Does the severity of tissue eosinophilia of colonic neoplasms reflect their malignancy potential?

Kolon neoplazmalarında doku eozinofil yoğunluğu malignite potansiyelini gösterir mi?

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Background/aims: *It was speculated that there was a relationship between the intensity of tissue eosinophilic infiltration in colonic malignancies and their prognosis. This retrospective study aimed to investigate the frequency and intensity of tissue eosinophilia in various colonic neoplasms, including serrated adenomas.* ***Methods:*** *We evaluated 448 colonic neoplasms to determine eosinophilic infiltration: 96 hyperplastic polyps, 50 serrated adenomas, 19 flat adenomas, 154 tubular adenomas, 71 tubulovillous adenomas, 13 villous adenomas and 45 adenocarcinomas. The eosinophilic infiltration was categorized into three groups by evaluating the percentage of eosinophils relative to total stromal inflammatory cells: mild (0-5%), moderate (5-40%), and marked (>40%). Chi-square and Fisher's exact tests were used for analyses. P value <0.05 was considered statistically significant.* ***Results:*** *Moderate (46.7%) and marked (52.9%) intensity were noted in all colonic adenomas. Most of the hyperplastic polyps (96%) and adenocarcinomas (75.6%) showed mild intensity. Mostly moderate eosinophilic infiltration was observed in serrated adenomas.* ***Conclusions:*** *Our findings suggest that the intensity of tissue eosinophilia is most prominent in adenomas including serrated adenomas and is diminished from adenoma to carcinoma. This finding may be used as a diagnostic indicator.*

Key words: Tissue eosinophilic infiltration, colonic neoplasms, serrated adenomas

Amaç: *Kolon malignitelerinde doku eozinofil yoğunluğu ile prognoz arasında ilişki olduğu ileri sürülmektedir. Bu retrospektif çalışma serrated adenomları da içeren çeşitli kolon neoplazmalarında doku eozinofil sıklığı ve yoğunluğunu araştırmayı amaçlamaktadır.* ***Yöntem:*** *Eozinofil infiltrasyonunu saptamak için 448 kolon neoplazmasını değerlendirdik: 96 hiperplastik polip, 50 serrated adenom, 19 flat adenom, 154 tubuler adenom, 13 villöz adenom ve 45 adenokarsinom. Eozinofil infiltrasyonu, eozinofillerin toplam inflamatuar hücrelere oranı hesaplanarak 3 gruba ayrıldı. Hafif (%0-5), orta (%5-40) ve belirgin (>%40). Analizler için Chi-square ve Fisher's exact test kullanıldı. P değerinin < 0.05 olması istatistiksel anlamlılık olarak kabul edildi.* ***Bulgular:*** *Kolon adenomlarının %46.7'sinde orta, %52.9'unda belirgin eozinofil yoğunluğu vardı. Hiperplastik poliplerin %96'sında ve adenokarsinomların %75.6'sında hafif yoğunluk mevcuttu. Serrated adenomlarda çoğunlukla orta derecede eozinofil infiltrasyonu gözlendi.* ***Sonuç:*** *Bulgularımız, doku eozinofil yoğunluğunun serrated adenomları da içeren adenom grubunda en belirgin olduğunu ve adenomdan adenokarsinomaya gidişte azaldığını göstermektedir. Bu bulgu tanısal bir ayıraç olabilir.*

Anahtar kelimeler: Doku eozinofil infiltrasyonu, kolon tümörleri, serrated adenomlar

INTRODUCTION

Galen (1) first noted the association between cancer and inflammation in his writings *Opera Omnia* almost 2000 years ago. Tissue eosinophilia has been reported in various malignancies (2-9); however, this relationship remains controversial (9-17). Clinical observations have shown that the presence of eosinophils in solid tumors is common and occurs in several tumor types, particularly in those

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of epithelial origin (2-9).

The frequency and intensity of stromal eosinophilia in benign, premalignant and malignant colonic epithelial tumors were first described by Moezzi et al. (18) in 2000. In that study, they found markedly increased frequency and intensity of stromal eosinophilia in colorectal adenomas compared to benign hyperplastic polyps and colorectal carcinomas (18).

