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REVIEW ARTICLE

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The significance of atypical adenomatous hyperplasia and prostatic intraepithelial neoplasia for the development of prostate carcinoma

An update

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Abstract The term prostatic intraepithelial neoplasia (PIN) is an accepted diagnosis in pathology of the prostate. The diagnostic difference between atypical adenomatous hyperplasia (AAH) and adenosis is still under debate. A number of questions remain about the significance of grading of AAH and PIN, the biology of AAH and PIN as precursors of carcinoma, the possibility of treatment of AAH and PIN and whether AAH- and PIN-associated cancers differ from non-associated carcinoma. This paper reviews the results and discussions at the First International Consultation Meeting on Atypical Adenomatous Hyperplasia and Prostatic Intraepithelial Neoplasia and the Origins of the Prostatic Carcinomas. AAH is an architectural atypia of the prostate. The histological and cytological features of AAH are intermediate between BPH and low-grade carcinoma of the prostate. Cell kinetic findings show no distinct neoplastic pattern. AAH may be a precursor of transition zone carcinoma but the findings to date are inconclusive. Follow up studies should address whether the association of AAH and carcinoma is incidental or whether transition occurs between AAH and carcinoma. In contrast, PIN is an accepted preneoplastic lesion and the most likely precursor of the dorso-peripheral zone carcinoma. The diagnosis of high-grade PIN is clinically important, because high-grade PIN is associated with carcinoma in a high percentage of patients (38–100%). AAH- and PIN-associated cancers may not differ from other prostatic cancers. At present treatment for AAH and PIN without carcinoma is not indicated, but high-grade PIN warrants surveillance and follow up of the patient to identify a possible coexisting cancer. It must be stressed that AAH and PIN are multifocal lesions and both are age-associated.

Key words Prostate · Carcinoma · Atypical adenomatous hyperplasia · Prostatic intraepithelial neoplasia

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Introduction

Thorough examination of prostatectomy specimens, needle biopsies, and transurethral resection specimens from patients with prostate carcinoma has shown that atypical glandular proliferations without invasive features may be detected in the vicinity of carcinoma in more than half of cases. These alterations have been referred to as atypical adenomatous hyperplasia (AAH) and prostatic intraepithelial neoplasia (PIN). The preneoplastic nature of PIN has been established by histological and immunohistochemical studies [1, 8, 9, 10, 13, 47], whereas the preneoplastic potential of AAH is still under debate [1, 11, 14, 17, 34]. Brawn [14] proposed the term "adenosis", and it has been redefined by Epstein and Gaudin [17, 19]. In a recent consensus statement, however, the term "atypical adenomatous hyperplasia" was recommended by 21 urological pathologists [12]. Apart from the problems with terminology and definition of AAH and PIN, the following questions are of interest: Can low- and high-grade AAH and PIN be distinguished, and is this distinction meaningful? What is the biology of AAH and PIN? What is the relationship between grades of AAH and PIN and grade of cancer? Is AAH- and PIN-associated cancer different from PIN- and AAH-non-associated cancer? And, finally, how should AAH or PIN be treated? Before reviewing the different features of AAH

and PIN and the evidence supporting the concept of AAH and PIN as precursors of prostatic carcinoma, a brief discussion of the zonal anatomy of the prostate is useful in order to understand some of the topographic characteristics that AAH, PIN, and prostatic carcinoma share.

Prostatic anatomy

The prostate gland contains four glandular compartments: the peripheral zone, the central zone, the transition zone and the periurethral gland region (Fig. 1a, b).

The peripheral zone is the largest glandular region, constituting approximately 70% of the glandular tissue. It forms the posterior, lateral, and apical regions of the prostate and surrounds the central zone and partially surrounds the transition zone. The peripheral zone is readily visualized by transrectal ultrasound and is the area that is primarily sampled by transrectal biopsies [35] (Fig. 1a, b).

The central zone constitutes approximately 25% of the prostate. It is cone-shaped. The base of the cone forms the major part of the base of the prostate (seminal vesicle/bladder junction). The apex of the cone is located at the verumontanum. The ejaculatory ducts pass through the central zone (Fig. 1a).

The transition zone consists of two lobes that surround the proximal urethral segment laterally and anteriorly. The transition zone is surrounded posteriorly and laterally by a band of fibromuscular tissue, the so-called transition zone boundary or "surgical capsule" that separates the transition zone from the peripheral zone. The transition zone is the region sampled predominantly by transurethral resection procedures. Because the transition zone is the region where benign prostatic hyperplasia (BPH) occurs, its volume is variable. Prior to the development of BPH with increasing patient age, the transition zone constitutes only 5–10% of the prostatic volume. BPH may also arise in the periurethral gland region (Fig. 1a, b).

The periurethral gland region is a minor glandular region surrounding the proximal urethral segment of the prostate; it is confined by the preprostatic sphincter and constitutes less than 1% of the prostatic volume (Fig. 1a, b).

The prostate is surrounded posteriorly and laterally by the outer fibromuscular rim (the so-called capsule) that separates the prostate from the surrounding tissue. At the prostatic base and along the anterior surface of the prostate, there is no well-defined anatomical separation between the prostate and adjacent tissues and bladder neck [2].

