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Case Report

Tumor associated tissue eosinophilia: a case report with review

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ABSTRACT

Cancer is one of the most deadly diseases. Even today a lot of research is going on to understand the various aspects of this neoplasm in order to improve the treatment modalities and thus the life of the affected. The role of tumor associated tissue eosinophilia (TATE) has gained much impetus as it is believed to play important role in the biological behavior of the tumor. There are contradictory reports with respect to malignancy and hence its functional role remains ambiguous. We report a case of oral squamous cell carcinoma (OSCC) with TATE and review of literature of the same. A 58 year old female patient presented with a shallow ulcer on the palate. On clinical examination, left submandibular lymph nodes were enlarged and tender on palpation with slightly raised surface temperature. Fine needle aspiration cytology from submandibular lymph nodes was suggestive of squamous cell carcinoma. Incisional biopsy from ulcer confirmed the diagnosis of moderately differentiated squamous cell carcinoma, with the striking feature of tissue eosinophilia. Haematological investigations revealed differential & absolute eosinophil count which was not significant. The review of literature revealed contradictory findings with respect to TATE as a prognostic factor in OSCC patients. It has been found to have a favourable, a poorer or even no influence on patient's outcome, thus remaining a matter of controversy.

Keywords: Tumor associated tissue eosinophilia, Oral squamous cell carcinoma, Tumor associated blood eosinophilia, Eosinophils, prognostic indicator

INTRODUCTION

Tumor-associated tissue eosinophilia (TATE) is defined as stromal infiltration of eosinophils in a tumor, but not associated with tumor necrosis or ulceration. It was first described in cervical carcinoma by Przewoski in 1896.[1] It is characterised by the presence of eosinophils as a component of peritumoral and intratumoral inflammatory infiltrate.[2,3] TATE is seen in malignancies associated with different sites such as cervix, external genitalia, skin, gastrointestinal tract, colon, nasopharynx, larynx, esophagus, and oral cavity. Correlation of tissue eosinophilia as prognostic indicator has shown variable results in oral squamous cell carcinoma (OSCC). Its presence has been related to a varied inference ranging from a favourable to unfavourable or even having no influence on prognosis.[4]

CASE REPORT

A 58 year old female patient presented with a shallow, well defined ulcer on palate in relation to 27 and 28, involving marginal and attached gingiva. It measured about 1.0×1.5 cms, had erythematous floor and was tender on palpation (Figure 1). Patient had history of chewing pan, 1-2 times per day for the past 30 years. Left submandibular lymph nodes were enlarged and tender on palpation with a slightly raised surface temperature. A provisional diagnosis of malignant ulcer was given. Patient was subjected to necessary radiological and

laboratory investigations. Complete haemogram, serological tests and radiological investigations were done and all parameters were within normal range. FNAC from submandibular lymph nodes showed clusters of atypical squamous cells in a background of haemorrhage, necrotic tissue fragments and many keratin flakes. It was suggestive of squamous cell carcinoma. Incisional biopsy from ulcer revealed parakeratinised dysplastic stratified squamous epithelium and dysplastic tumor islands invading into the connective tissue stroma. (Figure 2) The tumor islands were seen in proximity to the muscle tissue (Figure 3). The tissue section shows abundant inflammatory infiltrate, predominantly composed of eosinophils in the connective tissue which was later confirmed by congo red staining (Figure 4 and 5). A definitive diagnosis of moderately differentiated squamous cell carcinoma (SCC), with the striking feature of tumor associated tissue eosinophilia (TATE) was established. To rule out tumor associated blood eosinophilia (TABE), absolute eosinophil count was 420 cell/cu. mm of blood which was not significant. Hence, it was a case of OSCC with TATE and without TABE. The patient was referred to a cancer institute for further treatment and follow up.

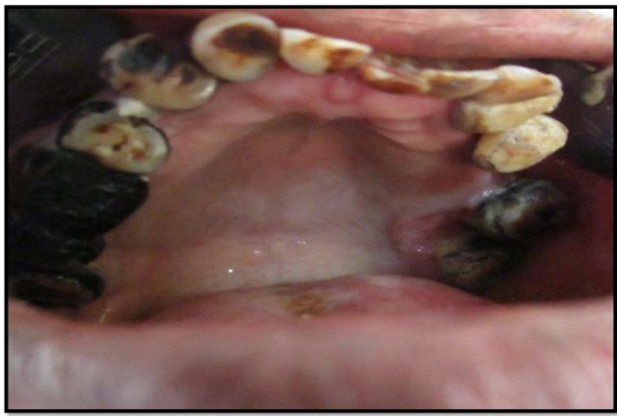

Figure 1: Intra-oral photograph showing well defined ulcer on palate i.r.t. 27 & 28.

