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Programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) expressions in type 2 endometrial cancer

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Abstract

Purpose The aim of this study was to evaluate prognostic importance of programmed death-1 (PD-1) and/ or programmed death-ligand 1 (PD-L1) expressions in type 2 endometrial cancer.

Study design

Formalin-fixed, paraffin-embedded tissue samples from 53 cases with type 2 endometrial cancer were analyzed. One-third of our cases had serous adenocarcinoma (32%), 11 had clear cell (21%) and 25 had mixed-type adenocarcinoma (47%). PD-1 and PD-L1 expressions in tumor tissue and microenvironment were detected by immunohistochemistry. Clinical and pathological characteristics including age, stage, initial symptom, surgical procedure, myometrial invasion, lymphovascular space invasion (LVSI), lymph node invasion, adjuvant therapy, and survival were reviewed. The Kaplan–Meier and Cox proportional hazards models were used to evaluate the prognostic factors.

Results PD-1 expression in tumor tissue and microenvironment was detected in 22 (42%) and 28 (53%) cases, respectively. PD-L1 expression was detected in tumor and microenvironment in 8 (15%) and in 15 cases (28%), respectively. Expression of PD-1 and PD-L1 expressions in tumor area was associated with shorter survival ($p=0.006$ and 0.001, respectively) but PD-1 and PD-L1 expressions in microenvironment were not found to be related with survival. PD-1 ($p=0.006$) and PD-L1 expressions ($p=0.001$) in addition to LVSI ($p=0.005$), myometrial invasion ($p=0.015$), lymph node involvement ($p=0.019$), and suboptimal cytoreduction ($p=0.042$), were found to be associated with poor prognostic indicators. PD-1 and PD-L1 expressions in tumor and lymph node involvement were determined as independent prognostic factors.

Conclusion PD-1 and PD-L1 expressions in type 2 endometrial cancers were found to be poor prognostic indicators.

Keywords Programmed death-1 (PD-1) · Programmed death-ligand 1 (PD-L1) · Prognostic factors · Type 2 endometrial cancer · Uterine clear cell carcinoma · Uterine serous carcinoma · Uterine mixed type adenocarcinoma

Introduction

There are two groups of endometrial cancer, type 1 and type 2, defined by Bokhman [1]. Non-endometrioid tumors, known as type 2, compose 15% of endometrial cancers and the cause of the majority of deaths together with advanced stage tumors and grade 3 endometrioid tumors [2]. From epidemiologic, clinic, histopathologic and molecular perspective, endometrial cancer is a heterogeneous and complex disease [3]. Molecular and histopathologic features have become important in the identification and more importantly the precise management of the disease [4].

Immune checkpoints play an essential role in providing self-tolerance and regulating the T-cell responses. PD-1 acts as an immunosuppressive co-inhibitory molecule and has two cognate ligands known as PD-L1 and PD-L2. PD-L1 is expressed in tissues such as tonsils, trophoblasts, lung; PD-L2 is expressed predominantly in dendritic cells and they have important effects in autoimmunity and inflammatory response [5]. The therapeutic effects of PD-1 and

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PD-L1 blocking antibodies have been investigated in various tumors and approved in various malignant tumors by FDA [5]. The most important point is to determine the patients that might get benefit from these agents. In last years, it has been shown that immunotherapy will have significant potential for the treatment of endometrium cancer [6].

To the best of our knowledge, this is the first study exploring prognostic value of the PD-1 and PD-L1 expressions in type 2 endometrial carcinomas both in tumor and microenvironmental areas.

Material and methods

Formalin-fixed, paraffin-embedded tissue samples from 53 cases with type 2 endometrial cancer who were operated and followed in our university clinic between January 1996 and December 2015 were analyzed. The patients who were operated in our clinic during this period but could not reach the paraffin blocks or were not followed up were not included in the study. Their pathologic diagnoses were established based on hysterectomy material evaluated by expert gynecological pathologists (E.K.B., D.G.) and the evaluation of the PD-1, PD-L1 staining was performed by one pathologist (E.K.B). This study was approved by Çukurova University, Faculty of Medicine, local ethical committee (2015.037.IRB.044) and was supported by the coordination unit of Scientific Research Projects (BAP–TSA-2015–4843) of Çukurova University.

