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Analysis of Hematological and Histological Parameters Among Individuals with Pre-Cancerous and Cancerous Lesions

***Alvina Ali Shaikh*[1]**
***Bushra* [2]**
***Uzma Tarique*[3]**
***Arhama Surwaich* [4]**
***Muhammad Rafique Tagar*[5]**
***Surwaich Ali Channa* [6]**

[1]*Assistant Professor, Isra Dental College, Isra University*
[2]*Senior registrar, Assisstant professor Department of oral medicine Isra dental college, Isra University,*
[3]*Associate Professor, Isra Dental College, Isra University*
[4,6]*Associate Professor, Bhitai Dental and Medical College Mirpurkhas*
[5]*Associate Professor, Shaheed Mohtarma Benazir Bhutto Medical University*

Address for Correspondence
Dr. Muhammad Rafique Tagar
Associate Professor, Shaheed Mohtarma Benazir Bhutto Medical University
hafiztagar@gmail.com

Abstract

Objective: To evaluate the hematological and histological parameters among individuals with pre-cancerous and cancerous oral lesions by comparing them with healthy controls

Methodology: A cross-sectional comparative study was conducted at the Department of Biochemistry, Basic Medical Sciences Institute (BMSI), from Mar 2024 to Sept 2024 in collaboration with the Clinical Oncology Ward of Jinnah Postgraduate Medical Centre (JPMC), Karachi. Individuals aged 14 years and above, with confirmed diagnoses, were enrolled and divided into three groups: Group A (34 oral cancer patients), Group B (34 oral precancerous cases), and Group C (34 healthy controls). Blood sample of 5 ml was collected, processed, and stored under aseptic conditions for CBC. Initial biopsy was done under local anesthesia targeting the areas of lesions. Sections were then stained utilizing the Hematoxylin and Eosin "H&E" for routine histological evaluations. Data were statistically analyzed using SPSS version 21.0.

Results: Overall mean age of the cases was 42.79 ± 4.12 years. Out of 102 subjects, 55 (53.9%) males and 47 (46.0%) were female. In cancer cases, the buccal mucosa and tongue were the most commonly affected sites (23.5% each), with other regions also involved. In the pre-cancer group, leukoplakia was the most frequent lesion (58.8%), followed by erythroplakia and submucous fibrosis. Most cancer patients had well-differentiated SCC (67.6%), while 32.4% had moderately differentiated SCC, with males being more commonly affected in both types. Hematological markers (Hb, hematocrit, RBC, TLC, neutrophils, lymphocytes) were significantly elevated ($p < 0.01$) in both oral precancer and cancer groups compared to controls. Monocyte and platelet counts showed no significant differences.

Conclusion: Distinct alterations o hematological parameters observed among individuals with oral precancerous and cancerous lesions compared to healthy individuals. Histologically, leukoplakia emerged as the most frequent pre-cancerous lesion, while well-differentiated squamous cell carcinoma (SCC) predominated among cancer cases, especially among males.

Key Words: Oral lesions, Precancer, Cancer, Hematology, Histopathology

Introduction

Oral squamous cell carcinoma (OSCC) accounts for over 90% of all oral malignancies, making it a major public health burden globally, especially in developing countries.[1] The occurrence of OSCC differs widely across regions; in Southeast Asia, it ranks as the leading cancer type, while in Finland, it holds the 16th position among cancers. This global disparity in incidence may stem from differing levels of exposure to harmful agents like smokeless tobacco, cigarette use, and alcoholic consumption. South Asia, including Pakistan, reports high incidence rates due to widespread habits such as tobacco use, areca nut chewing, and alcohol consumption. More than 120,000 cases of oral cancer globally were caused by smokeless tobacco and areca nut use, accounting for one-third of oral cancer cases worldwide. Notably, nearly 88% of these cases occurred in South-Central Asia, highlighting the significant public health burden in this region due to these risk factors.[2] These risk factors act synergistically, increasing the probability of malignant transformation in the oral mucosa.[3] Oral cancer often develops through a multistep carcinogenesis process that begins with oral potentially malignant disorders (OPMDs) such as leukoplakia, erythroplakia, and oral submucous fibrosis.[4] Oral epithelial dysplasia (OED) lesions are histologically characterized by varying degrees of epithelial dysplasia and may progress to invasive cancer if not diagnosed and managed. Oral malignant disorders exhibit varying levels of malignant transformations, ranging from 1.1% to 40.8%, cases of leukoplakia while 33.1% and 49.5% cases of erythroplakia and proliferative verrucous leukoplakia respectively.[5]

Authorship Contribution: [1,5] Conceived and planned the idea of the study, [4,5]final approval of the version to be published, Collecting the data, [2,3]drafting the work or revising it critically for important intellectual content.

