Prostate inflammation

Association with benign prostatic hyperplasia and prostate cancer

Taha A. Abdel-Meguid, *MSc, MD (Urology),* ***Hisham A. Mosli,*** *FRCSC, FACS,* ***Jaudah A. Al-Maghrabi,*** *MD, FRCPC.*

ABSTRACT

الأهداف: دراسة العلاقة المحتملة بين التهابات البروستات و كلا من تضخم البروستات الحميد وسرطان البروستات في المرضى السعوديين.

الطريقة: تمت مراجعة الملفات الطبية للمرضى السعوديين الذين أجريت لهم دراسة باثولوجية لأنسجة عينات البروستات في مستشفيات مدينة جامعة الملك عبد العزيز الطبية –المملكة العربية السعودية خلال الفترة من شهر يونيو 2003 حتى يونيو 2008. اشتملت العينات على عينات أخذت بتوجيه الموجات الفوق صوتية الشرجية. تم انتقاء العينات التي بها التهابات أو سرطان أو تضخم حميد. وتم تصنيف العينات إلى أقسام: الالتهابات فقط – الالتهابات مع التضخم الحميد – التهابات مع سرطان – التضخم الحميد فقط – سرطان فقط. وقسمت أنواع الالتهابات إلى مزمن – مزمن مع حاد – أو حاد.

النتائج: تم تحليل 214 عينة لمرضى يتراوح عمرهم بين 37–100 عام متوسط= 68. من بين الحالات، ظهر التهاب حاد في حالة واحدة، بينما ظهر التهاب مزمن مصاحب للالتهاب الحاد أو بدونه في 87/88. وجدت الالتهابات فقط في (5.6%) في حين وجد تضخم البروستاتBPH في 126 مريض (58.9%) و كان مصحوبا بالالتهابات في 20.1% بينما وجد السرطان في 76 مريض (35.5%) وكان مصحوبا بالالتهابات في 15.4%. اشتمل النوعين الأخيرين على حالات مصاحبة بالالتهاب. في تحليل 214 عينة وجد تضخم البروستات المصاحب للالتهاب منتشر بشكل أكثر من السرطان المصاحب للالتهاب .versus 33/214=15 214/43=20.1%(4%). وفي التحليل الجزئي في كل صنف، انتشر الالتهاب بشكل أقل في مجموعة تضخم البروستات مقارنة بمجموعة السرطان(126/34=34.1% versus 33/76=43.4%).

خاتمة: تشير الدراسة إلى فرضية ارتباط الالتهابات مع التضخم الحميد للبروستاتBPH و السرطان. المزيد من الدراسة و البحث مطلوب لتأكيد مدى صحة هذه الفرضية و توضيح العلاقة الجوهرية المرتبطة بين الالتهاب وتضخم البروستات BPH مقارنة مع السرطان.

Objectives: To study the association and possible relationship of prostate inflammation with benign prostatic hyperplasia (BPH), and prostate cancer.

Methods: The medical records and pathological findings of all Saudi patients who underwent transrectal ultrasound guided prostatic needle biopsies in King Abdulaziz University Medical City, Jeddah, Kingdom of Saudi Arabia from June 2003 to June 2008 were reviewed retrospectively. The indications for biopsy were elevated levels of serum prostate specific antigen, abnormal findings on digital rectal examination, or both. The specimens harboring inflammation, adenocarcinoma, BPH, or their combinations, were selected and included in the study.

Results: A total of 214 patients were selected with an age ranging from 37-100 years (median=68). Inflammation was histologically evident in 88 patients. Of them, only one demonstrated acute inflammation, while 87/88 demonstrated chronic inflammation with, or without acute inflammation. Histopathologic features were categorized into 3 main categories: inflammation alone (12/214, 5.6%), BPH category (126/214, 58.9%), and cancer category (76/214, 35.5%) patients. The last 2 categories also included cases associated with inflammation. In the overall analysis of 214 specimens, BPH with inflammation was more prevalent than cancer with inflammation (43/214 [20.1%] versus 33/214 [15.4%]). In a subgroup analysis within each category, inflammation was less prevalent in the BPH category compared to the cancer category (43/126 [34.1%] versus 33/76 [43.4%]).

