Original Article

Comparison between the concentration of mast cells and risk criteria of malignancy in intestinal adenomas

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ABSTRACT: Intestinal adenomas are benign neoplasms that present a risk of malignancy associated with three independent characteristics: the polyp size, the histological architecture and the severity of epithelial dysplasia (or atypia). Current evidence suggests that mast cells (CM) contribute to the tumorigenesis of colorectal carcinomas. Objective: Compare the concentration of CM in intestinal adenomas and risk criteria for malignancy in these tumors (size, histological type and degree of cellular atypia). Methods: We conducted a retrospective study with 102 anatomopathological reports of intestinal adenoma excision. We selected paraffin blocks with the central area of the tumor. The CM were stained with toluidine blue. Results: In most cases (89.2%, n=91), the mast cells concentration (MC) was less than 6 CM/10 high power field (HPF) (p=0.0001). Most adenomas, regardless of their histological type, showed 0 CM/10 HPF (p=0.083). In most adenomas, regardless of their size, MC was 0 CM/10 HPF (p=0.665). Presence or absence of atypia was associated, in most cases, with MC of 0 CM/10 HPF (p=0.524). Conclusion: This study did not show association between the MC and histological type, size or presence of atypical cells in intestinal adenomas.

Keywords: mast cell; adenoma; intestinal cancer; histology; pathology.

RESUMO: Adenomas intestinais são neoplasias benignas que apresentam risco de malignização relacionado a três características independentes: o tamanho do pólipo, a arquitetura histológica e a gravidade da displasia (ou atipia) epitelial. Evidências atuais sugerem que os mastócitos contribuem para a tumorigênese do carcinoma colorretal. Objetivo: Analisar comparativamente a concentração de mastócitos em adenomas intestinais e os critérios de risco para malignização nesses tumores (tamanho, tipo histológico e grau de atipia celular). Métodos: Realizou-se um estudo retrospectivo, com seleção de 102 laudos anatomopatológicos de exérese de adenoma intestinal. Foram selecionados os blocos de parafina com a área central da neoplasia para a realização da coloração de azul de toluidina para evidenciar os mastócitos. Resultados: Na maioria dos casos (89,2%, n=91) a concentração de mastócitos (CM) foi menor que 6 mastócitos/10 campos de grande aumento (CGA) (p=0,0001). A maioria dos adenomas, independente do tipo histológico, mostrou 0 mastócito/10 CGA (p=0,083). A maioria dos adenomas, independentemente do tamanho, tinha CM de 0 mastócito/10 CGA (p=0,665). A presença ou a ausência de atipias esteve associada, na maioria dos casos, a CM de 0 mastócito/10 CGA (p=0,524). Conclusão: Este estudo não mostrou associação entre a concentração de mastócitos e tipo histológico, tamanho ou presença de atipias celulares nos adenomas intestinais.

Palavras-chave: mastócito; adenoma; câncer intestinal; histologia; patologia.

INTRODUCTION

In terms of incidence, colorectal cancer is the third most frequent cause of cancer in the world, in both genders, and the second cause in developed countries. Around 9.4% of all cancers are colorectal cancer, corresponding to one million new cases[1]. The estimated number of new cases of colorectal cancer in Brazil in 2010 was 13,310 cases in men and 14,800 in women. These values correspond to the estimated risk of 14 new cases in each 100,000 men and 15 new cases in each 100,000 women[1].

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The family history of colorectal cancer and the genetic predisposition to developing chronic bowel disease (such as APC) are the most important risk factor for the development of this type of neoplasm[1,2].

The early detection of colorectal adenomatous polyps (precursors of colorectal cancer) and local cancers is possible through the fecal occult blood test and endoscopic methods[1]. The natural history of colorectal cancer enables ideal conditions for its early detection. However, even countries with abundant resources have had difficulties in performing diagnostic assessments using endoscopic exams in patients with the presence of fecal occult blood, not allowing the population screening. The purpose of this strategy is not to diagnose more polyps or more flat lesions, but reduce the incidence and mortality of this type of cancer in the target population[1].

