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High Serum Prostate Specific Antigen as A Risk Factor for Moderate-Severe Prostate Inflammation in Patient with Benign Prostatic Hyperplasia

Gede Wirya K. Duarsa[1], *Rika Lesmana*[2], *Tjokorda G. B. Mahadewa*[3]

[1]Urology Department, Sanglah General Hospital, Denpasar, Indonesia
[2]Surgery Department, Medical Faculty, Udayana University, Denpasar, Indonesia
[3]Neurosurgery Department, Sanglah General Hospital, Denpasar, Indonesia

Background: Benign Prostatic Hyperplasia (BPH) is one of the most common degenerative disease found in men. Theories have been delivered to elucidate etiology, one of them is the theory of inflammation, and PSA is considered as one of risk factor for prostate inflammation. Undetected chronic inflammation could be a problem in BPH due to the obstructive and irritative symptoms it causes. Assessing risk factor could provide a better treatment outcome. **Methods**: A retrospective case control study in Sanglah Hospital, Indonesia. 70 men with BPH who underwent TURP in 2014, prostate inflammation is evaluated histologically from prostate specimens by one pathologist to avoid subjectivity. Those without inflammations and with mild inflammations are categorized as control group (n=35), and those with moderate and severe inflammations are categorized as case group (n=35). Preoperative total serum PSA retrieved from medical record **Results**: Median PSA is higher in case group, 2,83 compared to 14,12, with odd ratio 1,18 (p<0,001). Multivariate analysis is done for high PSA, bacteriuria, duration of urinary catheter insertion, and obesity, and still high PSA is the independent risk factor (adjusted OR=14,6 p<0,001). **Conclusion**: PSA is a risk factor for moderate-severe prostate inflammation in men with BPH. Bacteriuria, urinary catheter usage, and obesity did not differ significantly as risk factors for moderate-severe prostate inflammation.

Keywords: prostatitis, prostate inflammation, high PSA

INTRODUCTION

Benign Prostatic Hyperplasia (BPH) is a common degenerative condition in men from all over the world. Although generally BPH is not life threatening, the symptoms or complication could affect quality of life significantly. Histologically, 20% men of age 41-50 had BPH, 50% in the age of 51-60 years, >90% above the age of 80 years[1]. In 45-80 years old men with BPH, 90% have Lower Urinary Tract Symptoms (LUTS)[2].

Etiology of BPH remains unclear, although some hypotheses have been emerged. The role of inflammation has been suggested as the pathogenesis of BPH in 1937, and now BPH is hypothesized as an immune-mediated inflammatory disease[3]. Inflammation process stimulates tissue destruction, growth factor released, increases cellular proliferation and differentiation, and leads to prostate hyperplasia[3].

Prostate Specific Antigen (PSA) is hypothesized as a self antigen[4]. Men with PSA higher than 4 ng/ml, incidence rate of obstruction due to prostate is 89%, while those with PSA less than 2 ng/ml, the incidence is 33%[5]. PSA may increase due to primary condition such as prostate tissue damage, or secondary due to physical activities, infection, and drugs[2]. It is proven that CD4 T-cell in men with prostatitis reacted with seminal plasma, and the antigen being recognized is derived from the prostate[4].

METHODS

This is a retrospective study, included 70 men with BPH who underwent Transurethral Resection of the Prostate (TURP) in Sanglah Hospital, Denpasar, Indonesia, from January 2014 until April 2015. Subjects were selected with consecutive sampling, those with prostate cancer, diabetic, and with incomplete medical records data were excluded.

Retrieved from medical records were age, body mass index, duration of preoperative urinary catheter usage, concomitant bacteriuria, and preoperative total serum PSA value. All existed prostate tissue specimens were reviewed to determine grade and aggressiveness of inflammation, based on grading adapted from Sciarra, 2007[3,6]. Subjects with no inflammation or with inflammation grade 1 (mild inflammation) are categorized as control group, and subject's inflammation grade 2 and 3 (moderate and severe inflammation) are categorized as case group. Bivariate analysis was done for age, obesity, bacteriuria, and PSA as risk factors for prostate moderate-severe inflammation.

