THE PREVALENCE OF HIGH GRADE PROSTATIC INTRAEPITHELIAL NEOPLASIA IN PROSTATIC BIOPSIES DIAGNOSED AS BENIGN PROSTATIC HYPERPLASIA AT MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM

HA Mwakyoma

Abstract

Setting: The study was conducted at Muhimbili National Hospital in Dar es Salaam in the department of Histopathology and Morbid Anatomy.

Study design: The study was a retrospective cohort type in which prostatic biopsy reports of patients with histological diagnosis of BPH were microscopically re-evaluated in order to reveal whether there was any presence or absence of HGPIN, which is a significant risk factor for the development of prostatic adenocarcinoma.

Objective: To determine the prevalence of high-grade PIN in BPH as diagnosed at Muhimbili National Hospital and relate it to its histomorphological types as well as the ages of the patients and its distribution in different types of prostatic biopsies and also compare the distribution of HGPIN with that of adenocarcinoma in prostatic biopsies during the same period of study.

Methodology: The data was retrieved from register books, histological reports and computer files. The data was used as a source of information in order to determine the number of PC and BPH histologically reported , types of prostatic biopsies, and age of the patients. H&E stained slides on which the diagnosis of PC or BPH was previously made were retrieved from archives and then microscopically reviewed for histological confirmation of the diagnosis. The slides with the diagnosis of BPH were further re-examined for the presence or absence of HGPIN. For those slides which were missing, their corresponding paraffin blocks were re-cut, stained with H&E and reported for the presence or absence of high-grade PIN.

Results: Out of 687 specimens of prostatic biopsies received in 3 years (mean 229 per year), 321(46.7%) were diagnosed as adenocarcinoma and 366 (53.3%) were supposedly diagnosed as BPH. The mean age of patients with prostatic cancer (PC) was 75.6 years while that of BPH was 67 years. The number of patients with PC below 60 years was 23 (7.2%) and those with BPH was 46 (12.6%). However, 122 (38%) patients with PC were between 60-70 years of age while in those with BPH, 172 (47%) were in the same age range. Of the 366 patients who were diagnosed as having BPH, 163 (44.5%) were also found to have HGPIN. The mean age of patient with high-grade PIN in PBH was 69.6 years. In the 163 patients with HGPIN, 20(12.3%) were below 60 years of age , 83 (50.9%) were between 60-70 years and 60 (36.8%) were above 70 years. Of the 366 prostatic specimens in which the diagnosis of BPH was made, 238 (65%) were from needle biopsy (NB), 47 (12.9%) from transurethral resections of prostate (TURP) and 81(22.1%) were from open prostatectomy (OP). Similarly, out of 238 NB, 82 (34.5%) had HGPIN while in 47 TURP biopsies, 21 (44.7%) had HGPIN and in 81 RP specimens, 60 (74.1%) had HGPIN. With regard to morphological patterns of PIN, tufting was the most frequent in all types of biopsies followed in descend order by Cribriform, micropapilary, and flat.

Conclusion: The study has conclusively shown that there is a high prevalence of HGPIN in prostatic biopsies diagnosed and reported solely as BPH at our hospital as has been suspected before. The age distribution of HGPIN has indicated that the lesion is an intermediate stage between BPH on one hand and PC on the other, further confirming that HGPIN is precursor or pre-invasive stage to invasive prostate carcinoma. The identification of increased number of HGPIN in biopsy specimens has an important implication for the management of the patient.

Recommendations: Bearing in mind that HGPIN is strongly predictive of the presence of prostatic carcinoma, HGPIN should be included in pathology report. The finding of HGPIN in a patient should clinically be closely followed-up with serum PSA, digital rectal examination (DRE) and ultrasound, preferably trans rectal ultrasound or repeated needle biopsy for a defined period of time.

Key words: Benign prostatic hyperplasia (BPH), High grade PIN, Prostatic cancer (PC), Prevalence.

Correspondence to: HA Mwakyoma, P. O. Box 65001, Muhimbili university of Health and Allied Sciences.