Conclusion: The association between chronic inflammation and both BPH and cancer is obvious in our study. Further studies are needed to substantiate this observation, and to clarify the magnitude of association of inflammation with BPH compared to cancer.

Saudi Med J 2009; Vol. 30 (11):

From the Departments of Urology (Abdel-Maguid, Mosli), and Pathology (Al-Maghrabi), King Abdulaziz University Medical City, Jeddah, Kingdom of Saudi Arabia.

Received 13th July 2009. Accepted 13th October 2009.

Address correspondence and reprint request to: Professor Hisham A. Mosli, Department of Urology, King Abdulaziz University Hospital, PO Box 80215, Jeddah 21589, Kingdom of Saudi Arabia. Tel. +966 (2) 6408307. Fax. +966 (2) 6408308. E-mail: hmosli@hotmail.com

Inflammation of the prostate is associated with prostate cancer and benign prostatic hyperplasia (BPH).[1] Studies suggest a common relationship between inflammation and prostate cancer. This hypothesis was supported by the identification of some common molecular pathways in the development of both processes,[2] as well as by the possible association of prostate cancer with sexually transmitted infections.[3] On the other hand, histological inflammation can also be demonstrated in most BPH pathological specimens.[4] Chronic histologic inflammation was found in more than 78% of men in the recently published Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study,[5] reflecting its almost ubiquitous nature in aging men. Some studies on the pathogenesis of BPH have provided an evidence-based thesis that strongly suggests a role of inflammation in the progression and propagation of histological BPH.[6-8] The objective of this study is to evaluate the association and possible relationship of prostate inflammation with BPH and prostate cancer in transrectal ultrasound guided (TRUS) prostatic biopsies obtained from Saudi patients.

Methods. The medical records and pathological findings of Saudi patients who underwent TRUS guided prostatic needle biopsies in King Abdulaziz University Medical City, Jeddah, Kingdom of Saudi Arabia from June 2003 to June 2008 were reviewed retrospectively. The institutional Ethics Committee approved the study protocol, and written informed consent was obtained for each patient prior to TRUS guided biopsies. The indications for biopsy were either due to elevated levels of serum prostate specific antigen (PSA), abnormal findings on digital rectal examination, or both. Biopsy cores were obtained from various sites in the prostate according to the standard sextant technique, 3 cores from each of the lateral aspects of the prostate. A single pathologist analyzed the specimens. Specimens harboring inflammation, adenocarcinoma, BPH, or their combinations were selected and included in the study. Excluded from the study, were other types of prostatic malignancies. The selected prostatic specimens were categorized according to their pathological features into 3 main categories: inflammation alone, BPH category, and cancer category. The BPH category was sub-classified into BPH alone and BPH with inflammation, while the cancer category was sub-classified into cancer alone and cancer with inflammation. Specimens having both cancer and BPH were considered as cancer. Histopathologically, hyperplasia was characterized by an increased number of epithelial and stromal cells; with papillary infolding, projections or cystic dilatation; and an increase in the fibrous and muscular components. Inflammations were regarded as acute (AI), chronic (CI), or both. Inflammation was determined by the presence of inflammatory infiltrates with the presence of neutrophils in AI, lymphocytes and/or plasma cells in CI, and all these cells in mixed inflammation. Overall analysis of data was carried out in all selected patients, and then subgroup analysis was carried out within each specific histological category of BPH, cancer, and inflammation alone.

Study data were compiled and examined with Microsoft Office Excel 2007 (12.0.6331.5000) SP1 MSO (12.0.6320.5000) software.

Results. A total of 214 patients were selected with ages ranging from 37-100 years (median of 68 years). The age distribution in patients harboring inflammation is shown in **Table 1**. The standard sextant technique was utilized. The different histological categories encountered in the examined specimens are demonstrated in **Table 2**.

Table 1 - Age distribution in patients with inflammation.