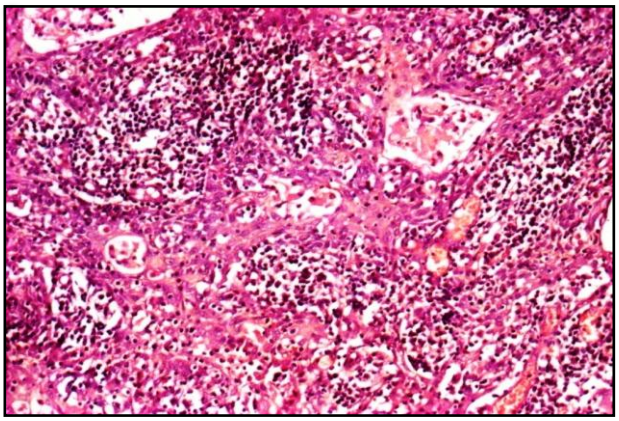

Figure 2: H and E stained section showing dysplastic tumor islands in connective tissue stroma (100 X magnification).

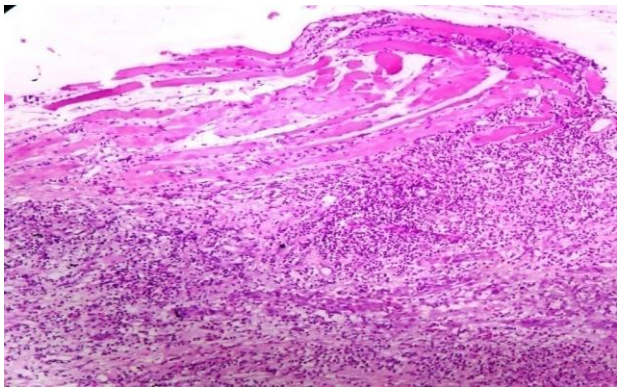

Figure 3: H and E stained section showing tumor islands in proximity to muscle tissue (100 X magnification).

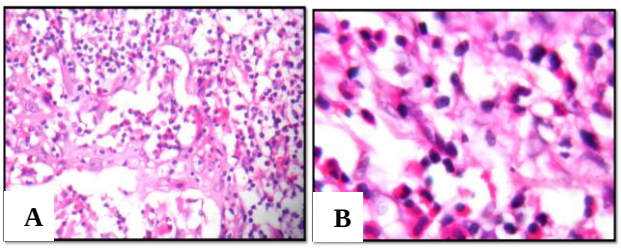

Figure 4 (A and B): H & E stained section reveals numerous eosinophils in connective tissue stroma (400 X magnification).

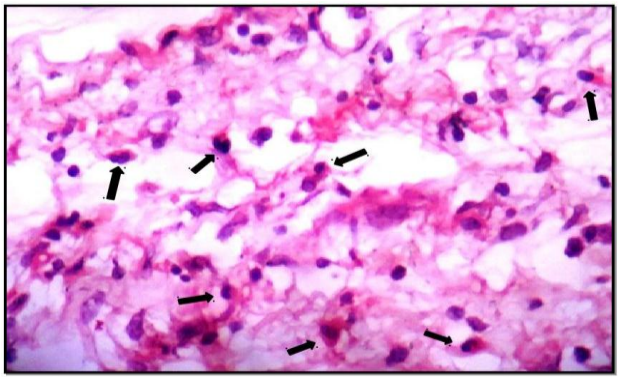

Figure 5: Congo red staining showing eosinophils (100 X magnification).

DISCUSSION

Wharton Jones was the first to describe eosinophils as "coarse granular cells" in 1846 and later Paul Ehrlich termed it as "eosinophils" in 1880.[5] The presence of abundant cytoplasm with coarse reflective granules are the characteristic features of eosinophils[6] and are distinguished by their tinctorial properties of bright red staining with acid aniline dye.[7] Eosinophils are multifunctional leucocytes with pleiotropism and play an important role in health and disease. They are vital in initiation and propagation of diverse inflammatory responses including allergic diseases, parasitic, bacterial

and viral infections, tissue injury, and are modulators of innate and adaptive immunity as well.[8] Many cancers including OSCC have shown extensive tissue eosinophilia. Eosinophils have direct tumoricidal activity by the release of cytotoxic proteins and also act indirectly by enhancing the permeability into tumor cells, which inturn facilitates penetration of tumor-killing cytokines. Additionally, they promote tumor angiogenesis by the production of several angiogenic factors. They also contain matrix metalloproteinases (MMPs); MMP-9 as well as their inhibitors, tissue inhibitor of metalloproteinases (TIMP); TIMP-1 and TIMP-2 which are indicative of their property of modulation of extracellular matrix formation. Eotaxin, a highly potent and selective eosinophil chemoattractant, mainly derived from tumor-associated eosinophils is also involved in eosinophilic chemotaxis to the tumour.[9] Likewise, histamine and eosinophil chemoattractant factor (ECF) which is secreted by mast cells further attracts eosinophils in tissues.[10]