Department of histopathology and morbid anatomy

Introduction

High grade prostatic intraepithelial neoplasia (PIN) is the most significant risk factor for prostate cancer in needle biopsy specimens. Its role as the pre-invasive stage of cancer was recently confirmed conclusively in two separate models,[1,2] coexists with cancer in more than 85% of cases[3,4] but retains an intact or fragmented basal cell layer, unlike cancer which lacks a basal cell layer.[5] The clinical importance of recognizing PIN is based on its strong association with prostatic carcinoma. PIN is strong predictive of adenocarcinoma, and its identification in biopsy specimens of prostate warrants further search for concurrent cancer.[8] PIN alone has no apparent influence on serum PSA concentration[7] and it is not apparently visible by current imaging techniques. Patients with PIN may be ideal candidate for chemoprevention.

Prostatic intraepithelial neoplasia is found predominantly in the peripheral zone of the prostate (75% - 80%), rarely in the transition zone (10% -15%), and extremely rarely in the central zone (< 5%). This distribution parallels the frequency of zonal predilection for prostatic carcinoma.[9] The frequency of HGPIN in needle biopsy series ranges from 5% to 16% and in transurethral resection of prostate specimens between 2.3% and 4.2%. [9] The multifocality of this process has been observed by McNeal and others.[4,5,9]

Prostatic intraepithelial neoplasia (PIN) refers to the putative precancerous end of continuum of cellular proliferations within the lining of prostatic ducts, ductules and acini. High grade PIN (HGPIN) refers to the archtecturally benign prostatic acini and ducts lined by atypical cells, which is an intermediate lesion between BPH and prostatic carcinoma (PC), and which is also known to be a significant risk factor for the development of prostatic adenocarcinoma. These atypical cells share morphological, histochemical, immunohistochemical, and genetic changes[6,12] with cancer but lack invasion of the basement membrane of the prostate gland. Because of these similarities, HGPIN and inflammation are believed to lead to development of prostate cancer.[11]

HGPIN is characterized by cellular proliferations within pre-existing ducts and acini with cytologic changes mimicking cancer, including nuclear and nucleolar enlargement, hyperchromasia, nuclear overlapping or pseudo-stratification, prominent nucleoli and fragmentation of basal cell layer. There are four main morphologic patterns of HGPIN, these include tufting, micropapillary, cribriform and flat patterns. Tufting pattern is the most common and present in 87% of cases, the micropapillary pattern 85%, the cribriform pattern 32%, and the flat pattern 28%, although in some cases multiple patterns are encountered.[6)]

High grade PIN, patients' age and serum PSA are highly significant predictors of Prostatic cancer (PC) with PIN having the highest risk factor. PIN is more predictive of PC in older patients and those with PSA of > 4ng/ml [(8)] Repeat biopsies should be performed on patients with high grade PIN at regular intervals. [(13)] This may be anytime between three to twelve months depending on circumstances relating to the findings of changes in PSA levels and Digital rectal examination (DRE).

The objective of this study therefore was to determine the prevalence of High Grade Prostatic Intraepithelial Neoplasia in Benign Prostatic Hyperplasia (BPH) as diagnosed at the department of Histopatholgy and Morbid Anatomy from 2005 to 2007.

Study design

This was a retrospective study in which prostatic biopsy reports of patients with histological diagnosis of benign prostatic hyperplasia (BPH) were microscopically re-evaluated in order to determine the presence of High Grade Prostatic Intraepithelial Neoplasia.

Study setting

The study was done at the department of Histopathology and Morbid anatomy at MNH for a period of 5 months from October 2007 to February 2008.

Methods

The data was retrieved from register books, histological report files and computer files in the department of Histopathology and Morbid Anatomy. The medical records were studied to determine the number of all prostatic cancer (PC) and Benign Prostatic Hyperplasia (BPH) reported from prostatic biopsies from 2005 to 2007. The information retrieved included age of patients, types of prostatic biopsies and histological diagnosis of prostatic lesions.

Haematoxylin &Eosin (H&E) stained slides on which the diagnosis of prostatic cancer and BPH were previously made were retrieved from archives and were then microscopically reviewed for histologic confirmation of the diagnosis. The slides with the diagnosis of BPH were then thoroughly and meticulously re-examined for the presence of PIN. For those slides which were missing, their corresponding paraffin blocks were re – cut and stained by H&E and eventually reported for the presence or absence of PIN.

