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RESEARCH ARTICLE
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Androgen Receptor Expression In Benign Prostatic Hyperplasia And Prostate Cancer

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ABSTRACT

Background: Benign prostatic hyperplasia (BPH) and prostate cancer (PCa) require androgen/androgen receptor (AR) signals. It plays an important role in the development of BPH; the initiation, growth, and progressivity of PCa, but the mechanism of AR in both of them remains unclear.

Objective: This study aims to evaluate the expression of AR in BPH and PCa.

Methods: Analytical study with cross-sectional design on a sample of 56 cases of BPH and PCa, respectively. The sampling was from the Anatomic Pathology laboratory in West Sumatera. Immunohistochemical (IHC) staining of AR to analyze protein expression semi-quantitatively. High expression of AR was set as strong interpretation.

Results: Mostly AR expression was high in BPH at 98.21% (55 cases) whereas high AR expression of PCa in tumor cells was slightly more in 51.79% (29 cases) than low AR expression. Most cases of PCa were Gleason score 9, namely 25 (44.64%) cases, and high AR expression in 29 (51.79%) cases. High-grade Gleason score (Gleason score 8-10) with high AR expression was more than low-grade Gleason score (Gleason score ≤ 7). There was a statistically significant association between AR expression and Gleason score (p=0.018).

Conclusion: Activation of AR pathway is crucial for the development and progression of BPH and PCa. High AR expression was revealed most in epithelial and stromal cells of BPH, but it showed half of the tumor cells in PCa. The AR expression in tumor cells of PCa should be examined in cases to determine patient prognosis.

Keywords: *AR expression, benign prostatic hyperplasia, prostate cancer*

INTRODUCTION

Prostate enlargement remains a common urologic problem in men today. Benign prostatic hyperplasia, also called BPH is a significant source of morbidity in aging men by causing lower urinary tract symptoms (LUTS) and acute urinary retention. It is reported in 30-40% of men over 40 years of age, increasing to 70-80% over 80 years (Madersbacher et al., 2019; Lim, 2017). Prostate cancer (PCa) is the second most common cancer in the world after lung cancer in men. The incidence of new cases is reported to be 1.4 million, an increase compared to 2018, ranking 5th cause of cancer deaths in men in the world, an increase compared to 2018 (Sung et al., 2021; Bray et al., 2018; Andry et al., 2023). New cases of PCa in Indonesia are reported to be 7.4% or 5th most common cancer in men (The Global Cancer Observatory, 2020).

BPH and PCa are strongly influenced by AR signaling, a ligand-dependent transcription factor that controls specific gene expression. Androgens as ligands bind to AR in the epithelial and stromal nuclei of the prostate. The binding activates the AR signaling pathway thus inducing prostate tissue growth. However, the detailed mechanism of androgen/AR signaling, especially its role in the pathogenesis of BPH, is still debated (Devlin et al., 2021). PCa has an imbalance between proliferation and tumor cell death. The loss of this balance leads to higher proliferation than cell death, resulting in continuous tumor cell growth. Androgens/ARs play an important role in this ratio, as well as in tumor cell progressivity and metastasis (Andry et al., 2022). The mechanism of AR signaling switching from homeostatic to proliferative, progressive and metastatic is still unknown (Crumbaker et al., 2017). Our several studies have been conducted previously AR related to PCa (Putriyuni & Nurwiyeni, 2022; Putriyuni & Oktora, 2020).

MATERIALS AND METHODS

The observational study used a total of 56 cases of BPH and PCa from Department of Anatomical Pathology archieves in West Sumatera. The study was approved by the local research and ethical review committee. Hematoxylin and eosin (HE) stained slides and paraffin blocks were retrieved. Slides of all cases were evaluated to review Gleason score, histopathological grading, and WHO grade group based on ISUP 2014/WHO 2016 for PCa. Gleason score was grouped into a low grade (Gleason score < 8) and high grade (Gleason score 8–10). Specimens included prostatic chips and prostatectomies. Moreover, representative tissue blocks of BPH and PCa cases were selected for immunohistochemistry (IHC) examination.