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Research studies highlight that OED is a premalignant histopathological diagnosis with grading systems that suffer from significant inter- and intra-observer variability, and do not reliably predict malignancy progression.[6] Early detection and intervention are critical, as survival rates drop significantly with advanced-stage diagnosis.[7]

In Pakistan, OSCC is among the most prevalent malignancies, with a significant prevalence observed among males. The affected intraoral sites by this carcinoma include buccal mucosa, tongue, and floor of the mouth, with Buccal mucosa (45.5%) being the most commonly affected site. Additionally, chronic indurated ulcers are a common manifestation of OSCC. Areca nut chewing, tobacco use in both the smoke free and smoking forms, and, to a lesser extent, alcohol consumption have been recognized as the primary risk factors contributing to the high occurrence rates of OSCC among the population of Pakistan.[8]

Recent advances suggest that changes in hematological and biochemical profiles can provide vital information about the onset and progression of malignancies, including OSCC.[9] Inflammation plays a major role in cancer diagnosis and prognosis. Systemic inflammatory markers like the neutrophil, lymphocyte and platelet counts have been suggested as prominent indicators of tumor behavior.[10] Elevated neutrophil counts and decreased lymphocyte counts have been associated with systemic inflammation and poorer prognosis in OSCC patients, indicating their association with poor prognosis and disease progression.[11] Significant alterations in the levels of other hematological indicators such as TLC, hemoglobin concentration, and ESR have also been linked to malignant alterations.[12] Despite the availability of data on individual hematological parameters in oral cancer, there is a lack of comprehensive comparative studies evaluating these parameters across three distinct groups healthy controls, patients with OPMDs, and confirmed OSCC cases.[14] A systematic comparison could enhance our understanding of disease progression and offer potential biomarkers for early diagnosis and prognosis.

Methodology

This cross-sectional study was conducted at the Department of Biochemistry, BMSI, from Mar 2024 to Sept 2024 in collaboration with the clinical oncology ward of JPMC, Karachi. A total of 102 adult participants of age range 14 years and above, with or without tobacco habits and confirmed diagnoses were enrolled in the study. Based on the clinical, haematological, and histopathological findings, subjects were categorized into three groups: 34 oral cancer patients (Group A), 34 oral precancerous cases (Group B), and 34 healthy controls (Group C). Individuals with nephropathy, malignancies other than oral cancer, diabetes mellitus, Cardiovascular and chronic liver disorders, and severe depression were excluded. Blood samples (5 ml each) were collected, processed, and stored under aseptic conditions for the estimation of CBC, and platelet count using spectrophotometric and automated methods. Initial biopsy was done under local anesthesia targeting the areas of lesions. Obtained specimens were fixed in 10% neutral buffered formalin immediately and sent to the pathology laboratory. Furthermore, after gross examination the tissues of the specimens were processed under standard protocol as clearing, dehydration, paraffin embedding and microtomy to obtained the 4-5µm sections. Sections were then stained utilizing the Hematoxylin and Eosin “H&E” for routine histological evaluations. Data were analyzed using SPSS version 21.0, ANOVA and Student’s t-test were applied. A p-value of 0.05 was considered statistically significant.

