CLINIC RESEARCH

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Mast Cell Density in Hyperplastic Gastric Polyps: Correlations with Polypogenesis and Metaplasia

Hiperplastik Gastrik Poliplerde Mast Hücre Dansitesi: Polip Oluşumu ve Metaplazi ile Korelasyonu

ABSTRACT

Objective

Mast cells play pivotal roles in tumorigenesis dynamics, yet the specific factors driving hyperplastic gastric polyp formation remain unclear. This study aims to elucidate this gap by examining mast cell quantities in incidental gastric polyps, with a specific focus on hyperplastic lesions, and exploring their correlation with polypogenesis and metaplasia.

Material and Methods

Forty-five endoscopy specimens exhibiting anterior non-atrophic chronic inactive gastritis (2014-2023) were examined. Following histological evaluations, the cases were classified into three groups: hyperplastic gastric polyps with or without intestinal metaplasia, and chronic inactive gastritis as the control. Mast cell density per unit area was assessed from toluidine blue-stained sections. Polyp diameter and demographic information were also recorded for statistical analysis.

Results

The average ages of patients with hyperplastic polyps, metaplasia, and gastritis were 51.2±12.84, 55.93±13.58, and 56.2±14.68, respectively ($p>0.05$). In each group, the proportion of women was higher. Mast cell density, which varied within each group, did not show a statistically significant difference ($p>0.05$). The average polyp diameters for the metaplasia and hyperplastic polyp groups were 0.26 and 0.30 mm, respectively ($p>0.05$). There was no correlation between mast cell density and polyp diameter ($p>0.05$).

Conclusions

Intestinal metaplasia did not significantly influence mast cell density in non-dysplastic, low-malignant gastric polyps. Mast cell density and diameter in hyperplastic gastric polyps of 1 cm or smaller showed no correlation. Overall, non-cancerous gastric polypogenesis and mast cell count lack a unidirectional relationship.

Key Words

Gastritis, Mast Cells, Polyps, Stomach Disease

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ÖZ

Amaç

Mast hücreleri tümör gelişimin dinamiklerinde önemli roller oynamaktadır, ancak hiperplastik gastrik polip oluşumunu yönlendiren spesifik faktörler net değildir. Çalışma, bu boşluğu açıklığa kavuşturmak amacıyla rastlantısal gastrik poliplerde mast hücre miktarlarını inceleyerek, özellikle hiperplastik lezyonlara odaklanarak, polip oluşumu ve metaplazi ile korelasyonlarını araştırmayı amaçlamaktadır.

Gereç ve Yöntemler

2014-2023 yıllarına ait antral non-atrofik kronik inaktif gastrit gösteren 45 endoskopik örnek incelendi. Histolojik değerlendirmelerin ardından, vakalar intestinal metaplazisi olan ve olmayan hiperplastik gastrik polipler ve kontrol olarak kronik inaktif gastrit olacak şekilde üç gruba ayrıldı. Toluidin mavisi ile boyanmış kesitlerden birim alan başına mast hücresi yoğunluğu değerlendirildi. İstatistiksel analiz için polip çapı ve demografik bilgiler de kaydedildi.

Bulgular

Hiperplastik polip, metaplazi ve gastritli hastaların ortalama yaşları sırasıyla 51,2±12.84, 55,93±13.58 ve 56,2±14.68 idi (p>0,05). Her grupta kadın oranı daha yüksekti. Mast hücre yoğunluğu, her grup içinde varyasyon göstermekle birlikte, istatistiksel olarak anlamlı bir fark göstermedi (p>0.05). Metaplazi ve hiperplastik polip grupları için ortalama polip çapları sırasıyla 0,26 ve 0,30 mm idi (p>0,05). Mast hücre yoğunluğu ile polip çapı arasında bir korelasyon bulunmadı (p>0,05).

Sonuç

İntestinal metaplazi non-displastik, düşük malignite gösteren gastrik poliplerde mast hücre yoğunluğunu önemli ölçüde etkilemedi. Bir santimetre veya daha küçük hiperplastik gastrik poliplerde mast hücre yoğunluğu ve polip çapı arasında bir korelasyon bulunmadı. Sonuç olarak, kanseröz olmayan gastrik polip oluşumu ile mast hücre sayısı arasında tek yönlü bir ilişki bulunmamaktadır.

