IMMUNOHISTOCHEMICAL EXPRESSION OF PROGRAMMED DEATH-LIGAND 1 (PD-L1) IN COLORECTAL ADENOCARCINOMA AT H. ADAM MALIK GENERAL HOSPITAL MEDAN

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Abstract

Background: Colorectal cancer is the third most common malignancy in the world. Based on GLOBOCAN data, colorectal cancer in 2020 ranks 3rd most in the world with 1.9 million new cases (10%) and the second most common cause of death, 935 thousand (9.4%). Ligands from PD-L1 can be expressed on tumor cells, T cells and B cells, macrophages. The objective of this study is to determine PD-L1 expression based on age, sex, tumor location, histopathological subtype, clinical stage, grading, PNI, vascular invasion, lymphatic invasion, stromal TILs, tumor budding, depth of invasion, lymph node involvement, tumor metastasis, and lesion growth patterns in patients with colorectal adenocarcinoma.

Methods: This study was a descriptive study with a cross-sectional approach on 40 samples from surgical resection, diagnosed histologically as colorectal adenocarcinoma and stained with PD-L1 immunohistochemical staining.

Results: In this study, PD-L1 expression was found in 15 male colorectal adenocarcinoma patients (77.8%), with an age range of 50-59 years in 15 samples (68.2%), the most common histopathological subtype was adenocarcinoma NOS 21 sample (70.0%). The location is the left colon of 15 samples (71.4%). The depth of tumor invasion (T) is T3 in 19 samples (79.2%). Most without involvement of the KGB 21 samples (72.4%), most without metastasis 26 samples (74.3%). The most stage II stage 14 samples (87%). Grading low grade 19 samples (76.0%). Lymphatic invasion was positive in 12 samples (70.6%). Vascular invasion from EMVI and IMVI results were the same in 8 samples. The most expressed perineural invasion was negative in 21 samples (72.4%). Tumour budding had low budding in 17 samples (73.9%). Stromal TILs rich 23 samples (74.2%). Growth patterns of infiltrating lesions in 24 samples (80.0%).

Conclusion: The expression of PDL-1 was found mostly positive in 29 samples of 40 samples (72,5%) of colorectal adenocarcinoma.

Keywords: colorectal, adenocarcinoma, PD-L1

Introduction

World Health Organization defines colorectal cancer as a malignant epithelial tumor originating in the large bowel with invasion of tumor cells through the muscularis mucosa into the submucosa. Ninety percent of all colorectal cancer are adenocarcinoma. Based on the Global Burden of Cancer (GLOBOCAN) data, the incidence of colorectal cancer in 2020 ranks third in the world, which is 1.9 million new cases (10%) and the second leading cause of death after lung cancer, which is 935 thousand cases (9.4%). In developed countries the incidence of colorectal cancer is 4 times more than in developing countries.[1,2] By 2030 the number of newly diagnosed cases and deaths related to colorectal cancer is expected to reach more than 2.2 million and 1.1 million cases, respectively. Mortality rate of colorectal cancer ranks third of all common malignancy in men and woman worldwide.[3,4] In Indonesia, colorectal cancer ranks fourth with 34,189 new cases (8.6%), and the second most common cancer in men after lung cancer.1 Chronic inflammatory bowel disease (Crohn's disease and ulcerative colitis) may increase the

risk of colorectal cancer. The risk of colorectal cancer is higher in men than in women which is thought to be due to hormonal differences.[5]

Programmed death-1 (PD-1; CD279) is one part of regulatory T cells that is expressed on the surface of active T cells, B cells and natural killer (NK) cells.[6] PD-1 may also be selectively upregulated due to persistent exposure to antigens, so the expression of PD-1 on T cells is one of the markers of exhausted T cells.[7] Meanwhile, the ligand of programmed death-ligand 1 (PD-L1; B7-H1 and CD274) may be expressed on tumor cells, T cells and B cells, macrophages, and certain types of cells. The binding between PD-L1 and PD-1 sends the inhibitory signals to reduce cytokine production and T cell proliferation thus ultimately lead to increased apoptosis in T cells.[8]