Mast cells (CM) were described infiltrating the interface between developing tumors and healthy tissues in 1891 by Westphal, a student of Paul Erlich (apud[3,4]). CM are common in several human cancers, including carcinoma of Merkel cells, breast, lung, skin and Hodgkin's lymphoma[5]. Some studies suggest that CM can promote tumor growth in some types of cancers, but opposed results in others[6,7].

Several studies have evaluated the association between CM and colorectal cancer, showing greater concentration of CM in tumors when compared to adjacent healthy tissues[3], high level of metalloproteinase (MMP) of CM in normal tissue adjacent to tumor[8], significant correlation between MC and microvascular density[9], greater concentration of CM in poorly differentiated tumors, but no correlation with invasion depth[10], longer survival in patients with lower concentration of CM and lower vascular density[9,11] and better prognosis in patients with lower concentration of CM in the tumor[12].

The study conducted by Gounaris et al.[13] showed a MC in adenomatous polyps (lymphocyte-independent), which is required for polyp formation, the initial step for colon cancer.

Understanding the mechanisms that lead to neoplasm aggressiveness is important when trying to institute more effective therapeutic methods that mainly prevent its local infiltration and systemic dissemination. In this context, the tumor microenvironment plays an important role, and knowing possible differences in the microenvironment of cancer-precursor lesions is essential.

The literature does not have studies that compare MC to risk criteria for malign transformation into intestinal adenomas.

Based on that, the purpose of this study was to compare MC in intestinal adenomas and the risk criteria for malignancy in these tumors (size, histological type and degree of cellular atypia).

METHODS

Selection of cases

A retrospective study was conducted, with the selection of 102 anatomopathological reports of intestinal adenoma excision made by the Laboratory of Pathological Anatomy at the Universidade do Oeste Paulista (UNOESTE), between January 2005 and August 2009.

The cases of intestinal adenoma incision biopsy were excluded, as they are performed for the preoperative diagnosis of lesions, but do not allow to assess the lesion size.

Data related to patients' gender, adenoma size, histological type (tubular, tubulovillous and villous), presence and degree of cellular atypia (absent, mild, moderate and severe) and presence of associated lesion in another bowel area and, if present, what lesion was found, were obtained from the exam reports. Then, the adenomas were sorted according to their size into the following categories: adenomas smaller than 1.0 cm, 1.0–1.9 cm, 2.0–2.9 cm, 3.0–3.9 cm and 4 cm or larger.

The evaluation of histological parameters (histological type and atypia) was made by the same pathologist (GAN).

Determination of mast cell concentration

Paraffin blocks with the central area of the tumor were selected for CM staining with toluidine blue (Merck, Darmstadt, Germany) to evidence the CM, as determined by Michalany[14]. The CM count of each plate was made in the adenoma stroma, with 10 HPF (objective lens 40×), which corresponds to around 1 mm^2, using an optical microscope. Regardless of the adenoma size, all of them presented a proportional quantity of stroma.

The MC was sorted into five categories: 0 CM in 10 HPF; 1 to 5; 6 to 15; 16 to 25; and more than 25.

Statistical analysis

The quantitative variables were primarily tested to verify the adequacy to normal distribution, through the Kolmogorov-Smirnov test and, as they did not present normal distribution, non-parametrical tests were used. The Kruskal-Wallis test was used to compare the histological type and cellular atypia in the adenomas to the patients' age; the histological type to the adenoma size; the adenoma size to cellular atypia; and the MC to the histological type of adenomas and cellular atypia. The Mann-Whitney test was used to compare the adenoma size to the patients' gender, the adenoma size to the presence or absence of adenoma-related lesions and the MC to the presence or absence of adenoma-related lesions. The Spearman correlation was used to verify the association between the MC and the adenoma size and the patients' age, and the association between the patients' age and the adenoma size. The χ^2 test was used to compare the histological type of adenomas to cellular atypia; and the patients' gender and the histological type to the presence or absence of associated lesions. The likelihood ratio was used to compare the histological type to cellular atypia and cellular atypia to the presence or absence of adenoma-related lesions, as in the χ^2 test, 20% or more of boxes presented expected frequencies lower than 5. All tests were made considering the significance level of 5% using the *Statistical Package for the Social Sciences* (SPSS), version 15.0.

