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Original Contributions

Juxtatumoral desmoplastic stromal reaction is associated with high tumor cell dissociation in squamous cell carcinomas of the uterine cervix

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Abstract There are different types of tumoral growth patterns invading host tissue. During tumor infiltration, cancer cells not only destroy the pre-existing extracellular matrix, but usually induce new matrix formation by activating the peritumoral stromal cells; that is, desmoplastic stromal reaction (DSR) at the front of invasion (juxtatumoral stroma). This study evaluates the association between different types of invasion and DSR. Eighty-eight squamous cell carcinomas (Fédération Internationale de Gynécologie et d'Obstétrique [FIGO] stage IB to IV) were evaluated histologically for different patterns of invasion (PI) using a 3-level scoring system (pushing, finger-like, and spray-like). Desmoplastic stromal reaction was scored from none to weak, moderate, or strong. The pattern of invasion and DSR were compared with patients' age, FIGO stage, clinical tumor size, tumor grade, and the presence of lymphovascular space involvement. Finger-like PI was the most common (72.7%), followed by the spray-like PI (27.3%), whereas pushing PI was not seen. Of the tumors, 23.9% showed no DSR; 51.1%, weak; 14.8%, moderate; and 10.2%, strong DSR.Tumors with spray-like PI showed a significantly stronger desmoplastic reaction compared with the finger-like PI ($P < .0001$) and were significantly associated with poor tumor cell differentiation ($P = .018$). Moderate or strong DSR was associated with G2 and G3 carcinomas ($P = .027$). No correlation was seen neither for PI and DSR to lymphovascular space involvement, FIGO stage, and tumor size. The intensity of DSR, as understood in the context of a remodeling of the juxtatumoral stroma to the infiltrative tumor growth, might be indicative of a highly dissociative tumor growth and is correlated to poorly differentiated tumors.

Keywords: Cervix; Carcinoma; Pattern of invasion; Desmoplastic change; Tumor grade; Tumor cell dissociation

1. Introduction

Different types of tumoral growth patterns have been described in various types of carcinomas, for example, gastric and endometrioid adenocarcinomas, as well as in squamous cell cancers of the head and neck, the skin, and the cervix uteri [1-6].

Some of these investigations have described a prognostic significance of the growth pattern of tumors, particularly at the front of the tumoral invasion [1,2,5,6].

Different scoring systems for the description of the different patterns of invasion (PI) have been described in the literature for several types of carcinomas [4,6-8]. The most useful system for squamous cell carcinomas is a 3-level scoring system [4,6,9,10]. Briefly, this scoring system differentiates between a pushing, a finger-like, and a spray-like pattern of invasion. The pushing or closed pattern of invasion is characterized by a cohesive tumor growth with well-delineated infiltrating borders and "pushing" margins. A finger-like PI, on the contrary, shows a

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trabecular tumor growth in solid cords, whereas the spray-like PI is defined by tumor growth in small groups of infiltrating cells. The spray-like PI has been determined as the most dissociative kind of growth pattern [4,6,11,12].

Cancer cells not only destroy the pre-existing extracellular matrix, but cancer invasion per se usually induces new matrix formation by activating the peritumoral stromal cells; that is, desmoplastic stromal reaction (DSR) [13]. The DSR at the front of invasion (juxtatumoral stroma) contains proliferating myofibroblasts, inflammatory cells, trapped residual atrophic parenchymal components of the invaded organ, and also the process of neovascularization [13,14]. The DSR is one hallmark of the morphologic diagnosis of an invasive tumor and is the result of a complex cross-talk between the tumor cells and the surrounding tissue [15,16].

The link between the intensity of the tumoral cell dissociation as represented by the different PI and the intensity of the DSR is not well described.

The aim of this study was therefore the evaluation of a potential relationship between the pattern of invasion and the DSR in squamous cell carcinomas of the uterine cervix.

2. Materials and methods

Cervical biopsies from 88 consecutive patients who presented to the Departments of Obstetrics and Gynecology of the University of Leipzig and the University of Mainz, Germany, with Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stages IB to IV were selected for this study.

The H&E–stained tissue slides were evaluated for a potential correlation between the intensity of the DSR, the peritumoral inflammatory response and the pattern of invasion. The different PI were described with a 3-level scoring system which differentiates between a pushing, a finger-like, and a spray-like pattern (see above; [4,6,9,10]).

The intensity of the peritumoral desmoplastic reaction and of the peritumoral inflammatory response was evaluated semiquantitatively. The scoring system ranged from negative desmoplastic reaction/inflammatory response (0) to weak (1), moderate (2), and strong (3) desmoplastic/inflammatory reaction. The scores were obtained from a microscopic field using a 10-fold objective.

The grade of DSR was compared with the patients' age, FIGO stage, clinical tumor size, tumor grade according to World Health Organization classification [17], as well as the presence of lymphovascular space involvement.

