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Correlation between Immunohistochemical Caveolin -1 Expression and Clinicopathological Parametres in Gastric Adenocarcinomas

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Abstract

Objective: Caveolin- 1 protein encoded by CAV1 gene regulates many different biological processes including carcinogenesis. Its correlation with prognosis in various tissue malignancies has been indicated in many investigations. The objective of this study is to evaluate the relationship between immunohistochemical caveolin-1 expressions with other clinicopathological parameters.

Material and Method: All clinical information about 116 cases with gastric carcinoma who had been undergone gastrectomy between 2011, and 2014 were reviewed. Caveolin-1 expression was evaluated using immunohistochemical methods.

Results: As is the case with normal tissues, tumors with limited caveolin-1 expression observed in the perivascular area were accepted as caveolin-1 negative tumors. Caveolin-1 expression was of stromal or tumoral pattern in 58 cases. In Kaplan- Meier survival analysis caveolin-1 expressing cases had lower survival rates (p=0.04).

Conclusion: Contribution of tumoral caveolin-1 expression to tumor aggressiveness, and contrarily antitumoral activity of stromal caveolin-1 expression have been reported in many studies. In compliance with literature findings, our study results suggested adverse prognostic impact of caveolin-1 expression in gastric carcinomas. However since tumoral caveolin-1 expression was detected in only 5 cases, cases expressing tumoral or stromal caveolin-1 could not be subjected to intragroup comparisons. Therefore these findings should be confirmed in larger case series.

Keywords: Gastric adenocarcinoma, Caveolin-1, HER2, prognosis, survival.

Introduction

Gastric carcinomas rank second among the most frequently seen life-threatening cancer types in the whole world. Since 90 % of them are in advanced stage at the time of diagnosis, survival rates are relatively low. Interactions between various environmental factors as dietary habits, and *Helicobacter pylori* (HP) infection, and individual factors as genetic predisposition lead to development of gastric cancer (1-4).

HER2 protooncogene localized on chromosome 17 encodes erbB2 receptor protein situated on cell membrane (5). This protein is one of the epidermal growth factors. When it is activated it exerts its effects on cellular differentiation, apoptosis, adhesion, migration and growth through tyrosine kinase pathway (1). Since it is localized on signal conduction pathway responsible from cellular proliferation, it is effective in many types of cancer. HER2- positivity is seen in 5-30% of gastric carcinomas (1-5). Variable incidence rates of HER2- positivity in gastric tumors have been associated with regional, and ethnic factors, and also lack of any standardization of HER2 scoring criteria (5, 6). HER2- positivity is frequently (32%) seen in intestinal type gastric carcinomas (5). More rarely it is seen in diffuse (6%), and undifferentiated carcinomas (1). HER2- positivity is observed most frequently on gastroesophageal region (5). HER2 expression in intestinal subtype is associated with poorly differentiated tumors, and lymph node metastasis (5). HER2 immunhistochemistry (IHC) and insitu hybridization (ISH) procedures have been routinely performed in stomach tumors because they provide prognostic, and predictive information (1-7).

Caveolin-1 is one of the 3 submembers of the caveolin protein family (8). The term caveola means small cave. Caveolas are localized on cell membrane, and involved in signal conduction, in macromolecular transport vesicles, endocytosis, cellular metabolism, cholesterol homeostasis and tumorigenesis. Caveolin- 1 is the most widely observed member of this protein family (9). In many studies potential prognostic importance of caveolin-1 expression in various organ cancers has been emphasized (10). Besides variations in caveolin-1 expression have been correlated with various clinopathological data priorly related to histological subtypes in gastric carcinoma (10-13).

In this study, we aimed to investigate the correlation between caveolin-1 expression, and other clinicopathological parameters, and test caveolin-1 as a potential target marker in the treatment of gastric carcinoma.