Serrated polyps of the colorectum form a group of morphologically related lesions, which include aberrant crypt foci, hyperplastic polyps, mixed polyps, serrated adenomas and sessile serrated adenomas (19-21). Although the serrated adenoma has become an established entity in the field of pathology, the clinical and morphological features of these polyps have not been described thoroughly.

The aim of our study was to evaluate the frequency and intensity of stromal eosinophilia in benign and premalignant and malignant colonic epithelial neoplasms. The present study is the first to include serrated adenomas in addition to other types of adenomas, hyperplastic polyps and colorectal cancers.

MATERIALS AND METHODS

A computer list was generated of all patients whose endoscopic specimens of polyp and cancer of the colon were reviewed by pathologists at the Marmara Pathology Center in İstanbul from 2006 to 2007. Unsatisfactory specimens such as those showing crush-artifact or having insufficient stroma were excluded from the study.

Table 1. Distribution of the polyps according to diagnosis

Type of Colonic Neoplasm	Number of cases (n)	Percentage
Hyperplastic Polyp (HP)	96	21.4%
Serrated Adenoma (SA)	50	11.2%
Flat Adenoma (FA)	19	4.2%
Tubular Adenoma (TA)	154	34.4%
Tubulovillous Adenoma (TVA)	71	15.8%
Villous Adenoma (VA)	13	2.9%
Adenocarcinoma (CA)	45	10.0%
Total	448	100%

A total of 448 colonic neoplasms, including those containing serrated adenomas, were retrospectively reviewed and scored for tissue eosinophilia by two pathologists (96 hyperplastic polyps, 50 serrated adenomas, 19 flat adenomas, 154 tubular adenomas, 71 tubulovillous adenomas, 13 villous adenomas and 45 adenocarcinomas). The distribution of the polyps by morphologic type is presented in Table 1. All of the adenomatous polyps were classified into low- (n=202) and high-grade (n=55) dysplasia groups.

In adenocarcinomas, the area between normal tissue and tumor - the transitional mucosa- was also evaluated to determine the degree of eosinophilic infiltration.

The histological specimens were cut 4-5 micrometer thick and stained with hematoxylin and eosin. Interobserver differences at the diagnosis of hyperplastic polyp-serrated adenoma and in the classification of grades were reviewed again by the pathologists under Olympus – CX31 microscope and a consensus was reached. The intensity of tissue eosinophilia was scored according to three grades by evaluating the percentage of eosinophils relative to total stromal inflammatory cells: Mild 0-5%, moderate 6-40% and marked >40%. At least 5 high-power fields (HPF) were screened to evaluate the intensity of eosinophilic infiltration.

After all the data were categorized, chi-square and Fisher's exact test were used for analyses. P values < 0.05 were considered statistically significant.

RESULTS

The intensity of tissue eosinophilia in various colonic neoplasms, including serrated adenomas, is shown in Table 2. Moderate intensity was found in 46.6% and marked intensity in 53% of all colonic adenomas. Peak incidence of marked intensity was observed in flat (n=19, 78.9%) and in tubular (n=154, 55.2%) adenomas. Minimal intensity of tissue eosinophilia was found in only 0.4% of all colonic adenomas.

Hyperplastic polyps generally showed mild (n=87, 90.6%) and moderate (n=9, 9.4%) intensity of the tissue eosinophilia. There was no marked inten-

Table 2. The distribution of the colonic neoplasms according to the intensity of tissue eosinophilia

Tissue Eosinophilia	Minimal intensity (<5%)	Moderate intensity (6-40%)	Marked intensity (>40%)
Hyperplastic polyps (n=96)	87 (90.6%)	9 (9.4%)	0
Adenomatous polyps (n=257)	1 (0.4%)	120 (46.6%)	136 (53%)
Serrated adenomas (n=50)	1 (2%)	42 (84%)	7 (14%)
Adenocarcinomas (n=45)	34 (75.6%)	11 (24.4%)	0

sity of tissue eosinophilia in any of the hyperplastic polyps. Tissue eosinophilia was found with moderate or marked intensity in all adenomatous polyps (98%), except two. Intensity of tissue eosinophilia was mild in most of the adenocarcinomas (n=34, 75.6%), and no case of adenocarcinoma showed marked intensity of eosinophilic infiltration.