There is few research on PD-L1 expression in colorectal adenocarcinoma. Previous research with colorectal cancer samples conducted by Rosenbaum et al. found that PD-L1 was more often positively expressed in tumors with poor differentiation.[9] Meanwhile, research conducted by Masugi et al. stated that PD-L1 expression in colorectal tumors was not associated with multivariable analysis.[10] A study by Janzic et al. found a significant association between PD-L1 and 54 samples of squamous cell carcinoma and lung adenocarcinoma, where PD-L1 expression was higher in tumor cells of squamous cell carcinoma variants compared to adenocarcinoma.[11,12] The role of PD-L1 in colorectal adenocarcinoma requires further research. The things mentioned above and some results of the previous research which are still controversial, became the basis for the author to conduct this research. The aim of this study is to determine the frequency distribution and PD-L1 expression characteristics of colorectal adenocarcinoma patients based on age, gender, tumor location, histopathological subtype, clinical stage, grading, PNI, vascular invasion, lymphatic invasion, stromal TILs, tumor budding, depth of invasion, lymph node involvement, tumor metastasis, and lesion growth pattern in patients with colorectal adenocarcinoma at H. Adam Malik Hospital Medan.

Methods

The design of this research is a descriptive study with cross-sectional approach to assess the expression of PD-L1 immunohistochemistry in colorectal adenocarcinoma. The study was conducted at the Anatomic Pathology Laboratory of H. Adam Malik Hospital Medan using paraffin blocks and slides from surgical resection that had been histologically diagnosed as colorectal adenocarcinoma which met the inclusion criteria. The exclusion criteria were incomplete clinical data and missing or unrepresentative paraffin blocks/slides which could not be processed, cut and re-staining.

Histopathology grading was assessed microscopically on the components of glandular differentiation, in which divided into low-grade tumor if ≥50% glandular formations were found, and categorized as high-grade tumor if 0-49% of glandular formations were found. Location of tumor was divided into 3 categories as follows: right colon, left colon, and rectum. Depth of invasion was divided into T1 (tumor invades submucosa), T2 (tumor invades muscularis propria), T3 (tumor invades subserosa, or into non-peritonealized pericolic or perirectal tissue), and T4 (tumor invades the other organ, and/or perforates visceral peritoneum). Regional lymph node involvement was divided into N0 and N1, tumor metastasis was divided into M0 and M1. The stage of tumor was classified according TNM system (AJCC): stage I, II, III, and IV. Perineural invasion, vascular invasion, and lymphatic invasion were also assessed. Vascular

invasion was divided into 3 categories: no invasion, IMVI, and EMVI. Both perineural and lymphatic invasion were divided into 2 categories: there is invasion and no invasion. Peritumoral budding was assessed according to ITBCC and divided into 3 categories, as follows: low budding (0-4 buds), intermediate budding (5-9 buds), and high budding (≥10 buds). Stromal TILs was categorized into TILs rich (stromal TILs ≥ 60%) and TILs poor (stromal TILs < 60%). The growth pattern of lesion was divided into 3 categories: exophytic, infiltrative, and exophytic + infiltrative.

Immunohistochemical staining of PD-L1 was performed using rabbit monoclonal antibody that was diluted at 1:100. PD-L1 expression was percentage of tumor cells which identified by the presence of brownish staining in membrane and/or cytoplasm of tumor cells either completely or partially circular with any color intensity.[9,13] Assessment was performed in 10 high power field with 400x magnification.[9] The expression of PD-L1 was scored as follows: score 0 (< 5%), score 1 (5-49%), score 2 (≥ 50 %) and categorized into negative (score 0) and positive (score 1-2). Immunohistochemical staining was evaluated and scored by two independent pathologists and the researcher.

Results

Forty samples of colorectal adenocarcinoma were obtained in this research. Table 1 shows the distribution of sample characteristics based on gender, age, histopathological subtype, location, depth of invasion, lymph node involvement, metastasis, stage, tumor grade, lymphatic invasion, vascular invasion, perineural invasion, tumor budding, stromal TILs, lesion growth pattern, and PD-L1 immunohistochemical expression.

Table 1. Characteristics of colorectal adenocarcinoma patients

Characteristics	N=40	%
Gender		
Male	22	55,0
Female	18	45,0
Age		
< 30 years	2	5,0
31-39 years	4	10,0
40-49 years	3	7,5
50-59 years	22	55,5
60-69 years	6	15,0
70-79 years	1	2,5
≥ 80 years	2	5,0
Histopathology subtype		
Adenocarcinoma NOS	31	77,5
Micropapillary	5	12,5
Mucinous	3	7,5
Serrated	1	2,5
Location		
Right colon	7	17,5
Left colon	21	52,5
Rectum	12	30,0
Depth of tumor invasion		
T1	2	5,0
T2	11	27,5
T3	24	60,0
T4	3	7,5
Regional lymph node involvement		
N0	29	72,5
N1	11	27,5
Metastasis		
M0	35	87,5
M1	5	12,5

