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Clinical significance of prostatic proliferative inflammatory atrophy

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Tittle: Clinical significance of prostatic proliferative inflammatory atrohpy

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ABBREVIATIONS

%fPSA: percent free PSA

95% CI: 95% confidence interval

ABBREVIATIONS

AIP: Asymptomatic inflammatory prostatitis

CBP: Chronic bacterial prostatitis

CDKN1B:

COX-2: Cyclooxygenase 2

CTL: cytotoxic T lymphocytes

DRE: Digital rectal exam

FDA: Food and drug administration

GSTP1:

HGPIN: High-grade prostatic intraepithelial neoplasia

IL-17: Interleukin-17

mCRPC: metastatic castration resistant prostate cancer

MRI: magnetic resonance imagin

NIH: National Institutes of Health

NO: nitric oxide

OR: Odds ratio

PAH: Postatrophic hyperplasia

PB: Prostate biopsy

PCa: Prostate cancer

PCA3: *prostate cancer antigen* 3

PD-1L: inhibitor receptor programmed death 1 ligand

PD1: inhibitor receptor programmed death 1

phi: Prostate Health Index

PhiP: 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine

PIA: Proliferative inflammatory atrophy

PSA kinetics: PSAV and PSADT

PSA: prostatic specific antigen

PSAD: PSA density

PSADT: PSA doubling time

PSAV: PSA velocity

PV: prostate volume

ROS: reactive oxygen species

RP: Radical prostatectomy

RR: relative risk

SA: Simple atrophy

STI: sexually transmitted illness

T_{reg}:Regulatory T cells

UTI: urinary tract infection

ABSTRACT

Background: Proliferative inflammatory atrophy (PIA) has been involved in prostatic carcinogenesis. Proliferative epithelium in PIA may progress to high-grade prostatic intraepithelial neoplasia (HGPIN) or adenocarcinoma or both. However, little is known about the clinical significance of a PIA finding in negative prostate biopsies (PBs). A preliminary review of the current literature has been done.*(1st article)*

Objectives: 1)Determine the incidence of PIA in PBs with and without prostate cancer (PCa) and RPs, its association to HGPIN and tumor aggressiveness.*(2nd article)*

2)Determine the prognostic value of PIA finding in a negative PB regarding PCa risk and agressiveness.*(3rd article)*

Methods: Retrospective and observational study of PIA lesion in 528 extended PBs and 200 RPs. Outcome measurements: PIA, HGPIN, PCa incidence, Gleason score, clinical and pathologic tumor stage and insignificant tumor rate.*(2nd article)*

Retrospective and observational study of 474 men scheduled to repeated PBs. Assessment of PIA and its extension in the previous biopsy. PCa detection rate and tumor aggressiveness. Age, serum total PSA, free PSA, percent free PSA (%fPSA), digital rectal exam (DRE), prostate volume (PV), PSA density (PSAD), PSA kinetics (PSAV and PSADT) findings of PIA and HGPIN and number of affected cores in previous PBs were included in the univariate and multivariate analysis. Aggressive tumors were considered when any Gleason pattern 4 was found.*(3rd article)*

Results: Overall incidence of PIA and HGPIN was 30.3% and 54% in extended PBs. In RPS, the incidence was 30.5% and 72%, respectively. No significant association was found between PIA and HGPIN. Overall PCa detection rate in PBs was 38.1%. PCa was found in 27.5% PBs with PIA and 42.7% of those without PIA, $p<0.001$. In contrast, PCa was detected in 50.9% of PBs with HGPIN and 23% of those without HGPIN, $p=0.001$. Multivariate analysis revealed that PIA decreased the risk of PCa, OR: 0.59 (95%CI:0.37–0.95), $p=0.029$, while HGPIN increased OR: 3.16 (95%CI:2.04–4.90), $p=0.001$. PIA was not related to Gleason grade and clinical stage, however it was associated to an insignificant tumors increase, OR:3.08 (95%CI:1.09–8.7), $p=0.033$. The information in RPs suggests that PIA is associated with less aggressive tumors and a higher probability of insignificant tumors.*(2nd article)*

In the analysis of 474 men that underwent repeated PBs, PCa was detected in 133 men (28.1%). Age, serum total PSA, %fPSA, PV, PSAD, PSAV, PSADT and PIA finding were significantly associated to PCa detection. However, only age, OR:1.061 (95%CI:1.025-1.098), $p=0.001$; DRE, OR:1.755 (95%CI:1.054-2.923), $p=0.031$; %fPSA, OR:0.963 (95%CI: 0.933-0.996), $p=0.028$; PV, OR:0.983 (95%CI:0.972-0.994), $p=0.002$ and PIA

finding, OR:0.491 (95%CI:0.291-0.828), p=0.008, were independent predictors of PCa detection. PCa was found in 18% of 159 men with previous PIA finding while in 33% of 315 men without previous PIA (p=0.001). None of the studied parameters including PIA in the previous biopsy were related with subsequent PCa aggressiveness. *(3rd article)*

Conclusions: 1)PIA lesion is found in 30% of extended prostate biopsies, only 27% of PBs with PIA had PCa. PIA incidence in RPs was 32%.