Results

Overall mean age of the cases was 42.79 ± 4.12 years. Out of 102 subjects, 55 (53.9%) males and 47 (46.0%) were female. In the pre-cancer group, the most common site was the buccal mucosa (35.3%), followed by the tongue (26.5%) and right cheek (14.7%). In the cancer group, the buccal mucosa and tongue were equally affected (23.5%), with additional involvement of the cheeks, submandibular and juxta mandibular regions, lip, alveolus, gingiva, nasopharynx, and hard palate. Histopathological findings in the pre-cancer group included leukoplakia (58.8%), erythroplakia (29.4%), and submucous fibrosis (11.8%). In contrast, cancer patients showed 67.6% with well-differentiated squamous cell carcinoma and 32.4% with moderately differentiated SCC, with a higher proportion of males affected in both histological subtypes. (Table I)

Pre-cancer patients showed significantly reduced hemoglobin, hematocrit, and RBC counts compared to healthy controls, all with strong statistical significance (p=0.001). In contrast, their TLC, neutrophil, and

lymphocyte levels were notably higher. Monocyte levels remained unchanged, and platelet counts were slightly raised but without statistical significance as shown in table II.

Patients with oral cancer showed markedly lower hemoglobin levels (9.2 g/dl vs. 11.8 g/dl), haematocrit (29.6% vs. 41.5%), and RBC count (3.6 vs. 4.3 million/µl), all with highly significant (p-0.001). In contrast, TLC and neutrophil percentage were significantly elevated in the cancer group, along with an increase in lymphocyte percentage (38.5% vs. 26.5%), also (p-0.001). Monocyte levels remained almost the same in both groups, with no

Table I: Gender distribution of affected sites and Histopathological patterns

Variables	Pre cancer (N=34)			Cancer (N=34)		
	Total (N=34)	Male (N=15)	Female (N=19)	Total (N=34)	Male (N=23)	Female (N=11)
Affected site						
Buccal Mucosa	12 (35.3%)	7 (46.7%)	5 (26.3%)	8 (23.5%)	7 (30.4%)	1 (9.1%)
Tongue	9 (26.5%)	2 (13.3%)	7 (36.8%)	8 (23.5%)	6 (26.1%)	2 (18.2%)
Right cheek	5 (14.7%)	3 (20.0%)	2 (10.5%)	5 (14.7%)	3 (13.0%)	2 (18.2%)
Left cheek	3 (8.8%)	-	3 (15.8%)	5 (14.7%)	3 (13.0%)	2 (18.2%)
Submandibular	-	-	-	3 (8.8%)	2 (8.7%)	1 (9.1%)
Juxta mandibular	3 (8.8%)	1 (6.7%)	2 (10.5%)	-	-	-
Lip	1 (2.9%)	1 (6.7%)	-	2 (5.9%)	-	2 (18.2%)
Alveolus	-	-	-	1 (2.9%)	1 (4.3%)	-
Gingiva	-	-	-	1 (2.9%)	1 (4.3%)	-
Nasopharanx	-	-	-	1 (2.9%)	-	1 (9.1%)
Hard Palate	1 (2.9%)	1 (6.7%)	-	-	-	-
Histopathological findings						
Leukoplakia	20 (58.8%)	8 (53.3%)	12 (63.2%)	-	-	-
Erythroplakia	10 (29.4%)	5 (33.3%)	5 (26.3%)	-	-	-
Submucous Fibrosis	4 (11.8%)	2 (13.3%)	2 (10.5%)	-	-	-
Well Differentiated SCC	-	-	-	23 67.6%)	15 (65.2%)	8 (72.7%)
Moderately Differentiated SCC	-	-	-	11 32.4%)	8 (34.8%)	3 (27.2%)

Table II: Comparison of haematological parameters in controls and pre cancer.

Parameters	Controls (n=34) (Mean ± S.D)	Pre cancer (n=34) (Mean ± SD)	P-value
Hb. (g/dl)	11.8 ± 1.48	9.2 ± 2.26	0.001
Haematocrit (%)	41.5 ± 3.31	28.9 ± 6.88	0.001
RBC count x 10^5 µl	4.3 ± 0.50	3.4 ± 0.77	0.001
TLC x 10^3 µl	8.6 ± 2.43	14.6 ± 3.39	0.001
Neutrophil (%)	63.0 ± 6.21	74.4 ± 11.40	0.001
Lymphocytes (%)	26.5 ± 7.69	49.8 ± 7.56	0.001
Monocytes (%)	1.4 ± 0.50	1.4 ± 0.50	0.810
Platelets x 103 µl	176 ± 25.7	192 ± 58.0	0.132

Table III: Comparison of bio-chemical and haematological parameters in controls and oral cancer