The development of invasive cancer is determined not only by the genetic alterations within tumor cell, but also by the profound changes in host stromal, endothelial, and inflammatory cells.[3] The peritumoral and intratumoral inflammatory infiltrates found in tumors have been considered as the host's immune response to the neoplasia.[2,3] The mechanism by which eosinophils are activated and initially recruited towards the tumour microenvironment is complex and is mediated by inflammatory cytokines and chemokines. This process is principally related to Th2 response. Eotaxin chemokines such as IL-4 and IL-13 are potent inducers of this process which inturn explains the eosinophilia associated with Th2 responses. The eosinophils are activated by various chemotactic factors which include histamine and eosinophilic chemotactic factor A in mast cells, eosinophil stimulator and promoter substances in lymphocytes, neutrophil peptides, C5a complement, and eotaxin.[6]

The functional role of eosinophils in malignancy still remains an ambiguity. The literature has shown a tendency to consider TATE as a favourable prognostic indicator, unfavourable prognostic indicator or no influence on prognosis in head and neck squamous cell carcinoma (HNSCC), and hence remains a matter of controversy.[2,3]

Factors which consider TATE as good prognostic indicator:

1. Immune system activation by eosinophils by release of different substances like interleukins (ILs), cytotoxic proteins, platelet activating factor (PAF), leukotrienes (LTs), neuromediators, indoleamine-2,3-dioxygenase (IDO).[11,12]
2. IL-13 has anti-tumor immune response mediated mainly by neutrophils and macrophages.[13]
3. Cytotoxic proteins like eosinophil peroxidase (EPO), major basic protein (MBP), eosinophilic cationic protein (ECP), eosinophil derived neurotoxin (EDN). EDN induces dendritic cells (DC) maturation and activation.[14,15]
4. Anti-apoptotic property by IL – 4 which promotes tumor growth.[16]
5. Various substances produced by eosinophils e.g. vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), TNF-gamma, GM-CSF, TGF-beta, IL-8 promote angiogenesis.[17]

Factors which consider TATE as poor prognostic indicator:

1. IL-4 presents anti-angiogenic properties which could inhibit the tumor growth.[18]
2. Immune system inhibition by following mechanisms:
   a. Downregulate anti-tumor immunity mainly through IL-10 and IDO production. IL-10 suppresses DC differentiation.[19,20]
   b. TGF-beta is strong immunosuppressive cytokine which is capable of inhibiting T cell proliferation & differentiation and also inhibits cytotoxic activity of NK.[21]
3. IDO catalyses amino acid tryptophan to kynurenine which causes apoptosis.[22]

The exact pathogenesis of blood eosinophilia is not known. Many investigators have linked its presence with necrosis in the primary tumour or in metastases or, in the cases of pancreatic carcinomas with widespread fat necrosis. An increase in bone marrow eosinophils is seen in cases of metastatic carcinomas. Hypoxia and cigarette smoking is thought to cause blood eosinophilia and possibly contribute to TABE in carcinoma of the lung. Chemotaxis for eosinophils by T lymphocytes and antigen/antibody complexes has been described. It is suggested that immune complex formation with tumour antigen may produce large amounts of C3a, with subsequent histamine release, and perhaps account for the occasional finding of a Loeffler-like endocarditis in patients with marked blood eosinophilia and carcinoma.[5]

In the present case, OSCC was associated with TATE but not with TABE. Thorough evaluation of the patient did not show metastatic or any necrosis associated with the primary tumor, which could be the reason for its absence.

CONCLUSION

Every day, thousands of lives are taken by oral squamous cell carcinoma. Despite tremendous efforts for finding a cure, overall survival of cancer patients has not increased and the main barrier is the limited understanding of the tumor biology. So, there is continuous search for predictive and prognostic factors for OSCC, we conclude that increased tissue eosinophils (TATE) in OSCC should be used as a prognostic indicator. However, the prognostic value of eosinophils in oral carcinoma still

remains a matter of ambiguity. Further studies on eosinophils and their state of activation and long term follow up of OSCC patients with TATE will elucidate these findings. Thus, assessment of eosinophils quantitatively should also be considered in microscopic evaluation of OSCC.

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