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EVALUATION OF MITOTIC INDEX, APOPTOTIC INDEX AND TUMOUR ASSOCIATED TISSUE EOSINOPHILIA IN CERVICAL CARCINOMAS.

Pathology

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ABSTRACT

Introduction / Background: Cervical cancer is one of the commonest causes of cancer and cancer related deaths in women in India as well as across the world. To assess the net tumour growth, we tried to study mitotic index and apoptotic index of different types of carcinoma cervix. Cervical cancers were the first ones in which Tumour Associated Tissue Eosinophils (TATE) were firstly described. Also recently TATE are being evaluated for their prognostic roles in various carcinomas. Hence the study also tried to assess the pattern of TATE in different types of cervical carcinomas. **Materials & Methods:** Study included 40 consecutive diagnosed cases of cervical carcinomas including biopsies and complete resections. We calculated mitotic index(MI) and apoptoic index (AI) in hot spot areas where maximum mitotic and apoptotic activity was there. Mitoses, apoptotic cells & bodies were counted per 1000 tumour cells and expressed as percentage for Mitotic and Apoptotic indices respectively. We also evaluated tumour associated tissue eosinophils (TATE) in hot spot areas where maximum number of stromal peritumoral eosinophils present and counted them per 10 high power fields. Results were compared with type and grade of cervical cancer. **Results:** Mean age of patients was 57.67 years. Most of the cases were of keratinizing Squamous cell carcinomas (30/40) followed by non keratinizing (6/40) and adenocarcinoma of the cervix (4/40). Mean Mitotic index for keratinizing SCC, non keratinizing SCC and adenocarcinoma cases were 2.236%, 3.966% & 3% respectively while mean Apoptotic index were 1.833%, 2.816% and 2.975% respectively. Out of total cases, 80% cases showed presence of TATE. Mean TATE were higher in non keratinizing SCC (63.833 cells/10 hpf) compared to keratinizing SCC (32.277 cells /10 hpf). **Conclusion:** Mitotic index and apoptotic index gives idea about net growth of the tumour. All indices were higher in non keratinizing Squamous cell carcinomas as compared to keratinizing ones. Tumour associated tissue eosinophils noted variably in both Squamous and adenocarcinomas with variable densities.

KEYWORDS

Carcinoma cervix, Mitotic index, Apoptotic index, Eosinophils, Tumour associated tissue eosinophils.

INTRODUCTION:

Carcinoma cervix is fourth most frequently diagnosed cancer & fourth leading cause of cancer death in women worldwide as per Globocan 2020. In India, It ranks third in cancer incidence while second in cancer associated deaths.[1,2] Dysplasia and malignancies are characterized by cell proliferation. Cell proliferation and cell death in a tumour can give idea about cell turnover and overall net growth of tumour or tissue. Measuring cell proliferation and death these parameters may help in identify at risk individuals as well as they have prognostic value. [3]

Apoptotic activity have shown therapeutic and prognostic implications during chemotherapy or radiotherapy. Cell proliferation is traditionally being assessed with Mitotic activity while cell death mainly by apoptosis and can be measured by counting apoptotic cells and apoptotic bodies.

Apoptosis is genetically controlled death which leads to removal of cells that have been damaged. The cancer cells that undergo apoptosis may have important implications for tumour progression and response to treatment. Apoptosis is a programmed cell death which is essential and complex process required cellular homeostasis. Morphologically it is characterized by cell and nuclear shrinkage, chromatin condensation, disassembly of the nuclear and cytoplasmic networks, membrane blebbing and DNA fragmentation. [4].

The role of mitotic count / index has been evaluated in various tumours in differentiating types or grades of tumour. Similarly apoptosis has been evaluated & shown to correlate with tumour grade and subtype in some malignant lesions including those of large intestine, endometrium, prostate, breast, etc. [5,6]

Tumour associated tissue eosinophils (TATE) is defined as the stromal infiltration of eosinophils in the tumour which can be intratumoural or peritumoural in nature. Over the last few years, role of eosinophils in carcinogenesis and its role in immune resposnes related to progression of cancers are being studied with interest and hope. They were first described by Przewoski in 1896 in cervical carcinomas. TATE is seen involving tumours of various organs such as the oral cavity, esophagus, larynx, bile duct, lung, gastro-intestinal tract and genito-urinary tract. Recently TATE is being evaluated for their prognostic roles and possible therapeutic role in various carcinomas. [7,8] In carcinoma Cervix TATE are being proposed as marker of invasion to differentiate from non invasive premalignant lesions. [8,9].

