Original Article

Tumor-associated tissue eosinophilia versus tumor associated blood eosinophilia: A ratio of diagnostic importance in oral squamous cell carcinoma

Flora Verma, Saurabh Juneja, Ankita Tandon, Devi Charan Shetty

Department of Oral Pathology and Microbiology, ITS-CDSR, Muradnagar, Ghaziabad, Uttar Pradesh, India

For correspondence: Dr. Ankita Tandon, Department of Oral Pathology and Microbiology, ITS-CDSR, Muradnagar, Ghaziabad, Uttar Pradesh, India. E-mail: drankita tandon7@gmail.com

ABSTRACT

Introduction: Eosinophils are multifunctional granulocytes, which play a pivotal role in health and disease. Tumor Associated Tissue Eosinophilia (TATE) has long been evaluated in the diagnosis and progression of oral squamous cell carcinomas (OSCCs). However, their association with Tumor Associated Blood Eosinophilia (TABE) in OSCCs is still far fetched. We, therefore, attempted to evaluate their individual roles and to achieve a ratio between TATE and TABE in order to signify its usage in objectifying the diagnosis.

Materials and Methods: TATE was evaluated using H and E stain per 10 high power fields in 33 previously diagnosed cases of OSCC which were retrieved from department archives. TABE values were achieved from complete blood hemogram reports of patients. TATE/TABE ratio was calculated. All the parameters were clinicopathologically correlated and statistically evaluated using SPSS.

Results: TATE represented higher values in well-differentiated squamous cell carcinoma (WDSCC) and poorly differentiated squamous cell carcinoma (PDSCC) and was least in moderately differentiated squamous cell carcinoma (MDSCC), whereas TABE linearly increased from WDSCC to PDSCC. TNM Stage II cases revealed the highest TATE and lowest TABE. TATE/TABE ratio was the highest in WDSCC.

Conclusion: Due to the dual nature of eosinophils in early and late carcinogenesis events, evaluation of only TATE might not be conclusive in determining tumor grade. Hence, in a first of its kind attempt, the TATE/TABE ratio may be suitable to achieve a criterion for the determination of tumor grade and may also help to unfold the underlying biologic events.

KEY WORDS: Eosinophils, oral squamous cell carcinoma, tumor-associated tissue eosinophilia, tumor associated blood eosinophilia

INTRODUCTION

Wharton[1] first described "coarse granule cells" in 1846 which were later referred to as "eosinophils" by Ehrlich.[2] They are bone marrow-derived minority circulating (1%–5%)[3] multifunctional granulocytes.[4,5]

The spectrum of eosinophil activity in human health and disease has long been focused. Besides their involvement in tissue remodeling and in innate and acquired immune response modulations;[6] they are active participants in pathogenesis of allergic reactions and parasitic infections.[4,6] Eosinophils are strongly considered among destructive cells with cytotoxic activities which are usually attributed to their granules containing cationic proteins such as the major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin, and the eosinophil peroxidase.[7,8]

In the premise of advancing research, the importance of the tumor microenvironment (TME) has outgrown. Collaborative interactions between neoplastic cells and their supporting stroma coalesce to form chronically proliferative (and often disseminating) malignancies.[9] Infiltrating immune cells such as eosinophils supply direct and indirect mitogenic

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growth mediators that stimulate proliferation of neoplastic cells, as well as educate other stromal cell types to induce paracrine and juxtacrine mitogenic signaling molecules to support neoplastic growth which also appears true for oral squamous cell carcinomas (OSCCs).[9]

In India, OSCCs account for about 30% of all new cases annually and 22.9% of cancer-related deaths. The high-mortality and high-morbidity rates of OSCCs[10] indicate an urgent need of the development of therapeutic targets in the prevention and control of OSCC epidemic.

In evidence of current scientific literature, the association between tissue and blood eosinophilia has not been studied in OSCCs. Tumor-associated tissue eosinophilia (TATE), observed and described in many tumors, including the head-and-neck neoplasia was first described by Prezewoski in 1896 as "eosinophilic stromal infiltration of a tumor not associated with tumor necrosis or ulceration.[11,12] Furthermore, the term "Tumor-Associated Blood Eosinophilia (TABE)" was given to emphasize the possible clinical and/or biological significance of eosinophils in patients with various malignancies.[13,14] However, the binal significance of eosinophils in tumor growth and differentiation is the topic of ongoing debate, and several studies have reported inconclusive evidence of the same.

