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Review Article

Prostatic intraepithelial neoplasia- the story evolves

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ABSTRACT

Prostatic intraepithelial neoplasia is preneoplastic lesion described from early of this 20th century. PIN includes a spectrum of features ranging from low grade to high grade neoplasia. The studies are focused on their influence to predict the occurence of prostatic carcinoma. This review analyses the various development in the identification and differentiation of PIN and their clinical implication.

INTRODUCTION

Prostate cancer is the sixth most common cancer in the world, the second most common cancer in men during the last decades of the 20th century contributing to three fourth of the registered cases across the globe. The incidence of prostate cancer estimated was 513,000 patients in 2000, while the number of new cases projected was 1.1 million people in 2012. It is expected that by 2030, 1.7 million new cases and 499,000 deaths will occur in the entire world simply due to the growth and aging of the global population.[1-3]

Incidence rates of prostate cancer vary by more than 25 fold worldwide, the highest rates being in Australia/New Zealand (104.2/100,000), Western and Northern Europe, North America. Though the incidence is low in Asian Countries, the trend is increasing. The incidence rate of Asian countries is compared in the following table1. The rates are low in Bangladesh and Bhutan and Nepal.

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In one of the study conducted in Nepal – Eastern Part, the hospital based cancer detection rate in this study was 0.73% and those detected were locally advanced.[3,4] The increase in the incidence is related with newer efforts for identification and recent refined criteria. This has led to proper management of the patient and early identification of precursors. There are various spectrum of benign and precursors lesion including prostatic intraepithelial neoplasia (PIN), inflammation with or without atrophy, and adenosis, atypical adenomatous hyperplasia, intraductal hyperplasia, and acinar atypical hyperplasia and intraductal carcinoma.

Prostatic intraepithelial neoplasia – the story begins

Prostatic intraepithelial neoplasia (PIN), first described in 1969 is a proliferation of prostatic epithelial cells that is confined to preexisting prostatic ducts or acini (glands). PIN was further characterized and initially termed intraductal dysplasia in 1986 .The currently used term "prostatic intraepithelial neoplasia" was introduced in 1987 by Bostwick and Brawer and endorsed by consensus at a 1989 Workshop on Prostatic Dysplasia (Bethesda, Md; March 1989) as the preferred nomenclature till date for this

preneoplastic change which was similar to the terminology used in cervix.[5,6]

Prostatic intraepithelial neoplasia (PIN) is defined as an intraluminal proliferation of the secretary cells of the prostatic duct–acinar system. PIN usually involves single acini or small clusters of acini, but is occasionally more extensive.

PIN is found predominantly in the peripheral zone of the prostate (75 – 80%), rarely in the transition zone (10 – 15%), and very rarely in the central zone (5%). This distribution mirrors the frequency of the zonal predilection for carcinoma of the prostate.

The continuum from low grade PIN to high grade PIN and early invasive carcinoma is characterized by basal cell layer disruption, progressive loss of markers of secretory differentiation, and increasing nuclear and nucleolar abnormalities, proliferative activity, microvessel density, genetic instability, and DNA content.

Table 1: Incidence of Prostatic cancer in different Asian countries

Country Name	Incidence
Israel	84.3/100,000
Turkey	40.6/100,000
Lebanon	37.2/100,000
Singapore	33.1/100,000
Japan	30.4/100,000
India	4.2/100000
Bangladesh	1.7/100,000
Bhutan	1.5/100,000
Nepal	1.2/100,000

Histomorphology of PIN

In PIN, acini appear hyperchromatic due to proliferation, crowding, and irregular spacing of the inner secretory cells, in contrast with benign acini. The acini are medium-sized or large, with smooth-sculpted rounded contours. The presence of partial acinar involvement is particularly helpful in identifying PIN. Nuclei overlapping are prominent, and cell borders are usually inapparent. Along the luminal surface, the majority of cells display cytoplasmic blebs reminiscent of apocrine secretion.[6,7]

PIN can be easily identified even at low power view (fig.1). They have (1) darker lining cells, (2) are thicker than the surrounding normal ducts, and (3) may have a complex intraluminal pattern of growth. At high magnification, there is a cytological triad including (1) varying degrees of nuclear enlargement with nuclear stratification, (2) hyperchromasia, and (3) nucleolar prominence.[5]

Morphologically PIN was initially divided into three strata, PIN 1, 2 and 3. In grade 1 PIN, nuclei are enlarged, vary in size, have normal or slightly increased chromatin content, and possess small or inconspicuous nucleoli.