With this background the study also tried to assess mitotic index and apoptotic index as well as pattern of TATE in different types of cervical carcinomas.

MATERIAL & METHODS:

In this retrospective cross sectional descriptive study, we included & re-evaluated all consecutive diagnosed cases of carcinoma cervix either on cervical biopsies or complete surgical resection specimens whose formalin-fixed paraffin embedded tissue blocks and / or slides are available in the repository of the Department of Pathology of a tertiary care hospital over a period of one year (January 2020 to December 2020). Cases in which, patients received preoperative radiotherapy or chemotherapy, or where slides or FFPE blocks were not available for review were excluded. Relevant archived records were assessed. Pathological diagnoses were reconfirmed as per WHO classification of female genital tumours-2020 and grading was carried out. Both mitotic index and apoptotic index were calculated as per criteria by previous studies [5,6,10]

Slides of all selected cases were screened for apoptosis, mitoses and

tumour stromal eosinophils at scanner magnification. The areas with maximum activity and density were selected for counting and evaluation with both low (10x) and high power (40x) examination. Actual counting of apoptosis and mitoses was carried out in oil magnification (100x). While stromal eosinophils measured at high power (40x) magnification.
Apoptotic cells identified with features like cell shrinkage, condensation and deep eosinophilia of cytoplasm and pyknotic, round or irregular nucleus and counted in areas of maximum activity. While Apoptotic index (AI) was calculated as the number of Apoptotic cells and Apoptotic bodies per 1000 tumour cells and expressed as percentage.

Mitotic count included both typical & Atypical ones in areas of maximum activity. Similarly, mitotic index (MI) was also calculated by counting mitosis among 1000 tumour cells and expressed as percentage. Tumour associated tissue eosinophils (TATE) calculated number of eosinophils in tumour stroma per 10 high power fields in areas with maximum density (hotspots) of the eosinophils. [5,6,10]

Aims & Objectives of the study were as follows 1. To assess the mitotic index (MI) and apoptotic index (AI) in cases of Cervical carcinomas. 2. To assess tumour associated tissue eosinophils (TATE) in cases of Cervical carcinomas 3. To analyse any difference between means of mitotic index / apoptotic index / Tumour associated tissue eosinophilia in different types of cervical carcinomas. Standard statistical analysis was carried out using MS excel and MedCalc software online.

RESULTS:
We evaluated total 40 cases of cervical malignancies for Mitotic index (MI), apoptotic index (AI) & TATE and tried to correlate these parameters with different types of cervical malignancies. The mean age of all cases was 57.67 years with range from 41 to 76 years. Out of 40 cases, there were 30 (75%) Keratinising Squamous cell carcinoma (SCC), 6(15%) Non-Keratinising SCC, and 4(10%) cervical Adenocarcinomas. (Figure 2**)** Among keratinised Squamous cell carcinomas, Moderately differentiated 26(65%) tumours predominated while rest were well differentiated 3(7.5%) and poorly differentiated 1(2.5%) tumours. The mean age for Keratinised SCC, Non-Keratinised SCC and Adenocarcinoma are 58.03, 56.0, 57.5 respectively.

Where as in Keratinizing SCC, the mean age distribution for Well differentiated (WD) SCC, Moderately differentiated (MD) SCC and Poorly differentiated (PD) SCC are 52.33 yrs, 59.23 yrs and 44.0 yrs respectively. Representative images of various malignant cervical lesions from the study and representative images of apoptosis and mitoses are shown in Figure 2. The mean mitotic index, apoptotic index and tissue associated tissue eosinophils (TATE) in all cervical malignant lesions are also shown in **(Table 1)**.

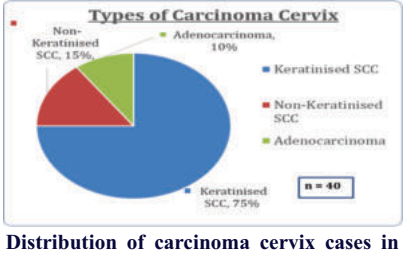

Figure- 1 Distribution of carcinoma cervix cases in the study (n=40)

Table 1- Mean Mitotic index (%), Apoptotic index (%) and Tumour associated tissue eosinophils (TATE) (per 10 hpf) in Cervical Malignancies.