Table 1
Patient characteristics

Median age	47 y (range, 24-79 y)
Median tumor diameter	4.5 cm (range, 1.5-10.0 cm)
FIGO stage distribution	
FIGO IB	20 (22.8%)
FIGO II	39 (44.3%)
FIGO III	22 (25.0%)
FIGO IV	7 (7.9%)

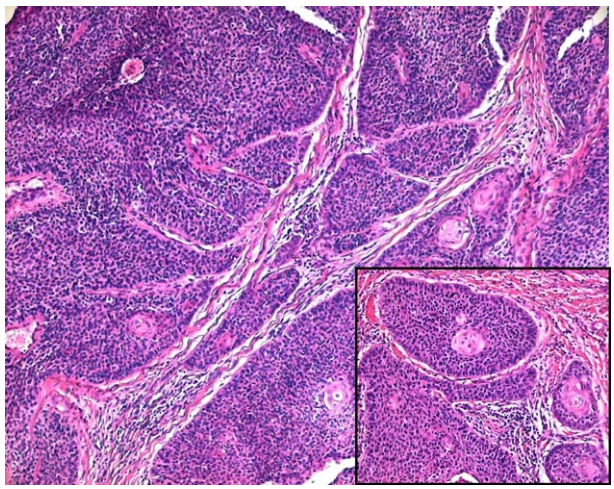

Fig. 1. Squamous cell carcinoma of the cervix uteri: well-differentiated tumor with small foci of keratinization and finger-like pattern of invasion representing a trabecular tumor growth. Inset, No DSR in the juxtatumoral stroma.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 11.5; SPSS GmbH, Munich, Germany). χ^2 and Fisher exact tests were used for the correlation of categorized parameters, the t test was used for statistical evaluations with numerical variables. $P < .05$ was considered as statistically significant.

3. Results

Most patients presented with tumors of FIGO stages I and II. The patients' characteristics are given in Table 1.

Most carcinomas (72.7%) showed a finger-like pattern of invasion (PI), whereas 24 (27.3%) grew in a spray-like pattern. A pushing border of infiltration was not seen.

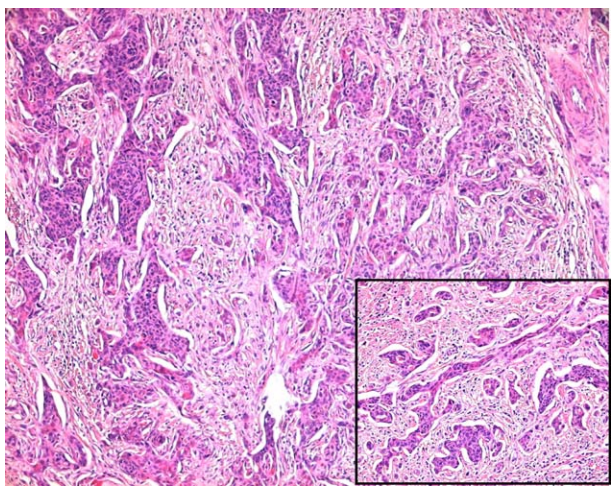

Fig. 2. Squamous cell carcinoma of the cervix uteri: poorly differentiated tumor with spray-like pattern of invasion representing a tumor growth in small groups of infiltrating cells. Inset, Strong DSR in the juxtatumoral stroma.

About 23.9% of the tumors showed no peritumoral desmoplastic reaction; 51.1% showed weak; 14.8%, moderate; and 10.2%, strong peritumoral desmoplastic reaction.

There was a strong correlation ($P < .0001$) between the strength of the DSR and the pattern of invasion (Figs. 1 and 2). Spray-like PI showed a significantly stronger desmoplastic reaction compared with the finger-like PI (Table 2). In addition, spray-like PI was significantly associated with poorly differentiated (G3) carcinomas ($P = .018$; Table 2). Moderate or strong DSR was strongly correlated with G2 and G3 carcinomas ($P = .027$; Table 3).

In about one fifth of the carcinomas (23.9%), no peritumoral inflammatory response was detected. Of the carcinomas, 51.1% presented weak; 14.8%, moderate; and 10.2%, strong inflammatory response (Table 3).

Neither the intensity of the DSR nor the peritumoral inflammatory response showed any correlation to the age of the patients ($P = .739$ for desmoplasmic stromal reaction; $P = .847$ for peritumoral inflammatory response).

There was no significant correlation between DSR and the grade of the peritumoral inflammatory response ($P = .879$) or between the pattern of invasion and the inflammatory response ($P = .069$). In addition, neither the pattern of invasion nor the intensity of the peritumoral desmoplastic reaction showed any correlation to the lymphovascular space involvement of the carcinomas ($P = .60$ for pattern of infiltration; $P = .565$ for desmoplastic reaction).

The clinical tumor size showed no correlation to the pattern of invasion ($P = .859$), DSR ($P = .195$), and peritumoral inflammatory response ($P = .538$).