Approval from the Research Ethics Committee

This study was approved by the Research Ethics Committee of the Universidade do Oeste Paulista (CEP/UNOESTE – Process n° 584/10).

RESULTS

The patients' age varied between 22 and 94 years, mean age was 63.96 years (standard deviation of 13.27 years and median value of 66 years), and 56.9% of them were males.

Regarding the histological type, 39.2% (n=40) were tubular adenomas, 42.1% (n=43) were tubulovillous adenomas and 18.7% (n=19) were villous adenomas. The adenoma size ranged from 0.20 to 4.50 cm in the greatest axis (mean of 1.29 cm, standard deviation of 0.84 cm and median of 1.00 cm), with most cases (81.3%, n=83) measuring less than 2 cm and only two cases measuring 4 cm or more. Regarding cellular atypia, 22.5% (n=22) had no atypia, 37.2% mild atypia, 29.4% (n=30) moderate atypia and 10.9% (n=11) had severe atypia.

A statistically significant difference was observed between the histological type of adenomas and the patients' gender (p=0.019), with tubular and tubulovillous types more frequent in women, and also in relation to age (p=0.025). No statistically significant difference was observed between cellular atypia and the patients' gender (p=0.495) or the patients' age (p=0.241). Regarding the adenoma size, a difference was observed in relation to the patients' gender (p=0.035), but not in relation to the patients' age (p=0.555).

Most cases did not present other associated lesions in the bowel (78.4%, n=80). Nineteen cases were associated with adenocarcinoma (18%) and three (2.9%) with hyperplastic polyp.

Most tubular adenomas measured less than 2 cm (92.5%, n=37) and presented mild atypia (45%, n=18) or no atypia (35%, n=14). Tubulovillous adenomas measured between 1.0–1.9 cm in 48.8% of the cases (n=21) and presented moderate atypia in 34% (n=15) of the cases. The two adenomas measuring 4 cm or more were tubulovillous and presented mild and moderate atypia. Only one villous adenoma measured between 3.0–3.9 cm, the others measured up to 1.9 cm and most of them presented mild (42.1%, n=8) or moderate atypia (42.1%, n=8) (Figure 1). A statistically significant difference was observed between the histological type of adenomas and the size (p=0.0001) and cellular atypia (p=0.007) of the adenomas.

When comparing the size to cellular atypia, most cases of all categories presented mild atypia (p=0.414).

Regarding the associated lesions, adenocarcinoma was associated with tubular adenomas in most cases (68.4%, n=13), adenomas smaller than 1 cm (57.9%, n=11) e absence of atypia (36.8%, n=7). One case associated with adenocarcinoma and 10 without associated lesions (12.5%) presented severe atypia. A statistically significant difference was observed