Diagnosis	Grade	Mean Mitotic Index% +/- (SD)	Mean Apoptotic Index +/- (SD)	Mean TATE per 10 hpf +/- (SD)
Keratinizing SCC	-	2.236 +/- (1.495)	1.833 +/- (1.555)	32.277 +/- (55.163)
	Well differentiated	2.166 +/- (1.415)	0.666 +/- (0.152)	72.333 +/- (96.074)
	Moderately differentiated	1.859 +/- (1.110)	1.744 +/- (1.427)	20.814 +/- (26.502)
	Poorly differentiated	2.2	1.9	1.0
Non – Keratinizing SCC	-	3.966 +/- (2.018)	2.816 +/- (2.074)	63.833 +/- (105.306)
Adenocarcinoma Cervix	-	3 +/- (2.603)	2.975 +/- (3.092)	6.5 +/- (9.949)

Difference between mean using t test was calculated for all three parameters between Squamous CC & Adenocarcinoma, Keratinising & Nonkeratinising SCC and Well & Moderate keratinizing SCC Difference mean MI of Keratinizing SCC and non- Keratinizing SCC was statistically significant (p=0.0010).

Also Difference mean TATE of well differentiated keratinizing SCC and moderately differentiated keratinizing SCC was found statistically significant (p=0.0286)

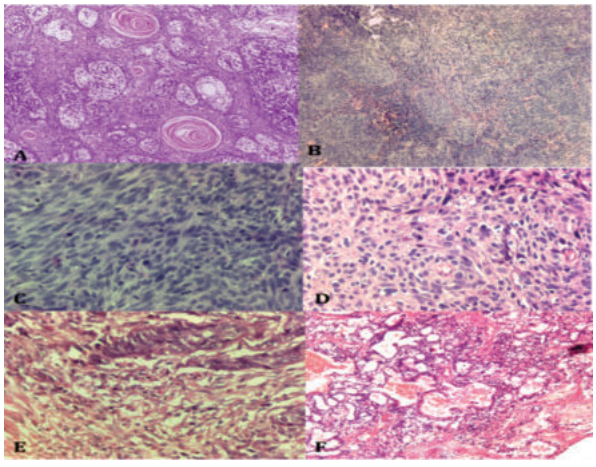

Figure 2- Representative microphotographs of **A)** Keratinizing Squamous cell carcinoma of cervix (40x, H&E stain), **B)** Non-Keratinizing Squamous cell carcinoma of cervix (40x, H&E stain), **C)** Mitoses (40x, H&E stain), **D)** Apoptotic cells and apoptotic bodies (40x, H&E stain), **E)** Tumour associated tissue eosinophils (40x, H&E stain) and **F)** Adenocarcinoma of cervix.

DISCUSSION:
Role of mitotic index and apoptotic index are studied in association with tumour proliferation and therapy response. Durgaprasad G et al [11]studied apoptotic index and mitotic index as a predictor of response to radiation in subjects of squamous cell carcinoma of uterine cervix treated by radical radiotherapy. They found better radiation therapy response in patients with Apoptotic Index (AI) less than median value of 0.75% and Mitotic Index (MI) greater than median value of 0.2%. However difference was not statistically significant. Also they found statistically significant better control of disease in cases with AI/MI median value ratio of less than 0.3 than that of median value more than 0.3. (p = 0.03).

Suzuki et al [12] suggested that high MI is an indicated poorer prognosis, and MI can be a important prognostic factor in patients of cervical squamous cell carcinomas treated with carbon ion beam therapy. ZHU Xue-qiong et al [13] also found that high proliferation (Mitotic) index (PI) was an indication for neoadjuvant intraarterial chemotherapy. They suggested one more cycle of chemotherapy for patients with significantly increased AI or AI/PI after chemotherapy. While immediate surgery and / or radiotherapy to patients with low AI or AI/PI.

Various authors like Chauhan et al [5], Mysorekar et al [14], Bharadwaj et al [6], Singh et al [15], Gupta et al [16], Sagol et al [17] have studied AI & MI in cases of various grades of cervical dysplasia and cervical carcinomas. All of them found increasing trends in all indices as grade increased from cervical intraepithelial neoplasia (CIN) I to CIN II to CIN III. Similar increasing trend noted in cases, from cervical dysplasia to invasive cervical carcinomas. Bharadwaj et al also included cases of various grades of Squamous cell carcinomas, non keratinizing Squamous cell carcinoma and adenocarcinomas along with CIN cases. Gupta et al included cases of various grades of Squamous cell carcinomas and adenocarcinomas along with CIN cases. While Singh et al studied only keratinizing Squamous and non keratinizing Squamous cell carcinomas along with CIN cases.

