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Immunoexpression of E-cadherin, P-cadherin and fibronectin in gastric carcinomas

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Abstract

One of the mechanisms involved in gastric carcinomas progression is represented by epithelial–mesenchymal transition (EMT), a complex process during which tumor cells acquire an invasive and migratory mesenchymal phenotype. In this study, we analyzed the immunoexpression of E-cadherin, P-cadherin and fibronectin in 50 gastric carcinomas, in relation with the tumoral type, differentiation grade and lesions stage. The reactions presented variable patterns related to lesions stage. Membrane and cytoplasmic reactions were present in 62% of cases for E-cadherin and in 56% of cases for P-cadherin, being present only cytoplasmic in 34% of cases for fibronectin. The immunoexpression for E-cadherin and P-cadherin was superior in tubular gastric carcinomas, of low grade and early stage, while fibronectin expression was superior in discohesive or mixed gastric carcinomas, of high grade and in advanced stages. Negative E-/P-cadherin and positive fibronectin immunophenotype may be associated with aggressive gastric carcinomas and supports the EMT involvement in gastric carcinogenesis.

Keywords: gastric carcinoma, E-cadherin, P-cadherin, fibronectin.

Introduction

Epithelial–mesenchymal transition (EMT) represents a process during which epithelial cells loose their polarity and cell–cell adhesion and are subjected to a dramatic remodeling of the cytoskeleton [1, 2].

Concurrently with epithelial cells adhesion lose, cells undergone EMT acquire the expression of mesenchymal components and a migratory phenotype [2].

Recent studies indicated that aberrant activation of EMT plays a crucial role in genesis, invasion and metastasis of different tumors, including gastric cancer [3, 4].

EMT phenotype in gastric cancer seems to be correlated with advanced tumor stage and it is significantly correlated with unfavorable prognosis [5, 6]. Kim *et al.* found that in gastric cancer, EMT is associated with diffuse type, low grade of differentiation and unfavorable prognosis, suggesting that EMT inhibition could be a promising method in invasion and metastasis prevention [7].

Consequently, systematic exploration of EMT role in gastric cancer allows a deeper understanding of gastric cancer tumorigenesis and progression, which may be helpful for an early diagnosis and an efficient personalized treatment. In this study, we followed the E-cadherin, P-cadherin and fibronectin expression in 50 cases of gastric cancer in relation to different histopathological forms and tumor stages of lesions.

Materials and Methods

We investigated a number of 50 cases of gastric carcinomas from Surgery Clinics of the Emergency County Hospital of Craiova, Romania. Surgical excision specimens fixed in 10% buffered formalin were processed by paraffin embedding technique and stained with Hematoxylin–Eosin (HE). Lesions classification was performed according to *World Health Organization* (WHO) 2010 Criteria [8].

Subsequently, from the paraffin blocks we obtained serial sections, which were immunohistochemically processed by a detection system based on amplification polymer [polymer–Horseradish peroxidase (HRP) Histofine, Nichirei, Japan, ready-to-use, code 414151F]. Reactions visualizing was performed with 3,3'-Diaminobenzidine (DAB) chromogen (code 3467, Dako), for reactions validation being used positive and negative external controls (by omitting the primary antibody) (Table 1).

Examination of semicantitative expression of the analyzed markers was performed by an adapted system, awarded independently by two specialists, based on the staining intensity and positive cells percentage assessment. Score intensity was noted with 1 (low), 2 (moderate) and 3 (high), with a cutoff value of 5% for reactions positivity. The percentage of immunostained cells was marked with 1 (6–25% positive cells), 2 (26–50% positive cells), 3 (51–75% positive cells) and 4 (>75% positive cells). By multiplying the intensity and percentage scores, we were able to calculate the final staining score (FSS), considered low for values between 1–4 and high for values between 6–12.