Characteristics	N=40	%
Stage		
I	13	32,5
II	16	40,0
III	6	15,0
IV	5	12,5
Grade		
Low grade	25	62,5
High grade	15	37,5
Lymphatic invasion		
Negative	23	57,5
Positive	17	42,5
Vascular invasion		
Negative	21	52,5
IMVI	8	20,0
EMVI	11	27,5
Perineural invasion		
Negative	29	72,5
Positive	11	27,5
Tumor budding		
Low budding	23	57,5
Intermediate budding	5	12,5
High budding	12	30,0
Stromal TILs		
Rich	31	77,5
Poor	9	22,5
Growth pattern		
Infiltrating	30	75,0
Exophytic	6	15,0
Infiltrating + exophytic	4	10,0
PD-L1 Expression		
Negative	11	27,5
Positive	29	72,5

According to table 1, most patients were men (55%) and in the group of age 50-59 years (55,5%), with the oldest was 83 years old and the youngest was 22 years old. The most common histopathological subtype in this study was adenocarcinoma NOS (31 samples, 77,5%), followed with 5 samples (12,5%) of micropapillary, 3 samples (7,5%) of mucinous subtype, and 1 sample (2,5%) of serrated subtype. The location of the tumor was predominantly found in left colon (52,5%). Most of samples was T3 (60%), no metastasis found (87,5%), and stage 2 tumor (40%). The grade of colorectal adenocarcinoma in this study was predominantly low-grade tumor (62,5%), with 27,5% samples had extramural vascular invasion, negative perineural invasion (72,5%), low budding tumor (57,5%), and had rich stromal TILs (77,5%). The most common growth pattern of tumor found in this study was infiltrating pattern (75%). Most tumor had positive expression of PD-L1 which was found in 29 samples (72,5%).

Table 2. The expression of PD-L1 based on characteristics of colorectal adenocarcinoma patients

Variable	PD-L1 expression			
	Negative (n = 11)		Positive (n = 29)	
	n	%	n	%
Gender				
• Male	7	31,8	15	68,2
• Female	4	22,2	14	77,8
Age				
• < 30 years	0	0	2	100
• 31 – 39 years	0	0	4	100
• 40 – 49 years	1	33,3	2	66,7
• 50 – 59 years	7	31,8	15	68,2
• 60 – 69 years	3	50,0	3	50,0
• 70 – 79 years	0	0	1	100
• ≥ 80 years	0	0	2	100
Histopathological subtype				
• Adenocarcinoma NOS	9	30,0	22	70,0
• Micropapillary	1	20,0	4	80,0
• Mucinous	0	0	3	100
• Serrated	1	100	0	0
Location				
• Right Colon	1	14,3	6	85,7
• Left Colon	6	28,6	15	71,4
• Rectum	4	33,3	8	66,7
Depth of Tumor Invasion				
• T1	1	50,0	1	50,0
• T2	5	45,5	6	54,5
• T3	5	20,8	19	79,2
• T4	0	0	3	100
Regional lymph node involvement				
• N0	8	27,6	21	72,4
• N1	3	27,3	8	72,7
Metastasis				
• M0	9	25,7	26	74,3
• M1	2	40,0	3	60,0
Stage				
• I	6	45,2	7	53,8
• II	2	12,5	14	87,5
• III	1	16,7	5	83,3
• IV	2	40,0	3	60,0
Grade				
• Low Grade	6	24,0	19	76,0
• High Grade	5	33,3	10	66,7
Lymphatic invasion				
• Negative	6	26,1	17	73,9
• Positive	5	29,4	12	70,6
Vascular invasion				
• Negative	8	38,1	13	61,9
• IMVI	0	0	8	100
• EMVI	3	27,3	8	72,7
Perineural invasion				
• Negative	8	27,6	21	72,4
• Positive	3	27,3	8	72,7
Tumor Budding				
• Low Budding	6	26,1	17	73,9
• Intermediate Budding	0	0	5	100
• High Budding	5	41,7	7	58,3
Stromal TILs				
• Rich	8	25,8	23	74,2
• Poor	3	33,3	6	66,7
Growth pattern				
• Infiltrating	6	20,0	24	80,0
• Exophytic	3	50,0	3	50,0
• Infiltrating + exophytic	2	50,0	2	50,0

In this study, most samples showed positive expression of PD-L1 immunohistochemistry which was found predominantly in male (68,2%). All samples in group of age < 30 years, 31-49 years, 70-79 years and ≥ 80 years showed positive expression. Most adenocarcinoma NOS and micropapillary subtype showed positive expression of PD-L1, 70% and 80% respectively, while all mucinous subtype had positive PD-L1 expression. Most left colon tumor, T3 tumor, N1, stage 2, low grade tumor, positive perineural invasion tumor, rich stromal TILs, and infiltrating growth pattern tumor had positive PD-L1 expression. All tumor with IMVI had positive expression of PD-L1.

