Frequency and Outcome of Metaplasia in Needle Biopsies of Prostate and Its Relation With Clinical Findings

Alireza Abdollahi,[1] Mohsen Ayati[2]

Introduction: Metaplasia is a reversible change in which one adult cell type is replaced by another adult cell type. Our aim was to determine the frequency and outcome of metaplasia in specimens from needle biopsies of the prostate and its relation with clinical findings.

Materials and Methods: Among 1566 prostate specimens referred to 2 pathology centers of Tehran, we studied on cases with a diagnosis of metaplasia, during a 2-year period. The clinical and laboratory data of the patients with metaplasia were collected, and they were followed-up for 2 years. Age, serum total and free prostate-specific antigen levels, ultrasonography findings, and results of digital rectal examination were recorded at baseline and the follow-up period.

Results: Ten prostate specimens (0.6%) had metaplasia, of which 6 were transitional and 4 were squamous metaplasia. Serum total PSA levels ranged from 0.7 ng/mL to 14.5 ng/mL, and free PSA levels ranged from 0.1 ng/mL to 1.3 ng/mL in the patients with metaplasia. None of the patients developed carcinoma of the prostate during the 2-year follow-up, and no significant changes were seen in the follow-up studies.

Conclusion: Metaplasia of the prostate are often associated with BPH. Clinical findings on DRE and TRUS resemble those found in benign lesions of the prostate, such as BPH. We found no sign of developing malignancy in our 2-year follow-up. However, in the differential diagnosis of this benign lesion, malignant lesions, such as squamous cell carcinoma or urothelial transitional cell carcinoma, should also be taken into consideration.

INTRODUCTION

[1]Department of Pathology, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Urology, Tehran University of Medical Sciences, Tehran, Iran

Corresponding Author:
Alireza Abdollahi, MD
Imam Khomaini Hospitals Complex, Keshavarz Blvd, Tehran, Iran
Tel: +98 21 6119 2337
E-mail: dr_p_abdollahi@yahoo.com

During the past decade, there was a sudden increase of interest in research on diseases of the prostate. This is largely due to the recently perceived high incidence of prostatic carcinoma in different geographical areas. Attention has naturally focused on premalignant, as well as malignant, lesions of the prostate. An example is the necessity of periodically evaluation of benign lesions such as metaplasia.[1] Squamous and transitional epithelial metaplasia are relatively common in the prostate. They can occur as a result of infections, traumatic lesions, or infarcts.

Squamous metaplasia is frequently observed in men under estrogen therapy. While the squamous metaplasia is seen in the areas of the acinar and ductal epithelium,

transitional cell metaplasia is characteristically found in the ductal epithelium.[1,2] Metaplasia is a reversible change, in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type.[3] This is cellular adaptation whereby cells sensitive to a particular stress are replaced by other cell types which are better able to withstand the adverse environment.[3] Metaplasia is thought to arise by genetic reprogramming of epithelial stem cells or of undifferentiated mesenchymal cells in connective tissue.[2,3] This study was performed to determine the frequency and outcome of metaplasia in needle biopsies of the prostate, and its connection with the clinical findings, including digital rectal examination (DRE), transrectal ultrasonography (TRUS), and serum levels of total prostate-specific antigen (PSA) and free PSA.

MATERIALS AND METHODS

In a cross-sectional study, all prostate samples that had been sent to one of the largest pathology centers (Danesh Pathology Laboratory) in Tehran, Iran and Imam Khomeini Hospital (Tehran, Iran) were examined. The study was carried out for 2 years, from 2004 to 2005. All of the received needle biopsy specimens taken from the prostate were studied without any restrictions. The hematoxylin-eosin-stained histological slides were reviewed by 2 pathologists and the specimens with a diagnosis of metaplasia were determined according to the defined microscopic properties.[2]

All of the patients were informed of the study protocol and provided written consent. They were examined with DRE and their serum levels of total and free PSA were measured. Transrectal ultrasonography was carried out in the axial and sagital planes using a 7.5-MHz multiplaner transducer. Sextant biopsies from the prostate were obtained using an 18-gauge biopsy gun. Nineteen to 22 tissue specimens of each patient (depending on ultrasonographic observations and suspected zones) were taken, and a total of 6 to 7 cut sections from each specimen were prepared for microscopic examination.

Patients with metaplasia were followed up for 2 years. On a regular basis (every 6 months), they were assessed for signs and symptoms of prostate diseases and serum levels of total and free PSA. They also underwent DRE and TRUS at each follow-up visit. In case of increased PSA levels or abnormal findings on examinations, biopsy of the prostate would be repeated.

RESULTS

Of the total number of 1566 prostate specimens, 10 (0.6%) were diagnosed with benign prostatic hyperplasia (BPH) with metaplasia (6 cases of transitional metaplasia and 4 cases of squamous metaplasia; Figures 1 and 2). The age range of the patients with transitional metaplasia was 51 to 75 years, and the age range of patients with squamous metaplasia was 57 to 68 years (Table).