2)The finding of PIA in prostate biopsies is not related with HGPIN finding in PBs nor in RPs. PIA finding is related to a lower risk of associated PCa. If PCa is present in prostate biopsies, the finding of PIA is associated to less aggressive and insignificant tumors. The presence of PIA in RPs was associated to less aggressive and insignificant tumors.

3)PIA lesion can be identified in 30% of patients with a negative PB. PIA finding in negative prostatic biopsies represents a decreased risk of PCa detection in future repeated PBs due to persistent PCa suspicion. There is no relation between PIA lesion in negative prostate biopsies and PCa aggressiveness in further biopsies.

SUMMARY

Acknowledgements

Abbreviations

Abstract

Introduction

       Motivation

       Work hypothesis

       Objective

       Methodology

Main part / Body of the thesis

- Clinical Significance of Proliferative Inflammatory Atrophy in Prostate Biopsy. Celma, A., Servian, P., Planas, J., Placer, J., Quilez, M. T., Arbos, M. A., de Torres, I., and Morote, J. 2013. Actas Urol Esp. 10.1016/j.acuro.2013.04.008.

- Clinical Significance of Proliferative Inflammatory Atrophy Finding in Prostatic Biopsies. Servian, P., Celma, A., Planas, J., Placer, J., de Torres, I., Olivan, M., Morote, J. 2015. Prostate 2015;75(14):1669-1675

- Clinical Significance of Proliferative Inflammatory Atrophy in Negative Prostatic Biopsies. Servian, P., Celma, A., Planas, J., Placer, J., de Torres, I., Morote, J. *Submitted to Prostate April 2016.*

Discussion

Conclusions

Bibliography

Annex 1

Introduction

PCa is the most frequent neoplasm in men and will be diagnosed in approximately 180890 US men in 2016. It is the second cause of cancer death among men, around 26120 men will die from this disease in 2016[1].

Age, race and genetic factors have been described as casual factors, however some exogenous factors have also been described. With the improvement of life expectancy and quality of live of western countries, prostate cancer has become a more prevalent illness. Its natural history, allows early diagnosis of the illness and the chance to select a curative treatment in many cases.

As exogenous factors we should highlight inflammation produced by different factors such as infections, diet, hormonal changes and urinary reflux. Prostatic inflammation is a very common entity. The NIH classification of prostatitis syndromes includes: Type I: Acute bacterial prostatitis which is associated with severe prostatitis symptoms, systemic infection and acute bacterial urinary tract infection (UTI). Type II: Chronic bacterial prostatitis (CBP), which is caused by chronic bacterial infection of the prostate with or without prostatitis symptoms and usually with recurrent UTIs caused by the same bacterial strain. Type III: Chronic prostatitis/chronic pelvic pain syndrome, which is characterized by chronic pelvic pain symptoms in the absence of UTI. Type IV: Asymptomatic inflammatory prostatitis (AIP) which is characterized by prostate inflammation in the absence of genitourinary symptoms[2]. Type IV prostatitis is described in many prostate biopsies, autopsies and in the tissue obtained during transurethral resection of the prostate.

Prevalence of chronic inflammation of the prostate varies from 77% of the REDUCE study[3] to 35% of Ugurlu et al. study[4]. The high prevalence of chronic inflammation may be due to inclusion criteria of the study that selected older men and excluded men with clinical prostatitis or severe lower urinary tract symptoms. The most accepted prostatic inflammatory factors are infections, diet, *corpora amylacea*, hormonal changes and urinary reflux.

Only in 5-10% of prostatitis episodes a bacteria is detected, the most frequent are *E.coli, Enterococcus spp, Pseudomonas spp, Proteus mirabillis, Klebsiella spp and Serratia spp.* Many studies have tried to find a correlation between prostatitis and prostate cancer Dennis et al. conducted a meta-analysis where they found an increased risk of prostate cancer among men with a history of prostatitis OR:1.6 (95%CI:1.0-2.4), particularly with population-based case-control studies OR:1.8 (95%CI:1.1-3.0). Increased relative risk

estimates were also seen among men with a history of syphilis and a history of gonorrhea[5].

Sarma et al. explored the chronic inflammation hypothesis of prostate cancer development among black men by examining sexual activity, sexually transmitted diseases and prostatitis in a population based study of 129 patients and 703 controls 40 to 79 years old. After adjusting for age, income, cigarette smoking, and history of digital rectal examination and prostate specific antigen tests in the last 5 years, they observed that a history of gonorrhoea infection and prostatitis increased prostate cancer OR:1.78 (95%CI:1.13-2.79) and OR:4.93 (95%CI:2.79-8.74), respectively. Men reporting 25 or more sexual partners were more likely to be diagnosed with cancer OR:2.80 (95%CI:1.29-6.09) compared to men with 5 or fewer partners. They concluded that their findings support the significance of prior sexual practices, exposure to sexually transmitted microbial agents and history of prostatic infection in the natural history of prostate cancer in black men[6].

