Journal of Cellular Biochemistry, Supplement 16G:171-174 (1992)

Prostatic Intraepithelial Neoplasia: A Premalignant Lesion

Michael K. Brawer

Department of Urology RL-10, University of Washington, Seattle, Washington 98195

Abstract Putative premalignant changes in the prostate have been recognized for a number of years. A variety of synonyms have been given to the most commonly described lesion, characterized by proliferation and dysplasia of the normal two cell layers lining prostatic acini and ductules; prostatic intraepithelial neoplasia (PIN) is the term most often used.

A premalignant prostatic lesion should have morphologic features similar to invasive carcinoma (CA), a spatial association with microinvasive cancer arising from the lesion, and should occur at a greater frequency, severity and extent in organs harboring CA. Most definitively, progression from the premalignant lesion into CA should be observed over time. PIN fulfills all but the last of these requirements.

High grade PIN is cytologically indistinguishable from prostate carcinoma (CAP). The major differentiating feature between PIN and CAP is the presence, although frequently disrupted, of the basal cell layer in the former. We have studied the basal cell layer in PIN using antibodies to high molecular weight cytokeratins and have found a correlation between PIN grade and the percent disruption of the basal cell layer. The cells making up PIN are phenotypically similar to those of CAP. We have used a variety of markers including cytokeratins, vimentin and the lectin *Ulex euroapaeus* to demonstrate this similarity. Additionally, we and others have noted decreased PIN immunoreactivity with antibodies directed against prostate specific antigen (PSA) and prostatic acid phosphatase. Other investigators have noted additional phenotypic similarities between PIN and CAP, including the ABH and Lewis antigens. PIN incidence and grade correlate well with the presence of CAP elsewhere in the prostate. In fact, we have noted PIN in all cases of peripheral zone CAP in which radical prostatectomy specimens were available for review. The definitive requirement for a premalignant lesion is that it undergoes invasion over time. This requirement has not been satisfied with PIN because it is impossible to serially biopsy the same acinar-ductule system on separate occasions.

The clinical importance of PIN follows from three primary observations. We and others have demonstrated that PIN may be associated with elevated serum PSA levels. On transrectal ultrasound of the prostate (the optimum imaging modality for this organ) PIN may appear to give rise to a hypoechoic lesion similar to the most common presentation for CAP. Finally, we have noted that, when PIN is detected on a prostate biopsy, there is a very high incidence of CAP on a repeat biopsy. It would thus appear that PIN represents a major premalignant lesion in the human prostate. The potential for strategies of chemoprevention to inhibit further transformation or progression of PIN into invasive carcinoma seems tenable and worthy of further investigation.

Key words: chemoprevention, intermediate biomarker, premalignant lesion, prostate, prostate specific antigen (PSA), prostatic intraepithelial neoplasia (PIN)

Premalignant changes in the prostate have been recognized for a number of years. The literature is confusing because of the fact that a number of synonyms have been utilized to describe these entities including atypical hyperplasia, atypical glandular hyperplasia, cytologic atypia, duct-acinar dysplasia, glandular atypia, intraglandular dysplasia, large acinar atypical hyperplasia, intraductal dysplasia and prostatic intraepithelial neoplasia [1-21]. A consensus conference in 1989 resulted in standardization of diagnostic criteria, grading, and in the decision to utilize the term prostatic intraepithelial neoplasia (PIN) for the most typical lesion [22].

Criteria for considering a lesion premalignant include morphologic features similar to invasive carcinoma; spatial association between the premalignant change and cancer; microscopic foci of invasion arising from the

premalignant change; frequency, severity and extent of the lesion greater in organs with invasive carcinoma; and progression of the premalignant lesion into invasive cancer as evidenced by serial biopsy.

Grade one PIN is associated with stratification and crowding of the proliferating luminal cell associated with minimal cytologic atypia. Nuclei may be variable in size but chromatin is normal and there is no prominence of nucleoli [11,15]. In contrast high grade PIN is associated with increased crowding of the luminal cells. Disruption of the basal cell layer may be frequently observed [15]. Cytologic features suggestive of malignancy include marked variability of nuclear size, clumping of chromatin and large prominent nucleoli. The disruption of the basal cell layer may be difficult to identify on hematoxylin and eosin preparations. We have previously described our observations with immunohistochemical labeling of the basal cell with high molecular weight anticytokeratin antibody [15, 23-26].

Phenotypic evidence of the similarity between PIN and carcinoma is demonstrated by a number of immunohistochemical investigations. An antibody directed against cytokeratins 14, 15, 16 and 19 (KA 4 developed by R.B. Nagle, Department of Pathology, University of Arizona) [27] as well as the lectin *Ulex euroapaeus* (Ulex) [27] show expression in both PIN and carcinoma but not in the luminal cells of benign prostate. Moreover, vimentin, which is expressed in the luminal cell of benign prostate is not seen in PIN or carcinoma [27]. We and others have noted decreased immunohistochemical reaction with antibodies directed against prostate specific antigen in PIN relative to benign tissue [28, 29]. Other investigators have shown additional phenotypic similarity between PIN and carcinoma with antibodies directed against leu-7 [28] and the blood group antigens ABH and Lewis [30].