Material And Method

A total of 116 cases with gastric carcinoma who had been diagnosed, in the Pathology Laboratory of Hospital, and undergone gastrectomy between the years 2011, and 2014 were included in this study. In these cases with adequate viable tumor tissue cerbB2 was examined using IHC methods. Hematoxylin-eosin (HE) stained slides were re-evaluated based on WHO 2010 classification. In all cases age of the patients at the time of diagnosis, tumor size, location, histological type, differentiation, neuroendocrine differentiation, presence of lymphovascular, and perineural invasion, lymph node metastasis, TNM stage, and HER2-positivity and similar parametres were evaluated. The most appropriate paraffin block which most accurately reflects tumor tissue was selected for IHC evaluation, and labeled both on the slide, and on the block Then cylindrical paraffinzed tissue samples with a diameter of 2 mm were cut from donor blocks, and microarray blocks were prepared using mapping, and addressing techniques. From each prepared block, tissue

samples from placenta, and spleen were used for addressing. Immunohistochemistry (IHC) was performed by the streptavidine biotin peroxidase method (Invitrogen, Camarillo, 85-9043). Serial 5-µm sections were obtained and the slides were baked overnight at 60ºC, dewaxed in xylene, and hydrated in distilled water through decreasing concentrations of alcohol. All slides were treated with heat-induced epitope retrieval in the microwave (in 10mM/L citrate buffer, pH 6.0, for 20 minutes, followed by cooling at room temperature for 20 minutes). Endogenous peroxidase activity was blocked using avidin-biotin blocking solution. An affinity- purified monoclonal mouse antibody against caveolin-1 (Novus Biologicals, Littleton, NB100-615, USA) was used at a dilution of 1:200. The evaluation was blinded to any of the clinical features and staining patterns were classified as stromal, perivascular or tumoral (Figure 1, 2 and 3). HER2 was evaluated, and scored using immunohistochemical methods in accordance with CAP 2013 protocol as follows: 0= membranous staining seen less than 10 % of cells or lack of any staining; 1+, faint membranous staining seen in more than 10% of tumor cells; 2+, faint, moderately complete, basolateral or lateral membranous staining in more than 10% of cells; 3+, strong, complete, basolateral or lateral membranous staining in more than 10% of tumor cells. Accordingly only 3+ cells were considered as HER2- positive cells. Spearman Correlation analysis, Mann-Whitney U test, Kruskal-Wallis test, *chi*-square test and Kaplan-Meier Survival Analysis were performed for statistical analysis using SPSS *v.* 15.0 package program. *P*-value of less than 0.05 was considered as statistically significant.

Results

Study population consisted of 78 (67.2%) male, and 38 (32.8%) female patients. Mean age of the patients was 64.3±12.5 (range, 36 – 92) years. Tumors were localized on cardia (n=22;19%), corpus (n=52;44.8%), antrum/pylorus (n=42; 36.2%). Mean diameter of tumoral masses was 6.22cm± 3.1cm (range, 1-15 cm). Distribution of histopathological subtypes of tumors was as follows: poorly cohesive adenocarcinoma (n= 55; 47.4%), and tubular type adenocarcinoma (n=46, 39.6%). In only 5 tumor samples neuroendocrinological differentiation was seen. Lymphovascular invasion (n=77; 66.4%), perineural invasion (n=70; 60.3%), and lymph node metastasis (n=93; 80.2%) were detected in indicated number of patients. Number of metastatic lymph nodes changed between 0, and 44 (mean, 7.38±8.5). Tumors were evaluated according to TNM classification as follows: T4 (n=34 :29.3%); T3 (n=68:58.6%);T2 (n=7:6%); T1b (n=7:6%); N0 (n=23:19.8%); N1, (n=17: 14.7%); N2 (n=30: 25.9%); N3 (n=26 :24.4%), and N3b (n=20:17.2%). Distant metastases were seen in 34 (29.3%) patients.