Results

From 2005 to 2007 the department of histopathology and morbid anatomy, Muhimbili national hospital received a total of 687 specimens of prostatic biopsies from surgical wards (mean of 229 per year). Out of these, 321 (46.7%) were diagnosed as prostatic adenocarcinoma and 366 (53.3%) as Benign Prostatic Hyperplasia (BPH)

The mean age of patients with prostatic cancer (PC) was 75.6 years while that of patients with BPH was 67 years. The number of patients with PC below 60 years was 23 (7.2%) while for those with BPH it was 46 (12.6%). One hundred and twenty two (38%) patients with PC were between 60-70 years of age and among those with BPH 172 (47%) belonged to this age group. Also 176 (54.8%) patients with PC were above the age 70 years and those with BPH in the same age range were 148 (40.4%). (Table 1)

Table 1: The distribution of prostatic lesions by age groups.

Age in years	Type of Prostatic lesions		
	BPH	PIN in BPH	PC
< 60 years	46 (12.6%)	20 (12.3%)	23 (7.2%)
60 – 70 years	172 (47%)	83 (50.9%)	22 (38.0%)
> 70 years	148 (40.4%)	60 (36.8%)	176 (54.8%)
Total	366 (100%)	163 (100%)	321 (100%)

Out of 366 patients who were diagnosed as BPH, 163 (44.5%) were also found to have high grade PIN. The mean age of patients with high grade PIN in BPH was 69.6 years. In 163 patients with PIN, 20 (12.3%) were below the age of 60 years while 83 (50.9%) were between 60 – 70 years of age and 60 (36.8%) were above 70 years.

Of the 366 prostatic specimens with the diagnosis of BPH, 238 (65%) were from needle biopsies ((NB), 47 (12.9%) were from transurethral resections of prostate (TURP) and 81 (22.1%) were from radical prostatectomy. Out of the 238 needle biopsy specimens, 82 (34.5%) had high grade PIN while in the 47 TURP biopsies, 21(44.7% had high grade PIN and in 81 radical prostatectomy specimens, 60 (74.1%) had high grade PIN. (Table 2)

With regard to the morphological patterns of PIN, tufting was the most frequent in all types of biopsies followed in that descending order by cribriform, micropapillary and flat architectural patterns. With regard to needle biopsies, the frequency distribution of architectural patterns of PIN was 47.6% tufting, 19.5% cribriform, 12.2% micropapilary, and 20.7% flat. (Table 3 and figures 1, 2, 3, 4, 5, and 6)

Table 2: The prevalence of high grade PIN in BPH in prostatic biopsies

Type of biopsy	No. of PIN	(%)
Needle biopsy	82	50.3
TURP	21	12.9
Radical prostatectomy	60	36.8
Total	**163**	**100.0**

Table3: Frequency distribution of histomorphological types of high grade PIN in biopsies.

Morphology	Frequencies PIN in biopsies			Total
	NB	TURP	RP	
Tufting	39 (47.6%)	13 (54.2%)	79 (41.8%)	131
Cribriform	16 (19.5%)	8 (33.3%)	49 (25.3%)	73
Micropapillary	10 (12.2%)	8 (33.3%)	50 (26.3%)	68
Flat	17 (20.7%)	5 (20.8%)	12 (12.3%)	34
Total frequency	**82**	**24**	**190**	**206**

