

Prostatic Intraepithelial Neoplasia and Endocrine Manipulation

Th.H. van der Kwast F. Labrie B. Têtu

Department of Pathology, Erasmus University, Rotterdam, The Netherlands, and Centre Hospitalier
Université de Québec, Canada

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Abstract

Prostatic intraepithelial neoplasia (PIN) is the most common precursor lesion of prostatic adenocarcinoma. In 50- to 70-year-old participants of a randomized screening program for prostate cancer (Rotterdam section of the ERSPC) the frequency of high-grade PIN as an isolated finding in sextant prostatic needle biopsies was estimated to be about 1%. As yet, data in literature on the impact of androgen deprivation on PIN lesions are limited, showing discrepant outcomes. In part this may be the consequence of the application of different criteria for the identification of PIN under conditions of androgen deprivation. Foci of PIN could be distinguished in the majority of radical prostatectomy specimens of men treated for 3 or 6 months with combined endocrine therapy. Endocrine manipulation led to architectural changes (remodelling) in residual PIN which were more pronounced at 6 months of endocrine therapy. This is consistent with a prolonged effect of androgen deprivation on this precursor lesion. The presence of MIB-1 immunopositive nuclei in PIN lesions suggests that they still have the potential to expand after cessation of therapy.

Introduction

Prostatic intraepithelial neoplasia (PIN) is regarded as the most likely precursor lesion for prostatic adenocarcinomas arising in the peripheral zone of the prostate [1, 2]. The histological and cytological characteristics of high-grade PIN are now well established. An important feature of high-grade PIN is the presence of prominent nucleoli in the majority of the dysplastic cells [3]. High-grade PIN is found in association with prostatic adenocarcinoma in 80-90% of radical prostatectomy specimens [2, 4]. It has been reported that in 5-16% of diagnostic needle biopsies, high-grade PIN is diagnosed in the absence of accompanying adenocarcinoma [5, 6]. The incidence of high-grade PIN as an isolated finding may be influenced by the nature of the population under study and the needle biopsy strategy. Data on the frequency of high-grade PIN in a nonselected population are limited [6]. The detection of an isolated high-grade PIN in men with elevated PSA levels could mean that a focus of adenocarcinoma has been missed owing to a sampling error, particularly if a limited number of biopsies was taken. Nevertheless, its presence in men with low PSA levels is also frequently associated with the finding of an adenocarcinoma in subsequent biopsies [7, 8]. This has been interpreted as evidence for the commonly held view that prostatic adenocarcinoma may evolve from high-grade PIN.

After androgen deprivation both the benign peripheral and transitional zone prostatic glands and adenocarcino-

mas show regressive changes associated with a considerable reduction in prostatic size and tumor volume [9–11]. Characteristically, the benign luminal cells undergo vacuolization and shrinkage, while the basal cells become relatively more prominent [9, 10]. Recently, we demonstrated that these luminal cells retain the potential to proliferate, although this proliferative activity does not match cell loss as a consequence of programmed cell death [12]. Since the dysplastic cells in PIN share morphological and biochemical features with prostatic secretory epithelial cells, it may be anticipated that androgen deprivation leads to comparable morphological and functional changes. Several studies have reported a decrease in the incidence and extent of PIN following 3 months of androgen deprivation therapy [9, 11, 13–15]. This observation has been attributed both to the real loss of PIN lesions and to a loss of features helping to distinguish high-grade PIN from normal luminal cells [11].

In untreated prostatectomy specimens, at least four histological patterns of PIN can be distinguished: tufting and micropapillary in the majority of cases and cribriform and flat in a minority [16]. Analogous to the remodelling of benign prostatic glands observed after androgen deprivation, it is conceivable that the architecture of PIN lesions undergo similar changes. The availability of prostatectomy specimens of patients randomized to a 3- or 6-month regimen of neoadjuvant endocrine combination therapy allowed us to study the effects of androgen deprivation on (1) the frequency of residual PIN lesions, (2) the morphological changes of PIN-involved glands and (3) the potential of dysplastic cells of residual PIN to proliferate.

Materials and Methods

Tissue Specimens and Patient Material

The presence of isolated high-grade PIN in sextant needle biopsies of 3,607 men was recorded. The men were aged between 55 and 75 years with a PSA level >3 ng/ml and participated in a randomized screening program on prostate cancer (Rotterdam section of the ERSPC study).