The prostatic zones display different histological features [36, 37] based on the glandular architecture, the appearance of the glandular epithelium, and stromal characteristics. The glandular elements of the peripheral and transition zone are similar; in both zones the glands are relatively small with round or oval contours. The glandular elements are lined by two cell layers, the outer basal cell and the inner luminal secretory cells. The luminal epithelium is cuboidal or columnar with small round basal or centrally located nuclei and absent or inconspicuous nucleoli. The cytoplasm is pale or clear. In the absence of BPH, the difference between the peripheral and transition zones is mainly in the stroma, which is denser and more compact in the transition zone.

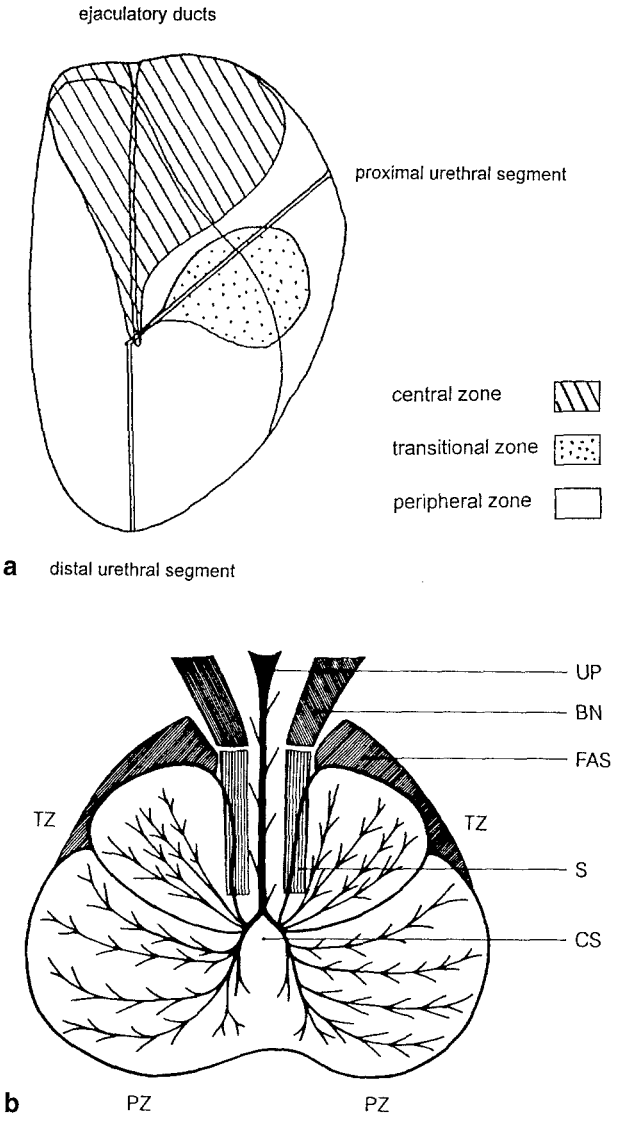

Fig. 1 **a** Three-dimensional representation of the central zone, transitional zone, and peripheral zone of the glandular prostate with proximal and distal urethral segments and ejaculatory ducts (modified after McNeal [37]). **b** Zonal subdivision of the prostate gland (modified after McNeal [37] and from Helpap [28]. Location of outer and inner zones of the prostate: *pz* peripheral zone, *tz* transition zone, *cs* colliculus seminalis, *s* preprostatic sphincter, *up* urethral segment, *bn* bladder neck, *fas* fibromuscular aglandular stroma of anterior region

The glands of the central zone are larger and architecturally different from those of the peripheral and transition zone. They have a polygonal appearance with complex intraluminal projections. These glands are also lined by an outer basal cell layer and an inner luminal cell layer. The luminal epithelium is different from that of the peripheral and transition zones in that the nuclei are not all basal in location and the cytoplasm is more abundant,

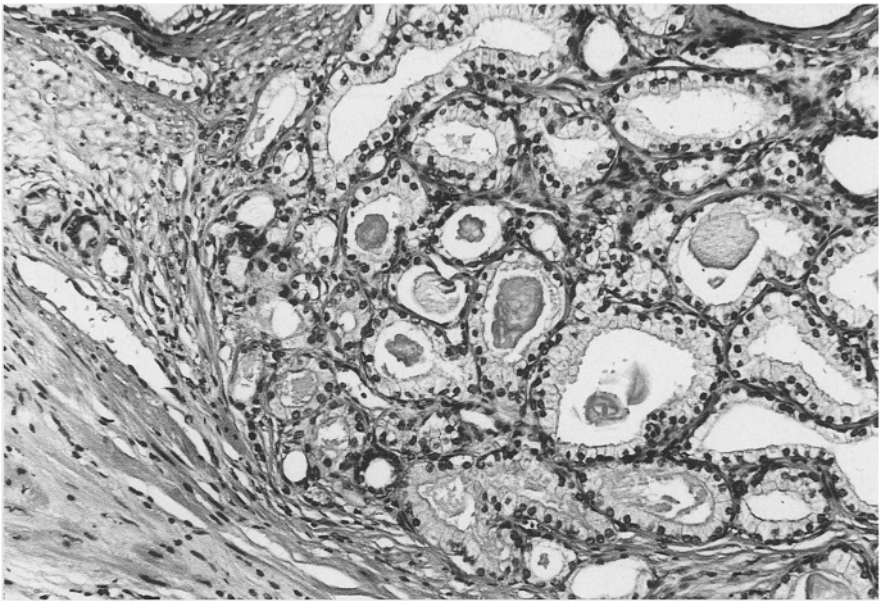

Fig. 2 Nodule of atypical adenomatous hyperplasia (AAH) of the prostate with architectural disturbance and with minimal infiltrative growth pattern. H&E, ×130