Morphological Patterns of High Grade- PIN

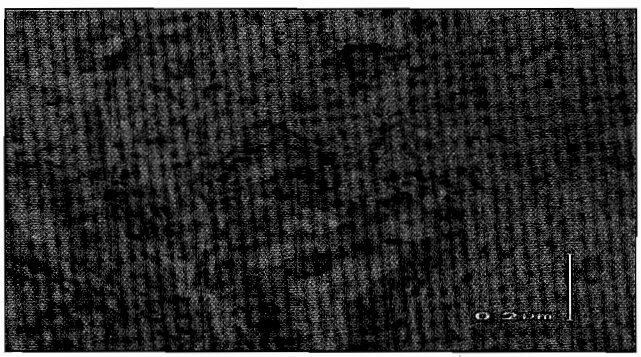

Figure 1: Cribriform pattern x 40

Figure 2: Flat pattern x 40

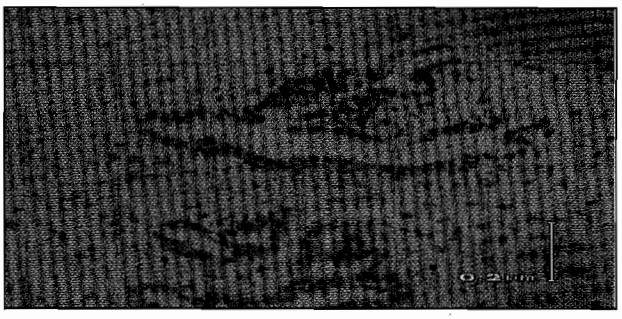

Fig 3: Cribriform and Tufting patterns x 40

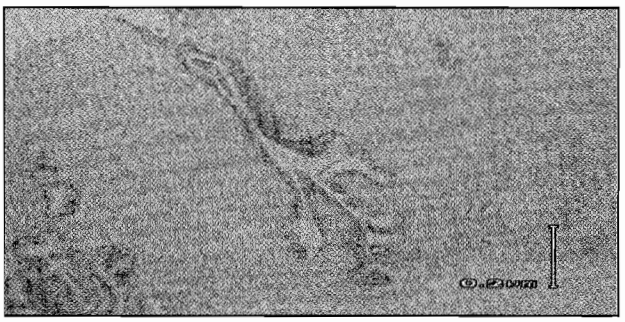

Fig 4: Tufting pattern x 20

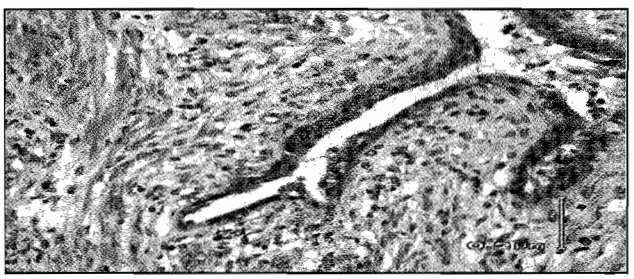

Fig 5: Tufting pattern x 40

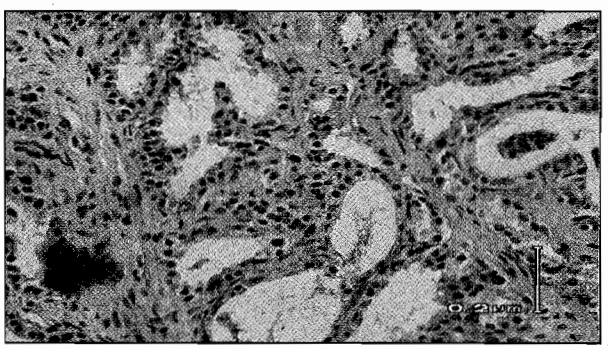

Fig 6: Micropapillary pattern x 40

Discussion

Specimens from prostatic biopsies examined during a period of 3 years revealed that prostatic cancer (PC) which was exclusively adenocarcinoma, was encountered in 46.7%

of the patients while benign prostatic hyperplasia (BPH) was seen in 366 patients (53.3%). However, out these BPH cases, 163 (44.4%) had High grade PIN. This confirms the hypothesis that there is a high prevalence of high grade PIN in prostatic biopsies diagnosed as BPH at our hospital (MNH). Thus, there is a need to include in our histological reports a component of high grade PIN as it is known that this entity is a pre-invasive stage, most likely a precursor of adenocarcinoma[13,14]; has a high predictive value as a marker of adenocarcinoma and therefore its identification warrants repeat biopsy, especially in needle biopsies for concurrent or subsequent invasive carcinoma.[14]

The mean age of PC was 76.6 years while that of high grade PIN was 69.6 years and that of BPH was 67 years. This age distribution is in agreement with the hypothesis that high grade PIN is an intermediate stage between PC and BPH and is thus a pre-malignant lesion for most if not all cases of PC. Some clinical studies [14] suggest that PIN predates carcinoma by ten years or more. However, the finding of a mean age difference of 7 years between PC and high grade PIN in our study is slightly less than theirs and this may suggest that the period of occurrence from high grade PIN to carcinoma is variable, probably depending on some environmental influences. In the same setting of age, the age distribution of BPH, HGPIN, and PC below 60 years was 12.6%, 12.3% and 7.2% respectively while the distribution between 60 -70 years was 47% for BPH, 50.9% for HGPIN and 38% for PC. For patients above 70 years the distribution of the three lesions was 40% for BPH, 36.8% for HGPIN and 54% for PC. This trend indicates that there is a proportional increase with age from BPH through HGPIN to PC and this further confirms that HGPIN is a precursor to invasive carcinoma [14] and that it is associated with progressive abnormalities of phenotype and genotype which are intermediate between normal prostatic epithelium and cancer, indicating impairment of cell differentiation and regulatory control with advancing stages of prostatic carcinogenesis [12, 16]. Similarly, studies have shown that both HGPIN and PC share an increase in incidence and severity with advancing age and with high rates of occurrence in the peripheral zone of the prostate [16] .