PIN is much more commonly found in prostates with invasive carcinoma. In a compilation of the literature, in 876 organs without carcinoma obtained at postmortem examination PIN was observed in 32% of cases (range 20-72) [8, 11, 13, 18-20]. In contrast in organs exhibiting invasive carcinoma (731 cases) 73% displayed PIN (range 59-100) [8, 11, 13, 15, 18]. We have not seen any cases of peripheral zone carcinoma that were not associated with PIN when the entire radical prostatectomy specimen was available for study (unpublished observation).

PIN grade correlates with the presence of carcinoma. If the worst grade of PIN in the specimen is noted, grade 1 PIN is found in between 7 and 46% of prostates with carcinoma (mean 21%) [8, 11, 13, 19]. Grade 2 PIN occurs more commonly in glands with carcinoma with a mean incidence of 35% (range 21-48) [11, 13, 19]. Grade 3 PIN is found in between 6-90% of organs with invasive carcinoma, and the mean amongst the published series is 54% [8, 11, 13, 19]. Whereas grade 1 PIN is found in 14-81% of prostates without carcinoma (mean 55%), grade 3 PIN is rarely found without invasive carcinoma (mean 17%, range 5-32) [8, 11, 13, 19]. McNeal and Bostwick [11] as well as Troncoso and associates [19] have correlated the volume of PIN in a specimen with the presence of carcinoma. Additionally Troncoso observed that only 15% of prostates without invasive carcinoma had multifocal PIN [19].

Troncoso and associates [19] demonstrated a predilection of PIN for the peripheral zone of the prostate. Similar observations have been made by Kovi and associates [13]. This observation is salient because the vast majority of prostatic carcinomas arise in the peripheral zone [31].

In addition to the zonal relationship there appears to be a subzonal spatial realtionship between PIN and carcinoma. Of 1093 ducts and acini with PIN which we quantitated in radical prostatectomy specimens, 41% were found within one high powered microscopic field of invasive carcinoma [15]. Proximity to carcinoma appears to correlate with PIN grade. Eighty-seven percent of the acini juxtaposed to carcinoma were high grade PIN. Finally micro-invasive carcinoma arising from PIN has been described by ourselves and others [15, 31].

The above observations illustrate that PIN fulfills the majority of criteria for a premalignant lesion. Morphologic similarities to carcinoma as shown both by hematoxylin and eosin preparations as well as immunohistochemical phenotypic similarity has been demonstrated. The frequency of PIN is greater in organs with carcinoma than in those without. Zonal and spatial association between PIN and invasive carcinoma has been demonstrated. Because of the inability to repeatedly biopsy the same duct-acinar system, it is impossible to demonstrate conclusively progression of PIN into invasive carcinoma. Intermediate evidence of progression comes from our observation that disruption of the basal cell layer is more commonly associated with higher grade PIN as well as recognition of the foci of microinvasive carcinoma arising from PIN.

In addition to the increasing evidence that PIN is a premalignant condition, this entity is clinically significant. Prostate specific antigen (PSA) may be elevated in patients exhibiting PIN. PSA is a 34 kilodalton glycoprotein which is specific to the prostate but not cancer specific [32]. This marker which represents a major advance in our oncologic armamentarium is useful primarily for monitoring patients with a diagnosis of carcinoma. Investigations into its utility for staging and early detection are ongoing.

In a series of patients undergoing prostatectomy for relief of bladder outlet obstruction owing to presumed

benign etiology we noted that a significant percentage of patients with PIN had elevated PSA. Of the 25 patients with PIN the mean PSA was 5.6 ng/ml, range 0.3-32.0 [33]. Thirteen of the patients with PIN had a PSA above the established normal range of 4.0 ng/ml (Hybritech, Inc., San Diego, CA). We have noted similar findings in a series of patients undergoing ultrasound guided prostate needle biopsy who demonstrated PIN [34]. In this series of 36 patients with PIN the mean PSA was 7.8 (range 0.2-19.2). Lee and associates reported similar findings [35].

Transrectal ultrasound represents the optimum imaging modality for the prostate. We have described 8 men undergoing ultrasound guided prostate needle biopsy of hypoechoic peripheral zone lesions (the most common change associated with carcinoma) who had PIN without carcinoma in their biopsy specimen. Of note 3 of the 8 patients on repeat biopsy demonstrated invasive carcinoma.

The significance of finding PIN on prostate needle biopsy is reinforced by our recent observation of 21 patients who had PIN identified on biopsy because of a palpable prostatic abnormality and underwent repeat ultrasound guided biopsy [37]. Twelve of the patients (57%) demonstrated carcinoma on the second biopsy procedure. This included 2 of those with low grade PIN and all 10 men with high grade PIN. We obtained prostate specific antigen level in 16 of the patients prior to the second biopsy. This demonstrated stratification of higher PSA's in those who had high grade PIN on the initial biopsy as well as those who subsequently were shown to have carcinoma.

The clinical management of men with PIN is predicated on the reporting of this change when observed on simple prostatectomy or prostate needle biopsy specimens by pathologists. Additional tissue which may not have been submitted for histologic examination, should be sectioned and examined. Prostate specific antigen may be useful in identifying patients needing further investigation. In the case of high grade PIN on needle biopsy we immediately perform repeat needle biopsy of the region demonstrating PIN. If this biopsy is negative, the patients are carefully followed with digital rectal examination and serum PSA levels.

PIN has great potential for research. This entity may well serve as a model for carcinogenesis and invasion. In addition, the clinical significance of PIN makes this a potential entity for chemoprevention trials. Further research is indicated in both of these arenas.

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