Thirty-five (30.2%) HER2-positive tumors were detected immunhistochemically. Median age of the cases with HER2- positive, and HER2-negative tumors were 61.34, and 65.69 years, respectively. Median diameter of HER2-positive, and HER2-negative cases were 6.88, and 5.94 cm, respectively. HER2-positive cases were localized on cardia (n=4:11.4%), corpus or pylorus (n=31: 88.6%). HER2-negative cases were localized on cardia (n=18: 22.2%), corpus or pylorus (n=63: 87.8%). A statistically significant correlation was not detected between HER2 status, and tumor size (p: 0.33), age (p: 0.087), tumor location (p:0.087), lymph node metastasis (p:0.742), lymphovascular invasion (p:0.449), perineural invasion (p:0.197), T stage (p:0,270), and N stage (p=0.435). Caveolin -1 expression was observed in 58 of 116 (50%) cases. Caveolin-1 expression demonstrated stromal (n=53:

91.4%) or tumoral (n=5: 8.6%) patterns Tumoral or stromal staining was detected in 19 of 35 (54.3%) HER2-positive, and 39 of 81 (48.1%) HER2- negative patients. Caveolin-1 expression, and histological subtypes were compared, and caveolin-1 expression was detected in 46.7% of poorly cohesive, and 50.5% of other types of carcinomas. Mean tumor diameter of 58 cases with positive caveolin-1 expression was 6.52±3.177 cm, while mean diameter of caveolin-1 negative cases was 5.93 ±3.113 cm. We compared tumors based on their T stages, and caveolin-1 expression was seen in 60% of early-stage, and 48.5% of advanced stage tumors. A significant correlation was not found between caveolin- 1 expression, tumor size (p:0,316), histological subtype (p:0,770), and T stage (p:0.689). Among 80 deceased cases, 1-, and 2-year survival rates were 37.5%, and 68.8%, respectively. Caveolin-1 expression of deceased, and survived cases were 55, and 38.9 %, respectively. A statistically significant correlation was found between caveolin-1 expression, and survival rates (p:0,044).

Discussion

HER2 amplification in gastric carcinomas is a negative prognostic factor (1, 2). In the literature HER2 expression in gastric carcinomas was found to be correlated with decreased survival rates (1-4). However in recent studies thanks to targeted treatments added to management of HER2-positive tumors, negative prognostic factor of HER2 has become debatable (1-4). In the literature rates of HER2-positivity change between 5, and 30 percent (5). It is most frequently seen in proximal gastric cancers, and especially those localized on gastroesophageal junction, and intestinal type tumors (5). Correlation between HER2 expression, and intestinal subtype, poorly differentiated tumors, and lymph node metastasis has been also reported (1-6). In our study only 4 (11.4%) of 35 HER2-positive cases were localized on cardia. In 20 (57.1%) cases tumor was of pure intestinal type. A statistically significant correlation was not found when we compared HER2-positive, and negative tumors as for age, gender of the patients, tumor size, location, differentiation, histological subtype, T , and N stages, lymph node metastasis, lymphovascular, and perineural invasion, and survival rates. In our series rates of HER2-positivity were at the upper limit of those reported in the literature. This high rate can be attributed to the fact that our hospital is a reference hospital where complicated cases have been diagnosed, and treated. In addition, referral of the endoscopically diagnosed patients with cErbB expression who will receive targeted treatment increases HER2-positivity rates.

The role of the Cav1 protein in cell proliferation, tumor development and progression of some cancer types remains controversial whether Cav-1 acting as a tumor-promoter or suppressor. The different roles of Cav-1 in cancer may be depend on the stage of cancer and its interaction with multiple different signaling molecules in specific tissues and cell types. In some cell types, Cav-1 interacts with multiple members of the EGF-R/RAS/ERK and PI3/AKT pathways to modify signaling activity (14). Previous studies showed that Cav-1 facilitates both, ERK and AKT signaling in cancer cells from kidney, colon, prostate, epidermis, muscle, and brain, and it is associated with promotion of cell invasion, proliferation, angiogenesis and multi-drug resistance (14- 18). Similar association between Cav-1 expression and mutations of B-RAF in melanomas was also reported (19). Most authors suggest that Cav-1-positive tumor cells function as tumor promoters mediated by these signaling pathways (14- 20). It has been also demonstrated that, Cav-1 displays its role as a tumor-suppressor requiring the presence of E-

cadherin. When E-cadherin is still expressed in cancer cells, Cav-1 remains its anti-proliferative and pro-apoptotic role, whereas the depletion of E-cadherin resulting in loss of Cav-1 function (12). In our study, we determined tumoral Cav-1 expression in a limited number of tumors. Therefore, we were not able to determine any statistically significant relationship between the presence of Cav-1 expression in tumor cells and tumor behavior.

