Original Article

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Pathology Section

Evaluation of Tumour Eosinophilia and Histological Grade in Squamous Cell Carcinomas of the Upper Aerodigestive Tract: A Cross-sectional Study

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ABSTRACT

Introduction: Tumour-Associated Tissue Eosinophilia (TATE) refers to the presence of eosinophilic infiltration within and around tumour tissue. Its role in Squamous Cell Carcinoma (SCC) of the upper aerodigestive tract remains controversial, with studies suggesting both tumour-promoting and tumour-suppressing effects.

Aim: To assess the degree of tissue eosinophilia in SCC of the upper aerodigestive tract and to correlate it with tumour differentiation.

Materials and Methods: This cross-sectional study was conducted over a period of two years, from May 2023 to April 2025 at a tertiary care medical center, Vijayapura, Karnataka, India. A total of 70 biopsy specimens of histologically confirmed SCC of the upper aerodigestive tract (oral cavity, larynx, and oesophagus) were included. Eosinophils were counted in 10 High-Power Fields (HPF) in both intratumoral and peritumoral regions using Hematoxylin and Eosin (H&E) stained sections. Cases were graded as Grade I (0-20 eosinophils), Grade II (21-40 eosinophils), and Grade III (>40 eosinophils). Tumours were classified as well, moderately, or poorly differentiated. Data were analysed using SPSS® version 17.0. Descriptive statistics were used to summarise eosinophil grades and tumour differentiation, and Spearman's rank correlation coefficient was applied to assess the association between TATE grade and tumour differentiation, with $p<0.05$ considered statistically significant.

Results: Of the 70 cases, 25 were well-differentiated, 35 moderately differentiated, and 10 poorly differentiated. Grade III TATE was most common in well-differentiated SCC with 16 cases (64%), while Grade II was predominant in moderately differentiated tumours, with 23 cases (65.7%). Poorly differentiated SCCs showed minimal eosinophilic infiltration, with 8 cases (80%) exhibiting only Grade I TATE. A statistically significant inverse correlation was observed between TATE grade and tumour differentiation (Spearman's $\rho=-0.78$, $p<0.001$).

Conclusion: High eosinophil infiltration was associated with better tumour differentiation. TATE may serve as a supplementary histopathological marker in assessing tumour differentiation and biological behaviour in SCC of the upper aerodigestive tract, although further studies with larger cohorts and clinical follow-up are warranted.

Keywords: Eosinophils, Tumour-associated tissue eosinophilia, Tumour differentiation

INTRODUCTION

The TATE refers to the infiltration of eosinophils within and around tumour tissue, a phenomenon first documented by Przewoski in cervical carcinoma [1]. Since then, TATE has been observed in various malignancies, particularly those of squamous cell origin, including those affecting the upper aerodigestive tract [2-4]. These include carcinomas of the oral cavity, larynx, and oesophagus, sites known for their exposure to environmental carcinogens and chronic inflammation [2,5].

Eosinophils are multifunctional granulocytes known primarily for their role in allergic reactions and parasitic infections [4]. However, their role in tumour biology has gained increasing attention [6-8]. In response to tumour-associated stimuli, eosinophils migrate to the tumour microenvironment, where they release a wide array of bioactive mediators, including interleukins, interferon-gamma, Transforming Growth Factors (TGF-α and TGF-β), eosinophil cationic proteins, major basic protein, eosinophil peroxidase, eosinophil-derived neurotoxin, tumour necrosis factor-alpha, chemokines, platelet-activating factor, leukotrienes, and indoleamine 2,3-dioxygenase [4,8].

These mediators can contribute to tumour dynamics in various ways. Some may promote tumouricidal activity through direct cytotoxic effects or by enhancing the penetration of immune cells and cytokines into tumour tissues [8,9]. Conversely, eosinophils may also facilitate tumour progression by promoting angiogenesis and modulating the immune microenvironment in favour of tumour survival [10]. Thus, their role appears to be dualistic and context dependent.

The prognostic and predictive significance of TATE in SCC of the upper aerodigestive tract remains a subject of ongoing investigation [11-13]. While some studies suggest a favourable prognosis associated with increased eosinophil infiltration, others report neutral or even adverse effects [4,11]. This variability highlights the need for further research to clarify the clinical utility of TATE in SCC. Moreover, data correlating TATE with histological grade in upper aerodigestive tract SCCs remain limited, particularly in the Indian population.

