ORIGINAL ARTICLE   Open Access

The role of tumour-associated tissue eosinophilia as a prognostic indicator in head and neck squamous cell carcinoma

Naveen Sharma, Neha Salaria[*], Surender Kumar, Nimmy Thomas, Nidhi Beniwal and Ranvir Singh

Abstract

Background: Eosinophils are bone marrow-derived granulocytes known to have an imperative role in tissue inflammation. The mechanism of tumour-associated tissue eosinophilia (TATE) in head and neck cancers is however not well understood, and its role as a prognosticator is under evaluation. The aim of this study was to evaluate the association of TATE with factors associated with head and neck cancer and to assess its role as a prognostic marker in such patients.

Results: 102 males and 24 females comprised the study population, and 34.9% of which were in the age group of 41 to 50 years. Amongst these 126 patients, most (37.3%) presented in stage III followed by stage IV (28.6%). 29.4% had well-differentiated SCC, 55.6% had moderately differentiated SCC, and 15% were diagnosed with poorly differentiated SCC. 42.8% had TATE grade II, followed by grade III (29.4%) and grade I (27.8%). Correlation studies showed that factors significantly associated with TATE were age, site and tumour differentiation. While 45.7% poorly differentiated tumours showed grade I eosinophilia, 51.4% of well-differentiated tumours had grade III TATE.

Conclusions: TATE showed a highly significant association with tumour differentiation, suggestive of eosinophils partaking a tumouricidal role. This association may be utilised as a convenient early prognosticator for head and neck cancers and should be made a regular feature of biopsy reports. Furthermore, it may be utilised in planning and adopting appropriate treatment modalities in malignancies predicted to have an aggressive course.

Keywords: Eosinophilia, Head and neck cancer, Tumour, Tissue

Background

Squamous cell carcinoma (SCC) of the head and neck region is the 6th leading cancer by incidence worldwide and accounts for more than 550,000 cases and 380,000 mortalities every year [1]. Males belonging to 40–60 years of age are affected more significantly than females. It usually begins in the squamous cells lining the mucosal surfaces. Cancers of the head and neck are further categorised by the subsites in which they begin namely oral cavity, oropharynx, larynx, hypopharynx, nasophar-ynx, nasal–paranasal cavities and salivary glands. At least 75% of head and neck cancers are attributed to tobacco, its products and alcohol abuse [2]. Human papilloma virus (HPV) infections (especially HPV 16), paan, preserved or salted food, poor oral health and radiations are some other plausible causes. Over the past decades due to a high risk of exposure to oncogenic HPV, there has been a drift in primary site distribution with a steady upsurge of oropharyngeal squamous cell carcinoma than cancers of the larynx and hypopharynx.

Tumour-associated tissue eosinophilia (TATE) was foremost described precisely by Przewoski in cervical cancer in 1896 and was characterised by infiltration of

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eosinophils as peritumoural and intratumoural infiltrates. Eosinophils are derivatives of the bone marrow characterised by the existence of specific granules containing cationic proteins which are intensely stained by eosin. It has been long hypothesised that eosinophils have tumouricidal action by releasing cytotoxic proteins, interleukins (IL) and cytokines which also affect the permeability of the malignant cells. In tumour microenvironment, after receiving an appropriate stimulus from the tumour antigen, eosinophils release several mediators such as IL-1, 2, 4, 5, 6, 8, 10, 12, 13, and 18; interferon-γ; transforming growth factor-α and β; eosinophil cationic protein; major basic protein; eosinophil peroxidase; eosinophil-derived neurotoxin; and tumour necrosis factor [3–5].

Inflammatory infiltration with eosinophils results from an immune reaction to counter tumour antigens in or around the tumoural tissue which varies amid cases with squamous cell carcinoma of the upper aero-digestive tract [6]. Recent studies have indicated that eosinophil infiltration in oesophageal SCC may correlate with a less aggressive tumour [7, 8]. While several studies have established TATE as a favourable prognostic indicator, certain contrary studies consider it not to be a good prognosticator [9–15]. Hence, the role of TATE as a prognosticator is still controversial as the mechanism of tumour-associated eosinophilia is not well understood and literature regarding TATE is also ambiguous. The other factors related to the tumour growth are age, sex, habit of smoking, anatomic location of tumour, lymph node involvement and final stage of the tumour.

This study is an effort to assess the association between age, sex, habit of smoking, site of cancer, lymph node involvement, final stage and tumour differentiation with TATE and to assess the use of TATE as a prognostic indicator in SCC of the head and neck.

