Original Paper

Histological Profile of Chronic Inflammation in Gastric Adenocarcinomas

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ABSTRACT: Gastric adenocarcinomas (GAC) constitute a major problem in clinical practice, for which late diagnosis and heterogeneity contribute greatly to maintaining epidemiological mortality rates. One of the recent approaches related to the prognosis and therapy of GAC refers to the activation of an effective antitumor immune response, which is not fully known in terms of cellular substrate or interaction with the tumor parenchyma. In this study, we analyzed the chronic mononuclear inflammatory infiltrate in 125 primitive GAC, in relation to the classic histological parameters of tumor aggressiveness, based on a composite histological score (CHS) that took into account the distribution and density of the elements tracked. The results indicated significant differences, most GAC having a predominantly peritumoral infiltrate except for poorly cohesive signet ring cell carcinomas (PC-SRC) in which intratumoral elements predominated. Density and CHS were higher in PC-SRC GAC and MX-GAC (mixed), in high-grade, stage III tumors with vascular invasion. Although the pattern or density of inflammation in GAC does not necessarily reflect the orientation or antitumor efficacy of immune elements, the data obtained may be useful for the development of histological criteria to assist in stratifying patients for therapy.

KEYWORDS: *Gastric adenocarcinoma, inflammation, histological score.*

Introduction

Despite the improvement in the epidemiological trend in the last 30 years, gastric cancer remains in fifth place in terms of incidence and mortality today and continues to represent a challenge in oncological pathology [1].

The biological aggressiveness of gastric adenocarcinomas (GAC), which are the most common forms of gastric cancer, is reflected in the relatively rapid evolution of tumors and death rates worldwide, reflected in all age groups [2,3].

Also, late diagnosis and tumor heterogeneity seem to be directly related to the reserved prognosis of lesions [4].

However, in the last decade, targeted therapies on the mechanisms of tumor development have been approached and implemented, including for advanced forms of GAC, some of them addressing the host immune response in the sense of stimulating and inhibiting immune checkpoints [5].

In this context, immune elements in the tumor microenvironment or in contact with the tumor advancing edge appear to play an important role in regulating tumor growth, both directly and through the release of cytokine mediators, proteinases and membrane-perforating agents through autocrine/paracrine mechanisms [6-8].

Studies investigating the pattern and distribution of immune inflammatory elements in GAC, in relation to histological prognostic parameters are rare and with relatively variable results. While some studies have indicated the association of immune inflammatory infiltrate with a better prognosis in GAC and in carcinomas in general, others have not identified this aspect [9-11].

Also, some authors have indicated the association of certain types of immune elements with a better physiological and therapeutic antitumor response, such as regulatory T lymphocytes or dendritic cells, some of which also have a preventive role for tumor initiation [10].

Along with chronic mononuclear elements, in GAC there is frequently a neutrophilic inflammatory substrate with dual anti- and protumorigenic effect, located both peritumorally and intratumorally [12], which must be taken into account in the sense of the existence of signaling mechanisms between the two inflammatory populations and through the secretion products. Thus, the mixed intratumoral and peritumoral inflammatory microenvironment, through composition, distribution and quantity, can influence tumor behavior, response to therapeutic agents and tumor development mechanisms, representing an area of interest, in the context of the need to improve the prognosis of GAC.

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Objective

In this study, we investigated the density and pattern of chronic inflammation in gastric adenocarcinomas in relation to tumor prognostic parameters, which may have an impact on the prognostic criteria of lesions.

Methods

In this study, 125 gastric adenocarcinomas (GAC) were analyzed, diagnosed within the Pathology Department of the Craiova County Emergency Clinical Hospital between 2019-2023, in patients operated on in the Surgical Departments of the same hospital.

The biological material was represented by total gastrectomy specimens, which were fixed in 10% neutral formalin for 24-36 hours and processed by the classical technique of paraffin embedding and standard staining with Hematoxylin-Eosin. The diagnosis of tumors was made based on the criteria developed by the World Health Organization for GAC [13].

The study aimed to quantify chronic inflammation associated with GAC in relation to the main prognostic parameters represented by tumor type, tumor grade and stage, and lymphovascular invasion (LVI).

For the analysis of the associated chronic inflammatory infiltrate, descriptive evaluation was used, in the sense of the predominance of inflammatory elements at the intratumoral, peritumoral compartments or with balanced distribution (Mixed). The intratumoral compartment was designated any area within the tumor that was adjacent to other tumor areas at least at a distance of 200x, while the peritumoral compartment was designated any area outside the tumor at a distance of maximum 200x.