Eosinophilic infiltration in the tumor stroma was lower than that in peritumoral tissue, and the difference was statistically significant (p=0.011). In serrated adenomas, moderate (n=42, 84%) and marked (n=7, 14%) eosinophilia were observed. Only one case showed mild intensity.

There was a significant difference in the intensity of tissue eosinophilia between hyperplastic and adenomatous polyps (p<0.001). The difference was also significant between hyperplastic polyps and adenocarcinomas (p=0.022).

The intensity of tissue eosinophilia declined with increasing malignancy potential, which was statistically significant (p<0.001). There was no significant difference in terms of intensity of tissue eosinophilia between low- and high-grade dysplasia (p=0.073).

High-grade dysplasia (n=55, 65.6% marked) was significantly different from adenocarcinoma (n=45, 75.6% mild) in terms of eosinophilic infiltration (p<0.001). The severity of tissue eosinophilia was higher in high-grade dysplasia compared to adenocarcinomas.

There was a significant difference in terms of the intensity of tissue eosinophilia between serrated adenomas and other adenomatous polyps (p<0.001) and hyperplastic polyps (p<0.001). The eosinophil count was significantly low in the hyperplastic polyps and high in adenomatous polyps compared to serrated adenomas. The severity of the intensity of tissue eosinophilia in various colonic neoplasms is shown in Figure 1.

Tubular adenoma with prominent eosinophilia and hyperplastic polyps with mild eosinophilia are shown in Figures 2 and 3, respectively. Serrated adenoma with moderate eosinophilia and adenocarcinoma with mild eosinophilia are shown in Figures 4 and 5, respectively.

DISCUSSION

It has long been known that the presence of an inflammatory host response to colon carcinoma is a significant prognostic factor (22,23). The association of inflammation with malignancy was described about two millenniums ago (1).

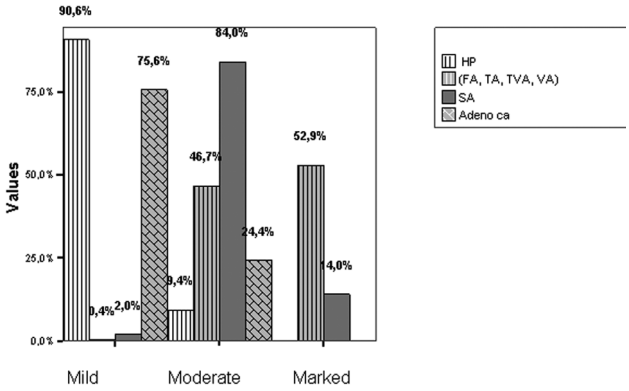

Figure 1. The frequency and intensity of tissue eosinophilic infiltration in various colonic neoplasms (Kızıltaş et al 2007).

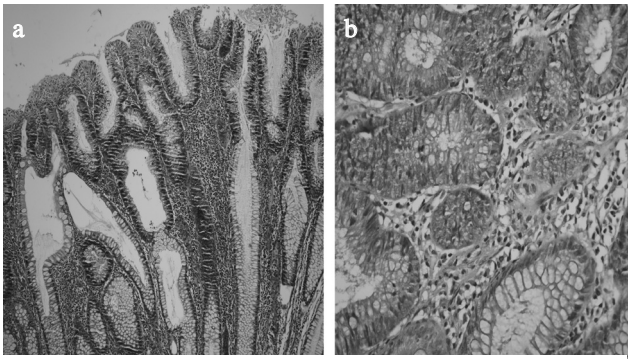

Figure 2. Tubular adenoma with prominent stromal eosinophilia (**2a:** H-Ex100) (**2b:** H-Ex400)

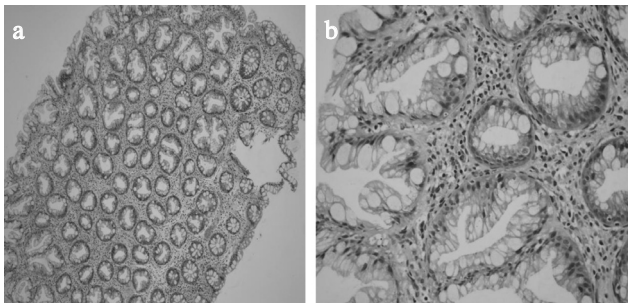

Figure 3. Serrated adenoma **a)** H-E, x40; **b)** H-E, x400)