Methods

An observational study was conducted at a tertiary level centre in the northern part of India. A total of 126 patients with growth in the head and neck area were included in the study. Patients who had received radiotherapy/chemotherapy in the past and those with benign lesions of head and neck, recurrence/residual disease or with an immunocompromised state were excluded from the study. Appropriate clearance was taken from the institutional scientific research committee and ethical committee.

The aims which we targeted to achieve were to establish association if any between tumour-associated tissue eosinophilia with age, gender, addictions, primary site involved, lymphatic spread, final composite stage and differentiation of tumour in squamous cell carcinoma in head and neck region. We also targeted

to evaluate tumour-associated tissue eosinophilia as a prognostic marker in squamous cell carcinoma in the head and neck.

All patients encompassed in the study were biopsied after detailed history, clinical examination and taking informed consent. The slides were prepared with haematoxylin and eosin staining, and histopathological specimens were studied concerning the differentiation of tumour and infiltration of eosinophils. The tissue eosinophils were tallied in randomly chosen 10 high-power fields at ×40 magnification. The classification was done in 3 grades as follows:

1. Grade I: 0–10 eosinophils/10hpf
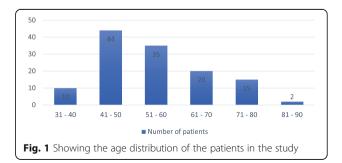2. Grade II: 11–20 eosinophils/10hpf
3. Grade III: >21 eosinophils/10hpf

Squamous cell carcinoma was also categorised into 3 grades on basis of the degree of keratinisation and nuclear atypia:
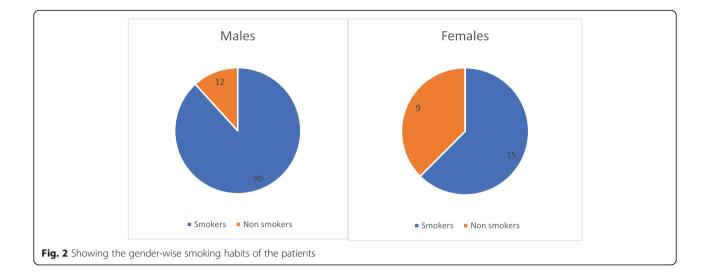
1. Well-differentiated SCC
2. Moderately differentiated SCC
3. Poorly differentiated SCC

The results were analysed with SPSS software by descriptive-analytic method (mean ± standard deviation) and chi^2 test was applied to find the association between tumour-associated tissue eosinophilia and age, gender, addictions, primary site involved, lymphatic spread, final composite stage and differentiation of tumour in squamous cell carcinoma in head and neck region. A p value of less than 0.05 was considered significant.

Results

There were a total of 126 patients included in the study with ages ranging from 33 to 82 years. Most patients were in the age group of 41 to 50 years, and the mean age was 55.12 ±12.98 years (Fig. 1). Out of 126 patients, there were 102 males and 24 females with M: F = 4.2:1. Of 102 male patients, 90 (88%) were smokers and 12 (12%) were non-smokers, whereas amongst 24 female

Fig. 1 Showing the age distribution of the patients in the study

Fig. 2 Showing the gender-wise smoking habits of the patients
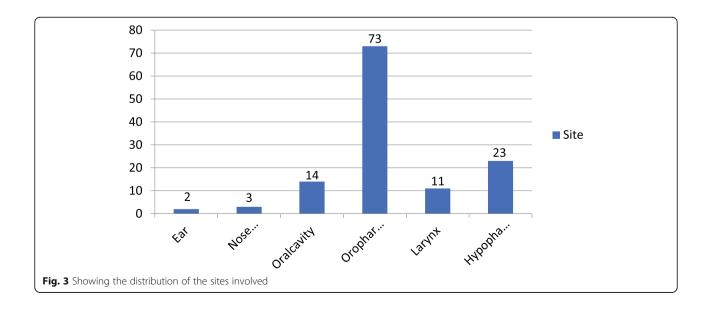
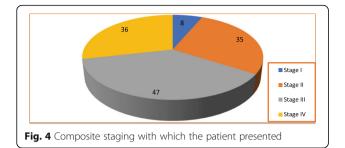patients, 15 (63%) were smokers and 9 (37%) were non-smokers (Fig. 2).

In the current study, the oropharynx 73 (58%) remained the most common site of SCC followed by the hypopharynx 23 (18.2%). Oral cavity 14 (11.1%), larynx 11 (8.7%), nose and paranasal sinuses 3 (2.3%) and ear 2 (1.6%) were the other sites found to be involved (Fig. 3).

