Annals of Diagnostic Pathology 24 (2016) 55–61

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

Inflammation and focal atrophy in prostate needle biopsy cores and association to prostatic adenocarcinoma

Ines Benedetti, MD [a,*], Alfonso Bettin, MSc [b], Niradiz Reyes, MSc, PhD [b]

[a] Histopathology Research Group, School of Medicine, Zaragocilla campus, University of Cartagena, Colombia
[b] Genetics and Molecular Biology Research Group, School of Medicine, University of Cartagena

ARTICLE INFO

Keywords:
Prostate cancer
Inflammation
Atrophy

ABSTRACT

The possible origin of proliferative inflammatory atrophy in the regenerative proliferation of prostate epithelial cells in response to injury caused by inflammation, and their relation to prostate adenocarcinoma have not been defined. Inflammation and focal atrophy are common pathological findings in prostate biopsies, currently not routinely included in surgical pathology reports. The objective of the study was to determine the correlation between inflammation and focal atrophy with prostate adenocarcinoma. Prostate needle biopsies from 203 patients with clinical parameters suspicious for malignancy were evaluated for the presence and extent of chronic inflammation, type and grade of focal atrophy, high-grade intraepithelial neoplasia, and adenocarcinoma. Relations among them and with age were also analyzed. χ^2 tests and binary logistic regression were used to estimate associations. Chronic inflammation was observed in 77.3% of the biopsies, significantly associated to adenocarcinoma ($P = .031$). Moderate/severe inflammation in at least 1 biopsy core increased the risk of prostate adenocarcinoma (odds ratio, 2.94; 95% confidence interval, 1.27-6.8), whereas glandular localization of inflammation decreased the risk. Focal atrophy was present in 72.9% of the biopsies, proliferative inflammatory atrophy was the most common type, and its grade was significantly associated to inflammation ($P < .0001$) and inflammation intensity ($P = .003$). An association between prostate adenocarcinoma and inflammation was found, with higher odds in presence of moderate/severe inflammation in at least 1 biopsy core. Increasing grades of proliferative inflammatory atrophy were associated to high levels of inflammation, supporting its previously proposed inflammatory nature.

1. Introduction

Prostate adenocarcinoma (PCa) is the second most frequently diagnosed cancer and the fifth leading cause of death from cancer in men worldwide, with 70% of cases from developed countries and incidence rates relatively high in developing areas such as the Caribbean, South America, and sub-Saharan Africa [1]. According to the American Cancer Society, this is the most common cancer expected to occur in men in 2015, accounting for about one-quarter of new diagnoses, and the second cause of cancer-related death in men in the same period in the United States [2].

Although the most well-established risk factors for this cancer type are older age, race (black), and family history, some environmental factors have been included as well. One such potential environmental factor which has gained a great deal of recent attention is the development of chronic prostatic inflammation and its link with the pathogenesis of PCa, and extensive research efforts have been devoted to its study [3].

Substantial work has been conducted in the last years, but the study of chronic prostatic inflammation has been difficult [4]. The histological term *prostatitis* implies the presence of inflammatory cells in the glands and stroma of the prostate. The pathologist has usually given little attention to prostatic inflammation unless it is particularly florid because the clinical meaning of this observation remains largely undefined. For the pathologist, *prostatitis* is defined as an increased number of inflammatory cells within the prostatic parenchyma. Prostatic inflammation may be an important factor contributing to increased levels of prostatic-specific antigen (PSA) in men without PCa [5], and a high percentage of men subjected to prostatic needle biopsy because of an elevated PSA or an abnormal digital rectal examination (DRE) result had histological evidence of chronic inflammation [6].