Anahtar Kelimeler

Gastrit, Mast Hücreleri, Polipler, Mide Hastalığı

INTRODUCTION

Mast cells play a significant role in tumor angiogenesis, tumor invasion, and the immunosuppressive tumor microenvironment (1). Notably, mast cells have been observed within adenomatous polyps of the colon, which are recognized as precancerous lesions. Intriguingly, reducing mast cell populations within these polyps can lead to remission (2). Furthermore, a recent discovery has linked the frequency of circulating mast cell progenitors to advanced stages of colorectal cancer (3). Despite the extensive research on mast cells in colorectal and other types of cancers, there is a noticeable gap in the literature regarding the quantification of mast cells in gastric polyps. Gastric polyps are commonly encountered as incidental findings during esophagogastroduodenoscopies, with their prevalence estimated to range from 0.5% to 23% of all upper gastrointestinal endoscopies (4). Gastric polyps are a diverse group, with fundic gland and hyperplastic polyps being the most prevalent (5-7). Hyperplastic polyps, characterized by their extended and irregular cystic expansions within the foveolar epithelium, are often associated with chronic gastritis (approximately 85% of cases) (7). While factors like heightened regenerative mechanisms and enterochromaffin-like cell accumulation may contribute to their formation, exact causes remain unclear (8, 9).

Hyperplastic polyps are generally considered to have a low risk of neoplastic transformation, with an average transformation rate of approximately 2.1% (10). Malignancy is correlated with polyp size, and the potential of malignant transformation is higher in hyperplastic polyps that exceed 1 cm in size (5, 8). In the context of this study, our primary aim is to investigate the correlation between mast cells and hyperplastic gastric polyps that develop on the basis of inactive chronic gastritis. To achieve this, we conducted a comprehensive histochemical quantification of mast cells per unit area within hyperplastic gastric polyps. Our approach involves quantifying mast cell density within these polyps and comparing it with cases of intestinal metaplasia or chronic inactive gastritis (those without polyps). Furthermore, we explored the potential correlation between mast cell density and the diameter of polyps, aiming to provide a deeper understanding of the intricate relationship between mast cell density and the process of gastric polyp formation.

MATERIALS and METHODS

Analysis of Patient Data, Inclusion, and Exclusion Criteria for Samples

In this retrospective analysis, we examined cases of chronic inactive gastritis from the archives of a Pathology Department, covering the years 2014-2023. Biopsies were taken from the antrum, with or without the corpus depending on the macroscopic appearance, for histopathological examination and assessment of Helicobacter pylori following polypectomy. Patients with non-antral gastritis, atrophic gastritis, active gastritis, or Helicobacter pylori-related gastritis were excluded. The resulting dataset included 45 cases, categorized into three groups (n=15): a control group (chronic inactive gastritis), a polyp group (hyperplastic polyps), and a metaplasia group (hyperplastic polyps with intestinal metaplasia).

We collected demographic data, including patient ages, genders, and polyp diameters, to identify potential patterns or associations. Ethical approval was obtained from the Bilecik University Ethics Committee (approval number: 2022/8-1), ensuring compliance with the Declaration of Helsinki's ethical guidelines.

Histopathological examination

Following endoscopic biopsy, tissues were fixed in 10% neutral buffered formaldehyde and underwent standard tissue processing procedures, including dehydration, clearing, and paraffin embedding. Tissue sections of 5-micrometer thickness were prepared and mounted on glass slides. After deparaffinization and dehydration with ethanol, the sections were rinsed with water. Rehydrated sections were stained with hematoxylin-eosin or 1% toluidine blue. Stained sections were then examined under a brightfield microscope (Olympus CX23), and relevant histological features were captured using an attached Olympus camera (Olympus EP50).

Histopathological Classification

The tissue samples obtained from gastritis cases were classified according to the Sydney classification system, which considers parameters such as localization, gastritis type (acute, chronic, or other), and grading based on factors like Helicobacter pylori presence, inflammation, atrophy, and intestinal metaplasia. Gastric atrophy and intestinal metaplasia (IM) were scored based on Sydney scoring (11). Gastric hyperplastic polyps are predominantly located in the antral region and commonly associated with chronic gastritis (7). Therefore, our study specifically recruited individuals diagnosed with non-atrophic (score 0), inactive chronic gastritis in the antral region.

Mast Cell Quantification

To quantify mast cells, we utilized toluidine blue staining. Due to the non-uniform distribution of mast cell infiltration, we identified areas with the highest mast cell concentration within each sample at 100x magnification. For mast cell density analysis, three regions were randomly selected from these identified areas at 400x magnification. The field of view of the microscope was calculated in mm^2, and mast cells per mm^2 were used for statistical comparisons between the groups (12, 13).

