Immunohistochemical expression of MUCIN 1 in benign prostatic hyperplasia, prostatic intraepithelial neoplasia and prostate adenocarcinoma at the Haji Adam Malik General Hospital, Medan

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ABSTRACT

Background*: Benign prostatic hyperplasia (BPH), prostatic intraepithelial neoplasia (PIN) and prostate adenocarcinoma are lesions that can be found on the prostate. In 2013 there were 9.2 million cases of BPH in Indonesia while 25,012 cases of prostate cancer alone. MUC1 is a transmembrane glycoprotein that can be expressed in both benign and malignant prostate lesions. In malignancy, MUC1 plays a role in cell proliferation, apoptosis and cell adhesion, thus increasing mortality from prostate cancer. MUC1 can also be associated with a poor prognosis in prostate malignancy. Currently, target therapies are being developed for prostate malignancies from several signaling pathways. Anti MUC1 as one of the therapeutic targets, is expected to be one of the therapeutic treatments in prostate malignancies.*

Objective: *To determine the expression of MUC1 in BPH, PIN and prostate adenocarcinoma with histopathological grading according to WHO 2016.*

Materials and Method*: This research is a descriptive study with a cross-sectional design. The sample of this study was BPH slaid, PIN and prostate adenocarcinoma which was stained with MUC1 immunohistochemistry and its expression was assessed in three categories: negative, weak positive and strong positive.*

Result*: From 34 samples in this study found 19 cases of BPH, 14 cases of prostate adenocarcinoma and 1 case of PIN. In BPH, MUC1 expression was negative in 9 (47.37%) cases, MUC1 expression was weak in 8 (42.11%) cases, strong positive expression in 2 (10.52%) cases. In prostate adenocarcinoma, MUC1 expression was negative in 1 (7.14%) cases, MUC1 expression was weak 9 (64.29%) cases, MUC1 expression was strongly positive 4 (28.57%) cases. On the positive MUC1 expression PIN is strong in 1 (100%) cases.*

Keywords*: benign prostatic hyperplasia, prostate adenocarcinoma, MUC1*

1. Introduction

Abnormalities in the prostate are one of the causes of impaired quality of life in men, including inflammation, benign prostatic hyperplasia (BPH) and prostate adenocarcinoma.[1] In BPH there is proliferation of stromal and epithelial elements which results in enlargement of the prostate gland and can rarely cause obstruction in the prostate urinary tract.[2] Meanwhile, prostate adenocarcinoma is an invasive carcinoma consisting of neoplasms of prostatic epithelial cells with differentiation of secretory cells. Prostatic intraepithelial neoplasia (PIN) is a precancerous lesion characterized by neoplastic transformation of the epithelial lining on the prostate.[3] PIN has a benign gland architecture, but is limited by cells with atypical features.[4]

In 2013 in Indonesia there were 9.2 million cases of BPH, among them men over 60. While the prevalence of prostate cancer in Indonesia was estimated at 0.2 0/00 (25,012 patients) in 2013.[6] Cancer deaths prostate ranks second highest after death from cancer in the lungs.[7]

MUC1 is a type I membrane glycoprotein of the mucin family that has a broad extracellular domain, consisting of hundreds of tandem repeating units, transmembrane domains, and C-terminal cytoplasmic tail. [8,9,10] MUC1, which is expressed on the surface of apical cells in normal secretory epithelial cells , serves to prevent adhesion and increase the development of metastases.[11] So that MUC1 can be used to determine the prognosis in prostate cancer.[12]

In a study conducted by Garbar in 2008, MUC1 was expressed in benign, PIN and malignant prostate glands.[12] Meanwhile, according to Eminaga et al (2016), MUC1 is positively expressed in prostate cancer in radical prostatectomy patients and has to do with the level of prostatic histopathological grading.[13] However, in the study of Rabiau et al (2009) it was found that MUC1 was expressed in prostate adenocarcinoma, PIN and normal prostate gland.[14]

Research using MUC1 immunohistochemistry in prostate tissue in some literature is still quite limited. Therefore, researchers are interested in conducting research on how the expression of MUC1 immunohistochemistry in BPH, PIN and prostate adenocarcinoma.

2. Material and Methods

We investigated the slides of prostate lesions, which consisted of BPH patients who were diagnosed histopathologically by staining hematoxilin-eosin, adenocarcinoma and PIN, each diagnosed using p63 immunohistochemistry and AMACR at the Anatomic Pathology Laboratory of USU Faculty of Medicine and H. Adam Malik Hospital. Field. All samples were obtained from operative actions.