Grade 2 PIN is a subtle transition from PIN 1 and consists of cells with larger nuclei and nucleoli that are more obvious and larger than in PIN 1. In PIN 2, prominent nucleoli are observed only in some cells, but these are more numerous than in PIN 1; however the difference is very subtle.

The grade 3 PIN is easy to identify. Criteria for diagnosing PIN 3 have also evolved in recent years, and definitions have focused on nucleolar prominence, nuclear enlargement, hyperchromasia, and presence of one or more nucleoli that are usually large, often with prominent clear halos.[7,8]

In less severe foci of high grade PIN, greater variability in nuclear size is observed, with some markedly enlarged forms. The definition of prominent nucleoli is unclear and subjective. Nucleolar prominence has been variably defined as nucleolar size greater than 1 mm, greater than 1.6 mm, or even greater than 3 mm by various authors. Nucleoli may be single or multiple, and are often eccentric and in contact with the chromatin rim.[6] Pathologists cannot be expected to measure nucleolar diameter in their daily practice. Although there is no consensus as to what constitutes prominent nucleoli; however, if distinct nucleoli can be visualized at 20x magnification, it qualifies for prominent nucleoli. Generally at least 10% of the luminal cells should show these features to make the diagnosis.[8,9]

The basal cell layer is usually inconspicuous and may be difficult to appreciate by routine light microscopy; rarely, it is prominent at low power, partially or completely encircling acini containing PIN. Discontinuity of the basal cell layer is a distinctive finding in about half of acini with high grade PIN, but often requires immunohistochemical studies with high molecular weight keratin for identification. Mitotic figures are rare in HGPIN and are not included in the grading criteria of PIN.

There was lack of reproducibility in reporting of the PIN 2 so in the 1989 Workshop on Prostatic Dysplasia,[9] it was agreed to designate ductal dysplasia grade 1 as low-grade PIN and to combine ductal dysplasia grades 2 and 3 together as high-grade PIN (HGPIN).[9,10]

The differences in between low grade PIN and HGPIN is listed in the following table (Table 2).

Despite the modification in nomenclature, Low grade PIN failed to show clinical significance in terms of patient management. Once again the terminology of Low grade PIN disappeared from reporting. The focus was directed more towards high Grade PIN. There were different studies analyzing various patterns in HGPIN.

Table 2: Difference between LPIN and HPIN

	Low grade PIN	High Grade PIN
Architecture	Epithelial crowding and stratification with irregular spacing.	More crowding and stratification
Cytology		
Nuclei	Enlarged with marked size variation	Enlarged with some size and shape variation
Chromatin	Normal	Increase density and clumping
Nucleoli	Rarely prominent	Occ. to frequently large and prominent , sometimes multiple
Basal Cell Layer	Intact	May show some disruption
Basement membrane	Intact	Intact

Architectural patterns of HGPIN

The architecture shows a spectrum, varying from a flattened epithelium to a florid cribriform proliferation. Four basic patterns that often coexist have been described by Bostwick and colleagues flat, tufting, micropapillary, and cribriform. .

The *flat pattern* shows nuclear atypia without significant architectural changes ;*Tufting pattern* has piled up nuclei, resulting in undulating mounds of cells, *Micropapillary pattern* shows columns of atypical epithelium that typically lack fibrovascular cores; and *Cribriform pattern* with complex architectural patterns showing Roman bridge and cribriform formation (fig.2).

There are other histological variants named as:

- *Signet-ring cell PIN*
- *Mucinous cell PIN*
- *Foamy cell PIN*
- *Inverted PIN*
- *Small cell neuroendocrine*

However these various architectural patterns have no apparent clinicopathological significance.

