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# MMR deficient undifferentiated/dedifferentiated endometrial carcinomas showing significant programmed death ligand-1 expression (sp 142) with potential therapeutic implications

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ABSTRACT

*Background:* Uterine undifferentiated (UEAC)/dedifferentiated (DEAC) carcinomas are rare malignant neoplasms. They appear to pursue an aggressive clinical course with an advanced stage at presentation. Recently, it was discovered that the use of immunotherapeutic drugs targeting programmed cell death protein 1 (PD1)/programmed death ligand-1 (PD-L1) was associated with improved survival in several types of cancer (especially in patients with mismatch-repair (MMR) deficient patients). Whether these findings can be applied to UEAC/DEAC remains a question. Herein, the aim of this study is to evaluate the expression of PD-L1/PD-1 in UEAC/DEAC and its relationship to MMR status. This could offer useful therapeutic information.

*Design:* Review of endometrial carcinoma (EC) diagnosed over the period of 2011 to 2017 in our institution identified 14 UEAC/DEAC cases (n = 14). All cases had immunohistochemistry performed for MMR (MLH1, PMS2, MSH2 and MSH6), PD-L1 and PD-1. The protein expression was examined and in DEAC cases both the undifferentiated component and the low grade component were recorded separately. The expression of PD-L1 and PD-1 was scored in both the tumor and the peritumoral lymphocyte infiltration.

*Results:* Overall variable degrees of tumoral or immune stromal PD-L1 staining (from 1% to 5%), was present in 50.0% (7/14) of UC/DEACs. Seven cases (50%) were PD-1 positive (immune stromal). Five cases (35.7%) showed co-expression of PD-1 and PD-L1 (Figure 1). Worth noting is that PD-1 staining was exclusively present in peritumoral immune cells. Following this the 14 cases were further divided into MMR deficient and MMR proficient groups (Table 1). A total of 8 cases had MMR deficiency (57.1%). There was a statistically significant association for PD-L1 positivity in the MMR deficiency group ($p = 0.05$). However there was no statistically significant differences regarding PD-1 positivity between MMR groups.

*Conclusions:* PD-L1 and PD-1 were expressed in majority of MMR-deficient UEAC /DEAC cases. PD-L1 was not expressed in MMR-proficient carcinomas. These findings might help support potential immunotherapy trials in MMR-deficient UEAC /DEAC.

## 1. Introduction

Endometrial carcinoma (EC) is the most common gynecologic malignancy in the USA [1]. EC represents a heterogeneous group of tumors, characterized by a spectrum of histomorphological and molecular changes [2]. The most common histologic type is endometrioid followed by serous carcinoma [2]. Undifferentiated endometrial carcinoma (UC) and dedifferentiated endometrial carcinoma (DAEC) are less common, accounting for less than 9% of ECs [3]. With regards to prognosis, UC/DAEC behaves more aggressively, having higher rates of recurrence and metastasis [3,4]. Currently, there is an urgent need to develop novel therapies in order to improve patient outcomes.

With this in mind, immonotherapies have gained much attention in the oncology world, secondary to their antitumor effects observed in several traditional chemo-resistant solid and hematological malignancies: such as melanoma, renal cell carcinoma, bladder carcinoma, breast carcinoma, non-small-cell lung carcinoma, and Hodgkin's lymphoma [5]. Current immunotherapy targets include programmed death ligand 1 (PD-L1) and programmed death receptor 1 (PD-1) [5].

Furthermore, PD-1 is a transmembrane receptor expressed by activated T cells, natural killer cells, B cells, and antigen-presenting cells [6]. PD-L1 (one of the PD-1 ligands) is expressed at the surface of either

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inflammatory or non-inflammatory cells [7]. Normally the interaction of PD-1/PD-L1 can avoid over activation of the immune system through inhibition of T-cell proliferation [6,7]. Worth mentioning is that the key role of the PD-L1/PD-1 axis in tumor microenvironment formation and immune escape is now well established [6,7]. In many cancers however, tumor cells can also aberrantly express PD-L1, inhibiting the normal immune surveillance functions (by binding with PD-1 on immune cells), thus favoring tumor growth and metastasis [6,7]. Therefore, disruption the PD-1/PD-L1 axis in tumors can potentially activate immune system and facilitate elimination of cancer cells. This constitutes the rationale for PD-L1/PD-1 immune checkpoint therapies [7,8]. Importantly, in many clinical trials, the response rates of various tumor types to PD-L1/PD-1 targeting therapies correlated with the immunohistochemical expression of PD-L1 [9]. This suggests that PD-L1 expression may be predictive of a tumors sensitivity to immunotherapy. Therefore, proper evaluation of PD-L1 status may become clinically significant in the management of these cancer patients.