Table 1. Histologic Grading and Aggressiveness of Prostatic Inflammation (Adapted from Sciarra et al[6])

Histologic grading:
0: No inflammation
1: Scattered inflammatory cell infiltrate without nodules
2: No confluent lymphoid nodules
3: Large inflammatory areas with confluence
Histologic aggressiveness:
0: No contact between inflammatory cells and glandular epithelium
1: Contact between inflammation and epithelium
2: Interstitial infiltrate with glandular disruption
3: Glandular disruption on >25%

RESULT

70 samples are collected consecutively, 35 from both control and case group. Both group has normal distribution for age based on Shapiro-Wilk normality test. Mean age for control group was 68.5±7.4, and 66.3±8.1 for case group. Characteristics of subjects on both group is shown in Table 2. From men with moderate-severe prostate inflammation, 21 (60%) had bacteriuria, 11 (31.4%) used urinary catheter for 30 days or more before operation, and 6 (17.1) were with obesity.

Table 2. Characteristic of Subjects based on Group

Characteristics	Group		Total
	Control (n=35) f (%)	Case (n=35) f (%)	
Age, mean ± SD	68.5 ± 7.4	66.3 ± 8.1	67.4 ± 7.8
min-max	55-84	52-79	52-84
Bacteriuria			
No	20 (57.1)	14 (40.0)	34 (48.6)
Yes	15 (42.9)	21 (60.0)	36 (51.4)
Catheter duration			
<30 days	25 (71.4)	24 (68.6)	49 (70.0)
≥30 days	10 (28.6)	11 (31.4)	21 (30.0)
Obesity			
No	29 (82.9)	26 (71.4)	54 (77.1)
Yes	6 (17.1)	10 (28.6)	16 (22.9)

Histopathological review categorized subjects into control and case group. In control group, 5 were found without inflammatory cell and 30 with scattered inflammatory cell. In case group, 26 had lymphoid nodules and 9 with confluent nodules or large inflammatory areas (Table 3).

To determine risk factor for each variable, bivariate analysis was used with 95% confidence interval and significant p value is <0.05. Here, we analyzed PSA value as a categorical variable, PSA >4 ng/ml was categorized as high, and PSA ≤4 ng/ml was normal. From our study, men with high PSA had risk for moderate-severe prostate inflammation 11.6 times higher than men with normal PSA (OR=11.6, p <0.001). Other variables that we analyzed, bacteriuria, long term urinary catheter usage, and obesity did not differ significantly (Table 4).

Table 3. Inflammation Grading and Inflammatory Cell Aggressiveness Based on Group

Characteristics		Group	
		Control (n=35) f (%)	Case (n=35) f (%)
Inflammation	grade 0	5 (14.3)	0 (0)
	grade 1	30 (85.7)	0 (0)
	grade 2	0 (0)	26 (74.3)
	grade 3	0 (0)	9 (25.7)
Aggressiveness	grade 0	18 (51.4)	1 (2.9)
	grade 1	16 (45.7)	13 (37.1)
	grade 2	1 (2.9)	18 (51.4)
	grade 3	0 (0)	3 (8.6)

Table 4. Bivariate Analysis of Risk Factors for Moderate-Severe Prostate Inflammation

Variable Risk Factors	Group		Crude OR	95% CI	p value
	Control (n=35) f (%)	Case (n=35) f (%)			
PSA					
Normal	21 (60.0)	4 (11.4)			
High (>4ng/ml)	14 (40.0)	31 (88.6)	11.6	3.0-53.3	<0.001
Bacteriuria					

No	20 (57.1)	14 (40.0)			
Yes	15 (42.9)	21 (60.0)	2.0	0.7-5.8	0.151
Catheter duration					
<30 days	25 (71.4)	24 (68.6)			
≥30 days	10 (28.6)	11 (31.4)	1.1	0.4-3.6	0.794
Obesity					
No	29 (82.9)	25 (71.4)			
Yes	6 (17.1)	10 (28.6)	1.9	0.5-7.4	0.255

We also analyzed PSA value as a numerical variable. Median value of PSA in control group was 2.83 (IQR=8.57) while in case group was 14.12 (IQR=16.40). Our study showed that every 1 ng/ml increase of PSA, risk for moderate-severe prostate inflammation raised 1.18 times higher, or 18% more likely to have moderate-severe prostate inflammation (p <0.001).