For quantification, the most representative sections for the analyzed GAC were selected, avoiding areas of necrosis and normal submucosal follicular structures. Only chronic mononuclear inflammatory elements with a role in the immune response (lymphocytes, plasma cells, macrophages, histiocytes) were quantified, excluding from the evaluation areas with leukocyte infiltration present especially on the surface of the epithelium in the case of ulcerations or in areas of tumor necrosis.

For qualitative and quantitative evaluation we used two scores, respectively the pattern score (PS) and the density score (DS). PS was designated as follows: score 1 (focal), score 2 (diffuse compact), score 3 (diffuse with lymphoid follicles with/without germinal centers), taking into account the areas with the highest inflammatory infiltration.

DS was designated: score 1 (weak- under 100 inflammatory elements/400x), score 2 (moderate- 100-200 inflammatory elements/400x), score 3 (increased >200 inflammatory elements/400x), for each case the richest 10 microscopic fields of 400x were analyzed, subsequently calculating the arithmetic mean. By multiplying the two scores (PS and DS) the composite histological score (CHS) was obtained, for which values 1-3 were considered low, and values 4-9 high.

Only cases without primary processing defects, without oncological treatments, anti-inflammatory or local or systemic immune status modulators were included in the study.

The acquisition and evaluation of the inflammatory infiltrate was performed with the Nikon Eclipse Ei-R microscope, with the KoPa Pro camera and software, by two pathologists, who in case of disagreement resumed the quantification until consensus was reached.

Statistical analysis used SPSS 12 (Statistical Package for the Social Sciences) and the chi-square (χ^2)/Fisher comparison tests, values being considered significant for $p<0.05$ and at the limit of significance for $p<0.1$.

Results

In this study, the 125 cases of gastric adenocarcinomas (GAC) belonged to a group of patients with a mean age of 66.6±11.2 years, tumors with tubular histological pattern (TGUC) being the most frequent (52%), followed by those with discohesive pattern (not otherwise specified-PC-NOS and signet ring cells-PC-SRC) (25.6%), mixed (MX-GAC) and mucinous (MC-GAC) (12% and 10.4%).

GAC were more frequently high-grade (50.4%), in tumor stage III (56%) and with lymphovascular invasion (LVI) present (60%). (Table 1).

Table 1. Distribution of gastric adenocarcinomas in relation to the histopathological parameters analyzed.

HP Parameter	No. cases
Histopathological type	TGAC=65
	PC-NOS GAC=11
	PC-SRC GAC=21
	MX-GAC=15
	MC-GAC=13
Tumor grade	Low grade=62
	High grade=63
Tumor stage	I=7

	II=40
	III=70
	IV=8
Lymphovascular invasion (LVI)	Present=75
	Absent=0

TGAC: Tubular gastric adenocarcinoma;
PC-NOS GAC: Poorly cohesive-no other specifications gastric adenocarcinoma;
PC-SRC GAC: Poorly cohesive-signet ring cells gastric adenocarcinoma;
MX-GAC: Mixed gastric adenocarcinoma;
MC-GAC: Mucinous gastric adenocarcinoma.

For the entire analyzed group, inflammatory elements predominated in the peritumoral compartment (56.8%), with a both pattern score (PS) and density score (DS) score of 1.9 and a composite histological score (CHS) of 3.7.

In relation to the tumor type, inflammatory elements predominated at the peritumoral level, except for PC-SRC GAC in which they were mostly intratumoral. Mixed distribution was present in 35 cases (28%), especially in the case of TGAC and PC-SRC GAC, and the differences observed were statistically significant (Table 2, Figure 1A).

Although inflammation predominated peritumorally regardless of the degree of differentiation, almost half of the low-grade GAC showed mixed or intratumoral predominance of immune elements, which was at the limit of statistical significance (Table 2, Figure 1B).

Also, although the intratumoral and mixed response was more consistent in the case of tumor stages II/III, compared to I/IV, the differences were not significant in relation to tumor progression (Table 2, Figure 1C).

Also, inflammation predominated peritumorally in relation to LVI, with non-significant aspects, but in the absence of GAC invasion with intratumoral or mixed inflammatory infiltrate predominated (Table 2, Figure 1D).