On the other hand, Sutcliffe et al.[7] conducted a study from 1992 to 2002, where participants were asked to report their histories of gonorrhoea, syphilis, and clinical prostatitis by mailed questionnaire. Prostate cancer diagnoses were ascertained by self-report on the 1994 and each subsequent biennial follow-up questionnaire and confirmed by medical record review. Of the 36033 participants in this analysis, 2263 were diagnosed with prostate cancer between the date of return of the 1992 questionnaire and 2002. No association was observed between gonorrhoea RR:1.04 (95%CI:0.79-1.36) or syphilis RR:1.06 (95%CI:0.44-2.59) and prostate cancer. Overall null results were also observed between clinical prostatitis and prostate cancer RR:1.08 (95%CI:0.96-1.20), although a significant positive association was observed among younger men (<59 years) screened for prostate cancer RR:1.49 (95%CI:1.08-2.06). Therefore these authors concluded that gonorrhoea and syphilis did not seem to be risk factors for prostate cancer in this cohort of men with a lower burden of sexually transmitted infections. Clinical prostatitis was also unlikely to be a risk factor, although possible roles for prostatitis in younger men and asymptomatic prostatic infection and inflammation could not be ruled out.

As Palapattu et al. said in 2004, novel insights into the development of human prostate cancer have emerged that implicate the process of chronic inflammation in prostate carcinogenesis. Epidemiological studies of prostatitis and sexually transmitted infections and genetic epidemiological investigations of key somatic genetic alterations and germ line variants have formed the foundation of the proposed link between inflammation and prostate cancer. Inflammation regardless of aetiology is thought to incite carcinogenesis by

causing cell and genome damage, promoting cellular replacement and creating tissue microenvironment rich in cytokines and growth factors that can enhance cell replication, angiogenesis and tissue repair[8].

Advances in molecular pathology and in our understanding of inflammatory toxicology have reinforced this hypothesis even further. Some diets contain recognised mutagens such as heterocyclic amines. Nakai et al.[9] exposed rats to 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), a heterocyclic amine in cooked meat. As a result this amine caused cancer in the rat ventral prostate. They examined the prostate and other organs for mutation frequencies using transgenic Fisher344 rats (Big Blue rats) after PhIP treatment. After PhIP treatment for as early as 4 weeks, the colon, spleen, seminal vesicles, and all lobes of the prostate had significantly elevated mutation frequencies compared with the saline-treated control group, and the differences became even greater after 8 weeks. G:C→T:A transversions were the predominant type of mutation. After 8 weeks of treatment with PhIP, the Ki-67 index was increased (p<0.001) in the ventral prostate, but not in the dorsolateral or anterior prostate. An increase in the number of stromal mast cells and macrophages was seen in the ventral prostate, but not in the other prostatic lobes. The apoptotic index also increased in the ventral lobe only. The increased proliferation and cell death in response to PhIP indicates that in addition to PhIP acting as an "initiator" of cancer, PhIP is also acting like an organ- and lobe-specific tumor "promoter." The prostate lobe-specific infiltration of mast cells and macrophages in response to PhIP suggests a potential new mechanism by which this dietary compound can increase cancer risk-by prompting inflammation.

Animal models of prostate inflammation provide a unique laboratory venue in which the development of prostate cancer can be studied. The future examination of known animal models of prostate cancer and prostate inflammation, and the relationship between the two, may uncover new perspectives on prostate carcinogenesis and reveal novel targets for prevention and therapy[8].

Inflammation is a complex phenomenon consisting of humoral (cytokines and chemokines) and cellular components (leukocytes, lymphocytes and granulocytes) The purpose of the inflammatory response is thought to be the creation of a tissue microenvironment that promotes the recognition and repair of cellular damage as well as the eradication of foreign particles, infected cells and irreparably damage cells. The primary mediators of the non specific host immune defence system are free radicals, predominantly

nitric oxide (NO) and reactive oxygen species (ROS) are the most commonly linked to the deleterious oxidative effects of inflammation. These reactive species can alter protein structure and function and induce somatic gene changes[10]. Free radicals have been shown to cause post-translational modifications of several key proteins, including those involved in DNA repair, apoptosis, cell signalling and essential enzymatic pathways[11-13]. Experimental non-prostatic models of chronic inflammation have revealed that NO is able to cause structural changes to p53 that can affect its function[14].