Clinical correlative studies of patients in other human malignancies with either blood or tissue eosinophilia, or both, have suggested that tissue eosinophilia at the tumor sites can be "protective," whereas blood eosinophilia may be an indicator of tumor metastasis.[11] However, due to the ambiguous evidence of either of the two in oral cancer pathogenesis, the ratio of TATE/TABE in OSCC could be decisive of the pathology.

In light of limited literature available, the current study was designed to correlate the tumor-associated tissue and blood eosinophilia with various clinicopathological parameters of OSCC.

MATERIALS AND METHODS

Study samples

The study was conducted in the Department of Oral and Maxillofacial Pathology and Microbiology, after obtaining consent from the Institutional Review Board. The retrospective study sample composed of a total of 33 cases of previously diagnosed OSCC (according to WHO 2005 grading criteria) as well, moderate and poorly differentiated OSCC. Cases with a history of another concomitant primary tumor, history of previous radiotherapy/chemotherapy, known history of diseases interfering with WBC counts, history of recent infectious diseases, tumors with extensive ulceration, or necrosis were excluded from the study sample. Demographic and clinicopathologic data of the patients including age, gender, tumor size (T), nodal status (N), and metastasis (M) were obtained from the records.

Procedure

Tumor-associated tissue eosinophilia

Formalin-fixed and paraffin-embedded archival tissues were retrieved to obtain 3 μm sections for routine H and E staining. The number of eosinophils was counted per 10 high power fields at X400 magnification and the mean numbers were calculated.

Tumor-associated blood eosinophilia

Peripheral blood eosinophil count was obtained from preoperative complete blood count (CBC) report of patients using Mindray; BC3600, Auto Hematology Analyzer.

Statistical analysis

The data were analyzed using the SPSS software version 19 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp). Data were expressed using mean and standard deviation. Differences between the different variables were analyzed using ANOVA and Kruskal–Wallis test. Value of $P \leq 0.05$ was considered statistically significant, with 95% of the confidence interval.

RESULTS

Demographic data

A total of 33 cases were included in the study. Mean TATE in patients <50 years was 6.47, which was slightly lower to patients >50 years (6.86) of age. Mean TABE values also showed a similar trend with mean values of 1.9 and 2.2 in patients <50 years and >50 years, respectively.

As per the gender analysis, females showed a lower mean value of TATE (6.76) but a higher TABE (2.78) over males (TATE = 6.79; TABE = 1.86).

Quantitative assessment of Tumor Associated Tissue Eosinophilia (TATE) and Tumor Associated Blood Eosinophilia (TABE) in different grades of oral squamous cell carcinoma

Among the randomly selected cases within the study group, 14 cases belonged to well-differentiated squamous cell carcinoma (WDSCC), 15 and 4 cases each for moderately differentiated squamous cell carcinoma (MDSCC) and poorly differentiated squamous cell carcinoma (PDSCC). The mean numbers of eosinophils in TATE did not represent a linear gradation from well through moderately differentiated to poorly differentiated cases. A sudden decrease in their count in MDSCC was observed over well and poorly differentiated cases. However, mean TABE demarcated a linear increase from well to PDSCCs [Figure 1a] ($P \leq 0.05$).

Quantitative assessment of Tumor Associated Tissue Eosinophilia (TATE) and Tumor Associated Blood Eosinophilia (TABE) in different clinical stages of oral squamous cell carcinoma

The study group comprised two cases each of Stage I and II, 9 cases of Stage III and 20 cases of Stage IV OSCC. On comparison