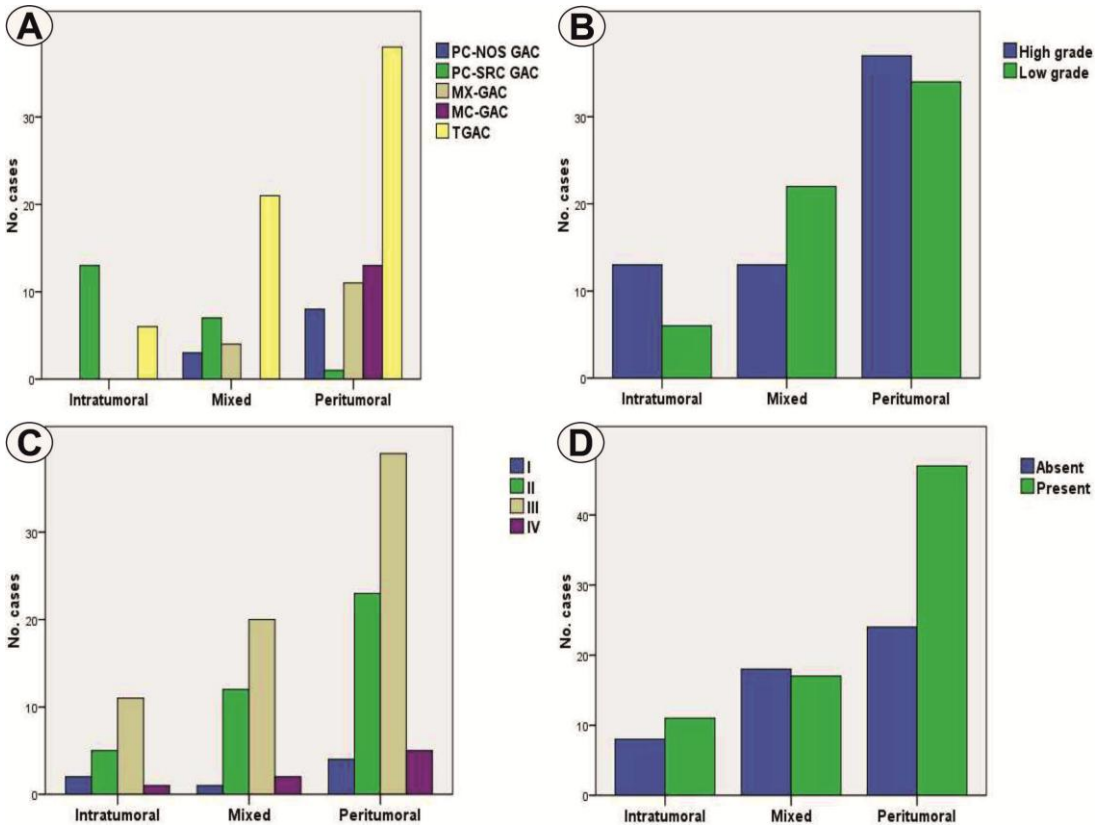

Figure 1. Distribution of inflammatory elements in tumor compartments in relation to tumor type (A), tumor grade (B), tumor stage (C) and lymphovascular invasion (D).

Regarding the value of the scores analyzed in this study, we found some differences. The pattern scores (PS) indicated the predominance of the diffuse compact in TGAC, MX-GAC and PC-NOS GAC, of the one with lymphoid follicle formation in PC-SRC GAC and of the focal pattern in MC-GAC.

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Table 2. Distribution, pattern and density of chronic inflammation in gastric adenocarcinomas.

Parameters/ p value		Distribution predominance	p value (χ^2/ Fisher tests)	Composite histological score (CHS)	p value (χ^2/ Fisher tests)
Histopathological type	TGAC	Peritumoral	<0.001	3.2	<0.001
	PC-NOS GAC	Peritumoral		3.0	
	PC-SRC GAC	Intratumoral		6.1	
	MX-GAC	Peritumoral		4.6	
	MC-GAC	Peritumoral		1.8	
Tumor grade	Low grade	Peritumoral	0.082	2.7	<0.001
	High grade	Peritumoral		4.6	
Tumor stage	I	Peritumoral	0.946	2.4	0.021
	II	Peritumoral		3.6	
	III	Peritumoral		3.9	
	IV	Peritumoral		3.7	
Lymphovascular invasion (LVI)	Present	Peritumoral	0.215	4.2	0.001
	Absent	Peritumoral		3.0	

TGAC: Tubular gastric adenocarcinoma; PC-NOS GAC: Poorly cohesive–no other specifications gastric adenocarcinoma; PC-SRC GAC: Poorly cohesive-signet ring cells gastric adenocarcinoma; MX-GAC: Mixed gastric adenocarcinoma; MC-GAC: Mucinous gastric adenocarcinoma.