The inflammation identified in prostate cancer is most commonly chronic, composed by lymphocytes and macrophages, acute inflammation is less present and is composed by neutrophils. Over the last years the inflammatory cells infiltrating the prostate have been characterized. Regulatory T cells (T_{reg}), identified by high coexpression of CD4 and CD25 markers, have been investigated for a role as suppressors of antitumor immune responses[15]. $CD4^+$ $CD25^{high}$ T cells were first reported in tumour tissues and peripheral blood of prostate cancer patients in 2006[16]. The presence of infiltrating T_{reg} in solid tumours have been correlated with poor prognostic outcome[17]. The significance of elevated levels of T_{reg} in the prostate remains unclear, but T_{reg} in prostate tumors may have a potential effect on cancer immunotherapy strategies.

Another protein of interest is PD1 (inhibitor receptor programmed death 1), a cell surface protein associated with inhibition of T cell responses. A number of human tumours have been found to express PD-1L (B7-H1) [18], and expression of PD-1 on cytotoxic T lymphocytes (CTL) inhibits antitumor effector function[19]. The binding of PD-1 with its major ligand (PD-1L) determines the inhibition of T lymphocyte proliferation. This serves to minimize the inflammatory damage to the surrounding tissues and promote CD4+ T cell differentiation into regulatory T cells (T_{reg}), thus preventing the development of autoimmunity by ensuring self-tolerance as well as the development of tolerance to tumor cells.

Recent therapeutic strategies for castration-resistant prostate cancer have focused on immunomodulation, especially the PD-1/PD-L1. Few cases of castration-resistant prostate adenocarcinoma have been tested simultaneously for presence of PD-1, PD-L1 and T lymphocytes in cancerous tissue. Massari et al. have quantified the PD-1/PD-L1 immune pathway and T lymphocyte infiltrates in patients with castrate-resistant prostate adenocarcinoma. Approximately 19 % of patients showed simultaneous high PD-1/PD-L1 immunoscores. Those ones were the best candidates for receiving targeted anti-PD-1/PD-L1 immunotherapy[20].
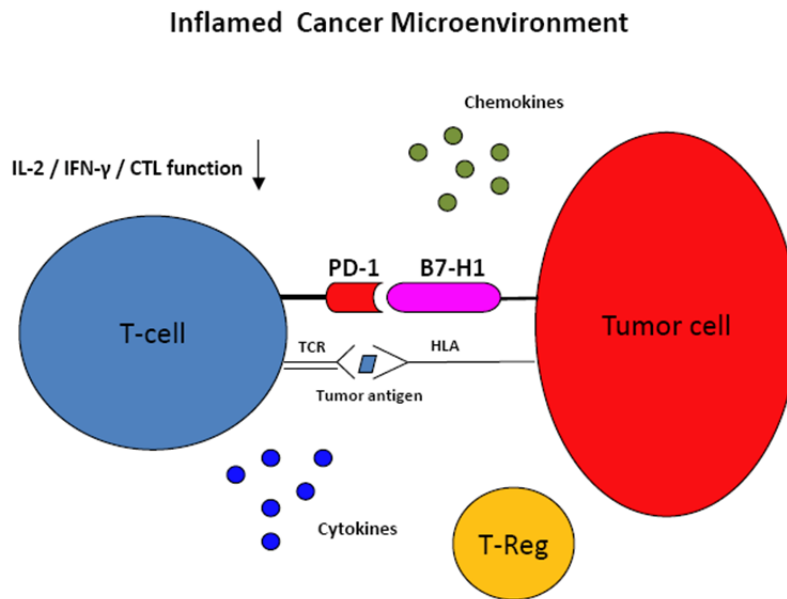
Inflamed Cancer Microenvironment

Figure 1. The B7-H1/PD-1 pathway in cancers associated with infections and inflammation: opportunities for therapeutic intervention[21]

Another example of treatment involving the immune system is Sipuleucel-T. It was approved in 2010 by the FDA for the treatment of minimally symptomatic metastatic castration resistant prostate cancer (mCRPC) based on the results of the IMPACT trial, a phase III double blind placebo controlled trial in which 512 patients were randomly assigned to receive sipuleucel-T every two weeks for a total of three doses or placebo[22]. Although logistical and financial constraints have somewhat limited the use of Sipuleucel-T in the clinic. In recent years, therapeutic cancer vaccines have emerged as a viable and promising treatment for prostate cancer.

Beyond Sipuleucel-T, phase III trials are evaluating multiple vaccine platforms in men with this disease. Growing data evaluating vaccine therapies suggests that these agents are more effective in patients with more indolent and possibly also earlier stages of disease. In addition, a variety of preclinical data has shown that traditional prostate cancer treatments including anti androgens, cytotoxic and radiation therapies may provide immunologic synergy when given in combination with vaccines. Numerous clinical trials are evaluating therapeutic cancer vaccines in early stage prostate cancer and also in combination with traditional prostate cancer therapies. While studies have suggested that single agent immune checkpoint inhibitors may have limited clinical utility with this disease, there is data supporting the idea that therapeutic vaccines have the potential to turn T-cell poor tumors into T-cell rich tumors and potentiate the efficacy of anti-PD1/PDL1 therapies. Ultimately vaccines added to definitive therapy, perhaps with anti-androgens and/or

PD1/PDL1 inhibition, could be used in the neoadjuvant or adjuvant settings to enhance the cure rate of clinically localized disease at high risk for recurrence. We are just beginning to understand the antineoplastic capability of the immune system and it seems likely that vaccine therapies will have a crucial role in optimizing these anti-tumor immune responses[23].

