Eosinophil Infiltration of Human Colonic Carcinomas as a Prognostic Indicator

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ABSTRACT

In experiments with suspensions of cells from colonic carcinomas, we noted that some colon carcinomas contain large numbers of eosinophils. We therefore carried out a prospective study with 67 almost consecutive colon carcinomas in our medical center after optimal fixation and staining for the demonstration of eosinophils. Infiltration of the primary tumor by eosinophils was found to have marked prognostic significance. The proportion (4 of 17 or 23.5%) of carcinomas with more than 30 eosinophils/sq mm that had metastases was significantly less (p = 0.01) than the proportion (31 of 50 or 62.0%) of carcinomas with less than 30 eosinophils/sq mm that had metastases. At 18 months, following the resection of tumor in patients without metastases, all of the patients (9 of 9) with greater than 30 eosinophils/sq mm were alive in contrast to 73.7% (11 of 15) of the patients with less than 30 eosinophils/sq mm. The number of survivors at 18 months for the total population without regard to metastases was significantly greater (p = 0.028) for those with greater than 30 eosinophils/sq mm than for those with less than 30 eosinophils/sq mm. We conclude that the quantitative assessment of eosinophils is one of the most important aspects of the microscopic evaluation of this common human tumor.

INTRODUCTION

In 1977, we described the purification of epithelial cells from human colonic carcinomas (6, 7). During this work, we noticed large numbers of eosinophils in the suspensions of cells from a proportion of these tumors. Since there was a marked difference in the number of eosinophils from different colon tumors, we wondered if these differences were associated with any prognostic significance. While eosinophils have received relatively little attention as stromal cells in recent decades, Yoon (47) noted that eosinophilic infiltration of tumors including carcinomas of the lung, skin, intestine, breast, and cervix, and cervix. The significance of this eosinophilic infiltration has been widely debated. In the 129 new cases of gastrointestinal carcinoma studied by Yoon (47), the percentage mortality, especially during the first year after surgery, decreased with increasing amounts of eosinophilic infiltration as measured semiquantitatively. Although stromal eosinophils are frequently reported in carcinoma of the uterine cervix (1, 4, 20, 25-27), their significance in that disease is still unclear. Stromal eosino-
RESULTS

Of our original 70 patients with colonic carcinoma in this prospective study, mast cells and eosinophils were evaluated in 67 specimens, since the remaining 3 specimens were largely necrotic tissue. There were 25 females and 42 males with a combined mean age of 65.3 years. With a modified Dukes classification (28), this study included no Stage A, 32 Stage B, and 35 Stage C colonic carcinomas. The degree of differentiation and the locations of the tumors from these 2 populations are presented in Table 1; the extent of eosinophilic infiltration of the tumors is presented in Chart 1. The rate of tissue eosinophilia did not appear to be different in patients with or without prior biopsies. A range of 0 to 233 eosinophils/sq mm was seen in the subpopulation without metastases, and a range of 0 to 119/sq mm was noted in the subpopulation with metastases. The Wilcoxon 2-sample test, normal approximation, confirmed that there were significantly more eosinophils per sq mm in the subpopulation without metastases than in the subpopulation with metastases ($Z = 2.027, p > |Z| = 0.04$).