Most of the patients presented with stage III (37.3%) followed by stage IVA (28.6%), stage II (27.7%) and stage I (6.3%). None of the patients presented with stage IVB and IVC malignancy (Fig. 4).

The tumour differentiation was done on the basis of keratinization and nuclear atypia. Out of 126 patients, 37 (29.4%) had well-differentiated SCC, 70 (55.6%) had moderately differentiated SCC, while 19 (15%) were diagnosed with poorly differentiated SCC. The grading of the TATE score was done as grades I, II and III as per the predefined grading system. Out of 126 patients, 35 (27.8%) patients were in grade I, 54 (42.8%) patients were in grade II and 37 (29.4%) patients were in grade III.

Chi^2 test was then applied to find the association between the above various factors and the TATE grades. On evaluating the association between age and TATE grade, the p value came out to be less than 0.05, hence implicating a significant relation between the two. The highest association was found in the age group 51–70 years (Table 1). However, no significant association was found between the sex of the patient and TATE score using chi^2 test as the p value was more than 0.05 (Fig. 5).

Fig. 3 Showing the distribution of the sites involved

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Fig. 4 Composite staging with which the patient presented

Chi^2 test was also applied to find the connotation between the habit of smoking and the TATE grades. The p value came out to be more than 0.05 which was deemed insignificant (Table 2).

The correlation between the site of cancer and TATE by chi^2 test showed a significant association between the two parameters. Amongst head and neck cancer sites, oral cavity malignancies presented with the highest eosinophil infiltration compared to others (Table 3).

Amongst 126 cases of head and neck cancer, lymph node involvement was found in 74 (58.7%) cases. Association between the lymph node involvement and TATE score using chi^2 test discovered no significant association between the two factors (Table 4). Evaluation of relation between the final stage of cancer and TATE score using chi^2 test revealed no significant association, as the p value was more than 0.05 (Table 5).

To find the association between tumour differentiation and the TATE grades, chi^2 test was applied which revealed that the p value in this case was less than 0.05 indicating a significant relation between the two as shown in Table 6.

Discussion

Eosinophils are long-lived multifunctional cells which hold and produce many biologically active constituents. Even though traditionally eosinophilia was thought to be associated mainly with parasitic contagions or allergic disorders, current studies suggest eosinophil infiltration

Table 1 Showing association between age and TATE score

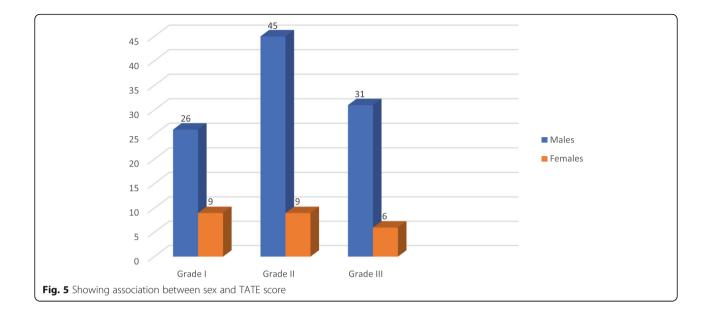| TATE score	Age (years)	30–50	51–70	71–100
Grade I		8	10	17
	% within TATE score	22.9%	28.6%	48.6%
Grade II	Count	15	39	0
	% within TATE score	27.8%	72.2%	0.0%
Grade III	Count	31	6	0
	% within TATE score	83.8%	16.2%	0.0%

*P value 0.001, highly significant

is likewise existing in target tissues during physiological and pathological processes like angiogenesis, embryogenesis, immune regulation and neoplasia resulting in tissue damage or remodelling. Tumour-associated tissue eosinophilia was first described by Prezewoski in 1896 as "eosinophilic stromal infiltration of a tumour not related with tumour necrosis or ulceration" [15]. It is typified by the presence of eosinophils as an element of peri- and intratumoural inflammatory infiltrates. MEDLINE search of the literature showed that TATE has been allied with malignancies of diverse sites such as the oral cavity, nasopharynx, larynx, oesophagus, colon and cervix [4, 8, 12, 16–20].

A total of 126 patients of either sex with ages ranging from 32 to 82 years were assessed in the study. The mean age was found to be 55.12 years with a major proportion belonging to 4th and 5th decades of life. The study conducted by Vaibhav et al. [21] and Bankur [22] found that the main age group of the presentation was above 5th decade. An early age of presentation in the current study could be attributed to the habit of smoking in this area. The patient's influx in the study is mainly from surrounding rural areas where there is early onset of smoking owing to acceptance of the concept of community smoking.

