The Correlation Between Immunohistochemical Expression of Cluster of Differentiation 5 (CD5) and Stromal Tumor Infiltrating Lymphocytes (sTILS) Grade in Prostate Adenocarcinoma

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Abstract

Background: Adenocarcinoma of the prostate is an invasive carcinoma, a neoplasm of prostate epithelial cells with secretory cell differentiation. Histomorphology is glandular. The cells are sheets or single cells with neoplasia, basal cells are not seen in this carcinoma. Tumor-Infiltrating Lymphocytes (TILs) are lymphocytes that migrate to tumor cells or peritumoral cells. In a malignancy, T lymphocyte infiltration can be found, indicating an immune response to malignancy. The cluster of Differentiation 5 (CD5) is a transmembrane receptor that plays a role in regulating the function and development of T cells.
Objective: To determine the correlation between Immunohistochemical expression of Cluster of Differentiation 5 (CD5) and the Stromal Tumor-Infiltrating Lymphocytes (sTILs) grade in Prostate Adenocarcinoma.
Methods: This study was conducted on slides of 32 prostate adenocarcinoma patients. Each slide was stained with hematoxylin and eosin (H&E), and the grade of STILs was observed on the slide. Furthermore, CD5 immunohistochemical staining was carried out to see and analyze whether the appearance was positive or negative.
Results: Among 32 specimens of prostate adenocarcinoma patients, it was found 10 mild STILs, 22 moderate STILs and no severe STILs on hematoxylin and eosin (HE) staining, CD5 immunohistochemical staining was obtained 16 positive expressions and 16 negative expressions.
Conclusion: There is no correlation between immunohistochemical expression of Cluster of Differentiation 5 (CD5) and the grade of stromal Tumor-Infiltrating Lymphocyte (sTILS) in prostate adenocarcinoma.
Keywords: Adenocarcinoma of the prostate; prostate; sTILs; Cluster of Differentiation 5 (CD5).

1. Introduction

Adenocarcinoma prostate is an invasive carcinoma consisting of neoplastic prostatic epithelial cells with secretory differentiation arranged in a variety of histomorphology patterns, including glands: cords, single cells, and sheets. Basal cells are typically absent.[1] According to data from the Global Burden of Cancer (GLOBOCAN) 2020, prostate cancer in the world is in fifth place. New cases of prostate cancer have reached 1,414,259 (7.3%), with deaths reaching 375,304 (3.8%). This is the ninth most cases in the world. Most prostate cancer occurs in European countries with an incidence of 449,761 cases.[2] According to data from the American Cancer Society 2021, new cases of prostate cancer reached 248,530, there were 34,130 deaths in America,[3] in Asian countries with an incidence of 297,215 cases, the most deaths were in Asian countries reaching 118,427 deaths and the second most deaths in European countries reaching 109,315 death.[2]

Tumor-Infiltrating Lymphocytes (TILs) are part of the immune system against tumors that have an essential role for invasion, growth, and metastasis. TILs are divided into intratumoral TILs, those that infiltrate the tumor nest and reside in the tumor, and stromal TILs, which surround the tumor nest.[4] TILs always attack tumor cells, so they are effective in inhibiting cancer growth. There have been many studies

that prove this. [5,6] Histopathological measurement of TILs was carried out to see the immune reaction to tumors, where TILs can also affect the stage and grading of various types of cancer.[4]

The cluster of Differentiation 5 (CD5) is a type-1 transmembrane glycoprotein consisting of three cysteine receptor scavenger (SRCR) domains. CD5 is a transmembrane receptor that plays a role in regulating the function and development of T cells.[7] CD5 is a receptor for T cells, B1-a cells, and B-CLL. In several studies, it is stated that the role of CD5 is to promote the survival of T cells and B cells. CD5 also plays a role in the differentiation of effector T cells and immune tolerance. CD5 can be useful for targeting immune intervention in pathology, such as cancer, autoimmune disease or infection. The cluster of Differentiation 5 (CD5) is expressed on thymocytes and mature T cells.[8]