This study is a descriptive cross sectional study evaluating the immunohistochemical expression of MUC1 in benign prostatic hyperplasia, prostatic intraepithelial neoplasia and prostate adenocarcinoma. Then the semiquantitative assessment of MUC1 immunohistochemical expression and immunocystactivity patterns of MUC1 immunohistochemical expression by researchers and two supervisors. Outward immunohistochemistry using the direct method. The primary antibodies used are MUC1, polyclonal antibody, human rabbit, with a dilution of 1: 100. MUC1 expression sees brown appearance on cytoplasm which is stated as Negative (-) if it fails to display brown color, positive (+) is weak if it can display brown color with weak intensity, positive (+) strong if it can display brown color with strong intensity. [14]

3. Result

The sample in this study, obtained 34 slaid prostate lesion patients who met the inclusion and exclusion criteria consisting of 19 BPH samples, 14 prostate adenocarcinomas and 1 PIN sample. All samples were obtained from operative measures, 31 cases (91.2%) were from Transurethral resection prostatectomy (TURP) and 3 cases (8.8%) were from Radical Prostatectomy.

Based on medical records, the sample in this study had an average age of 70.85 years, with the youngest age being 44 years and the oldest was 91 years. The highest number of prostate lesion sufferers at the age of <60 years were 32 patients (94.12%) and> 60 years were 2 patients (5.88%).

Based on the results of histopathological examination of prostate adenocarcinoma, grade 2 adenocarcinoma was the most frequently encountered, as many as 5 patients (35.71%). Prostate adenocarcinoma with grade 1 group was 4 patients (28.57%), grade 3 group and grade 4 group were 2 patients (14.29%) and grade 5 group was 1 patient (7.4%). (Table 1)

Table 1. Sample distribution based on characteristics of prostate lesion sufferers

Characteristics of Sufferers	Amount (n)	Percentage (%)
Usia		
< 60 years old	2	5,88%
≥ 60 years old	32	94,12%
Adenocarcinoma		
Grade Group 1	4	28,57%
Grade Group 2	5	35,71%
Grade Group 3	2	14,29%
Grade Group 4	2	14,29%
Grade Group 5	1	7,14%
PIN	1	2,94%
BPH	19	55,88%

From 34 samples of benign and malignant prostate lesions, immunohistochemical expression of MUC1 was found to be positively weak in 17 cases (50%), strong positive in 7 cases (20.59%) and negative in 10 cases (29.41%) (table 2).

Table 2. Frequency distribution of MUC1 immunohistochemical expression in prostate lesions

MUC1 immunohistochemical expression	Amount (n)	Percentage (%)
Positive		
Weak	17	50%
Strong	7	20,59%
Negative	10	29,41%
Total	34	100%

MUC1 expression that showed a weak positive was found in adenocarcinoma and BPH, but not in the PIN. MUC1 expression that displays a weak positive is found in both benign and malignant prostate lesions. While MUC1 expression was negative, the majority found in BPH and 1 adenocarcinoma sample also displayed negative MUC1 expression .(table 3)

Table 3. Frequency distribution of MUC1 immunohistochemical expression by type of prostate lesion

Prostate Lesion	MUC1 immunohistochemical expression					
	Positive				Negative	
	Weak		Strong			
	n	%	N	%	n	%
Adenocarsinoma	9	64,29%	4	28,57%	1	7,14%
PIN	0	0%	1	100%	0	0%
BPH	8	42,11%	2	10,53%	9	47,37%
Total	17		7		10	

From 14 prostate adenocarcinoma samples, MUC1 expression that showed a weak positive was found in grade 1 in 3 cases, grade 3 in 4 cases and grade 4 in 2 cases. The MUC1 expression showing strong positive was found in grade 1 and grade 2 each in 1 case while grade 3 was 2 cases. A negative MUC1 expression was only found in grade 5 group in 1 case (table 4)

Tabel 4. Frequency distribution of MUC1 immunohistochemical expression of prostate adenocarcinoma based on histopathological grading

Histopathology Grading	Ekspresi imunohistokimia *MUC1*					
	Positive				Negative	
	Weak		Strong			
	n	%	n	%	n	%
Grade Group 1	3	33,33%	1	25%	0	0%
Grade Group 2	4	44,44%	1	25%	0	0%
Grade Group 3	0	0%	2	50%	0	0%
Grade Group 4	2	22,22%	0	0%	0	0%
Grade Group 5	0	0%	0	0%	1	100%
Total	9	100%	4	100%	1	100%