For the statistical analysis, we used mean values and comparative tests [χ^2 (*chi*-square) and Pearson] in the

Statistical Package for the Social Sciences (SPSS) 10 automatic software. The study was approved by the local Ethics Committee (No. 201/October 24, 2017), and written informed consent was obtained from all the patients.

Table 1 – ***Used antibodies: clone, dilution, antigen retrieval and external control***

Antibody	Clone	Manufacturer	Dilution	Antigen retrieval	External control
E-cadherin	Mouse monoclonal NCH 38	DAKO	1:50	Microwaving in citrate buffer, pH 6	Mammary gland
P-cadherin	Rabbit polyclonal	Atlas Antibodies	1:75	Microwaving in citrate buffer, pH 6	Placenta
Fibronectin	Rabbit polyclonal	DAKO	1:200	Microwaving in citrate buffer, pH 6.1	Kidney

Results

Histopathological analysis of the 50 selected tumors revealed: six (12%) cases in stage I, which included only low-grade tubular gastric carcinomas (LG-TGC); 20 (40%) cases in stage II, including 10 cases of LG-TGC, eight cases of poorly cohesive gastric carcinomas (PCGC) and two cases of mixed gastric carcinomas (MGC); 22 (44%) cases in stage III, including eight cases of LG-TGC, three cases of high-grade tubular gastric carcinomas (HG-TGC), eight cases of PCGC and three cases of MGC; two (4%) cases in stage IV, represented by one case of PCGC and one case of MGC.

For the selected tumors, E-cadherin, P-cadherin and fibronectin immunoexpression indicated some differences regarding the staining distribution and intensity, but also the immunoreactive cells percentage, aspects observed by comparing the FSS mean values for different lesions categories (Table 2).

Table 2 – ***Gastric carcinomas distribution depending on E-cadherin, P-caderin and fibronectin FSS***

Marker	Tumor type		No. of cases / FSS	Stage I	Stage II	Stage III	Stage IV
E-cadherin	LG-GC	tubular	No. of cases	6	10	8	
			FSS	9.5	9.3	8.3	
	HG-GC	tubular	No. of cases		1		
			FSS		8		
		poorly cohesive	No. of cases		2	4	
			FSS		7	4	
		mixed	No. of cases				
			FSS				
P-cadherin	LG-GC	tubular	No. of cases	6	7	6	
			FSS	9	8.5	4	
	HG-GC	tubular	No. of cases			1	
			FSS			4	
		poorly cohesive	No. of cases		5	3	
			FSS		5.2	3.3	
		mixed	No. of cases				
			FSS				
Fibronectin	LG-GC	tubular	No. of cases			3	
			FSS			1.6	
	HG-GC	tubular	No. of cases			2	
			FSS			7.5	
		poorly cohesive	No. of cases		4	4	1
			FSS		5	7.5	9
		mixed	No. of cases		1	1	1
			FSS		2	6	9

FSS: Final staining score; LG-GC: Low-grade gastric carcinoma; HG-GC: High-grade gastric carcinoma.

E-cadherin immunoexpression was identified in 31 (62%) of the investigated cases, in the epithelial component of tumors, with different pattern. E-cadherin expression analysis indicated for the stage I carcinomas the presence of membrane pattern expression in all of the investigated cases (Figure 1A), for stage II carcinomas E-cadherin expression in tubular and discohesive carcinomas with cytoplasmic and membrane pattern (Figure 1, B and C), in stage III carcinomas cytoplasmic and membrane expression for tubular carcinomas regardless the differentiation grade and cytoplasmic expression for discohesive carcinomas (Figure 1, D and E), while in stage IV gastric carcinomas, we observed the absence of E-cadherin immunoexpression. Regardless the tumoral stage, FSS scores were high for LG-TGC and variables for high-grade lesions (HG-TGC, PCGC) (Table 2).