Parameters	Controls (n=34) (Mean ± S.D)	Cancer (n=34) (Mean ± S.D)	P-value
Hb. (g/dl)	11.8 ± 1.48	9.2 ± 2.53	0.001
Haematocrit (%)	41.5 ± 3.31	29.6 ± 7.78	0.001
RBC count x 105 µl	4.3 ± 0.50	3.6 ± 0.94	0.001
TLC x 103 µl	8.6 ± 2.43	13.0 ± 4.13	0.001
Neutrophil (%)	63.0 ± 6.21	83.9 ± 8.39	0.001
Lymphocytes (%)	26.5 ± 7.69	38.5 ± 17.43	0.001
Monocytes (%)	1.4 ± 0.50	1.5 ± 0.50	0.338
Platelets x 103 µl	176 ± 25.7	177 ± 44.7	0.908

Table IV: Comparison of Bio-chemical and Haematological parameters in Pre cancer and Cancer

Parameters		Pre cancer (n=34) (Mean ± S.D)	Cancer(n=34) (Mean ± S.D)	P-value
Hb. (g/dl)		9.2 ± 2.26	9.2 ± 2.53	0.984
Haematocrit (%)		28.9 ± 6.88	29.6 ± 7.78	0.704
RBC count x 105 µl		3.4 ± 0.77	3.6 ± 0.94	0.579
TLC x 103 µl		14.6 ± 3.39	13.0 ± 4.13	0.106
Neutrophil (%)		74.4 ± 11.40	83.9 ± 8.39	0.001
Lymphocytes (%)		49.8 ± 7.56	38.5 ± 17.43	0.001
Monocytes (%)	1.4 ± 0.50	1.5 ± 0.50	0.474	
Platelets x 103 µl	192 ± 58.0	177 ± 44.7	0.219	

significant difference (p=0.338), and platelet counts were nearly identical, showing no statistical difference (p=0.908). (Table III)

On the comparison between pre-cancer and cancer patients the hemoglobin levels, haematocrit, RBC count, TLC, monocytes, and platelet counts did not differ significantly, as indicated by P- 0.05. However, significant differences were observed in the white blood cell subtypes. Cancer patients had a notably higher neutrophil percentage (83.9% vs. 74.4%), while pre-cancer patients had a significantly higher lymphocyte percentage (49.8% vs. 38.5%), both (p- 0.001). (Table IV)

Discussion

The present study investigated hematological parameters among control, oral precancer, and oral cancer groups, revealing significant alterations that align with existing literature. In this study, buccal mucosa was the most commonly affected site (35.3%) in the pre-cancer group, followed by the tongue (26.5%) and right cheek (14.7%). While, in the cancer group, the buccal mucosa and tongue were equally affected (23.5%), followed by equal involvement of left and right cheeks 5 (14.7%). The outcomes of this study were consistent with Global findings. A recent Indian study by Shah and Dubby reported 34.4% involvement of Oral Submucous Fibrosis, being the most frequently effect sites, with a higher prevalence among males (81.1%) than the females. Another more recent study by Siddiqui et al.,[16] from Pakistan stated cheek mucosa (36.2%) as the commonest affected site, followed by, lips (25.7%) and tongue (20%), with male predominance (61%). On the other hand, a US study by Stepan et al. reported that the most frequently involved site was oral tongue (41.7%), followed lip, floor of mouth, gingival, buccal mucosa, retromolar trigone, and hard palate (16.5%, 16.5%, 10.6%, 6.7%, 5.6%, 2.3%) respectively. with 2.3% higher prevalence among women. Moreover, previous research studies suggest that the frequent involvements of buccal mucosa and tongue in malignant transformations have been attributed to the practices of areca nut chewing and consuming tobacco products, making them the key risk factors.[17-19]

In this study, leukoplakia (58.8%) was the most prevalent histopathological finding in the pre-cancer group, followed by erythroplakia (29.4%), and submucous fibrosis (11.8%). In contrast, cancer patients showed 67.6% with well-differentiated squamous cell carcinoma (SCC) and 32.4% with moderately differentiated SCC, with a higher proportion of males affected in both histological subtypes. In proportion to these findings, a systematic review and meta-analysis by Kumbhalwar et al.[20] reported leukoplakia (6.7%) as the most prevalent finding, followed by submucous fibrosis (4.5%), and erythroplakia (2.5%). However, in their study, erythroplakia was less common, but is noted for its higher malignant potential. Contrasting to our findings, a research study by Lin et al.[21] reported 17.2% well-differentiated oral squamous cell carcinoma (OSCC), 77.5% moderately-differentiated, and 5.4% poorly-differentiated OSCC cases. The disparity in OSCC differentiation may be attributed to the variations in sample populations or diagnostic criteria. The male predominance in our study aligns with the global trends in gender disparity explained by the higher rates of tobacco, alcohol, and betel nut use among men.

