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ORIGINAL ARTICLE

Blood Vessel Invasion in Endometrial Cancer Is One of the Mechanisms of Spread to the Cervix

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Abstract

To evaluate the association between type of invaded vessels (blood or lymphatic) and cervical involvement in endometrial cancer (EC). Pathological slides of 93 patients with EC who had vascular space invasion in hematoxylin-eosin staining underwent immunohistochemical assay with CD31 and podoplanin. CD31 and podoplanin were used to identify blood and lymphatic invaded vessels, respectively. Cervical stromal invasion (CSI) was determined in 21 (30%) patients. The rate of CD31-positivity was significantly higher in patients with CSI than without (76.2 and 34.7%, $p = 0.001$; respectively). Podoplanin-positivity was determined in 47.6 and 81.6% of patients with and without CSI, respectively ($p = 0.005$). Age, myometrial invasion and the combination of CD31-positivity with podoplanin-negativity were found as independent predictors for CSI. Blood vessel invasion is an important factor for CSI in EC. Blood vessel invasion rather than lymphatic vessel invasion is one of the predominant ways by which EC spreads to the cervix.

Keywords Lympho-vascular invasion · Podoplanin · CD31 · Blood vessel · Endometrial cancer

Introduction

Endometrial cancer (EC) is the most common gynecologic cancer of the female genital tract [1]. EC involves the uterine cervix in 5.8–20% of patients [2–4], and the presence of cervical involvement is associated with poor oncologic outcomes [5–8].

The most prominent mechanisms for cervical spread are direct surface or stromal extension, secondary to implantation and via vascular invasion [6, 9, 10]. However, the literature lacks data about distinct effects of blood or lymphatic vessel invasion in the cervical involvement of EC.

Vascular invasion is determined by the presence of malignant cells within the endothelial-lined space of blood vessels and/or lymphatic channels, using conventional hematoxylin-eosin (H&E) staining [11]. There is a great inter- and intra-observer variability in the detection of vascular invasion, and distinguishing blood vessels from lymphatic channels is particularly difficult via H&E staining [12–14]. In comparison, immunohistochemical (IHC) assay is suggested to provide more precise results in determining vascular invasion and for identification of the type of invaded vessels [15]. In recent years, podoplanin (D2–40) and CD31 immunostaining have been recommended to discriminate lymphatic and blood vessels, respectively [14, 16–18].

The primary objective of this study was to evaluate the association between the type of invaded vessels (blood or lymphatic) and cervical involvement in EC.

Materials and Methods

Data for 188 patients with EC who underwent a total hysterectomy, bilateral salpingo-oophorectomy and bilateral pelvic-

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paraaortic lymphadenectomy, and whose definitive pathology report revealed the presence of lympho-vascular space invasion (LVSI) in H&E staining between January 2000–January 2016 in our gynecologic oncology clinic, was obtained from electronic database searches and patient files. The study protocol was approved by the institutional review board (2016/216; 1). Patients who had EC, including sarcoma components, patients with secondary tumors and patients who received neoadjuvant therapy, were excluded initially.

Pathologic slides of uterus were reviewed by a specialized pathologist on gynecologic-oncology. LVSI is determined by the presence of tumoral cells or cell clusters that adhere to the vessel wall without differentiation between blood and lymphatic vessels in H&E staining sections, which include both tumor and adjacent tumor-free tissue. After exclusion of the patients ($n = 95$) whose pathologic slides and paraffin-embedded blocks were absent or unsuitable for evaluation, 93 patients' paraffin-embedded blocks were obtained.