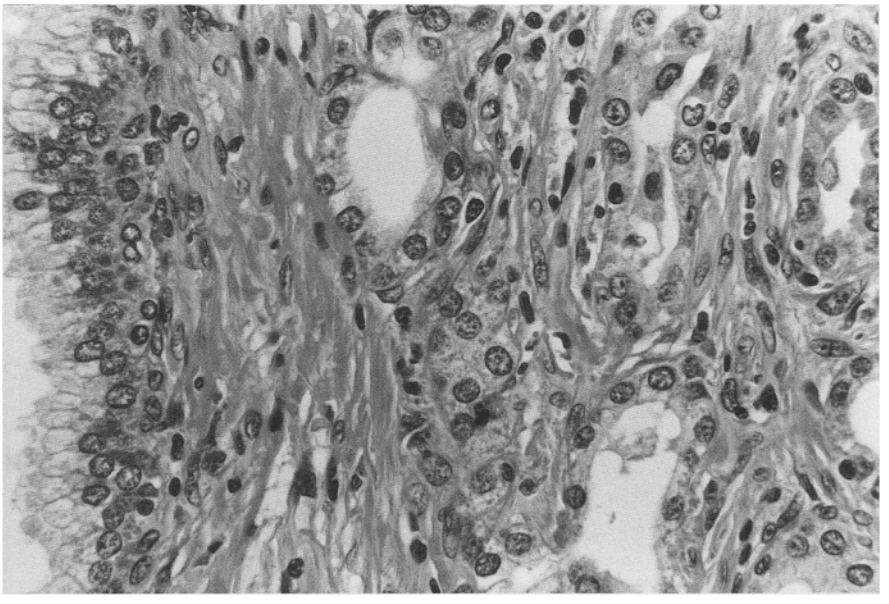

Fig. 3 Secretory cells with mild nuclear atypias and singular small nucleoli of AAH and normal basal and secretory cells of benign prostatic hyperplasia (BPH). H&E, ×400

eosinophilic, and granular. The stroma of the central zone contains more smooth muscle than that of the peripheral and transition zones and is more compact than that of the peripheral zone.

Prostatic carcinoma

The incidence of prostatic adenocarcinoma is different in the three prostatic zones. Overall, approximately 70% of prostatic carcinomas arise in the peripheral zone, 20–25% in the transition zone, and 5–10% in the central zone [3, 39]. Prostatic carcinoma is usually multifocal. Over 90% of prostatectomy specimens demonstrate multiple, discrete tumour foci and approximately 65% of cases with multiple tumours contain foci in the peripheral zone and transition zone. Carcinomas of peripheral and transition zone origin differ in their clinical presentation and in their histopathological characteristics [21, 26, 39]. Transition zone carcinoma constitutes the majority of cases of incidental carcinoma detected in specimens derived from transurethral resection procedures for urinary obstruction.

Definition and diagnostic features of AAH and PIN

AAH is characterized by architectural atypia, and consists of a new formation of well-circumscribed small crowded tubular glands in an adenomatous pattern which may resemble well differentiated prostate carcinoma (Figs. 2, 3). The glands are smaller than the surrounding benign hyperplastic glands of BPH. Three features which

Table 1 Diagnostic criteria for atypical adenomatous hyperplasia and comparison with low-grade adenocarcinoma. (From [11])

	Atypical adenomatous hyperplasia	Carcinoma (Gleason grades 1 and 2)
Architectural and associates features		
Low power	Circumscribed or limited infiltration	Circumscribed or limited infiltration
Lesion size	Variable	Variable
Gland size	Variable	Less variable
Gland shape	Variable	Less variable
Crystalloids	Infrequent (16%)	Frequent (75%)
Corpora amylacea	Frequent (32%)	Infrequent (13%)
Basophilic mucin	Infrequent	Frequent
Nuclear features		
Nuclear size variation	Less variable	Variable
Chromatin	Uniform/granular	Uniform or variable
Parachromatin clearing	Infrequent	Frequent
Nucleoli	Inconspicuous	Prominent
Nucleoli (largest)	2.5 μm (rare)	3.0 μm
Nucleoli (mean)	<1.0 μm	1.8 μm
Nucleoli>1 μm	18%	77%
Basal cell layer		
Haematoxylin and eosin stain	Inconspicuous	Absent
Anti-keratin stain (high molecular weight)	Fragmented	Virtually absent