Demographic variables (age, parity, menopausal status, presenting symptoms, medical history) and clinicopathologic variables (histopathological type, stage, the degree of myometrial invasion, lymph node involvement, LVSI, choices of adjuvant therapy, and survival outcomes) were evaluated. The staging was performed according to the FIGO 2009 guidelines. Open or laparoscopic total hysterectomy and bilateral salpingo-oophorectomy (TH + BSO) and pelvic/paraaortic lymphadenectomy with or without omentectomy were the main surgical procedures.

Chemotherapy and radiotherapy were administered for systemic and local controls, respectively. Patients were followed up every 3 months in the 1st year and then every 6 months up to 5 years. During follow up, patients underwent gynecological examination, transvaginal sonography, and thoracic and abdominopelvic computed tomography (every 6 months in the first 2 years and then per year). OS was defined as the time (months) between the date of surgery/diagnosis and the date of the death or last follow up.

Immunohistochemical staining

Immunohistochemical staining was performed on 5-mm sections of formalin-fixed, paraffin-embedded tissues. Monoclonal antibody MRQ-22, Ventana, was used to detect PD-1 and CD274/PDL1 AM26531AF-N and Acris, Germany, was used to detect PD-L1 expression. The visualization system used was the BenchMark XT with enzymatic digestion (ISH protease 2, Ventana) and the iView Blue Detection Kit (Ventana). Tumor samples stained with anti-PD-1 and PD-L1 were scored according to the intensity of cytoplasmic and/or membranous positivity as follows: 0 (no staining), 1 + (weak or equivocal staining), 2 + (moderate staining) or 3 + (strong staining). Tumor cells and microenvironment were considered as positive staining if they have more than 5% staining [7]. Since 2 + and 3 + staining were not found in our cases, the assessment was performed as positive or negative. Tumor microenvironment contains immune cells (mainly T lymphocyte), vasculature and lymphatics as well as fibroblasts and pericytes [8]. The practical implication of evaluating PD-1 and PD-L1 expressions in the microenvironment is the assessment of expression in tumor-infiltrating lymphocytes (TILs). Tonsil tissue was used as a positive and negative control.

Statistical analysis

Data were analyzed using the SPSS software version 20.0 (IBM, Armonk, NY, USA). The variables were tested to determine whether or not they were normally distributed using visual (histograms, probability plots) and analytical methods (Shapiro–Wilk test). Descriptive analyses were presented using mean ± SD. Chi-square and Fisher's exact tests were used for cross-tables. p value < 0.05 was considered statistically significant. The p value was presented as a two-tailed test. Expression of PD-1 and PD-L1 and survival times were computed using the Kaplan–Meier method. The Cox proportional hazard model was used to assess the significance of multiple variables.

Results

Analyses were performed on 53 patients followed regularly in our unit. The mean age of patients was 61.8 ± 9.2. The main symptom was abnormal uterine bleeding (n = 46, 87%). About half of the patients had a comorbidity (n = 27, 51%). Demographics and main clinical characteristics were shown in Table 1. Sixty-eight percent of the patients (n = 36) had an early-stage disease (stage 1–2). The myometrial invasion was higher than 50% in half of the patients (n = 27). Thirty-five patients (66%) had a LVSI. Lymph node involvement was found in 18 (42%) cases. Chemotherapy and radiotherapy as adjuvant treatments were given in 72% (n = 38) and 53% (n = 28) of the cases, respectively (Table 2).