P-cadherin immunoexpression was identified in 28 (56%) of the investigated cases, in the epithelial component of tumors, with different pattern. P-cadherin expression analysis for stage I carcinomas showed the presence of membrane and cytoplasmic pattern expression with moderate/high intensity for all the investigated cases (Figure 2A). For stage II and III, we observed the presence of membrane and cytoplasmic pattern with moderate/high intensity in tubular carcinomas regardless the tumoral grade and low intensity in discohesive carcinomas (Figure 2, B–E). For stage IV carcinomas, the immunoexpression was cytoplasmic with low intensity and present only in discohesive carcinomas (Figure 2F). FSS scores were variable for LG-TCG and low for high-grade lesions (HG-TGC, PCGC), regardless the tumoral stage (Table 2).

Fibronectin immunoexpression was identified in the epithelial component of tumors in 17 (34%) of the investigated cases, but we also noticed the intense and diffuse positivity of tumoral stroma for all the investigated cases. Fibronectin expression analysis for stage I carcinomas showed the absence in all cases (Figure 3A). In stage II carcinomas, we observed the presence of cytoplasmic expression with low intensity in tubular carcinomas and with high intensity in discohesive carcinomas (Figure 3, B–C). In stage III gastric carcinomas, fibronectin expression was also cytoplasmic moderate/high predominantly for tubular carcinomas, regardless the differentiation grade, and also for discohesive carcinomas (Figure 3, D and E). On the contrary, for stage IV gastric carcinomas, fibronectin immunoexpression was cytoplasmic but present only in mixed and discohesive carcinomas (Figure 3F). FSS scores were low for LG-TCG and predominantly high for high-grade lesions in advanced stages (HG-TGC, PCGC, MGC) (Table 2).

The statistical analysis indicated significant superior differences of FSS values for E-cadherin in tubular carcinomas, compared to discohesive carcinomas ($p<0.001$, χ^2 test), also in low-grade carcinomas ($p<0.001$, χ^2 test) and in early stages ($p=0.042$, χ^2 test) (Figure 4, A–C). For P-cadherin, differences were superior but non-significant regarding FSS values in tubular carcinomas, compared to discohesive carcinomas ($p=0.096$, χ^2 test), respectively significant superior in low-grade carcinomas ($p=0.041$, χ^2 test) and in early stages ($p<0.001$, χ^2 test) (Figure 4, D–F). FSS mean values for fibronectin were significant superior in mixed and discohesive carcinomas, compared to tubular carcinomas ($p=0.023$, χ^2 test), and also in high-grade lesions ($p=0.003$, χ^2 test), respectively superior values but statistically non-significant in advanced stages carcinomas ($p=0.567$, χ^2 test) (Figure 4, G–I).