Correlation of HGPIN with Carcinoma –Then and Now

For many years the pathologists were concentrated on identifying the precursor lesion of the prostatic carcinoma. The initial study had focused on both low grade and high grade PIN. Later there was disagreement regarding the identification of LPIN among pathologist, most pathologists no longer report the presence of LGPIN.

The studied were then directed at high grade intraepithelial neoplasm. There are various studies which show the

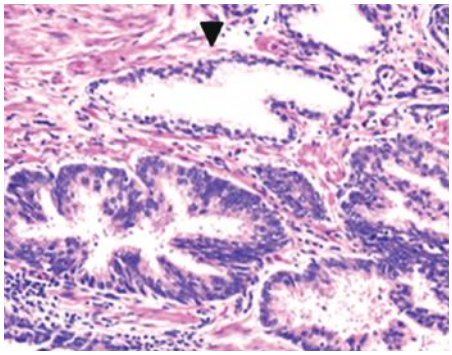

Figure 1: *Normal looking glands (arrow head) along with PIN (arrow) (HE stain, X100).*

predictive value for prostate carcinoma after HGPIN. In previous studies the risk of carcinoma on follow-up biopsy for a HGPIN diagnosis has been reported to be as high as 50%. According to the study conducted by Aboseif et al the incidence is as high as 79%. Table 3 shows the data conducted by different studies where percentage of prostatic carcinoma was seen following HGPIN.

The identification of HGPIN gained importance in this era with identification of prostatic carcinoma on repeat biopsy. People became more aggressive in the management. However these studies were based on sextant biopsy - the original systematic biopsy scheme with 1 core from the base, mid and apex bilaterally. This technique missed the biopsy and gave false negative result; up to 30 % of the Cancer was missed on first biopsy.[23]

The technique was later modified with extended biopsy including samples from the peripheral region which included 5 region biopsy with 10-13 core . With increase in representative core biopsy, the dectection of prostatic cancer on first biopsy increased and need for repeat biopsy was redundant.

During the sextant era the cancer detection rate on repeat biopsy for HGPIN was 25-70%. However in extended biopsy scheme with the increased number of fragments, the diagnosis of HGPIN lost its power to predict PC in subsequent biopsies. The detection rate on repeat biopsy for HGPIN decreased dramatically to 2.5-4.5%, which was not higher than the rate of cancer detection rate on repeat biopsy in case of normal findings on first biopsy. There have been different studies comparison of which is given in the following table (table 4).[23,24]

The table shows that the chances of identifying prostatic carcinoma in case of unifocal HGPIN was similar to that of normal biopsy even in the third year of diagnosis. The above table shows that immediate repeat biopsy is not necessary in unifocal HGPIN. HGPIN is said to be multifocal when

Table 3: Prostatic carcinoma following HGPIN in different studies

Reference	% HPIN	Year
Aboseif et al13	79	1995
Berner et al14	38	1993
Davidson et al15	35	1995
Krishnamurthi et al16	31	1999
Markham et al17	41	1989
Langer et al18	27	1996
Perachino et al19	71.1	1997
Raviv et al20	48	1996
Rovner et al21	31.6	1997
Shepherd et al22	58	1996

there is presence of HGPIN in more than 3 cores. In these multifocal biopsies there is a 10% chance of detection in rebiopsy.

HGPIN or IDC

There has been a major change in the identification of HGPIN which earlier included a feature which is now described as Intraductal carcinoma. IDC-P initially coined by McNeal. But later Bostwick and Brawer had introduced the concept of "HGPIN" when referring to intraductal neoplastic lesions of prostatic origin. Consequently, diagnosis of IDC-P was reported only infrequently, as many pathologists tended to place these intraductal malignancies under the diagnostic category of HGPIN. As their original concept included IDC-P, all atypical intraductal proliferative lesions fell under the unifying term of HGPIN, hence may be contributing to higher incidence of carcinoma on follow up.

McNeal and Yemoto investigated these proliferation which showed a higher Gleason score, greater tumor volume and advanced pT stage. Guo and Epstein then proposed histological criteria for differentiating IDC-P from HGPIN.[25]

The diagnostic criteria for IDC-P are more defined than that for HGPIN.