In contrast to these studies, we included only invasive cervical carcinomas with different types including keratinizing Squamous cell carcinomas, non keratinizing Squamous cell carcinomas and adenocarcinomas. Age range for cervical carcinomas in our study was 41-76 years. Similarly Bharadwaj et al, Mysorekar et al and Singh et al had age range for malignant lesions between 45-64 yrs, 35-64 years, and 35-74 years respectively.

Mean MI +/- SD for Squamous cell carcinoma in our study was 2.236 +/- 1.495 as compared to Chauhan et al, Bharadwaj et al, Singh et al and Mysoerkar which were 1.08 +/- 0.216, 0.57 +/- 0.55, 0.81 +/- 0.227 and 4.49 +/- 2.23 respectively. Mean MI +/- SD for non keratinizing Squamous cell carcinoma in our study was 3.966 +/- 2.018 on a higher side as compared to Bharadwaj et al and Singh et al were 0.42 +/- 0.26 and 0.711 +/- 0.190 respectively. Mean MI +/- SD for adenocarcinoma in our study was 3.0 +/- 2.603 as compared to Bharadwaj et al= 0.2 +/- 0.07 which was lower as compared to our study.

Chauhan et al showed that mean MI was found to increase from WD-SCC to MD-SCC to PD-SCC. The difference between WD-SCC and MD-SCC was found to be extremely significant ($p<0.0001$) while between MD-SCC and PD-SCC it was not found significant. In our study, mean MI was increased from well to poor as well as from moderate to poor SCC however it was slightly decreased in cases from well to moderate SCC. However we did not found any statistical significant difference between these grades. Bhardwaj et al found no statistically significant difference between the MI of well differentiated and less differentiated carcinomas of cervix.

AI was increased as grades of Squamous cell carcinoma were increased similar to that of Chauhan et al and Gupta et al. However the difference between various grades was not statistically significant.

Mean AI +/- SD for Squamous cell carcinoma in our study was 1.883 +/- 1.555 comparable with Chauhan et al where it was 1.226 +/- 0.532, while it was lower as compared to Bharadwaj et a, Singh et al and Mysorekar et al where it was 3.38 +/- 1.15, 3.34 +/- 0.37 and 4.70 +/- 2.03 respectively. Mean AI +/- SD for non keratinizing Squamous cell carcinoma in our study was 2.816 +/- 2.074 which was comparable to Bharadwaj et al & Singh et al where it was 2.92 +/- 1.41 and 3.055 +/- 0.320 respectively. Mean AI +/- SD for adenocarcinoma in our study was 2.975 +/- 3.092 which was higher as compared to Bharadwaj et al and Gupta et al where it was 1.76 +/- 1.2 & 0.567 +/- 0.153 respectively.

Sagol et al. (1999) [17] reported no statistically significant difference in the apoptotic and mitotic cell counts between non-keratinizing and keratinizing squamous cell carcinoma. Also no siginificant diference between grades of SCC. Bharadwaj et also did not find any statistical difference between mean indices of differentiated SCC and less differentiated tumours like non keratinizing SCC, Adencarcinoma and adenosquamous carcinomas.

Our study showed statistically significant ($p=0.0010$) Difference between mean MI of Keratinizing squamous cell carcinoma and non-Keratinizing squamous cell carcinoma. While difference between mean MI of SCC & Adenocarcinoma and Well & Moderate keratinizing SCC were non-significant.

However, Difference between mean calculated for rest parameters mean AI and mean TATE between Squamous cell Ca & Adenocarcinoma, Keratinising & Non-keratinising SCC and Well & Moderate keratinizing SCC were non-significant.

While mean TATE were higher in non keratinizing SCC as compared to keratinizing SCC, however with no statistical significance demonstrated. We found difference between mean TATE of well differentiated keratinizing squamous cell carcinoma and moderately differentiated keratinizing squamous cell carcinoma statistically significant ($p=0.0286$) Lowe et al [18] assessed 460 cervical malignancies where in 3% of cases showed severe tissue stromal eosinophilia with over 100 eosinophils per high power field.