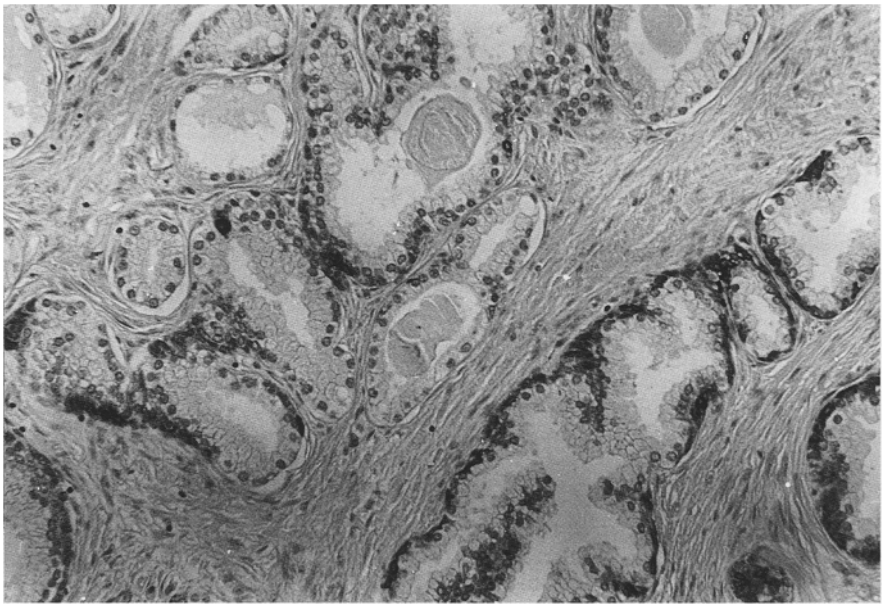

Fig. 4 AAH with fragmented basal cell layer and a few glands with complete loss of basal cells. Glands of BPH with distinctly labelled basal cells. Cytokeratin staining 34-β-E12, ABC method, ×150

are helpful in recognizing this entity include the low-power histological architectural appearance, the nuclear characteristics, and the identification of the basal cell layer. Prominent nucleoli are found more frequently than in regular hyperplastic glandular cells, but they are single and in the mean not larger than 1 μm in diameter (Fig. 3). In 15–18% prominent nucleoli may be found which are larger than 1 μm [11, 19]. Luminal crystalloids within glands (a relatively specific feature of low-grade glandular carcinoma of the prostate), corpora amylacea and, rarely, blue-tinged luminal mucinous secretions are characteristic findings in AAH [5, 11], although Epstein [17, 18] and Gaudin and Epstein [19, 20] stress that no significant differences in these features exist between AAH and glandular carcinoma. In most cases of AAH, these cellular features are less conspicuous than those seen in glandular carcinoma (Table 1). The confusion with glandular carcinoma is due to the irregular arrangement within the fibromuscular stroma. The glands of AAH may be in a back-to-back position without clearly visible stromal elements. Furthermore, the growth pattern sometimes mimics that of carcinoma. This minimal infiltrative growth pattern is present in >15% of AAH [19] and is the result of disorganization of the morpho-

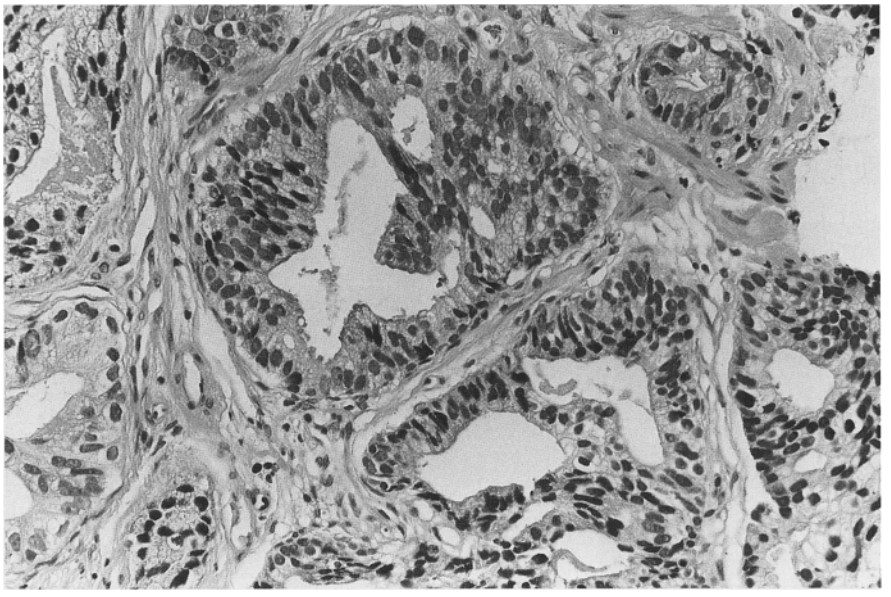

Fig. 5 Prostatic intraepithelial neoplasia (PIN) with micropapillary and cribriform pattern and distinct nuclear atypias with prominent nucleoli. H&E, ×180