Several years ago, focal atrophy was proposed as a possible precursor lesion in PCa [7,8]. Some supporting evidence of this has been shown recently. In this regard, a new "injury-and-regeneration" model, linking the effects of chronic inflammation to the molecular and cellular modifications underlying the pathogenesis of PCa, has been proposed by De Marzo and coworkers, who introduced the term *proliferative inflammatory atrophy* (PIA) to refer to focal atrophic lesions associated with chronic inflammation, with an increased fraction of proliferating epithelial cells compared with normal epithelium, and

* Corresponding author. Tel.: +57 5 6698176.
E-mail addresses: inebenedetti@hotmail.com, ebenedettip1@unicartagena.edu.co (I. Benedetti), alfonsobettin@yahoo.es (A. Bettin), nreyesr@unicartagena.edu.co (N. Reyes).

http://dx.doi.org/10.1016/j.anndiagpath.2016.04.010
1092-9134/

often directly adjacent to lesions of prostatic intraepithelial neoplasia, PCa, or both [9].

PIA contains atrophic epithelial cells that appear to be regenerating in response to cellular damage [9]. This atrophic lesion frequently merges with the only, until now, recognized direct precursor for PCa, high-grade prostatic intraepithelial neoplasia (HGPIN). Furthermore, PIA has some of the hallmark somatic genome alterations found in PCa and HGPIN, and it has been proposed as "risk factor lesion" for the development of this neoplasia [12,13]. Epithelial cells in PIA lesions show high levels of molecules induced in response to oxidative stress or to signals associated to cellular activation and proliferation [9,14,15]. Several key molecular pathways involved in PCa have also shown to be altered in PIA lesions [16,17]. All these changes could potentially lead to genetic instability and high risk of mutations, in addition to the accumulation of genetic changes and persistent proliferation, and ultimately to progression to invasive carcinoma [12]. Furthermore, some studies have described and documented morphological transitions between PIA and HGPIN, as well as between PIA and PCa [9,18-20].

Postulation of PIA as a possible precursor lesion for PCa or HGPIN remains controversial [21,22], and its possible origin in the regenerative proliferation of prostate epithelial cells in response to injury caused by inflammatory oxidants [9] has not been defined. Considering all these information and given that inflammation and focal atrophy are common findings in prostate biopsies, without an established association to PCa, and that currently they are not routinely included in surgical pathology reports, we studied morphological details in prostate biopsies from patients with suspicion of PCa to determine the relationships between these histopathological findings and their association with PCa and age.

2. Methods

2.1. Design and study population

We performed a prospective observational study between December 2010 and December 2013 at the Hospital Universitario del Caribe, Cartagena, Colombia. The studied population corresponded to patients referred to transrectal ultrasound–guided prostate needle biopsy because of a PSA level greater than 4.0 ng/mL and/or abnormal result from DRE who were invited to participate in the study and signed an informed consent. The study was approved by the Ethics Committee of the Universidad de Cartagena and the Ethics Review Board of the Hospital Universitario del Caribe. Clinical data were obtained from hospital records and pathology reports.

As part of the routine process of biopsy, patients received antibiotic prophylaxis by oral route with 500 mg of ciprofloxacin daily for 10 days, starting 3 days before and ending 7 days after the procedure. The biopsies were performed by an experienced radiologist, and the anesthetic agent used during the procedure was topical lidocaine.

All biopsies were performed with a spring-loaded biopsy gun and 18-gauge Tru-Cut needle (Carefusion, UK). A Sonosite Titan (Fujifilm Sonosite Inc, USA) ultrasound probe was used for diagnostic ultrasonography, and octant biopsies were typically performed if no hypoechoic lesions were found. For patients with hypoechoic lesions, additional site-specific biopsy cores were taken. Eight to 12 cores of approximately 1 cm in length were taken from the peripheral zone and suspect nodules. Tissue specimens were fixed in 10% buffered formalin, processed, and subjected to hematoxylin and eosin (H&E) staining according to routine protocol.

The hospital pathologist evaluated stained tissue sections for their respective histopathological diagnosis. Tissue slides were later forwarded to our research laboratories and examined by another pathologist, who was blinded with regard to the original diagnosis and other clinical data. The second pathologist evaluated the slides for the presence of chronic inflammation, focal atrophy, high-grade prostatic intraepithelial neoplasia, and adenocarcinoma. Cores containing gland-free prostatic stroma or nonprostatic tissue (rectal mucosa, or accessory glands as seminal vesicles or Cooper's glands) were discarded. Histological grading of biopsies with adenocarcinoma was based on Gleason scoring system [23].

