ORIGINAL PAPER

INFECTIONS

Association between pre–biopsy white blood cell count and prostate biopsy – related sepsis

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Introduction Despite all preventive measures and improved biopsy techniques, serious, life–threatening complications of prostate biopsy, including sepsis, still exist. In the present study, in order to identify the risk factors that may be associated with sepsis development after prostate–biopsy, we aimed to analyze retrospectively the data of our patients who underwent transrectal ultrasound–guided prostate biopsy.

Material and methods We retrospectively reviewed the data of 889 patients who underwent prostate biopsy at our clinic. We compared pre–biopsy parameters (age, prostate volume, white blood cell (WBC) count, fasting blood glucose, free and total prostate specific antigen levels) between patients who developed sepsis and those who were sepsis–free following prostate biopsy.

Results 28 patients (3.1%) developed sepsis. Among the risk factors evaluated, only pre–biopsy WBC count was found to be a significant risk factor for biopsy–related sepsis. A 5.1 fold increase was detected in the risk for sepsis development, when the cut–off value of WBC was accepted as 11.165/μL, OR: 5.1 (95% CI: 2.3–11.5). The post–biopsy sepsis development rate in patients with pre–biopsy WBC count greater and less than 11.165/μL was 13.7% (n = 10) and 3% (n = 18) respectively.

Conclusions Patients with a pre–biopsy WBC count greater than 11.165/μL should be informed of the increased risk of developing post–biopsy sepsis.

Key Words: prostate ‹› biopsy ‹› sepsis ‹› leukocytosis

INTRODUCTION

In developed countries, prostate cancer is the most frequently diagnosed cancer in men after middle–age and the associated mortality rate ranks second only to lung cancer. Prostate cancer is detected in 20–67% of biopsies; the remaining are reported as non–cancerous lesions [1].

Despite all preventive measures and new biopsy techniques, complications of prostate biopsy still exist, ranging from minor hematuria, urethral or rectal bleeding, prostatitis and hematospermia to major complications, in the form of severe anemia, febrile urinary tract infection, syncope and sepsis. Sepsis is the most serious and life–threating one among these complications [2].

Nowadays, the necessity for prophylactic antibiotic use prior to prostate biopsy is accepted scientifically. In a prospective, randomized study by Puig et al., the infection rate was 3.7% in patients who received antibiotic prophylaxis, and 10.3% without prophylaxis [3].

Although there is no doubt regarding the necessity for antibiotic prophylaxis, it is not clear how much and what type of antibiotics should be used. There are more than 20 existing protocols in the literature [4]. Broad spectrum antibiotics are recommended for prophylaxis of transrectal ultrasound (TRUS)–guided prostate biopsy. According to several centers, administering a quinolone derivative prior to the procedure and 1–3 days thereafter is a reasonable choice [5, 6].

Antibiotic prophylaxis minimizes life–threatening septic complications. However, septic complications can not be avoided completely. For this reason, a more rational approach would be to predetermine the patients in whom the risk of development of sepsis is higher after biopsy.

Sepsis is defined as the presence of clinically or microbiologically documented infection in conjunction with Systemic Inflammatory Response Syndrome (SIRS) [7, 8]. SIRS describes the evolving response in the host against different clinical criteria. It is characterized by the presence of at least two of the following:

- Body temperature >38°C or <36°C
- Heart rate >90 beats/minute
- Respiratory rate >20 breaths/minute or PaCO2 <32 mmHg
- White blood cell (WBC) count >12000/μL or <4000/μL or >10% detection of young neutrophils

The importance of predicting such a serious and potentially fatal complication is obvious. Certain parameters such as diabetes mellitus (DM), large prostatic size and number of biopsy cores, have been determined to effect biopsy–related complications negatively [9, 10].

In this study, we analyzed the data of our patients who underwent TRUS–guided prostate biopsy, and compared the patients with or without post–biopsy sepsis regarding several risk factors.

