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Full Length Article

Basal cell hyperplasia (BCH) versus high grade prostatic intraepithelial neoplasia (HGPIN) in tiny prostatic needle biopsies: Unusual diagnostic dilemma

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KEYWORDS

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Abstract *Background:* Histopathological differentiation between BCH and HGPIN in prostatic needle biopsies is a diagnostic challenge. The gold standard for detection of HGPIN and BCH is histopathological examination; however subjectivity in interpretation and tiny volume of obtained tissue hamper reliable diagnosis.

Aims: The aim of this study was to assess usefulness of using the p63 and p504s to solve this problem. Although the use of p63 and p504s is now well established in differentiation between preneoplastic and neoplastic prostatic lesions, their usefulness in tiny tissue material is, however, not fully studied.

Abbreviations: BCH, Basal cell hyperplasia; HGPIN, High grade prostatic intraepithelial neoplasia; PSA, prostatic specific antigen; PIN, i Prostatic intraepithelial neoplasia; PAC, prostatic adenocarcinoma; LGPIN, Low grade prostatic intraepithelial neoplasia; AMACR, alpha- methylacyl coenzyme a racemase; BPH, Benign prostatic hyperplasia

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Methods: The study included a spectrum of 30 prostatic needle biopsies (5 BCH, 10 HGPIN, 10 indefinite luminal proliferations where BCH and HGPIN could not be distinguished from each other and 5 adenocarcinomas). H&E stained sections were examined for histopathological features. Other sections were stained immunohistochemically with p63 and p504s.
Results: The mean age of patients was 69 (SD = 7.6) years. PSA range was 1.3–2.7 ng/ml. Ultrasongraphic findings were unremarkable. All BCH showed p504s−/p63+ pattern, All HGPIN had p504s+/p63+ pattern while carcinomas were p504s+/p63−. After immunostaining combined with histopathological features; the 10 indefinite specimens could be diagnosed as 4 BCH and 6 HGPIN. The article explains how applying this staining pattern on the challenging specimens, combined with histopathological features, can be helpful in proper identification of prostatic proliferations.

Introduction

Prostatic epithelial cell proliferations span a spectrum of lesions starting from ordinary BCH, florid BCH to PIN ending by adenocarcinoma [1]. BCH arises from terminal ducts and acini usually of peripheral glands. The lesion is reported in about 10% of prostatic needle biopsy [2]. Two types of BCH were described; Typical and atypical. Proliferating basal cells in typical type consist of two or more cell layers. Cells are characteristically larger than usual cells, basophilic in appearance with scanty cytoplasm, have round to slightly ovoid nuclei with absent to inconspicuous nucleoli [2]. Cells in atypical BCH are characterized by having prominent nucleoli, but are otherwise identical to ordinary BCH [3]. Atypical BCH is diagnosed if more than 10% of the basal cells exhibited prominent nucleoli [2]. Prostatic intraepithelial neoplasia (PIN) is characterized by a neoplastic transformation of the secretory epithelium within preexisting benign prostatic acini or ducts [4]. The lesion was originally graded from 1 to 3 [5], but currently a simplified, two-tier classification has been recommended: low grade (grade 1) and high grade (grades 2 and 3) [5]. Low-grade PIN (LGPIN) is not a risk factor for subsequent adenocarcinoma [4], whereas HGPIN is a precancerous lesion possessing most of the phenotypic, biochemical, and genetic changes of prostatic carcinoma but without invasion of the basement membrane [5]. Early stromal microinvasion, the earliest evidence of carcinoma, occurs at sites of acinar outpouching and basal cell disruption in acini with HGPIN in about 2% of high-power microscopic fields of PIN [6,7].

P63 is a member of the p53 gene family, located on human chromosome 3q27–29. The encoded protein is widely expressed in human tissues, particularly in basal cells of many epithelial tissues such as the epidermis, cervix, urothelium, and prostate [8]. P63 staining is a sensitive marker in identifying basal cells in benign lesions and therefore was reported to help to avoid misdiagnoses of malignancy in prostatic needle biopsies where diagnosis of malignancy is often based on the absence of basal cells [9].