The density score (DS) was predominantly moderate, except for MC-GAC where the density was weak; the increased density was more consistent in PC-SRC GAC. Thus, in terms of tumor type, the highest CHS values were recorded in PC-SRC GAC and MX-GAC (6.1 and 4.6), followed by TGAC and PC-NOC GAC (3.2 and 3.0) and MC-GAC (1.8) (Table 2, Figure 2A-D).

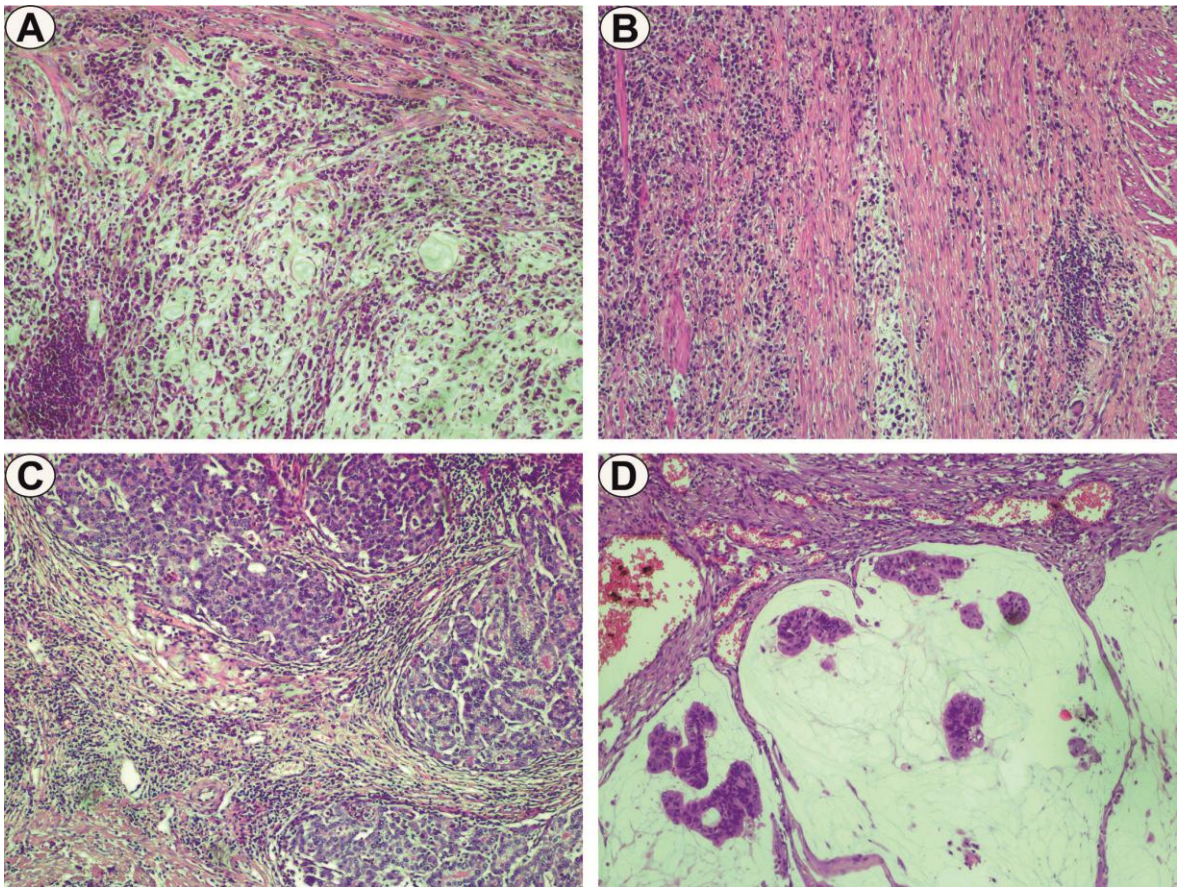

Figure 2. Inflammatory immune infiltrate in GAC, HE staining, x100.
A. Intratumoral compartment, follicular pattern, increased density, PC-SRC GAC;
B. Peritumoral compartment, diffuse compact pattern, moderate density, PC-NOS GAC;
C. Peritumoral compartment, diffuse compact pattern, moderate density, TGAC;
D. Peritumoral compartment, focal pattern, weak density, MC-GAC.