IHC staining has been carried out at the Anatomical Pathology Department of General Hospital Dr. Cipto Mangunkusumo Jakarta. The antibodies were primary mouse monoclonal anti-human AR antibody (clone AR441, DAKO, dilution of 1:100) and secondary antibody (Starr Trek Universal Link, Biocare Medical). Epithelial and tumor cells staining was semi-quantitatively evaluated. Percentage of positive cell was scored into 0, 1, 2, 3, 4 (0, 1 = <10%, 2 = 10–50%, 3 = 51–80%, and 4 = >80%) and staining intensity was scored 0, 1, 2, 3 (0 = negative, 1 = weak, 2 = intermediate, and 3 = strong). Percentage and intensity scores were multiplied to generate an immunoreactive score ranging from 0 to 12. The interpretation was 0–1 = negative, 2–3 = mild, 4–8 = moderate, and 9–12 = strong. A cut-off value of 9 was used to categorized AR expression into low (negative, mild, and moderate interpretation) and high (strong interpretation). AR expression was scored by pathologist with clinical data blinded.

AR expression in PCa was compared with tumor grade using the Gleason score grouped. Statistical analysis for quantitative variables was a mean and standard deviation. Frequency and percentage were evaluated for qualitative variables. Fisher test was applied to determine correlation. $p < 0.05$ was taken as significant.

RESULTS

The mean age of patients was 68.59 ± 6.85 years with BPH and 70.68 ± 7.99 years with PCa. The histopathology of BPH showed proliferation of epithelial cells and stromal components. Epithelial hyperplasia is characterized by nodular lesions composed of variably sized glandular structures lined by luminal epithelial and basal

cells. Glandular dilatation with papillary infoldings and cysts, often containing corpora amylacea. The most PCa cases were Gleason score 9 (44.64%) and then Gleason score 8 (28.57%), histopathological grading poorly differentiated/undifferentiated (76.78%) and WHO grade Group 5 (48.21%) (Table 1).

Mostly AR expression was high in BPH (Figure 1) 98.21% (55 cases) in epithelial cells. High AR expression of PCa in tumor cells (Figure 2) was slightly more in 51.79% (29 cases) than low AR expression as shown in Table 2.

TABLE 1: The subject characteristic of study

Characteristics	F (n = 56)	%
BPH		
Age (years)		
Mean ± SD	68,59 ± 6,85	
PCa		
Age (years)		
Mean ± SD	70,68 ± 7,99	
Gleason score		
6	1	1.79
7	12	21.43
8	16	28.57
9	25	44.64
10	2	3.57
Histopathological grading		
Well-differentiated	1	1.79
Moderately-differentiated	12	21.43
Poorly-differ/undifferentiated	43	76.78
WHO grade-group		
Grade 1	1	1.79
Grade 2	8	14.29
Grade 3	4	7.14
Grade 4	16	28.57
Grade 5	27	48.21

BPH: benign prostatic hyperplasia, PCa: prostate cancer

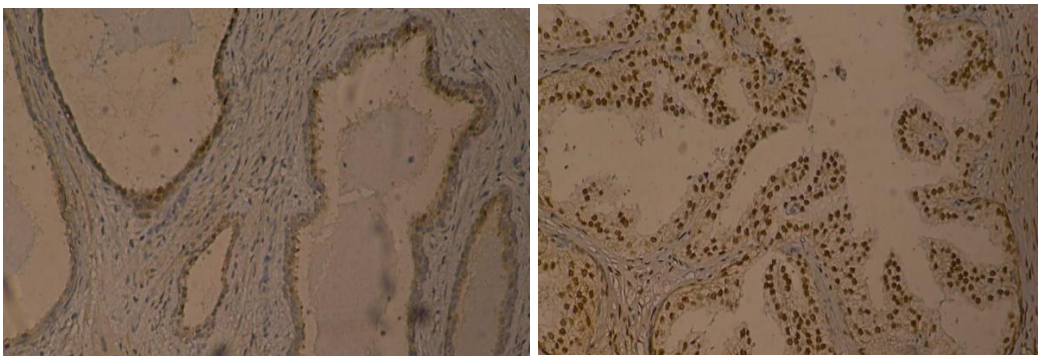

FIGURE 1: AR expression in BPH, A. Low expression, B. High expression (100x).

