Original Research

Prognostic value of tumor budding in Oral Squamous Cell Carcinoma

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Received: 08 May, 2023 Accepted: 12 June, 2023 Published: 14 July, 2023

Abstract

Introduction: Oral squamous cell carcinoma (OSCC) is one of the most common malignancies globally, particularly in regions with high-risk behaviors and environmental factors that promote carcinogenesis. The most progressed layers of tumor reside in the invasive tumor front, which forms the advancing edge of the cancer and gives excellent details of prognosis. " Tumor budding" is the histological phenomenon seen as a detached single or cluster of tumor cells in the invasive tumorfront.The present study aims to assess the prognostic significance of the tumor budding by assessing its association with clinicopathological parameters in oral squamous cell carcinoma

Material and method: Ten patients who had undergone excision of the primary lesion along with radical neck dissection for oral squamous cell carcinoma were retrospectively included in the study from the period of one year i.e. from May 2022 to April 2023 conducted in National Institute of Medical Sciences & Research, Jaipur.

Result: Of the 10 patients included in the study 8 patients were male (80%) and 2 patients were female (20%). The mean age was 57.82 year (range from 30-65 years). The most common site was buccal mucosa (90%). The tumor buds were seen at the advancing edge of invasive tumor front in standard hematoxylin and eosin-stained sections. All of the 10 cases demonstrated tumor budding (100%) in the stroma. Of the 10 cases, only 2 cases shows tumor budding of Grade 3.

Conclusion: Tumor budding is the frequently observed histological feature in OSCC. It was correlated with deep invasion, the worst pattern of invasive front along with minimal host response conditions in OSCC.Thus this study emphasizes the importance of tumor budding evaluation in regular pathology practice in assessing the prognosis of OSCC cases.

Keywords- Tumor budding, Oral Squamous Cell Carcinoma, Histological evaluation

Introduction

Oral squamous cell carcinoma (OSCC) is one of the most common malignancies globally, particularly in regions with high-risk behaviours and environmental factors that promote carcinogenesis. It accounts for a significant proportion of all cancer cases worldwide, with substantial variation in incidence and mortality rates across different geographic regions.[1] Globally, oral cancer ranks as the sixth most prevalent cancer, affecting millions of individuals annually.[1] Its impact is particularly severe in low- and middle-income countries where access to preventive healthcare and early detection services is limited. OSCC constitutes over 90% of all oral malignancies and presents a considerable public health burden due to its aggressive nature, high morbidity, and poor survival rates.[1]

India bears a disproportionate share of the global burden of oral cancer, with more than one-third of global cases reported in the country. OSCC is the most prevalent cancer among men and the third most common cancer among women in India. Tobacco use is a well-established carcinogen that directly damages oral tissues, leading to cellular changes and the development of malignancies.[2]

The most progressed layers of tumor reside in the invasive tumor front, which forms the advancing edge of the cancer and gives excellent details of prognosis. " Tumor budding" is the histological phenomenon seen as a detached single or cluster of tumor cells in the invasive tumor front.[3]

Even though tumor budding is detected frequently in oral squamous cell carcinoma, its role as histological predictive marker has not been explored until recently. The present study aims to assess the prognostic significance of the tumor budding by assessing its association with clinicopathological parameters in oral squamous cell carcinoma.

Material and method

Ten patients who had undergone excision of the primary lesion along with radical neck dissection for oral squamous cell carcinoma were retrospectively included in the study from the period of one year i.e. from May 2022 to April 2023 conducted in National Institute of Medical Sciences & Research, Jaipur. Patients with primary lesion of oral squamous carcinoma with radical neck dissection who had given consent were selected regardless of age and gender. Patients who had incisional biopsy, post chemotherapy status and had autolysed sample were excluded. The clinical details of the patient were collected from the biopsy requisition form and digital record management system central to the hospital. The details obtained include age, sex, presence/absence of habits, site, tumor size and TNM staging. The excisional specimens of oral squamous cell carcinoma were routinely fixed in 10% neutral buffered formalin, processed and paraffin embedded. 2-3 um paraffin sections were prepared and stained with hematoxylin and eosin. To evaluate tumor budding, Slides were scanned under 4x first to select five areas displaying good intensity of budding. Then these five selected fields were counted under 10x to score the tumor budding intensity/budding index. Cases with 10 tumor buds were grouped into grade 3, cases with 5-9tumor buds into grade 2, cases with 1-4tumor buds into grade 1 and no tumor buds were considered negative.

Data collected were tabulated and were assessed using chi-square test and fisher's exact test. Ethical approval was obtained from the institution standard review board prior to the commencement of the study.

Result

The study comprised ten patient specimens who had undergone excision for oral squamous cell carcinoma. The results obtained are summarized in Table 1. Of the 10 patients included in the study 8 patients were male (80%) and 2 patients were female (20%). The mean age was 57.82 year (range from 30-65 years). The most common site was buccal mucosa (90%). Most of them had the history of tobaccochewing/smoking/arecanut chewing /alcohol with a mean duration of 10-15 years. Patients included were in TNM stage 1 (30%) and stage 2 (70%). The tumor size of patients ranged from 2 to 5 cm with the majority of them in the T2 group (70%). The histologic grading or differentiation at the invasive front showed 2 well differentiated tumors (20%),6 moderately differentiated tumors (60%) and 2 poorly differentiated tumors(20%). The most common type of invasive front encountered was tumor edge with small groups or cords of infiltrative cells /nests (60%). Lymphovascular invasion was present in two tumors (20%) and perineural invasion was absent in all of the tumors.