Regarding tumor grade, although PS indicated a predominance of diffuse compact infiltrate in most GACs, the focal pattern was more frequent in low-grade GACs and that with lymphoid follicles in high-grade GACs.

Also, DS indicated a moderate density in most cases, but with a higher frequency of weak density in low-grade GACs and increased in high-grade ones. Mean CHS were higher in high-grade tumors compared to low-grade ones (4.6 and 2.7) (Table 2).

In relation to tumor stage, the most frequent PS were those with diffuse compact infiltrate, followed by focal and lymphoid follicles. DS indicated an increase in the density of inflammatory elements in stages II/III and a decrease in stage I/IV. Thus, CHS indicated the highest value in stage III (3.9) and the lowest in stage I (2.7) (Table 2).

In the case of LVI, diffuse compact PS predominated, followed by those with lymphoid follicles, more frequent than in the case of GAC without invasion. Also, although moderate DS predominated in both categories, those with increased density were more frequent in the case of invasion. Final mean CHS were higher in the case of GAC with LVI compared to those that did not present invasion (4.2 and 3.0) (Table 2).

Statistical analysis indicated significantly higher differences in CHS in PC-SRC GAC and MX-GAC ($p<0.001$, χ^2 test), high-grade ($p<0.001$, Fisher test), stage III ($p=0.021$, χ^2 test) and with LVI present ($p=0.001$, Fisher test) (Table 2, Figure 3A-D).

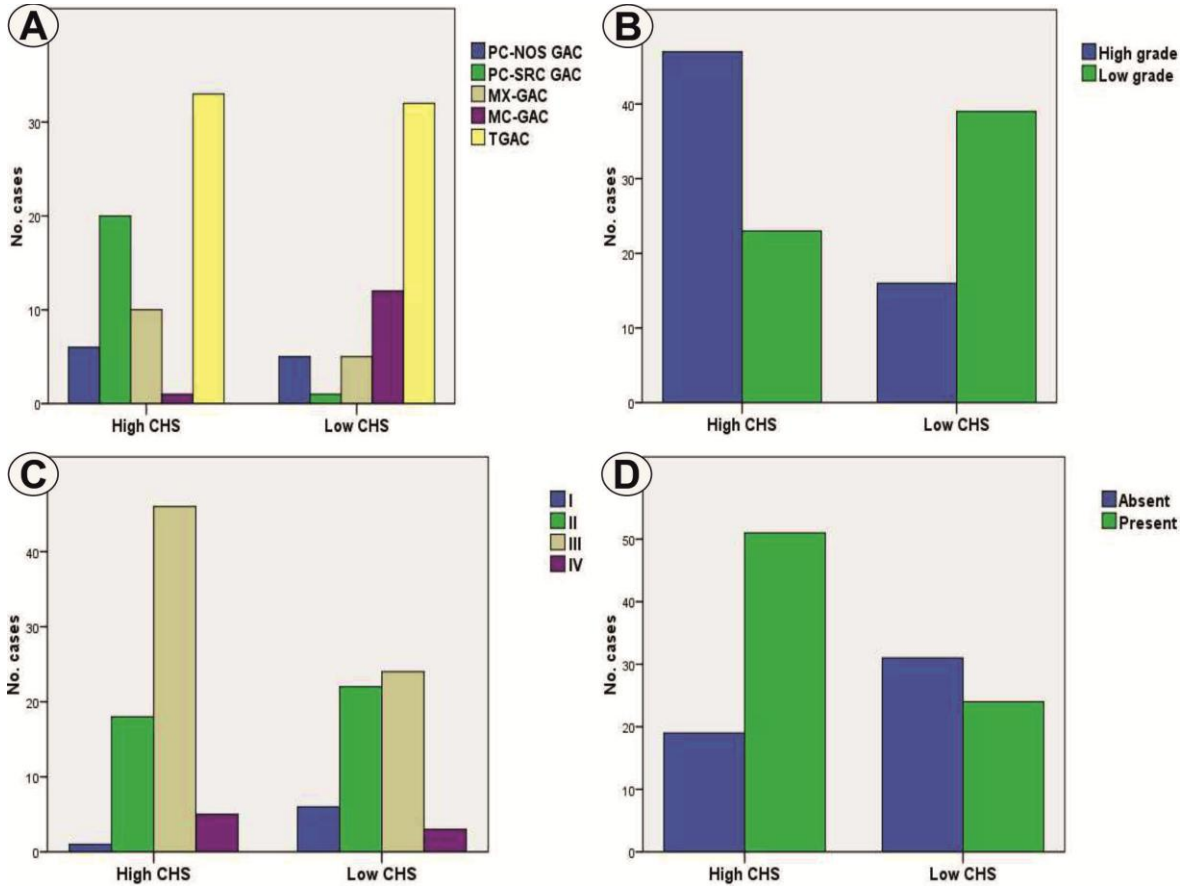

Figure 3. Distribution of cases according to composite histological score (CHS) and tumor type (A), tumor grade (B), tumor stage (C) and lymphovascular invasion (D).

