and oral cancer is the sixth most frequent cancer globally. Oral squamous cell carcinomas, or OSCCs, account for more than 90% of malignant tumours of head and neck that originate from oral squamous epithelial cells. It has a tendency to spread to the cervical lymph nodes and deviates to differing degrees. Despite advancements in research and treatment over the last few decades, survival rates have not increased significantly. Oral cancer continues to have a high five-year survival rate, with 40% morbidity and 46% mortality. [3]

Furthermore, the 5-year death rate for patients with oral cancer is extremely close to 50%, demonstrating that the significant mortality frequency has not decreased significantly over the previous 40 years.

Oral squamous cell carcinomas (OSCC), which account for over 90% of oral neoplasms, account for the vast majority of oral malignancies in addition to the time needed for the difficult process of obtaining at an accurate diagnosis of oral cancer, other data demonstrates that 30% of oral cancer patients who delay seeking care for longer than 3 months after they first discover signs and indications of the disease. [4]

It is noteworthy that numerous risk factors have been linked with the development of oral squamous cell carcinoma (OSCC). The most substantial risk factor, accounting for roughly 75% of cases, is the habit of chewing or smoking tobacco. [5]

Oral premalignant lesions affect 1.5% to 4.5% of people worldwide, with men being affected more frequently than women. [6]

The oral cavity is lined by stratified squamous epithelium, which is highly susceptible to carcinogenic shock. Tobacco, betel nut, alcohol, and HPV exposure can all create a cellular microenvironment that leads to the development of hyperkeratotic or dysplastic epithelium. Clinically, this presents as lichen planus, erythroplakia, or oral leukoplakia above pathologies could cause dysplastic epithelium. However, there is variation in the rates at which these entities develop into carcinoma, emphasizing the significance of histopathological examination. [7]

Tumor marker research in oral carcinoma has not been extensive. Additional research is required on a number of tumor markers that show clinical promise (nacetyl neuraminic acid, ferritin, CEA, phosphohexose isomerase). Serum β2-Microglobulin (β 2-m) is one of these tumor markers.

β2-Microglobulin was initially evaluated by Crispian Scully as a marker for oral premalignant lesions. Berggard and Bearn first defined and isolated it in 1968 from the urine of patients suffering from tubular proteinuria. All cells, with the exception of erythrocytes, have the low molecular weight protein known as b2-microglobulin, which has a mass of 11,600 Da.

It has also been proven to exist in trace amounts in the normal human plasma, urine, and cerebrospinal fluid. The light or b-chain of the human leukocyte antigen (HLA) is represented by this protein. It is an invariant component of HLA molecules and exists in two main forms: free and noncovalently linked to the HLA antigens.

The B2-microglobulin in serum is present in free form. It is made up of one intrachain disulfide bridge and one polypeptide chain. There are no carbohydrates in it. There are only a few studies that link serum ß2-microglobulin levels to precancer and oral cancer, despite the fact that raised levels have also been observed in patients with oral cancer.[8]

The dysfunction of the kidneys and cell turnover lead to an increase in the concentration of β2M. [9].

Thus, an increased amount of β2M in individuals with healthy kidneys indicates the proliferation of the changed cells. Serum levels of β2M have been found to increase in certain pathologic cases, such as autoimmune diseases, immune deficiencies, and kidney diseases. Furthermore, at the time of diagnosis, certain solid and hematologic cancers had elevated levels of β2M. [10-11]

MATERIAL AND METHODS

This study was a cross sectional study. It was collaboratively conducted in the Department of biochemistry, Oncology and Radiotherapy and Oral Pathology, Krishna Vishwa Vidyapeeth, Karad. Total samples studied were 384. The samples were categorized into 4 groups, each group had 96 samples.

Group A involved healthy control subjects who did not have any clinical conditions or diseases. Group B involved subjects who had a history of tobacco/areca nut chewing and smoking habit. Group C involved patients with oral potentially malignant lesions such as leukoplakia, submucous fibrosis and lichen planus.

Group D included newly diagnosed cases of oral squamous cell carcinoma.

This study was approved by Ethics Clearance Committee (157/2020-2021) by Krishna Vishwa Vidyapeeth, Karad.