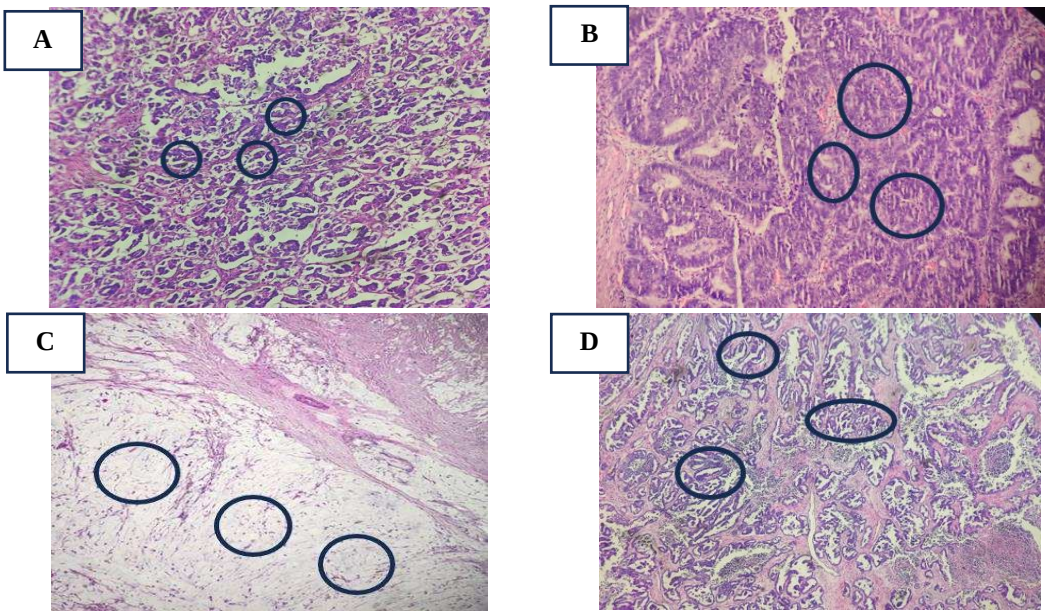

Figure 1. Histopathological subtypes of colorectal adenocarcinoma. **A**. Micropapillary (H&E, 10x). **B.** Adenocarcinoma NOS (H&E, 10x). **C.** Mucinous (H&E, 10x). **D.** Serrated (H&E, 4x).