The proposed criteria include five major criteria are:

(i) large-caliber glands twice the diameter of normal peripheral zone gland structures;

(ii) surrounded by basal cells identified with cell markers;

(iii) occupied with cytologically-malignant cells; nuclei 6X larger than the adjacent benign cells.

(iv) always span the gland lumen;and

Table 4: Chance of progression into carcinoma

Findings	Chance of cancer on follow up		
	1yrs	2yrs	3yrs
Normal biopsy	3.6%	12.5%	22.4%
Unifocal HGPIN	4.4%	14.7%	26.1%
Multifocal HGPIN	9.1%	29.0%	47.8%

(v) the presence of central comedonecrosis.

The first four criteria are always present in IDC-P, whereas central comedonecrosis is not always observed.

The three minor criteria proposed were: (i) right angle branching; (ii) smooth and rounded contour; and (iii) two cell populations, an outer perimeter cell group that is elongated, pleomorphic, mitotically active and have low PSA immunoreactivity, and a central group that is cuboidal, monomorphic, abundant cytoplasm and has high PSA immunoreactivity. The central group of cells is cuboidal, monomorphic and quiescent with abundant cyto-plasm containing copious PSA, and occasional extracellular mucin (secretory layer).[26]

Recently, Pathologist now have appreciated its cliniopathological significance and included intraductal carcinoma as separate entity . the presence of these of IDC-P in radical prostatectomy specimens is well-known to correlate with other adverse prognostic factors, such as Gleason score, tumor volume, tumor stage and presence of lymph node metastasis rather than HGPIN.

Should we report HGPIN?

Now after a decade of defining and redefining PIN, where do we stand? The main purpose of identifying the preneoplastic lesion is to stop the progression cancer by some intervention and reduce the disease related mortality.

The recent studies does not demonstrate significant difference in the occurrence of prostatic carcinoma in follow up of Low grade PIN, High grade PIN and normal patient . We accepted the relative low risk associated with LGPIN and dropped the concept of LGPIN way back. Now the data show a similar correlation with unifocal HGPIN. Though multifocal HGPIN still needs some attention, the chance of having a carcinoma in case of unifocal HGPIN is not different from the normal. Therefore we can now omit the diagnosis of unifocal HGPIN as we have done for LGPIN in the past and for Gleason grade 6(3+3) in 2014 by International Society of Urological Pathology.

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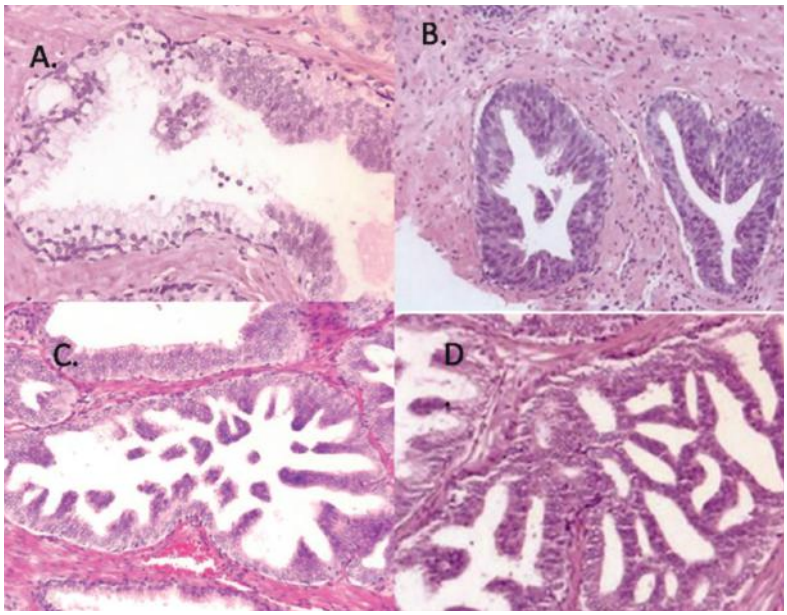

Figure 2: *Moropholgical pattern of high grade prostatic intraepithelial lesion. A. Flat type, B. Tufting, C.Micropapillary and D. Cribiform (HE stain, X100)*

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