In 2000, Xu and colleagues identified three genes: p503s, p504s and p510s that showed differential expression in benign and malignant prostate glands using cDNA subtraction in conjunction with cDNA microarray screening. p504s; one of the gene products named with cDNA clone number, was clearly identified as human alpha-methylacyl coenzyme A racemase (AMACR) [10]. Ordinary BCH lacks AMACR/p504s immunoreactivity however, rarely, scant individual positive AMACR/p504s cells could be found in florid BCH [11]. In contrast, both HGPIN and prostate cancer show expression of AMACR/p504s in several reports [12,13].

Basal cell proliferations have the same immunophenotype of basal cells present in normal ducts and acini [1]. Montironi et al. suggested that basal cell proliferations should be strongly positive for p63 and negative for p504s. HGPIN might have a high degree of basal cell disruption. This feature is best demonstrated with disruption of nuclear p63 immunohistochemical expression [4]. HGPIN adjacent to prostatic adenocarcinoma shows a greater degree of basal-cell disruption than HGPIN distal to cancer [14]. Similar to adenocarcinoma, the cytoplasm of cells in most cases of HGPIN showed positive AMACR [15].

Because both BCH and HGPIN do not result in a significant elevation of serum PSA [16,17] and both cannot be detected clinically or through imaging, the histopathological evaluation is considered the gold standard for the diagnosis of the two entities [18]. Although the use of p63 and p504s markers is now well established in differentiation between preneoplastic and neoplastic prostatic lesions, their usefulness in tiny tissue material is, however, not fully studied. The aims of the current study were (1) to assess the usefulness of p63 and p504s markers in the histopathological differential diagnosis between BCH and HGPIN in tiny prostatic needle biopsies and (2) to examine histopathological morphological characteristics of both lesions with assessment of the interobserver variability in lesion diagnosis.

Material and methods

Patients and tissue samples

One hundred specimens of prostatic needle biopsy were retrieved from the Pathology Department, Sohag University Hospital during the period from 2009 to 2010. Revision of 100 H&E stained slides revealed the following diagnoses; thirty definite prostatic adenocarcinoma (PAC), 20 pure BPH, 15 HGPIN with foci of adenocarcinoma, 4 solid pattern of BCH and 6 LGPIN. Because the aim of the study was to examine usefulness of using immunohistochemical tools for differentiation between BCH and HGPIN, only specimens which carry foci with luminal proliferations were identified for the study (25 specimens). These specimens fulfill the following inclusion criteria:

1. Stratification of epithelium within the pre-existing ducts or acini (two layers or more) with preservation of the lumen even if it was small or eccentric.

2. Presence of cellular atypia; ranged from mild to moderate atypia (mainly; prominent nucleoli).
3. Absence of true cribriform glands (single glandular units with punched out lumina) while the pseudocribriform glands (fused individual hyperplastic acini) could be included [19].
4. The glandular architecture is still retaining a benign pattern.
5. Exclude cases of PIN associated with prostatic adenocarcinoma.
6. Benign prostatic hyperplasia can be considered as an associated finding.

Five cases of definite prostate adenocarcinoma were also included as the control group, their Gleason's Score ranged from 6 to 8. Foci of BPH were considered as internal control. Clinicopathological data of the 30 (25 luminal proliferations and 5 control) prostatic needle biopsy specimens were retrieved from the clinical reports to assess the clinicopathological criteria, PSA level and sonographic findings.

After reviewing the literature a constellation of features distinguishing BCH from HGPIN including architecture, cytological features were used in the following study to identify each of the 25 specimens on H&E sections as mentioned in Table 1.(Modified from [1]). According to the criteria in Table 1, the 25 studied specimens were grouped as follows after examination of H&E sections: **First group**: BCH (5 cases) associated with BPH. **Second group**: HGPIN (10 cases). **Third group**: 10 cases in which the nature of basal or luminal epithelial cell proliferation was difficult to be assessed (these cases were previously diagnosed as BPH).

Immunohistochemistry

Representative formalin-fixed, paraffin embedded routinely-processed, tissue sections from each specimens were stained with 1:50 Rabbit Polyclonal p504s (AMACR) antibody (CP 200 AK, BK, CK, Biocare Medical, USA in Renaissance Background Reducing Diluent; PD905, BioCare Medical, USA) and 1:100 Mouse Monoclonal p63 antibody (Clone 4A4, Lab Vision Corporation, USA in phosphate buffered saline; PBS, pH 7.2).