2. Materials and Methods

We studied 32 cases of prostate adenocarcinoma histology slides at the Anatomic Pathology Laboratory, North Sumatra University and Anatomic Pathology Unit H. Adam Malik Hospital using an analytical study design with a cross-sectional approach to analyze the relationship between CD5 immunohistochemistry expression and the degree of stromal Tumor-Infiltrating Lymphocytes (TILs) in patients with prostate adenocarcinoma with CD5 immunohistochemical staining.

The authors reviewed histopathological specimens stained with CD5 immunohistochemical staining after fixation with 96% ethanol and dry fixation. The histopathological slides were examined for the presence or absence of stained CD5 immunohistochemical expression on the cytoplasmic membrane viewed with 400x magnification using a CX21 microscope.

3. Results

The research sample was histopathological slides diagnosed as prostate adenocarcinoma at the Anatomic Pathology Laboratory, Faculty of Medicine, University of North Sumatra and the Anatomic Pathology Unit at H. Adam Malik Hospital. The total sample was 32 slides that met the inclusion criteria. The following are the results of the research obtained.

Table 1. Distribution of Prostate Adenocarcinoma Samples by Age, Degree of TILs and CD5 expression

Variable	N	%
Age		
• ≤ 60 years	3	9,38
• 61-70 years	17	53,12
• ≥ 70 years	12	37,50
Derajat sTILS		
• mild (<10%)	10	31,25
• moderate (11 - 49%)	22	68,75
• poorly (≥ 50%)	0	0
Ekspresi CD5		
• Positive	16	50,00
• Negative	16	50,00

From the medical record data, as many as 32 samples in this study, the average age was 68.5 years, most patients with prostate adenocarcinoma were aged > 60 years, namely 31 patients (53.13%) and the youngest age was 58 years, as many as 1 patient, and the oldest age is 93 years with 1 patient.

From the microscopic results of patients with prostate adenocarcinoma with HE staining. TILs were assessed for stromal tumors in the category of mild (<10%), moderate (11-49%), and severe (⩾50%). In this study, 10 (31.25%) mild stromal TILs were found, moderate 22 (68.75%), and severe stromal TILs were not found in this study sample.

In this study, immunohistochemical staining of the cluster of differentiation 5 (CD5) was used. CD5 expression was assessed in positive and negative categories. In this study, the results were obtained with positive CD5 expression of as many as 16 (50.00%) and negative CD5 expression of as many as 16 (50.00%).

Table 2. Relationship of TILS Stromal Degree with CD5 expression

No	sTILs Degrees	Exspression CD5				P-Value
		Positive		Negative		
		n	%	n	%	
1	<10%	6	60,0	4	40	
2	11- 49%	10	45,5	12	54,5	0,446
3	≥50%	0	0	0	0	

*** Mann-Whitney.**

This study examined the relationship between the degree of stromal TILs and CD5 expression in patients with prostate adenocarcinoma. In this study, the results showed that the degree of sTILs was mild (<10%) in as many as 10 samples, of which there were 6 samples with positive CD5 expression and 4 negative CD5, moderate sTILs (11-49%) as many as 22 samples of which 10 samples with expression CD5 positive and 12 samples negative, and the degree of severe sTILs in the sample was not found. In this study, the Mann-Whitney test was carried out to assess the relationship between the degree of sTILs and CD5 expression, and the p-value = 0.446 (p> 0.005) showed an insignificant relationship.