Statistical Analysis

For statistical analysis, we used a dedicated statistical software package. A significance level of $p<0.05$ was considered statistically significant. The Shapiro-Wilk test assessed the normal distribution of continuous variables. Non-parametric data underwent pairwise comparisons with the Kruskal-Wallis test, while parametric data were analyzed using One-way ANOVA followed by Tukey's multiple comparison test. Additionally, Spearman's test was used for correlation analysis.

RESULTS

Histopathological Results

Upon conducting histopathological examinations, the following observations were made:

In the control group, individuals with chronic inactive gastritis exhibited mild lymphocytic inflammatory cell infiltration, edema, and benign glandular structures in the lamina propria. Hyperplastic polyp samples showed dilated and tortuous gland structures on the surface, a decrease in glandular mucus load, and mild chronic inflammation in the lamina propria. In the metaplasia group of polyps, a distinct pattern of intestinal metaplasia was observed, including cystic, dilated, and tortuous gastric glands, presence of goblet cells, as well as mild edema, lymphocytes, and vascular structures in the lamina propria (Figure 1A). The Sydney scoring system was utilized to assess atrophy and metaplasia. All samples in the groups were categorized as score 0 for atrophy. Control and hyperplastic polyp samples were obtained from patients classified as score 0 for intestinal metaplasia. The metaplasia group primarily comprised low-grade metaplasia, with 66.7% scoring 1 (+) and 26.7% scoring 2 (++) (Table I).

Number of Mast Cells per Square Millimeter

Notably, the differences in mast cell counts per square millimeter were not statistically significant across the groups ($p>0.05$). It's crucial to highlight that there was variation in mast cell counts within each group. The control group displayed an average cell count of 138.74±40.89, the hyperplastic polyp group had 69.60±16.90, and the hyperplastic polyp + metaplasia group had 48.46±18.97 mast cells per square millimeter. In the benign intratumoral area, although there is a tendency of decreased mast cell count from control to metaplasia, no significant difference could be found due to high variability. Additionally, the medians of the groups were close to each other (Figure 1B).

Polyp Diameter Analysis

In terms of polyp diameter, no significant differences were observed between the hyperplastic polyp and metaplasia groups ($p>0,05$). Mean polyp diameters were as follows in the hyperplastic polyp group 0.30±0.21 and the metaplasia group 0.26±0.22 (Table I).

Relationship Between Polyp Diameter and Mast Cell Density

After conducting a correlation analysis, it was established that there was no statistically significant association between polyp diameter and mast cell density ($p>0.05$) (Table I).

Analysis of Demographic Data

The average age of the patients did not reveal any statistically significant differences among the groups, with mean ages as follows: Control 51.2 ± 12.84, Hyperplastic Polyp 55.93 ± 13.58, Metaplasia 56.2 ± 14.68. It's also worth noting that there were more female patients than male patients in all groups (Control 66.7%, Hyperplastic Polyp 86.7%, Metaplasia 80.0 %) (Table I).