PD-1 was positive in 42% (n = 22) in the tumor and 53% (n = 28) in the microenvironment, while PD-L1 was positive

Table 1 Demographics and main clinical characteristics of the patients (*n*: 53)

		n%	*p*
Age	< 55	13 (24.6)	0.155
	55–64	20 (37.7)	
	> 64	20 (37.7)	
Parity	0	10 (18.8)	0.804
	≥ 1	43 (81.2)	
Menopause	Premenopausal	8 (15.0)	0.101
	Postmenopausal	45 (85.0)	
Medical history	Cancer	0	
	Accompanying comorbidity	27 (51.0)	
Presenting symptom	Abnormal uterine bleeding	46 (87.0)	
	Bloating	4 (7.5)	
	Pain	3 (5.5)	

in 15% ($n = 8$) of the patients for tumor and 28% ($n = 15$) of the patients for microenvironment (Fig. 1). PD-1 and PD-L1 expressions in the tumor were found to be associated with poor survival times ($p = 0.006$, $p = 0.001$, respectively) (Fig. 2). The results of PD-1 and PD-L1 expression and their association with prognosis have been demonstrated in Table 2.

Age ($p = 0.155$), menopausal status ($p = 0.101$), stage ($p = 0.206$), histopathological subtype ($p = 0.711$) and PD-1 and PD-L1 expressions in microenvironment ($p = 0.062$, $p = 0.100$, respectively) were not found to be prognostic factors. However, optimal cytoreduction ($p = 0.042$), LVSI ($p = 0.005$), myometrial invasion ($p = 0.015$), nodal involvement ($p = 0.019$), PD-L1 expression ($p = 0.001$) and PD-1 expression in tumor ($p = 0.006$) were found to be associated with OS (Table 2). In multivariate analysis, PD-1 and PD-L1 expressions in the tumor and nodal involvement were found to be independent prognostic factors (Table 3).

Table 2 Clinical-pathological characteristics and PD-1/PD-L1 expressions in the tumor and microenvironment

		n (%)	Mean survival (month) ± SD	*p*
Surgery	Laparotomy	40 (75)		
	Laparoscopy	13 (25)		
LND	Unable to	10 (19)	25 ± 0.0	0.566
	PPALND	37 (67)	44 ± 9.5	
	PLND	6 (11)	27 ± 13.6	
Optimal cytoreduction	No	23 (43)	55.9 ± 9.5	0.042
	Yes	30 (57)	31.9 ± 4.2	
Histopathologic type	Serous	17 (32)	23.6 ± 2.8	0.711
	Clear	11 (21)	30.1 ± 5.9	
	Mixed	25 (47)	43.4 ± 7.4	
Stage	1 + 2	36 (68)	42.6 ± 5.7	0.206
	3 + 4	17 (32)	30.5 ± 6.6	
Nodal involvement	Negative	25 (58)	45.4 ± 5.7	0.019
	Positive	18 (42)	26.3 ± 6.2	
Myometrial invasion	< 50%	26 (49)	48.1 ± 6.0	0.015
	≥ 50%	27 (51)	25.2 ± 3.9	
LVSI	Negative	18 (34)	55.2 ± 7.6	0.005
	Positive	35 (66)	27.8 ± 3.8	
PD-L1 TM expression	Negative	45 (85)	45.7 ± 5.4	0.001
	Positive	8 (15)	15.8 ± 4.9	
PD-L1 MCE expression	Negative	38 (72)	24.2 ± 6.3	0.100
	Positive	15 (28)	28.7 ± 7.3	
PD-1 TM expression	Negative	31 (58)	49.2 ± 6.6	0.006
	Positive	22 (42)	24.9 ± 4.4	
PD-1 MCE expression	Negative	25 (47)	46.1 ± 5.3	0.062
	Positive	28 (53)	32.4 ± 6.1	
Radiotherapy	None	25 (47)	39.0 ± 7.5	0.911
	Received	28 (53)	37.2 ± 4.6	
Chemotherapy	None	15 (28)	39.3 ± 8.4	0.712
	Received	38 (72)	40.9 ± 6.2	
Status	Alive	24 (45)		
	Exitus	29 (55)		