Of the 366 prostatic biopsies which were diagnosed as BPH, there were 238 needle biopsy specimens in which 82 (22.1%) contained HGPIN while 47 were TURP specimens, 21(44.7%) contained high grade PIN and in 81 simple open prostatectomies, 60 (74.1%) had HGPIN. The prevalence of high grade PIN in both needle biopsy (NB) and TURP specimens in our study is significantly higher than those found in other series where it varied from 5% to 16.5% [9,16] and between 2.3% and 4.2% [13,16] respectively. The prevalence of PIN in open prostatectomy specimens was higher compared to NB and TURP specimens presumably because of the multifocality of this lesion as mentioned by McNeal in 1969[3] and has been also corroborated by others since then[4,16] The differences in the distribution of high-grade PIN in our study from other series might be attributed to the same risk factors as those which are responsible for the variability of occurrence of prostatic carcinoma in different parts of the world which include age, race, hormonal factors (testosterone), a positive family history of PC, Diet-high in animal fat and low in fruits and vegetables. It is also noteworthy that high-grade PIN and prostate cancer share genetic and molecular markers[12,16] with PIN representing an intermediate stage between benign epithelium and invasive carcinoma.

Prostatic intraepithelial neoplasia may display a spectrum of architectural patterns. The 4 most common patterns of HGPIN observed in other studies and also confirmed in ours include the tufting, the Micropapillary, the Cribriform, and the flat patterns. The highest frequency of the morphologic pattern encountered in all 3 types of biopsy specimens was tufting, 47.6% in needle biopsy, 54% in TURP and 41.8% in radical prostatectomy specimens followed by cribriform (19.5% to 33%), Micropapillary (12.2 to 33%), Cribriform and flat (12.3% to 20.8%) in that order respectively. This distribution does not generally differ significantly from other studies [6].

The age distribution of HGPIN in BPH and prostatic cancer observed in this study show that PIN in BPH tended to increase with age from below 60 years to its peak between 60 and 70 years (50.9%) and thereafter decreasing to 36.8% after 70 years while PC tended to increase progressively from 7.2% below 60 years, through 38.% between 60 and 70 years to 54.8% above 70 years. The decrease (downward trend) of HGPIN after 70 years might indicate that there is a continuum of HGPIN into invasive carcinoma and thus a increase of PC, further confirming that HGPIN is a precursor to invasive carcinoma, the continuum of which culminates in early invasive cancer.

Conclusion

This study has conclusively shown that there is a high prevalence of high-grade PIN in prostatic biopsies reported as BPH at our hospital as we had suspected before. The age distribution of high-grade PIN (HGPIN) has indicated that this lesion is an intermediate stage between that of Benign Prostatic Hyperplasia (BPH) and Prostatic cancer (PC) further confirming that HGPIN is a precursor lesion or pre-invasive stage to invasive carcinoma and is thus an important risk factor to the development of adenocarcinoma.

The increase in number of HGPIN in needle biopsies (NB) as compared to TURP and Radical prostatectomy biopsies at our hospital should be taken strongly as predictive of the presence of carcinoma because the identification of HGPIN in biopsy specimens has important clinical implications for the management of the patient.

Recommendation

Bearing in mind that HGPIN is strongly predictive of the presence of prostatic carcinoma, HGPIN should be included in the pathology report. The finding of HGPIN in a patient should clinically be closely followed-up with serum PSA, digital rectal examination (DRE), and ultrasound examination, preferably trans rectal ultrasound or repeated

prostatic needle biopsies for a defined period of time, say 3 to 6 moths for 2 years and thereafter can be repeated annually for life.

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