Staining procedure

Briefly, tissue sections were deparaffinized and rehydrated, antigens were retrieved by incubating sections in 0.01 mol/L sodium citrate buffer (pH 6.0) in a 800w microwave for 20 min. After blocking nonspecific reactions by endogenous hydrogen peroxidase, sections were incubated at room temperature with p63 and p504s for one hour and two hours, respectively. Visualization of staining was conducted using strept-avidin-bioten; ABC staining kit (Catalog # TA-015-HP, LabVision Corporation Fremont, USA), according to the manufacturer's instructions. Immunohistochemical reactions were developed with 3,3-diaminobenzidine; chromogenic peroxidase substrate (DAB). Counterstaining of tissue sections was done using Myer's Hematoxylin and mounted using DPX and cover slipped.

Sections of definite prostatic adenocarcinoma and benign prostatic hyperplasia (BPH) associated with BCH were used as positive controls for p504s and p63, respectively. Both positive and negative controls were consistently immunoreactive and lacking reactivity respectively. This confirms the validity of the staining results.

Assessment of p504s immunostaining

Positive p504s staining was identified as cytoplasmic and/or luminal staining within the epithelial cells. P504s expression was evaluated in BPH, BCH, PIN, and prostatic adenocarcinoma. *The extent of staining* was evaluated as follows: **0:** (none) absent. **1:** ($<5\%$) minimal. **2**: (5–50%) focal, or **3:** ($>50\%$) diffuse. *The intensity* was graded as follows: **0:** negative**, 1:** weak**, 2:** moderate **or 3:** strong [20].

Assessment of p63 immunostaining

P63 appeared as brown nuclear staining in the basal cells. Staining results were continuous, patchy or negative. Internal positive control in the form of nuclear staining of either entrapped or dispersed basal layer of benign glands was found in some sections.

Statistical analysis

Statistical analysis was performed using the software package SPSS for Windows, version 15: (a) a 2×2 table and Fisher's

Table 1 Comparing histopathological features between BCH and HGPIN.

	BCH	HGPIN
Architectural patterns	Cells form small solid basal cell nests – acinar or pseudocribriform	Stratification of epithelium form; flat-tufting – micropapillary and cribriform but do not occlude the glandular lumina
Cells	Atypical looking basal cell can be seen underlying the benign appearing secretory cells	Full thickness cytological atypia seen in luminal cells while the basal cells appear unremarkable
Nuclei	Rounded and central	Round to ovoid and perpendicular to the basement membrane
Nucleoli	May be present in atypical BCH	Usually present, their absence may be due to poor fixation or staining
Atypia	Minimal to mild, mainly in the form of prominent nucleolus	Minimal, moderate and severe
Associated conditions	Inflammation, BPH and/or atrophy	Adenocarcinoma of the prostate

Exact test were conducted to examine for statistical significant differential expression of p63 and p504s in the BCH, HGPIN, and adenocarcinoma. All statistical analyses were two-sided and significance was defined as $P < 0.05$.

Results

The thirty specimens of prostatic needle biopsy included 5 cases of definite prostatic adenocarcinoma. The main attribute in the other 25 cases is the presence of glandular profiles lined by several layers of epithelial cells with retained central lumen. In the 25 patient cohort, patient ages ranged from 54 to 86 years with mean age of 69 (SD = 7.6) years. Their PSA level ranged from 1.3 to 2.7 ng/ml. Their sonographic findings were unremarkable.

Histomorphological features of BCH; N = 5 and HGPIN; N = 10 in H&E stained sections

BCH

The included five cases of BCH revealed variable sized prostatic acini with focal or diffuse circumferential proliferation of basal cells; at least two cell layers' thickness. The lumen of prostatic acini is usually preserved. The recognized patterns