Hence, the present study aimed to evaluate the pattern and intensity of tumour-associated eosinophilic infiltration in histologically confirmed cases of SCC of the upper aerodigestive tract and to correlate tissue eosinophilia with the histopathological grade of the tumour.

MATERIALS AND METHODS

Study Design and Sample Selection

This cross-sectional study was conducted over a two-year period, from May 2023 to April 2025, at Shri B M Patil Medical College Hospital and Research Center, Vijayapura, Karnataka, India. Institutional ethics committee approval was obtained (IEC

No: 61/2023) prior to the commencement of the study. In view of the retrospective nature of the study utilising archived biopsy specimens, informed consent was waived.

Archived biopsy specimens of histopathologically confirmed SCC of the oral cavity, larynx, and oesophagus were included. Only solid epithelial tumours confirmed as SCC were included. Cystic neoplasms and poorly preserved tissue samples were excluded from analysis to ensure consistency and diagnostic reliability.

Histological Evaluation

All tissue specimens were fixed in 10% formalin, processed routinely, and stained with H&E. Eosinophilic infiltration was assessed both within the tumour mass (intratumoral) and at the periphery of the tumour (peritumoral) using light microscopy.

Eosinophil counts were performed manually by two independent pathologists. Ten randomly selected HPFs were evaluated per slide at ×400 magnification with a field number of 20 (FN20). The average eosinophil count across these fields was recorded for each case. In cases of initial disparity in counts or grading, the slides were re-examined together under a multi-headed microscope, and disparities were resolved through consensus.

Grading of TATE

Based on the number of eosinophils per 10 HPFs, each case was categorised into one of the three grades [2], as detailed in [Table/Fig-1].

Tumour Differentiation

SCC cases were also categorised according to their histological differentiation as:

- Well-differentiated
- Moderately differentiated
- Poorly differentiated

This classification was based on established histopathological criteria [14,15] including the degree of keratinisation, cellular pleomorphism, mitotic activity, and architectural disorganisation.

STATISTICAL ANALYSIS

Data collected from the histological evaluations were entered into Microsoft® Excel 2016 and statistically analysed using SPSS® version 17.0 (IBM Corp.). Descriptive statistics including frequency distributions and percentages were used to describe eosinophil grades and tumour differentiation categories. Spearman's rank correlation coefficient (ρ) was used to assess the monotonic relationship between ordinal TATE grade and tumour differentiation. A p-value of <0.05 was considered statistically significant. Results were visually represented through tables and charts. Interobserver variability was resolved through pathologist consensus.

RESULTS

This study analysed 70 histopathologically confirmed cases of SCC of the upper aerodigestive tract, comprising lesions from the oral cavity (n=46), larynx (n=5), and oesophagus (n=19). The study population consisted of 38 males (54.3%) and 32 females (45.7%), with patient ages ranging from 34 to 90 years (mean age 58.4±12.75 years). The demographic peak was in the fifth to seventh decades of life, which accounted for the majority of the cohort.

Based on histopathological evaluation, 25 cases (35.7%) were classified as well-differentiated SCC, 35 cases (50%) as moderately differentiated SCC, and 10 cases (14.3%) as poorly differentiated SCC. TATE was assessed by counting eosinophils in 10 HPFs in both intratumoral and peritumoral regions. Based on the average eosinophil count per 10 HPFs, cases were categorised into three TATE grades: Grade I (0-20 eosinophils), Grade II (21-40 eosinophils), and Grade III (more than 40 eosinophils).

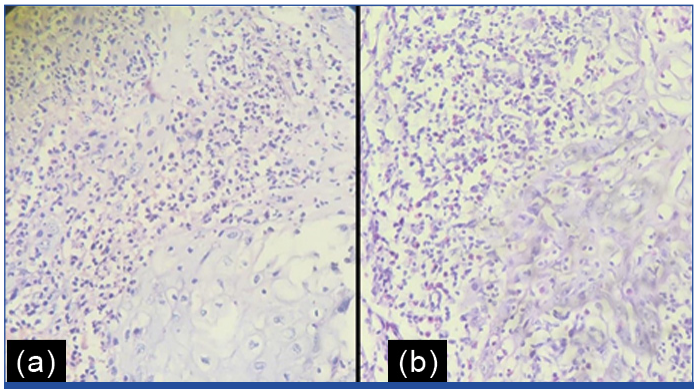
Grade	Eosinophil Count (per 10 HPFs)
Grade-I	0-20 eosinophils
Grade-II	21-40 eosinophils
Grade-III	>40 eosinophils

[Table/Fig-1]: Grading of tumour-associated tissue eosinophilia.