MATERIAL AND METHODS

We retrospectively reviewed the data of 889 patients who underwent prostate biopsy between December 2005 and March 2012. All biopsies were performed in our clinic by two urologists. Indications for biopsy included abnormal digital rectal examination findings and/or high prostate specific antigen (PSA) levels. Patients with bleeding disorders, severe cardiovascular disease and those taking immunosuppressive drugs did not undergo biopsy.

In all patients, pre–biopsy free and total PSA levels were determined with the Tandem–R monoclonal kit (Hybritech Inc., San Diego, CA, USA). Total PSA values under 4 ng/mL were considered normal. Complete blood count and fasting blood glucose (FBG) levels were also measured.

Midstream urine samples were taken prior to biopsy for urinalysis and urine cultures. Those with urinary tract infections were first treated medically, and the biopsies were taken after their control urine cultures returned negative. Patients were requested to come to clinic in the morning on an empty stomach and without performing any bowel or rectal cleaning.

The biopsies were taken 3 and 7 days after the discontinuation of warfarin and aspirin respectively.

A Hitachi EUB–400 device (Hitachi Medical Corp., Tokyo, Japan) with a bipolar 6.5 MHz probe was used to perform TRUS. Prostate volumes were calculated using the prolate ellipsoid formula (volume = 0.52 × length × width × height). Using an 18 gauge cut needle, 10 core (base, middle, apex, lateral and far lateral of both left and right peripheral zones) biopsies were performed with the patient in the left lateral decubitus position. All patients received ciprofloxacin 500 mg twice–daily for five days, starting two days before biopsy.

Age, prostate volume, WBC count, (FBG), free–total PSA levels and biopsy results of all patients were reviewed. The presence of urinary tract infections after biopsy and urine culture results of those with infection were also recorded.

Sepsis is defined as the presence of clinically or microbiologically documented infection in conjunction with SIRS [7, 8]. Complications after biopsy were classified as minor and major. The patients were followed up for 7 days post–biopsy to monitor any development of biopsy–related complications. Hematuria, rectal bleeding and hematospermia were regarded as minor complications, while fever, acute urinary retention, epididymitis, and sepsis were classified as major. Urine and blood cultures of patients who developed sepsis were sent for microbiological evaluation.

We compared pre–biopsy parameters between patients who developed sepsis and those who were sepsis–free following prostate biopsy.

Statistical analysis

The results were analyzed using student's t–test and Pearson's chi–square tests with the SPSS (Statistical Package for Social Sciences) software program version 18.0 (SPSS Inc., Chicago, IL, USA). A Receiver Operating Characteristics (ROC) curve was drawn to evaluate the performance of serum WBC count in diagnosing sepsis and to determine the best cut–off value for serum WBC count. A p–value less than 0.05 was considered statistically significant.

RESULTS

TRUS–guided 10 core prostate biopsies were taken from a total of 889 patients. The mean age of patients was 64.22 ±8.4 (39–90) years. The mean PSA value was 13.9 ±39.3 (0.55–50) ng/mL, free PSA 2.1 ±3.5 (0.01–50) ng/mL, WBC count 6077.9 ±4116.8/μL (3500–15400/μL), prostate volume 56.6 ±26.5 (15–205) mL and FBG 93.8 ±272.6 (77–400) mg/dl.

Benign prostate hyperplasia was observed in 707 patients (79.5%), prostate adenocarcinoma in 170 (19.1%), atypical small acinar proliferation in 4 (0.44%), low–grade prostatic intraepithelial neoplasia (PIN) in 6 (0.67%), high–grade PIN in 2 (0.22%) patients, and prostatitis in 330 patients. PIN was formerly classified as low and high grade PIN. The diagnosis of "low–grade PIN" derived from old data. There was no significant association between biopsy pathology and the presence or absence of sepsis ($p > 0.05$).

Of the minor biopsy–related complications, hematuria occured in 110 patients (12.3%), rectal bleeding in 82 patients (9.22%) and hematospermia in 135 patients (15.1%). Major complications included fever in 35 patients (3.9%), acute urinary retention in 22 patients (2.4%), epididymitis in 8 patients (0.89%) and sepsis in 28 patients (3.1%) (Table 1). Sepsis developed in those patients between 2–5 days after the biopsy.