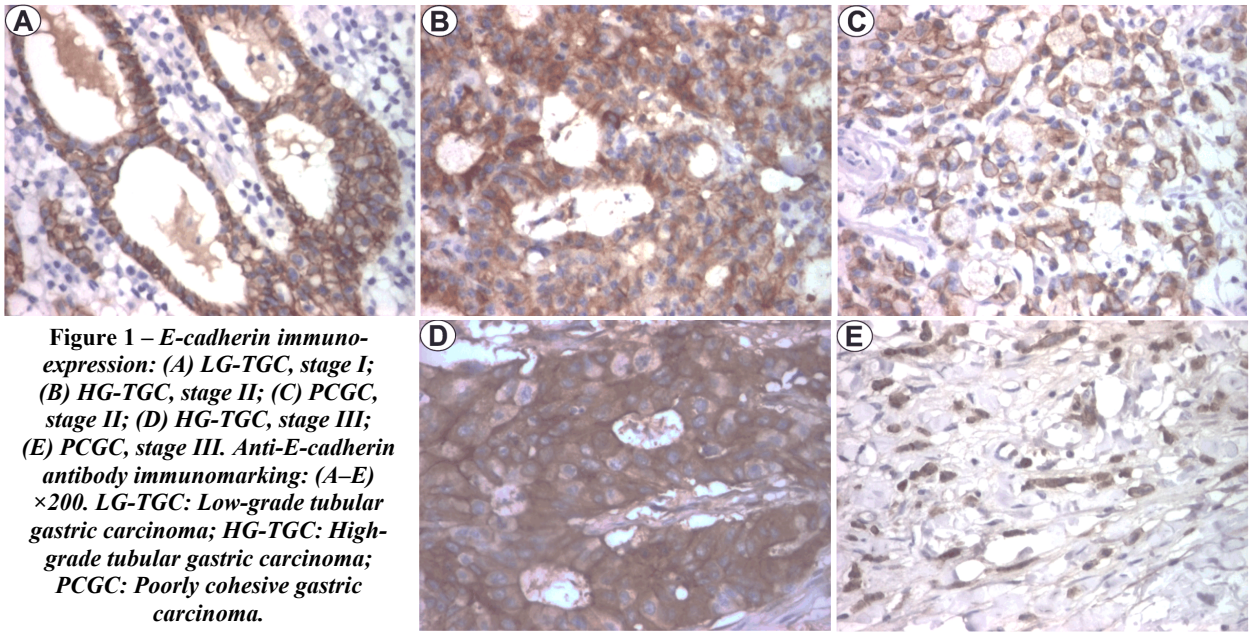

Figure 1 – ***E-cadherin immunoexpression: (A) LG-TGC, stage I; (B) HG-TGC, stage II; (C) PCGC, stage II; (D) HG-TGC, stage III; (E) PCGC, stage III. Anti-E-cadherin antibody immunomarking: (A–E) ×200. LG-TGC: Low-grade tubular gastric carcinoma; HG-TGC: High-grade tubular gastric carcinoma; PCGC: Poorly cohesive gastric carcinoma.***