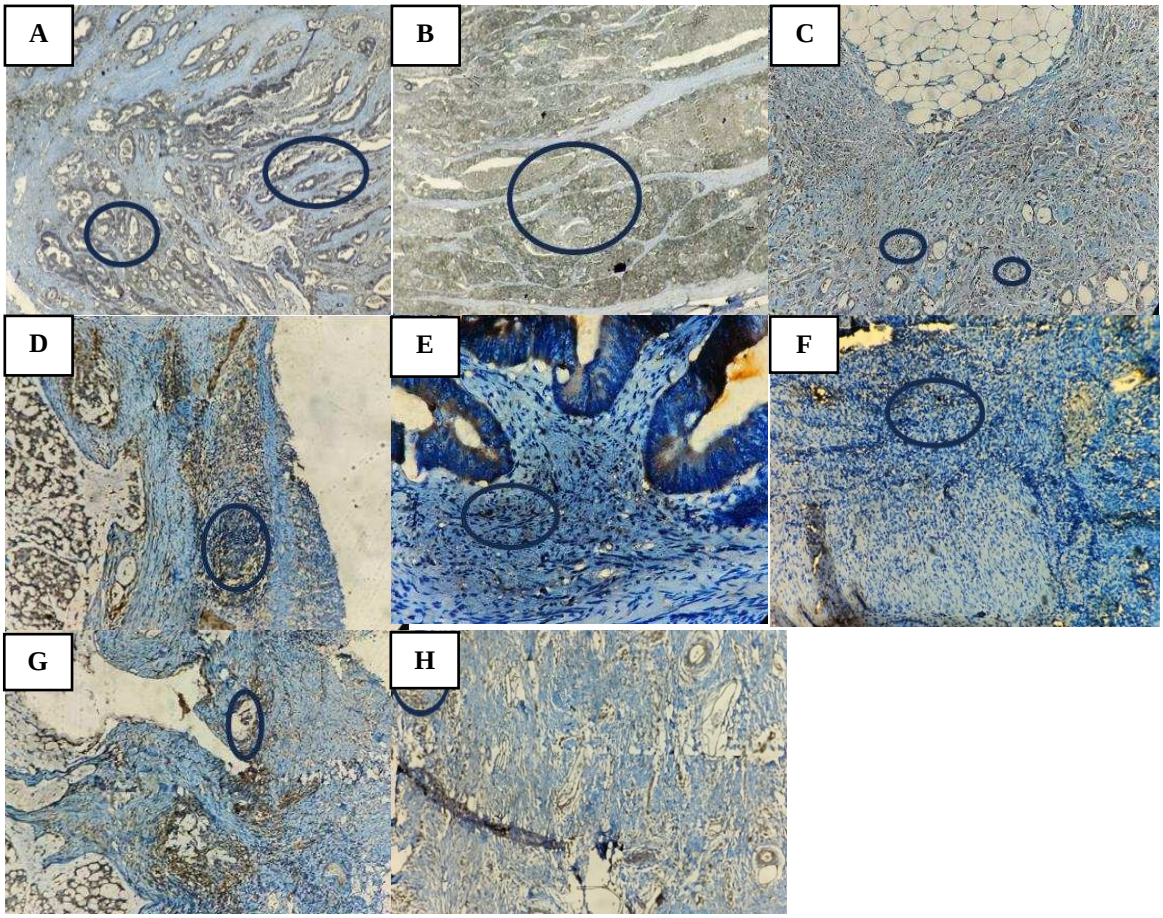

Figure 2. Positive PD-L1 immunohistochemical expressions. **A.** Low grade tumor**. B**. High grade tumor. **C.** Tumor budding**. D.** Perineural invasion **E.** TILs poor. **F.** TILs rich**. G.** Vascular invasion. **H.** Lymphatic invasion.

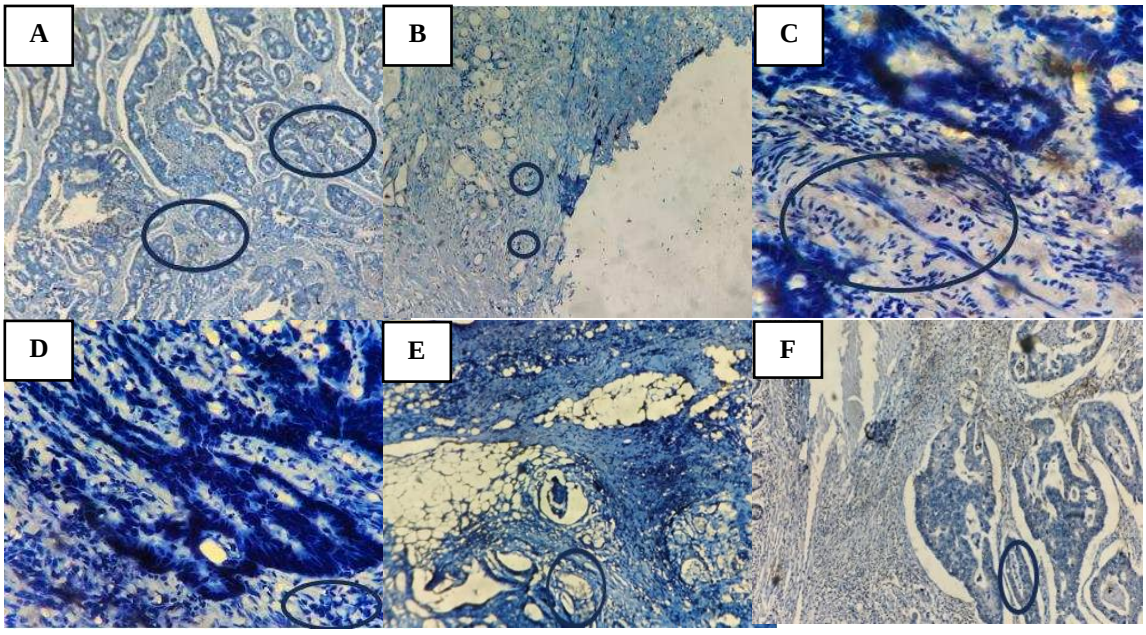

Figure 3. Negative PD-L1 immunohistochemical expressions. **A.** Low grade tumor**. B**. Tumor budding. **C.** Perineural invasion**. D.** TILs poor **E.** Lymphatic invasion. **F.** Vascular invasion**.**