PD-1 programmed death-1, *PD-L1* programmed death-ligand 1, *LND* lymph node dissection, *TM* tumor, *MCE* microenvironment, *LVSI* lymphovascular space invasion, *PPALND* pelvic–paraaortic lymph node dissection, *PALND* pelvic lymph node dissection

Discussion

Immunotherapy has been inevitably included in our current oncology practice. Immunotherapy has shown promising effects in non-small cell lung cancer, malignant melanoma, and Hodgkin's lymphoma, but there is no clear data about the efficacy of immunotherapy for gynecologic tumors including endometrial cancer [5, 6, 9]. Furthermore, there is a lack of evidence regarding survival based on intratumoral PD-1 and PD-L1 expressions in endometrial cancer. This study aimed to assess the expressions of PD-1 and PD-L1 in patients with type 2 endometrial cancer and to demonstrate the prognostic value of PD-1/PDL-1 expression in type 2 endometrial cancer. The results demonstrated that PD-1 and PD-L1 expressions can be considered as independent poor prognostic factors in this disease. Vanderstraeten et al. [10] reported PD-L1 expression in 83% (*n*: 29) and 100% (*n*: 9) of the cases with primary and metastatic endometrial cancer, respectively. Another study demonstrated no evidence between PD-1, PD-L1 expressions and OS in endometrial cancer unlike our results but reported an association between PD-1, PD-L1 expressions and higher microsatellite instability (MSI) [11].

We know that the fundamental difficulty is to elucidate the tumor and host characteristics that can determine the response to immunotherapeutic agents. Mismatch repair