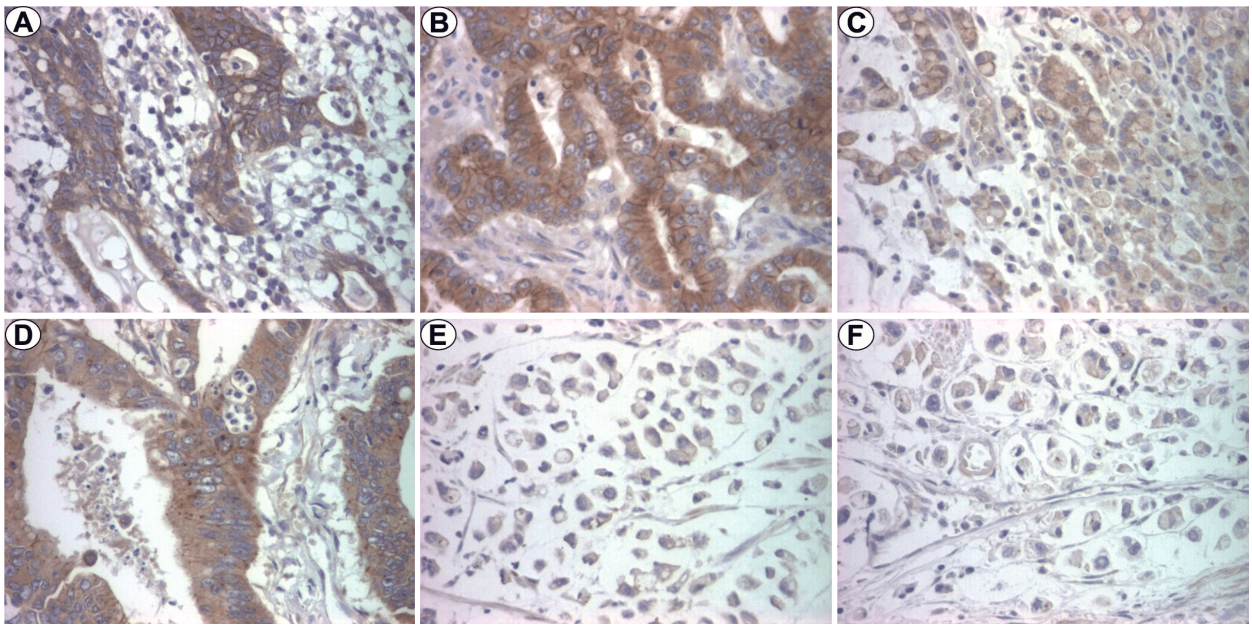

Figure 2 – ***P-cadherin immunoxpression: (A) LG-TGC, stage I; (B) HG-TGC, stage II; (C) PCGC, stage II; (D) HG-TGC, stage III; (E) PCGC, stage III; (F) PCGC, stage IV. Anti-P-cadherin antibody immunomarking: (A–F) ×200. LG-TGC: Low-grade tubular gastric carcinoma; HG-TGC: High-grade tubular gastric carcinoma; PCGC: Poorly cohesive gastric carcinoma.***

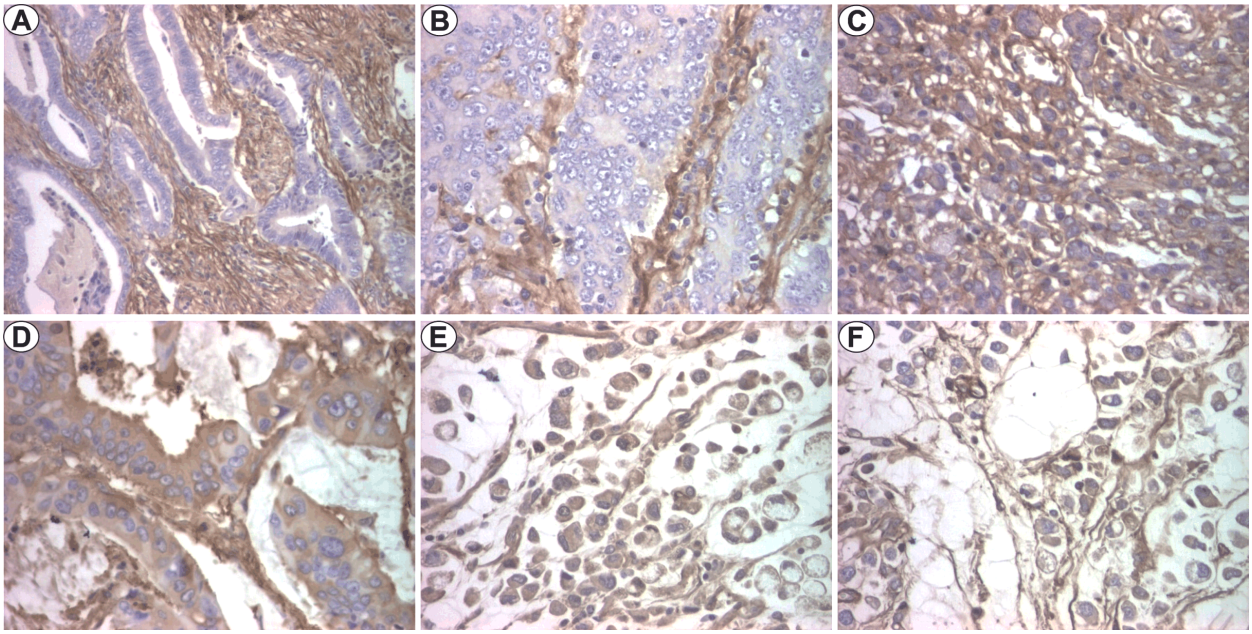

Figure 3 – ***Fibronectin immunoxpression: (A) LG-TGC, stage I; (B) HG-TGC, stage II; (C) PCGC, stage II; (D) HG-TGC, stage III; (E) PCGC, stage III; (F) PCGC, stage IV. Anti-fibronectin antibody immunomarking: (A–F) ×200. LG-TGC: Low-grade tubular gastric carcinoma; HG-TGC: High-grade tubular gastric carcinoma; PCGC: Poorly cohesive gastric carcinoma.***