The tumor buds were seen at the advancing edge of invasive tumor front in standard hematoxylin and eosin-stained sections. All of the 10 cases demonstrated tumor budding (100%) in the stroma. Of the 10 cases, only two cases shows tumor budding of Grade 3.

All the clinical and histological parameters were cross tabulated individually against tumor budding. All the High-intensity tumor budding was seen in older age groups 40 years age, males, buccal mucosa cancers and stage 2 cancers with tumor size of < 4cms. Histologically, they were deep and extensive tumors, having an invasive front with infiltrative cells in groups or cords, dense stromal type in association with mild inflammation invariably. In the present study, only two cases werelymphovascular invasion positive and was associated with high intensity bud score.

Table 1: Clinical and Histological parameters evaluated in the study

Variables	No of patients (n=10)	Negative tumor budding	Grade 1 tumor budding	Grade 2 tumor budding	Grade 3 tumor budding	P value
Age (in years)						
<40 years	3 (30%)	2 (25%)	0	0	1(50%)	
>40 years	7 (70%)	6 (75%)			1(50%)	
Sex						
Male	8 (80%)	6 (75%)	0	0	2 (100)	
Female	2 (20%)	2 (25%)	0	0	0	
Site						
Buccal Mucosa	9 (90%)	7 (87.5%)	0	0	2 (100%)	
Maxilla	1(10%)	1 (12.5%)	0	0	0	
Tumor Size						
pT1: 2cm	3 (30%)	3 (37.5%)	0	0	0	
pT2: ≥2cm and ≤4cm	7 (70%)	5 (62.5%)	0	0	2 (100%)	
pT3: >4cm	0	0	0	0	0	
pT4: advanced disease	0	0	0	0	0	
Habits						
No	0	0	0	0	0	
Yes	10(100%)	2(100%)	1(100%)	1(100%)	6(100%)	

Histological grading						
Well differentiated	2(20%)	2 (25%)	0	0	0	
Moderately differentiated	6 (60%)	6 (75%)	0	0	0	
Poorly differentiated	2 (20%)	0	0	0	2(100%)	
Types of invasive front						
1) Pushing well defined borders	4 (40%)	3(42.85%)	0	0	1(33.33%)	
2) Infiltrative solid cords/ bands/strand	0	0	0	0	0	
3) Small group or cords of infiltrative cells (nests)	6 (60%)	4(57.14%)	0	0	2 (66.67%)	
Inflammation						
Present	4 (40%)	2 (25%)	0	0	2 (100%)	
Absent	6 (60%)	6 (85%)			0	
Lymphovascular invasion						
Present	2 (20%)	0	0	0	2 (100%)	
Absent	8 (80%)	8 (100%)			0	
Perineural invasion						
Present	Absent	Absent	Absent	Absent	Absent	
Absent						

Discussion

Oral squamous cell carcinoma is a heterogeneous disease with high variations in treatment response and prognosis. Detailed histopathological grading with scoring of specific features can help individualize treatment and predict prognosis. Tumour budding is a histopathological phenomenon that symbolizes cellular dissociation and invasion.[4]

Although studies had indicated evaluation of tumor budding by using markers such as cytokeratin andEpithelial Mesenchymal Transition(EMT) markers, tumor budding can easily be identified in H&E with good objectivity.[5,6,7] In the present study, we have used only routine hematoxylin and eosin slides to evaluate and score tumor buds into high intensity and low intensity. Grading criteria proposed by Ueno et al was used which had been reported to have more objectivity and good inter observer agreement.[3,8]

Worst pattern of invasive tumor front (WPOI), with small groups or cords of infiltrative cells /nests (60%) and dense stromal type was observed in association with tumor budding in most of the OSCC cases. The WPOI was previously also strongly associated with mortality from oral tongue SCC. Invasive patterns with cohesive cells (collective cell invasion) show good prognosis than those with discohesive cells that penetrates into normal surrounding tissues and acquires increased capacity (undergo Epithelial Mesenchymal Transition changes) for migration and invasion on exposure to increased levels of pro migratory signal molecules and a microenvironment produced by cells in stroma.[9,10]

Inflammatory cells infiltrate, considered as a result of tumor host interaction, activate cellular pathways by the chronic inflammation that can restrict the initial cancer cell transformation and progression.[7] A previous study has demonstrated dense lymphocytic host response to produce complete response to therapy for oral tongue SCC.[11] Absence or minimal inflammation favors the restriction free tumor invasion through tumour bud formation.

All the two OSCC cases with lymphovascular invasion were tumor budding positive. Whereas all of the tumor budding cases did not have lymphovascular invasion suggesting that tumor budding precedes and the isolated tumor buds acquire the cell motility to invade the vasculature and lymphatics effecting the metastasis process.

Conclusion

Tumor budding is the frequently observed histological feature in OSCC. It was correlated with deep invasion, the worst pattern of invasive front along with minimal host response conditions in OSCC.Thus this study emphasizes the importance of tumor budding evaluation in regular pathology practice in assessing the prognosis of OSCC cases.

Conflict of interest- None

Financial support- None

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