Male patients were more compared to female patients and M to F ratio was 4.2:1 which was comparable to several other studies. However, an increasing incidence of head and neck cancer in females was found in this study as compared to certain other reports [6]. It could be ascribed to the habit of smoking in females which is more prevalent in this region due to unrestricted smoking practices and general communal acceptance.

A significant association between the age of the patient and TATE grade was found on chi^2 test. Interestingly, patients of age above 70 years were more associated with TATE grade I, while grade II was more in ages 51–70 years and grade III in 30–50 years, respectively. It indicates as age increases TATE grade decreases, since the immune system is stronger in younger adults as compared to old age patients. Nonetheless, we could not find any significant association between gender and TATE grade. Most studies found no correlation of TATE with age and sex however Ercan et al. [23] found a negative correlation between TATE and age which was consistent with the current study. He also suggested that a lesser incidence of TATE over the age of 60 years could be due to decreased inflammatory response to tumour as age advances which is reasserted due to consistency with the current study.

There was an 83.33% incidence of smoking in patients included in the study, amongst which 71.4% were males and 11.9% were females. The main forms of tobacco consumption in these patients were non-chewable

Fig. 5 Showing association between sex and TATE score

tobacco products such as bidi and hukkah (waterpipes). Intake of these products is more prevalent in the population included in the study. Especially unique was a positive history of chronic hukki (smaller hukkah) smoking in females explicitly seen in this section of the state. In the current study, we also understood that there is no association between the habit of smoking and TATE in case of head and neck cancers. Dorta et al. [4] and Oliveira et al. [14] found a high prevalence of head and neck cancers in patients with smoking habits. They revealed that intense TATE is significantly linked with alcohol consumption only or with a long history of collective alcohol intake and cigarette smoking in oral cavity squamous cell carcinoma.

Dorta et al. [4] and Oliveira et al. [14] also assessed TATE in squamous cell carcinoma of the tongue, floor of the mouth, retromolar area and inferior gingiva, but they could not find any statistically significant variances in the distribution of eosinophils amid these sites. In the current study, the oropharynx remained the most common site of SCC contributing to about 58% of cases followed by the hypopharynx, oral cavity, larynx, nose–

paranasal sinuses and ear. We however found a significant association between TATE and site of cancer in head and neck cancers as the *p* value was 0.009. Chi^2 test showed hypopharyngeal, oropharyngeal and laryngeal cancers were associated with grade II TATE, and grade I TATE was observed in the ear, nose and paranasal sinuses while grade III TATE was seen in oral cavity cancer. It could be gathered that a major proportion of head and neck cancers are associated with grade II TATE; however, this needs to be further evaluated in a larger number of patients to establish a conclusive association.

Most of the patients presented with stage III (37.3%) cancer followed in frequency by stage IVA (28.5%), stage II (27.7%) and stage I (6.3%), respectively. No significant association could be established between the stage of cancer and the grade of tissue eosinophilia in the current study. Late presentation in head and neck cancer in this area may be attributed to lack of awareness, fear of surgical procedures and treatment from local quacks. Oliveira et al. observed that patients with oral SCC in early stages T1/T2 presented absent or mild TATE whereas intense eosinophilia was accompanying tumours in advanced stages T3/T4 [14]. Oliveira et al. [14] and Thompson et al. [17] also noticed a statistically insignificant association between TATE status and tumour category of patients. Even though statistically insignificant, higher eosinophilic infiltration was found in stage 3 and stage 4A. Dorta et al. [4] revealed that TATE is an independent prognostic factor and does not correlate with the stage of cancer which was advocated by the current study too. The current study also gauged the association between lymph node metastasis and TATE grade which

Table 2 Showing association between habit of smoking and TATE score

TATE grade	Addiction	
	Smokers. *n* (% within TATE score)	Non-smoking *n* (% within TATE score)
Grade I	28 (80.0%)	7 (20.0%)
Grade II	48 (88.9%)	6 (11.1%)
Grade III	29 (78.4%)	8 (21.6%)

P value >0.05, not significant

Table 3 Showing association between site of cancer and TATE score

Site of cancer	TATE grade			Total
	Grade I *n* (% within TATE score)	Grade II *n* (% within TATE score)	Grade III *n* (% within TATE score)	
Hypopharynx	8 (34.8)	11 (47.8)	4 (17.4)	23
Ear	2 (100)	0	0	2
Larynx	2 (18.2)	5 (45.5)	4 (36.4)	11
Oropharynx	21 (28.8)	33 (45.2)	19 (26)	73
Oral cavity	0	4 (28.6)	10 (71.4)	14
Nose & PNS	2 (66.7)	1 (33.3)	0	3
Total	35 (27.8)	54 (42.9)	37 (29.4)	126

*P value 0.009, highly significant

divulged insignificant association between the two factors which was consistent with results observed in similar studies.