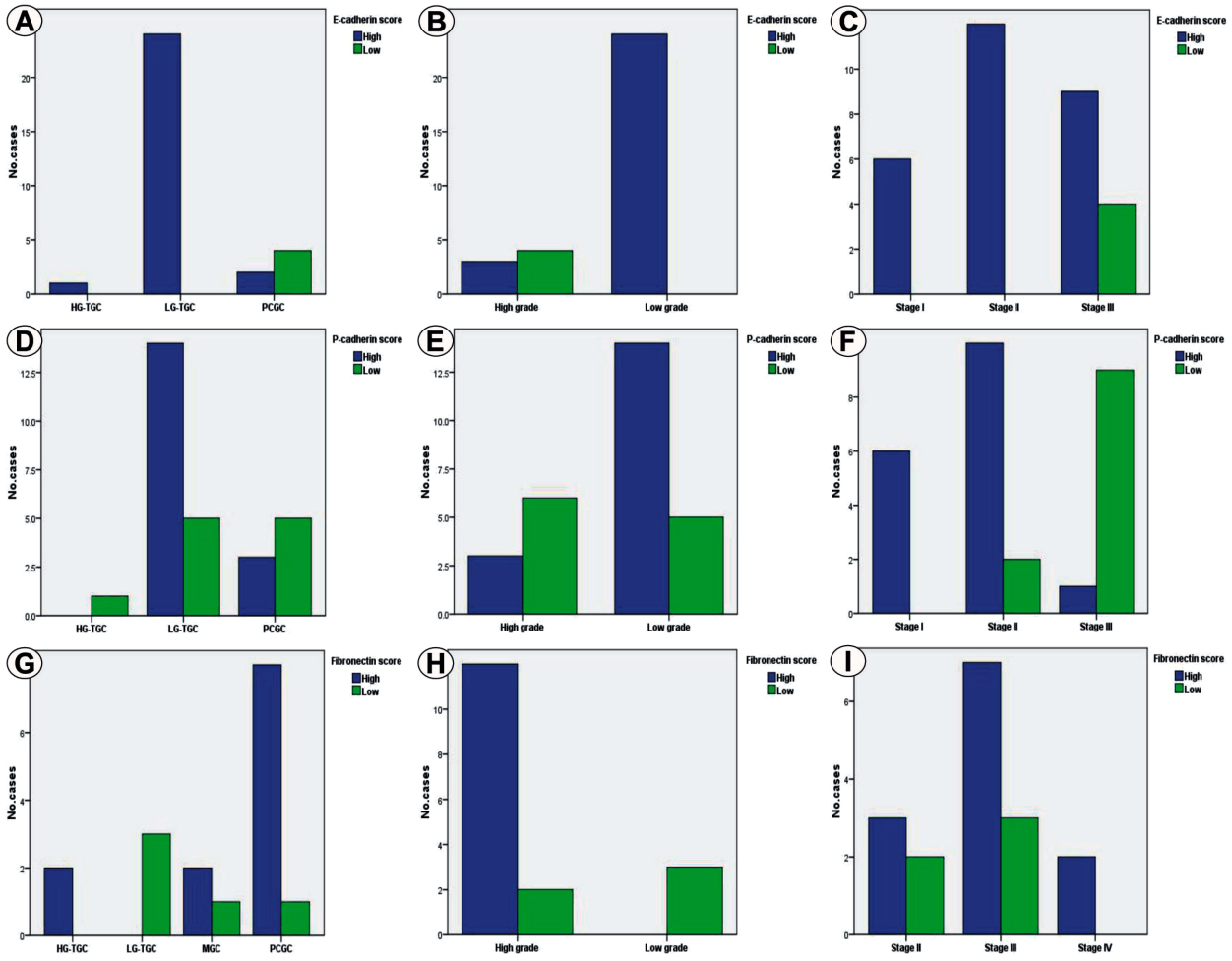

Figure 4 – ***Case distribution related to lesions type (A, D and G), tumoral grade (B, E and H), tumoral stage (C, F and I) and FSS mean values for E-cadherin (A–C), P-cadherin (D–F), fibronectin (G–I). FSS: Final staining score; HG-TGC: High-grade tubular gastric carcinoma; LG-TGC: Low-grade tubular gastric carcinoma; PCGC: Poorly cohesive gastric carcinoma; MGC: Mixed gastric carcinoma.***