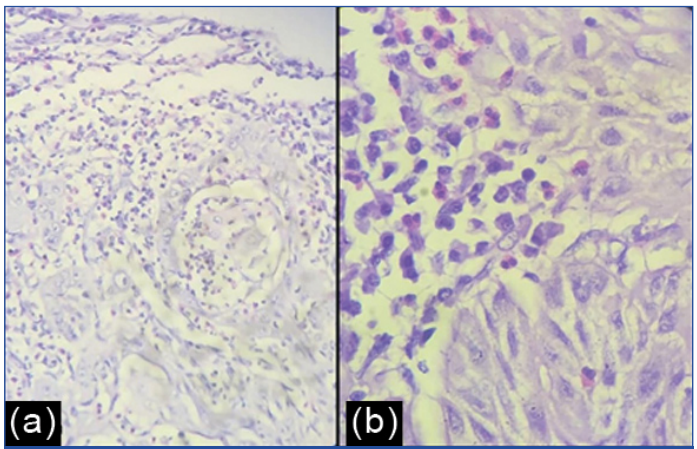
The distribution of TATE grades across histological differentiation categories is summarised in [Table/Fig-2]. In the well-differentiated SCC group, a significant proportion of cases demonstrated high eosinophilic infiltration, with 16 cases (64%) showing Grade III TATE [Table/Fig-3], while 7 cases (28%) had Grade II, and only 2 cases (8%) showed Grade I TATE. In moderately differentiated SCC, most cases were associated with an intermediate level of eosinophilic infiltration; 23 cases (65.7%) exhibited Grade II TATE [Table/Fig-4], followed by 6 cases each (17.1%) for Grades I and III.

Histological grade	Grade-I n (%)	Grade-II n (%)	Grade-III n (%)	Total
Well differentiated	2 (8.0)	7 (28.0)	16 (64.0)	25
Moderately differentiated	6 (17.1)	23 (65.7)	6 (17.1)	35
Poorly differentiated	8 (80.0)	1 (10.0)	1 (10.0)	10
Total	16 (22.9)	31 (44.3)	23 (32.9)	70

[Table/Fig-2]: Distribution of Tumour-Associated Tissue Eosinophilia (TATE) grades according to histological differentiation.



[Table/Fig-3a, b]: Photomicrograph showing dense peritumoral eosinophilic infiltration (TATE Grade III, mean eosinophil count >40/10 HPF) in well-differentiated squamous cell carcinoma of the upper aerodigestive tract (H&E stain, ×400).



[Table/Fig-4a, b]: Photomicrograph showing moderate eosinophilic infiltration (TATE Grade II, mean eosinophil count 31/10 HPF) in moderately differentiated Squamous Cell Carcinoma (SCC) of the upper aerodigestive tract (H&E stain, a-100x, b- 400x).

Conversely, poorly differentiated SCCs displayed a markedly reduced eosinophilic infiltrate. A striking 80% (8/10) of these cases demonstrated only Grade I TATE, indicating minimal eosinophil presence, while just one case each (10%) showed Grade II and Grade III TATE.

When all cases were considered collectively, Grade II TATE was the most common overall, observed in 44.3% (31/70) of cases. Grade III TATE was present in 32.9% (23/70), and Grade I in 22.9% (16/70).

Spearman's rank correlation analysis demonstrated a statistically significant inverse correlation between tumour differentiation and TATE grade (Spearman's ρ=-0.78, p<0.001).

DISCUSSION

The present study demonstrates a statistically significant inverse correlation between TATE grade and histological grade in SCCs of the upper aerodigestive tract. Higher grades of eosinophilic infiltration were predominantly observed in well-differentiated tumours, whereas poorly differentiated carcinomas were more frequently associated with lower eosinophil counts. These findings indicate a consistent relationship between the degree of tumour differentiation and the extent of eosinophilic infiltration within the tumour microenvironment. This gradation of TATE across different tumour differentiation categories highlights the potential role of eosinophils as biomarkers for tumour behaviour.

