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Original Article

Tumor-associated tissue eosinophilia in preinvasive and invasive squamous cell carcinoma of cervix

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ABSTRACT

Background: Differentiating between preinvasive and invasive squamous neoplasms of the cervix can be a challenge in small, superficial fragments of cervical biopsy, particularly when inflammatory infiltrates obscure the epithelial stroma interface and due to tangential sectioning of the acanthotic squamous epithelium. This study evaluates whether thresholds of eosinophils in stroma serve as a morphological marker for the presence of tumor invasion in squamous neoplasms of the cervix.

Materials and methods: Sixty-five cases of invasive squamous cell carcinoma and preinvasive squamous neoplasia were evaluated. In each case, the number of eosinophils per HPF and per 10 HPF in the tissue adjacent to the neoplastic epithelium was counted. For statistical purposes, the elevated eosinophils were categorized as > 3 eosinophils/HPF, > 5 eosinophils/HPF, and >10/10 HPF.

Results: Stromal eosinophils were present in 1/5 cases of LSIL, 3/8 HSIL cases, 15/16 cases of microinvasive squamous cell carcinoma, and 34/36 cases of invasive squamous cell carcinoma, signifying an increase in eosinophil count from a spectrum of preinvasive to invasive carcinoma. Greater than 5 eosinophils/HPF and >10 eosinophils/10 HPF had sensitivity, specificity, and positive predictive values of 55%, 100%, 100%, and 75%, 100%and 100%, respectively. The difference of >5 eosinophils/HPF and >10 eosinophils/10 HPF between SIL and SCC was statistically significant.

Conclusions: Our study suggests that the presence of increased eosinophils in squamous neoplasia of the cervix can be associated with tumor invasion and should prompt a thorough evaluation when evidence of invasion is absent.

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INTRODUCTION

Tumor-associated tissue eosinophilia (TATE) is defined as stromal infiltration of a tumor by eosinophils, not associated with tumor necrosis or ulceration.[1] The presence of eosinophils as a component of intra-tumoral and peritumoral inflammatory infiltrate was first described by Przewoskin in 1896 in carcinoma cervix.[2] TATE has been reported in many cancers including squamous cell carcinoma of the cervix, lung, vagina, penis, skin, nasopharynx, adenocarcinoma of the stomach, large bowel, uterine body, and in transitional cell carcinoma of the urinary bladder.[3]

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Squamous cell carcinoma is the most common malignant tumor arising in the cervix.[4] Differentiating between preinvasive and invasive lesions can be challenging in small, superficial, and fragmented specimens, particularly when a prominent inflammatory infiltrate obscures the epithelial stroma interface and is further complicated when sectioning the acanthotic squamous epithelium is tangential.

Even in larger excised specimens, the recognition of superficial invasion may be difficult in cases such as doubtful invasion, abnormal morphological features of cells, presence of tangential cut nests, or infiltration particularly when the desmoplastic reaction is marked. Adjunct features may help in close observation for invasion or such a feature should raise the suspicion that the lesion may harbor foci of invasion in the specimen that otherwise lacks conventional diagnostic criteria of invasion.

The relations between the tumor tissue and adjacent stroma have been a major area of concern in cancer research with features such as varying degrees of infiltration of inflammatory cells, increased angiogenesis, micro-invasion, and desmoplastic stromal reaction. The association between proliferating tumor cells and lymphocytic infiltrate has been recognized for over 50 years, whereas the literature on the relation between eosinophils and tumor is relatively less studied.[5] Thus, this study was carried out to assess whether stromal eosinophilia may provide a diagnostic criterion for distinguishing invasive squamous neoplasms from non-invasive neoplasms in the cervix.

MATERIALS AND METHODS

The present study included a total of 65 cases, both biopsy and hysterectomy specimens of squamous neoplasms of the cervix. The specimens received were fixed in 10%formalin and processed using conventional histopathological techniques. Hematoxylin and Eosin stain was done on these sections. For both the incisional biopsy and excisional specimens, the high-power field (HPF) with the maximum number of eosinophils in the stroma adjacent to and within the neoplastic epithelium was identified and the eosinophils were counted, followed by the number eosinophils in nine contiguous HPF adjacent to this field were counted and these counts were recorded as eosinophils/HPF and eosinophils/10HPF, respectively (fig. 1). Cells only with brightly eosinophilic cytoplasmic granules were interpreted to be eosinophils. Eosinophils present in the vascular spaces were excluded.

