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RESEARCH ARTICLE

TUMOR ASSOCIATED TISSUE EOSINOPHILIA - A PROGNOSTIC MARKER IN MALIGNANT TUMORS

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ABSTRACT

Tumor associated tissue eosinophilia (TATE), is characterized by the presence of eosinophils as a component of peri and intra tumoral inflammatory response. The present study on 92 cases of diagnosed malignant tumors was undertaken to assess the role of tissue eosinophilia as a prognostic factor in malignant tumors; to verify the association between tumor associated tissue eosinophilia, microscopic neoplastic characteristics as well as tumor tissue inflammatory response and to evaluate the role of blood eosinophilia on the prognosis of malignant tumors. The study concluded that tumor associated tissue eosinophilia is associated with absence of metastasis and has a protective role in the spread of squamous cell carcinomas, with a high grade TATE being a favourable prognostic indicator in squamous cell carcinomas.

INTRODUCTION

The idea that a tumor may induce a protective reaction in its host, antedated by many years the modern concept of immune surveillance of tumors (Goldsmith *et al.,* 1992). Many types of human cancer are associated with extensive eosinophilia either within the tumor itself or in the peripheral blood or in both locations. Tumor associated tissue eosinophilia is characterized by the presence of eosinophils as a component of peri and intra tumoral inflammatory infiltrate. Although the exact role of eosinophils in tumors in not yet defined, it has been related to a good, (Van Driel *et al.,* 1999) to a poor prognosis, (Leighton *et al.,* 1996) or having no influence on patients outcome (Dorta, 2002). One possible explanation for this controversy, is the fact that the definition and measurement of tumor associated tissue eosinophilia is not uniform among authors, precluding the comparison of results obtained from different studies (Samoszuk, 1997). Although the presence or absence of eosinophilia, within the tumors does not appear to have a major influence on the prognosis of the patient, eosinophils may play an important role in the host interaction with the tumor, perhaps by promoting angiogenesis and connective tissue formation adjacent to the tumor. In addition, tumor related tissue eosinophilia provides some interesting clues into tumor biology, particularly with regards to the production of cytokines by the tumor cells.

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Cellular and molecular interactions of eosinophils in tumor sites may contribute to the treatment and establishment of prognosis for these tumors in the future (Lovi, 1987). The present study was undertaken to assess the role of tissue eosinophilia as a prognostic factor in malignant tumors; to verify the association between tumor associated tissue eosinophilia (TATE), microscopic neoplastic characteristics as well as tumor tissue (acute or chronic) inflammatory response and to evaluate the role of blood eosinophilia on the prognosis of malignant tumors.

MATERIALS AND METHODS

The present study included 132 cases of diagnosed malignant tumors in the Department of Pathology, JN Medical College, AMU, Aligarh. A thorough clinical history and detailed examination of each patient was obtained. Surgically resected specimens were processed, cut into 3-5µm thick sections and stained with Haematoxylin and Eosin stain. Histopathological variables (Goldsmith *et al*., 1992) studied were–

- **Broder's scale:** tumors were graded 1 to 4 on the basis on increasing percentage of undifferentiated epithelium
- **Bauer's scale:** tumors were designated as keratinizing or non-keratinizing
- Pattern of spread at the periphery of tumor (borders) - either pushing or infiltrative
- Percentage of tumor composed of pleomorphic cells. Grades 1, 2, 3 and 4 corresponded to 10%, 30%, 50% and 75% respectively of the tumors cells being pleomorphic (v)

Presence or absence of perineural, vascular involvement and koilocytosis

- Amount of desmoplasia in the adjacent connective tissue was graded 1+ to 4+ (vii) Post inflammatory response was subjectively graded as mild, moderate and intense and the cells of inflammation whether lymphocytes, polymorphs or mast cells were identified
- (viii) Finally, the prominence of eosinophilia within the inflammatory infiltrate was graded 1+ to 4+; '0' = none to 2/HPF, '1+' = 2-10/HPF, '2+' = 10-20/HPF, '3+' = 20-30/HPF and '4+' = >30/HPF. Ten high power fields were assessed for each specimen and the average number of eosinophils/HPF represented the assigned value, for which grades of eosinophilia were determined. Peripheral blood smears prepared by finger prick for assessment of differential eosinophil count and absolute eosinophil count using Dunger's fluid was also performed.

RESULTS

Out of the total of 92 cases, 70 were males (53.0%) and 62 females (46.9%), with a mean age of 49 years and 47 years respectively. Majority of the cases were of head and neck tumors, 50 cases (54.3%), followed by female genital tract tumors, 28 cases (30.4%) and Gastrointestinal tract, 14 cases (15.2%).