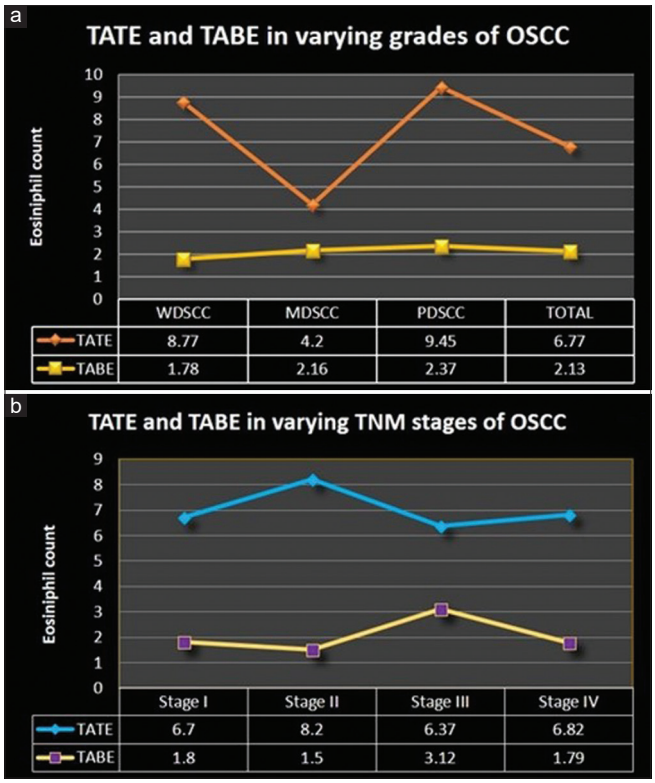

Figure 1: (a) Mean TATE and TABE values in varying grades of oral squamous cell carcinoma; (b) mean TATE and TABE values in varying clinical stages of oral squamous cell carcinoma

of mean values with clinical stages of OSCC, Figure 1b suggests the highest TATE and lowest TABE in Stage II OSCC cases ($P > 0.05$, Kruskal–Wallis test).

Association between the ratio of mean TATE and TABE values in varying stages and grades of oral squamous cell carcinoma

The TATE/TABE ratio, as suggested in Table 1, is the highest for Stage II and least for Stage III SCCs. TATE/TABE ratio did not attain statistical significance for the stage of tumor. The ratio is also the highest for WDSCC and least for MDSCC ($P \leq 0.05$).

DISCUSSION

OSCC represents 95% of all forms of headandneck cancers and is on the rise globally.[15] The majority of OSCC cases are diagnosed at a late phase,[16] in Stages III or IV,[17] which markedly decreases the chances of survival and leads to a significant deterioration in patient quality of life. Despite the currently available therapeutic strategies, patients present with high mortality[18] and the 5-year survival rate is only 53%.[19]

Well recognized checkpoints mediated through immune system posits that the immune mechanism recognizes malignant cells as foreign agents. Bone marrow-derived myeloid cells such as macrophages, neutrophils, eosinophils,

Table 1: Ratio of mean TATE and TABE values in varying stages and grades of oral squamous cell carcinoma

	TATE/TABE ratio	*P*
Clinical stages		
Stage I	20.5	0.158
Stage II	24.25	
Stage III	10.94	
Stage IV	17.11	
Histopathologic grades		
WDSCC	22.08	0.003
MDSCC	10.21	
PDSCC	16.5	

WDSCC=Well-differentiated squamous cell carcinoma, MDSCC=Moderately differentiated squamous cell carcinoma, PDSCC=Poorly differentiated squamous cell carcinoma, TATE=Tumor associated tissue eosinophilia, TABE= Tumor associated blood eosinophilia

mast cells, and dendritic cells infiltrate malignant tumors in large numbers.[20]

Eosinophils are granule containing cells that are 8 μm in diameter, and their nuclei are usually bilobed although three or more lobes are often observed. The eosinophils are characterized by their bright red granules that can be visualized with the dye such as eosin under light microscope.[21] Intact eosinophils can usually be readily detected in tissue sections of tumors that are stained with hematoxylin and eosin or phloxine B.[22]

With regards to TATE analysis, it has been postulated that the initial stages of oral carcinoma are said to be characterized predominantly by T-helper 1 (Th1) response (interleukin [IL]-12 and INF-γ, cellular immunity response). In turn, these T-helper 1 cells release various chemokines among which IL-2 and INF-γ are potent inducers of eotaxin, an eosinophil chemoattractant which binds to CCR3 receptor of eosinophils and recruits more eosinophils to the tumor site. Thus, the tumors associated with Th1 response are said to have a better prognosis.[23,24] However, in advanced stages of OSCC, with increasing tumor load, lymph node invasion and metastasis, the T-cell function is impaired with higher antibody response. This immune dysregulation is associated with alteration of Th phenotype leading to distinct profiles of cytokines. Tumor cells in cases exhibiting lymph node metastasis and poorer differentiation have higher Indoleamine 2,3-Dioxygenase (IDO) expression.[25] IDO-dependent tryptophan catabolites, including 3-hydroxyanthranilic and quinolinic acids, are known to induce selective apoptosis of Th1 but not Th2 cells, thereby evading immune surveillance. It could, therefore, be rightly said that eosinophils are like a "Double-edged sword in tumor battlefield" that support cell-mediated tumor immunity in early stages while inhibiting the same in advanced stages through IDO and cytokines and promoting tumor angiogenesis [Figure 2]. Besides, eosinophils also act as potent drivers in tumor pathogenetic model. They also activate mast cell and angiogenetic bystander pathways through cytokines and chemokines within the TME, thereby establishing successful crosstalk to facilitate tumor growth and development.[26]

Numerous authors have confirmed the presence of elevated eosinophil counts in invasive squamous cell carcinoma compared to noninvasive tumors of the head-and-neck region.[27,28] Tostes Oliveira *et al.*[29] found that intense eosinophilia was strongly associated with advanced stage T3/T4, whereas patients with OSCC in early stages T1/T2 presented absent/mild TATE.