To the best of our knowledge, this is one of the first studies on PD-L1 expression (clone SP142) in UC/DEAC. From our literature search, it is evident that the relationship of PD-L1 with the clinical/histopathological features of these cancers remains unknown. Worth noting is that PDL-1 is a surrogate marker with potential therapeutic benefits from Atezolizumab [10]. Lastly, our study will aim to characterize the expression of PD-1 and PD-L1 in UC/DEAC and correlate this with clinical and pathologic features.

## 2. Materials and methods

### 2.1. Case selection and classification

A total of 14 cases of 'endometrial UC/DEAC carcinoma' were identified in our institutional database from 2000 to 2017. All cases were reviewed independently by two senior gynecological pathologists in order to confirm the diagnosis and to identify the best tumor-containing slide. All samples were obtained with informed consent from the Institutional Review Board of the respective hospitals that the patients were treated in.

### 2.2. Immunohistochemistry

Formalin fixed and paraffin embedded tumor sections were cut at 4 μm thickness and were stained on the Ventana Bench Mark Autostainer (Ventana Medical System, Tucson, Arizona) for the following antibodies: PD-L1 antibody (Clone SP142 from Ventana), PD-1 antibody (Clone NAT 105 from Ventana), MLH-1(M1, Ventana), PMS2 (EPR 3947, Ventana), MSH2(G219-1129, Ventana), and MSH6 (44, Ventana). These assays utilize rabbit monoclonal primary antibodies on paraffin-embedded tissue sections. The specific antibody were visualized using OptiView DAB IHC Detection Kit (Cat. No. 760-700 / 06396500001) followed by the OptiView Amplification Kit (Cat. No. 760-099 / 06396518001 (50 test) or 860-099 / 06718663001 (250 test)). All the staining was performed at the Immunopathology Laboratory of Long Island Jewish Medical Center (Northwell Health System, New Hyde Park, NY).

The expression of PD-L1 and PD-1 was scored in both the tumor and the peritumoral lymphocytes (immune stroma), a definitive membranous stain that was present in more than 1% of tumor cells or lymphocytes was considered positive. For this study, as recommended by Kulangara et al, we used the combined positive score (CPS) to calculated percent staining [28]. The CPS incorporates PD-L1 expression by both tumor cells and immune cells into a single score that can be assessed directly by a pathologist [28]. Given that the TPS (tumor proportion score) is the ratio of the number of PD-L1–expressing tumor cells to that of all tumor cells, it is mathematically feasible to combine it with the MIDS (both are fractions with a common denominator) [28]. The result of this combination—the combined positive score (CPS)—is then, the ratio of the number of all PD-L1–expressing cells (tumor cells, lymphocytes, macrophages) to the number of all tumor cells [28]. A cut-off of 1% was used because of the US Food and Drug Administration (FDA) granting of pembrolizumab for the treatment of cancers with scoring > 1% [28]. MLH1, PMS2, MSH2, and MSH6 were scored as retained (+) if > 10% of tumor cells were positive, a cutoff proposed by Shia et al. [29]. Finally, positive and negative controls were performed for all stains used in this study.

### 2.3. Statistical analysis

Statistical analysis was performed using the two-tailed Fisher exact test and Student t tests
(vassarstats.net) depending on the type of variables being analyzed.

## 3. Results

### 3.1. Case review

A total of 14 cases with available tissue blocks were used for immunohistochemical analysis. Out of 14 cases, 12 were underwent TAH-BSO (Total abdominal hysterectomy with bilateral salpingo-oophorectomy) procedures. Two cases underwent biopsy only. During follow-up the two biopsy only cases were included for the analysis of immunohistochemical expression, however were not included for the assessment of clinicopathologic variables.