Tumor microenvironment has a crucial role in the development and progression of malignancies. It has been clearly evidenced that during tumorigenesis micro-vessel density increases, reactive stromal fibroblasts, and different inflammatory cells recruit, and peptide-signaling molecules and proteases release. An altered extracellular matrix (ECM), produced by cancer-associated fibroblasts (CAFs) can induce epithelial–mesenchymal transition (EMT) or other types of behaviors associated with a more aggressive phenotype in the neighboring epithelial cells (13, 20). The exact mechanisms of this relationship remain to be fully elucidated. However, the transforming growth factor β (TGF-β), which is involved in modulation of cell growth and tumorigenesis, seems to play a major role (13, 20). In many studies, reduced levels of Cav-1 in the extratumoral stroma have been reported (13- 21). Functional studies have also demonstrated that down-regulation of stromal Cav-1 expression can alter the impact of stromal factors on tumor epithelium, tumor angiogenesis, cholesterol and androgen metabolism. Atala et al (20), used myofibroblasts to investigate the relationship between cancer cells and tumor microenvironment so as to clarify the pathogenesis of this process. Their results indicated that Cav-1 down-regulation in the stroma with concomitantly increased expression of some reactive markers, induces a number of gene alterations, including up-regulation of TGF-β1 and down-regulation of some genes with a proangiogenetic effect. They also showed that Cav-1 silencing stimulates proliferation and provokes oncogenic cell signaling in prostate stromal cells together with increased levels of intracellular cholesterol and activation of steroidogenic enzymes with resultant acceleration of tumor cell migration (20). Contrary to this suggestion, we found that Cav-1 expression both in tumor cells and in the peritumoral stroma was associated with a lower survival rate in gastric carcinomas.

The role of tissue expression of Cav-1 used as a marker of cancer progression remains controversial. Its level of expression in peritumoral stromal cells has been accepted as a better predictor for cancer progression. In the majority of English-language reports, stromal Cav-1 appears to be down-regulated and its decreasing expression seems to play a negative role in tumorigenesis. Many oncogenes such as SRC, RAS, BCR-ABL, transcriptionally down-regulate Cav-1 expression (8). Albeit with controversial results, recent studies have focused their attention on Cav-1 expression in the peritumoral stromal cells rather than in tumor cells. For example, Goetz et al. (22), suggested that there may be an important role for stromal Cav-1 in promoting tumor progression and metastasis (22). However, in most other studies, loss of stromal Cav-1expression in association with a high tumoral Cav-1 expression, has been reported to be poor prognostic factors in different malignancies (10- 15, 20, 23, 24). Taken together, no matter Cav-1 expression in the tumor or stromal cells, Cav-1 shows paradoxical role in different tumors, even in vivo and in vitro. In this study, stromal Cav-1 expression was an independent prognostic factor. Besides contrary to other studies, presence of Cav-1 expression seemed to be correlated with shorter survival times. However very

small number of cases with tumoral Cav-1 expression precluded our detailed interpretation of tumoral, and stromal Cav1 expression.

In summary, the role of Cav-1 in tumorigenesis including dysregulation of cell cycle, apoptosis and autophagy, adhesion, and in invasion and metastasis, as well as modulation of autophagy and regulation of miRNAs to affect tumor progress. In this study we evaluated the expression of Cav-1 in the gastric carcinomas and determined tumoral Cav1 expression in only 5 tumors. Although tumoral Cav-1 expression has been extensively studied in several carcinomas, there is little or no data on the expression and significance of Cav-1 in gastric tumors (25- 29). We observed that the expression status of Cav-1 in the peritumoral stroma did not change dependent on the status of most prognostic and predictive factors, including HER2-expression. Contrarily, regardless of Cav-1 expression in the tumor or stromal cells, presence of Cav-1 expression was a poor prognostic clinical factor. In conclusion, the results of our study demonstrate that Cav-1 may act as a predictive marker in gastric carcinomas, but our findings should be investigated, and supported in larger series.

Conflict of interest

The authors declare that they have no conflicts of interest.