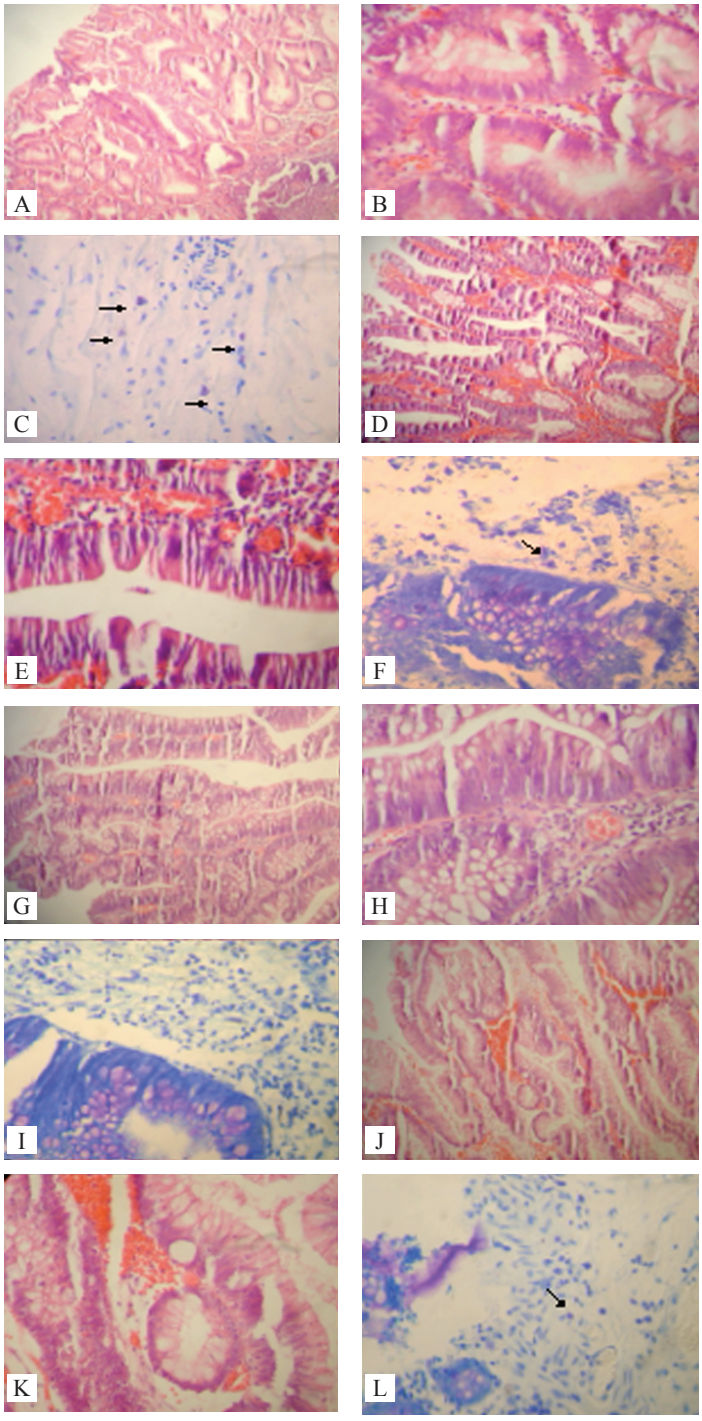

Figure 1. *(A) Tubular adenoma of 1 cm (hematoxilin-eosin, 100x enlargement). (B) Absence of cellular atypia (hematoxilin-eosin, 400x enlargement). (C) Concentration of mast cells (CM) above 25 (toluidine blue staining, 400x enlargement). (D) Tubulovillous adenoma of 1.5 cm (hematoxilin-eosin, 100x enlargement). (E) Absence of cellular atypia (hematoxilin-eosin, 400x enlargement). (F) CM between 6 and 15 (toluidine blue staining, 400x enlargement). (G) Villous adenoma of 1 cm (hematoxilin-eosin, 100x enlargement). (H) Absence of cellular atypia (hematoxilin-eosin, 400x enlargement). (I) CM of 0 (toluidine blue staining, 400x enlargement). (J) Tubulovillous adenoma of 4.5 cm (hematoxilin-eosin, 100x enlargement). (K) With mild cellular atypia (hematoxilin-eosin, 400x enlargement). (L) CM between 1 and 5 (toluidine blue staining, 400x staining).*

between associated lesions and histological type of adenomas (p=0.019) and size (p=0.016), but no difference was observed in relation to cellular atypia (p=0.51) of adenomas.

The MC ranged from 0 to 28 CM/10 HPF (mean was 2.28, standard deviation of 4.57 and median was 1) (p=0.0001) (Figures 1 and 2). No statistically significant difference was observed between the MC and the patients' age (p=0.790) and gender (p>0.05).

The comparisons between mast cell concentration and histological type (p=0.083), size (p=0.665) and cellular atypia (p=0.524) of adenomas and the presence of associated lesions (p=0.202) are illustrated in Figures 3, 4, 5 and 6, respectively.