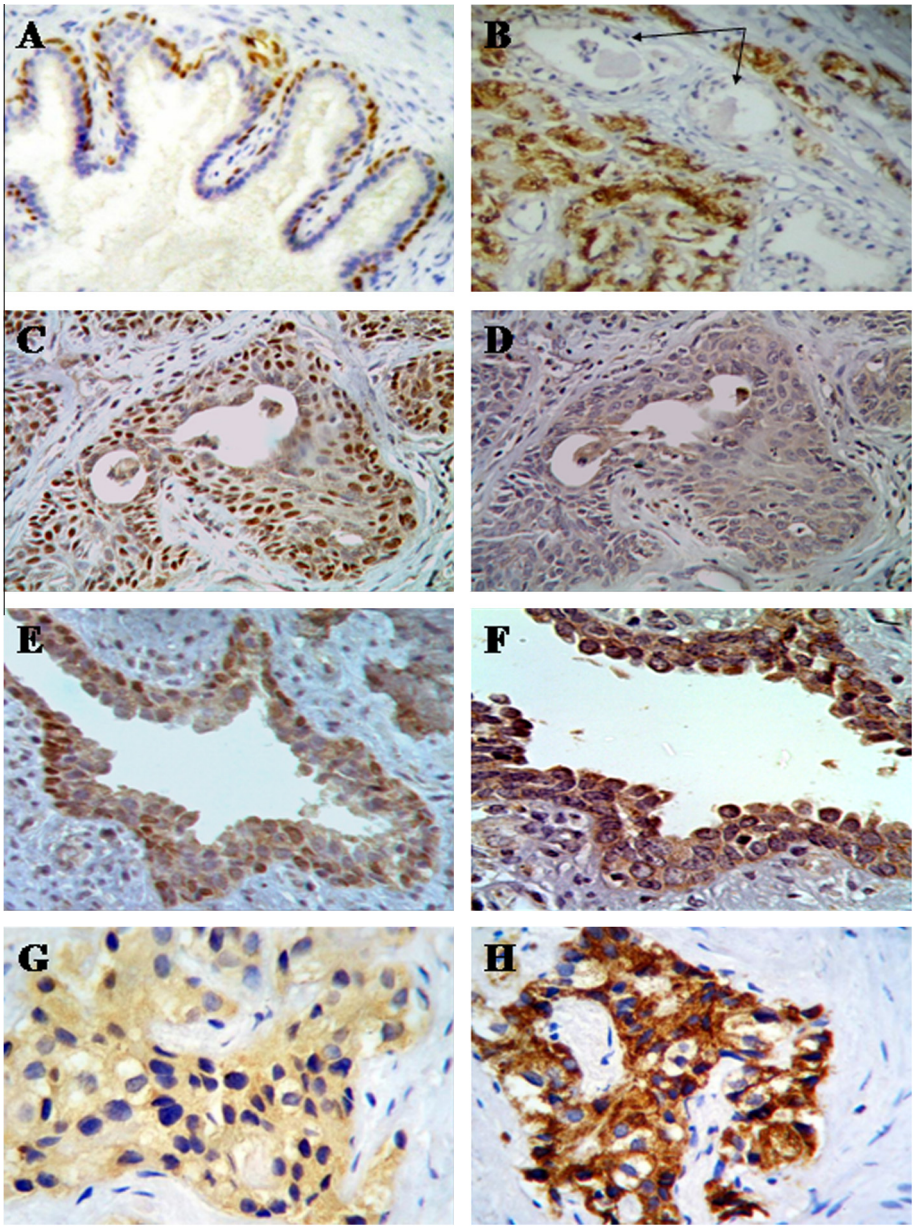

Figure 1 A spectrum of prostatic lesions including normal prostatic acini (fist raw) left, benign acini (arrows) within adenocarcinoma (first raw right), BCH (2nd raw), HGPIN (3rd raw) and PAC (raw at the bottom). Four panels in left column are stained with p63. Four panels in right column are stained with p504s. Single continuous layer of p63-positive basal cells is seen in normal acini (A × 100). Positive multiple layers of p63 basal cells are seen in BCH (C × 100). Basal cells are interrupted in HGPIN (B × 200) and absent in PAC (G × 200). Staining with p504s showed negative staining in benign acini among strongly positive PAC glands (A × 200), negative in BCH (D × 100), moderate to strong positive cytoplasmic reactivity detected in HGPIN (F × 200) and PAC (H × 200), respectively.

of glandular profiles were acinar in four cases and pseudocribriform in one case. The basal cells had small, rounded to slightly ovoid nuclei, with absent to inconspicuous nucleoli. The cytoplasm of basal cells appeared as a dark narrow rim with inconspicuous cell margins. Preservation of an inner layer of luminal cells was often noted. The luminal cells showed abundant cytoplasm with a slightly basophilic appearance, an easily identifiable cell membrane and nuclei with open chromatin and occasional small nucleoli. The borders between the basal and the luminal cells were not easily recognized. The surrounding prostatic tissue showed BPH.

