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Research Article

Prostate Intraepithelial Neoplasia in Prostate Core Biopsies done for Suspected Prostate Cancer

Rahma Rashid, Shaheera Shakeel, Muhammed Mubarak

Department of Histopathology, SIUT, Karachi, Pakistan

Abstract

Objectives: Prostate intraepithelial neoplasia (PIN) is a premalignant lesion of the prostate with little and varied information on its prevalence in prostate biopsies. This study aimed to determine the prevalence of PIN in tansrectal ultrasound (TRUS)-guided prostate core biopsies in suspected prostate cancer.

Methods: Between July 2012-June 2017, 919 adult males of age ≥ 40 years underwent TRUS-guided biopsies. These were processed for histopathological evaluation. Data was entered into SPSS version 20.0.

Results: The mean age of all patients was 66.14±8.91 years with a median serum total PSA (tPSA) of 16.6 ng/ml (IQR: 9.4-55.0). Of the 919, 80 (8.7%) were diagnosed with PIN. Among these, 66 (82.5%) had concurrent cancer and 14 (17.5%) had isolated PIN. Mean age of patients with PIN and cancer was 66.06±9.8 years and only PIN was 65.43±5.4 years (p=0.817). The median serum tPSA was higher in patients with PIN and cancer, 66.7 ng/ml (IQR: 24.77-183.50) than in isolated PIN, 9.15 ng/ml (IQR: 7.22-19.00) (p=0.124). There was a positive correlation between increasing PSA levels and findings of PIN with adenocarcinoma (p=0.001).

Conclusion: In conclusion, majority of cases of PIN were found in association with adenocarcinoma. Isolated PIN was distinctly low in our setup.

Keywords: Men, prostate intraepithelial neoplasia, prostate cancer

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Prostatic intraepithelial neoplasia (PIN) is considered a likely precursor lesion of invasive prostate adenocarcinoma and is characterized by proliferation and anaplasia of cells lining prostatic ducts, ductules and acini (Fig. 1).[1,2] However, unlike prostate carcinoma, the impact of PIN on the serum prostate prostate specific antigen (PSA) concentration is controversial.[3-6] The term 'PIN' is used as synonymous with high grade PIN (HGPIN).[3] PIN is often multicentric and may extend into the prostatic utricle.[4] The incidence and extent of PIN increases with advancing age and its rate of occurrence is high in peripheral zone of the prostate. Race and geographic location also have great influence on the incidence of PIN.[3,5]

This study aims to determine the prevalence of PIN in TRUS-guided needle biopsies specimens and to compare the pathological findings of the biopsies with the age and total serum prostate specific antigen levels.

Methods

This descriptive cross-sectional study was conducted between July 2012-June 2017 at the Department of Histopathology, Sindh Institute of Urology and Transplantation

Address for correspondence: Muhammed Mubarak, MD. Department of Histopathology, SIUT, Karachi, Pakistan
Phone: 03222206346 **E-mail:** drmubaraksiut@yahoo.com

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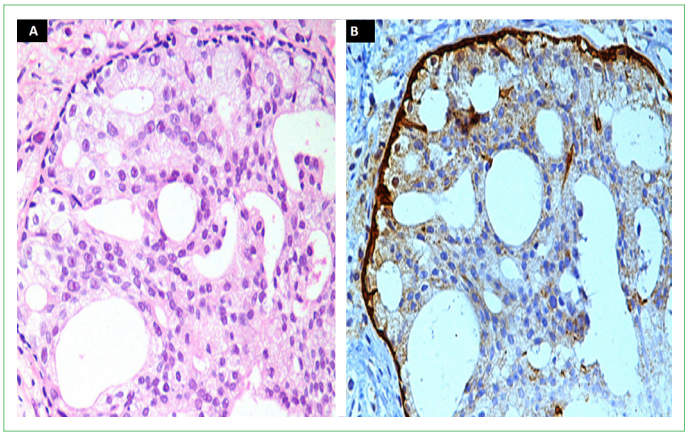

Figure 1. (a) Duct showing proliferation and anaplasia of cells (hematoxylin & Eosin, x400). **(b)** IHC stain highlighting the intact basal layer, and it stains the cytoplasm of cells.