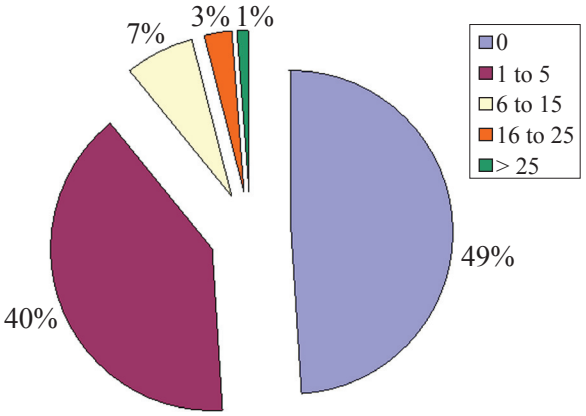

Figure 2. *Distribution of cases according to the concentration of mast cells in the intestinal adenomas (n=102), p=0.0001.*

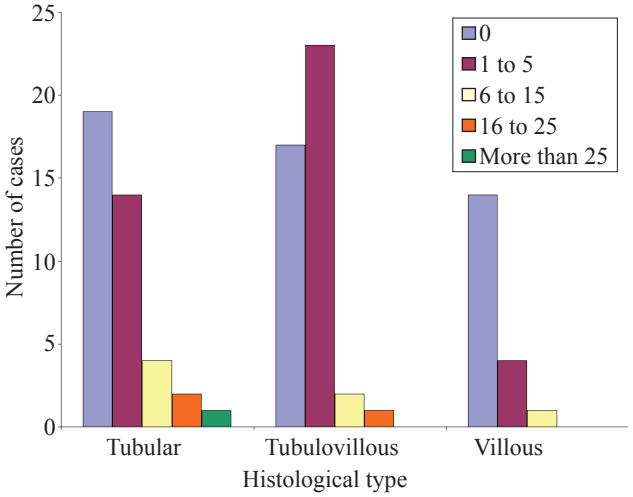

Figure 3. *Distribution of cases according to the concentration of mast cells and histological type of the intestinal adenomas (n=102), p=0.083.*

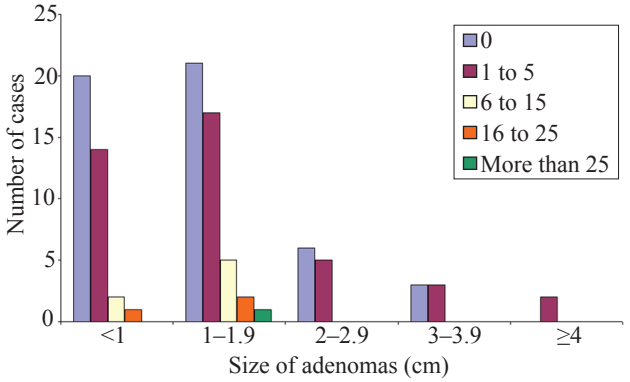

Figure 4. *Distribution of cases according to the concentration of mast cells and the size (in cm) of the intestinal adenomas (n=102), p=0.665.*

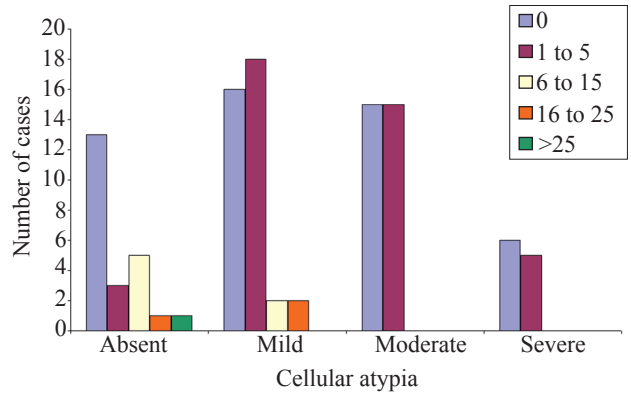

Figure 5. *Distribution of cases according to the concentration of mast cells and the degree of cellular atypia of the intestinal adenomas (n=102), p=0.524.*