Table 2. PSA Value in Control and Case Group

Variable	Group		OR	95% CI	p value
	Control (n=35)	Case (n=35)			
PSA, median (IQR)	2.83 (8.57)	14.12 (16.40)	1.18	1.08-1.29	<0.001
min-max	0.14-21.39	2.13-93.71			

PSA: Prostate Specific Antigen, IQR: Interquartile Range

DISCUSSION

Prostate inflammation is a challenge for health care provider these days, due to unclear etiology and wide variety of symptoms, from asymptomatic to chronic pelvic pain[7]. Data that we collected in Sanglah Hospital, Denpasar from January 2014 until April 2015, from 112 men with BPH, 95 (84.8%) were with prostatitis based on histopathological examination. This number is slightly higher than Piovesan's study, 78% within 145 men with BPH[7], and also a study from Nickel who showed 77% prostatitis in men with BPH[8].

Normal value of total serum PSA was ≤4 ng/ml, and PSA >4 ng/ml was considered high[9]. From our research, we found that subjects with high PSA had 11.6 times higher risk for moderate-severe prostate inflammations, and every 1 ng/ml increase of PSA, the risk for moderate-severe prostate inflammation increase 1.18 times (p<0.001).

There are several conditions that have been proposed as risk factors for prostatitis. In this research, we put urinary catheter usage, bacteriuria, and obesity as controlled variables. Referencing to Infectious Diseases Society of America Guidelines and review from Nicolle et al (2014), short term urinary catheterization is less than 30 days, and long term urinary catheterization is 30 days or more[10,11]. Jayakumar et al (2011) stated that 80% patients with bacteriuria were correlated with urinary catheter[12]. We consider this since men with BPH frequently had urine retention and catheterization. In our study, subjects with urinary catheter 30 days or more had OR=1,1 for moderate-severe prostate inflammation, but statistically not significant (p=0,794). Not much different, subjects with bacteriuria had twice higher risk for developing moderate-severe prostate inflammation (OR=2), but statistically not significant (p=0,151).

Obesity has been known related to metabolic syndrome, and both correlated with systemic inflammation[13]. It was stated that obesity may stimulate the increase of pro inflammatory substances[14]. In our study, subjects with obesity had 1.9 higher risk for moderate-severe prostate inflammation, but statistically not significant (p=0,255). This was similar to Wu et al (2013) that investigate correlation between obesity and prostatitis with results OR=1,1 but statistically not significant (p=0,55)[15].

Prostatitis is a non-malignant condition that most diagnosed in patients with elevating PSA[16]. PSA was hypothesized as a self antigen that stimulates inflammation process in the prostate. There was a proliferative reaction on CD4-T cell when inserted with seminal plasma, where the antigens were from prostate tissue[4]. Hou et al (2009) inserted protein expression or extract from prostate to mice, and found that there was a specific immune response to that antigen, that led to prostatitis-like conditions due to lymphoid infiltration[16]. They also found the specific protein in prostate, which was seminal vesicle secretory 2 (SVS2), that induced the CD4- T cell reaction and spontaneously form an antibody then caused prostatitis.

CONCLUSION

PSA is a risk factor for moderate-severe prostate inflammation in men with BPH. Men with PSA >4 ng/ml has 11.6 times higher risk compared to those with normal PSA. Bacteriuria, urinary catheter usage, and obesity did not differ significantly as risk factors for moderate-severe prostate inflammation.

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