HGPIN

The glandular profiles of the ten cases of HGPIN were varied from tufted, flat to micropapillary patterns. Within the proliferating acini there is crowding and stratification of the nuclei with occasional nucleoli. Nuclei toward the center of the gland tend to have bland cytology compared to peripherally located nuclei. The individual cells are uniformly enlarged with increased N/C ratio. Most of cells showed coarse clumped chromatin along the nuclear membrane and frequent nucleoli were noticed.

Immunohistochemical profiles of the control and the third (unknown) groups

Control group (prostatic adenocarcinoma; PAC)

P504s immunostaining. Diffuse positive strong cytoplasmic expression of P504s was detected in all five prostatic needle biopsy specimens of prostatic adenocarcinoma. The staining was circumferential and luminal (Fig. 1H).

P63 immunostaining. There was negative nuclear staining (absence of basal cells) in all five prostatic needle biopsy specimens of prostatic adenocarcinoma (Fig. 1G). Positive internal control appeared clearly in the adjacent benign glands (Fig. 1A).

The third (unknown) group (N = 10)

Four cases showed continuous nuclear p63 immunostaining of the stratified epithelium and complete negative cytoplasmic p504s staining within the prostatic acini indicating the basal cell nature of the stratified epithelium. The other six cases showed fragmented nuclear p63 immunostaining of the basal layer and moderate circumferential luminal cytoplasmic p504s of the stratified luminal cells.

After application of immunohistochemical p63 and p504s to the 3rd group, and constellation of the previous histopathological features of BCH and HGPIN; the 10 unknown specimens were diagnosed as: 4 BCH and 6 HGPIN.

Summary of the immunohistochemical features of BCH (N = 9 cases) and HGPIN (N = 16 cases) as follows (Table 2)

Expression of p63 in BCH versus HGPIN

The nine (100%) specimens of BCH showed dark brown nuclear p63 staining in the basal cells in the form of multilayer

Table 2 Detailed staining pattern of p63 and p504s in HGPIN and BCH.

HGPIN	Number	BCH	Number
Histopathological patterns			
Tufted	6	Stratification with preservation of lumen (Acinar)	6
Flat	9		
Micropapillary	1	Pseudocribriform	3
P504s staining			
Staining pattern		Negative	All
Positive focal moderate luminal	4		
Positive focal weak luminal	2		
Positive diffuse weak luminal	2		
Positive diffuse moderate luminal	6		
Positive diffuse strong luminal	2		
P63 staining (nuclear/basal)			
Positive(continuous)	3	Strongly positive in 2–3 layers	All
Positive (fragmented)	13		

Table 3 Summary for P63 and p504s in a spectrum of prostatic lesions.

	Control group of p504s (PAC) (N = 5)	HGPIN (N = 16)	BCH (N = 8)	Control of p63 (BPH)
P63 (nuclear stain)	Negative 5/5 (100%)	Positive Continuous 3/16 (19%) Fragmented 13/16 (81%)	Positive Multilayer 8/8 (100%)	Positive Continuous single layer
P504s (cytoplasmic stain)	Positive Strong 5/5 (100%)	Positive Weak 4/16 (25%) Moderate 10/16 (62.5%) Strong 2/16(12.5%)	Negative 8/8 (100%)	Negative

PAC, prostatic adenocarcinoma; HGPIN, high grade intraepithelial neoplasia; BCH, basal cell hyperplasia.

Table 4 Summary for the statistical analysis tables in Fisher's Exact test.

Lesion type	Number	P504s		P63	
		Negative	Positive	Negative	Positive
BCH	8	8	0	0	8
HGPIN	16	0	16	0	16
PCA	5	0	5	5	0
Fisher's Exact test *P* values		< 0.001		< 0.001	

(ranged from 2 to 4 cell thick) (Fig. 1C). Negative p63 staining of luminal cells was noticed. The basal cell layer was identified as a single layer with p63 brown nuclear staining in 16/16 (100%) of HGPIN; 3/16 (19%) were in a continuous fashion and 13/16 (81%) were fragmented (Fig. 1E).