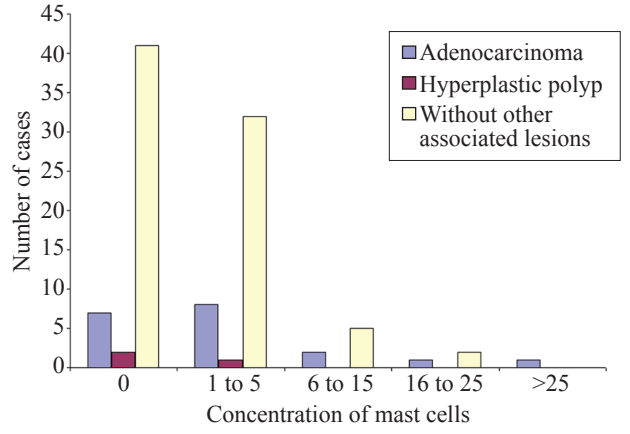

Figure 6. *Distribution of cases according to the concentration of mast cells and the intestinal lesion in other areas associated with the adenomas (n=102), p=0.202.*

DISCUSSION

Intestinal polyps can be non-neoplastic (inflammatory, hamartomatous or hyperplastic) and neoplastic (adenomatous polyps or adenomas). Adenomas can be of three types, according to their histological architecture: 1) tubular adenomas, composed of tubular glands similar to the mucosa topology, are the most frequent types; 2) villous adenomas, with villous projections, corresponding to 1% of the adenomas; 3) tubulovillous adenomas, a combination of the two types described above, corresponding to 5 to 10% of the adenomas[15]. In this study, most cases of intestinal adenomas occurred in male patients, with median age of 66 years, as described in the literature. However, tubulovillous adenomas were predominant (42.1%), followed by tubular adenomas (39.2%). The median size was 1 cm and mild atypia predominated in the studied sample (29.4%). Such data show that the adenomas had early diagnosis, reducing the risk of malignancy of these tumors.

In this study, the histological type of adenomas was associated with the patients' gender and age, while the adenoma size was associated with gender only, and cellular atypia was not associated with either parameter. In addition, a statistically significant difference was observed between the histological type and size (p=0.0001) of adenomas and histological type and cellular atypia (p=0.007), but no association was observed between the adenoma size and cellular atypia (p=0.414). The absence of association observed between adenoma size and cellular atypia may be explained by the fact that most cases had adenomas measuring up to 1.9 cm, with moderate and severe cellular atypia as the most frequent types observed in adenomas larger than 2 cm[15]. On the other hand, most cases had tubular and tubulovillous adenomas, which tend to be smaller and with lower degree of cellular atypia[15], which predominated in this study.

The risk of malignancy for an adenoma is associated with three independent characteristics: polyp size, histological architecture and epithelial dysplasia (or atypia) severity, described as follows: 1) cancer is rare in tubular adenomas with diameter of less than 1 cm; 2) the probability of cancer is high in villous adenomas with diameter of more than 4 cm, reaching up to 40%; 3) severe dysplasia, when present, is frequently found in villous areas[15]. This study showed a statistically significant difference between the presence of associated lesions and the histological type of adenomas (p=0.019) and adenoma size (p=0.016), partially confirming the data above, as no association was observed between these other lesions and the degree of cellular atypia of the adenomas (p=0.51). This fact may have occurred due to the small number of adenocarcinomas (18%) in the sample of associated lesions, as well as the small number of adenomas with severe atypia (10.9%), which are more associated with the progress into malign neoplasm.

The role of stroma-epithelium interaction in the initial events of carcinogenesis was proposed around 30 years ago[6]. An interaction between tumor cells and their microenvironment is important for their growth and survival. In this context, the involvement of inflammatory cells in the initiation, promotion and progression of cancer has indicated a new therapeutic opportunity in the treatment of cancer. The main immune cells involved in tumor-associated inflammation are macrophages, dendritic cells, lymphocytes, neutrophils, eosinophils and CM[16].

CM are metachromatic cells from hematopoietic pluripotent stem cells of the bone marrow[17], first described by Erlich, in 1878[3,4]. The CM can be found in most tissues, but are found in greater number in the skin, airways and digestive tract[4]. The study conducted by McGinnis et al.[18] showed that the use of a histochemical method, with toluidine blue staining, or the immunohistochemical method for CM detection, has similar results.