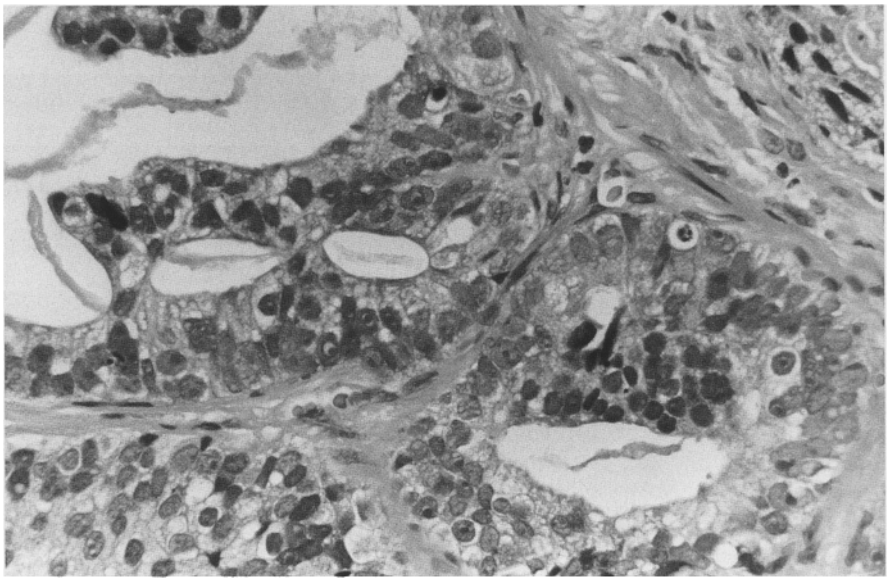

Fig. 6 High-grade PIN with cell crowding, stratification, multiple nucleoli and an apoptotic body. H&E, ×400

logical integrity between glandular epithelium and surrounding stroma (Fig. 2). The question as to whether the proliferating glands are invasive can be answered reliably only by finding splitting of the fibromuscular stroma or by confirming disruption of basal cell layers [11]. With immunohistochemical techniques, especially with specific anticytokeratin antibodies against basal cells, it is possible to distinguish between low-grade glandular carcinoma and AAH (Fig. 4). Prostatic carcinoma lacks basal cells completely, whereas the glands of AAH, depending on the degree of atypia, show distinct or weaker and spotted expression of cytokeratin of high molecular weight (anti-cytokeratin antibody 34β-E12). Prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) are heterogeneously expressed in AAH [11]. Such fragmentation of basal cell layer and expression pattern of PSA are not typical for BPH and adenosis.

PIN refers to a tufted, papillary, and cribriform epithelial proliferation in preexisting ducts, ductuli, and acini. This is characterized by multilayering of glandular epithelial cells with cytological atypia of varying degree. Sometimes a flat pattern may be also observed, and the cells are crowded and more basophilic (Fig. 5). They form micropapillary structures and epithelial bridges superficially resembling the pattern of cribriform carcinoma. The nuclei of the proliferated cells are enlarged with variable size and prominent nucleoli mainly in eccentric position (Figs. 5, 6). The cytological atypia of PIN is, as a rule, more conspicuous than that of AAH, and is similar to that seen in intermediate and high-grade carcinomas with mainly cribriform pattern (Fig. 5, 6). Immunohistochemical studies have shown a reduction in basal cells demonstrated by staining by cytokeratin of high molecular weight (anti-cytokeratin antibody 34ß-E12)

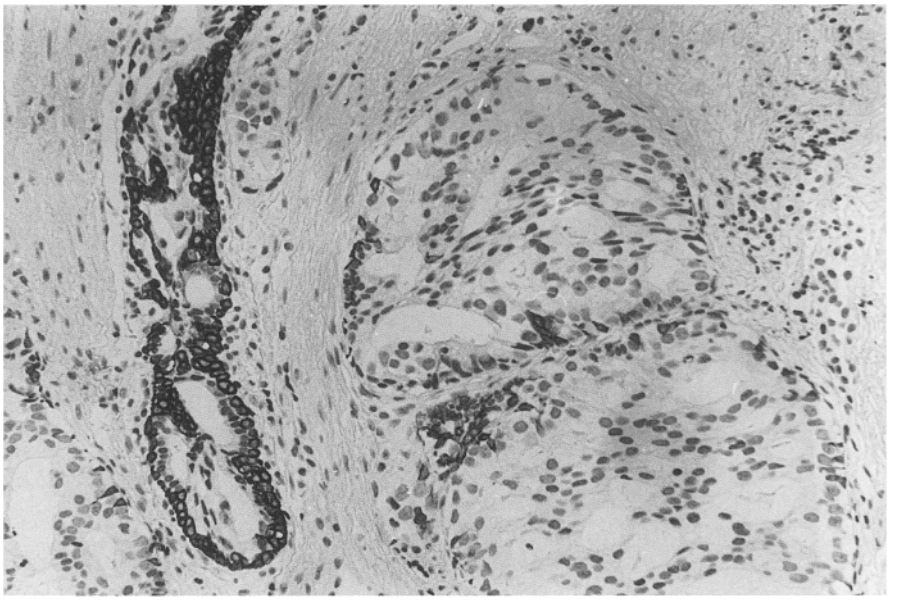

Fig. 7 High-grade PIN with fragmentation and loss of basal cells in contrast to intact basal cell layer in surrounding hyperplastic glands. Cytokeratin staining 34 β-E12, ABC method, ×150

(Fig. 7) and a reduction in the intensity and distribution of lectin binding capacity. The diagnosis of AAH and PIN requires an evaluation of combination of cytological and architectural features.