References

1. Bang YJ, Van Cutsem E, Feyereislova A et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2 positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open label, randomized controlled trial. Lancet 2010;376:687-697.
2. Gomez-Martín C, Lopez-Rios F, Aparicio J, Barriuso J, García-Carbonero R, Pazo R ve ark. A critical review of HER2-positive gastric cancer evaluation and treatment: from trastuzumab, and beyond. Cancer Lett 2014; 351(1): 30-40. doi:10.1016/j.canlet.2014.05.019.
3. Gravalos C, Jimeno A. Her2 in gastric cancer: a new prognostic factor and a novel therapeutic target, Ann. Oncol 2008; 19 (9): 1523-1529.
4. Gomez Martin C, Garralda E, Echarri MJ, Ballesteros A, Arcediano A, Rodriguz-Peralto JL et al. HER2/neu testing for anti HER2 based therapies in patients with unresectable and/or metastatic gastric cancer. J.Clin.Pathol 2012: 65 (8): 751-757.
5. Irkkan SC. HER2 Assessment in Gastric Carcinoma. Acta Onkologica Turcica 2014, doi: 10.5505/aot.2014.24633.
6. Sheffield BS, Garratt J, Kalloger SE, Li-Chang HH, Torlakovic EE, Gilks CB et al. HER2/neu testing in gastric cancer by immunohistochemistry: assessment of interlaboratory variation. Arch Pathol Lab Med 2014;138(11):1495-502. doi: 10.5858/arpa.2013-0604-OA.
7. Ieni A, Barresi V, Caltabiano R, Caleo A, Bonetti LR, Lanzafame S et al. Discordance rate of HER2 status in primary gastric carcinomas and synchronous lymph node metastases: a multicenter retrospective analysis. Int J Mol Sci 2014;15(12):22331-41. doi: 10.3390/ijms151222331.
8. Senetta R, Stella G, Pozzi E, Sturli N, Massi D, Cassoni P. Caveolin-1 as a promoter of tumour spreading: when, how, where and why. J Cell Mol Med 2013; 17(3):325-36. doi: 10.1111/jcmm.12030.
9. Engelman JA, Zhang X, Galbiati F, Volonte D, Sotgia F, Pestell RG,et al. Molecular genetics of the caveolin gene family: implications for human cancers,

diabetes, Alzheimer disease, and muscular dystrophy. Am J Hum Genet 1998;63(6):1578-87.