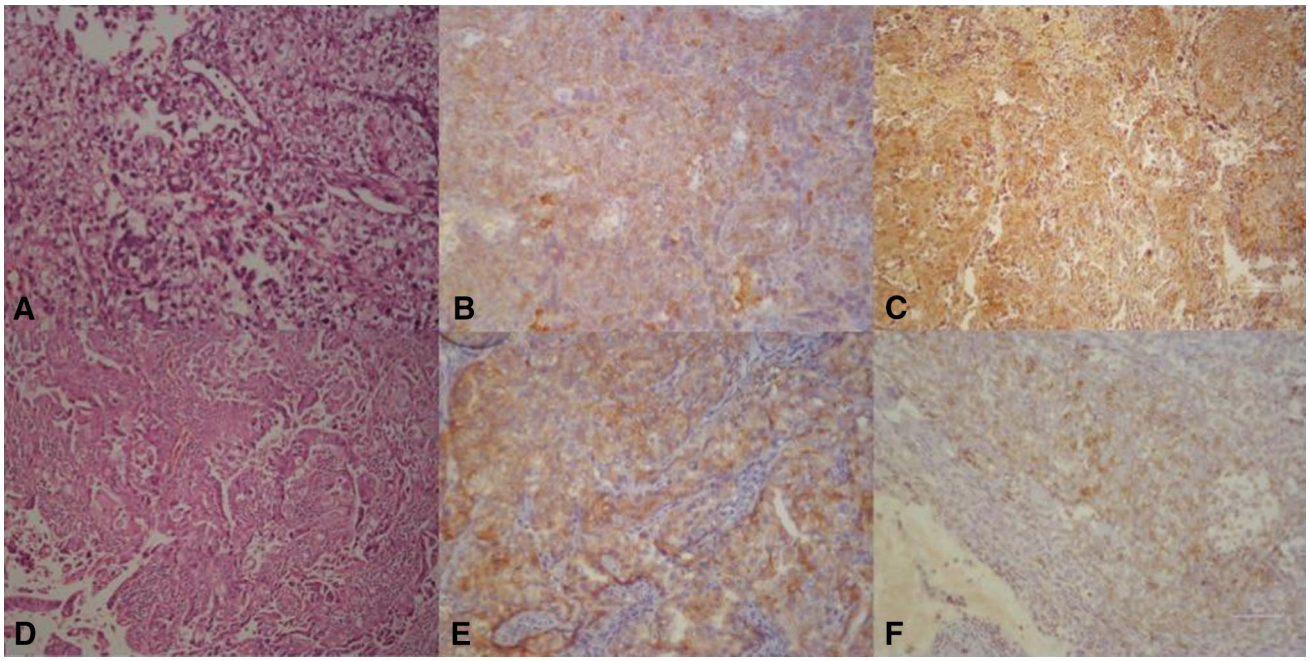

Fig. 1 Hemotoxylin–eosin sections of clear cell carcinoma (**a**, H&Ex100), and serous adenocarcinoma (**d**, H&Ex100), immunohistochemically PD-L1 positivity of the tumor cells in clear cell carcinoma (**b**, IHCx100), serous adenocarcinoma (**e**, IHCx100) and PD-1 positivity clear cell carcinoma (**c**, IHCx100), serous adenocarcinoma (**f**, IHCx100)

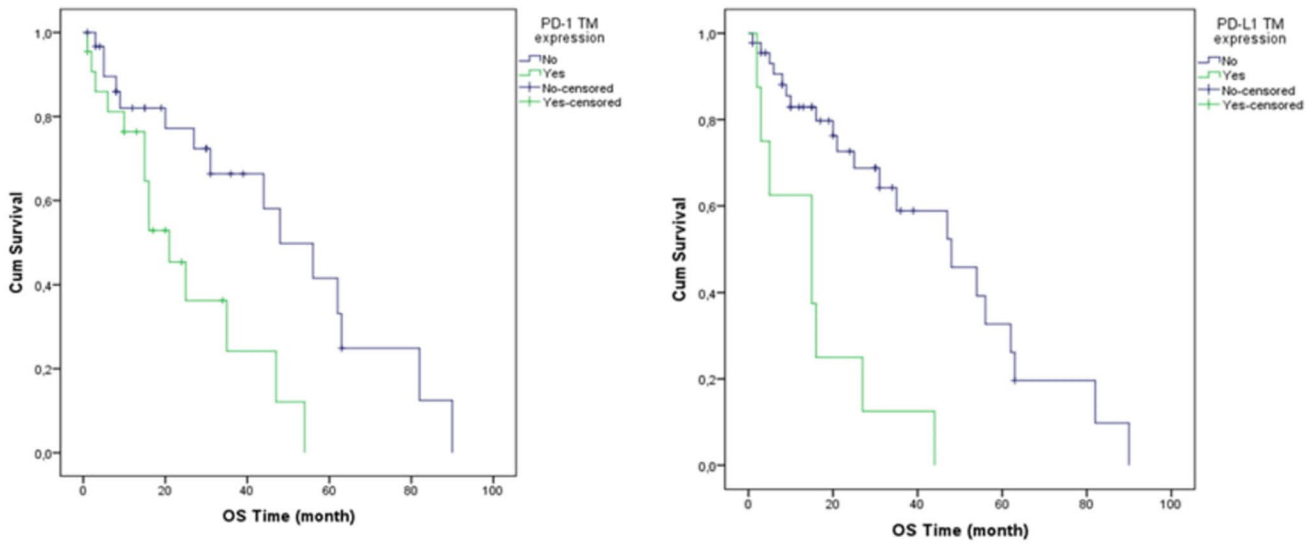

Fig. 2 Survival times according to the PD-1 and PD-L1 staining in tumor area

(MMR)-deficient status is predictive for response to checkpoint blockers [12, 13]. When comparing PD-L1 expression in MMR-deficient endometrial cancer ($n=38$) with those who have MMR intact endometrial cancer ($n=29$), Sloan et al. demonstrated a significant increase in tumoral and immune stromal PD-L1 expression in patients with MMR-deficient endometrial cancer than those with MMR intact tumors. Furthermore, MMR deficiency may be a better predictor of response to PD-1 and PD-L1 inhibitor therapy than the grade of endometrial carcinoma [14]. Bregar et al. reported the correlation between PD-L1 expression in MSI status and also high-grade tumors in 70 cases with endometrial tumors, including 10 serous type tumor; three of the serous tumors (30%) were positive for the PD-L1 expression [15]. Eggink et al. explored the immune infiltration and PD-1, PD-L1 expression in 116 high-risk