Four-micron sections were obtained from paraffin blocks. Sections on the laminae were dried in an incubator at 45 °C for 12 h. CD31 (Roche®) and podoplanin (Roche®) were used for IHC detection. The IHC assay was performed by an automated Ventana Benchmark XT (Ventana™, Tucson, AZ) machine staining technique. Antibody features were as follows: for CD31: JC70; Cell Marque; Antigen Retrieval (AR): ethylenediaminetetraacetic acid (EDTA), 1/50 dilution, 95 °C, 64 mins; Roche®, and for podoplanin: D2–40; Cell Marque; AR: EDTA, 1/50 dilution, 95 °C, 64 mins; Roche®. Next, adhesive laminae were washed with detergent water, followed by rinsing under running water. Afterward, the laminae were dehydrated in 98% alcohol and then cleared in xylene. Spleen for CD31 and pleural tissue for podoplanin were used as a positive control. Vascular space involvement was defined as positive in the presence of tumoral cells or cell cluster(s) that adhere to the vessel wall, as evident by IHC assay. In the IHC assay, CD31 and podoplanin were used to identify blood and lymphatic invaded vessels, respectively (Figs. 1 and 2).

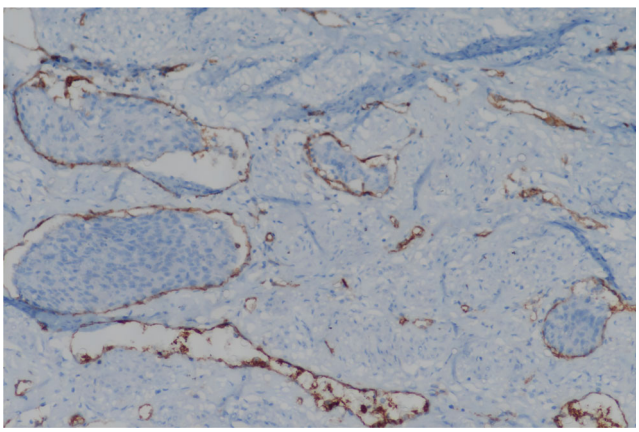

Fig. 1 CD31 positivity, tumoral invasion of vessel, Immunohistochemical assay, ×100

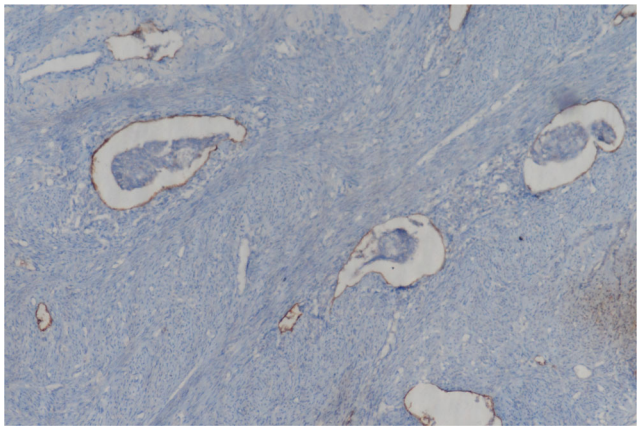

Fig. 2 Podoplanin positivity, tumoral invasion of vessel, Immunohistochemical assay, ×100

Patients whose slides did not exhibit immunoreactivity with both CD31 and podoplanin ($n = 23$ (24.7%)) were determined to be artifact rather than true LVI.

Tumors were staged according to the International Federation Obstetricians and Gynecologists (FIGO) 2009 criteria. Histologic type of EC was categorized into two groups, namely endometrioid and non-endometrioid type EC. According to the FIGO, tumor architecture was classified as either grade 1, 2 or 3. Clear cell carcinoma, serous carcinoma and undifferentiated carcinoma were defined as grade 3. Presence of cervical stromal invasion (CSI) was regarded as the presence of stromal invasion, with or without glandular invasion. Patients with only cervical glandular involvement, without any malignant cells and with free migrants in the cervix were included in the group without cervical invasion.

Statistical analysis was performed using SPSS Statistics for Windows v.17.0 (SPSS, Inc., Chicago, IL). Descriptive statistics were expressed as mean ± SD and median (range) for continuous variables, and number and percentage for categorical variables. Categorical variables were compared by using Chi-square or Fisher's exact test, as appropriate. Multivariate analysis was performed by using multinomial logistic regression analysis. Odds ratios, 95% confidence intervals and Wald statistics for each independent variable were also calculated. The level of statistical significance was set at $p < 0.05$.