DISCUSSION

Forty samples were obtained and as many as 22 samples (55.0%) were men. In line with Nasution's research, the results of colorectal adenocarcinoma patients were mostly men as many as 44 samples (54.3%).[14] Research conducted by Noh et al., found that most colorectal adenocarcinoma patients were men as many as 291 samples (60.1%).[15] In contrast to research by Rosenbaum et al., found that most patients with colorectal adenocarcinoma were women as many as 100 samples (53%).[9] Research by Masugi et al., with the results of research on colorectal adenocarcinoma patients in women 458 samples (56%).[10]

According to the researchers, most results were obtained in men because they were influenced by hormones, where in women estrogen levels are higher than in men. Estrogen hormone is protective factor in colorectal adenocarcinoma. This is in accordance with research conducted by Li et al., stating that in women the estrogen has a protective role against colorectal carcinogenesis, estrogen can regulate the growth of colonic epithelial cells and inhibit the proliferation of colorectal adenocarcinoma through estrogen receptors, and indirectly by reducing secondary bile acids and Insulin-like Growth Factor-I (IGF-1).[16] Another study mentioned that in women, progesterone can also reduce the risk of colorectal adenocarcinoma, because of its activity in helping synthesize endogenous sex hormones.[17] Unhealthy lifestyles, such as frequent consumption of alcoholic beverages and heavy smoking for a long period of time, are factors that develop this malignancy in men. This may cause changes in the normal mucosa of the digestive tract, due to the oxidation of acetaldehyde from ethanol metabolism which causes inflammation of the digestive tract mucosa and abnormal cell growth.[18]

The largest age group of patients was 50-59 years (55.0%) which in line with previous researches conducted by Zhu et al. and Li et al.[19,20] In contrast to research by Wang et al., and Noh et al. found the results of age over 60 years more suffer from colorectal adenocarcinoma.[8,15] Old patients with colorectal adenocarcinoma may be caused by a lack of awareness about health, low endurance in old age and unhealthy lifestyle factors at a young age. WHO states that most colorectal carcinoma patients are found in the age group > 50 years associated with diet and lifestyle patterns that accumulate with age. Patients with colorectal adenocarcinoma at the age of < 40 years generally have a family history, such as a history of HNPCC, FAP, intestinal infection Crohn's disease, and ulcerative colitis.[2] In this study, the highest age range of PD-L1 expression was between 50 - 59 years with 15 samples (68.2%). In line with previous research conducted by Li et al., getting the most PD-L1 expression at the age of ≤ 60 years.[20] In contrast to previous research conducted by Wang et al., getting results at the age of over 60 years with 35 samples (22.9%).[8] The decrease of immune system in old age may cause PD-L1 was more expressed.

The most common histological subtype in this study was colorectal adenocarcinoma NOS (75.0%), this is in accordance with research conducted by Schwarz et al.[21] but contrast to the Rosenbaum et al. research which medullary subtype was predominantly found.[9] The histological subtype that expressed PD-L1 was colorectal adenocarcinoma NOS as many as 21 samples (70.0%), in line with research by Schwarz et al.[21] Research conducted by Srivastava et al., obtained 29.6%, samples and mentioned that there was an association between PD-L1 expression in tumors.[22]

In this study, tumors were mostly found in the left colon (52.5%), this is in accordance with previous research of Valentini et al. and Park et al, 50.79% and 74,2% respectively. Different research conducted by Srivastava et al., obtained the most common location was in the right colon.[22-24] Left colon expressed PD-L1 mostly compared to the other location (71.4%) in this study. In contrast to research conducted by Srivastava et al. and Valentini et al., getting the most results in the right colon.[22,23] According to research by Li yan et al., stated that PD-L1 expression significantly correlates with unfavorable clinical outcomes, right-sided colorectal adenocarcinoma shows a poor prognosis.[24]