More than 50% of patients had moderately differentiated SCC which was followed by well-differentiated SCC and poorly differentiated SCC in frequency. TATE grade III was found in 51.4% cases of well-differentiated cancers and in 48.6% cases of moderately differentiated cancers. Most cases of poorly differentiated cancers had grade I eosinophilia followed by grade II while none had grade III eosinophilia as depicted in Table 6. Chi^2 test disclosed a significant association between tumour differentiation and TATE grade. Well-differentiated head and neck cancers were more associated with higher TATE grade than poorly differentiated cancers. It indicates that as TATE grade increases, tumour becomes more differentiated, i.e. the higher the TATE grade, the better the prognosis. Poorly differentiated carcinomas are known to metastasize more as compared to well-differentiated carcinomas [24]. Hence, a significant association of TATE with tissue differentiation could potentially be used as an indicative prognostic indicator.

Researchers offer varying opinions regarding the role of TATE as a prognostic factor in cancer. While most authors such as Dorta et al. [4] indicated that tissue eosinophils have an antitumoural role, contradictory views indicate no prognostic value in cancers [14]. Comparable results were encountered in a study by Yellapurkar et al. [25] where it was suggested that eosinophils have a tumouricidal effect in early carcinoma but a contrary effect in advanced carcinoma which is reaffirmed and corroborated by our study. Hence, a more locoregional effect of tissue eosinophilia on the primary site of tumour especially in the early stages is likely. This fact may be utilised to establish the importance of reporting tissue eosinophilia at an early stage preferably during diagnostic biopsy to predict the outcome and plan treatment modalities effectively.

Conclusions

HNSCC is a disease with critical implications, not only socioeconomic but more importantly on patient survival. There is hence the need for definitive prognosticators for early evaluation and for predicting the progress of disease and response to treatment modalities. TATE has been shown to have a certain role in tumour biology. This study reaffirms the same and elucidated a significant correlation of TATE with factors such as the age of patient, site of tumour and grade of tumour differentiation. Especially significant was the association between tumour differentiation and TATE grade, which could be used as a potential prognostic indicator to plan aggressive treatment modalities. There is hence the need of

Table 4: Showing association between lymph node involvement and TATE score

TATE score	Lymph node involvement	
	No *n* (% within TATE score)	Yes *n* (% within TATE score)
Grade I	20 (57.1)	15 (42.9)
Grade II	20 (37.0)	34 (63.0)
Grade III	12 (32.4)	25 (67.6)

P value 0.073, not significant

Table 5 Showing association between final stage and TATE score

TATE score	Carcinoma stage			
	Stage 1 *n* (%)	Stage 2 *n* (%)	Stage 3 *n* (%)	Stage 4a *n* (%)
Grade I	2 (5.7)	14 (40.0)	6 (17.1)	13 (37.1)
Grade II	3 (5.6)	14 (25.9)	24 (44.4)	13 (24.1)
Grade III	3 (8.1)	7 (18.9)	17 (45.9)	10 (27.0)

P value 0.148, not significant

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Table 6 Showing chi^2 test to find association between TATE and tumour differentiation

TATE score	Tumour differentiation		
	Well *n* (%)	Moderate *n* (%)	Poor *n* (%)
Grade I	5 (14.3)	14 (40.0)	16 (45.7)
Grade II	13 (24.1)	38 (70.4)	3 (5.6)
Grade III	19 (51.4)	18 (48.6)	0

P value <0.05, significant

incorporating grade of TATE in routine biopsy reports as it could play a significant role in the future to outlay the course of treatment in a conducive manner so as to reduce patient morbidity and mortality.

Abbreviations
TATE: Tumour-associated tissue eosinophilia; SCC: Squamous cell carcinoma; HPV: Human papilloma virus; IL: Interleukins

Availability of data and materials
Yes, all data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
The approval for this study was received from the institutional ethics committee of BPS Government Medical College for Women, Khanpur Kalan, Sonepat, Haryana, India, vide letter no. BPSGMCW/RC 447/IEC/19. Written informed consent to participate was taken.

Consent for publication
No individual patient data, not applicable.

Competing interests
The authors declare that they have no competing interests.

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