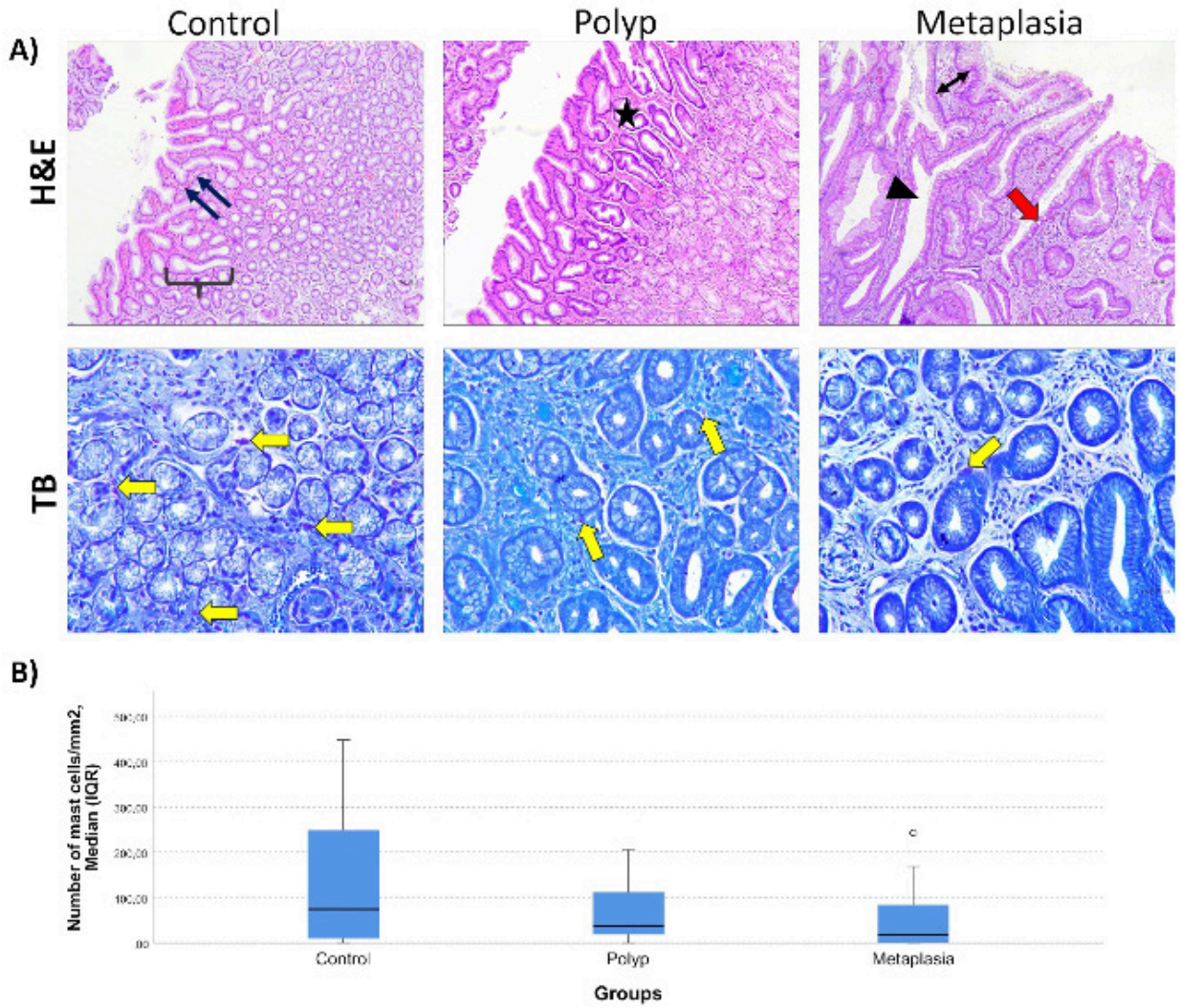

Figure 1. Histochemical staining of the groups and comparison of mast cell density. A) H&E: Hematoxylin-eosin, TB: Toluidine blue staining of gastric samples. In the control group, mild lymphocytic inflammatory cell infiltration and edema (double arrow), benign glandular structures (brackets). In the hyperplastic polyp group, dilated and tortuous gland structures (star). In the metaplasia group cystic, dilated, tortuous gastric glands (arrowhead) and goblet cells (thick red arrow) along with mild edema, lymphocytes, and vascular structures (two-headed arrow). Mast cells in histological sections (thick yellow arrow). Scale bars: H&E 100 µm, TB 30 µm. B) Boxplot graph of mast cell counts per mm2 (Median) for each group, IQR: interquartile range, Kruskal-Wallis test, p>0.05

Table I. Demographic and histopathologic characteristics of patients with statistical analysis.

	Control	Hyperplastic Polyp	Metaplasia	p value
Gender				
Male (%)	33.3%	13.3%	20.0%	
Female (%)	66.7%	86.7%	80.0%	
Total (%)	100%	100%	100%	
Intestinal Metaplasia				
0	100%	100%	0%	
+	0%	0%	66.7%	
++	0%	0%	26.7%	
+++	0%	0%	6.7%	
Age (Mean±SD)	51.2±12.84	55.93±13.58	56.2±14.68	0.538
Polyp diameter, mm (Mean±SD)		0.30±0.21	0.26±0.22	0.528
Correlation			**r**	**p value**
Polyp diameter	**Mast cell density**		-0.064	0.677

SD: Standart deviation, r: Correlation coefficient, +: Score 1, ++: Score 2, +++: Score 3. One-way ANOVA, Kruskal-Wallis test, Spearman test, p>0.05

DISCUSSION

Gastric hyperplastic polyps are among the most common types of gastric polyps, yet their pathogenesis is still not fully understood. In this study, we explored mast cell density dynamics during hyperplastic gastric polyp development, considering the presence or absence of intestinal metaplasia. Our approach was influenced by the findings of Gounaris et al. who showed that depleting mast cells could lead to the remission of precancerous adenomatous polyps (2). A histomorphological analysis by Amarapurkar et al. in 2021 found that gastric polyps were present in 4% of upper gastrointestinal endoscopies, with 29.4% of these being hyperplastic polyps (14). Gastric polyps are infrequently encountered in clinical settings and there is a notable gap in our understanding of mast cell distribution within this specific context.