50 tumors studied were in Broder's grade 1, of which 17 (85%) were well differentiated and 3 (15%) moderately differentiated (Table 1). Thirteen of the grade 1 tumors (65%) exhibited moderate or marked tissue eosinophilia, while 7 cases (35%) showed absent or mild tissue eeosinophilia. This feature was of equal incidence in grade 2 tumors. Blood eosinophilia was low (< 6%) in 15 cases (75%) of Broder's grade 1 tumor whereas 5 cases (25%) exhibited a high blood eosinophilia. (Table-2) Mean AEC in Broder's grade 1 tumor was 740 cells/ cu mm and it was 510, 890 and 830 cells/ cu mm in tumor grade 2, 3 and 4 respectively. The pattern of tumor spread at periphery (borders) with tissue eosiniphilia was evaluated in 47 cases (94%) of head and neck tumors. In 3 cases (6%) borders could not be commented upon due to extensive tissue necrosis or inadequacy of surgically resected specimens. Sixteen out of 25 cases (72.7%) with absent to mild tissue eosinophilia exhibited infiltrating borders in contrast to 9 cases (27.2%) with marked tissue eosinophilia. Pushing borders were observed in 19 (76%) cases with marked eosoniphilia (Figure 1). Ten out of 13 cases (76.9%) of 1 + TATE were associated with marked pleomorphism whereas 71 cases with 4+ TATE were associated with mild to moderate pleomorphism. Four out of 13 cases (30.7%) of 1+TATE were associated with low grade of desmoplasia whereas 5 out of 7 (71.0%) of 4+ TATE were associated with high grade of desmoplasia (Figure-2).

Table 1. Tumor Grade in relation to differentiation of Head and Neck Tumors

Broder's Grade	No. of cases	Well- ifferentiated	Moderately differentiated	Poorly Differentiated
		No. of cases	No. of cases	No. of cases
1	20	17 (85.0)	3 (15)	-
2	16	02 (12.4)	13 (80.6)	01 (6.2)
3	05	01 (20.0)	2 (40.0)	02 (4.0)
4	09	-	2 (22.2)	07 (77.7)

Table 2. Broders grade in relation to TATE and TABE (Head and Neck tumors)

Broder's grade	Total no. of cases	Tissue Eosinophilia (TATE)		Blood Eosinophilia (TABE)	
		Absent/ Mild	Moderate/ Marked	< 6%	> 6%
		No. of cases (%)	No. of cases (%)	No. of Cases (%)	No. of Cases (%)
1	20	7 (35)	13 (65)	15 (75)	5 (25.0)
2	16	8 (50)	8 (50)	11 (68.7)	5 (31.3)
3	05	4 (80)	1 (20)	2 (40)	3 (60.2)
4	09	6 (66.7)	3 (33.3)	3 (33.3)	6 (66.6)
Total	50	25 (50)	25 (50)	31 (62)	19 (38)

Table 3. Correlation of tissue eosinophilia with Broders' Grade in squamous cell carcinoma of cervix

Broder's Grade	Total no. of cases	Mild to Moderate (1+ to 2+)	Marked (3+ to 4+)
		No. of cases (%)	No. of cases (%)
1	2	-	2 (100.0)
2	8	2 (25)	6 (75.0)
3	3	2 (66.7)	1 (33.0)
4	4	3 (75.0)	1 (25.0)
Total	17	7 (41.2)	10 (58.8)

Head and Neck tumors

Out of a total of 50 cases, 39 (78%) were males and 11 (22%) were females, with a sex ratio of 3.5: 1. Microscopically,42 cases (84%) were squamous cell carcinoma, 3 (6%) mucoepidermoid carcinoma, 2 (4%) adenocarcinoma and 1 (2%) each acinic cell carcinoma, undifferentiated chondrosarcoma and adenoid cystic carcinoma. Twenty of the Inflammatory infiltrate was mild to moderate in 12 out of 13 cases (92.3%) with 1+ TATE and intense in 55.5% of 3+ TATE and 71.4% of 4+ TATE.

Female Genital Tract Tumors

Tumors of female genital tract comprised 19 cases (67.8%) of cervix, 6 cases (21.4%) of ovary and 3 cases (10.7%) of

endometrium with mean age of 40.5 years, 45.3 years and 42.1 years respectively.