Results

The study included 70 cases. The median age of the entire cohort was 59 (range; 37–79) years, at the time of diagnosis. Histologic type was endometrioid EC in 57 (81.4%) patients. The non-endometrioid type EC group (18.6%) included clear cell carcinoma in 2 patients, serous carcinoma in 5 patients and undifferentiated carcinoma in 6 patients. Fifty-three percent ($n = 37$) of the patients had stage 2 disease and above. Thirty-three (47.1%) patients had grade 3 tumor. CSI was

identified in 21 (30%) patients. Two patients had only cervical glandular involvement. The other pathologic findings were uterine serosal involvement in 4 (5.7%) patients, adnexal involvement in 10 (14.3%) and omental spread in 5 (7%). The median number of removed lymph nodes was 67 (range; 34–122). Lymph node metastasis was detected in 36% of the entire cohort. The clinical-pathological findings of the patients are shown in Table 1.

The pathologic slides exhibited immunoreactivity with CD31 only in 20 (28.6%) patients, with podoplanin only in 37 (52.9%) patients and with both markers in 13 (18.6%) patients. CD31 and podoplanin immunostaining were significantly associated with CSI status only. More cases showed involvement of CD31-positive vessels only in patients with CSI compared to those without CSI (76.2 and 34.7%, $p = 0.001$; respectively). Podoplanin-positive immunostaining was determined in 47.6 and 81.6% of patients with and without CSI, respectively ($p = 0.005$). Age (<59 vs. ≥59 years), histologic type (endometrioid vs. non-endometrioid EC), stage (1 vs. ≥2), status of lymph node metastasis (negative vs. positive), grade (1 vs. 2&3), myometrial invasion (<1/2 vs. ≥1/2), adnexal involvement (negative vs. positive), uterine serosal involvement (negative vs. positive) and omental spread (negative vs. positive) were not significantly associated with CD31 or podoplanin immunostaining (Table 2).

In univariate analysis, a young age (<59 years), deep myometrial invasion (≥1/2) and CD31 positive and podoplanin-negative immunostaining were significantly associated with CSI in EC (Table 3). Histologic type, grade, the tumor diameter and uterine serosal involvement were not related to CSI. In multivariate analysis; age, myometrial invasion and togetherness of CD31 positivity with podoplanin negativity were found as independent predictors for CSI (Table 4).

Table 1 Clinical-pathological findings of the entire cohort

Characteristics		*n*	%
Histology	Endometrioid	57	81.4
	Non-endometrioid	13	18.6
Stage	Stage 1	33	47
	1A	15	21.3
	1B	18	25.7
	Stage 2	4	6
	Stage 3	27	38.5
	3A	5	7.1
	3B	1	1.4
	3C	21	30
	3C1	8	11.4
	3C2	13	18.6
	Stage 4 (all 4B)	6	8.6
Grade	Grade 1	17	24.3
	Grade 2	20	28.6
	Grade 3	33	47.1
Depth of myometrial invasion	<1/2	20	28.6
	1/2≤	50	71.4
Uterine serosal involvement	Negative	66	94.3
	Positive	4	5.7
Cervical invasion	Negative	49	70
	Positive	21	30
Adnexal involvement	Negative	60	85.7
	Positive	10	14.3
Omental spread	Negative	64	91.5
	Positive	5	7
	NR	1	1.5
Status of lymph node metastasis	Negative	45	64
	Positive	25	36
Status of immunostaining	Only CD31 positive	20	28.6
	Only Podoplanin positive	37	52.9
	Both positive	13	18.6

n number of patients, *NR* not reported

Discussion

In the present study, age, myometrial invasion and blood vessel invasion were associated with CSI as independent factors. Blood vessel invasion, rather than the lymphatic route, could have a role in the dissemination of EC to the cervix, as evident by dual CD31 and podoplanin immunostaining.