Site of AAH and PIN

AAH is found mainly in TUR specimens of benign prostatic hyperplasia and is therefore more frequent in the transition zone than in the peripheral zone (6.0%) [11, 19] (Fig. 1a, b). However, Troncoso and Ayala [54] found no topographical association between AAH and cancer and no difference in the prevalence of AAH in prostates with and without cancer. The number of AAH foci was greater in the vicinity of glandular carcinoma than distant from it. AAH was multicentric in 46% of the cases. The mean volume of AAH was much higher in the transition zone than in the non-transition zone. AAH was more common in older patients with greater prostatic weight, greater percentage of BPH, and greater volumes of cancer similar to PIN. There was no correlation of volume of AAH with pathological stage, DNA ploidy, and seminal vesicle invasion of carcinoma (Qian and Bostwick, Ancona 1994, unpublished data). AAH is only rarely diagnosed in needle biopsies (less than1%).

PIN does not appear to be related to AAH. PIN is a multifocal lesion (64.5%) that is predominantly detected in the dorsoperipheral zone (63.0%) of the prostate (Fig. 1a, b) and in the vicinity of clinical cancer (86%) (Qian and Bostwick, Ancona 1994, unpublished data). A positive correlation was found between total volume of PIN and volume of cancer. This correlation was significant only for PIN in the immediate vicinity of cancer (within 2 mm). The volume of PIN correlated positively with age, pathological stage, grade (Gleason score), capsular perforation, and lymph node status of cancer (Qian and Bostwick, Ancona 1994, unpublished data). PIN, therefore, has mainly been diagnosed in biopsy specimens and rarely in transurethral resection specimens [55].

Grading and proliferative activity of AAH and PIN

Low-grade AAH

The alterations differ only slightly from typical hyperplasia. The glands are close to each other and stromal bridges are distinctly reduced. The secretory epithelium is single layered, with clear cytoplasm. The nuclear/cytoplasmic ratio is about 1 : 4.The basal layer is intact. The nodular arrangement is somewhat blurred.

High-grade AAH

The histological pattern is similar to the alterations in well to moderately differentiated glandular carcinoma. The cells are small and clear. The nuclear/cytoplasmic ratio is shifted in favour of the nucleus. The secretory epithelium shows a single, cuboidal layer. Focally, prominent but singular nucleoli with a mean diameter of more than 1.0 μm are found in an eccentric location within the nucleus in 15–18% of cases [11,19]. The basal cell layer is fragmented (Table 1).

Low-grade PIN

The architecture of epithelial cells is altered, with crowding, stratification, and irregular spacing. Cytologically, nuclei are enlarged, with marked size variation. The chromatin is normal, and nucleoli are rarely prominent. The basal cell layer and basement membrane are intact (Table 2).

Table 2 Prostatic intraepithelial neoplasia (PIN); diagnostic criteria. (From [9])

	Low-grade PIN (formerly PIN 1)	High-grade PIN (formerly PIN 2 and 3)
Architecture	Epithelial cell crowding and stratification, with irregular spacing	Similar to low-grade PIN; more crowding and stratification; 4 patterns: tufting, micropapillary, cribriform, and flat
Cytology		
Nuclei	Enlarged, with marked size variation	Enlarged, some size and shape variation
Chromatin	Normal	Increased density and clumping
Nucleoli	Rarely prominent	Occasionally to frequently large and prominent, similar to invasive carcinoma; sometimes multiple
Basal cell layer	Intact	May show some disruption
Basement membrane	Intact	May show some disruption

High-grade PIN

The disturbance of the architecture is similar to that in low-grade PIN but with more crowding and stratification. There are four histological patterns: tufting, micropapillary, cribriform, and flat, with a frequency of 87%, 85%, 32%, and 28%, respectively [9,10]. The majority of nuclei are enlarged, with less variation in size and shape. The chromatin shows increased density and clumping. The nucleoli are large and prominent, similar to invasive carcinoma, sometimes multiple and predominantly in an eccentric position. The neoplastic cells replace the normal luminal secretory epithelium with preservation of the basal cell layer. Sometimes high-grade PIN is indistinguishable by routine light microscopy from intraductal spreading of cribriform carcinoma. PIN may also show direct invasion through the ductal or acinar wall, with disruption of the basal layer. Pagetoid spreading of PIN with invagination of neoplastic cells between basal cell layer and secretory cells is very rare (Bostwick, Ancona 1994, unpublished data) [9, 40] (Table 2).

Invasion into and beyond the basal cell layer corresponds to high-grade PIN with early invasion, present in 56% of the cases of high-grade PIN. The frequency of disruption of basal cell layer is 0.7–15.5% of cases of low-grade PIN. The percentage of disruption of basal cell layer increases with increasing grade of PIN. The disruption of the basal cell layer is more common in acini and ducts adjacent to invasive carcinoma than in distant acini or ducts [9].

Cell-proliferation kinetics of AAH and PIN

After ^{3}H-thymidine incorporation by use of the in vitro method, scattered radioactively labelled nuclei are seen in the basal cell layer and very rarely in the luminal layers of secretory cells of AAH. Overall, however, the labelling index is very low. Only in high-grade AAH are results comparable with those in well to moderately differentiated glandular carcinoma. The labelling index of high-grade PIN is twofold that in low-grade PIN and AAH (1.5% versus 0.8%) [25]. Moreover there is a distinct difference in the topography of the proliferative cell compartment. In AAH, as in BPH, basal cells are chiefly labelled by ^{3}H-thymidine autoradiography or Ki-67/MIB1 immunohistochemistry. In contrast, in PIN basal cells and luminal cells may be labelled by Ki-67/MIB1, and/or PCNA immunohistochemistry, as in poorly differentiated carcinoma (Fig. 8) [7]. Similar results may be found after measurement of nuclear DNA content in cases of BPH, low- and high-grade AAH, PIN, and carcinoma. BPH, AAH and low-grade PIN show diploid DNA pattern. Many cases of high-grade PIN and carcinoma are triploid and aneuploid [4, 6, 16, 41].