Discussion

The frequent association of GAC with Helicobacter pylori, which induces a mixed inflammatory response associated with the initiation of metaplastic, dysplastic and cancerous transformation of epithelial cells, designates a particular model of carcinogenesis, which is incompletely elucidated and which may have an impact on the prognosis of the lesions [14].

In this study, we found a distribution of mononuclear inflammatory elements, which presented variable patterns, respectively focal, diffuse or with the formation of lymphoid follicles and germinal centers, along with

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different degrees of their density both intratumorally and peritumorally. Similar studies investigating GAC-associated lymphocytes indicated that both the density and the localization of immune elements are relevant in these tumors, suggesting a differentiated therapeutic management [15,16].

In our study, most GAC, except PC-SRC, presented a predominantly peritumoral distribution of inflammatory elements, with a mixed distribution being consistent in TGAC and an intratumoral/mixed distribution in low-grade GAC and those in stages II/III. Most studies have investigated the distribution of inflammatory elements using immunomarkers.

Thus, in the study conducted by Soeratram TTD et al. the authors indicated a predominantly peritumoral distribution of T lymphocytes in intestinal-type gastric carcinomas and intratumoral in the case of diffuse and mixed types [16].

The distribution of immune elements also seems significant in other types of carcinomas, such as pancreatic ductal adenocarcinoma where only intratumoral lymphocytes are associated with a better prognosis, while the peritumoral compartment has no relationship with the survival rate [17].

Also, in breast carcinomas, tumor-infiltrating lymphocytes (TILs), which constitute a histological parameter that is reported, although correlations of intra- or peritumoral distribution of these elements with clinical parameters are not described, the peritumoral compartment seems to be linked to better survival and response to treatment, especially in triple-negative lesions [18].

However, massive tumor lymphocytic infiltration is not always associated with a good response to immunotherapy or chemotherapy, as is the case in ovarian carcinomas [19].

Intra- or peritumoral inflammatory response also appears to be important in rectal carcinomas, since its absence in both compartments is associated with a poor prognosis [19].

In contrast, in clear cell renal cell carcinoma, immune-excluded tumors have a higher survival rate and reduced metastasis, and peritumoral infiltration is associated with a poor prognosis [20].

As such, the distribution patterns of immune elements and their significance are highly variable in carcinomas, suggesting that this histological parameter should be interpreted in the context of location and probably other clinical, histological, and molecular features.

The density of immune elements and composite histology scores obtained in this study were generally moderate, but significantly higher in PC-SRC GAC and MX-GAC, in high-grade, stage II/III and vascular invasion. There are studies in the literature that have indicated the association of an increased density of T lymphocytes in the tumor compartments of GAC with a longer survival, lower stage and less lymph node metastasis [16].

In a recent meta-analysis, Cao X et al. indicated a higher survival and a better prognosis in the case of an increased density of infiltrating lymphocytes intratumorally and in the resection margins of GAC, but subject to incomplete or non-existent results to support the general aspect described [21].

In other locations of carcinomas, although the increased density of immune elements seems to be associated with a better prognosis, the aspects are not generally valid [17,20].

On the other hand, there are numerous studies that have indicated the dual anti- and pro-tumor role of inflammatory elements in general and immune elements in particular.

Thus, lymphocytes have an anti-tumor cytolytic role, but by releasing proteases and other pro-tumor growth factors they can also favor the growth and development of cancers [8,22].

Also, due to functional plasticity, macrophages have a dual anti- and pro-tumor role, with classical or alternative activation, the latter being linked to the inhibition of the immune response and tumor promotion [23].

Last but not least, neutrophils that can participate in a chronic inflammatory climate of GAC play a dual role in tumor evolution [12].

Moreover, the neutrophil/lymphocyte ratio is an independent prognostic factor in gastric cancer, the consequences of neutrophilia and lymphopenia being represented by tumor development and progression, since the majority role of neutrophils is pro-tumor, and that of lymphocytes is the opposite [22].