After tabulation of the eosinophil counts, both sets of eosinophil counts were compared to investigate whether values for one or the other were more diagnostic of stromal invasion or whether there were values for each set that were complimentary for the diagnosis of an invasive tumor.

RESULTS

Out of the 65 cases, 52 (80%) were incisional cervical biopsy specimens and 13(20%) were hysterectomy specimens. Of the 65 cases 5 (7.70%) were low-grade squamous intraepithelial lesions (LSIL), 8 (12.31%) were high-grade squamous intraepithelial lesions (HSIL), 16 (24.61%) were micro-invasive squamous cell carcinoma (Micro SCC) and 36 (55.38%) were invasive squamous cell carcinoma (SCC) (Table 1).

Table 1: Distribution of eosinophils in LSIL, HSIL, micro-invasive SCC, and SCC

	>3 Eos/HPF	>5 Eos/HPF	>10/10HPF
LSIL (5)	0/5	0/5	0/5
HSIL (8)	1/8(12.5%)	0/8	0/8
Micro SCC (16)	12/16 (75%) [p value <0.001]	2/16 (12.5%) [p value <0.001]	10/16 (62.5%) [p value <0.001]
SCC (36)	31/36 (86.11%) [p value <0.001]	27/36 (75%) [p value <0.001]	29/36 (80.55%) [p value <0.001]

The predominant age in cervical lesions was between 41-50 years, with 24 cases (36.92%) in this age group. The youngest age was 28 years, which was a case of LSIL and the eldest age was of 70 years, a case of SCC (Table 2).

Table 2: Age distribution of patients

Age	LSIL (%)	HSIL (%)	Micro SCC (%)	SCC (%)	Total (%)
21-30	-	1 (1.54%)	1 (1.54%)	-	2 (3.08%)
31-40	3 (4.62%)	1 (1.54%)	2 (3.08%)	4 (6.15%)	10 (15.38%)
41-50	2 (3.08%)	3 (4.62%)	5 (7.70%)	14 (21.54%)	24 (36.92%)
51-60	-	2 (3.08%)	5 (7.70%)	7 (10.77%)	14 (21.54%)
61-70	-	1 (1.54%)	3 (4.62%)	11 (16.92%)	15 (23.08%)
Total	5 (7.70%)	8 (12.30%)	16 (24.62%)	36 (55.38%)	65 (100%)

Four (80%) out of 5 cases of LSIL had no eosinophils in the stroma. Only one case had 1-2 eosinophils/HPF and the same case showed <3 eosinophils/10 HPF. None of the cases of LSIL had >3 eosinophils/HPF or > 3 eosinophils/10 HPF (fig. 1).

Of the 8 cases of HSIL, 5 cases (62.5%) had no eosinophils in either per HPF or per 10 HPF. Two cases (25%) had 1-2 eosinophils/HPF and 1 case (12.5%) showed 3-4 eosinophils/HPF. Three cases (37.5%) had >5 eosinophils/10 HPF. None of the cases had >10 eosinophils either per HPF or per 10 HPF (fig. 2).

Of the 16 cases of microinvasive squamous cell carcinoma, only 1 (6.25%) had no eosinophils per HPF or 10 HPF. All the other cases showed the presence of eosinophils (fig. 3). Of the 36 cases of SCC, only 2 cases (5.56%) showed no eosinophils per HPF and in 10/HPF. All other cases showed

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a high number of eosinophils (fig. 4).