Regarding the depth of tumor invasion (T), T3 tumor was mostly found in this study (24 samples; 60.0%). This result is in line with the research conducted by Masugi et al and Noh et al (65% cases and 16,8% respectively).[10,15] In contrast to Wang et al.'s research, which found the most depth of invasion in T4.[8] The depth of invasion and the local resection margin of tumor are very important in determining the risk of local recurrence. Invasion depth beyond T1 allows infiltration into vascular, lymphatic, and distant metastasis as well as affecting the prognosis of colorectal carcinoma. In this study, the depth of tumor invasion (T) stained by PD-L1 was mostly at T3 as many as 19 samples (79.2%). This indicates that PD-L1 expression is increased in colorectal adenocarcinoma compared to normal colonic mucosa. Tumors that cross the muscularis propria may cause peritoneal perforation or infiltrate surrounding visceral structures.[2] High PD-L1 expression plays a role in tumor genesis, growth, metastasis, and mesenchymal epithelial transition (EMT).[25]

Lymph node involvement (N1) was found in 11 cases (27.5%). In this study, the most common PD-L1 stained was without lymph node involvement (N0) as many as 21 samples (72.4%). In line with the research of Zeynep et al., but in contrast with Tan et al, which positive lymph node involvement was mostly found.[26,27] In colorectal adenocarcinoma lymph node involvement as a poor prognostic indicator associated with survival rates, where lymph node involvement has a shorter survival rate compared to without lymph node involvement.[2]

In this study, the most PD-L1 stained was without metastasis (74.3%) and in line with research conducted by Tan et al.[27] According to Wang et al., PD-L1 expression for metastasis is still not fully understood, but several regulatory mechanisms can be considered such as examining the PD-L1 gene, where the PD-L1 gene can change in metastatic lesions, these genomic changes are believed to be involved in colorectal adenocarcinoma metastasis.[28] The most clinical stage obtained by researchers was stage II (40.0%) and also the most common stage that expressed PD-L1 (87,5%). In contrast to research conducted by Tan et al., who got the most results were stage III.[25]

Histopathologic grading of colorectal adenocarcinoma is more in low grade, as many as 25 samples (62.5%) found in this study. This may be due to increasing awareness about health, knowledge, and information about colorectal adenocarcinoma. Colonoscopy or other imaging support tools may help colorectal adenocarcinoma detected at an early stage. The most PD-L1 stained grading was low grade (76.0%) and this is in accordance with research conducted by Al-Jussani and Zeynep, et al.[26,30] This may be attributed to the increase in exhausted T cells along with the increase in tumor histopathology grade.[31]

Negative lymphatic invasion was found in most samples (57.5%). In contrast to research conducted by Betge et al., which found 33% samples had lymphatic invasion.[32] WHO states that the presence of lymphatic invasion is associated with lymph node metastasis and is a poor prognostic indicator in colorectal adenocarcinoma patients associated with lower survival rate compared to patients without lymphatic invasion.[2] In this study, the most lymphatic invasion that expressed PD-L1 was negative as many as 17 samples (73.9%). In line with research conducted by Schwarz et al., who obtained the most negative results of lymphatic invasion as many as 35 samples (16.6%).[21]

Vascular invasion consisted of inside the intestinal wall (Intramural Vascular Invasion /IMVI) and outside the intestinal wall (Extramural Vascular Invasion/ EMVI). From the results of the study obtained EMVI as many as 27.5% and IMVI 20.0%. The incidence of EMVI is higher than IMVI. The prognosis of EMVI is worse than IMVI. EMVI is an independent predictor of poor prognosis after resection in colorectal adenocarcinoma, but IMVI has no known role.[2] In this study, PD-L1 expression in vascular invasion in both EMVI and IMVI was found to be the same in 8 samples. Research conducted by Schwarz et al. did not distinguish between EMVI and IMVI, but assessed PD-L1 expression with vascular invasion and found that 17.9% samples did not have vascular invasion.[21] In colorectal adenocarcinoma, the involvement of vascular invasion associated with poor prognostic indicator and survival.[33]

Negative perineural invasion results were obtained in 27.5% samples which in line with research conducted by Srivastava et al.[22] In contrast to metaanalysis research conducted by Knijn et al., found perineural invasion 24.3% of 7653 cases. The presence of perineural invasion indicates a more severe disease and has a much lower 5-year survival rate.[34] In this study, many perineural invasions stained with PD-L1 were negative as many as 21 samples (72.4%) which in line with research conducted by Zhao et al. and Rosenbaum et al.[9,35] In colorectal adenocarcinoma perineural invasion as a poor prognostic indicator associated with survival rates, where perineural invasion has a shorter survival rate compared to colorectal adenocarcinoma patients without perineural invasion.[2]