Expression of p504s in BCH versus HGPIN

Basal cell layers within the proliferating prostatic acini showed complete cytoplasmic **AMACR/p504s** negativity in all 9 specimens of BCH (Fig. 1D). Two specimens of HGPIN showed strong **AMACR/p504s** immunostaining, ten specimens showed moderate staining and four specimens showed weak staining (Fig. 1F). **AMACR/p504s** expression was diffuse in 10 and focal in 6 specimens of HGPIN. The distribution was circumferential in 10 specimens of HGPIN and luminal in the other 6 specimens. Using Fisher's Exact test, there was a high significant difference in staining patterns of both p63 and p504s between BCH and HGPIN, $P < 0.001$ for p63 and $P < 0.001$ for p504s. Detailed staining pattern of p63 and p504s in HGPIN and BCH is mentioned in Table 2. Summary for p63 and p504s in the spectrum of prostatic lesions including PAC and BPH is mentioned in Tables 3 and 4.

Discussion

BCH is a well recognized entity on TUR specimens however; its presence on prostatic needle biopsies is a diagnostic challenge [21]. Growth of BCH is often focal in the prostatic peripheral zone causing difficulty in differentiation from HGPIN on needle core biopsies [2,22]. The gold standard for detection of HGPIN and BCH is histopathological examination of biopsy samples because both lesions cannot be suspected clinically [1]. BCH is not a precursor of HGPIN or adenocarcinoma, whereas HGPIN is a pre-malignant lesion [18]. Therefore, the management of both lesions differs. Accurate diagnosis should be done to avoid over-diagnosis of BCH or under-diagnosis of HGPIN. This study was designed to differentiate between both lesions using an immunohistochemical tool.

Peripheral BCH and HGPIN share the following features: both lesions are histological mimickers [4]. Both conditions are not uncommon findings on prostatic needle biopsies. Thorson and colleagues reported BCH in 10% of needle core biopsies from the peripheral zone [2], a figure close to what was found in the current study (9%). The frequency of HGPIN on needle biopsies ranges from 0.7% to 20% [23], this comes in agreement with our results which lie within the same range (16%). Tiny volume of prostatic tissue on needle biopsy makes the distinction between BCH and HGPIN problematic. Furthermore, the technical problems like poor fixation or staining of the slides making the reliability of histological atypical signs like prominent nucleolus is uncertain or unreliable [18]. Both BCH and HGPIN cannot be suspected clinically or by ultrasonographic examination. Imaging of all BCH and PIN specimens in the current study did not detect any suspicious mass similar to what was reported previously [2]. The same findings were mentioned in a previous report [5] emphasizing that PIN is an accidental microscopic finding below the detection threshold by transrectal ultrasound. Both conditions do not elevate PSA level; it ranges from 1.0 to 2.5 ng/ml in BCH [17] which is considered a normal range. Similar findings were detected in the current study (1.3–2.7 ng/ml). It was reported that isolated HGPIN is not associated with an elevated serum PSA because of the intact basement membrane. PSA produced by neoplastic cells in PIN is not released into serum at clinically significant levels. Any elevated PSA level in PIN should raise an alarm to search for adjacent focus of cancer prostate [16].

The management of patients with HGPIN differs from others with BCH. BCH is not a precursor of HGPIN or adenocarcinoma. Additionally, the presence of BCH in the peripheral zone needle biopsy samples was significantly associated with the absence rather than the presence of adenocarcinoma [2]. BCH is therefore a benign condition and no need for further biopsy [24]. In contrast, HGPIN is a premalignant condition, its identification warrants repeated biopsy for concurrent or subsequent invasive carcinoma that was reported in 30–75% of HGPIN [5,24,25]. The accurate diagnosis of both conditions (HGPIN and BCH) should be done to avoid over diagnosis of BCH or under diagnosis of HGPIN.

The distinction between BCH (with/without prominent nucleoli) and HGPIN may not be difficult at H&E stained sections if they have clear architectural and cytological features as mentioned in Table 1. The finding of small, solid, basaloid nests is a diagnostic clue pointing toward BCH because such nesting is not typical of HGPIN [26].