New roles of the CM have been identified, showing that these cells have a critical role, in innate immunity, or adaptive, normal or pathological immunity (e.g., acute or chronic bacterial or parasital infections, autoimmune diseases, pregnancy), including the immune tolerance[16,19-22].

The interaction between the CM and the tumor cells occur in three forms, recently described: 1) its effect on tumor angiogenesis; 2) for mediating the tissue remodeling; 3) mast cell-dependent immune regulation via immune cell recruitment and immunosuppression[4].

Tumor angiogenesis is essential for growth above 1 mm^3, invasion and metastases in solid tumors[4,9,16]. Several evidences have shown that the CM have an important role in tumor angiogenesis[9,16]. The CM secrete the vascular endothelial growth factor (VEGF), interleukin (IL)-8 and growth factors, which enable the formation of new vessels[6]. The infiltration of CM is well associated with tumor angiogenesis and metastases in gastric cancer, colorectal cancer, pulmonary adenocarcinoma, renal cell cancer and prostate cancer[5].

It has been suggested that, in the context of developing tumors, the tissue remodeling ability of CM is subverted, leading to the rupture of adjacent extracellular matrix, thus, increasing the tumoral dissemination, mainly through greater release of MMP-9[4].

Immunosuppression is another basic finding in the tumor microenvironment. Although the immunological vigilance occurs in the initial stages of tumorigenesis, the tumor establishment first induces immune tolerance. An absolute suppression of the immune response is generated in the tumoral microenvironment only in late stages of the tumor[23]. The CM have been identified as having a critical role in the suppression of immune responses[23]. The histamine released by the CM can cause the tumor cells to proliferate through H1 receptors and suppress the immune response through H2 receptors[6]. SCF (stem cell factor)-activated CM accentuate the tumoral immunosuppression through the release of adenosine, which inhibits the production of interferon (IFN)-γ and IL-2 by $TCD4^+$ cells and the increase of T regulatory (Treg) cells, which release IL-10, a cytokine with immunosuppressant effect[23,24].

Mutations in the tumoral suppressor, the colon adenomatous polyposis (APC) gene, are required to initiate hereditary or sporadic colorectal cancers. However, angiogenesis and tissue remodeling are required for the tumoral expansion[19].

The bowel, just as other mucosae exposed to the external environment, is an area where inflammation and cancer are closely linked. Bacterial infections, exposure to toxic molecules that damage the epithelial barrier, genetic predisposition and increased immune reactivity can promote chronic colitis, which induces cellular proliferation, stromal remodeling, neoangiogenesis and suppression of the adaptive antitumor immune response[25].

In the bowel, the CM play an important role in different processes, including cleaning of enteric pathogens, allergy to food, visceral hypersensitivity and intestinal cancer[22].

CM in the human bowel are the greatest source of tumoral necrosis factor (TNF)-α of the gastrointestinal tract[26]. The TNF is required for the growth of adenoma, the colorectal cancer precursor lesion. Thus, the TNF released by the CM can act in an autocrine manner. In the absence of CM, the genetically altered epithelium is not able to develop into a complete tumor[13]. In this study, most cases (89.2%) presented concentration of mast cells in intestinal adenomas of up to 5 CM/10 HPF, with 50% of them not presenting CM in the studied material. Then, no association of the MC was observed with the patients' age or gender, nor with the histological type, size and cellular atypia of the adenomas, nor with the presence of associated lesions. The sample evaluated in this study presented predominance of tubulovillous and tubular adenomas, of less than 2 cm and with mild cellular atypia, which would tend to have a lower concentration of CM, for presenting lower risk of developing into an adenocarcinoma. Perhaps the small number of villous adenomas, adenomas of more than 3 cm and adenomas with severe cellular atypia influenced the non association of risk criteria for malignancy of adenomas with MC.

CONCLUSION

This study did not show any association between the MC and the histological type, size of presence of cellular atypia in intestinal adenomas, nor any association with the presence of adenocarcinoma in other intestinal areas.

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