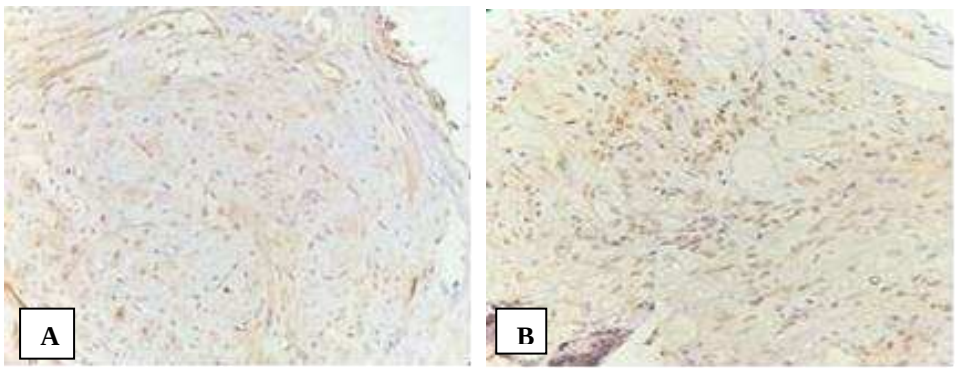

Fig. 1. (A,B). Positive stain Immunohistochemical CD5 of adenocarcinoma prostate

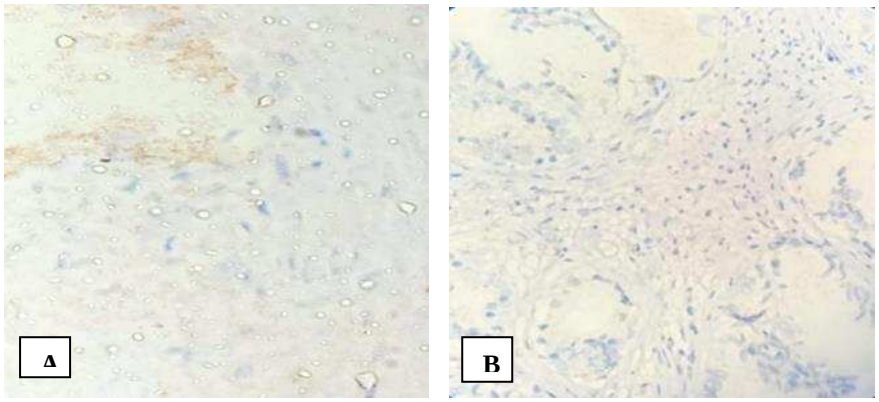

Fig. 1. (A,B). Negative stain Immunohistochemical CD5 of adenocarcinoma prostate

From table 4.1, most patients with prostate adenocarcinoma were at the age of 60-70 years, as many as 17 (53.12). This is in accordance with previous research conducted by Laksmi (2012), who reported that from 39 samples, prostate adenocarcinoma patients were often found at the age of 66-84. years (71.4%). This is in accordance with the literature, which states that prostate patients will increase according to age, only a few prostate patients are found under the age of 40 years, and 80% are found in the age above 80 years.[9] Research conducted by Siregar (2020) from 32 samples showed that the most prostate adenocarcinoma patients aged >71 years were 18 cases (56.3%). The risk of prostate adenocarcinoma is strongly related to age, where men aged 70-79 years have an almost 7 times higher risk of developing prostate adenocarcinoma.[10] Sah Mulia's study (2021) used 34 samples. The results showed that most patients with prostate adenocarcinoma were aged over 60 years, namely 23 people or 67.6%. Some literature states that increasing age tends to increase men's incidence of prostate adenocarcinoma. This may be related to reproductive activity.[11] This study also found the same thing where from 32 samples found, the average age of patients with prostate carcinoma was 68.5 years, with the youngest patient being 58 years old and the oldest being 93 years old, where the age group of patients with adenocarcinoma was >60 years old (53.13). %). This is also in accordance with the WHO, which states that most patients with prostate adenocarcinoma are found at the age of > 60 years. This is in accordance with some literature which states that increasing age causes an increase in the incidence of prostate adenocarcinoma in men, which may be related to reproductive activity. WHO also states that prostate adenocarcinoma in men aged <50 years is only found in 1%. Factors causing prostate adenocarcinoma at a younger age are closely related to a person's lifestyle and diet. Some growing evidence shows that glandular epithelial cell injury due to carcinogens, estrogens or oxidants is a trigger factor for chronic inflammation and is a stage of cancer cell development.[12]