### 3.2. Tumoral and peritumoral immune PD-1/PD-L1 expression together with MMR status in UC/DEAC

Overall, variable degrees of tumoral or immune stromal PD-L1 staining (from 1% to 5%) was present (in 50.0% (7/14) of UC/DEACs). Regarding these seven cases, 50% were PD-1 positive (in the immune stroma). Five cases (35.7%) showed co-expression of PD-1 and PD-L1 (Fig. 1). Worth noting is that PD-1 staining was exclusively present in peritumoral immune cells. Following this the 14 cases and their staining results were further divided into MMR deficient and MMR proficient groups (Table 1). A total of 8 cases had MMR deficiency (57.1%). There was a statistically significant association for PD-L1 positivity in the MMR deficiency group ($p = 0.05$) (Table 2). However there was no statistically significant differences regarding PD-1 positivity between MMR groups.

### 3.3. Expression of PD-L1 and clinicopathologic variables

All the 12 cases that underwent total hysterectomy with bilateral salpingo-oophorectomy were included in the analysis (Table 3). There was no statistically significant difference in the age at diagnosis between PD-L1 positive group and negative groups ($p > 0.05$). There was also no statistical difference between the two groups regarding FIGO stage at presentation, lymphovascular invasion, depth of myometrial invasion and positive lymph nodes ($p > 0.05$). During follow-up, one case was excluded because the patient expired due to a cardiovascular event. In the remaining 11 cases, 5 of them expired (5/11) within 2 years of surgery. There was no difference regarding overall two-year survival rate post initial diagnosis between the PD-L1 positive group and the PD-L1 negative group.

## 4. Discussion

In this pilot study, we studied the immunohistochemical expression of PD-L1 and PD-1 in endometrial UC/DEAC. To our best knowledge, this is one of the first studies to explore PD-L1 as a potential prognostic and therapeutic biomarker in these rare entities.

In recent years, inhibition of the PD-L1/PD-1 has shown impressive clinical results in various types of solid and hematological

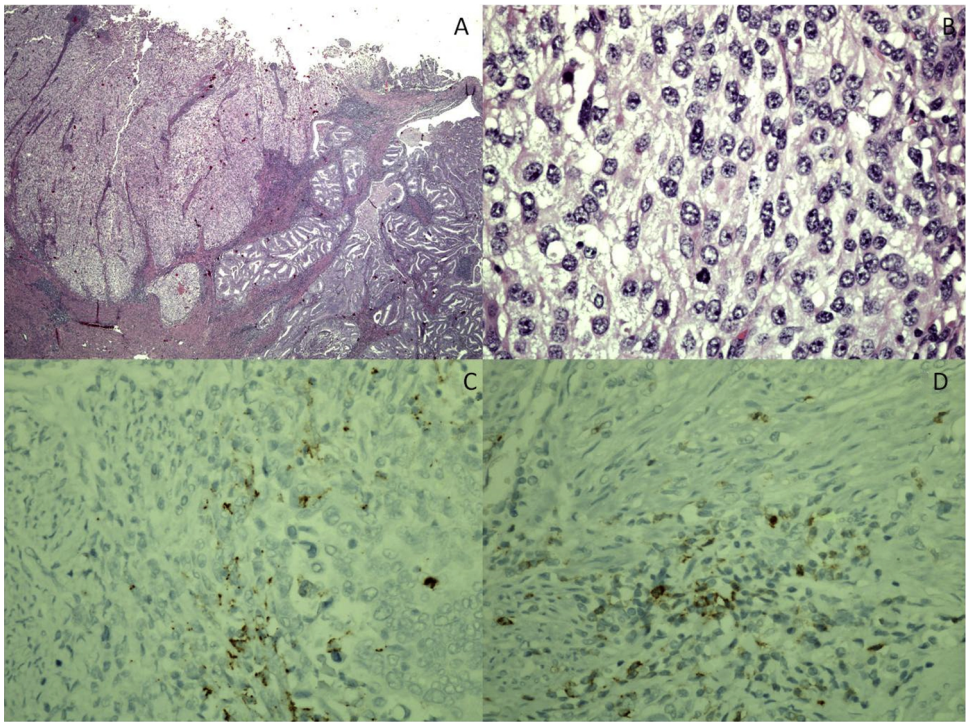


**Fig. 1.** Co-expression of PD-1 and PD-L1.
1A: 4x showing dedifferentiated component and undifferentiated component; 1B: 40x showing undifferentiated carcinoma; 1C: 40x PD-L1; 1D: 40x PD-1.