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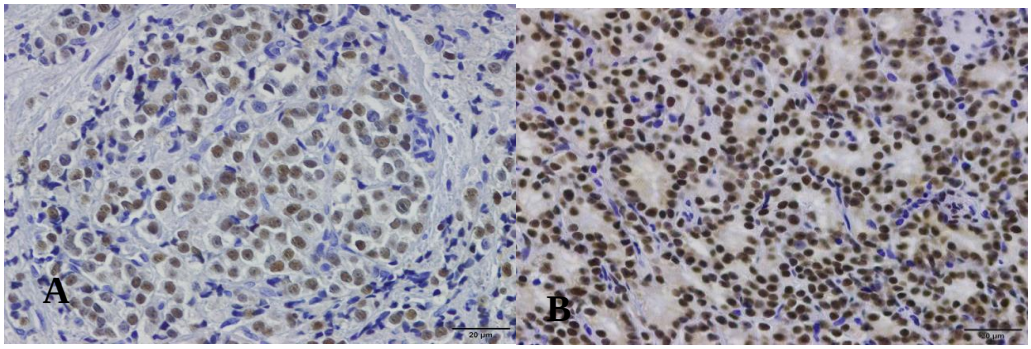

FIGURE 2: AR expression in PCa, A. Low expression AR, B. High expression (400x).

TABLE 2: Distribution of AR expression in epithelial and stromal cells

AR expression	F	%
BPH		
Low	1	(1.79%)
High	55	(98.21%)
PCa		
Low	27	(48.21%)
High	29	(51.79%)

BPH: benign prostatic hyperplasia, PCa: prostate cancer

PCa with a high-grade Gleason score showed high AR expressions (89.7%), compared to low-grade Gleason scores (10.3%). Statistically, the Fisher test showed a significant correlation between AR expression and Gleason score (p = 0.018) (Table 3).

TABLE 3: Correlation between AR expression with Gleason score

		Gleason score		Total	p
		Low Grade	High Grade		
AR Expression	Low	10 (37%)	17 (63%)	27 (100%)	
	High	3 (10.3%)	26 (89.7%)	29 (100%)	0.018
Total		13 (23.2%)	43 (76.8%)	56 (100%)	

DISCUSSION

Age is a significant predictor of both developments of BPH and PCa. Studies in UK (1990) revealed that the prevalence of BPH with lower urinary tract symptoms (LUTS) increased with age from 3.5% in 45-49 years to >30% in >85 years (Devlin et al., 2021; Vickman et al., 2020). The studies from Europe, US, and Asia also reported older age to be a risk factor for BPH progression (Lim, 2017). The study found the mean age of patients with BPH was 68.59 ± 6.85 years. PCa is rare before the age of 40, but the chance of developing prostate cancer rises rapidly after the age of 50. The aged especially 55 years and above had an almost 17-fold higher risk of developing prostate cancer as compared to age less than 55 years (Bashir, 2015). PCa in this study had a mean age of 70.68 ± 7.99 years.

Perhaps counter-intuitively as the incidence of BPH increases with age, the levels of circulating testosterone in the serum generally decreases. One answer to this may be that true

dihydrotestosterone (DHT) concentrations are higher in BPH than normal tissues but remain

stable during aging that induces the growth and enlargement of gland. It is therefore hypothesized that the prostate is insensitive to circulating testosterone level variations, because the AR in prostate cells is normally saturated by relatively low androgen intra-tissue concentrations. Thus, androgens can maintain the growth of prostate cells within BPH (Devlin et al., 2021).

This study revealed the most cases of Gleason score 9 and 8. The most histopathological grading was poorly-differentiated/undifferentiated (Gleason score 8-10) and WHO grade group 5 (Gleason score 9-10). The study of Hashmi et al. in the Pathology Department of Liaquat National Hospital Karachi got the most Gleason score 8-10, namely 64 (52.89%) cases and WHO grade group 5 as many as 37 (30.6%) cases (Hashmi et al., 2019). Lekshmy et al. from the Department of Pathology Government Medical College Trivandrum India found the most cases (50%) histopathological grading poorly-differentiated/undifferentiated (Gleason score 8-10) (Lekshmy & Prema, 2019). Collaborative research by Chen et al. in several countries in Asia reported Indonesia as the country with the highest prostate cancer cases with Gleason score >7 (70%) (R. Chen et al., 2014).

Whilst aging is considered essential for BPH development, another factor is the presence of androgens. The role of men sex hormones has been extensively examined; however, the exact mechanism of action or mechanistic importance is still disputed. Androgens, especially testosterone derived, play a central role in the normal functional development of the prostate. The main mode of action is via the transcription factor, the androgen receptor (AR), which is predominately located within the luminal epithelial cells, is almost non-existent in basal cells, and present at a lower density in a proportion of human prostate stromal cells. AR expression may be upregulated in BPH compared to normal tissue; however, no consistent evidence has been demonstrated for this (Devlin et al., 2021; Kishorebabu et al., 2019).