Prostatectomy specimens of men with clinically localized prostatic cancer were randomized at the Centre Hospitalier Université Laval, Québec, Canada, to 3 months (group A) and 6 months (group B) of neoadjuvant combined androgen blockade. Patients received either daily injections of a luteinizing hormone-releasing hormone agonist [*D*-Trp⁶, des-Gly-NH₂¹⁰]LHRH ethylamide (Tryptal) or monthly depot injections (Lupron). In addition, oral flutamide (Eulexin, 250 mg, 3 times/day) was given.

Processing and Histopathology of Prostatectomy Specimens

The prostatectomy specimens were fixed overnight in buffered formalin (pH 7.2), completely embedded in paraffin and processed to allow histopathological examination of tissue sections stained with hematoxylin and eosin. All slides, retrieved from the archives of the Hôtel Dieu de Québec, Canada, were reviewed by one pathologist (ThvdK) who was unaware of the treatment group. The presence and architectural pattern of PIN was recorded.

Immunohistochemistry

Proliferative activity was assessed by immunostaining with monoclonal antibody MIB-1 (Immunotech, France). Five-micrometer-thick sections were deparaffinized in toluene and rehydrated in ethanol. Endogenous peroxidase activity was quenched by 20 min treatment with methanol-0.3% H₂O₂ while rehydration was completed by rinsing in running tap water. Antigen retrieval was done by microwave treatment in 0.01 M citric acid (adjusted to pH 6.0). For visualization of primary antibody binding an avidin-biotin peroxidase complex method (Dako, Denmark) was used.

Results

In the ERSPC study, a total of 36 men were found to have isolated high-grade PIN corresponding with an incidence of 1% in men with a PSA level >3 ng/ml.

In radical prostatectomy specimens of patients treated for 3 or 6 months with endocrine therapy, PIN could be identified at high-power magnification on the basis of nuclear crowding, increased nuclear size, and disordered or irregular arrangement of nuclei.

The proportion of prostatectomies with PIN dropped from 72% at 3 months to 59% at 6 months. Strikingly, tufted PIN was much more frequent in 3-month- (48%) than in 6-month-treated cases (10%). Flat PIN was present in nearly all radical prostatectomy specimens which contained PIN lesions.

Immunohistochemical staining of 6-month-treated PIN-containing prostatectomy specimens revealed that some MIB-1-labeled nuclei were present in most PIN lesions, but no mitotic figures were detected.

Discussion

Here we show that in a nonselected population the incidence of high-grade PIN detected by sextant needle biopsies is rather low, i.e. 1%. The treatment of isolated high-grade PIN is not established as yet. It has been suggested that in the absence of detectable cancer after repeat biopsies, androgen deprivation therapy might be a suitable approach [15]. In the literature, the percentage of residual PIN during androgen deprivation varies from 6

to 83% [9, 11, 13–15]. Variation may be the consequence of different treatment regimens, but some of the discrepancies can be attributed to inter-observer variation among pathologists. Indeed, if the presence of large prominent nucleoli was considered as a prerequisite for a diagnosis of PIN, very few prostatic glandular lesions in treated prostatectomies would fit within this category.

It is well established that most residual prostatic adenocarcinomas lose the typical inclusion-like nucleoli as a consequence of androgen deprivation [11]. Therefore, we consider it very likely that loss of nucleoli as observed in regressive adenocarcinoma also occurs in PIN during androgen deprivation. In our opinion, (high-grade) PIN under endocrine therapy can still be identified by other criteria, namely increased nuclear size, nuclear crowding, and anisonucleosis. It is well established that androgen deprivation leads to a remodeling of benign prostatic glands, both in the peripheral and transitional zone [9, 10]. The alterations in the frequency of the various architectural patterns of PIN observed after 3 and 6 months of

combined androgen blockade indicate that PIN-involved glands undergo the same set of changes as benign glands.

The finding of MIB-1-positive dysplastic cells in the majority of PIN lesions, even after 6 months of combined endocrine therapy, implies that these cells still have the potential to replicate. This corresponds with our recent finding that under the condition of low androgen levels, luminal but not basal cells of benign prostatic glands show increased proliferative activity as defined by MIB-1 antibody immunostaining [12]. This further underlines the resemblance of dysplastic cells of PIN with benign prostatic secretory cells.

Chemoprevention of prostate cancer by reduction of androgen levels should act by elimination of PIN or by prevention of the transition of PIN to overt carcinoma. Given the observed slow decline in frequency of PIN after androgen deprivation, it can be concluded that eradication of PIN will require a very long androgen deprivation treatment.

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