The spread of cancer is a complex process that includes multiple steps, such as degradation of the basement membrane, adhesion, invasion of stroma, angiogenesis, cell proliferation, migration and anti-apoptosis [19]. Angiogenesis is a major step in the survival and uncontrolled proliferation of the malignant cells [17]. Concurrently with angiogenesis, increased permeability allows the penetration of tumor cells into the vascular space of blood vessels or lymphatic channels [17]. Therefore, vascular invasion plays a key role in local and distant dissemination of tumors [20–22].

Thus far, a limited number of studies have focused on the spreading mechanism of EC to the cervix, and conflicting results have emerged. In spite of the fact that asserted mechanisms for cervical dissemination are direct surface or stromal extension, secondary to implantation and vascular invasion [6, 9, 10], this issue is still debated. Furthermore, some of these reports are based on the examination of only endocervical curettage's specimens [9, 23].

Kadar et al. [9] reported histologic features of cervical involvement in EC. Based on the evaluation of endocervical specimens obtained from the fractional curettage, the authors subdivided this involvement pattern into four group. These included (1) free-floating malignant cells, (2) tumor confined exclusively to the surface epithelium (superficial endocervical

Table 2 Association between clinical-pathological findings and CD31 immunostaining, and podoplanin immunostaining in endometrial cancer

		Entire cohort						
			CD31 immunostaining			Podoplanin immunostaining		
Clinic-pathologic findings		*n*	N (%)	P (%)	*p* value	N (%)	P (%)	*p* value
Age	<59 years	34	52.9	47.1	0.989	32.4	67.6	0.496
	≥59 years	36	52.8	47.2		25	75	
Histologic type	Endometrioid	57	54.4	45.6	0.592	28.1	71.9	0.847
	Non-endometrioid	13	46.2	53.8		30.8	69.2	
Stage	1	33	57.6	42.4	0.455	21.2	78.8	0.195
	≥2	37	48.6	51.4		35.1	64.9	
Status of lymph node metastasis	Absent	45	51.1	48.9	0.694	31.1	68.9	0.525
	Present	25	56	44		24	76	
Grade	1	17	58.8	41.2	0.570	29.4	70.6	0.930
	2&3	53	50.9	49.1		28.3	71.7	
Myometrial invasion	<1/2	20	55	45	0.820	25	75	0.673
	≥1/2	50	52	48		30	70	
Uterine serosal involvement	Absent	66	51.5	48.5	0.616	28.8	71.2	1
	Present	4	75	25		25	75	
Cervical invasion	Absent	49	65.3	34.7	**0.001***	18.4	81.6	**0.005***
	Present	21	23.8	76.2		52.4	47.6	
Adnexal involvement	Absent	60	55	45	0.379	26.7	73.3	0.400
	Present	10	40	60		40	60	
Omental spread	Absent	64	53.1	46.9	0.665	28.1	71.9	0.623
	Present	5	40	60		40	60	

N negative, *P* positive, *n* number; *$p < 0.05$ is statistically significant

involvement), (3) tumor involving both the surface epithelium and stroma and (4) tumor with stroma only. Whereas only superficial endocervical involvement was determined in 13% of patients, 87% had stromal involvement. Also, 75% of patients with stromal invasion had no tumor present in the surface epithelium. Based on these findings, Kadar et al. [9] speculated that "dissemination of tumor in EC appears to predominantly occur by tissue spaces or via lymphatic channels

Table 3 Univariate analysis of association between pathologic features and cervical involvement

		Cervical involvement		
Pathologic features		N (%)	P (%)	*p* value
Age	<59 years	58.8	41.2	**0.046***
	≥59 years	80.6	19.4	
Histologic type	Endometrioid	73.7	26.3	0.188
	Non-endometrioid	53.8	46.2	
Grade	1	64.7	35.3	0.762
	2&3	71.7	28.3	
Myometrial invasion	<1/2	95	5	**0.004***
	≥1/2	60	40	
Diameter of tumor	<4 cm	85.7	14.3	0.054
	≥4 cm	62.5	37.5	
Uterine serosal involvement	Absent	72.7	27.3	0.078
	Present	25	75	
CD31 immunostaining	Negative	86.5	13.5	**0.001***
	Positive	51.5	48.5	
Podoplanin immunostaining	Negative	45	55	**0.005***
	Positive	80	20	

