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Original Research Paper

Pathology

ASSOCIATION OF PD-L1 EXPRESSION WITH HISTOLOGICAL GRADE OF ENDOMETRIAL CARCINOMA

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ABSTRACT A cross-sectional study to analyze PD-L1 expression in 38 endometrial specimens consisting of 23 low-grade endometrial carcinoma, and 15 high-grade endometrial carcinoma cases was conducted. Positive PD-L1 expression was defined as ≥5% of tumor cells staining positive. PD-L1 expressions and histological grade of endometrial carcinoma were significantly associated.

KEYWORDS : PD-L1, Endometrial carcinoma, grade.

Introduction

Endometrial carcinoma is the fourth most common malignancy among women and the sixth biggest cause of death among cancers in 2017. Most cases are at the age of ≥50 years. Endometrial carcinoma is divided into endometrioid and non-endometrioid histologically, which early stage cases having good survival rate while advanced stage cases having about 17% in 5-year survival rate. Management of endometrial carcinoma over the last decade has become more complex where there is no second-line therapy after surgery and chemotherapy.[1,2]

Recently immune checkpoint inhibitors in Programmed death ligand 1 (PD-L1) have shown promising results in several types of malignancy. This opens up a new approach to the management of endometrial carcinoma. PD-L1 expressions were commonly upregulated on the surface of solid tumor cells which were associated with tumor grade. The pattern of PD-L1 expression might be very important for the suitability of the therapeutic blockade of this pathway.[3,4]

PD-L1 expressions have been studied for the last two decades in many types of malignancy. In this study, PD-L1 expressions were observed in low-grade endometrial carcinoma, and high-grade endometrial carcinoma. This aimed to find out the association of PD-L1 expression with histological grade of endometrial carcinoma.

Methods

Sample Selection

This cross-sectional study was conducted on 38 endometrial cases in Anatomical Pathology Department of Universitas Sumatera Utara, Medan, Indonesia between 2014 and 2018. Inclusion criteria were specimens that were diagnosed histologically as grade 1-3 endometrioid carcinoma, mucinous carcinoma, serous carcinoma, clear-cell carcinoma, dedifferentiated carcinoma and mixed carcinoma of endometrial cancer. Exclusion criteria included all metastatic cancers that have similar histological features as primary endometrial carcinoma. Each case was reviewed by 3 observers. This study protocol was approved by the research ethics committee of Universitas Sumatera Utara.

PD-L1 staining and grouping procedure

PD-L1 staining was started by making a four-microns-thick section and deparaffinized it after section adhered to coated object glass. The section was put on the hot plate for 30 minutes then. Subsequent to the process, advanced staining using BOND-MAX fully automated immunohistochemistry (Leica Biosystems) was taken place. After staining, sample was dehydrated in alcohol for three minutes and immersed in xylene for three times. The process ended with mounting. PD-L1 expression was calculated on brown stained tumor cells using light microscope. It would be grouped as positive PD-L1 expression if stained tumor cells count was more or equal to 5% and vice versa.[5]

Statistical analysis

Analysis was done using the SPSS 22 version (SPSS Inc, Chicago) with 95% confidence interval. Analysis using Chi-square test with significant $p<0.05$ was performed.

Results

Thirty-eight cases of endometrial carcinoma in this study were in the age range of 32-85 years with the majority of cases in the age range of 45-75 years (84.2%). The youngest case of this study was grade 1 endometrioid carcinoma, while the oldest one was grade 3 endometrioid carcinoma. Mean age of this study was 57.4 years. Median value and range of age were divided based on histological type of endometrial carcinoma and described in **Table 1**.

Table 1. Frequency of endometrial carcinoma based on histological type and age

Histological type	n = 38 (100%)	Median (Min – Max)
Endometrioid carcinoma		55 (32 – 85)
Grade 1	13 (34.2%)	52 (32 – 71)
Grade 2	5 (13.2%)	65 (48 – 78)
Grade 3	2 (5.3%)	62 – 85
Variant of endometrioid carcinoma		57 (55 – 71)
Secretory carcinoma	1 (2.6%)	55
Villoglandular carcinoma	2 (5.3%)	57 – 71
Mucinous carcinoma	1 (2.6%)	37
Mixed carcinoma		57 (51 – 75)
Endometrioid-mucinous carcinoma	1 (2.6%)	52
Endometrioid-serous carcinoma	1 (2.6%)	75
Endometrioid-clear-cell carcinoma	1 (2.6%)	63
Serous-clear-cell carcinoma	1 (2.6%)	51
Serous carcinoma	5 (13.2%)	55 (45 – 77)
Clear-cell carcinoma	4 (10.5%)	60 (55 – 71)
Dedifferentiated carcinoma	1 (2.6%)	63

Low-grade endometrial carcinoma involved grade 1-2 endometrioid carcinoma, variants of endometrioid carcinoma, mucinous carcinoma, and mixed endometrioid-mucinous carcinoma. Total of these low-grade lesions were 23 (60.5%) cases. High-grade endometrial carcinoma comprised of grade 3 endometrioid carcinoma, serous carcinoma, clear-cell carcinoma, dedifferentiated carcinoma, and 3 others mixed carcinoma. Total of these high-grade lesions were 15 (39.5%) cases.