In our study, Pre-cancer patients had significantly lower levels of hemoglobin (9.2 g/dl vs. 11.8 g/dl), haematocrit (28.9% vs. 41.5%), and RBC count (3.4 vs. 4.3 million/µl) in comparison to controls (p<0.01). On the other hand, TLC, neutrophil percentage, and lymphocyte percentage were significantly higher in the pre-cancer group, indicating an inflammatory response (p<0.01). A case-control study by Sganzerla et al.[22] reported 15.7% prevalence of anemia in OSCC cases, with hemoglobin levels of moderate to very low levels in OSCC cases (OR; 6.49), suggesting normocytic and normochromic anemia, indicative of a chronic disease process rather than nutritional deficiency. Similarly, Singh et al.,[23] documented statistically significant differences in TLC, neutrophil count, and lymphocyte count among the pre-cancer, cancer, and control groups, suggesting a systemic inflammatory response indicating oral malignancies. They concluded that these white blood cell subtypes may be the potential indicators of malignant disorders.

In this study, in comparison to the healthy controls, oral cancer cases showed markedly lower hemoglobin levels (9.2 g/dl vs. 11.8 g/dl), haematocrit (29.6% vs. 41.5%), and RBC count (3.6 vs. 4.3 million/µl), with statistically significant difference (p-0.001). In contrast, TLC and neutrophil percentage were significantly elevated in the

cancer group, along with an increase in lymphocyte percentage (38.5% vs. 26.5%); p-0.001. Monocyte levels and platelet counts exhibited no significant difference (p=0.338 and p=0.908 respectively). Consistent research outcomes have demonstrated the prognostic value of hematological markers in oral squamous cell carcinoma (OSCC). Ge et al.[24] identified elevated red cell distribution width (RDW) as an independent prognostic factor in OSCC patients. Similarly, Singh et al.[22] observed significantly reduced hematocrit and red blood cell (RBC) counts in OSCC cases, further supporting the association between systemic inflammatory responses and disease progression. These findings suggest that hematological markers could serve as accessible, cost-effective indicators for evaluating disease burden and informing clinical decision-making in OSCC management. In this study, comparison between pre-cancer and cancer patients revealed no significant difference in hemoglobin levels, haematocrit, RBC count, TLC, monocytes, and platelet counts (P>0.05). However, significant differences were observed in the white blood cell subtypes, with notably higher neutrophil percentage (83.9% vs. 74.4%) in Cancer patients, while significantly higher lymphocyte percentage (49.8% vs. 38.5%) in pre-cancer patients, both (p- 0.001). These findings further support the study of Singh et al. [23] and Ram et al.[25], The authors collectively support the notion that while certain hematological parameters remain stable across disease progression, changes in specific white blood cell subtypes may reflect the transition from pre-cancerous to malignant states in oral tissues.

Conclusion

Study revealed the distinct alterations in hematological parameters among individuals with oral precancerous and cancerous lesions compared to healthy individuals. OC cases showed markedly reduced hemoglobin levels, hematocrit, and RBC count, alongside elevated total leukocyte count and neutrophil percentages, reflecting a systemic inflammatory and anemic state commonly associated with malignancy. In contrast, pre-cancerous individuals exhibited intermediate changes, suggesting a progressive hematological shift with disease advancement. Histologically, leukoplakia emerged as the most frequent pre-cancerous lesion, while well-differentiated SCC predominated among cancer cases, especially among males. Findings reinforce the importance of early detection and routine hematological assessment in identifying high-risk individuals, thereby enabling timely diagnosis and improving patient outcomes by earlier therapeutic interventions.

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