However, the distinction of BCH from HGPIN becomes difficult on H&E examination if they have the following criteria – as demonstrated by our work and others [24,27,28]: Similar growth patterns, stratification of epithelium within pre-exciting ducts and acini, little or no cellular atypia and benign looking of both conditions especially if HGPIN is not associated with micro invasion or definite prostatic adenocarcinoma.

As a point of interest, we and Thorson found the presence of inflammation in majority of BCH specimens [2]. Such finding suggests that peripheral zone BCH in untreated patients may represent a stereotyped response to injury such as that sustained because of inflammation. Thus, the multilayering of epithelium within prostatic ducts or acini could not be solved in all instances at level of H&E examination slides; therefore the use of immunohistochemical markers to identify the nature of the epithelial cell proliferation is mandatory.

P63 is a sensitive marker used to detect the presence of basal cells and to recognize the multilayered BCH. The marker therefore helps to avoid misdiagnoses of malignancy in prostatic needle biopsies. Moreover, staining of cells other than basal cells was not observed, indicating that its use would not lead to false-negative diagnoses [29]. Although HGPIN retains an intact or fragmented basal cell layer, prostatic adenocarcinoma does not [30]. Increasing grades of PIN were found to be associated with progressive disruption of the basal cell layer [31].

AMACR/p504s is a member of the gene family; over expressed in prostate cancer. Ordinary BCH was found to lack AMACR/p504s immunoreactivity however, rarely, scant individual positive AMACR/p504s cells could be found in florid BCH. Several reports showed that AMACR/p504s is expressed in both HGPIN and prostate cancer [12,13].

In the current study, the combined use of AMACR/p504s and p63 helped to distinguish BCH from HGPIN in prostatic needle biopsies. In nine cases (100%) of BCH immunostaining showed negative expression of AMACR/p504s and characteristic expression of basal cell marker (p63) in the form of continuous multilayer nuclear staining of the proliferating epithelium. The previous findings were similar to what was mentioned by Hosler and Epstein [21], they reported the use of the immunohistochemical method as a useful tool for the identification of the nature of basal cell proliferation. They found 100% (7/7) positivity for p63 in cases of basal cell hyperplasia with complete negative expression for p504s.

Yang and colleagues [8] conducted a comparative study between BCH (11 cases) and limited adenocarcinoma of the prostate (15 cases) by immunohistochemical methods. They found that p63 was positive in all BCH (100%) but negative in all prostatic carcinoma. On the other hand p504s was negative in hyperplastic basal cells but positive in carcinoma. Similar findings were also reported by other studies [4,27].

Immunostaining of AMACR/p504s showed moderate to strong expression in 16/16 (100%) of HGPIN biopsies. P63 expression in these lesions was limited to a single basal layer of challenging stratified epithelium; this expression profile of both AMACR/p504s and p63 came in agreement with previous studies and supported our diagnosis as HGPIN [4,23,32]. Whereas, Kunju and colleagues [12] found the same pattern of p504s/p63 expression in 89% of HGPIN. Another study [33] with larger numbers of cases reported positive expression of p504s in 90% (126 of 140 cases) of HGPIN. Moreover, Ananthranarayanan et al. [34] demonstrated the same staining profile of p504s/p63 in 45 patients with isolated HGPIN in needle core biopsy.

Although combined use of both markers (p504s & p63) is extremely helpful, they should be used cautiously and always in conjunction with conventional H&E histological assessment, as there is a spectrum of benign and malignant lesions sharing the previous immunoprofile which are outside our scope (e.g., atypical adenomatous hyperplasia).

Conclusion

The distinction between BCH and HGPIN is a challenging histopathological problem using conventional methods in tiny prostatic biopsies. Combined use of AMACR/p504s and p63 may be helpful in reaching a definite diagnosis where HGPIN are positive for both p63 and AMACR/p504s while BCH are positive for p63 and lack of AMACR/p504s expression. Because of the small number of specimens used in this study, we recommend conducting a similar study on bigger number of specimens before recommending use of both markers in daily practical histopathological diagnosis.

Conflict of interest

Authors declare no conflict of interest.

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