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·*Clinical Experience*·

Risk factors for prostatic inflammation extent and infection in benign prostatic hyperplasia

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Abstract

Aim: To investigate the risk factors for prostatic inflammation extent and infection in patients with benign prostatic hyperplasia (BPH) so as to manage prostatic inflammation more efficiently. **Methods:** Sixty patients with BPH undergoing TURP between September 2005 and December 2005 in West China Hospital of Sichuan University were studied. Prostate fluid (PF) was collected for the measurement of secretory IgA (SIgA) and complement 3 (C3). Prostate tissue were collected for testing bacterial 16S rDNA by real-time PCR, examining SIgA in the tissue and examining the inflammation. The possible clinical and immune risk factors for prostatic inflammation or infection were analyzed by using the logistic regression method. **Results:** Abnormal white blood cell count in urinalysis, prostatic infection and a high concentration of C3 in PF are the risk factors for prostatic inflammation extent (P = 0.025, 0.034 and 0.035, respectively and odds ratio [OR] = 18.269, 8.284 and 1.508, respectively). Risk factors for prostatic infection include the C3 concentration and the concentration of SIgA in PF (P = 0.003 and 0.013, respectively, and OR=1.645 and 0.993, respectively). **Conclusion:** The present study suggests that prostatic inflammation is associated with urinary tract infection, prostatic infection and the activated complement and that prostatic infection is associated with the activated complement and downregulated mucosal immunity in prostates of the patients with BPH. It is also suggested that individual immune regulation should be considered in the treatment of prostatic inflammation and infection of patients with BPH. *(Asian J Androl 2006 Sep; 8: 621–627)*

Keywords: inflammation; infection; logistic regression; benign prostatic hyperplasia; prostate

1 Introduction

It has been well recognized that benign prostatic hyperplasia (BPH) and inflammation can coexist in prostate. In the study of Nickel *et al*. [1] 100% (80/80) of prostatic samples of BPH gained during transurethral resection of the prostate (TURP) had periglandular inflammation.

The role of inflammation in the pathogenesis of BPH and prostate cancer (PCa) has generated much interest. At the 2005 Annual Meeting of the American Urological Association, Roehrborn *et al*. [2] reported that the treatment of prostatic inflammation was greatly associated with the symptom progression and incidence of acute urinary retention among men in their Medical Therapy of Prostatic Symptoms study. Another study suggests that

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cyclooxygenase-2 (COX-2) is released by the inflammatory cells in the atrophic lesions of prostate and that COX-2 expressing cells might be associated with the pathogenesis of PCa [3]. Proliferative inflammatory atrophy, PCa precursor lesion, share some molecular traits with prostate intraepithelial neoplasia and PCa [4]. Therefore, it is necessary to prevent and treat effectively the inflammation in prostates of patients with BPH, and it will be of benefit to study the risk factors for prostatic inflammation.

The etiology of prostatic inflammation in BPH remains unclear. Abnormal humoral immunity and bacteria play an important role in the pathogenesis of chronic prostatitis, and it is unclear whether prostatic inflammation in BPH is associated with abnormal humoral immunity in prostate. Secretory IgA (SIgA) is an essential component in mucosal immunity, which protects prostate from bacterial invasion, and complement is an important natural immunity, which can not only kill bacteria but also cause tissue inflammation. Activated complement in prostate can be estimated by checking complement 3 (C3) in prostatic fluid (PF), moreover, Nickel *et al.* [1] reported that bacteria were found in 44% (35/80) of the prostatic specimens of BPH gained during TURP by using the bacterial culture method. A meta-analysis indicated that the preoperative treatment with antibiotics could effectively reduce the infectional complications after TURP [5].

In this study, we analyzed the role of local humoral immunity (local SIgA and C3) and clinical factors (prostate infection, urianalysis, preoperative catheterization and age) in prostatic inflammation of BPH using a logistic regression model. To better understand the cause of the prostatic infection, we also analyzed the role of local humoral immunity (SIgA and C3) and clinical factors (urianalysis and preoperative catheterization) in prostatic infection of BPH by using another logistic regression model.