When 30 eosinophils/sq mm were taken as a threshold, the proportion (31 of 50 or 62.0%) of tumors with less than 30 eosinophils/sq mm with metastases was much greater ($p = 0.01$, Fisher's exact test) than the proportion (4 of 17 or 23.5%) of tumors with more than 30 eosinophils/sq mm with metastases. The exclusion of all patients with peripheral blood eosinophilia increased the significance ($p = 0.004$, Fisher's exact test) of the association of patients (24 of 39 or 61.5%) with less than 30 eosinophils/sq mm with metastases. In patients without metastases, all (9 of 9) with greater than 30 eosinophils/sq mm were alive at 18 months following colon resection. In contrast, 11 of 15 or 73.7% of patients with less than 30 eosinophils/sq mm of tumor were alive 18 months after colon resection. Survival at 18 months for the total population without regard to metastases was significantly greater ($p = 0.024$) for those with greater than 30 eosinophils/sq mm (11 of 13 or 84.6%) than for those with less than 30 eosinophils/sq mm (20 of 41 or 48.8%). Because of the short period of follow-up, the preliminary nature of this study must be stressed.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Degree of differentiation and the locations of the colonic carcinomas included in this study</th>
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<tbody>
<tr>
<td></td>
<td>No metastases $(n = 32)$</td>
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<tr>
<td></td>
<td>&gt;30 Eosinophils/sq mm</td>
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<tr>
<td>Total specimens</td>
<td>13</td>
</tr>
<tr>
<td>Differentiation</td>
<td>Good</td>
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<tr>
<td></td>
<td>Moderate</td>
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<td>Poor</td>
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<td>Location</td>
<td>Cecum</td>
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<td>Ascending</td>
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<td>Transverse</td>
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<td></td>
<td>Splenic flexure</td>
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<td>Descending</td>
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<tr>
<td></td>
<td>Sigmoid</td>
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<td>Rectosigmoid</td>
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<td>Rectum</td>
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Of the 17 patients with over 30 eosinophils/sq mm of tumor, only 3 had peripheral blood eosinophilia; 2 of these 3 had metastatic disease at the time of their colon resections. Peripheral blood eosinophilia was present in 9 of 35 patients with metastases compared to 4 of 31 (no data available on one) patients without metastases. Only 5 of 13 or 38.5% of the patients with peripheral blood eosinophilia survived for 11 months compared to 36 of 53 or 67.9% with less than 450 eosinophils/cu mm blood ($p = 0.062$). At 18 months, only 1 of 9 or 11.1% of patients with peripheral blood eosinophilia survived compared to 25 of 44 or 56.8% with less than 450 eosinophils/cu mm ($p = 0.024$).

We observed (Chart 2) a range of 0 to 87.4 mast cells/sq mm for tumors without metastases compared to 0 to 25.6 mast cells/sq mm for tumors with metastases. Although the 7 tumors with the highest numbers of mast cells per sq mm were from patients without metastases, the Wilcoxon 2-sample test, normal approximation, did not demonstrate a significant difference between these 2 populations ($Z = 1.580, p > |Z| = 0.11$). There was no strong correlation between the presence or absence of mast cells and the presence of eosinophils ($r = 0.309$).

DISCUSSION

The infiltration of human tumors by stromal cells has been the subject of much curiosity for over a century (38); however, the presence, type, or amount of stromal infiltration is seldom included in pathology reports (21). This continues to be true despite
The mechanisms by which eosinophils kill schistosomula and/or tumor cells are under intensive investigation. Pincus et al. (32) have demonstrated that oxidative metabolism is not necessary for the eosinophil-mediated killing of schistosomula. Rat eosinophils cytotoxicity against Schistosoma mansoni (9) and Dipetalonema viteae (19) has been shown to be IgE dependent. Capron et al. (10) have suggested that the presence of Fc receptors for IgE on human and rat eosinophils may be important in the killing of target cells: "The binding of IgE antibodies to their specific FcRs [Fc receptors for IgE] detected on phagocytic cells, such as ... eosinophils, should therefore be considered as a new mechanism of cell activation leading to killer activity ... and must be studied against various possible targets." Eosinophil peroxidase, when combined with hydrogen peroxide and a halide, is cytotoxic to mouse tumor cells in vitro (23). The possible participation of IgE with eosinophils in a tumor cytotoxicity reaction requires investigation.

Mass cells seemed of potential interest since mast cells are associated with eosinophils in immediate-type hypersensitivity reactions (2, 43) and are required in at least some antibody-dependent eosinophil cytotoxicity reactions (11). Mast cells contain eosinophil chemotactic factor of anaphylaxis (40). Our data, however, did not show a strong correlation between the presence of mast cells and eosinophils in the same specimens. It would be interesting to investigate the occurrence of a tumor-associated eosinophil chemotactic factor in colon carcinoma; such factors have been identified in squamous cell carcinomas of the lung (17, 41), in histiocytic lymphoma (16), and in cervical carcinoma (20). It should be noted, however, that each of these cases with chemotactic factors was associated with strong peripheral blood eosinophilia as well as with infiltration of tumor with eosinophils.

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REFERENCES


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