Table 3 Multivariate analysis of the clinical and pathological parameters and survival

	p	HR	95.0% CI	
			Lower	Upper
Stage	0.097	0.164	0.019	1.387
LVSI	0.148	2.521	0.720	8.829
Lymph node involvement	0.048*	8.709	1.024	74.070
Myometrial invasion	0.679	1.280	0.397	4.125
PD-L1 tumor	0.010*	3.868	1.384	10.808
PD-1 tumor	0.035*	2.561	1.070	6.132
Age	0.559	0.982	0.924	1.044

PD-1 programmed death-1, *PD-L1* programmed death-ligand 1, *LVSI* lymphovascular space invasion, *CI* confidence interval, *HR* hazard ratio

*p value < 0.05

endometrial cancers from the transPORTEC consortium and found an association between the presence of PD-1 and PD-L1 expression and increased immunological infiltration in highly mutated, neoantigenically rich POLE mutant and MSI endometrial tumors. With these results, they suggested that PD-L1 is primarily expressed by myeloid cells rather than tumor cells, especially in intratumoral stromal region [16]. This study results showed more expression of PD-Ll in the microenvironment as compared with tumor (28% vs 15%). Howitt et al. reported higher frequency for PD-L1 expression in intraepithelial immune cells and in POLE and MSI tumors [17].

There are conflicting results in the literature not only on the expression rate of PD1 and PD-L1 in tumors but also their prognostic value in different tumor types. These conflicting results may be due to the use of different IHC assays and cutoff points. Also, the possibility of PD-L1 expression from tumor cells, immune cells, and stromal cells shows substantial heterogeneity within the tumor and microenvironment. PD-L1 can be expressed in both tumor cells and immune/stromal cells. PD1 is usually expressed in T lymphocytes. We know that PD-1 is expressed in tumor cells in varied studies, while there is no clear findings about the expression mechanism [18, 19]. The time between sample collection and changes in PD-1/PD-L1 expressions after relapse is another important topic to focus on [5]. Although PD-L1 expression is the main marker, the current data cannot explain how the PD1 and PD-L1 blockade work due to technical difficulties and the ever-changing nature of the tumor and the microenvironment [6].

This study demonstrated the expression of the PD-1 and PD-L1 in non-endometrioid endometrial carcinoma as independent prognostic factors for survival as well as lymph node involvement. The results also demonstrated that optimal cytoreduction, LVSI, myometrial invasion and lymph node involvement are prognostic factors which was similar to some other studies [20–22]. This study could not reveal the prognostic difference between non-endometrioid type tumors such as serous and clear cell carcinoma due to the small number of the cases. There is no doubt that endometrial cancer is a heterogeneous group of diseases and the histopathologic diagnosis alone is sometimes insufficient to predict clinical outcome.

Currently, significant developments have occurred in the relationship between cancer genome and response to immune checkpoint inhibitors. Immune checkpoint inhibitors are an engaging and rational option in endometrial cancer especially for POLE ultramutated and MSI high endometrial cancer [23]. Of course, studies on immune checkpoint inhibitors for endometrial cancer are still in progress. There are 16 continuing clinical trials on the use of immune checkpoint inhibitors in endometrial cancer [23].

In conclusion, PD-1 and PD-L1 expressions are independent poor prognostic factors in type 2 endometrial cancer. Further studies are necessary to determine the role of immunotherapy in high-risk endometrial cancer classified by the molecular subtype.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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