2 Patients and methods

2.1 Patients

The present study included 60 patients diagnosed with BPH and scheduled for TURP from September 2005 to December 2005 in West China Hospital of Sichuan University (Chengdu, China). Patients were excluded if they had any history of prostatitis, prostatic surgery or documented urinary tract infection (UTI).

2.2 Clinical and laboratory data collection

Urinalysis was done before TURP, and it was considered abnormal when the white blood cell (WBC) count exceeded 5 per high power field (HPF) [6]. PF was collected before TURP, then SIgA and C3 concentration in PF were measured by radioimmunoassay and rate nephelometry assay, respectively. During TURP, deep random tissue after resection of the prostatic urethra were collected through the resectoscope sheath under sterile conditions, and then the specimens were washed repeatedly with sterile normal saline. The potential for contact with penile urethral and subsequent surface contamination was minimized before real-time polymerase chain reaction (PCR). Subsequently, more than 50 mg specimens were stored at –70ºC for testing bacterial 16S rDNA together by real-time PCR; 500 mg specimens were homogenized for examining SIgA content in the tissue by radioimmunoassay, and the remaining specimens were used to examine the inflammation under a light microscope.

2.3 Real-time PCR

The special primers and probe of bacterial 16S rDNA gene were designed according to the common bacteria in the prostate of patients with BPH, including *Escherichia coli*, *Staphylococcus epidermidis*, *Candida parapsilosis*, *Enterococcus spp*, *Streptococcus viridens* and *Pseudomonas aeruginosa* [1]. The forward primer sequence of 16S rDNA was 5'-TGG AAC TGA GAC ACG GTC CA-3', and the reverse primer sequence was 5'-CGC TTT ACG CCC AGT AAT TCC G-3'. The probe sequence was 5'-TGC CAG CAG CCG CGG TAA TAC-3'. They were synthesized in TaKaRa Biotechnology (Dalian, China). Real-time PCR was carried out in GeneAmp PCR System 9600 (Perkin Elmer, Norwalk, CA, USA). The other laboratory processes were similiar to those of a previous study [7]. Positive 16S rDNA was defined as the prostatic infection.

2.4 The diagnostic standard of prostatic inflammation extent

Nickel *et al.* [8] reported a consensus development of a histopathological classification system for chronic prostatic inflammation, which was adopted in the present study (Table 1). The grade 2 and 3 periglandular inflammation were classified together as moderate-severe inflammation.

2.5 Statistical analysis

All statistical analyses were performed using computer software SPSS 11.0 (SPSS, Chicago, IL, USA).

Logistic regression analysis was used to determine the independent association of the immune and clinical factors with prostatic inflammation or infection in BPH, and the backward stepwise (likelihood ratio) method was adopted in multivariate logistic regression models. Only factors with $P < 0.1$ in the univariate logistic regression model were involved into the related multivariate logistic regression model, and $P < 0.05$ was considered significant [9]. We also assessed the accuracy of the multivariate models by using the Hosmer and Lemeshow statistic with a nonsignificant *P*-value implying goodness of fit.

3 Results

3.1 General information

The mean age of the 60 patients was 69.6 ± 7.1 years. The percentage of abnormal WBC count in urinalysis was 58.3% (35/60), and 48.3% (29/60) of the patients had received catheterization before TURP. The C3 concentration in PF varied from 0.00 g/L to 0.91 g/L, and the median value was 0.11 g/L. Twenty-five and 75 percentiles of C3 concentration were 0.00 g/L and 0.29 g/L, respectively. The mean SIgA concentration in PF was 364.11 ± 164.70 μg/mL and the mean SIgA content per gram of hyperplastic prostate tissue was 19.72 ± 10.04 μg. Periglandular inflammation was identified in all patients, and mild inflammation was present in 76.7% (46/60) of patients and moderate-severe inflammation was present in 23.3% (14/60). Periglandular inflammation was the predominant pattern in the two inflammatory types (data not shown), and the following prostatic inflammation in this article was represented by periglandular inflammation. Of the prostate specimens, 28.3% (17/60) had been infected by bacteria. In the present study, there were five values absent, including four SIgA concentrations and one C3 concentration in PF, because we could not get enough PF from patients to test. The details of the absent data are illustrated in Table 2.