In the present study, we found that the mean numbers of eosinophils per 10 hpf were greatest in PDSCC (9.45) followed by WDSCC (8.77) and least in MDSCC (4.2) [Figure 3]. Although the findings were statistically significant, no positive linear association between advancing grades of SCC could be ascertained. The findings were similar to other studies where no correlation could be established between TATE and tumor histopathologic grade.[30-32] This could possibly be explained on the basis of the unequal and inconsistent distribution of OSCC cases according to histologic grades in this study.

Furthermore, Iwasaki *et al.*[33] in gastric cancers recognized marked eosinophilic infiltration more frequently in the poorly differentiated than the well-differentiated adenocarcinomas ($P \leq 0.05$) which is similar to the findings of our study. They presumed that some special histologic types of carcinoma may preferentially attract eosinophils into the lesion. However, contrasting results are put forth by Rahrotaban *et al.*[34] in the head-and-neck neoplasia, who found a significant relation between different tumor grades and the number of eosinophils ($P = 0.04$). As the tumor grade increase in their sample size and the differentiation of tumor decreased, the number of eosinophils declined. They stated that their results confirmed the anti-tumor activity of eosinophils, which may be attributed to the cytotoxic proteins (major basic protein and eosinophil cationic protein) produced by these granulocytes.

The variability could also be explained on the basis of difference in eosinophil counting method, staining method, and how the number of eosinophils were distributed in the tissue. Furthermore, abnormal and uncommon morphology of eosinophils, particularly in fibrous tissue, and the presence of severe inflammatory infiltration in the samples may pose difficulty in the distinction of these cells when conventional H and E stain is used for their identification.

On the other hand, the mean TABE was also the highest in PDSCC (2.37) followed by MDSCC (2.16) and least in WDSCC (1.78). Although there is a dearth of literature regarding the association between TABE in OSCC, our study found a positive correlation between TABE and OSCC and TABE and TATE. Their higher values in advanced cases signify more recruitment form peripheral blood to the stroma under the influence of eotaxin, IL-3, IL-5 thereby suggesting poor prognosis. It has been speculated that TATE may occur together or separately from TABE. Notably tumors with TATE