Age group, years	Inflammation alone (n=12)	BPH with inflammation (n=43)	Cancer with inflammation (n=33)
		n (%)	
<50	2 (16.7)	4 (9.3)	2 (6.1)
50-<60	5 (41.7)*	8 (18.6)	8 (24.2)
60-70	3 (25)	24 (55.8)*	10 (30.3)
>70	2 (16.7)	7 (16.3)	13 (39.4)*

*peak of incidence of each category among age groups,
BPH - benign prostatic hyperplasia

Table 2 - Histological categories and findings in specimens (n=214).

Histological categories	n (%)
Benign prostatic hyperplasia (BPH)	
BPH alone	83 (38.8)
BPH + inflammation	43 (20.1)
Total	**126 (58.9)**
Cancer	
Cancer alone	43 (20.1)
Cancer + inflammation	33 (15.4)
Total	**76 (35.5)**
Inflammation alone	
Chronic inflammation (CI)	7 (3.3)
Acute inflammation (AI)	0 (0)
CI + AI	5 (2.3)
Total	**12 (5.6)**

Disclosure. This study was supported by the Ahmad Hasan Fitiahi Chair for Research on Prostatic Diseases, Jeddah, Kingdom of Saudi Arabia.

Inflammation was histologically evident in a total of 88 patients. Of those patients, 87/88 demonstrated chronic inflammation with, or without acute inflammation. Chronic inflammation was evident in 51/88 patients (58%), chronic with focal acute inflammation in 36/88 (40.9%), and acute inflammation in 1/88 (1.1%). Within each of the 3 main categories, inflammation alone included 5.6% of patients, the BPH category involved 58.9% of patients, while the cancer category incorporated 35.5% of patients. In the overall analysis of all 214 specimens, BPH with inflammation was more prevalent than cancer with inflammation. In the subgroup analysis within each separate category, inflammation was less prevalent in the BPH category compared with the cancer category, as demonstrated in **Figure 1**. The prevalence of inflammation with BPH and cancer in different histologic study reports[1,5,9] from Western countries was compared to the current study as summarized in **Table 3**.

Discussion. It is nowadays widely accepted that inflammation has a role in many human cancers.[10] Chronic inflammation has emerged as a potential risk factor for carcinoma in many organs such as the liver, colon, bladder, lung, and pancreas.[11,12] The high prevalence of chronic inflammation infiltrates in pathological specimens of the prostate, including radical prostatectomy specimens, prostate biopsies, and transurethral prostate resection chips, has led to speculation that chronic inflammation may also be associated with prostate cancer.[1]

There is a body of literature of epidemiological and histological studies suggesting a link between chronic inflammation and prostate cancer. Sexually transmitted infections are hypothesized to play a role in the development of prostate cancer.[10] In epidemiological and meta-analysis studies,[3,13,14] aspects of sexual behavior and possible indicators of exposure to sexually transmitted infections, including number of sexual partners, age at first intercourse, and frequency of sex, have each been reported to be associated with prostate cancer risk. Epidemiological studies[3,13,14] linking chronic inflammation to prostate cancer, however, have limitations because an unknown proportion of chronic prostatic inflammation is not associated with any clinical sign or symptom (asymptomatic inflammatory prostatitis), and represent an incidental pathological finding. Data from the REDUCE study[5] failed to establish substantive links between the chronic prostatitis symptom index score and the presence of histologic inflammation.

Although pathological studies are more reliable than epidemiological studies to evaluate the association between inflammation and prostate cancer, pathological studies assessing the association between chronic inflammation and prostate cancer and BPH are conflicting. MacLennan et al[9] investigated the association and the influence of chronic inflammation on prostate cancer development by performing repeat biopsies in 177 patients with high PSA (4 ng/ml or greater), and/or abnormal digital rectal examination. Of them, 144 (81%) had chronic inflammation on initial biopsy, and 39 (22%) had cancer. Of the 39 patients with cancer, 29 also showed chronic inflammation on biopsy. The authors concluded that there was a strong