3.2 Analysis of the risk factors for prostatic inflammation extent

Risk factors for prostatic inflammation were analyzed in the univariate logistic regression mode of prostatic inflammation extent, including abnormal WBC count in urinalysis, prostatic infection, C3 concentration in PF, SIgA concentration in PF, content of SIgA per gram of hyperplastic prostate tissue, preoperative catheterization and age. Because $P < 0.1$ of abnormal WBC count in

Table 1. The diagnosis standard of prostatic inflammation [8].

Feature	Details
Anatomical location	Histological pattern
Periglandular	Inflammatory infiltrates lie within stroma, are centred around ducts/glands, and approach ducts/glands to within 50 μm
Glandular	Inflammatory infiltrates lie within duct/gland epithelium and/or lumens
Grade	Morphological description (typical inflammatory cell density, cells/mm^2)
Mild	Individual inflammatory cells, most of which are separated by distinct intervening spaces (< 100)
Moderate	Confluent sheets of inflammatory cells with no tissue destruction or lymphoid nodule/follicle formation (100–500)
Severe	Confluent sheets of inflammatory cells with tissue destruction or nodule/follicle formation (> 500)

Table 2. Details of the absent data because we could not get enough PF from patients. PF, prostatic fluid.

Patient number	Prostatic specimens		C3 Concentration in PF	SIgA concentration in PF
	Inflammation	Infection		
9	mild	Infection	Absence	
16	mild	No infection		Absence
20	mild	No infection		Absence
48	mild	No infection		Absence
50	mild	No infection		Absence

urinalysis, prostatic infection, the C3 concentration in PF and preoperational catheterization, respectively (Table 3), these four factors were involved into the multivariate logistic regression model of prostatic inflammation extent. As a result, the overall accuracy of the multivariate logistic regression model's prediction was 86%, and the model fitted the dataset well (Hosmer and Lemeshow statistic, $P = 0.86$). Abnormal WBC counts in urinalysis, prostatic infection and the C3 concentration in PF were associated with the extent of prostatic inflammation ($P = 0.025$, 0.034, 0.035, respectively, and OR =18.269, 8.284, 1.508, respectively) (Table 4). In other words, patients with an abnormal WBC count in urinalysis were 18.269 times more likely to develop a higher grade of prostatic inflammation than those with a normal WBC count in urinalysis, patients with prostatic infection were 8.284 times more likely to develop a higher grade of prostatic inflammation than those without prostatic infection, and patients with the C3 concentration in PF per increasing 0.1 g/L were 1.508 times more likely to have a higher grade of prostatic inflammation.

3.3 Analysis of the risk factors for prostatic infection

Risk factors for prostatic infection were analyzed in the

Table 3. Univariate logistic regression analysis of prostatic inflammation extent. Abnormal white blood cell (WBC) counts in urinalysis, prostatic infection, the C3 concentration in prostatic fluid (PF), the SIgA concentration in PF, the content of SIgA per gram of hyperplastic prostate tissue, preoperative catheterization and age were analyzed in the univariate logistic regression mode of prostatic inflammation extent. The *P*-values of abnormal WBC counts in urinalysis, prostatic infection, the C3 concentration in PF and preoperative catheterization were less than 0.1, and these four factors were involved into the multivariate logistic regression model of prostatic inflammation extent. B, the coefficient value of a variable involved in a logistic regression mode. OR, odds ratio.

Clinical/ immune factors	B	SE	*P*	OR	95% CI for OR	
					Lower	Upper
Abnormal WBC count in urinalysis (cases)	2.652	1.079	0.014	14.182	1.711	117.515
Yes (35)						
No (25)						
Prostatic infection (cases)	2.146	0.680	0.002	8.550	2.255	32.419
Yes (17)						
No (43)						
C3 concentration in PF (g/L) (cases)	0.624	0.168	0.000	1.867	1.342	2.597
0 (18)						
0.001–0.1 (9)						
0.101–0.2 (12)						
0.201–0.3 (6)						
0.301–0.4 (2)						
0.401–0.5 (2)						
0.501–0.6 (6)						
> 0.6 (4)						
SIgA concentration in PF (μg/mL)	–0.001	0.002	0.590	0.999	0.995	1.003
SIgA content in prostatic tissue (μg/g tissue)	–0.034	0.035	0.326	0.966	0.902	1.035
Preoperative catherterization	1.268	0.663	0.056	3.553	0.969	13.030
Yes (29)						
No (31)						
Age (years) (cases)	–0.227	0.524	0.665	0.797	0.285	2.224
53–64 (13)						
65–76 (39)						
77–88 (8)						