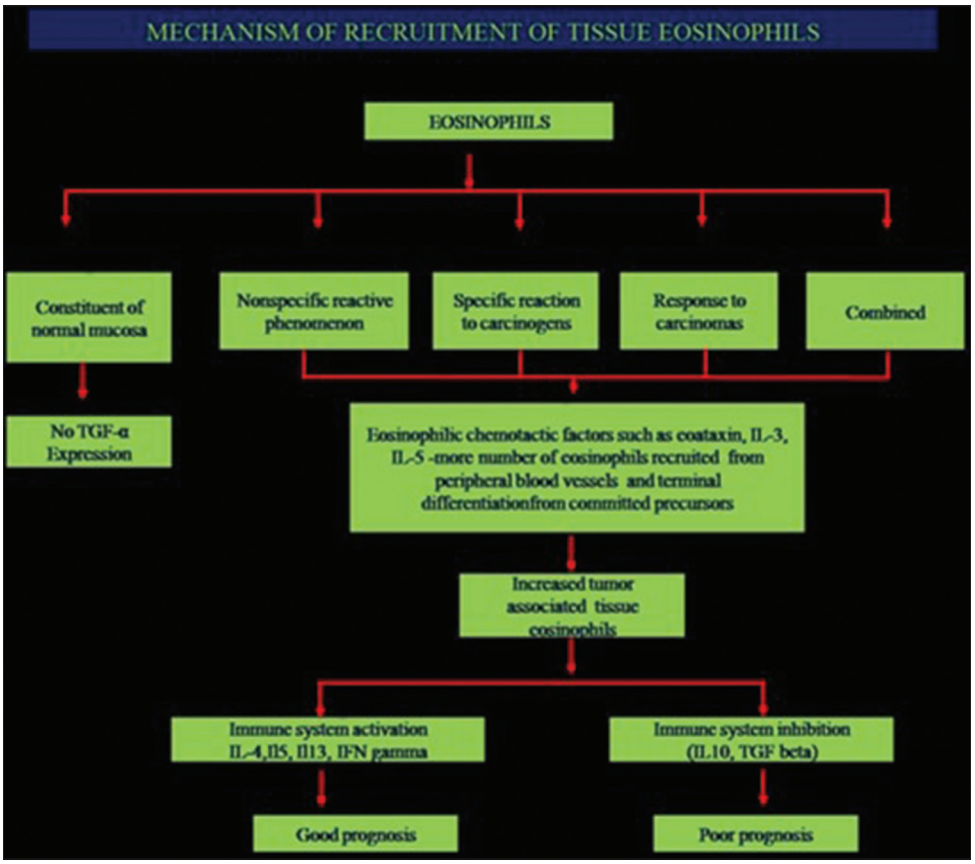

Figure 2: Functional significance of tissue eosinophils

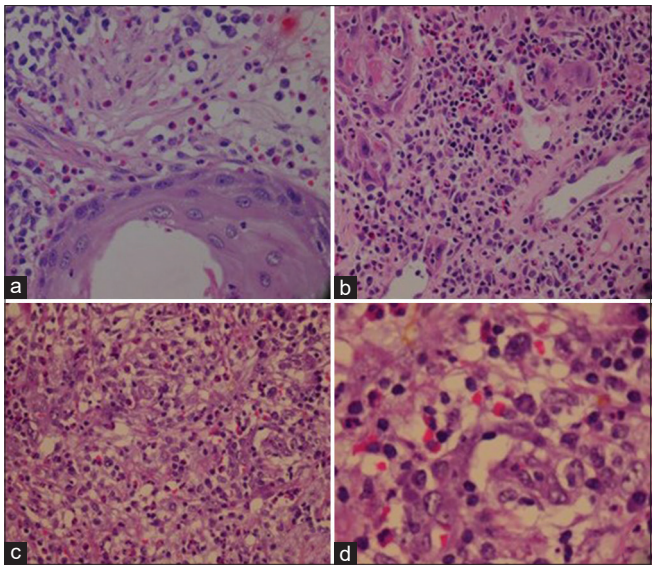

Figure 3: Tumor-associated tissue eosinophilia (TATE); (a) well-differentiated squamous cell carcinoma (H and E, X400); (b) moderately differentiated squamous cell carcinoma (H and E, X400); (c) poorly differentiated squamous cell carcinoma (H and E, X400); (d) eosinophils at higher magnification (H and E, X1000)

alone appears to have a better prognosis compared to those without TABE, whereas TABE is associated with tumor spread and poor prognosis.[35]

Since TNM is a well-accepted prognostic factor and the poor prognosis of poorly differentiated OSCCs is well documented, we decided to perform an objective evaluation of the primary tumor size, nodal status, and clinical staging in our cases.

On correlating the clinical staging, we found that the association of these parameters (T, N, M) with the TATE and TABE did not reach statistical significance. TATE was the highest in Stage IV (6.82) and TABE was the highest in Stage III (3.12). Our results for TATE were similar to Peter *et al*.[36] who reported a statistically significant increase in the eosinophil count with an increase in the size of the tumor. It was hence hypothesized that eosinophils increase with increase in tumor size as they are a part of host connective tissue response.

Our findings were also consistent with the results obtained by Aghbali *et al*.,[6] Etit *et al*.[37] who found that the correlation of eosinophil counts with lymph node metastasis in their study were statistically insignificant. Ercan *et al*.[38] stated that the presence of TATE in their study was not related to N staging in TNM classification.

As discussed previously, the role of eosinophils is binal with the involvement of both Th1 and Th2 type immune responses, thereby supporting TATE with both good[39-41] and poor[42-44] prognosis. On the contrary, Lowe *et al*.[35] mentioned that TATE without tumor associated blood eosinophilia is usually associated with a good prognosis. As per our knowledge, this is the first study which evaluated the TATE/TABE ratio and found a statistically significant association with histopathological grade ($P \leq 0.05$) but not with the clinical stage ($P > 0.05$).

CONCLUSION

It may hence be concluded that, in the world of advanced clinical research and ever-increasing usage of evidence-based therapeutic interventions, mere quantifying TATE and TABE in relation to diagnosis and prognosis carries less significance. As regards to pathfinder research in this direction, the ratio of TATE and TABE could provide an objective criterion to determine the biological basis of tumor progression and may carry prognostic significance in future research.

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Conflicts of interest
There are no conflicts of interest.

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