Clinical significance of proliferative inflammatory atrophy in prostate biopsy

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Abstract

Introduction: Proliferative inflammatory atrophy (PIA) is a frequently observed lesion in prostate biopsies and some authors have postulated its involvement in prostate carcinogenesis. However, the mechanisms that would permit its neoplastic transformation and the clinical significance of its finding in a prostate biopsy are currently not well known.

Objective: To analyze the characteristics of the PIA lesion, its possible role in prostate carcinogenesis and its relation with the tumor aggressiveness.

Materials and method: A systematic review was made of the literature in PubMed with the terms «proliferative inflammatory atrophy» or «PIA» and «prostate.» The most important findings are summarized in accordance with the study objective.

Results: PIA seems to be involved in prostate carcinogenesis. This hypothesis is based on its frequent association to cancer lesions (CaP) and on some genetic alterations that are common to the high grade prostatic intraepithelial neoplasia (HGPIN) and to the CaP, fundamentally deficit in GSTP1 expression and overexpression of AGR2. Currently, there are no epidemiological studies that evaluate the incidence of PIA or its association with HGPIN and CaP. Only one study, carried out by our group, has determined the global incidence of PIA in 30\% of the prostate biopsies, a lower association to CaP than the HGPIN lesion and an association between PIA and tumors of lower and insignificant grade.

Conclusions: PIA shares genetic alterations with HGPIN and CaP. Currently, there is no epidemiological evidence to consider that the PIA is associated to a greater incidence of CaP and the genetic and epidemiological data available suggest its association to not very aggressive tumors.

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Background

The prostate cancer (PC) is the most commonly diagnosed solid neoplasm and the second leading cause of death among men in industrial countries. Increased life expectancy and the slow natural progress of PC make it an increasingly prevalent disease. The use widespread of the prostate-specific antigen (PSA) test has enabled its early diagnosis, which has also resulted in a reduction in its mortality.¹

The traditional methods of diagnostic suspicion, PSA and/or rectal examination and random prostate biopsy are highly sensitive but nonspecific. This leads to the excessive performance of prostate biopsies. With the current prostate biopsy schemes, based on a minimum of 10–12 punctures, it is possible to achieve detection rates greater than 35% in first biopsies and approximately 20% in repeated biopsies.²

The theory of epithelial tissue damage followed by its regeneration, in the context of inflammation, is one of the more accepted in prostate carcinogenesis.³ Proliferative inflammatory atrophic (PIA) lesions have been proposed as precursor lesions of PC⁴;⁵; however, their role is still not well defined.

In the present article, we review the characteristics of PIA lesions and their biological potential in prostate carcinogenesis and in tumor aggressiveness.

Inflammation and prostate cancer

Tissue damage followed by cell repair in the presence of inflammation or various toxic, dietary or environmental agents promotes the formation of free oxygen radicals. It is thought that these radicals could be involved in prostate carcinogenesis, either by a genomic lesion or by creating an environment rich in cytokines and growth factors that promote replication and angiogenesis in the repair tissue. These disorders sustained over time can create a fertile environment for carcinogenesis.⁴³⁵⁷

A recent meta-analysis, which included 20 studies and a total of 25,768 patients, concluded that the continued consumption of nonsteroidal anti-inflammatory drugs was associated with a reduction in the risk of PC (OR=0.92; 95% IC: 0.86–0.97).⁸ The association between prostatitis and PC has been widely studied without conclusive results. Another meta-analysis, published in 2002, observed a slight increase in PC in patients with a history of sexually transmitted diseases, indicating that secondary inflammation could be related to this increase.⁹ Another suggested cause of prostate carcinogenesis is the increase in testosterone secretion as a result of an inflammatory process at a young age, suggesting that this increase could expose these patients to increased proliferative signals.¹⁰ In 2010 Cheng et al. observed similar results; however, they suggest the possibility that the increase in the detection of PC could be associated with the greater monitoring of these patients.¹¹

Characteristics of the proliferative inflammatory atrophic lesion

PIA is often associated with all types of inflammatory processes, acute and chronic, and it has been proposed as a precursor lesion of PC, directly or through the
development of high-grade prostatic intraepithelial neoplasia (HGPIN). In normal conditions, prostate cells are controlled by proliferative and antiproliferative signals that maintain the glandular balance. However, this balance could change in PIA lesions as a result of the repeated processes of tissue damage and repair secondary to the action of various toxic factors, which cause a cell instability that promotes carcinogenesis.

The lesions from prostatic atrophy and its anatomopathological variants were described in 1954. However, in 2006, the lesions were popularized as a result of the creation of a workgroup to standardize their classification. Androgenic suppression is associated with diffuse prostatic atrophy; however, it is the focal lesions that have been implicated in prostate carcinogenesis. Focal atrophy lesions include simple atrophy, with or without cystic formations; postatrophic hyperplasia; partial atrophy; sclerotic atrophy; and PIA. Although all variants are characterized as having acinar cells with scarce cytoplasm, hyperchromatic nuclei and monolayered structure, PIA lesions present a proliferative epithelium with morphological and molecular characteristics similar to those of PC. A number of authors have considered these PIA lesions as premalignant lesions. Supporting this hypothesis, Taking et al. in 2007 observed PIA lesions in specimens of radical prostatectomy with greater frequency than in specimens of prostatic adenomectomy, where foci of simple atrophy was preferentially observed.