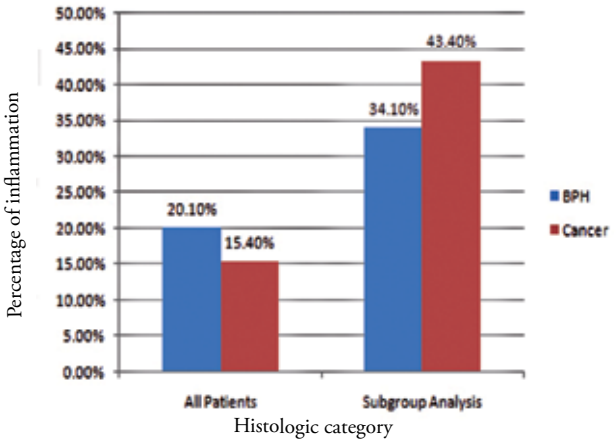

Figure 1 - The prevalence of inflammation with either benign prostatic hyperplasia (BPH) or cancer in all patients, and in each specific histologic category.

Table 3 - Prevalence of inflammation with benign prostatic hyperplasia (BPH) and cancer in different histologic studies.

Studies	Specimen	Inflammation (total) n/total (%)	BPH + inflammation n/total (%)	Cancer + inflammation n/total (%)
Current study	TRUS guided biopsy	88/214 (41.1)	43/214 (20.1)	33/214 (15.4)
MacLennan[9]	TRUS guided biopsy	144/177 (81)	-----	29/177 (16.4)
Gerstenbluth[15]	RP	40/40 (100)	40/40 (100)	20/40 (50)
Delongchamps et al[1]	Autopsy	113/167 (67.7)	70/167 (42)	27/167 (16.2)

TRUS - transrectal ultrasound, RP - radical prostatectomy

association between chronic inflammation and prostate cancer.

On the other hand, many pathological studies failed to demonstrate any clear association between chronic inflammation of the prostate and cancer, linking chronic inflammation to BPH instead.[9] Gerstenbluth et al[15] examined 40 whole mount radical prostatectomy (RP) specimens for the presence and distribution of chronic inflammation infiltrates. All the specimens contained multifocal areas of chronic inflammation. Inflammatory infiltrates were spatially associated with cancer in only half of the RP specimens. In comparison, chronic inflammation was noted within the areas of BPH in all the cases with chronic inflammation in the transition zone. The authors concluded that chronic inflammation was more associated with BPH than cancer in RP specimens. Additionally, in a more recent study, Delongchamps et al[1] prospectively analyzed 167 autopsied prostates to identify each focus of cancer, benign prostatic hyperplasia nodules, and areas of acute or chronic inflammation. The association of the prevalence of prostate cancer, BPH and inflammation were statistically assessed. Inflammation was present in 113 (67.7%) of 167 cases. Of the glands harboring BHP, 75% were also involved with chronic inflammation compared to only 50% of those without BHP. Comparatively, the glands with or without any evidence of cancer were similarly involved with chronic inflammation (55% versus 58%). Acute inflammation was not significantly associated with either BPH or cancer. Those authors concluded that chronic inflammation appeared to be directly associated with the presence of BPH, but not with cancer.

An obvious observation in the current study is the association between chronic- rather than acute-prostatic inflammation and both BPH and cancer. However, the magnitude of association of chronic inflammation with either BPH or cancer cannot be determined in our study, since the associations of inflammation with BPH and cancer in overall specimens compared to those within each separate histologic category are conflicting. In overall specimens, we identified 20.1% of all specimens having combined BPH and inflammation, while cancer with inflammation was less prevalent and was demonstrated in 15.4%. On the other hand, within each separate histologic category we found that inflammation was less prevalent in the BPH category (34.1 %) compared to 43.4% in the cancer category. When comparing the prevalence of histologic inflammation in Saudi patients in our study to those in a variety of histologic studies[1,5,9,15] reported in Western countries, clearly the prevalence of inflammation in the current study (41.1%) is lower than the 67.7%, 78.8%, 81%, and 100% prevalence in other reports involving TRUS guided biopsies, autopsy, or RP specimens. This finding, together with the obvious finding of association between inflammation and cancer, can explain, at least in part, our previous findings[16] that prostate cancer in Saudi patients has a low incidence, but commonly of high grade nature.