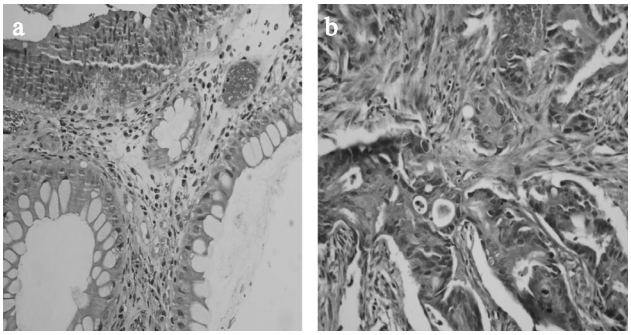

Figure 4. Invasive adenocarcinoma **a)** Normal colonic glands are seen in the peritumoral tissue, H-E, x400; **b)** Mild eosinophilic infiltration in adenocarcinoma, H-E, x100).

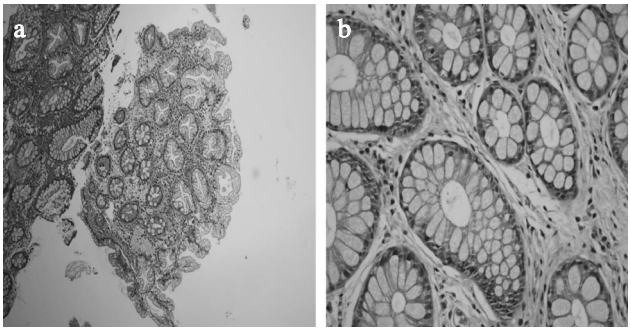

Figure 5. Hyperplastic polyp with mild stromal eosinophils (**5a:** H-E, x100; **5b:** H-E, x400).

Tumor-associated eosinophilia has been observed in numerous human cancers and several tumor models in animals; however, the relationship between eosinophilia and lesion types has remained largely undefined and anecdotal. The importance of tissue eosinophilia of tumors has been unclear. Within several tumor types, including gastrointestinal tumors, tumor-associated tissue eosinophilia has been associated with a significantly better prognosis.

There has been increasing interest recently in inflammatory cells of tumor stroma. Tumor infiltrating eosinophils have previously been investigated in colon carcinomas, but little data has been collated about their role in colonic polyps. Previous studies have suggested that eosinophils play a central role in immunologic response against tumors, but the underlying mechanisms of this role are not well known. The mechanism of tissue eosinophil infiltration in "low-high grade dysplasia – carcinoma sequence" has also not been understood.

According to recently published literature, tumor-associated eosinophils have at least two dominant non-overlapping activities. One of these is destructive effector functions potentially limiting tumor growth as well as causing recruitment and activation of other leukocytes. The second is immunoregulating and remodeling activity, which suppresses immune response and promotes tumor proliferation (36).

In 1983, Pretlow et al. (14) reported for the first time that high eosinophil counts were associated with an improved prognosis for patients with colorectal carcinoma. In addition, several groups have analyzed the prognostic significance of eosinophil counts in other kinds of tumors, with different results (7, 13, 14).

On the other hand, Fisher et al. (16) found that eosinophilic infiltration in the tumor tissue had no effect on prognosis, whereas mast cell had an inverse relationship with prognosis in patients with colorectal carcinomas.

Moezzi et al. (18) first demonstrated in their original article that the intensity of tissue eosinophilia increased in colonic adenomatous polyps rather than colonic adenocarcinoma and hyperplastic polyps. Our results support their findings.

The prototype of serrated lesions is the hyperplastic polyp. Since its recognition as a pathological entity different from adenomas, hyperplastic polyps have been regarded as innocuous, non-neoplastic lesions with no malignant potential (25-28). This view has remained unchanged for many years, despite several reports documenting occurrence of cancer in some hyperplastic polyps (29).

Serrated adenomas, which have sessile morphology, have recently been identified as a distinct entity among colorectal neoplasms (30). Wolber and Owen (31) and others speculated that serrated adenoma may be an independent precursor of colorectal cancer (32, 33). Therefore, it is very important to separate the serrated adenomas from hyperplastic polyp histologically.