In this study, tumor budding assessment was performed in front of the invasive tumor after selecting 1 hotspot with the highest number of buds and the most samples were low budding with 23 samples (57.5%). This is in line with a study conducted by Schwarz et al.[21] In colorectal adenocarcinoma, tumor budding is associated with an increased risk of metastasis to the lymph nodes and a decrease in life expectancy and recurrence.[36] In this study, tumor budding that expressed PD-L1 was low budding 73.9%. In line with research conducted by Schwarz et al., getting the most low-grade results as many as 19.5% of samples.[21] The high expression of PD-L1 plays a role in tumor genesis, growth, metastasis, and mesenchymal epithelial transition (EMT).[25]

The assessment of stromal TILs was evaluated at the front of the tumor, where this is the optimal area for assessing TILs. This study obtained rich TILs was the most common as many as 31 samples (77.5%). In contrast to the research by Hamzah who divided the degree of TILs with low, medium, and high, getting the most results in low degrees as many as 23 samples (44.2%). Many studies have reported the role of TILs histology assessment in predicting MSI status in colorectal adenocarcinoma. TILs are associated with host immune status and various reports have shown that TILs level is a favorable biomarker in the prognosis of various malignancies, including colorectal adenocarcinoma.[31] In this study,

the most stromal TILs stained with PD-L1 were rich (74.2%). The infiltration of T cells is one of the factors that can trigger the expression of PD-L1 tumor cells due to the interferon-γ released by T cells. This may be associated with the presence of samples with positive PD-L1 expression of tumor cells.[31]

There are two growth patterns in colorectal adenocarcinoma: infiltrative growth and pushing border growth. Pushing border is associated with good clinical outcomes and is found at lower stages. Whereas infiltrative growth is associated with poor clinical outcomes and is found at higher stages.[2] In this study, the most common lesion growth pattern was infiltrating (75.0%). In line with research conducted by Betge et al., but in contrast to research conducted by Papagiorgis et al., getting the mixed pattern was the most common results (48%).[29,32] In this study, the growth pattern of the lesion that most expressed PD-L1 was infiltrating (80.0%). In line with research conducted by Valentini et al., stated that the most growth pattern was infiltrating as many as 56.25%.[23] The high expression of PD-L1 in infiltrating growth patterns indicates a poor prognosis.

PD-L1 is an important molecule in the tumor microenvironment, and its upregulation is one of the mechanisms to evade the body's immune system. PD-L1 is an apoptosis-related protein that has an important role in the immune response. According to the researchers, based on the results of this study, it can be concluded that PD-L1 expression in colorectal adenocarcinoma with clinicopathological features and prognosis are still controversial. It is hoped that further research will be conducted linking PD-L1 with clinicopathology in colorectal adenocarcinoma.

Conclusion

Immunohistochemical expression of PD-L1 in colorectal adenocarcinoma predominantly was positive (72,5%) and the rest was negative (27,5%) of 40 samples. The most common age of colorectal adenocarcinoma patients in this study was 50-59 years old (55%) and mostly found in men (55%). The most common subtype of colorectal adenocarcinoma was adenocarcinoma NOS (75%), found mostly in left colon (52,5%). The highest depth of tumor invasion (T) was T3 (60.0%), lymph node involvement was mostly not found in 29 samples (72.5%). Tumor without metastasis was the most common (87.5%) with stage II as many (40.0%). Grading was mostly low grade (62.5%). Lymphatic invasion was mostly negative with 23 samples (57.5%). Most tumor had EMVI (27.5%) and perineural invasion was mostly negative. Tumor budding was mostly low budding (57.5%) and stromal TILs were mostly rich (77.5%). The lesion growth pattern was mostly infiltrating (75.0%). PD-L1 was expressed more in those without lymphatic invasion (73,9%), without perineural invasion (72.4%), low budding (73.9%), rich stromal TILs (74.2%), and infiltrating growth pattern (80.0%). Further research is needed to evaluate the prognosis and survival rate of colorectal adenocarcinoma patients. The limitation of this study is that several variables were assessed in one focus, and so other methods are needed to assess these variables more objectively.

Acknowledgments

Thank you to all staff and residents of the Department of Anatomical Pathology, University of North Sumatra / Central General Hospital H. Adam Malik Medan for their assistance.

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