CD5 is an essential physiological regulator of T cell immune responses. CD5 regulation is associated with homeostasis and immune tolerance.[13] Regulatory T cells are derived from T cells that are not eliminated even though their receptors bind to self-antigens during selection in the thymus. Regulatory T cells recognize self-antigens that are expressed by normal body cells but are known not for elimination but protection. Thus, eliminating problematic body cells (autoimmune) can be avoided. So the number of regulatory T cells is low in autoimmune cases. Regulatory T cells prevent the elimination of tumor cells, so high numbers of regulatory T cells are found in tumors.[14]

CD5 has a significant role in regulating antitumor immune responses, and downregulation of CD5 expression in TIL potentiates tumor-specific T-cell reactivity. CD5 downregulation of TIL occurs in the tumor microenvironment, and it may be in keeping with the strategy used by T cells to adjust their sensitivity to the strength of the TCR-pMHC interaction. The modulation of CD5 by tumor-infiltrating T lymphocytes expressing low levels of the pMHC complex and the subsequent increase in T cell reactivity may be a strategy used by the immune system to overcome tumor avoidance. In line with this hypothesis, we have reported that tumor-specific CTLs undergo a process of intratumoral adaptation depending on the strength of the TCR/pMHC interaction to enhance TCR signalling and overcome tumor escape due to altered pMHC expression through regulation of CD5. The absence of CD5 lowers the T-cell activation threshold, resulting in increased tumor-specific T-cell responses. Otherwise, CD5 expression renders wild-type murine TIL unresponsive to specific Ag stimulation. The silent status of CD5+ tumor-specific CTLs may partly explain the lack of a paradoxical correlation between the frequency of circulating pMHC-tetramer+ T cells induced in vaccination trials and tumor regression.[13] Previous research by Andrea Moreno-Manuel on small cell lung carcinoma stated that the higher the CD5 expression, the better the prognosis.[15] A study conducted by Rebecca on breast cancer noted that CD5 expression was more pronounced in low-grade cancers than in high-grade cancers.[16]

Lymphocyte cells are one of the immune cells that infiltrate solid tumors. Tumor infiltrates lymphocytes (TILs) are lymphocytes that migrate to the tumor and peritumoral. TILs are grouped with lymphocytes that infiltrate the tumor stroma (stromal TILs), defined as lymphocytes located and scattered in the stroma. Meanwhile, intratumoral TILs are defined as lymphocytes that infiltrate into tumor nests of tumor cells that are in direct contact with tumor cells.[17] Several studies have stated that stromal TILs are a

better parameter because they have a high reproducibility value and are relatively easy to observe on hematoxylin and eosin staining compared to intratumoral TILs.[18] TILs are known as one of the markers of tumor development associated with the involvement of the immune system, which controls and eliminates tumor cells so that the higher the tumor grade TILs are not found.[19] In a previous study conducted by Siregar on 32 prostate adenocarcinoma samples, the highest degree of sTILs was 22, the moderate grade was 8, and severe grade was 2 samples. In this study, after the Mann-Whitney U statistical test was carried out to assess the relationship between the degree of sTILs and CD5 expression in prostate adenocarcinoma, the results showed that there was no significant relationship between the degree of sTILs and CD5 expression in prostate adenocarcinoma, but in this study it was found that CD5 was overexpressed in prostate adenocarcinoma. moderate sTILs.

5. Conclusion

After conducting research on 32 samples, there was no correlation between the immunohistochemical expression of Cluster of Differentiation 5 (CD5) and the degree of stromal Tumor Infiltrating Lymphocyte (sTILS) in prostate adenocarcinoma.

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