At the same time, the presence of tertiary lymphoid structures, such as lymphoid aggregates with or without germinal centers, containing T and B lymphocytes, macrophages, and dendritic cells, which we also identified in this study, have an important

role in antitumor immunity, and at least theoretically should be associated with an efficient and superior immune response to other forms of mononuclear infiltration [24].

However, the immune response seems to be dependent on other histological features of GAC, suggesting the possibility of a bidirectional modulation of the immune and epithelial phenotype.

The limits of this study are further related to tumor heterogeneity, which is relatively difficult to quantify at the level of the entire tumor, to the histological identification of different types of immune elements, and to the composition of tertiary lymphoid structures.

In this context, as well as the data obtained and the results in the literature, it can be said that the density and pattern of the immune infiltrate are not absolutely related to the response of GAC to therapy and the prognosis of the patients. It is clear that the success of the effective activation of the immune system is dependent on the status of PD-L1 (Programmed Death-Ligand 1), Her2/neu (Human Epidermal Growth Factor Receptor 2), microsatellite instability/deficient mismatch repair (dMMR) and not only on the pattern or density of infiltration with tumor immune elements. Thus, with the individual personalized therapy of GAC remaining a basic principle, in-depth studies are needed on the histological and molecular significance of the immune infiltrate, which can establish the criteria for selecting tumors for effective therapy, also dependent on the native tumor histological aspects.

Conclusions

The immune inflammatory infiltrate in both tumor compartments of GAC shows differences in distribution, pattern and density, which may form the basis of future criteria for stratifying patient prognosis.

In this study, histological parameters of tumor aggressiveness were associated with a high score of infiltration with immune elements.

The relationship of inflammatory infiltrate with histological parameters of GAC, should be interpreted together with the molecular immunoprofile for targeted therapy and may refine the decision to interfere with different mechanisms of tumor progression.

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None to declare.

Author Contributions

Conceptualization, A.E.S. and R.A.P-I.; Methodology, R.A.P-I., A.M.B. and M.M.F; Investigation, R.A.P-I. and A.M.B.; Data analysis, A.E.S, R.A.P-I. and M.M.F.; Manuscript writing and initial draft preparation, R.A.P-I.; Manuscript review and editing R.A.P-I., A.M.B. and M.M.F.; Supervision, A.E.S. All authors read and approved the final manuscript

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Conflicts of interest

The authors declare no competing interests.

Institutional Review Board

The study was conducted according to the guidelines of the Declaration of Helsinki; the study and the protocols utilized therein were approved by the Ethics Committee of University of Medicine and Pharmacy of Craiova (11/16.03.2020).

Consent Statement

Not applicable for a retrospective descriptive study.

Data availability

All data presented in the manuscript are available from the authors upon request.

References

1. Inoue M. Epidemiology of Gastric Cancer-Changing Trends and Global Disparities. Cancers (Basel), 2024, 16(17):2948.
2. Liu L, Deng W. Gastric Cancer: Innovations in Screening, Diagnosis and Treatment. J Pers Med, 2023, 13(1):127.
3. Carcas LP. Gastric cancer review. J Carcinog, 2014, 13:14.
4. Sexton RE, Hallak MNA, Uddin MH, Diab M, Azmi AS. Gastric Cancer Heterogeneity and Clinical Outcomes. Technol Cancer Res Treat, 2020, 19:1533033820935477.
5. Sundar R, Nakayama I, Markar SR, Shitara K, van Laarhoven HWM, Janjigian YY, Smyth EC. Gastric cancer. Lancet. 2025, 405(10494):2087-2102.
6. Hsieh HL, Tsai MM. Tumor progression-dependent angiogenesis in gastric cancer and its potential application. World J Gastrointest Oncol, 2019, 11(9):686-704.
7. Mbeunkui F, Johann DJ Jr. Cancer and the tumor microenvironment: a review of an essential relationship. Cancer Chemother Pharmacol, 2009, 63(4):571-582.
8. Coussens LM, Werb Z. Inflammation and cancer. Nature, 2002, 420(6917):860-867.