malignancies, many of which were previous resistant to chemotherapy and carry poor prognosis [11]. The value of PD-L1 in endometrial carcinoma has also gained recent attention, the immune system plays an important role in endometrial carcinogenesis [12]. It has been shown that a high number of CD8 + T cells was independent favorable prognostic variable in overall survival in the endometrial carcinoma [13]. Some early ongoing clinical trials have been investigating the benefits of immune checkpoint drugs in endometrial carcinoma and Nivolumab has shown promising results in recurrent heavily pretreated and hyper-mutated endometrial cancer [14]. Therefore, endometrial UC/DEAC may be also an attractive target for immunotherapy due to its aggressive biological nature [3,4]. Multiple clinical trials have correlated the expression of PD-L1 in several types of cancers by immunohistochemistry with tumor response to PD-1/PD-L1 inhibitor therapy and prognosis [9]. Ultimately identification and validation of PD-L1 expression could offer important clinical information in order to guide immunotherapy.

Cancer studies have shown variable expression of PD-L1: dependent on the antibody clone, the cut-off value and histologic types [15–17]. In our study however we demonstrated that (7/14, 50%) of UC/DEAC have PD-L1 expression (in at least 1% of tumor cells or peritumoral lymphocytes). This finding is in conjunction with Sloan EA et al's observation (that 4/7, 57.1% of their DEAC showed tumoral PD-L1 expression) [18]. Additionally, our results are also congruent with that of Maysa Al-Hussaini's group, which showed that 66% of the 15 UEC cases were positive for PD-L1. [19]. While per contra, Chavez, J et al, found no relation between dMMR and PDL-1 expression using the Ventana clone SP263 [27]. The difference in results could be due to the different clones used (sp 142 vs 263), study designs and patient cohorts. Worth mentioning is that the primary aim in Chavez, J et al's. study was to look at differences between two main types of deficient MMR ECs, epigenetic due to MLH1 promoter methylation and mutated dMMR due to genetic mutation [20]. Furthermore, their study also did not look at a cohort of UC/DAECs such as presented in our study [20]. Importantly however, it has been shown that overall PD-L1 expression appears to be more relevant to mismatch repair status (MMR) endometrial cancers [18]. Endometrial cancers that were MMR deficient demonstrated positive PD-L1 expression in Sloan EA et al's study [18]. This finding is

**Table 1**
All 14 Cases and Staining Results.

| | Age | Number | Diagnosis | PD-L1 (HG) | PD-L1 (LG) | PD-L1 (TIL) | PD-1 (HG) | PD-1 (LG) | PD-1 (TIL) |
|---|---|---|---|---|---|---|---|---|---|
| Loss of MMR | 85 | 8 | EEC + DEAC | 1-5% | 0% | 0% | 0% | 0% | 5% |
| | 47 | | EEC + UD | N/A | 0% | 5% | N/A | 0% | 0% |
| | 71 | | EEC + DEAC | 0% | 0% | 1% | 0% | 0% | 30% |
| | 84 | | EEC + DEAC | 0% | 0% | 0% | 0% | 0% | 5% |
| | 87 | | EEC + DEAC | 1% | 0% | 0% | 0% | 0% | 80% |
| | 60 | | EEC + UD | 0% | n/a | 1% | 0% | n/a | 5% |
| | 58 | | EEC + DEAC | 0% | n/a | 1% | 0% | n/a | 1% |
| | 90 | | EEC + DEAC | 0% | 0% | 0% | 0% | 0% | 0% |
| Retain MMR | 64 | 7 | EEC + DEAC | 0% | 0% | 0% | 0% | 0% | 0% |
| | 74 | | UD | 0% | n/a | 0% | 0% | n/a | 5% |
| | 50 | | UD | 0% | n/a | 0% | 0% | n/a | 0% |
| | 46 | | EEC + UD | 0% | 0% | 0% | 0% | 0% | 5-10% |
| | 72 | | UD | 0% | 0% | 0% | 0% | 0% | 5% |
| | 68 | | Serous + UD | 0% | n/a | 0% | 0% | n/a | 5% |