(SIUT), Karachi, Pakistan. The study included 919 consecutive male patients (≥40 years) who presented in urology outpatients department (OPD) with signs and symptoms of prostatism and in whom TRUS-guided prostate needle biopsies were performed as per standard protocol. The serum total PSA levels were divided into four arbitrary categories: normal (0-4 ng/ml), mild (4.01-10 ng/ml), moderate (10.01-20ng/ml) and marked (>20.01ng/ml), which were then correlated with the biopsy findings. In the first 3 years (2012-2014), eight core biopsies (n=619 cases) were obtained in each case and during subsequent 2 and half years, twelve core biopsies (n=300 cases) were performed. The study was approved by the institutional ethics review committee and written informed consent was obtained from all patients for inclusion in the study. Each biopsy was classified as either benign, PIN with adenocarcinoma and isolated PIN. No patients had undergone previous biopsy. No patient had a previous diagnosis of prostatitis or cancer or any history of chemoradiation therapy. Diagnostic agreement was reached in all cases by two pathologists.

Histopathological studies:

All biopsy specimens were fixed in 10% formalin, routinely processed under standardized conditions for paraffin embedding, cut sections used 3-5 µm stained with hematoxylin and eosin (H&E) for detailed histopathologic examination. The histologic type of the lesion in each core of the biopsy were determined and recorded separately. In some cases, immunohistochemical staining was also applied where appropriate.

Statistical Analysis

The demographic, laboratory and histopathological variables of each patient were retrieved from the original biopsy request forms and case files, which included age, serum PSA levels and final histologic diagnosis. The collected data was entered in to SPSS version 20.0 and analyzed. Mean±SD and median (IQR) were used for continuous variables such as age and serum PSA levels. Numbers (percentages) were used for categorical data such as frequency of PIN and adenocarcinoma. We stratified patients according to the age groups and serum PSA levels to analyze the effects of these modifiers. For comparison between PIN with concurrent adenocarcinoma and isolated PIN, we used the independent samples t- and chi-square test. A P- value of less than 0.05 was considered significant.

Results

TRUS-guided prostate biopsies were performed in 919 patients in the study period. The mean age of the patients was 66.14±8.9 with a range was 40-95 years. Median serum tPSA was 16.60 ng/ml (IQR: 9.4-55.0), as shown in Table 1. The overall frequency of PIN in 919 patients was 80 (8.7%). The main characteristics of patients with PIN are given in Table 2. The mean age of the patients with PIN was 65.95±9.20 years. PIN with concurrent adenocarcinoma was found in 82.5% and isolated PIN was 17.5%. The mean age between two groups was similar (p=0.817).

Most of the cases of PIN were found within age group of 61-70 years, as shown in Table 2. There was no statistically significant difference among the age groups of PIN with concurrent cancer and isolated PIN (p=0.136). However, with advancing age, the detection of PIN was lower, as shown in Table 2. The reason for this decline in the incidence of PIN is unclear.

The overall median tPSA of the patients with PIN was 55.35 (IQR: 14.85-150.65) ng/ml. The median serum tPSA level was 66.7 (IQR 24.77-183.50) ng/ml and 9.15, (IQR 7.22-

Table 1. The main demographic and laboratory characteristics of all patients (n=919)

Variables	Results
Age, mean±SD (years)	66.14±8.91
Age, median (years)	65.00
Age groups years	(n,%)
40-50	46 (5.0)
51-60	233 (25.4)
61-70	412 (44.8)
>71 years	228 (24.8)
PSA*, mean±SD (ng/ml)	114.95±397.78
PSA, median (ng/ml)	16.60 (IQR: 9.4–55.00)
PSA levels (ng/ml)	**(n,%)**
0-4	35 (3.8)
4.01-10	221 (24.0)
10.01-20	260 (28.3)
>20.01	403 (43.9)