Table 2
Correlation between the pattern of invasion and clinicopathologic parameters

	Pattern of invasion		
	Finger-like	Spray-like	*P*
Clinical tumor size			
Median (cm)	4,5	4.5	
Range (cm)	1.5-10.0	1.9-8.0	.86
Tumor stage			
FIGO IB	14	6	
FIGO II	31	8	
FIGO III	14	8	
FIGO IV	5	2	.66
Lymphovascular space involvement			
No	24	9	
Yes	40	15	.60
Tumor grade			
G1	8	3	
G2	45	8	
G3	11	13	.018
Inflammatory response			
None	13	7	
Weak	25	9	
Moderate	7	2	
Strong	19	6	.44
Desmoplastic stromal reaction			
None	16	5	
Weak	38	7	
Moderate	10	3	
Strong	0	9	<.0001

Table 3
Correlation between the different grades of DSR and clinicopathologic parameters

	Desmoplastic stromal reaction				
	None	Weak	Moderate	Strong	*P*
Clinical tumor size					
Median (cm)	4.2	4.5	5.0	4.35	
Range (cm)	1.9-8.8	1.5-8.0	3.0-10.0	2.2-7.0	.195
Tumor stage					
FIGO IB	7	9	2	2	
FIGO II	5	25	5	4	
FIGO III	6	9	4	3	
FIGO IV	3	2	2	0	.361
Lymphovascular space involvement					
No	10	17	3	3	
Yes	11	28	10	6	.565
Tumor grade					
G1	4	5	0	2	
G2	13	29	10	1	
G3	4	11	3	6	.027
Inflammatory response					
None	6	12	0	2	
Weak	4	20	6	4	
Moderate	2	3	3	1	
Strong	9	10	4	2	.155
Pattern of invasion					
Finger-like	16	38	10	0	
Spray-like	5	7	3	9	<.0001

4. Discussion

Different PIs have been reported for squamous cell carcinomas of different sites, for example, the skin, tongue, head, and neck, as well as the cervix uteri [3-6,11], as well as for gastric and endometrial adenocarcinomas [2,9]. It has been reported that the spray-like PI represents a high grade of tumor cell dissociation [1,2,11,12]. Some studies have evaluated a potential impact of PI on the prognosis of patients with cervical cancer, with contradictory results [5,9,10,12]. Unfortunately, the short period between the date of the tumor biopsy along with the morphologic evaluation of the tumor tissue and the time of this study does not allow an evaluation of survival or recurrence data in our study population now.

In squamous cell carcinomas of the skin, a spray-like PI was associated with a strong DSR [11]. In our study, there was also a strong correlation between the spray-like PI and a strong DSR ($P < .0001$). To the best of our knowledge, this correlation has not, so far, been described for carcinomas of the cervix uteri. The intensity of DSR, as understood in the context of a reaction of the tumor-surrounding stroma (ie, juxtatumoral stroma) tissue to the infiltrative tumor growth, representing the grade of peritumoral stromal remodeling on a morphologic level [15,16], might be indicative of the dissociation of the tumor growth and, thus, of its invasive potential. Spiro et al [4] reported a significant prevalence of the spray-like PI in younger patients with oral tongue cancer. However, we have been unable to see any correlation between PI and the patients' age in this study (data not shown).

It has been reported that a strong DSR is associated with a high frequency of lymph node metastases, recurrences, advanced tumor stage, increased tumor diameter, and poor overall survival in squamous cell carcinoma of the skin and the oral tongue [4,11]. For cervical carcinoma, we failed to demonstrate any correlation between the grade of the DSR, the frequency of lymphovascular space involvement, and the clinical (FIGO) tumor stage. Regarding the testing of the prognostic value of DSR in our study, the same limitation as for the pattern of invasion must be recognized. Low tumor differentiation (G3) was significantly correlated with the spray-like PI and a moderate or strong DSR in the present study (Tables 2 and 3). This phenomenon was also seen in squamous cell carcinomas of the skin and the oral tongue [4,11], indicating that poorly differentiated tumors may induce a strong remodeling process in the juxtatumoral stroma. In breast cancer, Fox et al [18] reported that the plasminogen activator inhibitor 1, as a parameter of tumor-associated proteolysis, might be involved in this remodeling process.

Several factors such as the connective tissue growth factor, the c-met/HGF system, and several kinds of metalloproteinases and its inhibitors are involved in the interaction between cancer cells and the surrounding juxtatumoral stroma of the organ invaded by the tumor [19-21]. Recent molecular data have identified a cluster of genes representing markers of the host reaction to the malignant tumor [22] with strong differences comparing gene expression profiles of *in vivo* and *in vitro* systems of cancer cells. So far, no studies have evaluated these factors about the DSR or to the prognosis of patients with cervical cancer.

In this study, there was a significant association of the pattern of invasion (finger-like vs spray-like) at the tumoral front of invasion, as well as poorly differentiated (G3) carcinomas and the intensity of the DSR in squamous cell carcinoma of the cervix. Both of these morphologic parameters were independent of tumor stage, tumor size, patients' age, and the intensity of the peritumoral inflammatory reaction. This association could be explained in the highly dissociative growth pattern of spray-like growing tumors and the resulting higher degree of juxtatumoral stromal remodeling. However, further studies, including molecular techniques, are required in patients with cervical cancer for further evaluation of tumor-stroma interactions.

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