Our study is the first to search for tissue eosinophilia in serrated adenomas. Most of the serrated adenomas had moderate intensity of eosinophilic infiltration, whereas a small number of cases had marked infiltration.

However, all other adenomatous polyps had mostly moderate to marked eosinophilic infiltration; only two polyps had minimal intensity. Flat adenomas, which were generally considered to have a high malignancy rate (34,35), had the most prominent tissue eosinophilia.

Does this finding reflect that the host response was strongest in this adenoma type? We need further biological investigations to answer this question. The intensity of tissue eosinophilia diminished from tubular adenoma to adenocarcinoma at a statistically significant level. If the tissue eosinophilia in neoplasms is accepted as a host response to neoplastic tissue, we can postulate that this response undergoes exhaustion once invasive carcinoma has developed. Our findings also demonstrated that with regard to tissue eosinophilia, the difference between low- and high-grade tubular adenomas was not statistically significant. We think that stromal eosinophilia coexists with adenomatous polyps, but its intensity does not correlate with classical "low grade-high grade dysplasia-carcinoma sequence".

Our findings suggested that serrated adenomas were statistically different from hyperplastic polyps with respect to tissue eosinophilia. We can speculate that tissue eosinophilia may be a histologically good diagnostic indicator for separation of serrated adenomas from hyperplastic polyps.

Additionally, decreasing tissue eosinophilia from tubular adenoma to adenocarcinoma and the intensity of eosinophilic infiltration may help to determine patients at high-risk for developing adenocarcinoma.

In conclusion, the results of our study may help to modify the screening plans for the follow-up of patients with colonic neoplasms and to predict those patients who may have a high risk of developing colorectal carcinoma.