TATE is characterised by the presence of eosinophils within the tumour stroma and at its invasive margins and has been hypothesised to reflect either a host immune response or tumour-promoting inflammation, depending on the context [8,12]. In this study, the presence and extent of eosinophilic infiltration in 70 histologically confirmed cases of SCC of the upper aerodigestive tract was evaluated and correlated with tumour differentiation grades. The results demonstrate a significant association between tumour differentiation and the degree of eosinophilic infiltration. Well-differentiated SCCs showed the highest levels of eosinophilic presence, with 64% of cases exhibiting Grade III TATE, while poorly differentiated SCCs showed minimal eosinophilic involvement, with 80% of cases limited to Grade I TATE. This inverse relationship between tumour grade and TATE suggested that eosinophilic infiltration is more pronounced in tumours with more organised histoarchitecture and possibly less aggressive biological behaviour.

These findings are consistent with the study conducted by Bhan C et al., who reported a higher eosinophil count in well-differentiated SCCs of the upper aerodigestive tract and proposed that eosinophilic infiltration might be a marker of better prognosis [2]. Similarly, Yellapurkar S et al., found that higher eosinophil counts in oral SCC correlated with improved survival outcomes and reduced recurrence, supporting the hypothesis that TATE may serve as a surrogate marker for host immune response [4].

On the other hand, Etit D et al., in their evaluation of laryngeal SCC, reported that TATE did not have a significant association with lymph node metastasis and was not a definitive prognostic indicator [5]. Such conflicting observations highlight the complex, context-dependent role eosinophils may play in tumour progression. While some studies support a protective, tumour-suppressing role [12,14,15], others suggest that eosinophils may facilitate tumour growth and angiogenesis by releasing various mediators, including TGF-α and TGF-β, eosinophil cationic proteins, and vascular endothelial growth factor [10,16].

The dual role of eosinophils, either promoting or inhibiting tumour growth, may depend on various factors, including the type of tumour, the local immune microenvironment, cytokine signaling, and tumour-intrinsic properties [4,11]. Eosinophils are known to release cytotoxic granules such as major basic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin, all of which may contribute to tumouricidal activity [10]. In contrast, eosinophil-derived cytokines and chemokines can also contribute to immunosuppression, matrix remodeling, and neovascularisation, which may favour tumour progression [10].

In the context of SCC of the upper aerodigestive tract, the findings from the present study suggest that TATE may be indicative of a more robust local immune response in well-differentiated tumours, potentially contributing to tumour containment or slower progression. The diminished eosinophilic response observed in poorly differentiated tumours may reflect immune evasion mechanisms or an inherently less immunogenic tumour phenotype.

Limitation(s)

This study has certain limitations that should be acknowledged. The retrospective, cross-sectional design limits the ability to establish causal relationships between tumour-associated tissue eosinophilia and tumour behaviour. Clinical follow-up data, including lymph node status, treatment response, and survival outcomes, were not available, precluding assessment of the prognostic significance of TATE. The study was conducted at a single tertiary care centre with a relatively limited sample size, which may affect generalisability. Additionally, eosinophils were identified using routine haematoxylin and eosin staining without the use of immunohistochemical markers or special stains, which may have enhanced cellular characterisation.

While the findings align with the hypothesis that a higher degree of TATE correlates with better tumour differentiation and potentially more favourable outcomes, the role of eosinophils in cancer remains complex and multifactorial. Larger, multi-centric studies with long-term follow-up data are needed to evaluate the prognostic significance of TATE and its potential utility as a biomarker for predicting tumour behaviour, treatment response, or recurrence.

CONCLUSION(S)

This study demonstrates a clear correlation between TATE and histological grade in SCCs of the upper aerodigestive tract. Well-differentiated tumours exhibited significantly higher eosinophilic infiltration compared to poorly differentiated ones, suggesting that TATE may reflect an active local immune response associated with less aggressive tumour behaviour. These findings support the potential utility of TATE as a supplementary histopathological marker in the assessment of tumour differentiation and prognosis in upper aerodigestive tract SCCs.

Authors' contribution: PRV: Concept and design, data collection, literature search, manuscript writing; RDP: Concept and design, histological evaluation, data analysis, manuscript revision, corresponding author; SG: Histological evaluation, data collection, statistical analysis, manuscript writing; AKR: Study supervision, histological evaluation, critical review, final approval.

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