Percentage values analysis of the obtained reaction indicated a positive linear correlation of the two cadherins ($p<0.001$, Pearson's test) and non-significant negative linear correlations of E-cadherin/P-cadherin related to fibronectin ($p>0.05$, Pearson's test).

Discussions

The distinctive modification of EMT is loss of E-cadherin expression, the central component of cell–cell adhesion molecules junctions, which contributes to cellular polarity maintaining, with an essential role in suppressing tumoral progression. Several studies revealed the absence of E-cadherin expression for 17–82% of investigated cases [9–14], mainly observed in diffuse gastric carcinoma and rarely in the intestinal type, with direct correlations between E-cadherin and tumor differentiation grade [11, 15–18]. Recent studies showed that high expression of E-cadherin was more frequent in intestinal and well-differentiated type, while less differentiated tumors and diffuse type associated an increased rate of reactivity absence [9, 19].

Immunoreaction for E-cadherin was identified in 62% of analyzed cases, with membrane/cytoplasmic pattern, of variable intensity, FSS values being significantly superior in tubular type, low grade and early stages carcinomas, compared to discohesive type, high grade and advanced stages carcinomas.

Abnormal immunoreactivity of E-cadherin expression in gastric carcinomas was observed with higher incidence in diffuse carcinomas [15, 17, 20, 21], a recent study reporting in 48.6% of cases the abnormal expression of E-cadherin, considered as a common modification in gastric cancer [22]. Identification of E-cadherin expression in cytoplasm and not membrane is in conformity with the fact that the loss of membrane expression of E-cadherin promotes tumor dissemination. Since the role of E-cadherin is to maintain epithelial cells adhesion, it is postulated that its abnormal expression leads to cancerous cells cohesion loss and invasion facilitation [20]. Staining pattern analysis indicated also intense membrane staining in normal gastric epithelia, which decreases gradually in percentage and intensity, along with the staining pattern modification, which becomes cytoplasmic in chronic atrophic gastritis, intestinal metaplasia, dysplasia and carcinomas [13].

Although many studies on patients with gastric carcinomas were conducted, the prognostic value of E-cadherin remains controversial, most studies including a small number of cases. Gabbert *et al.* found that gastric cancer patients with positive tumors for E-cadherin had better 3- and 5-year survival rates compared to negative E-cadherin tumors [17]. In the same direction, Karayiannakis *et al.* found a significant correlation of E-cadherin expression with the differentiation grade, localization and lymph nodes involvement [23]. On the other hand, Anbiaee *et al.* found a significant correlation between the abnormal expression of E-cadherin, high-grade tumors and regional lymph nodes involvement [18]. In addition, a recent study reported that the abnormal expression of E-cadherin correlated significantly with tumor stage, grade, lymph node metastasis, tumor phenotype, tumor type, depth of invasion and patients' age, which concluded that E-cadherin could be a predictive factor for tumor invasiveness [22].

The role of P-cadherin in carcinogenesis is still under debate, as it could behave differently according to molecular context and studied tumoral model. Thus, it could act as a tumoral suppressor as its absence is associated with a more aggressive phenotype of cancerous cells, while its overexpression appears connected to a more aggressive behavior induction in tumors with different localizations [24].

In our study, the immunoexpression of P-cadherin was identified in 56% of cases with membrane/cytoplasmic pattern, with variable intensity in relation to tumoral stage. FSS values were significantly higher for P-cadherin in low-grade carcinomas and early stages. Although values were superior in tubular carcinomas compared to discohesive carcinomas, aspects were not statistically significant.