Table 2. The main demographic and laboratory characteristics of patients with PIN (n=80)

Variables	Overall n=80	PIN with adenocarcinoma n=66 (82.5%)	Isolated PIN n=14 (17.5%)	p
Age, mean±SD (years)	65.95±9.20	66.06±9.8	65.43±5.4	0.817
Age, median (IQR) (years)	65.00 (IQR: 60.00–70.00)	65.00 (IQR: 60.00–71.50)	66.00 (IQR: 60.00–70.00)	
Age group years	(n,%)	(n,%)	(n,%)	
40-50	4 (5.0)	4 (6.08)	0	0.999
51-60	21 (26.3)	17 (25.75)	4 (28.6)	0.999
61-70	37 (46.3)	28 (42.42)	9 (64.3)	0.136
>71 years	18 (22.5)	17 (25.75)	1 (7.1)	0.172
PSA*, mean±SD (ng/ml)	285.15±713.69	341.80±774.83	18.10 ± 20.72	0.001
PSA, median (IQR) (ng/ml)	55.35 (IQR: 14.85–150.65)	66.7 (IQR: 24.77–183.50)	9.15 (IQR: 7.22–19.00)	
PSA levels (ng/ml)	(n,%)	(n,%)	(n,%)	
0-4	2 (2.5)	1 (1.51)	1 (7.1)	0.321
4.01-10	9 (11.3)	3 (4.54)	6 (42.9)	0.001
10.01-20	16 (20.0)	12 (18.2)	4 (28.6)	0.463
>20.01	53 (66.3)	50 (75.75)	3 (21.4)	0.001

19.00) ng/ml in the group of patients with PIN with concurrent adenocarcinoma and isolated PIN, respectively (p=0.124). When correlated with serum PSA levels, the maximum number of cases of PIN was found with associated cancer 50/66 (75.5%) in the range of >20.01 ng/ml, which indicates a positive correlation between increasing PSA levels and chances of detecting PIN with adenocarcinoma (p=0.001), as shown in Table 2.

Discussion

In this retrospective study, 919 patients were consecutively taken in whom TRUS guided biopsies were performed. The mean age of all the patients was 66.14±8.9 with a range of 40-95 years. Median serum tPSA was 16.60 ng/ml (IQR: 9.4-55.0). Overall frequency of PIN in our population was found 80/919 (8.7 %). However, the overall frequency of isolated PIN was distinctly low i.e 14/919 (1.5%). The mean age of the patients with PIN was 65.95±9.20 years. PIN with concurrent adenocarcinoma was found in 66/80 (82.5%) and isolated PIN was 14/80 (17.5%). The mean age between two groups was similar (p=0.817).

In most of our cases, PIN was associated with concurrent prostate cancer, which underscores the close association between prostate cancer and PIN. This may partly be explained by overall delayed presentation of our cases.

Our results also showed the impact of PSA on prevalence of PIN was less striking and there is a trend of isolated PIN to be more common with lower PSA levels compared with PIN with adenocarcinoma which was associated with higher levels of PSA levels. These results are concordant with those reported by Fenely et al.[7] In one study by Brawer et al.,[8] the mean serum tPSA of the isolated PIN group was 7.8 ng/ml, which was also lower compared with our study. Weinstein and Epstein reported that serum tPSA levels were elevated in 90% of the patients with PIN and cancer compared with 50% of those with isolated PIN without cancer.[9] Majority of the cases of isolated PIN in our study also showed elevated levels of PSA, however, these elevations were of mild degree (4.01-10.00) ng/ml.