Blood samples of patients with PML and Malignancy were collected in the Department of Oral and Maxillofacial Surgery and Oncology Department after histopathological findings of the lesions. The healthy control individual samples were collected from the Krishna Vishwa Vidyapeeth campus whereas the subjects who had smoking and Tobacco/areca nut chewing habits were collected from the oral medicine department. Blood was collected in a plain bulb along

with the informed consent for each sample collected. History was taken accordingly. The blood samples were then centrifuged at 3000 rpm for 5-7 mins to obtain serum for further studies. The serum samples were separated and stored in -20°C for further use

Serum β2-Microglobulin was done by sandwich Enzyme-Linked Immunosorbent Assay (ELISA) method. Each Serum β2-M estimation kit contained 96 wells and they were obtained from Bioassay Technology Laboratory, Everon Life Sciences, Jiaxing Korain Biotech co., Zhejiang, China. 96 samples were processed at a time in the clinical laboratory, Biochemistry.

Statistical analyses was done using the SPSS software. P< 0.05 was considered significant.

RESULTS

Table 1: The Distribution of PMLs according to their histopathological findings

	PMLDs	Cases (n=96)	%
.	**Leukoplakia**	56	58.3
.	**Submucous Fibrosis**	33	34.3
.	**Lichen Planus**	7	7.2

Table 2: Mean values of Serum β2-Microglobulin (mg/L) in control and study groups

Groups	Mean ± S. D
A	1.211± 0.063
B	1.250±0.069
C	1.738±0.110
D	3.099±0.377

Graph 1: Comparison of mean differences of serum β2-Microglobulin (mg/L) among the control and study groups

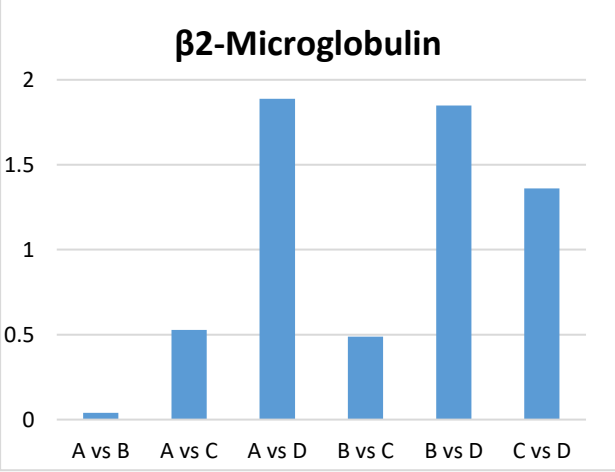

Table 1 shows distribution of patients having potentially malignant lesions according to their histopathological findings.

Table 2 shows mean values of serum β2-Microglobulin (mg/L) among the control and study groups which is expressed as Mean ± S.D, where S.D is the Standard Deviation.

Graph 1 Shows comparison of serum β2-Microglobulin (mg/L) among the control and study groups. One-way ANOVA test was done for comparison of serum β2-Microglobulin (mg/L) among the groups along with post Tukey Kramer's test which was statistically significant (P<0.001).

Discussion

In 2020, there were estimated to be 1.39 million newly diagnosed cases of cancer in India. Tobacco is one of the many known and most widely avoided cancer risk factors in the world. [12]

The WHO workshop of 2005 chose the term "Potentially Malignant Disorders" as it suggests that not all disorders falling into this category have the potential to progress to cancer. Erythroplakia, leukoplakia, submucous fibrosis, and lichen planus are the most frequently reported PMLs. [13]

Between 1.5% and 4.5% of people worldwide have oral premalignant lesions, which disproportionately affect men over women. [14]

Oral cavity lining is made of stratified squamous epithelium, which is highly sensitive to carcinogenic upset. Exposure to tobacco, alcohol, betel nut, or HPV can create a cellular microenvironment that leads to the formation of hyperkeratotic or dysplastic epithelium. When pathologies above cause dysplastic epithelium, the clinical manifestation is lichen planus, erythroplakia, or oral leukoplakia. The significance of a histopathological examination is emphasized by the differences in the rates at which these entities develop into carcinoma. [15]

According to a study by Kim et al., during the diagnosis of malignancy, the surface of the lesion in OPMD displayed verrucous, exophytic, papillary, corrugated, and ulcerative changes. The initial lesion's progression from dysplasia to malignancy took varying amounts of time. [16]