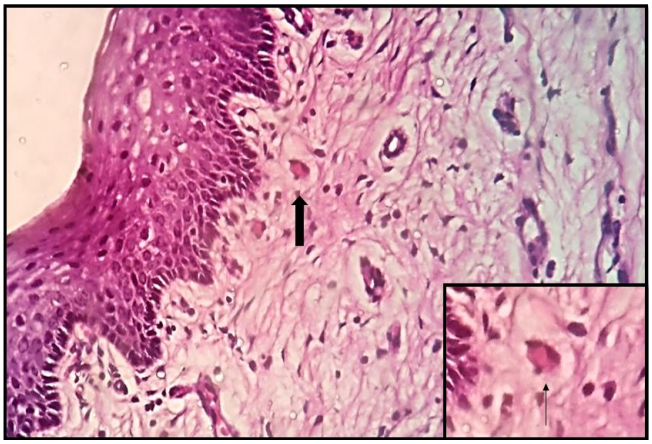

Figure 1: *Eosinophils in LSIL*

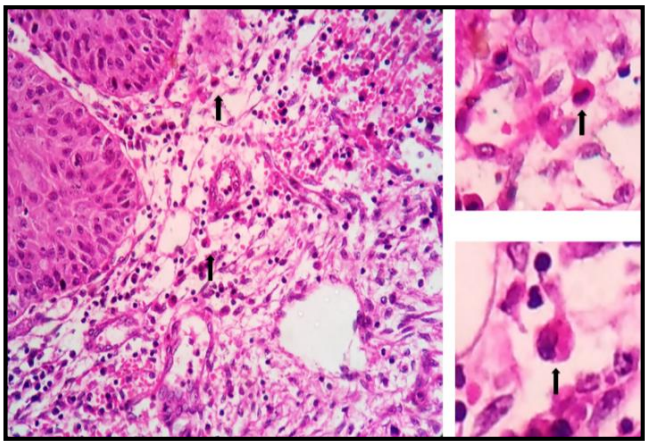

Figure 2: *Eosinophils in HSIL*

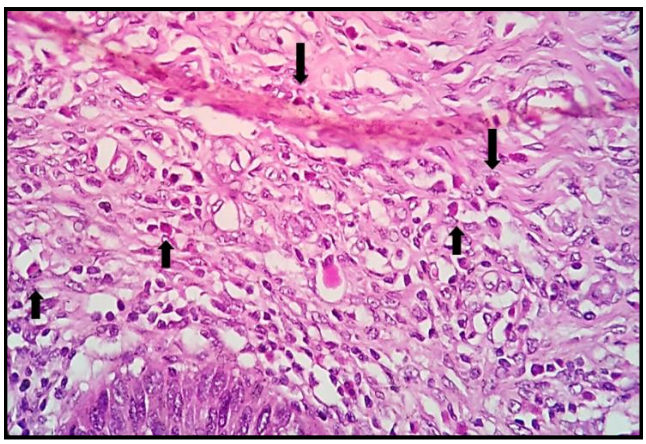

Figure 3: *Eosinophils in microinvasive SCC*

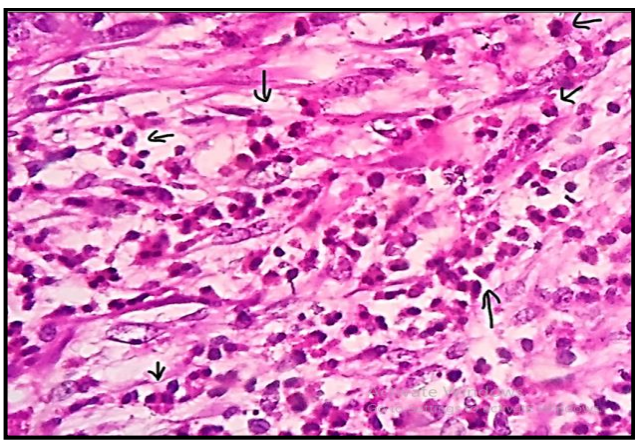

Figure 4: *Eosinophils in SCC*

DISCUSSION

In recent years, it has been shown through various studies and researches that eosinophils perform various functions in allergic conditions, presentation of antigens, and significant action in inflammatory responses by releasing a series of cytokines and lipid mediators.[6] Many studies have demonstrated the role of eosinophils in tumor progression or regulation.