The true incidence of PIN in needle biopsies is unknown and probably varies according to the patient population under consideration. African and American men have a greater prevalence of PIN than whites in 50-60 year age group. In contrast, Japanese men have a significantly lower incidence of PIN than men residing in the United States, while Asian men have the lowest rate of PIN. Worldwide reported frequency of PIN varies from 4 to 16.5%.[3, 6, 10] The prevalence of PIN in white males reported by Fowler et al was 5.9%[11] which is again higher than the frequency reported in our study. Comparatively higher frequencies of PIN were reported by Feneley et al, Bostwick et al and Lee et al., i.e 11 %, 16.5% and 11% respectively.[7,10,12]

A few Asian countries including India (2.1%)[13] and China (0.70%) [14] has also reported quite low frequency of PIN in TRUS guided biopsies, and these results are in concordance with our results. However, they did not specifically address the frequency of PIN in their population.

The American Cancer Society National Cancer Detection Project in screening program identified PIN and cancer in 17 (5.2%) and 58 (15.8%) men, respectively from the series of 330 biopsies obtained from men participating in an early detection project.[15] The frequency of PIN in our setup was also compared with the other international studies as shown in Table 3.

Table 3. Comparison of prevalence of PIN in TRUS- guided needle core biopsies in men with suspected prostate cancer in different studies.

Reference	Patient population	No. of patients	Incidence of PIN (%)
Present study	Consecutive biopsies of men with suspected cancer 2012-2017	919	8.7
Langer et al, 1996	Consecutive biopsies at University of Pennsylvania Medical Center	1275	4.4
Lee at el ,1989	Consecutive biopsies of hypoechoic lesions at St. Joseph Mercy Hospital, Michigan	256	11
Feneley et al ,1997	Consecutive biopsies at University College London Hospitals, London, England, 1988–1994	1205	11
Fowler et al, 2001	Consecutive biopsies of men with suspected carcinoma at the Veterans Affairs Medical Center, Mississippi, 1992-199	1050	8.9
Bostwick et al. (1995)	Consecutive biopsies at Mayo Clinic, Minnesota	200	16.5

However, in one study from our department reporting the spectrum of pathological lesions in TRUS-guided prostate needle biopsies in 50 patients, there was not a single case of PIN.[16] The reason was most probably the relatively small size of the study population, in that study.

The premalignant nature of PIN and particularly its spatial relationship with prostate cancer has been well documented.[1, 2] It is still unclear whether PIN alone causes elevated PSA or if it is reflecting the presence of undetected cancer. The observation that PSA is also elevated in patients with Benign prostate hyperplasia (BPH) makes it more difficult to use PSA as a sensitive marker for detection of prostate cancer in patients with PIN.[17,18] In one study with a multivariate analysis of 212 cases by Davidson et al.,[19] found that PIN on a needle biopsy had a greater relative risk (14.3) than serum PSA levels or patient age for prostate cancer, which supports the hypothesis that PIN on needle biopsy is a strongly predictive of cancer and it should be reported.

The strength of our study is that it is the first large scale study from this region. Our findings showed that frequency of PIN is lower in this territory and that of isolated PIN is even lower. This is probably due to decrease in incidence of PIN and prostate cancer in Asian countries including Pakistan. There is still little awareness of this lesion in Pakistan. This study will also help to increase the awareness of local pathologists and urologists for the detection of this lesion.

The limitation of our study is that it does not represent the true prevalence of PIN in our country as it requires data from different territories. Unfortunately, in developing countries, the detection rate of PIN was found to be lower as compared to international studies[3-9,16] likely due to the lack of availability of TRUS-guided needle biopsies and PSA screening programs. Our patients were selected for biopsy based upon the clinical findings of lower urinary tract symptoms (LUTS), abnormal DRE, TRUS findings and / or raised serum tPSA level. Currently, there is no screening program for prostate cancer in Pakistan.

In conclusion, the overall prevalence of PIN is low in this study and majority of these cases were found concurrently with prostate adenocarcinoma. Only in one fifth of cases, PIN was found alone. A prospective large scale multicenter is required to determine the true prevalence of PIN in our population.

Disclosures

Ethics Committee Approval: SIUT-ERC, Dated: 11 November 2020. Number: 2020/A-242.

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Conflict of Interest: None declared.

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