Yasui *et al.* performed an immunohistochemical and Western blot analysis of P-cadherin expression in gastric carcinomas [25]. By Western blot analysis, P-cadherin protein was expressed in 83% and 29% of well-differentiated, respective poorly differentiated gastric carcinomas and immunohistochemically, reactivity was localized in cellular surface or at cell–cell limit of well-differentiated adenocarcinomas [25]. In stage II carcinomas, P-cadherin expression was significantly higher compared to stage I and in stage II–IV carcinomas, P-cadherin expression decreased as the stage progressed, the difference between stage II and III and stage III and IV being statistically non-significant [26]. The authors suggest the fact that P-cadherin may play an important role in well-differentiated gastric adenocarcinomas development and decrease of P-cadherin expression could be responsible of gastric cancers growth and infiltrative progression [26]. In addition, the membrane or cytoplasmic aberrant expression of P-cadherin was associated with the aggressive behavior of tumors with different localizations, including gastric cancer [11].

In another study, non-neoplastic lesions from gastric cancer patients were negative for P-cadherin, after subjection to immunohistochemistry and Western blot evaluation, compared to gastric carcinoma which presented P-cadherin expression in 70.8% of cases, and positive cases presented a well or moderate differentiation histology and an early primary tumor (pT) stage; patients with tumors which expressed P-cadherin had a favorable survival prognosis in univariate and multivariate analysis [7]. Authors concluded that tumors which express P-cadherin represent a subset of intestinal-type gastric carcinoma and a favorable prognosis, findings that could be useful in patients' selection and targeted therapy with P-cadherin implementation [7].

Some studies already indicated a direct inactivation of P-cadherin as a therapeutic approach. Imai *et al.* reported that cancer immunotherapy using cytotoxic T-cells specific for P-cadherin peptides, which present anti-tumoral growth effect, could offer an efficient approach against many carcinomas, including gastric carcinomas [27].

Fibronectin represents one of the major structural components of basal membranes, with an important role in adhesion, growth, cell migration and differentiation [28–31]. During EMT, cytoskeleton junctions and inter-cellular junctions are reorganized by modifications of

differentiation markers expressions, like loss of E-cadherin and cytokeratin expressions and increase of vimentin, fibronectin and N-cadherin expression [32].

In our study, fibronectin was identified cytoplasmic, with a variable intensity in 34% of cases, FSS values being significantly higher in mixed and discohesive carcinomas compared to tubular and in high-grade lesions, compared to low-grade lesions. Although superior values were found in advanced stages, the aspects were not statistically significant. One study indicated that 90% of gastric carcinomas expressed fibronectin, especially in the connective tissue from the tumors invasion front, fibronectin expression being significantly connected to the neoplasms growth model [29]. Similarly, Grigioni *et al.* observed a more intense fibronectin staining in the connective tissue at the invasion front of gastric cancer [30]. Histopathological studies suggest that presence of large amounts of fibronectin in pericellular matrix is topographically associated with gastric carcinomas invasion advancing edges and it is correlated with an increased risk of local invasion and metastasis [29, 30, 33]. Sugihara *et al.* suggested that the invasive activity of signet ring cells carcinoma cannot be connected simply to presence or absence of fibronectin and laminin on the cellular surface but also to the quantity of stromal fibronectin, which may reflect an interaction between stromal cells [33].

Conclusions

In this study, the immunoexpression of E-cadherin and P-cadherin was associated with tubular gastric carcinomas, low grade and early stages, while fibronectin expression was associated with discohesive or mixed gastric carcinomas, high grade and advanced stages. Negative E-/P-cadherin and positive fibronectin immunophenotype could be associated with aggressive gastric carcinomas and supports the EMT involvement in gastric carcinogenesis. The used antibodies may provide support in patients' stratification for targeted therapy.

Conflict of interests

The authors declare that they have no conflict of interests.

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