On the other hand, T helper 17 CD4^{+} is a particular type of T cell that produces interleukin-17 (IL-17), which seems to be related with autoimmune illnesses and tumours related to inflammation processes. Many studies suggest that inflammation in and around prostate cancer is associated with worse disease outcome. The risk of prostate cancer and high-grade prostate cancer also increased with the number of biopsies that contained chronic inflammation[24]. Moreover, genetic polymorphisms in inflammation-related genes and pathways have been studied[25,26]. These studies underline the potential importance of the interactions between inflammatory cytokines and inflammation pathways in conferring prostate cancer risk. Cyclooxygenase 2 (COX-2) is an inducible isoform of the enzymes that convert arachidonic acid to proinflammatory prostaglandins. Some studies have indicated that COX-2 may be overexpressed in prostate cancer [27,28], overexpression of this enzyme may be limited to areas of PIA, a postulated premalignat lesion to prostate cancer[29].

The term " proliferative inflammatory atrophy" (PIA) was proposed by De Marzo et al in 1999 [30] to designate focal simple or postatrophic hyperplasia occurring in association with inflammation. Only atrophy with hyperplasia of the basal cells shows a marked proliferative activity of the epithelia and a lower frequency of apoptosis in atrophic glands[31].
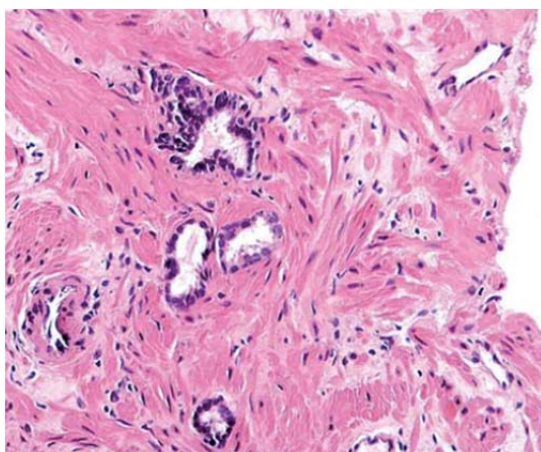

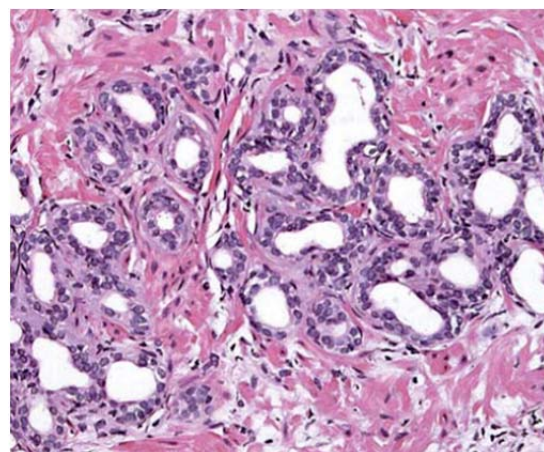Figure 2. Simple atrophy with inflammation[32]

Figure 3. Postatrophic hyperplasia with inflammation [32]

Morphologic transitions between PIA and high-grade prostatic intraepithelial neoplasia (HGPIN) occur frequently. The mere topographic relationship of the lesions is obviously not definitive proof of a continuum, but it is consistent with a model in which the proliferative epithelium in PIA may progress to HGPIN or adenocarcinoma or both[33].
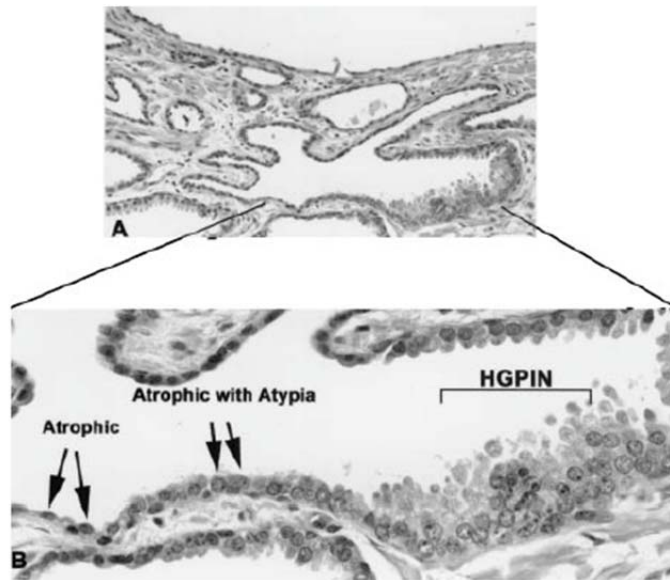
Figure 4. Morphologic transitions between atrophy and PIN. Apparent progression in atrophic cells from those containing no atypia (atrophic) to those containing mild nuclear atypia (atrophic with atypia) to those of PIN [33].