Nucleolar and AgNOR values of AAH are situated between BPH and low-grade carcinoma. PIN has increased nucleolar frequency, eccentrically located nucleoli, and a high number of AgNORs, similar to high-grade prostatic carcinoma [15, 23, 26, 27, 29, 30, 52]. Similar results may be found after immunohistochemical staining with proliferating cell nuclear antigen (PCNA) [42–44, 51].The values in low-grade PIN are comparable with values for low-grade carcinoma, and values for high-grade PIN correlate with the labelling index of growth fraction after PCNA staining of high-grade carcinoma. Also, increased frequency of apoptotic bodies (programmed cell death) supports the relationship between PIN and carcinoma, especially after total androgen ablation [44–46] (Montironi, Galluzzi, Prete et al., Ancona 1994, unpublished data).

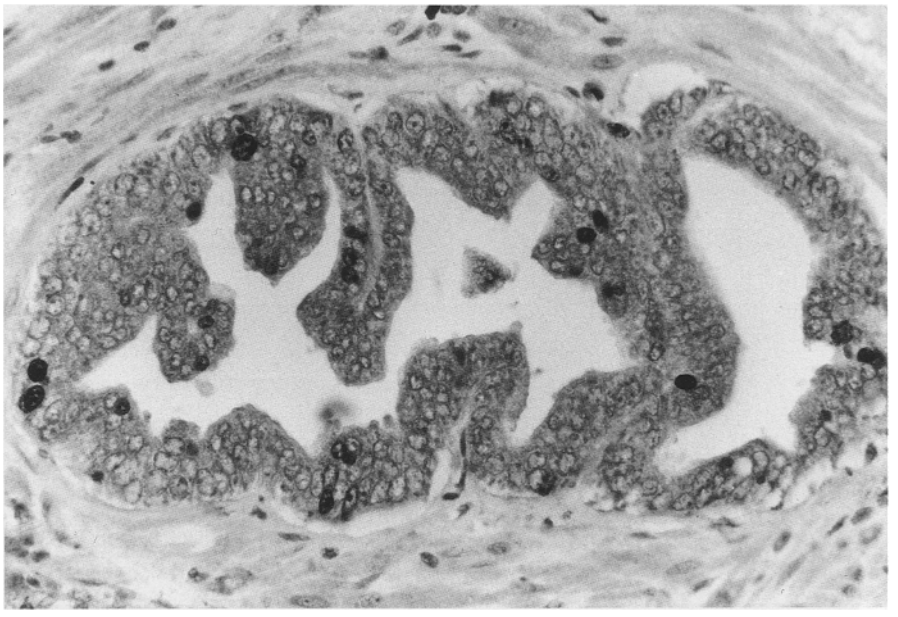

Fig. 8 High-grade PIN with Ki-67 antigen labelled basal and luminal cells. MIB1 staining, ABC method ×250

Cell kinetic data support the conception of progression of PIN to carcinoma, suggesting that there is transformation of diploid cells into a heterogeneous aneuploid cell population. This transformation may take place in high-grade PIN. High-grade PIN is thought to be a precursor of early invasive cancer according to the findings of basal cell layer disruption, progressive loss of markers of secretory differentiation, increasing nuclear and nucleolar abnormalities, increasing proliferative potential according to autoradiographic, histochemical, and immunohistochemical methods, and increasing variation in DNA content [8, 10, 49]. Cell kinetic data linking AAH and cancer are inconclusive, in contrast to PIN. Nuclear p53 immunostaining has suggested a close relationship between high-grade PIN and prostatic carcinoma (Humphry and Swanson, Ancona 1994, unpublished data).

Biology of AAH and PIN

The frequency of AAH is low (1.6–19.6%) [1, 19, 30, 53]. The coincidence of AAH with prostatic carcinoma ranges from 3% to 22% [19, 24], a frequency similar to that of incidental glandular carcinoma of the prostate (7–22%) [19, 24]. The coincidence of high-grade PIN and prostatic carcinoma, however, is very high (85.5%) [8, 9, 25, 26, 30, 31]. Carcinoma combined with AAH is in most cases low-grade glandular carcinoma, whereas carcinoma with high-grade PIN is of intermediate or high-grade malignancy, often with poorly differentiated glandular, cribriform or solid-trabecular architecture.