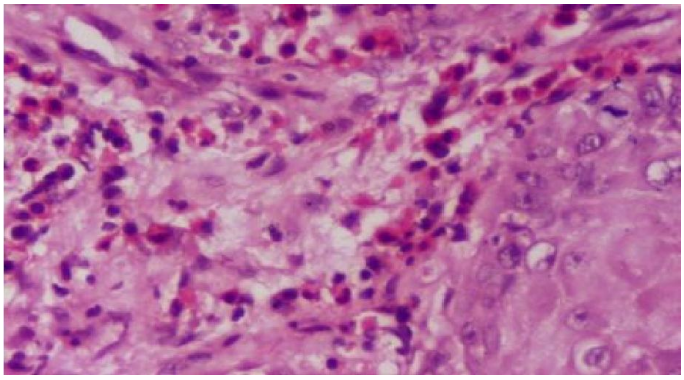

Figure 1. Squamous Cell Carcinoma: Well defined tumor border with intense eosinophilic response. H & E x 40

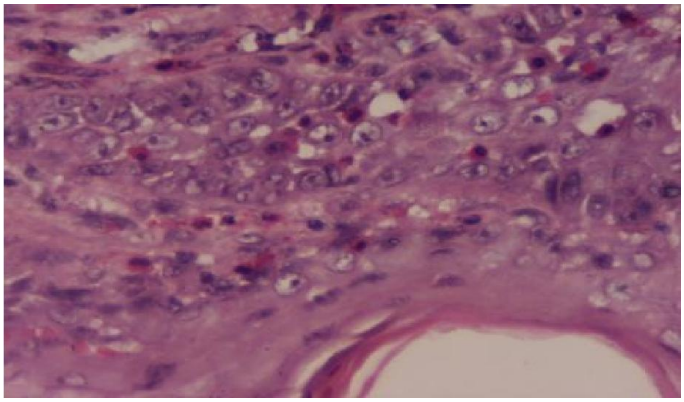

Figure 2. Squamous Cell Carcinoma: Intense tumor eosinophilia with high grade desmoplasia. H & E x 40

Cervix

Squamous cell carcinoma predominated the histologic cell type constituting 17 cases (89.5%) of all cervical tumors followed by adenocarcinoma in 2 cases (10.5%). Of the squamous cell carcinomas, 9 cases (47.5%) were large cell non keratinizing, while small cell and keratinizing large cell carcinoma had an equal incidence of 4 cases (21.2%) each. 8 cases (80.0%) in Broders' grade 1 and 2 were associated with marked tissue eosinophilia whereas only 2 (28.5%) cases in Broders' grade 3 and 4 showed such an association. In contrast a total of 5 cases (71.4%) in grades 3 and 4 were associated with mild to moderate tissue eosinophilia (Table 3). Seven cases (36.8%) of large cell non-keratinizing (LCNK) type of squamous cell carcinomas showed mild to moderate tissue eosinophilia whereas 2 cases (10.5%) showed marked tissue eosinophilia. Small cell carcinomas showed mild to moderate and marked tissue eosinophilia in 2 cases (50%) each. 5 cases (58.2%) with marked pleomorphism were associated with lesser degrees of eossinophilia whereas 7 cases (71.4%) with mild to moderate pleomophism showed high tissue eosinophilia. Ten cases (76.9%) with lesser degrees of TATE exhibited mild inflammatory infiltrate while 7 cases (70.0%) with higher degrees of TATE, were associated with intense inflammatory infiltrate. AEC was calculated in tumors showing raised blood eosinophilia with mean AEC being 720 cells per cu mm.

Ovary: Mucinous and serous cystadenocarcinomas constituted 50% each among the histologic cell types. Two of the 6 cases (33.3%) showed evidence of eosinophillic infiltration. 4 cases had evidence of metastasis and less than 6% of blood eosinophilia was observed in all the tumors irrespective of tumor spread.

Endometrium

All the cases were adenocarcinomas; of which 2 cases (66.6%) were moderately differentiated and 1 case (33.3%) was well-differentiated. A single case showed tissue eosinophilia and vascular invasion. Significant blood eosinophilia i.e., more than 6% was found in a single case (33.3%).

Gastrointestinal and gall bladder tumors

Of the 14 gastrointestinal tract tumors, there were 4 cases of eosophageal tumors, 6 of large intestine and 2 each of gall bladder and small intestine. There was 9 cases (64.2%) of adenocarcinoma, 4 cases (28.5%) of squamous cell carcinoma and a single case (7.1%) of non-Hodgkins lymphoma. Six cases (42.8%) of GIT cancers exhibited 1+ TATE of which 3 cases each were in early and late stage. Four cases (66.7%) each had evidence of spread and blood eosinophilia of more than 6%. Five cases (35.7%) had 2+ TATE with tumor metastasis in 2 cases and a high blood eosinophilia in a single case. High grades of TATE (+++ and ++++) showed no evidence of metastasis and exhibited low blood eosinophilia.

DISCUSSION

Tumor associated tissue eosinophilia (TATE) is characterized by the presence of eosinophils as a component of peri and intra-tumoral inflammatory infiltrate. Our study was designed to assess the role of tissue eosinophilia as a prognostic factor in malignant tumors; to verify the association between TATE, microscopic morphologic characteristics, as well as tumor tissue inflammatory response and to evaluate the role of blood eosinophilia on the prognosis of malignant tumors.