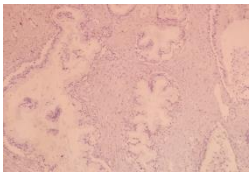

Figure 1. Negative MUC1 expression

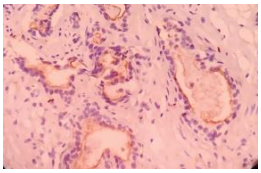

Figure 2. Weak positive MUC1 expression

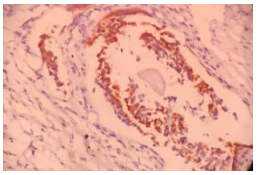

Figure 3. Strong positive MUC1 expression

4. Discussion

In this study of 34 samples that were diagnosed histopathologically with H&E staining consisted of 12 adenocarcinoma samples, 16 BPH samples and 6 PIN samples. However, after being confirmed with p63 immunohistochemistry and AMACR the results obtained were 14 adenocarcinoma samples, 19 BPH samples and 1 PIN sample. In this study also showed that the average sample age was 70.85 years. The youngest sample is 44 years old and the oldest sample is 91 years old. In accordance with the literature which states that prostate sufferers will increase according to age. This is in line with research conducted by Nurlaili, et al. (2017) of 50 prostate patients, age <60 years as many as 8 people and age> 60 years as many as 42 people.[15] Laksmi, (2012) also found prostate patients over 65 years of age more than those under 65 years of age.16 In the world, about three-quarters of prostate malignancies occur in men aged 65 years or older.[17] Only 1% of prostate cancer clinically detected is found in men <50 years old.[18]

In this study, the most positively expressed MUC1 among prostate lesions was adenocarcinoma in 13 cases. This is in line with research Rabiau, et al. (2009) of 24 patients with prostate lesions found 9 patients with positive MUC1 expression.[14] However, according to Garbar, et al. (2008) of the 65 prostate lesions studied, the

expression of positive MUC1 in adenocarcinoma had the same amount as the expression of positive MUC1 found in BPH, which was 24 cases.[12] This shows a tendency that MUC1 is more expressed in prostate adenocarcinoma compared with BPH. While on BPH itself, there is no tendency between positive and negative MUC1 expressions.

The most negative MUC1 expression among prostate lesions was found in BPH, which was 9 cases. This is in line with research conducted by Rabiau, et al. (2009) of 24 cases of benign lesions, 23 cases of MUC1 expression were negative. by Rabiau, et al. who found more negative MUC1 expression than positive MUC1 expression in all BPH samples.Pada penelitian ini, ekspresi *MUC1* negatif juga ditemukan pada 1 kasus adenokarsinoma. Hal ini disebabkan oleh karena gambaran histopatologi yang dijumpai pada sediaan ini, sel-sel tumor sudah menginvasi sampai ke stroma dan tidak dijumpai lagi kelenjar ganas pada sediaan ini.

Based on prostatic adenocarcinoma grading histopathology, the percentage of strong positive MUC1 expression was found in grade 3 group, which was 100% (table 4.4). This is different from the study of Rabiau, et al (2009) of 12 cases of gleason score 7, MUC1 was negatively expressed in 7 cases and weakly positive in 5 cases, none of which were found to be strongly positively expressed.[14] This might be due to Rubiau , et al categorize the histopathological grading of prostate adenocarcinoma based on the WHO gleason score in 2004, while this study categorizes based on the 2016 WHO gleason score, which divides grading by grade group 1 to grade group 5. According to WHO 2004, gleason score 7 shows the sum between the combination of gleason 1 to 5. Whereas according to WHO 2016, grade 7 is the sum of the gleason 4 + 3 pattern. What is interesting from this study is the negative MUC1 expression in grade 5 adenocarcinoma (table 4.4), this is caused by the gleason pattern found is 5 + 5 which shows a poor differentiation of glands and necrosal features is dominant.
The finding of different results on the expression of MUC1 on BPH with previous studies, according to the researchers is caused by differences in the level of glycosylation of MUC1 itself. According to the literature, MUC1 is a transmembrane glycoprotein from the results of variable number of tandem repeats (VNTR) which can be glycosylated 50-90% in the carbohydrate side chain.[19] This is also what the researchers say, causes why the expression of MUC1 in prostate adenocarcinoma in each gleason grade does not indicate the tendency for the higher level of gleason grade to be stronger the expression of MUC1.

5. Conclusions

Most prostate lesions occur at age> 60 years, the average age of 70.85 years. Immunohistochemical expression of MUC1 Prostate adenocarcinoma is weak positive, most benign prostatic hyperplasia is negative and prostatic intraepithelial neoplasia is only strongly positive. Group 2 prostate grade adenocarcinoma, showing the most number of weak positive MUC1 expressions and group 3 grade, showing the most strong positive MUC1 expression.

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