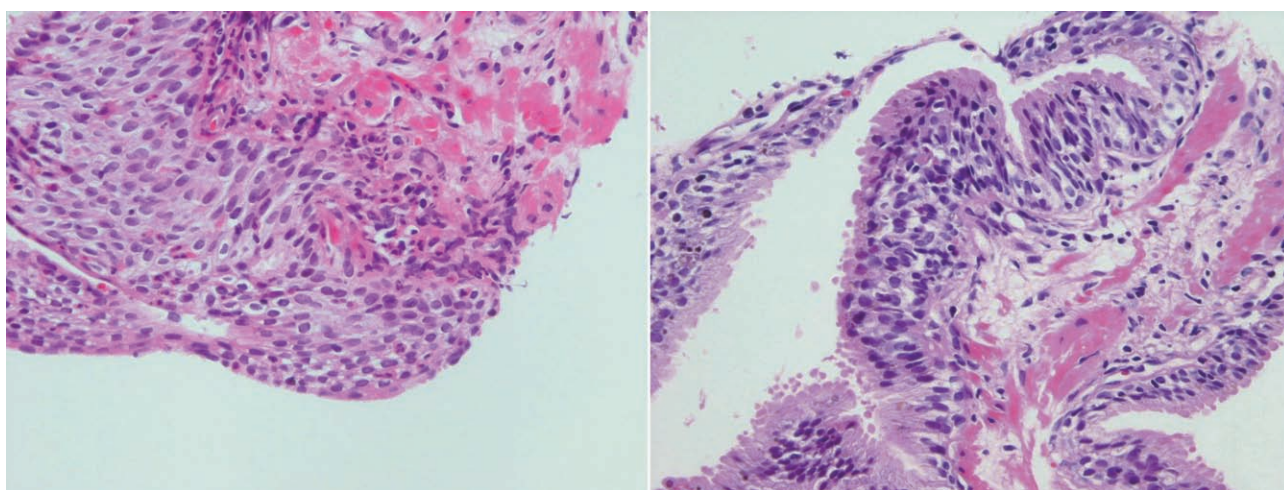Digital rectal examination revealed symmetric

Figure 1. Microscopic features of prostatic epithelial transitional metaplasia (hematoxylin-eosin, × 800).
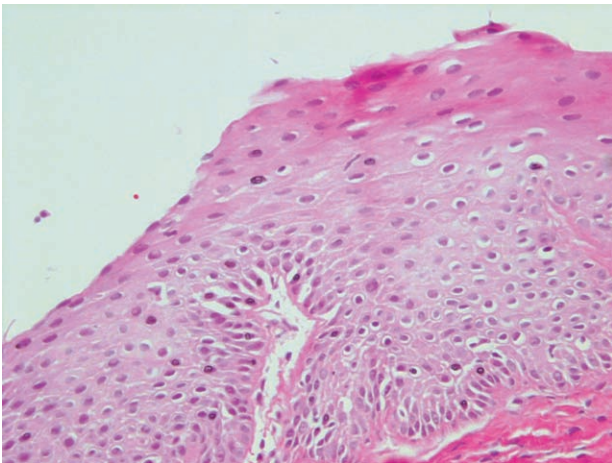
Figure 2. Microscopic features of prostatic epithelial squamous metaplasia: islands of squamous epithelial cell replace normal cuboidal prostatic epithelial cell (hematoxylin-eosin, × 800).

enlargement in all of the 10 patients. Other baseline clinical findings of the patients are summarized in the Table. Serum total PSA levels ranged from 5.5 ng/mL to 14.5 ng/mL in the patients with transitional metaplasia and from 0.7 ng/mL to 6.2 ng/mL in those with squamous metaplasia. Free PSA levels ranged from 0.1 ng/mL to 1.3 ng/mL in patients with transitional metaplasia and from 0.3 ng/mL to 0.7 ng/mL in those with squamous metaplasia. All prostate specimens showed mild to moderate chronic inflammation and 1 cases of the transitional metaplasia was associated with atrophy.

All of the patients completed the study up to the end of the follow-up period. None of the patients developed carcinoma of the prostate during the 2-year follow-up, and no significant increases were seen in the total and free PSA levels and the TRUS and DRE findings were the same as

they were at the beginning of the study. Since no indication was determined, repeat biopsy of the prostate was not performed during this period.