The PIA lesions share various aspects with HGPIN and PC. Morphologically, their epithelial cells resemble neoplastic cells, given that they exhibit an increase in nuclear size, a loss of the nuclear-cytoplasmic ratio and a prominent nucleolus (Fig. 1). They are frequently associated with HGPIN and PC lesions in specimens of radical prostatectomy and also have a peripheral arrangement that is typically multifocal.

**Involvement of proliferative inflammatory atrophy in prostate carcinogenesis**

A number of studies have found genetic abnormalities in PIA lesions, shared by HGPIN and PC, such as gains in chromosome 8p and 8q24. Both lesions are clearly involved in prostate carcinogenesis and contain genes whose alteration has been related to the development of PC (Table 1). Other studies have observed increased expression of the antiapoptotic Bcl-2 protein.

The glutathione S-transferase 1 (GSTP1) gene encodes an enzyme responsible for eliminating DNA damaged by oxidative stress. In the normal prostatic epithelium, its activity is limited to the basal compartment, although its expression increases in conditions of cellular stress, as well as in PIA lesions. However, in up to 90% of PC lesions and in 70% of HGPIN lesions, GSTP1 is underexpressed due to hypermethylation in its promoter region. In contrast to these data, this hypermethylation has been found in 6% of PIA lesions. Although we do not know the implication of this finding for clinical practice, the loss of GSTP1 functionality in PC could increase susceptibility to gene damage secondary to oxidizing agents, resulting in the transformation of its cells with characteristics similar to those of HGPIN and PC.

The anterior gradient 2 (AGR2) gene encodes the AGR2 protein that acts as a chaperone, binding proteins damaged by oxidative stress and facilitating their elimination to the extracellular space. There are a number of studies that have verified the overexpression of AGR2 in HGPIN and PC lesions compared with benign tissue. The overexpression of AGR2 has also been observed in PIA lesions. The increased expression of AGR2 in PC is mainly observed in low-grade tumors (Gleason 2 and 3), and its expression decreases as the grade increases. This fact has led to the suggestion that PIA could be involved in the initial process of prostate

![Figure 1](http://www.elsevier.es) Pathology characteristics of the PIA lesion. (A) PIA lesion characterized by angulated atrophic glands with proliferative epithelium and surrounded by active chronic inflammatory cellularity (H&E 200×). (B) At considerable magnification (H&E 1000×), the glandular proliferative epithelium is observed with nuclear disorder, large nuclei and the presence of nucleoli (arrow).
carcinogenesis. Recently, it has been observed that AGR2 expression is increased in the urine sediment of patients diagnosed with PC compared with that of patients without cancer. It has also been observed that the increase is greater in patients with low-grade cancer.

Our group has studied and compared the genetic signatures of PIA, HGPIN and PC lesions with the peripheral benign tissue in a series of 20 radical prostatectomy specimens that contained all the lesions. The RNA microarray study demonstrated that the PIA lesions expressed 379 genes differentially compared with normal tissue. In addition, the PIA lesions expressed 15 genes jointly with HGPIN and 83 genes jointly with PC; 14 genes were expressed simultaneously by the 3 lesions. These genes were primarily associated with processes of inflammation, apoptosis, angiogenesis and cellular adhesion. The verification of these findings was performed using reverse transcription polymerase chain reaction in the 10 genes that were expressed in a more differential manner. We also conducted the immunohistochemical study of AGR2. We confirmed that AGR2 expression was increased in the PIA, HGPIN and PC lesions, while its expression was silenced in the normal peripheral tissue.

The molecular changes related to PC show extensive heterogeneity both on an interindividual basis and within the same prostate. This diversity suggests that there is no dominant route in prostate carcinogenesis. This heterogeneity could also justify the variability in the clinical behavior of apparently similar tumors. All of these suggest a hypothesis that recognizes various mechanisms through which the tumors develop, including variations in aggressiveness.

Table 1 Genetic disorders in chromosome 8, shared by PC, HGPIN and PIA.

<table>
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<th>Function</th>
<th>PC</th>
<th>HGPINa</th>
<th>PIAb</th>
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<td>Losses 8 p (%)</td>
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<td>NKX3.1</td>
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<td>MSR1 (Macrophage scavenger receptor 1)</td>
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<td>Gains 8 q (%)</td>
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Source: Woenckhaus et al.15

a Samples obtained from patients with PC.
b Samples obtained from patients with no PC.

Incidence of proliferative inflammatory atrophic lesions and clinical significance

In order to analyze the clinical importance in regular practice of the finding of a PIA lesion in a prostate biopsy, our group analyzed 528 biopsies performed by serum increase of PSA and/or suspicious rectal examination. The overall incidence of PIA was approximately 30%. When PIA lesions were detected, the likelihood of finding PC was 27% compared to 42% when a PIA lesion was not detected (OR: 0.512; 95% CI 0.342–0.767). Additionally, when PC was diagnosed concomitantly with PIA, the tumor was insignificant in 48% of the cases. Lacking other studies confirming these results, we suggest that PIA lesions could be associated with a lower probability of PC, and when these are detected they increase the likelihood of PC when compared to an insignificant cancer.

Conclusions

PIA seems to be involved in prostate carcinogenesis. This hypothesis is based on the frequent association with cancer foci and in a number of genetic disorders that are common to HGPIN and PC, mainly GSTP1 expression deficit and AGR2 overexpression. Nevertheless, when PIA is associated with PC there is a greater likelihood that the tumor will be less aggressive.

Conflict of interest

The authors declare that they have no conflicts of interest.

References