REFERENCES

1. Kühn CG. Claudii galenii opera omnia. In: Kühn KG, Assmann FW, eds. Medicorum Graecorum Opera Quae Exstant, Vol. 7. Lipsiae, Germany: C. Cnobloch, 1821;705-32.
2. Przewoski E. Ueber die locale Eosinophille beim Krebs nebst Bremerkungen über die Bedeutung der eosinophilen Zellen im Allgemeinen. Zentralbl Allg Pathol 1896;5:177-91.
3. Lowe D, Fletcher CDM. Eosinophilia in squamous cell carcinoma of the oral cavity, external genitalia and anus – clinical correlations. Histopathology 1984;8:627-32.
4. Isaacson H, Rapoport P. Eosinophilia in malignant tumor: its significance. Ann Intern Med 1946;25:893-902.
5. Lowe D, Fletcher CD, Gower RL. Tumor associated eosinophilia in the bladder. J Clin Pathol 1984;37:500-2.
6. Yoon IL. The eosinophil and gastrointestinal carcinoma. Am J Surg 1959;97:195-200.
7. Caruson RA, Giuffre G, Inferrera C. Minute and small early gastric carcinoma with special reference to eosinophil infiltration. Histol Histopathol 1993;11:155-66.
8. Lowe DG. Carcinoma of the cervix with massive eosinophilia. Br J Obstet Gynaecol 1988;95:393-401.
9. Iwasaki K, Torisu M, Fujimura T. Malignant tumor and eosinophils. Prognostic significance in gastric cancer. Cancer 1986;58:1321-7.
10. Sassle LCDR, McClatchey KD, Wolf GT, et al. Eosinophilic infiltration in advanced laryngeal squamous cell carcinoma. Veterans Administration Laryngeal Cooperative Study group. Laryngoscope 1995;195:413-6.
11. Lowe D, Jorizzo J, Hutt MSR. Tumor-associated eosinophilia. A review. J Clin Pathol 1981;34:1343-8.
12. Lool LM. Tumor-associated tissue eosinophilia in nasopharyngeal carcinoma. A pathologic study of 422 primary and 138 metastatic tumors. Cancer 1987;59:466-70.
13. Leighton S, Teo J, Leung S, et al. Prevalence and prognostic significance of tumor associated tissue eosinophilia in nasopharyngeal carcinoma. Cancer 1996;77:436-40.
14. Pretlow TP, Keith EF, Cryar AK, et al. Eosinophils infiltration of human colonic carcinomas as a prognostic indicator. Cancer Res 1983;43:2997-3000.
15. Goldsmith MM, Bechis BDA, Cresson DH, et al. The importance of the eosinophil in head and neck cancer. Otolaryngol Head Neck Surg 1992;106:27-33.
16. Fisher ER, Paik SM, Rockette H, et al. Prognostic significance of eosinophils and mast cells in rectal cancer: finding from the national surgical adjuvant breast and bowel project (Protocol R-01). Human Pathol 1989;20:159-63.
17. Thompson AC, Bradley PJ, Griffin NR. Tumor associated tissue eosinophilia and long-term prognosis for carcinoma of the larynx. Am J Surg 1994;168:469-71.
18. Moezzi J, Gopalswamy N, Haas RJ, et al. Stromal eosinophilia in colonic epithelial neoplasms. Am J Gastroenterol 2000;95:520-3.
19. Urbanski SJ, Marcon N, Kossakowski AE, Bruce WR. Mixed hyperplastic adenomatous polyps: an underdiagnosed entity. Am J Surg Pathol 1984;8:551-6.
20. Gabbers JO, Laissue JA. Mixed hyperplastic and neoplastic polyp of the colon: an immunohistochemical study. Virchows Arch (A) 1986;410:189-94.
21. Longacre TA, Fenoglio-Preiser CM. Adenomas. In: Fenoglio-Preiser CM, Pascal RR, Perzin KH, eds. Tumors of the Intestines. Washington: Armed Forces Institute of Pathology, 1988;108-12.
22. Watt AG, House AK. Colonic carcinoma. A quantitative assessment of lymphocyte infiltration at the periphery of colonic tumors related to prognosis. Cancer 1978;41:279.
23. Swennevig JL, Lunde OC, Holter S, Bjorgovik D. Lymphoid infiltration and prognosis in colorectal carcinoma. Br J Cancer 1984;49:375.
24. Van Driel WJ, Hogendoorn PCW, Jansen FW, et al. Tumor-associated eosinophilic infiltrate of cervical cancer is indicative of less effective immune response. Hum Pathol 1996;27:904-11.
25. Morson B. Polyps and cancer of the large bowel. West J Med 1976;125:93-9.
26. Morson BC. Precancerous lesions of the colon and rectum. Classification and controversial issues. JAMA 1962;179: 316-21.
27. Estrada RG, Splut HJ. Hyperplastic polyps of the large bowel. Am J Surg Pathol 1980;4:127-33.
28. Goldman H, Ming S, Hickock DF. Nature and significance of hyperplastic polyps of the human colon. Arch Pathol 1970;89:349-54.
29. Jeeveratnam P, Cottier DS, Browett PJ, et al. Familial giant hyperplastic polyposis predisposing to colorectal cancer: a new hereditary bowel cancer syndrome. J Pathol 1996;179:20-5.
30. Torlakovic E, Snover DC. Serrated adenomatous polyposis in humans. Gastroenterology 1996;110:748-55.
31. Wolber RA, Owen DA. Flat adenomas of the colon. Hum Pathol 1991;22:70-4.
32. Rubio CA, Rodensjo M. Flat serrated adenomas and flat tubular adenomas of the colorectal mucosa: differences in the pattern of cell proliferation. Jpn J Cancer Res 1995;86: 756-60.
33. Rubio CA, Kato Y, Hirota T, Muto T. Flat serrated adenomas of the colorectal mucosa in Japanese patients. In Vivo 1996;10:339-43.

34. Parra-Blanco A, Gimeno-Garcia AZ, Nicolas-Perez D, Garcia C. Risk for high-grade dysplasia or invasive carcinoma in colorectal flat adenomas in a Spanish population. Gastroenterol Hepatol 2006;29:602-9.

35. Rubio CA, Kato Y, Hirota T, Muto T. Histologic classification of endoscopically removed flat colorectal polyps. A multicentric study. Jpn Y Cancer Res 1996;87:849-55.

36. Lotfi R, Lee JJ, Lotze MT. Eosinophilic granulocytes and damage-associated molecular pattern molecules (DAMPs): role in the inflammatory response within tumours. J Immunother 2007;30:16-28.