Positive PD-L1 expressions were found on 25 (65.8%) cases involving 13 (52%) cases of high-grade endometrial carcinoma (2

cases of grade 3 endometrioid carcinoma, 4 cases of serous carcinoma, 3 cases of clear-cell carcinoma, dedifferentiated carcinoma and 3 cases of mixed carcinoma) and 12 (48%) cases of low-grade endometrial carcinoma (6 cases of grade 1 endometrioid carcinoma, 3 cases of grade 2 endometrioid carcinoma, 1 case of villoglandular carcinoma, mucinous carcinoma, and mixed endometrioid-mucinous carcinoma). Negative expressions were found on 13 (34.2%) cases comprised of 2 (15.4%) others high-grade endometrial carcinoma and 11 (84.6%) others low-grade endometrial carcinoma (**Table 2**).

Table 2. Association of PD-L1 expression with histological grade of endometrial carcinoma

PD-L1 expression	High-grade endometrial carcinoma	Low-grade endometrial carcinoma	P	Prevalence ratio (CI=95%)
Positive	13 (52%)	12 (48%)	0.028	3.380
Negative	2 (15.4%)	11 (84.6%)		

Based on the comparison of the positive and negative PD-L1 expressions cases, there is a significant assotiation between PD-L1 expression and histological grade of endometrial carcinoma ($p = 0.028$). The positive rate of PD-L1 expression in high-grade endometrial carcinoma is 3.38 times greater than low-grade endometrial carcinoma.

Discussion

In this study, we included 65.8% endometrioid type and 34.2% non-endometrioid type of endometrial carcinoma when this was grouped by histological type. While grouping from the histological grade, we found 60.5% low-grade endometrial carcinoma and 39.5% high-grade endometrial carcinoma. Studies by Bregar et al and Li et al also classified cases of endometrial carcinoma into a two-tier grading system to do a comparison.[6,7]

In characteristics of age, this study has a mean age of 57.4 years with an age range of 32-85 years. Most cases of endometrial carcinoma in this study are in the age range of 45-75 years, whereas study by Li et al had a mean age of 60.5 years with a range of 26-91 years. The study by Li et al divided cases into 3 age groups, specifically the age group of 55-64 years with the highest proportion, followed by groups with age ≥ 65 years and <55 years. In general, the age characteristics of endometrial carcinoma in this study had a slightly lower mean age compared to the study by Li et al but had the similar highest proportion of cases in the age group of 55-64 years.[7]

PD-L1 expressions were seen in different histological types including endometrioid, serous, and clear-cell carcinoma. Cases of high-grade endometrial carcinoma including grade 3 endometrioid carcinoma or non-endometrioid carcinoma showed a higher proportion of tumoral PD-L1 expression. PD-L1 expressions were seen in 56% of high-grade endometrial carcinoma and 35% of low-grade endometrial carcinoma in the study by Bregar et al. The positive PD-L1 expressions in this study were found in 86.7% of high-grade endometrial carcinoma and 52.2% of low-grade endometrial carcinoma. Here we saw that positive PD-L1 expressions were more likely to occur in high-grade endometrial carcinoma.[6,7]

PD-L1 expressions were positive in 47.6% of low-grade endometrioid carcinoma cases, while the study by Ishak et al. found positive PD-L1 expressions in 46% of low-grade endometrioid carcinoma cases.[8] The expression of PD-L1 appeared to be predisposed to high-grade endometrioid carcinoma and non-endometrioid endometrial carcinoma, but when studied further quite a few positive PD-L1 expressions were seen in low-grade endometrioid carcinoma in both studies. Increased expression of PD-L1 may have something to do with the formation of high neoantigen load as in malignancies with microsatellite instability (MSI) status. When observed from the study by Sloan et al, PD-L1 was positive in low-grade endometrioid carcinomas more commonly found in cases with MSI status than microsatellite stable (MSS).[7,9,10]

The expression of PD-L1 is an additional tool for screening patient selection for the immunotherapy trial. Further research is needed to better determine whether PD-L1 expression can be used as a prognostic biomarker of endometrial carcinoma in addition to clinical trials.

Conclusion

There is significant association between PD-L1 expression and histological grade of endometrial carcinoma.

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