High-grade prostatic intraepithelial neoplasia was identified using criteria defined by Bostwick et al [10]. The inflammation was scored for grade, localization, and extension using the Histopathological Classification System of Prostatic Inflammation developed by Nickel et al. In this system, prostatic inflammation is classified according to its extent (1, focal; 2, multifocal; 3, diffuse) and grade (1, mild; 2, moderate; 3, severe) in each tissue compartment (stromal, periglandular, and glandular) [6] (Fig. 1). For cases with presence of inflammation in their biopsies, we determined the number of cores with moderate or severe inflammation; and for those cases with varying intensity of inflammatory infiltrate, the highest grade was recorded. In addition, we calculated an intensity score for chronic inflammation applying the system used by Gurel et al [5] with some modifications: to capture the combination of extent and grade, we multiplied in each biopsy its inflammation grade by its extension and classified them as none, 0; mild, 1-2; moderate, 3-5; or severe, 6-9.

Presence of focal atrophy and its most common type were evaluated and classified according to the Working Group Classification of Focal Prostate Atrophy Lesions that includes 4 categories—simple atrophy (SA), postatrophic hyperplasia (PAH), simple atrophy with cyst formation, and partial atrophy (PA)—using the morphological definitions of each type [24]. These lesions could be present in an isolated form or frequently in different combinations among them. Proliferative inflammatory atrophy includes only 2 lesions: SA and PAH [24]. In the present study, the other 2 types of focal atrophy, simple atrophy with cyst formation and PA, were categorized as "non-PIA."

Grade of focal atrophy was measured using categories described by Postma et al: 0, no atrophy; 1, 1 to 3 biopsy cores containing 1 or more separate small (less than 5 mm) foci of atrophy; 2, more than 3 biopsy cores containing 1 or more separate small (less than 5 mm) foci of atrophy; 3, greater than 5 mm of continuous atrophy (adjacent area) in 1 or 2 biopsy cores; 4, more than 5 mm of continuous atrophy (adjacent area) in more than 2 biopsy cores [25].

Relation of focal atrophy with age, HGPIN, intensity score of inflammation, and adenocarcinoma was evaluated. Topographic associations and transitions between lesions, PIA with HGPIN and/or adenocarcinoma, were evaluated according to descriptions by Putzi and De Marzo [18] as follows: merging, when the neoplastic-appearing epithelium of the HGPIN or carcinoma merged directly with PIA within a given acinus or duct; adjacent, when the neoplastic-appearing epithelium abutted but did not merge with PIA, and the 2 lesions were in very close proximity with only a small amount of intervening stroma but did not merge directly within a given acinus/duct; near, when the individual duct/acinus of HGPIN or carcinoma was separated from a distinct acinus/duct containing PIA by less than 1 mm; and distant, when the HGPIN or carcinoma lesion was separated by more than 1 mm [18]. Each PIA lesion with a fraction containing areas of HGPIN or adenocarcinoma was considered to be a separate focus of transition PIA-HGPIN or transition PIA-PCa.

2.2. Statistical analysis

Prevalence of inflammation, focal atrophy, and HGPIN in the prostate samples were examined globally at first and then separately in 2 biopsy groups: biopsies with and without adenocarcinoma. For chronic inflammation analyses, a 3-level ordinal variable was included for the categories of none, mild, and moderate/severe intensity score; localization was classified as stromal, periglandular, and glandular. For grade of focal atrophy, a 3-level ordinal variable was used for the categories of none, grade 1/grade 2, and grade 3/grade 4.

Nonparametric tests were used to compare age at diagnosis in relation with focal atrophy and inflammation. χ^2 tests were used to evaluate associations between the types of focal atrophy, presence of