N negative, *P* positive, * *p < 0.05* is statistically significant

Table 4 Multi-variant analysis for prediction of cervical stromal invasion

	Hazard Ratio (95% CI)	*p*
Age	5.2 (1.08–25.4)	**0.04***
Combination of CD31 positivity with Podoplanin negativity	10 (2.15–48.2)	**0.003***
Histologic type	5.8 (0.99–34.5)	0.051
Myometrial invasion	21 (2.09–219)	**0.01***
Diameter of tumor	4.3 (0.886–21.1)	0.07

CI confidence interval

*$p < 0.05$ is statistically significant

than by contiguous surface extension". However, the hypothesis of cervical invasion via lymphatic channels has not yet been evaluated by more objective techniques.

Rubin et al. [23] assessed the cervical involvement in specimens from the fractional curettage and determined the free tumor fragments and stromal involvement participation in 67.5 and 32.5% of patients with FIGO stage 2 EC, respectively. Jordan et al. [3] defined the free-floating malignant cells in the endocervical canal as tumor migrants. Tumor migrants were determined in 40% of patients with EC and 60% of those had real cervical involvement. The association between cervical involvement, tumor migrants and serous histologic type is found to be significant. The location of cervical involvement was at the surface only in 40.6% of patients, the surface and stroma in 50% of patients and the stroma only in 9.4% of patients. Jordan et al. [3] concluded that the spread pattern of EC to the cervix occurs most frequently by surface contiguity or by implantation. Additionally, a peculiar behavior of contiguous spread of endometrioid EC to the cervix, in what is termed a 'burrowing pattern', is described in the literature [4, 24]. There is a predominantly contiguous glandular neoplastic spread, with a minimal stromal reaction, in this extremely rare pattern that can lead to misdiagnosis as concomitant primary endocervical endometrioid adenocarcinoma [4, 24].

In the present study, tumors that exhibited CD31-positive and podoplanin-negative immunoreactivity were at risk for CSI. Combined CD31-positivity with podoplanin negativity is one of the independent factors for CSI. These features showed that blood vessel invasion of tumors is significantly associated with CSI. According to our results, vascular invasion has a non-negligible significance in the spread pattern of EC to the cervix. Moreover, blood rather than lymphatic vessel invasion appears to have a more significant role in the cervical spread of EC.

Although LVSI was detected in conventional H&E staining, it could not be confirmed by IHC assay [25–27]. The false-positive rate of vascular invasion in H&E staining ranged from 10 to 24% [25–27]. One of the underlying reasons is the occurrence of pinch artifacts (possible "pseudo invasion" by tumor cells) and the resulting misinterpretation pose challenges. Another explanation is that the use of serial sections and their separate assessment may lead to the disappearance of the area of vascular invasion in the subsequent section because of the small focus of vascular invasion [26]. The other possible reason is difficulties in IHC staining of superannuated paraffin-embedded blocks. The rate of overdiagnosis in conventional H&E staining is 24.7%, in our study.

The primary limitation of this study is the small sample size. Conversely, the major strengths are the evaluation of the vascular invasion by objective techniques and identification of the invaded vessel type by dual staining. CD31 is also weakly expressed on few lymphatic vessels; therefore, areas with distinct and strong staining are considered as blood vessels [17, 25, 28]. However, this approach is subjective and has a risk of inter- or intra-observer difference. In our study, we used dual staining and analyzed the "combined CD31-positivity with podoplanin negativity" group to avoid this confusion.

In conclusion, blood vessel invasion is an important factor for CSI in EC. This study highlighted that blood vessel invasion rather than lymphatic vessel invasion is one of the predominant ways by which EC spreads to than cervix. Additional large-scale studies are needed to further delineate the affected vessel type related to cervical spread pattern.

Compliance with Ethical Standards

Conflict of Interest Statement The authors declare that there is no conflict of interest.

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