10. Eliyatkin N, Aktas S, Diniz G, Ozgur HH, Ekin ZY, Kupelioglu A. Expression of Stromal Caveolin- 1 May Be a Predictor for Aggressive Behaviour of Breast Cancer. Pathol Oncol Res 2018;24(1):59-65. doi: 10.1007/s12253-017-0212-8.
11. Ayaz D, Diniz G, Kahraman DS, Sayhan S, Uncel M, Karadeniz T, Sanci M. The evaluation of the caveolin-1 and AT-rich interactive domain 1 alpha expressions in uterine smooth muscle tumors. Indian J Pathol Microbiol 2016;59(3):301-4. doi: 10.4103/0377-4929.181891.
12. Torres VA, Tapia JC, Rodriguez DA, Lladser A, Arredondo C, Leyton L,et al. E-cadherin is required for caveolin-1-mediated down-regulation of the inhibitor of apoptosis protein survivin via reduced beta-catenintcf/ lef-dependent transcription. Mol Cell Biol 2007; 27, 7703-7717.
13. Sayhan S, Diniz G, Karadeniz T, Ayaz D, Kahraman DS, Gokcu M, Yildirim HT. Expression of caveolin-1 in peritumoral stroma is associated with histological grade in ovarian serous tumors. Ginekol Pol 2015;86(6):424-8.
14. Sáinz-Jaspeado M, Martin-Liberal J, Lagares-Tena L, Mateo-Lozano S, Garcia del Muro X, Tirado OM. Caveolin-1 in sarcomas: friend or foe? Oncotarget 2011;2(4):305-12.
15. Campbell L, Gumbleton M, Griffiths DF. Caveolin-1 overexpression predicts poor disease-free survival of patients with clinically confined renal cell carcinoma. Br J Cancer 2003;89(10):1909-13.
16. Basu Roy UK, Henkhaus RS, Loupakis F, Cremolini C, Gerner EW, Ignatenko NA. Caveolin-1 is a novel regulator of K-RAS-dependent migration in colon carcinogenesis. Int J Cancer 2013;133(1):43-57.
17. Li L, Ren CH, Tahir SA, Ren C, Thompson TC: Caveolin-1 maintains activated Akt in prostate cancer cells through scaffolding domain binding site interactions with and inhibition of serine/threonine protein phosphatases PP1 and PP2A. Mol Cell Biol 2003, 23:9389-9404.
18. Quann K, Gonzales DM, Mercier I, Wang C, Sotgia F, Pestell RG, et al. Caveolin-1 is a negative regulator of tumor growth in glioblastoma and modulates chemosensitivity to temozolomide. Cell Cycle 2013;12(10):1510-20.
19. Wu KN, Queenan M, Brody JR, Potoczek M, Sotgia F, Lisanti MP, Witkiewicz AK. Loss of stromal Caveolin-1 expression in malignant melanoma metastases predicts poor survival. Cell Cycle 2011; 10(24):4250-5.
20. Ayala G, Morello M, Frolov A, You S, Li R, Rosati F, Bartolucci G,et al. Loss of Caveolin-1 in prostate cancer stroma correlates with reduced relapse-free survival and is functionally relevant to tumour progression. J Pathol 2013; 231(1):77-87.
21. Paskaš S, Janković J, Marečko I, Išić Denčić T, Tatić S, Cvejić D, Savin S. Caveolin-1 expression in papillary thyroid carcinoma: correlation with clinicopathological parameters and BRAF mutation status. Otolaryngol Head Neck Surg 2014;150(2):201-9.
22. Goetz JG, Minguet S, Navarro-Lérida I, Lazcano JJ, Samaniego R, Calvo E, et al. Biomechanical remodeling of the microenvironment by stromal Caveolin-1 favors tumor invasion and metastasis. Cell 2011;146(1):148-63.

23. Witkiewicz AK, Dasgupta A, Sotgia F, Mercier I, Pestell RG, Sabel M, et al. An absence of stromal Caveolin-1 expression predicts early tumor recurrence and poor clinical outcome in human breast cancers. Am J Pathol 2009; 174(6):2023-34.
24. Wiechen K, Diatchenko L, Agoulnik A, Scharff KM, Schober H, Arlt K,et al. Caveolin-1 is down-regulated in human ovarian carcinoma and acts as a candidate tumor suppressor gene. Am J Pathol 2001;159(5):1635-43.
25. Yang Ye, Shu-Han Miao, Rong-Zhu Lu, Jian-Wei Zhou. Prognostic Value of Caveolin-1 Expression in Gastric Cancer: a Meta-analysis. Asian Pac J Cancer Prev 2014;15(19):8367-70. DOI: 10.7314/APJCP.2014.15.19.8367.
26. Guo-yang Sun, Jun-xia Wu, Jian-sheng Wu, Yu-ting Pan, Rong Jin. Caveolin-1, E-cadherin and β-catenin in Gastric Carcinoma, Precancerous Tissues and Chronic Non-atrophic gastritis. Chin J Cancer Res 2012; 24(1): 23–28. doi: 10.1007/s11670-012-0023-0.
27. Nam KH, Lee BL,Park JH, et al; Caveolin 1 expression correlates with poor prognosis and focal adhesion kinase expression in gastric cancer. Pathobiology 2013; 80:87-94.
28. Şeker M, Aydın D, Bilici A, Yavuzer D, Ozgun M, Ozcelik M, Ozhan A, Aliustaoglu M, Correlation of caveolin 1 expression with prognosis in patients with gastric cancer after gastrectomy. Oncol Res Treat 2017;40(4):185-190. DOI: 10.1159/000456620.
29. Sagara Y, Mimori K, Yoshinaga K, Tanaka F, Nishida K, Ohno S et al. Clinical significance of Caveolin-1, Caveolin-2 and HER2/neu mRNA expression in human breast cancer. Br J Cancer 2004;91(5):959-65.