In 2019, Eissmann et al. analyzed mast cell counts in gastric tissue and found no significant differences between gastritis and cases with intestinal metaplasia (13). In contrast, Piazuelo et al. demonstrated a notable increase in mast cell density, especially between intestinal metaplasia and dysplasia scores based on the gastric histopathological score (15). Notably, hyperplastic polyps are characterized as low-malignancy gastric polyps, and the metaplasia group primarily comprised low-grade metaplasia in the study (66.7% score 1, 26.7% score 2) (10). We observed that the presence of intestinal metaplasia did not significantly influence mast cell density in non-dysplastic, low-malignant gastric polyps.

Han et al. identified a higher risk of malignancy in hyperplastic polyps larger than 1 cm in diameter; however, it is important to point out that the polyps examined in our study were all 1 cm or smaller in diameter (16). In a study conducted by Lv et al., it was found that gastric tumors larger than 5 cm had higher per-field mast cell numbers. In the same study, mast cell counts in low-stage gastric cancers (Stage I and II) did not show significant differences compared to those in the non-tumoral area (17). Even though size has been identified as a potential determinant, it's interesting to note that there was no relationship in our study between the diameter of these low-malignancy polyps and the density of mast cells ($p>0.05$). This finding implies that mast cell density in this size range does not significantly alter in relation to the size of hyperplastic gastric polyps. Continuing in this vein, we noted that mast cell density did not exhibit significant differences between cases of gastritis and hyperplastic gastric polyps. Based on these results, we can infer that mast cell density might be more closely associated with dysplastic and malignant lesions than with low-malignant polyps, aligning with the data from existing literature.

The role of mast cells in tumors and inflammation is complex and multifaceted. Existing literature suggests that mast cells can play opposing functional roles in both the tumor microenvironment and inflammation (1, 18). In a 2020 study conducted by de los Rios et al., using toluidine blue, a statistically significant difference in mast cell numbers was observed between the metastatic and non-metastatic colon cancer groups (19). However, similar to our study, there was a substantial level of variation within these groups. An immunohistochemical examination revealed that this disparity could be attributed to tryptase-positive mast cells. In our study, it is worth noting that there were slightly more mast cells in our control group. Nevertheless, the absence of statistically significant unidirectional changes can be attributed to the variation within the groups. The duality of mast cells may provide an explanation for the observed differences in cell distribution within the study groups.

In a study conducted by da Silva et al. in 2019, the mean age of individuals with chronic inactive gastritis was reported to be 49.0±17.3 years, with a 75% female ratio (20). Additionally, the literature suggests that individuals with hyperplastic gastric polyps tend to fall within the age range of 65 to 75 years, with a higher incidence among women (8). The demographic parameters observed in our study closely align with the findings in the relevant literature, despite the unique focus on mast cell density. Nonetheless, despite its originality, our study is restricted by its retrospective single-center design. The sample size remained limited due to the low overall incidence of incidental hyperplastic gastric polyps.

CONCLUSION

In conclusion, we found that intestinal metaplasia did not significantly influence mast cell density in non-dysplastic, low-malignant gastric polyps. Additionally, there was no significant correlation between polyp size and mast cell density within the studied size range. Our findings suggest that mast cell density may be more closely associated with dysplastic and malignant lesions rather than low-malignant polyps.

Ethics Committee Approval

This research complies with all the relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the Medical Faculty Ethical Committee, Bilecik Şeyh Edebali University (approval number: 2022/8-1).

Informed Consent

All the participants' rights were protected according to the Helsinki Declaration. Written informed consents were not obtained because of retrospective study design.

Author Contributions

Concept – D.F.; Design – D.F.; Resources - D.F., Ö.T.; Materials - D.F., Ö.T.; Data Collection and/or Processing - D.F., Ö.T.; Analysis and/ or Interpretation – D.F., E.Ş.; Literature Search - D.F.; Writing Manuscript - D.F., E.Ş., Ö.T.

Conflict of Interest

The authors have no conflict of interest to declare.

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