9. Wakatsuki K, Sho M, Yamato I, Takayama T, Matsumoto S, Tanaka T, Migita K, Ito M, Hotta K, Nakajima Y. Clinical impact of tumor-infiltrating CD45RO$^+$ memory T cells on human gastric cancer. Oncol Rep, 2013, 29(5):1756-1762.
10. Lee HE, Chae SW, Lee YJ, Kim MA, Lee HS, Lee BL, Kim WH. Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer. Br J Cancer, 2008, 99(10):1704-1711.
11. Fukuda K, Tsujitani S, Maeta Y, Yamaguchi K, Ikeguchi M, Kaibara N. The expression of RCAS1 and tumor infiltrating lymphocytes in patients with T3 gastric carcinoma. Gastric Cancer, 2002, 5(4):220-227.
12. Fridlender ZG, Albelda SM. Tumor-associated neutrophils: friend or foe? Carcinogenesis, 2012, 33(5):949-955.
13. Fukuyama M, Rugge M, Washington MK. Tumors of the stomach. In: WHO Classification of Tumours Editorial Board (Eds): Digestive system tumors. WHO Classification of Tumours, 5th Edition, International Agency for Research on Cancer, 5th ed, Lyon, 2019, 59-110.
14. Kang BW, Seo AN, Yoon S, Bae HI, Jeon SW, Kwon OK, Chung HY, Yu W, Kang H, Kim JG. Prognostic value of tumor-infiltrating lymphocytes in Epstein-Barr virus-associated gastric cancer. Ann Oncol, 2016, 27(3):494-501.
15. Kim HI, Kim SY, Yu JE, Shin SJ, Roh YH, Cheong JH, Hyung WJ, Noh SH, Park CG, Lee HJ. Contrasting Prognostic Effects of Tumor-Infiltrating Lymphocyte Density in Cardia and Non-cardia Gastric Adenocarcinomas. J Gastric Cancer, 2020, 20(2):190-201.
16. Soeratram TTD, Biesma HD, Egthuijsen JMP, Meershoek-Klein Kranenbarg E, Hartgrink HH, van de Velde CJH, Mookhoek A, van Dijk E, Kim Y, Ylstra B, van Laarhoven HWM, van Grieken NCT. Prognostic Value of T-Cell Density in the Tumor Center and Outer Margins in Gastric Cancer. Mod Pathol, 2023, 36(9):100218.
17. Pyo JS, Son BK, Lee HY, Oh IH, Chung KH. Prognostic Implications of Intratumoral and Peritumoral Infiltrating Lymphocytes in Pancreatic Ductal Adenocarcinoma. Curr Oncol, 2021, 28(6):4367-4376.
18. Della Mora A, Bastianelli L, Pistelli M, Santinelli A, Cantini L, Doria A, Merloni F, Lucarelli A, Savini A, Maccaroni E, Ballatore Z, Pagliacci A, Berardi R. Stromal peritumoral and intratumoral infiltrating lymphocytes: how immunity influences prognosis in triple negative breast cancer. Annals Oncol, 2017, 28(6):vi31-vi32.
19. Finkelman BS, Zhang H, Hicks DG, Rimm DL, Turner BM. Tumor infiltrating lymphocytes in breast cancer: A narrative review with focus on analytic validity, clinical validity, and clinical utility. Hum Pathol, 2025, 162:105866.
20. Brück O, Lee MH, Turkki R, Uski I, Penttilä P, Paavolainen L, Kovanen P, Järvinen P, Bono P, Pellinen T, Mustjoki S, Kreutzman A. Spatial immunoprofiling of the intratumoral and peritumoral tissue of renal cell carcinoma patients. Mod Pathol, 2021, 34(12):2229-2241.
21. Cao X, Kang Y, Tai P, Zhang P, Lin X, Xu F, Nie Z, He B. Prognostic role of tumor-infiltrating lymphocytes in gastric cancer: A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol, 2025, 49(1):102510.
22. Szor DJ, Dias AR, Pereira MA, Ramos MFKP, Zilberstein B, Cecconello I, Ribeiro-Júnior U. Prognostic Role of Neutrophil/Lymphocyte Ratio in Resected Gastric Cancer: A Systematic Review and Meta-analysis. Clinics (Sao Paulo), 2018, 73:e360.
23. Gambardella V, Castillo J, Tarazona N, Gimeno-Valiente F, Martínez-Ciarpaglini C, Cabeza-Segura M, Roselló S, Roda D, Huerta M, Cervantes A, Fleitas T. The role of tumor-associated macrophages in gastric cancer development and their potential as a therapeutic target. Cancer Treat Rev, 2020, 86:102015.
24. Wang Q, Shen X, An R, Bai J, Dong J, Cai H, Zhu H, Zhong W, Chen W, Liu A, Du J. Peritumoral tertiary lymphoid structure and tumor stroma percentage predict the prognosis of patients with non-metastatic colorectal cancer. Front Immunol, 2022, 13:962056.

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