In urine and blood cultures of 28 patients with sepsis, eosin methylene blue agar detected *Escherichia coli* (*E. coli*) in 23 patients (13 were sensitive to cefoperazone + sulbactam, 10 were sensitive to imipenem, and all 23 were resistant to fluoroquinolones), extended spectrum beta–lactamase–positive *E. coli* in 4 patients (all 4 were resistant to fluoroquinolones, but sensitive to cefoperazone + sulbactam) and *Brucella spp.* in only 1 patient. These 28 patients were hospitalized and treated with appropriate antibiotics according to culture antibiogram test results. Comparing data from the two groups (sepsis, no sepsis), no statistically significant difference was determined regarding age, PSA, free PSA, prostate volume and FBG. However, regarding pre–biopsy WBC count, the difference was found to be significant ($p < 0.05$) (Table 2). Post–biopsy sepsis development rate of patients who had a pre–biopsy WBC count of greater and less than 11.165/μL was 13.7% (n = 10) and 3% (n = 18), respectively. A 5.1 fold increase was detected in the risk of biopsy–related sepsis [the cut–off value for WBC count was 11.165/μL, OR: 5.1 (95% CI: 2.3–11.5)]. According to the ROC analysis, the best cut–off value for serum WBC count was found to be 11.165/μL. The area under the ROC curves for serum WBC count was 0.637 (95% CI: 0.521–0.753, p: 0.014).

Table 1. *Complications after biopsy*

	n	%
Minor complications		
Hematuria	110	12.3
Rectal bleeding	82	9.22
Hematospermia	135	15.1
Major complications		
Fever	35	3.9
Acute urinary retention	22	2.4
Epididymitis	8	0.89
Sepsis	28	3.1

Table 2. *Comparison of pre–biopsy data in patients with or without post–biopsy sepsis*

	Sepsis (Group 1, n=28)	No sepsis (Group 2, n=861)	p–value
Age	64.35 ±7.35 (49–76)	64.21 ±8.51 (39–90)	0.821
PSA	10.79 ±13.49 (2.4–64)	14.00 ±39.86 (0.5–750)	0.272
fPSA	2.02 ±2.01 (0.48–10)	2.15 ±3.56 (0.01–50)	0.746
Prostate Volume	53.5 ±21.96 (23–85)	56.7 ±26.6 (15–205)	0.576
WBC count	9943.9 ±3911.7 (5600 –15400)	5949.8 ±4063.1 (3500–15100)	<0.001
FBG	112.4 ±36.9 (72–206)	93.1 ±276.9 (77–400)	0.104

DISCUSSION

Today, TRUS–guided prostate biopsy is considered a safe procedure applicable to an outpatient setting without a need for sedative or anesthetic agents. With the widespread use of automatic biopsy instruments and fine needles, the duration of the biopsy has been shortened and patients' comfort increased [4]. In fact, TRUS biopsy is well tolerated by as many as 70–90% of patients [11].

However, side effects and serious complications have been reported [4]. In some studies, complication rates of between 20–50% after prostate biopsy have been reported [12, 13], however, in a recent study, this rate was reported to be below 10% [14]. In the study by Yoshiyuki et al. of complication rates, hematuria was reported as 12%, rectal bleeding 5.9%, hematospermia 1.2%, fever 1.1%, urinary retention 1.2%, epididymitis 0.06% and sepsis 0.07% [15]. Djavan et al. reported a post–biopsy complicated urinary tract infection ratio between 1.2–11.3%, fever 1.4–4.5%, sepsis 0.1–0.3%, hematuria 12.5–58.4%, hematospermia 5.1–45.3%, rectal bleeding 2.1–37.1% and urinary retention 0.2–2.6% [16]. Our complication rates were 12.3% for haematuria, rectal bleeding 9.22%, hematospermia 15.1%, fever 3.9%, acute urinary retention 2.4%, epididymitis 0.89% and sepsis 3.1%. The differences in complication rates may be due to the particular biopsy preparation protocol or actual biopsy method. Some authors favor pro-