Various studies were done to assess the role of eosinophils in cancer which showed a definite quantitative rise in eosinophils compared to normal and dysplastic tissue. They are hypothesized to have a direct tumoricidal activity by the release of cytotoxic proteins enhancing the permeability of the tumor cells and allowing penetration of cytokines causing tumor cell death. A moderate to marked degree of eosinophilia has been reported to be associated with invasion in cases of squamous neoplasms at different sites of the human body.[7]

Spiegel et al in their study "Eosinophils as a marker for invasion in cervical squamous neoplastic lesions" have reported an association of eosinophils with the presence of invasion in squamous neoplasms of the cervix. The study included 52 cases of which 40 were cervical incisional biopsy specimens of HSIL, 12 with an element of invasive carcinoma, two of HSIL suspicious for invasion, and follow-up excisional specimens of 27 cases of HSIL and 6 of micro-invasive and invasive carcinoma.[8] Spiegel et al found that 83 % of cases of HSIL had no eosinophils in their stroma. Agarwal et al reported 27.3% of HSIL cases with eosinophils in their stroma. While Bhatta et al reported a minimum of only 13% with eosinophils in their stroma. Our study had 62.5% of cases of HSIL without eosinophils. The comparison of findings of different studies with the present study has been shown in Tables 3-4.

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Table 3: Different studies showing the number of Eosinophils in SIL

Study	No of cases	Eosinophils/HPF			Eosinophils/10HPF		
		0	1-4	>5	0	1-9	>10
Spiegel et al[8]	40	33 (83%)	7 (18%)	1 (2.5%)	33 (83%)	7 (18%)	1 (2.5%)
Agarwal et al[9]	11	-	3 (27.3%)	-	-		1 (9%)
Bhatta et al[10]	23	-	3 (13%)	-	-	1 (4.3%)	-
Our study	**08**	**5 (62.5%)**	**3 (37.5%)**	**-**	**5 (62.5%**	**3 (37.5%)**	**-**

Table 4: Different studies showing eosinophils in Invasive SCC

Study	No of cases	Eosinophils/HPF			Eosinophils/10HPF		
		0	1-4	>5	0	1-9	>10
Spiegel et al[8]	12	1 (8%)	4 (33%)	7 (59%)	1 (8%)	4 (33%)	7 (58%)
Agarwal et al[9]	32	-	-	23 (71.8%)	-	-	19 (59.3%)
Bhatta et al[10]	27	-	11 (40.7%)	5 (18.5%)	-	-	20 (74%)
Our study	**36**	**2 (5.6%)**	**7 (19.4%)**	**27 (75%)**	**2 (5.6%)**	**5 (13.9%)**	**29 (80.5%)**

According to Spiegel et al, in both incisional biopsy and excisional specimens, the presence of >5 eosinophil/HPF and >10 eosinophils/10 HPF were both highly significantly associated with invasion with a high degree of specificity and positive predictive value, whereas counts below these thresholds had a high negative predictive value. The comparison of findings of different studies with the present study has been shown in Tables 5-6.

Table 5: Sensitivity and Specificity of Eosinophils in assessing invasion

Study	Sensitivity			Specificity		
	>3 eos/hpf	>5 eos/hpf	>10 eos/10hpf	>3 eos/hpf	>5 eos/hpf	>10 eos/10hpf
Spiegel et al[8]	58	83	77	88	58	97
Bhatta et al[10]			23			100
Our study	**83**	**55**	**75**	**92**	**100**	**100**

Table 6: Predictive Values of Eosinophils in assessing invasion

Study	PPV			NPV		
	>3 eos/hpf	>5 eos/hpf	>10 eos/10hpf	>3 eos/hpf	>5 eos/hpf	>10 eos/10hpf
Spiegel et al[8]	87	88	58	97	87	88
Bhatta et al[10]			100			69
Our study	**98**	**100**	**100**	**52**	**36**	**50**

CONCLUSIONS

Our study suggests that the presence of increased eosinophils (exceeding 3/HPF or 10/10 HPF) in squamous lesions of the cervix is a morphologic feature associated with tumor invasion and should prompt a thorough evaluation when evidence of invasion is absent.

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