DISCUSSION

Given the increasing trend in the prevalence of prostate carcinoma and BPH, it can be of help to detect any potential link between metaplasia and such diseases. The reason is that the development of metaplasia, followed by predictive measures and more screening, could prevent progress of carcinoma in a bid for minimizing consequences. Squamous metaplasia is usually an adaptive response of marginally viable epithelial cells to infarcts.[3,4] There are no specific gross features.[4,5] Since metaplastic change is a microscopic finding associated with BPH, the gross feature will be that of BPH. On microscopic appearance, the normal ductal and glandular epithelial cells of the prostate are transformed to squamous cells. The cells are no longer cuboidal or columnar, but flattened. These cells may show keratinization and squamous pearl formation.[5,6]

Squamous metaplasia in the prostate can be seen adjacent to infarcts. An infarct of the prostate is rare and is usually reported in transurethral resections of the prostate or in prostatectomy specimens.[6] In animals, such as canine, squamous metaplasia of prostatic epithelial cells results from excessive estrogenic stimulation. The most common endogenous cause of this is a functional Sertoli cell tumor. Exogenous administration of estrogenic compounds is another cause, but it has not been confirmed in human.[7]

Although rare, patients with metaplasia of the

Summary of Baseline Clinical Findings in Patients With Prostatic Metaplasia*

Patients	Age, y	Metaplasia	Total PSA, ng/mL	Free PSA, ng/mL	TRUS Findings
1	68.0	Squamous	6.2	0.6	Symmetric enlargement
2	57.0	Squamous	0.7	0.3	Symmetric enlargement
3	61.5	Squamous	6.0	0.4	Symmetric enlargement
4	63.5	Squamous	2.1	0.7	Symmetric enlargement
5	73.0	Transitional	11.3	0.1	Symmetric enlargement
6	70.0	Transitional	14.5	0.9	Symmetric enlargement
7	51.0	Transitional	10.2	0.9	Symmetric enlargement
8	64.0	Transitional	7.9	0.6	Symmetric enlargement
9	75.0	Transitional	5.5	0.5	Symmetric enlargement with focal calcification
10	69.0	Transitional	6.4	1.3	Symmetric enlargement

*PSA indicates prostate-specific antigen and TRUS, transrectal ultrasonography.

prostate tissue may present with acute urinary retention, consistent with a history of prostatic hypertrophy. Other patients may have hematuria. Also, infarct of the prostate occurs predominantly in large prostates that exhibit BPH. Its incidence is probably dependent on the thoroughness of the microscopic examination. In different studies on prostatic metaplasia, it has been found to be present in 0.07% of needle biopsies to 18% to 25% of cases. The size and number of the lesion are directly related to the degree of prostatic hyperplasia.[6-9] In our study, 0.6% of the samples taken from the prostate by needle biopsy were metaplasic. This wide discrepancy in the frequency of metaplasia may be a result of the method of biopsy and patient selection for biopsy. For instance, age of the patients can be an influential factor. In different studies, age range of patients with metaplasia were 57 to 84 years.[4,5] In our study, the age range was 51 to 75 years (mean, 65.2 years). In our study, metaplasia was seen in lower ages than in others, maybe due to the incidence of BPH at lower ages in Iran than in developed countries.[10] It is noteworthy that 2 of the our patients had hypertension, but no definite correlation could be found between this sign and metaplasia in the prostate.

Our patients had acute urinary retention, with markedly enlarged prostates (90 mL to 110 mL)—as in the patients of other studies. Two of them had hematuria. Ranges of serum total PSA level in the patients were 0.7ng/mL to 14.5 ng/mL. While other studies have even reported serum PSA level increases up to 287 ng/mL,[9] our measured values were below 4 ng/mL in 2 patients, between 4 ng/mL and 10 ng/mL in 6, and above 10 ng/mL only in 2. This indicates well that in metaplastic lesions of the prostate, serum PSA does not increase like in malignant lesions, and that serum total and free PSA levels might be similar to those in cases of BPH.[11-13] Also on TRUS, the prostate has been seen enlarged and no sign of malignancy such as hypoechoic nodules has been observed.[14,15] Nor has been seen any trace of malignancy, and we merely found the symmetric enlargement of the prostate core without any nodularity on DRE.

Immunohistochemistry can help differentiate squamous metaplasia from squamous cell carcinoma.[16] In the differential diagnosis, squamous cell carcinoma should be taken into account; cellular properties could help us discriminate them. In our 2-year follow-up of patients with metaplasia of the prostate, no increase in the serum PSA level or development of malignancy was found. A larger and longer study is required in order to be able to conclude whether metaplasia in the prostate could result in carcinoma. We recommend a prospective multicenter project with larger sample volumes be carried out with 5- to 10-year follow-up to reach conclusion.

CONCLUSION

Metaplasia of the prostate is often accompanied by BPH, and there is a direct relation between the enlargement of the gland and the incidence of metaplasia. Clinical findings in association with prostatic metaplasia on DRE and TRUS resemble those of benign lesions of the prostate, such as BPH. No malignancy was detected in our series, but a larger study is needed to confirm whether or not this lesion is premalignant. When conducting differential diagnosis of this benign lesion, malignant lesions, such as squamous cell carcinoma or urothelial transitional cell carcinoma, should also be taken into consideration.

CONFLICT OF INTEREST

None declared.

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