Actually, there is some evidence that supports PIA involvement in prostatic carcinogenesis suggested initially by De Marzo[34,35]. Secretory cells in PIA lesions have a proliferative phenotype, increased expression of Ki67 and decreased expression of p27. Similarly, signals of stress-induced response such as expression of Bcl-2 and heterogeneous areas of GSTP1 and COX-2 expression are also present. Several molecular pathways involved in PCa have also been shown to be altered in PIA lesions. Three prostate tumor-suppressor genes, NKX3.1, CDKN1B, and PTEN, highly expressed in normal prostate tissue and often decreased or absent in HGPIN and PCa, are all down regulated in PIA lesions[36]. Chromosomal abnormalities such as increases in chromosome eight centromere signals, loss of chromosome 8p and a gain of chromosome 8q24, similar to those found in HGPIN and PCa, also occur in PIA lesions.

Recent studies show that if we carefully select the sample population, we would be able to develop population-screening campaigns, in order to decrease cancer specific mortality[37-39]. Moreover, many studies indicate that age itself should not be the only

criteria to exclude healthy older patients from an early diagnosis or a curative treatment for prostate cancer[40].
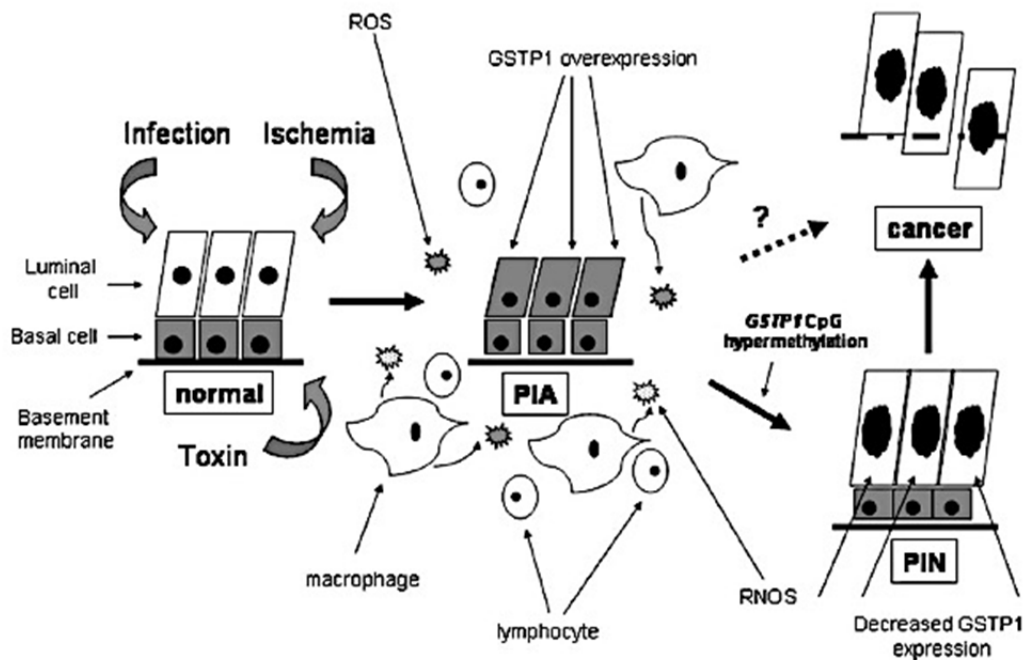
Figure 3. Proposed paradigm of proliferative inflammatory atrophy by Palapattu et al.[8].

DRE, PSA and ultrasound guided trans rectal PB are the classical diagnostic methods. All of them together are very sensitive but not very specific, this fact is the responsible of the huge amount of unnecessary prostate biopsies conducted every year all around the world. Prostate biopsy is a procedure that can lead to urinary sepsis and death in some patients. Only 30% of first prostate biopsies detect prostate cancer. That leads us to a big group of patients that will undergo repeated biopsies. The efficiency of the first repeated prostate biopsies oscillates from 18.7 to 39% [41].

Aware of these difficulties, many lines of research try to develop more specific diagnostic methods in order to make a better selection of the population that should undergo a prostate biopsy. New blood markers (prostate health index, 4K) and urine markers (prostate cancer antigen 3), seem to increase specificity when deciding to perform a prostate biopsy[42]. It would be interesting to find the best combination of markers to reduce the number of unnecessary prostate biopsies.

In this project we have focused in anatomo-pathological findings that could be related with the development of prostate cancer and therefore considered as premalignant lesions. The tissue damage theory followed by cellular reparation in presence of

inflammation or toxic factors has been proposed to play a role in prostate cancer carcinogenesis[34].