TATE are defined as the stromal infiltration of eosinophils. Role of TATE as prognostic marker remains controversial and role as biomarker or therapeutic target remains to be obscure yet. Over the last few years, role of eosinophils in carcinogenesis , its role in immune resposnes related to progression of cancers are being studied with interest and hope. Tumour associated tissue eosinophils were first described by Przewoski in cervical carcinomas. Eosinophilia is commonly associated with allergic conditions, parasitic infections and inflammatory reactions. TATE is observed in various malignancies from different sites such as uterine cervix, oral cavity, tongue, larynx, nasopharynx, esophagus, colon, etc. [5-7]

Varricchi et al [19] in their review on role of eosinophils in human and experimental tumours suggested that Eosinophils play important role in tumour regression via factors like Reactive Oxygen Species, TNF-alfa, granzyme, eosinophil cationic proteins, IL-18 and Interferron gamma. Also their role in tumour initiation and progression via protumorigenic factors like factors promoting tumour angiogenesis, tissue modelling and epithelial- mesenchymal transition. Protective antitumour role was noted in malignancies like melanoma, gastric, colorectal, oral and prostate cancer while protumour role seen in lung carcinoma, carcinoma cervix, ovarian carcinoma & hodgkins lymphoma. They also suggested that the role of eosinophils and their mediators could be cancer-dependent leading to such heterogenous effects in different malignancies.

Better clinical outcome in some of the tumours in presence of TATE is associated with various possibilities. Eosinophils in the tumour microenvironment may show antitumour response as they express same mediators and receptors like cytotoxic T lymphocytes (CTLs). [20] It is also thought that esoinophils secrete chemokines including CCL5, CXCL9 which attract CD8+ T cells as a part of anti-tumour immunity. [21] Also they release major basic protein (MBP), a highly cationic protein which helps in regulation of tumour immunity. [22]

Hu et al suggested that clinical application of biological response modifiers (BRM) such as carrier-assisted recombined human IL-2 /or IL-4 may have the potential to treat human solid tumors associated with TATE. Hu et al in their metaanalysis concluded that TATE were associated with better overall survival in various solid malignancies specially in esophageal and colorectal cancers, but not with disease free survival. This association suggested that it is a valuable prognostic biomarker and clinical application of biological response modifiers or agonists promoting TATE may be the novel therapeutic strategy for patients.[7]

Bethwaite et al (1993) [23]showed that tumour associated tissue eosinophilia in a modest proportions was associated with statistically significant improved survival in stage IB cervical carcinomas. Quantification of eosinophilic infiltration for all cases showed a range from 0 to 542 eosinophils/mm2- mean (SD) 61-5 (115.5).

Currently there are no standard methods to quantify TATE. We used method utilised by Yellapurkar et al [10] to quantify TATE. Spiegel et al (2002) proposed eosinophils as marker for invasion in cervical neoplastic lesions. Such that tumour stromal eosinophil counts ≥5 per single HPF and ≥10 per 10 HPFs in cervical biopsies should alert pathologists to look extensively for invasive component in case of CIN II and III. Otherwise deeper sections or repeat biopsies should be carried out. [8]

Agarwal et al in a similar study categorised cervical lesions into three groups- group 1 included non keratinizing and keratinising ca, group 2 included CIN II & CIN III cases while group 3 included cervicitis with Squamous metaplsia and CIN I cases. Stromal eosinophils were present in 23 of 32 (71.8%) cases of group 1. Also they found significant difference between groups of invasive ca and CIN II-III group as well as between Invasive ca and CIN I & Cervicitis with Squamous metaplasia groups. [9]

In cervical cancers TATE are mainly observed in Squamous cell carcinomas mainly large cell non keratinizing types. Other types like adenocarcinomas and adenosquamous carcinomas have also reported to be associated. While evaluating TATE other causes of eosinophilia like eosinophils at the sites of ulcer, parasitic infections, topical applications, and previous invasive procedures must be excluded. [24,25]

In our study, 80% of the cases showed stromal eosinophils with mean TATE per 10 hpf of 32.277 +/- (55.163), 63.833 +/- (105.306) and 6.5 +/- (9.949) for keratinizing Squamous cell carcinomas, non keratinizing Squamous cell carcinomas and adenocarcinoma of cervix

respectively. Mean TATE were higher in non keratinizing Squamous cell carcinomas.

CONCLUSION:

The current study utilizes simple light microscopy for morphological evaluation of AI and MI which can be easy and inexpensive method to assess net turnover of the tumour. Mitotic index can be helpful in differentiating Keratinizing from nonkeratinizing squamous cell carcinomas as later shows higher values. TATE are higher in non keratinizing squamous cell carcinomas as compared to the keratinizing ones, Though We could not find statistical significant difference. Role of TATE in cervical cancers need further rigorous research as prognostic marker or as potential therapeutic marker.

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