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univariate logistic regression model of prostatic infection including abnormal WBC count in urinalysis, C3 concentration in PF, SIgA concentration in PF, content of SIgA per gram of hyperplastic prostate tissue and preoperative catheterization. The *P*-values of the C3 concentration in PF, the SIgA concentration in PF and the content of SIgA per gram of hyperplastic prostate tissue were all less than 0.1 (Table 5). Therefore, these three factors were used in the multivariate logistic regression model of prostatic infection. The overall accuracy of the multivariate logistic regression model's prediction was 81.5%, and the model fitted the data well (Hosmer and Lemeshow statistic $P = 0.84$). The C3 concentration in PF and the SIgA concentration in PF were associated with prostatic infection ($P = 0.003$ and 0.013, respectively, and OR = 1.645 and 0.993, respectively) (Table 6). In other words, a patient was 1.645 times more likely to experience prostatic infection with a C3 concentration in PF per increasing 0.1 g/L and 0.993 times less likely to have prostatic infection with an SIgA concentration in PF per increasing 1 μg/mL.

Table 4. Multivariate logistic regression analysis of prostatic inflammation extent. An OR value greater than 1 suggests an increased risk of higher grade prostatic inflammation among patients with the specified level of the risk factor relative to those described by the reference level. For example, a patient with prostatic infection was 8.284 times more likely to experience a higher grade prostatic inflammation than one without prostatic infection. PF, prostatic fluid; WBC, white blood cell. B, the coefficient value of a variable involved in a logistic regression mode. OR, odds ratio.

Risk factors	Reference level	B	SE	*P*	OR	95% CI for OR	
						Lower	Upper
Abnormal WBC count in urinalysis	Normal WBC count in urinalysis	2.905	1.297	0.025	18.269	1.437	232.218
Prostatic infeciton	No prostatic infeciton	2.114	0.999	0.034	8.284	1.170	58.654
C3 concentration in PF	Per increasing 0.1g/L	0.410	0.195	0.035	1.508	1.029	2.208

Table 5. Univariate logistic regression analysis of prostatic infection. Abnormal white blood cell (WBC) counts in urinalysis, the C3 concentration in prostatic fluid (PF), the SIgA concentration in PF, the content of SIgA per gram of hyperplastic prostate tissue and preoperative catheterization were analyzed in the univariate logistic regression model of prostatic infection. The *P*-values of the C3 concentration in PF, the SIgA concentration in PF and the content of SIgA per gram of hyperplastic prostate tissue were less than 0.1, respectively, and the three factors were used in the multivariate logistic regression model of prostatic infection. B, the coefficient value of a variable involved in a logistic regression mode. OR, odds ratio.

Clinical or immune factors	B	SE	*P*	OR	95% CI for OR	
					Lower	Upper
Abnormal WBC count in urinalysis (cases)	0.373	0.593	0.530	1.451	0.454	4.642
Yes (35)						
No (25)						
C3 concentration in PF (g/L) (cases)	0.493	0.147	0.001	1.637	1.226	2.185
0 (18)						
0.001–0.1 (9)						
0.101–0.2 (12)						
0.201–0.3 (6)						
0.301–0.4 (2)						
0.401–0.5 (2)						
0.501–0.6 (6)						
> 0.6 (4)						
SIgA concentration in PF (μg/mL)	–0.006	0.002	0.006	0.994	0.990	0.998
SIgA content in prostatic tissue (μg/gram tissue)	–0.098	0.042	0.019	0.907	0.835	0.984
Preoperative catheterization(cases)	0.258	0.574	0.654	1.294	0.420	3.986
Yes (29)						
No (31)						

Table 6. Multivariate logistic regression analysis of prostatic infection. An OR value less than 1 suggests a decreased risk of prostatic infection among patients with the specified level of the risk factor relative to those described by the reference level. For example, a patient was 0.993 times less likely to experience prostatic infection with an SIgA concentration in prostatic fluid (PF) per increasing 1 μg/mL. B, the coefficient value of a variable involved in a logistic regression mode. OR, odds ratio.