**Table 2**
MMR Deficient vs MMR Proficient Groups.

| Cases N (%) | PD-L1 (+) N (%) | *p* | PD-1 (+) N (%) | *p* |
|---|---|---|---|---|
| MMR deficient n = 8 (57.1%) | 6 (42.8%) | = 0.05 | 2 (14.2%) | > 0.05 |
| MMR proficient n = 6 (42.8%) | 1 (7.1%) | | 5 (35.7%) | |
| Total n = 14 (100%) | 7 (50%) | | 7 (50%) | |

**Table 3**
Expression of PD-L1 and Clinicopathologic Variable.

| | PDL1 positive (n = 6) | PDL1 Negative (n = 6) | *p* |
|---|---|---|---|
| Age at Diagnosis | 68.0 ± 15.9 | 68.5 ± 15.2 | 0.47 |
| Stage at presentation | | | |
| Uterus Confined disease (FIGO stage I and II) | 4 | 3 | 0.62 |
| Extrauterine Disease (FIGO stage III and IV) | 2 | 3 | |
| Lymphovascular invasion present (n) | 3 | 4 | 0.49 |
| Myometrial invasion | | | |
| ≤50% (n) | 3 | 1 | 0.27 |
| > 50% (n) | 3 | 5 | 0.27 |
| Lymph nodes status | | | |
| positive | 1 | 2 | 0.49 |
| negative | 5 | 4 | 0.49 |

also observed in our current study with approximately 75% of our MMR deficient cases showing PD-L1 expression (while only 17% in MMR stable cases).

MMR deficient tumors are known to mutate rapidly, resulting in an accumulation of neoantigens [18,21]. This leads to increased immunogenicity (MSI high endometrial cancers are richly infiltrated with T lymphocytes) [19]. Howitt et al demonstrated that MSI-hypermutated endometrial cancers were characterized by high neoantigen loads and increased tumor infiltrating lymphocytes [21]. Studies have shown that UC/DEAC has a relatively high MMR deficient rate (50%–60%) [18,22,23]. Our study, as consistent with previous, shows that MMR deficiency is present in 57.1% of UC/DEAC. Patients in this disease cohort (MMR deficient with high PD-L1 expression) could be excellent candidates for immunotherapy.

In our series, we also evaluated PD-1 status in peritumoral/tumoral infiltrating lymphocytes. The association of PD-1 and its response to immunotherapy is not as well established (compared to PD-L1) [8]. Studies have shown that in advanced melanoma patients with CTLA-4 and PD-1-high double-positive infiltrating lymphocytes showed better response to Nivolumab or Pembrolizumab [24]. In our study most of our cases had PD-1 expression (78.5%), with no statistical difference in expression between MMR deficient and MMR intact groups. Notably, especially in the MMR intact group, PD-1 appears to be more prevalent than PD-L1 expression (5 cases versus 1 case). This discrepancy may raise the possibility of other involved immunomodulation pathways (besides PD-L1/PD-1) in MMR intact cancers. For example, PD-L2 can also serve a ligand for PD-1 [25]. It has been suggested that PD-L2 can be detected in the absence of PD-L1 [25,26]. PD-L2 status was also a significant predictor of progression-free survival with pembrolizumab independent of PD-L1 status [26]. Therefore, absence of PD-L1 in our cases may not exclude the potential therapeutic value of PD-L1 immunotherapy [26].

Finally, our study, in line with other studies, did not find a correlation between PD-L1 expression and clinicopathological features (including overall survival). Recently, in the largest study on correlation of PD-L1 and with clinicopathological features of 700 endometrial cancers, PD-L1 positivity was only statistically associated with lymphovascular invasion [27]. The absence of this finding in our study could be due to the limited sample size. Nevertheless, the correlation of PD-L1 expression with major clinicopathological features in endometrial carcinoma is ambiguous and currently not well understood [27]. This may reflect the dynamic nature of the immune response in tumor microenvironments; however, single evaluations of immune markers are not a summation of the complex immune responses seen in cancer.

In summary, in line with other studies, we herein demonstrate that some degree of tumoral and/or immune stromal PD-L1 is expressed in UC/DEAC, especially in MMR deficient patients. Finally, patients with these tumors could experience potential therapeutic benefits from Atezolizumab, warranting clinical trials.

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