Little is known about the age-dependent frequency of AAH and PIN and its relationship to prostatic carcinoma. In an autopsy study, a first peak of incidence was found, which preceded that of carcinoma by about 5 years. Similar results were reported by McNeal and Bostwick [38]. The frequency of PIN was 52% in the 6th decade, 62% in the 7th and 8th decades, and 78% by the 9th decade. In contrast, the frequency of carcinoma rose from 27% in the 6th decade to 51% in the 7th and 8th decades, and 74% by the 9th decade. These observations are consistent with the atypia–preneoplasia–carcinoma sequence in a multistep theory of carcinogenesis. McNeal and Bostwick [38] concluded that PIN and carcinoma are not independent, age-associated lesions, which is underlined by similar results published by Kovi et al. [32, 33]. In younger age groups (36–60 years) PIN was detected in 86.8% of prostates with carcinoma but only in 37.9% with BPH. No significant difference was found for those over 60 years of age. Clinical studies suggest that PIN predates carcinoma by 10 years or more, with low-grade PIN first emerging in men in the 3rd decade of life (Bostwick, Ancona 1994, unpublished data). In a study by Sakr et al. [50] PIN was identified in 0%, 9%, 20%, and 44% of patients in the 2th, 3rd, 4th, and 5th decades, respectively. Small foci of histological cancer were found in 0%, 0%, 27%, and 34% of patients of the same decades. The majority of the cases of PIN were low grade, with high-grade PIN first identified in the 5th decade. These cases contained histological carcinoma. Sakr et al. [50, 51] concluded that PIN preceded the development of carcinoma.

Clinical relevance of AAH and PIN

How should urologists respond to the diagnosis of AAH and PIN? AAH, almost always diagnosed by transurethral resection, does not require further diagnostic or therapeutic steps, but the patient should be watched and reevaluated. The clinical relevance of low-grade PIN is similar to that of AAH. The clinical importance of recognizing high-grade PIN is based on its strong associa-

tion with carcinoma (85%). The identification of this lesion in biopsy specimens of the prostate warrants a further search for concurrent invasive carcinoma. In a case control study of patients with multiple biopsies, prostate cancer was subsequently found in 36% of the PIN group and in 13% of the matched control group.The likelihood of finding cancer was greater in patients with PIN undergoing more than one follow-up biopsy than in those with only one biopsy (44–32%). PIN provides the highest risk ratio of all known predictive factors, including age, digital rectal finding, and serum PSA level. This indicates the need for repeat biopsy when high-grade PIN is identified on biopsy, especially with serum PSA levels over 4 ng/ml [54]. If all procedures fail to identify coexisting carcinoma in biopsies with high-grade PIN, surveillance and follow up is indicated at 6- to 12-month intervals for life (Bostwick, Ancona 1994, unpublished data).

Influence of hormonal and radiation treatment on AAH and PIN

In low- and high-grade PIN, cell loss or apoptotic index of basal cells and secretory cells is higher after total androgen ablation than in untreated cases, as in carcinoma [44–46, 48]. Studies of androgen receptor and *bcl*2 expression have also shown that most basal cells lack androgen receptor expression but contain *bcl*2, an intracellular protein that blocks apoptosis. The luminal secretory cells of benign prostatic glands usually show strong androgen receptor expression. In PIN, strong androgen receptor and *bcl*2 expression is noted. After androgen blockade therapy, benign prostatic glands show atrophy or basal cell hyperplasia. The basal cells do not express androgen receptor, but some persistent luminal cells still express androgen receptor and PSA under conditions of androgen ablation. PIN shows variable expression of androgen receptor similar to that of residual prostatic carcinoma after androgen ablation. Therefore, glandular secretory cells with the endocrine therapy resistance phenotype are present in benign glands, PIN, and carcinoma (van der Kwast, Ancona 1994, unpublished data). AAH after hormonal therapy shows squamous metaplasia, atrophy, and basal cell hyperplasia similar to benign glands in the vicinity of carcinoma [22].

Information on the sensitivity of PIN to radiation and the distribution of residual PIN after radiotherapy is scant. In prostates with cancer removed following radiation failure, there was no significant difference between carcinoma groups with and without high-grade PIN and various clinical factors such as preoperative PSA, age, dose of radiotherapy, interval from radiation therapy to prostatectomy, and survival. Also, no difference was observed in pathological factors such as extracapsular extension, positive surgical margins, seminal vesicle invasion and positive lymph nodes. Although PIN is reported to be common in prostates of patients who have failed radiation therapy, there is no evidence that recurrent tumours derive more from persistent PIN than from the initial incompletely eradicated tumour (Akrakawa, Scardino, and Wheeler, Ancona 1994, unpublished data).

Conclusions

High-grade PIN is the most likely precursor of prostatic carcinoma in the peripheral zone. In contrast, the clinical significance of AAH is uncertain, although it is suggested that AAH may be a precursor to transition zone carcinoma. The diagnosis of AAH and PIN often requires a combination of architectural, histological, cytological, immunohistochemical, and cell kinetic features.

The role of grading of AAH and PIN and the knowledge of the relationship of AAH and PIN to the zonal anatomy of the prostate and the relationship especially of grade of PIN and grade of cancers are important for pathologists and urologists. Low-grade AAH and PIN are of no apparent clinical significance, whereas high-grade AAH and PIN do appear to be clinically significant. PIN-associated cancer is not apparently different from AAH- and PIN-non-associated cancers. In high-grade PIN, surveillance and follow-up of the patient is necessary to identify the possible transition of high-grade PIN to carcinoma or to identify a coexisting cancer. The high rate of high-grade PIN associated with cancer and its age-related incidence in relationship to that of cancer suggest that PIN plays a more important part in the development of dorsoperipheral prostate cancer than does AAH in transition zone carcinoma.

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