Head and Neck tumors

Male to female sex ratio of 3.5: 1 was noted in head and neck tumors a mean age of 51.1 years and 47.6 years respectively in our study. Goldsmith *et al* 1992 reported male to female sex ratio of 1.75: 1 and a mean age of 58 years in their study on 149 cases. However, Lovi (1987) found no sex predilection in their study on nasopharyngeal tumors. Major histologic cell type was squamous cell carcinoma, 42 cases (84%) of which 31.7% were non keratinizing and 68.3% keratinizing. But Goldsmith *et al* 1992 reported corresponding figures of 13% and 87%. Well and moderately differentiated tumors accounted for 40% each in our study Quite similarly Goldsmith *et al* 1992 reported 38% and 56% well and moderately differentiated tumors respectively.

According to Broder's grade, 40% grade 1, 32% grade 2, 10% grade 3 and 18% grade 4 tumors were present in our study and the corresponding figures reported by Goldsmith *et al* 1992 were 20%, 56%, 23% and 1% respectively. Moderate to marked tissue eosinophilia was seen in 16 cases (65%); a finding concordant with the reports of Lowe and Fletcher

(Lowe and Fletcher, 1984) of 11.6% cases of oral cancer with massive tumor associated tissue eosinophilia (> 100 eosinophils/ hpf in 10 fields) and moderate eosinophilia (over 10/ hpf) in 50% cases each. However, the results of Sassler *et al*., 1995 were contradictory in their study of 248 cases of advanced laryngeal squamous cell carcinomas showing a tissue eosinophilia in 22.5% cases with only 1.6% cases exhibiting > 10 eosinophils/ hpf. 72.2% tumors in Broder's grade 1 and 2 exhibited a low blood eosinophilia whereas 64.2% tumors in grade 3 and 4 exhibited a high blood eosinophilia in our study which also showed 64% tumors with higher Broder's grade being associated with high grades of tissue eosinophilia.

Female Genital Tract tumors

Out of the total 28 cases, 89.5% were squamous cell carcinomas and 10.5% adenocarcinomas.

Cervix

Eight cervical tumors (42.1%) of Broders' grade 1 and 2 were associated with marked tissue eosinophilia, a finding similar to that of Lasersohn *et al* 1964 who observed tissue eosinophillia in 68% cases but in striking contrast to Linnell and Mansson (Linnel and Mannson, 1954) who found pronounced eosinophilia (> 50%) of the stromal cells in only 6.9% cases in their study on 291 cases of cervical carcinomas of various clinical stages. 77.7% of large cell non-keratinizing (LCNK) tumors showed association with mild to moderate tissue eosinophilia and 22.2% with marked tissue eosinophilia, unlike the study carried out by Lowe *et al* 1981in Malawi; which showed LCNK to be associated with massive eosinophilic infiltration. Five out of 6 tumors that had metastasized were associated with lesser grades of tissue eosinophilia and higher grades of circulating eosinophil, a finding in contrast to the study by Lange *et al* 1960, who claimed of a direct relationship of metastasis with marked tissue eosinophilia but Lowe *et al* 1981 reported a finding concordant to our study that circulating eosinophils appeared to be associated with poorer prognosis.

Ovary and endometrium

Six cases of ovarian tumors with a mean age of 46 years were studied of which three each (50%) were of mucinous and serous cystadenocarcinoma and all the three tumors of endometrium were adenocarcinomas. Only 3 of the 9 cases studied (33.3%) exhibited tissue eosinophilia (0-1/ hpf). Significant blood eosinophilia was found in just a single case. Vascular invasion/ ascitic fluid metastasis was seen in 66.6% of ovarian tumors and 33.3% of endometrial tumors but no correlation between tumor outcome and tissue eosinophilia was seen. Probably, the sample size was too small in our study but such association cannot be over ruled with certainty.

GIT and Gall Bladder Tumors

Of the 14 cases of GIT tumors, adenocarcinoma, constituted the main histological group, 64.2% cases followed by squamous cell carcinoma 28.5% cases and 7.1% of Non-Hodgkins lymphoma. Our study showed 11 cases (78.6%) with mild to moderate tissue eosinophilia, a finding consistent with that of Prozervoski 1896; who also identified mild to moderate tissue eosinophilia in all their adenocarcinomatous GI cases. Our study reported eosinophilic infiltrates in carcinomas of colon to be associated with a better prognosis which was comparable to Broder's and Dukes classification, a finding concordant to that of Yoon (Yoon, 1959). Reduced incidence of metastasis was associated with eosinophilic infiltration of a higher degree, a finding also reported by Pretlow *et al.,* 1983.

Conclusion

High tumor associated tissue eosinophilia is an important influential variable affecting tumor metastasis with vascular and lymphatic invasion. TATE is associated with absence of metastasis and has a protective role in the spread of squamous cell carcinomas, with a high grade tissue eosinophilia being a favourable prognostic indicator in squamous cell carcinomas of various sites.

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