According to Speight M. et al.'s evaluation of the risk factors, smoking, alcohol consumption patterns, sex, lesion type and location, and other factors were

major contributors to the progression of a potentially malignant lesion into malignancy. [17]

According to research by Jani et al., tobacco use in any form is harmful and increases the risk of several PMLs. Those who are exposed to tobacco habits have a risk that is 43.62 times higher. [18]

Oral squamous cell carcinoma (OSCC) causes a high grade of local invasiveness and a high degree of metastasis, which leads to its high incidence of mortality. Early detection of oral cancer would significantly improve long-term survival rates. Plasma biomarkers are believed to have a great potential for assisting the early detection of oral cancer and monitoring cancer recurrence or progression [19-21]

In the present study, Serum β2-Microglobulin was estimated and was statistically significant while comparing among the groups. Statistical analysis was done through ANOVA test followed by Tukey Kramer's post-test.

Table 1 shows the distribution of potentially malignant lesions. Among the 96 samples, Leukoplakia cases were 56 which was 58.3% of the 96 samples studied, Submucous Fibrosis were 33 which were 34.3% of the 96 samples studied, and Lichen Planus cases were 7 which were 7.2% of the 96 samples studied. Leukoplakia cases were more than the other potentially malignant lesions.

Table 2 shows mean values of β2-Microglobulin in all the 4 groups A, B C and D. values are expressed as mean ± S.D, where S.D is the standard deviation.

In group A the mean values were 1.211 ± 0.063 and the 95th % confidence interval was from 1.198 to 1.224.

In group B, the values were 1.250 ± 0.069 and the 95th % confidence interval was from 1.236 to 1.264.

In group C, the values were 1.738 ± 0.110 and the 95th % confidence interval was from 1.716 to 1.761.

In group D, the values were 3.099 ± 0.377 and the 95th % confidence interval was from 3.023 to 3.176.

In graph 1, Group A vs group B showed mean difference of 0.0392 (P>0.05, q = 1.895).

Group A vs Group C showed mean difference of 0.527 (P<0.001, q = 25.531)

Group A vs Group D shows mean difference of 1.889 (P<0.001, q = 91.386)

Group B vs Group C shows mean difference of 0.488 (P<0.01, q = 23.653).

Group B vs Group D shows mean difference of 1.849 (P<0.001, q = 89.491).

Group C vs Group D shows mean difference of 1.361 (P<0.001, q = 65.855).

The comparison of group A and Group B was statistically non-significant.

The comparison of Group A vs C, Group B vs C, Group A vs D, Group B vs D and group C vs D was statistically highly significant (P<0.001).

Similar findings were seen in S Reddy et al. study. Increased b2-microglobulin levels were reported in patients with oral cancer. This progressive increase in serum β2-M levels were highly significant. Their study established that β2-M can be used as a specific biological tumour marker for prognostic and diagnostic evaluation of OSCC. [22]

Another study by Singh AP et al showed β2-M levels in PMLD and OSCC were significantly increased when compared with the healthy controls. Their study concluded that β2- M can be used as an indicator for early detection of malignancy and therefore can be used for treating malignancy at an early stage. [23]

Saddiwal R et al.'s results showed that β2-M was increased in those exposed to carcinogens without having any precancerous and cancerous lesion. They projected the prognostic value of β2-M as a biochemical marker for the prognosis and diagnosis of OSCC. [24]

Jiang Q et al investigated β2-microglobulin expression in normal oral mucosa and OSCC and to evaluate the clinical significance of β2-microglobulin expression. the frequency of β2-M expression was significantly increased in metastatic OSCC lesion when compared with primary OSCC lesions. Therefore, they concluded that β2-M expression may contribute to the tumour invasion, metastasis and oncogenesis of human oral mucosa. [25]

Anand Pratap et al. estimated that β2-m levels progressively increased with OSMF and OSCC advancement. [26]

Another study concluded that Serum β2-microglobulin levels were found to be significantly increased in OSCC compared to controls. [27]

Conclusion

Serum β2-microglobulin levels were seen increased in PMLD and OSCC group when compared with Healthy controls. Therefore, it could be used as a and early detection marker for prognostic and diagnostic evaluation of OSCC.

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