PIA lesions share characteristics with PIN and PCa: a) morphological characteristics and peripheral disposition[43] b) molecular aspects, this cells react to oxidative stress by expressing high levels of Glutathione S-transferase A1 (GSTA1) and ciclooxigenase 2 (COX-2) [29], p53 mutations and hipermethilation of glutathione S-transferase-pi (GSTP1) promoter gene.

Loss of GSTP1 function in PIA lesion could generate PIN cells and PCa by increasing cells genomic susceptibility to oxidative agents[44]. Overexpression of Ki-67 (cell replication marker) and Bcl-2 were found (contributor to resistance to apoptosis) in PIA. Decreased expression of p27 was found, as in HGPIN and PCa. And overexpression of K5 and c-MET[43]. On the other hand, immunohistological studies reveal that AGR2 protein is present in very low level in normal prostatic cels and overexpressed in PCa and HGPIN lesions[45].

Due to the actual need to find new PCa diagnostic markers, our group designed a study of 20 RP specimens. Various slices of each specimen were analysed in which coexisted benign, tumoral, HGPIN and PIA areas. After analysing the expression of various genes we concluded that PIA, HGPIN and PCa share the regulation of genes that intervene in extracellular matrix and collagen and proteoglycans regulation.

Among all the studied genes, AGR2 was the most upstream gene; in fact, AGR2 protein was mostly found overexpressed in tumoral lesions, HGPIN and PIA. With these results we believe that PIA lesions share processes and biological pathways with PCa that could contribute carcinogenesis of a simple PIA lesion. Similar gene regulation among these different lesions could have a predictive value. AGR2 has been postulated as an early diagnostic biomarker of PCa[46].

Work hypothesis

"Proliferative inflammatory atrophy" is a premalignant lesion involved in prostate carcinogenesis. Its detection in negative prostate biopsies could help us to predict future prostate cancer detection and help us to predict illness outcome in case of prostate cancer finding.

Objectives:

1. Describe the incidence of PIA in extended prostate biopsies with and without PCa. Describe the incidence of PIA in radical prostatectomy specimens.
2. Analyse the relationship between PIA and HGPIN and PCa in prostate biopsies and radical prostatectomy specimens. Analyse the relationship between PIA and tumor aggressiveness in prostate biopsies and radical prostatectomy specimens.
3. Determine the prognostic value of PIA finding in a negative prostate biopsy regarding PCa risk and agressiveness.

Methodology:

Systematic review of literature in PubMed with the terms <<proliferative inflammatory atrophy>> OR <<PIA>> AND <<prostate>>. *(1st article)*

Retrospective and observational study carried out in 528 consecutive PBs done from January 2011 until December 2012 due to elevation of serum PSA (> 4.0 ng/ml) and/or abnormal DRE. After analysing PBs we selected 200 consecutive RPs done from January 2013 until December 2014 in order to verify the tumor aggressiveness findings in PBs. Patients receiving five alpha reductase inhibitors or any hormonal treatment before PB or RP were excluded from the study. Informed consent for both procedures and study participation was obtained. *(2nd article)*

Reprospective and observational study carried out between January 2010 and February 2014. A group of 474 men with a previous negative biopsy men scheduled to repeat PB, due to persistent suspicion of PCa based on PSA behaviour and DRE, were selected. Men receiving 5 alpha reductase inhibitors and those with ASAP (atypical small acinar proliferation) were excluded from the study. Informed consent for repeated PB and study participation was obtained. The median time between first and repeat PB was 10 to 44 months. *(3rd article)*

Prostate biopsy procedure

PB was performed as an outpatient procedure under local anesthesia. An end-fire ultrasound transducer (Falcon 2101, BK Medical, Inc.) and a 16-gauge automated biopsy needle (Bard, Inc.) were used. A minimum of 10 cores were obtained, and two to eight additional cores were taken as determined by age and prostate volume according to a modified Viena nomogram[47]. RP was performed either laparoscopically or robot assisted.

Pathology characterization of PBs and RPs

From 2007, an experienced pathologist (IT) always informs about the findings of PIA and HGPIN in all PBs and RPs. PIA is described as focal simple atrophy (SA) or postatrophic hiperplasia (PAH) occurring in association with inflammation. SA characteristics: little amount of cytoplasm compared with normal epithelium, acini of relatively normal caliber, number of acini per unit area similar to normal acini. Presence of chronic inflammatory cells and a variable fibrosis of stroma. Acute inflammatory cells may also be present, but in fewer proportion of cases. PAH characteristics: little amount of cytosplasm, small and

mostly round glands situated very close to each other in a lobular distribution. Most of these lesions contain at least some chronic inflammatory cells in the stroma, epithelium, or lumen. Acute inflammatory cells may also be present[48]. Primary and secondary Gleason grade of tumor areas are assessed based on 2005 ISUP Modified Gleason System[49], number of affected cores and size and percentage of tumor core invasion. Primary and secondary Gleason grades, biggest tumor nodule maximal diameter, multifocality and percentage of tumor to prostate volume were systematically informed in RPs.