Figure Legends

Figure 1: Perivascular CAV-1 expression pattern (DABX 200).

Figure 2: Stromal CAV-1 expression in a gastric carcinoma (DABX 200).

Figure 2: Stromal CAV-1 expression in a gastric carcinoma (DABX 200).

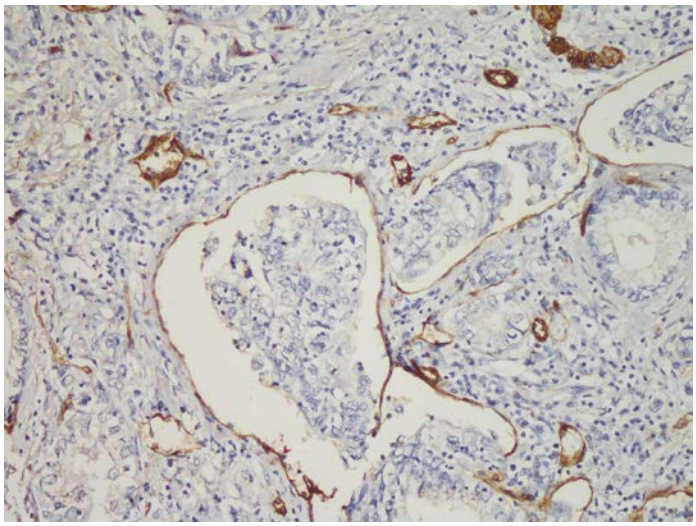

Figure 1: Perivascular CAV-1 expression pattern (DABX 200).

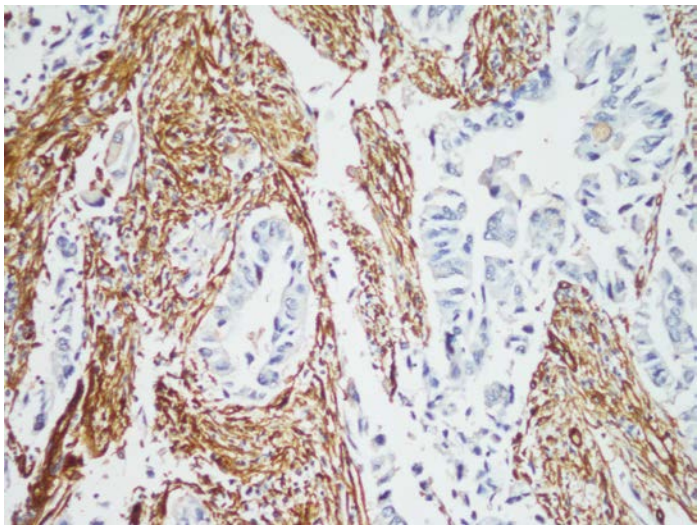

Figure 2: Stromal CAV-1 expression in a gastric carcinoma (DABX 200).

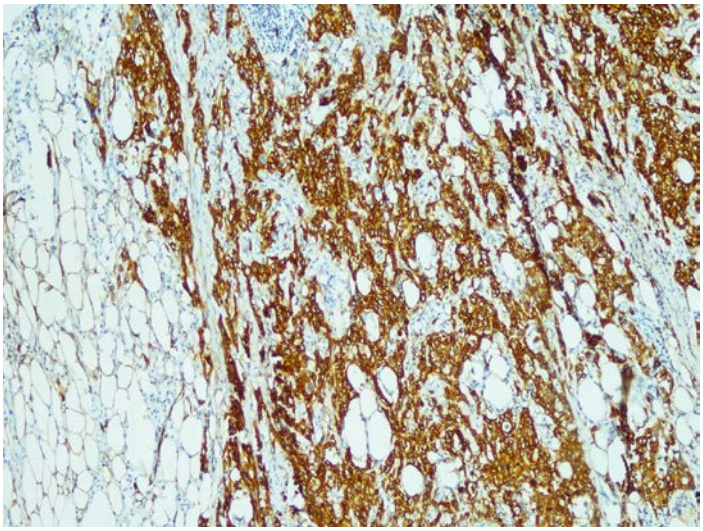

Figure 3: Tumoral CAV-1 expression in a gastric carcinoma (DABX 100).