phylactic antibiotic use before biopsy, while others support bowel cleansing. According to a Cochrane review, the use of enema did not decrease the risk of developing sepsis, it only lowered the risk of subsequent bacteremia [17]. Ruddick et al. reported that the 24–hour clear–fluid diet and the use of disposable enemas, combined with a regimen of ciprofloxacin, decreased the rate of post–biopsy sepsis, but the results, however, were not statistically significant [18]. Besides, according to Carey and Korman, pre–biopsy enemas increase cost and patients' discomfort without providing a clinically–significant outcome advantage [19].

In the present study, we used prophylactic antibiotics and did not attempt any bowel cleansing. The patients were instructed to come to the clinic on an empty stomach in the morning. In a study investigating the association between comorbidities in patients undergoing prostate needle biopsy and biopsy–related infections, Carignan et al. reported that DM, chronic obstructive pulmonary disease and a history of hospitalization within the preceding month are independent risk factors for post–biopsy infection [9]. After reviewing the medical background of our patients who developed sepsis, we noticed that 6 out of these 28 patients had DM. However, the relationship between the risk of developing sepsis and DM was not found to be statistically significant ($p > 0.05$). One of our sepsis–positive patients potentially had an occupational disease, as a butcher, who developed *Brucella spp.* sepsis. Nam et al. have found a significant relationship between the number of biopsy cores and post–biopsy sepsis [10]. In our study, we detected a significant association between pre–biopsy WBC count and biopsy–related sepsis ($p < 0.001$).

Signs and symptoms of sepsis are nonspecific. Altered WBC count or body temperature and demonstration of bacterial antigens in serum and in body fluids support the clinical diagnosis of sepsis. However, these tests are not specific for sepsis. The gold standard for the diagnosis of sepsis requires a positive blood culture in the presence of clinical symptoms [20].

White blood cells or leukocytes are cells of the immune system involved in defending the body against infectious disease. Leukocytosis is often observed in patients with sepsis. Neutropenia is seen in very few patients, and is a sign of an unfavorable disease course. Acute localized infections (pneumonia, meningitis, tonsillitis, abscesses) and acute generalized infections (acute rheumatic fever, sepsis, cholera) lead to an increase in the number of leukocytes. In acute infections, the number of leukocytes rises in direct proportion to the severity of infection. Resistance, age and patient bone marrow reserve are important determinants of this number. Leukocytosis is defined as a total WBC count more than two standard deviations above the mean, or a value greater than 11.000/μL in adults [21].

Pre–operative or pre–treatment leukocytosis has been shown to be associated with both infectious and non–infectious morbidity and mortality in several recent studies. For example, anal cancer patients with both leukocytosis (WBC count > 10.000/μL) and anemia (pre–treatment hemoglobin < 12.5 g/dL) had worse prognosis and 2–year disease–free survival compared with patients without these factors [22]. Pre–operative fever and leukocytosis, without an established source of untreated infection, are found to be independent risk factors for the development of deep post–operative wound infections after surgical treatment of pelvic and acetabular fractures [23]. Pre–operative factors, which include leukocytosis, are reported to be associated with peri–operative complications after pancreaticoduodenectomy [24]. In patients undergoing coronary artery bypass surgery, pre–operative leukocytosis was demonstrated to be a significant predictor of post–operative atrial fibrillation [25].

A retrospective analysis is a limitation of our study. Prospective, controlled studies are needed in the future to make more definitive comments regarding this subject.

CONCLUSIONS

In the present study, the value of pre–biopsy WBC count was found to be the only significant difference between patients with sepsis and those without. Pre–biopsy WBC count was also found to be an important factor for the development of post–biopsy sepsis. Therefore, we believe that pre–biopsy leukocytosis deserves more attention in the prediction of post–biopsy sepsis.

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