The AR expression in BPH were investigated in many studies, the results were not consistent. In this study, most samples of BPH showed high AR expression in the epithelial and also stromal cells. Song et al. revealed extensive and localized AR high expression in human BPH mainly to the epithelial and stromal cells (Song et al., 2016). However, the study of Husain et al. reported high AR expression only 20% cases and Hetzl et al. reported that the AR immune-reactivity in BPH was similar to that in normal prostate (Husain et al., 2016; Hetzl et al., 2012).

AR may contributed to BPH development via epithelial-stromal cells interaction with alterations of epithelial-mesenchymal transition, leading to proliferation of stromal cells (Izumi et al., 2013). The elevated serum or intraprostatic androgen levels may not be the causative factor in the activation of AR and etiology of BPH in humans, because the literature lack of conclusive data on serum or intraprostatic androgen level, DHT in particular. The review by van der Sluis et al. reported that no difference has been shown between DHT concentration in normal adult prostate and BPH tissue, nor is there a proven difference in androgen levels between histologically distinc regions of the prostate (Van Der Sluis et al., 2012). Further studies are required to clarify the mechanism of activation of AR and the downstream pathway of AR in BPH.

This study found high AR expression of tumor cells in 51.79% cases. The results of this study are similar to the study reported by Hashmi et al. found high AR expression in 56.2% cases (Hashmi et al., 2019). Meanwhile, Lekshmy and Prema's study found AR expression in almost all cases of PCa (Lekshmy & Prema, 2019). The AR signaling pathway plays pivotal role in pathogenesis of PCa. The classical model of AR signaling involves the recruitment of ligand-AR binding to induce transcriptional activity (Dai et al., 2017).

The higher proliferation and progressivity of tumor cells which means a worse degree of histopathological differentiation. High proliferation and progressivity indicate an increasingly bad biologic behavior, which in turn will affect the worse histopathological prognosis. Gleason score is the most important marker in determining the progressivity of PCa. This study found that high grade Gleason score (Gleason score 8-10) had more high AR expression in the

tumor cells than low expression. There was a significant correlation between AR expression and Gleason score (p=0.018). Hashmi et al. found a significant correlation between high AR expression in tumor cells and Gleason score (Hashmi et al., 2019). Another study by Chen et al. found high AR expression in PCa patients who metastasized to bone compared to those without metastasis (p<0.001) (Y. Chen et al., 2017). This suggests that high AR expression is associated with the progressivity of PCa. Therefore, examination of AR expression can be used as a prognostic predictor of PCa.

In BPH, AR function within luminal epithelial cells mimics that of a tumor suppressor, and there is little evidence of AR converting to a driver of cell proliferation such as in PCa. Thus, luminal epithelial cells remain differentiated and proliferatively quiescent. This supports a model whereby AR signaling within the prostate epithelium retains its normal adult function in BPH but instead inflammation and fetal reprogramming disrupt normal stromal/epithelial paracrine signaling. Such changes to the prostate microenvironment enable prostate epithelial cells to exit a steady-state of proliferation/death and enter into an abnormal growth phase leading to cellular overexpansion. It is not completely clear whether or not AR expression change throughout BPH progression. In general, it seems that both epithelial and stromal AR may be involved in this disease, and perhaps increase in the ratio stromal:epithelial AR in BPH compared to normal adult prostate influence disease outcome (Vickman et al., 2020).

In contrast, studies of AR in PCa have demonstrated that AR signaling acquires an oncogenic gain-of function that promotes cancer proliferation and progression. The vast majority of PCa express AR and androgen-deprivation therapy (ADT) is the predominant therapeutic strategy to reduce tumor burden and block cancer progression. furthermore, AR remains a critical oncogenic driver in castration-resistant PCa. Some studies have documented an oncogenic dependency of cancer cells to AR signaling and have justified continued development of novel anti-androgens targeting AR (Vickman et al., 2020).

CONCLUSION

AR activity is necessary for development and progression of BPH and PCa. Most samples showed high AR expression in BPH that indicates AR plays crucial role in the development of BPH. Therapies of BPH aimed to reduce AR activity have been used as treatment to diminish AR activity remains one of primary approach, but not all patients respond. It needs alternative therapies that also activated AR pathway. In PCa, high AR expression in tumor cells was a half of the samples and a statistically significant correlation between AR expression and Gleason score. AR expression in the tumor cells are important markers for the progressivity of PCa. Examination of AR expression can be a biomarker in determining the prognosis of PCa patients. The limitation of this study is using a cross sectional design. It needs a prospective cohort study of AR expression in BPH associated with resistance to therapy and in PCa associated with survival and resistance to therapy.

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