Ultimately, inflammation is complex in its nature and probably involves variable and concomitant mechanisms that cannot be distinguished by studying inflammatory infiltrates on pathological material. Additionally, our study has the limitations of a retrospective conduct. Accordingly, our observations still need further validation to provide better evidence in this regard. Further epidemiological, histological, and molecular studies are needed to enhance our understanding of the role of inflammation and its association with BPH and cancer.

In conclusion, the association between inflammation and both BPH and cancer is obvious in our study, providing some evidence that inflammation in the prostate gland appears to be closely related to both BPH and cancer. However, this observation still needs further validation to provide better evidence in this regard. Further studies are needed to expand our perception of the role of inflammation and to clarify the extent of its association with BPH compared with cancer.

References

1. Delongchamps NB, de la Roza G, Chandan V, Jones R, Sunheimer R, Threatte G, et al. Evaluation of prostatitis in autopsied prostates--is chronic inflammation more associated with benign prostatic hyperplasia or cancer? ***J Urol*** 2008; 179: 1736-1740.
2. Lu Y, Cai Z, Galson DL, Xiao G, Liu Y, George DE et al. Monocyte chemotactic protein-1 (MCP-1) acts as a paracrine and autocrine factor for prostate cancer growth and invasion. ***Prostate*** 2006; 66: 1311-1318.
3. Dennis LK, Dawson DV. Meta-analysis of measures of sexual activity and prostate cancer. ***Epidemiology*** 2002; 13: 72-79.
4. Nickel JC. Inflammation and benign prostatic hyperplasia. ***Urol Clin North Am*** 2008; 35: 109-115. Review.
5. Nickel JC, Roehrborn CG, O'leary MP, Bostwick DG, Somerville MC, Rittmaster RS. Examination of the relationship between symptoms of prostatitis and histologic inflammation: baseline data from the REDUCE chemoprevention trial. ***J Urol*** 2007; 178: 896-901.
6. Lee KL, Peehl DM. Molecular and cellular pathogenesis of benign prostatic hyperplasia. ***J Urol*** 2004; 172: 1784-1791.
7. Untergasser G, Madersbacher S, Berger P. Benign prostatic hyperplasia: age-related tissue remodeling. ***Exp Gerontol*** 2005; 40: 121-128.
8. Kramer G, Marberger M. Could Inflammation be a key component in the progression of benign prostatic hyperplasia? ***Curr Opin Urol*** 2006; 16: 25-29.
9. MacLennan GT, Eisenberg R, Fleshman RL, Taylor M, Fu P, Resnick MI, et al. The influence of chronic inflammation in prostatic carcinogenesis: a 5-year follow up study. ***J Urol*** 2006; 176: 1012-1016.

10. Vasto S, Carruba G, Candore G, Italiano E, Di Bona D, Caruso C. Inflammation and prostate cancer. ***Future Oncol*** 2008; 4: 637-645.
11. Coussens LM, Werb Z. Inflammation and cancer. ***Nature*** 2002; 420: 860-867.
12. Hussain SP, Hofseth LJ, Harris CC. Radical causes of cancer. ***Nat Rev Cancer*** 2003; 3: 276-285.
13. Clark LC, Dalkin B, Krongrad A, Combs GF Jr, Turnbull BW, Slate EH, et al. Decreased incidence of prostate cancer with selenium supplementation: results of a double blind cancer prevention trial. ***Br J Urol*** 1998; 81: 730-734.
14. Taylor ML, Mainous AG 3rd, Wells BJ. Prostate cancer and sexually transmitted diseases: a meta-analysis. ***Fam Med*** 2005; 37: 506-512.
15. Gerstenbluth RE, Seftel AD, MacLennan GT, Rao RN, Corty EW, Ferguson K, et al. Distribution of chronic prostatitis in radical prostatectomy specimens with up-regulation of Bcl-2 in areas of inflammation. ***J Urol*** 2002; 167: 2267-2270.
16. Mosli HA. Prostate cancer in Saudi Arabia in 2002. ***Saudi Med J*** 2003; 24: 573-581.