Risk factors	Reference level	B	SE	*P*	OR	95% CI for OR	
						Lower	Upper
C3 concentration in PF	Per increasing 0.1 g/L	0.497	0.167	0.003	1.645	1.187	2.279
SIgA concentration in PF	Per increasing 1 μg/mL	–0.007	0.003	0.013	0.993	0.988	0.999

4 Discussion

To avoid the adverse influence of TURP upon prostatic inflammation, measures were taken such as using smaller electrical flow when resecting samples, resecting piece of tissues as large as possible, cutting out the peripheral tissue of the samples and then choosing fresh cores of samples for pathologic examination. There was no statistical difference of the international prostate symptom score of patients between the mild inflammation group and the moderate–severe inflammation group (data not shown). Periglandular inflammation was the most predominant pattern but only represented 0.5% of the volume of the gland overall [1]. In the present study, severe inflammation had obvious gland destruction, and the percentage of severe inflammation in three grades was 10% (6/60).

Abnormal WBC count in urinalysis was associated with UTI. The diagnostic sensitivity was 90–96%, and specificity 47–50% when a patient with more than 5 WBCs per HPF in urinalysis was diagnosed as UTI [6]. UTI could result in prostatic inflammation and increasing serum prostatic specific antigen [10]. An inflammatory response in contiguous anatomic sites could be induced by the infection in the genitor-urinary tract, including the prostate [11].

The alternative pathway is activated when the complement C3b deposits on bacteria, and the classic pathway is activated by the antigen-antibody compound. Complement might damage the normal tissue when it is activated. The extent of tissue damage decreased accordingly when the activation of complement was inhibited [12].

Some bacteria might be culture resistant [13]. Takahashi *et al*. [7] applied real-time PCR technique to identify the nosogenetic bacteria in prostatitis, and found that bacterial 16S rDNA was positive in 26% (8/31) of prostatic specimens. The endotoxin concentration in prostatic secretions might provide a supplementary tool to quickly identify the bacterial cause of prostatic inflammation [14]. In the present study, real-time PCR was also adopted, which, to some extent, could exclude the adverse effect on bacterial identification from electric resection and the short-term treatment of antibiotics.

Some special complement receptors were used by some microorganisms to invade human somatic cells. For example, mycobacterium tuberculosis activated complement, resulting in the interaction of the bacterium with the complement receptors on macrophages promoting phagocytosis [15]. Human immune adherence happened when *Leishmania* entered into human blood circulation was a rapid reaction between complement receptor type one (CR1) on erythrocytes and few C3b ligands on promastigotes [16]. Springall *et al*. [17] found that C3 helps *Escherichia coli* combine with CR1-related protein y (Crry) on the renal epithelium of mice and, therefore, *E. coli* could enter proximal tubular epithelial cells of mice *in vitro*. We found that the C3 concentration in PF of the BPH patients with prostatic infection was significantly higher than that without prostatic infection (data not shown). A comprehensive study of the interrelationship between increased C3 in PF and prostatic infection is necessary.

SIgA plays an important role in the protection of mucosa against bacteria. Recurrent lower urinary tract infection results in weakened mucosal immunity, and decreasing secretion of SIgA is an important cause of recurrent infection [18]. Normally, there is some SIgA in human prostate, which protects not only the prostate but the urogenital tract. Mucosa-associated lymphoid tissue is the immune tissue of the prostate, which can synthesize SIgA increasingly when bacteria invade the prostate under normal conditions [19]. However, SIgA secretion is decreased in patients with long-term and recurrent prostatitis.

The following conclusions are drawn from the present study: (1) Prostatic inflammation was an common find-

ing in patients with BPH undergoing TURP in the present study. (2) Prostatic inflammation is associated with UTI, prostatic infection and the activated complement, and prostatic infection is associated with the activated complement and downregulated mucosal immunity in prostates of the patients with BPH. (3) Individual immune regulation should be considered in the treatment of prostatic inflammation and infection of patients with BPH. With the emerging insights into the role of inflammation in BPH and PCa, the importance of treating prostatic inflammation in BPH and prostatitis is being recognized.

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