PCa clinical staging

Patients with cancer were staged according to 2002 TNM classification. Multi-parametric magnetic resonance and bone scan were performed if Gleason score was higher than seven, serum PSA over than 20 ng/ml or suspected T3 by DRE.

Assessment of PCa aggressiveness

Was done according to the Gleason grade and clinical stage. We also considered the diagnosis of insignificant cancer as cT1c, PSA density lower than 0.15 ng/ml/cc, less than three positive cores with less than 50% of cancer and no Gleason pattern four or five[50]. In RPs, insignificant tumor was considered for unifocal organ-confined tumors, maximal tumor diameter was less than 0.5cm and Gleason score was six.

Statistical analysis

Quantitative variables were expressed as medians semi-interquartile range (range). Qualitative variables were expressed as rates. Univariate analysis included X^2 test to analyze the association between qualitative variables and Cochran test to evaluate their strength. Mann-Whitney U test was performed to compare quantitative variables. Multivariate analysis using binary logistic regression was carried out to examine independent predictors of PCa risk and tumor aggressiveness characteristics. Odds ratio and 95%CI were calculated. SPSS program V.20 was used to perform statistical analysis.

MAIN PART / BODY OF THESIS

This project has been developed through the publication of the following scientific articles

1. Clinical Significance of Proliferative Inflammatory Atrophy in Prostate Biopsy.

> Celma, A., **Servian, P.**, Planas, J., Placer, J., M. T., Arbos, M. A., de Torres, I., and Morote, J. 2013.
> *Actas Urol Esp.* 10.1016/j.acuro.2013.04.008.
> Impact factor: 1.002; Area: Urology

2. Clinical Significance of Proliferative Inflammatory Atrophy Finding in Prostatic Biopsies.

> **Servian, P.**, Celma, A., Planas, J., Placer, J., de Torres, I., Olivan, M., Morote, J. 2015.
> *Prostate* 2015;75(14):1669-1675
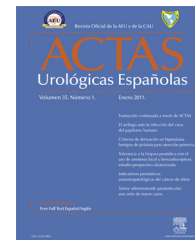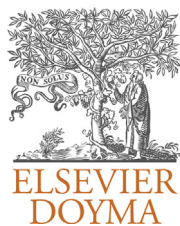> Impact factor: 3.565; Area: Urology

Annex

1. Clinical Significance of Proliferative Inflammatory Atrophy in Negative Prostatic Biopsies.

> **Servian, P.**, Celma, A., Planas, J., Placer, J., de Torres, I., Morote, J.
> *Submitted to Prostate April 2016.*
> Impact factor: 3.565; Area: Urology

Actas Urológicas Españolas

REVIEW ARTICLE

Clinical significance of proliferative inflammatory atrophy in prostate biopsy ☆

A. Celma [a,b,*], P. Servián [a,b], J. Planas [a,b], J. Placer [a,b], M.T. Quilez [b], M.A. Arbós [b], I. de Torres [c,d], J. Morote [a,b,d]

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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 epidemiologic 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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PALABRAS CLAVE
Atrofia proliferativa
inflamatoria;
Cáncer de próstata;
Agresividad tumoral

Significado clínico de la atrofia proliferativa inflamatoria en la biopsia prostática

Resumen

Introducción: La atrofia proliferativa inflamatoria (PIA) es una lesión frecuentemente observada en biopsias prostáticas, y algunos autores han postulado su implicación en la carcinogénesis prostática. Sin embargo, en la actualidad no se conocen bien los mecanismos que permitirían su transformación neoplásica ni el significado clínico de su hallazgo en una biopsia prostática.

Objetivo: Analizar las características de la lesión de PIA, su posible papel en la carcinogénesis prostática y su relación con la agresividad tumoral.

Material y método: Se realiza una revisión sistemática de la literatura en PubMed con los términos *proliferative inflammatory atrophy* o *PIA* y *prostate*. Se resumen los hallazgos más relevantes de acuerdo a los objetivos del estudio.

Resultados: La PIA parece estar implicada en la carcinogénesis prostática. Esta hipótesis se sustenta en su asociación frecuente con lesiones de cáncer (CaP) y en algunas alteraciones genéticas que le son comunes a la neoplasia intraepitelial de alto grado (HGPIN) y al CaP, fundamentalmente déficit en la expresión de GSTP1 y sobreexpresión de AGR2. Actualmente no existen estudios epidemiológicos que evalúen la incidencia de PIA ni su asociación con HGPIN y CaP. Un solo estudio, realizado por nuestro grupo, ha determinado la incidencia global de PIA en el 30% de las biopsias prostáticas, una menor asociación a CaP que la lesión de HGPIN y una asociación entre PIA y tumores de menor grado e insignificantes.

Conclusiones: La PIA comparte alteraciones genéticas con el HGPIN y el CaP. Actualmente no existe evidencia epidemiológica para considerar que la PIA se asocia a mayor incidencia de CaP y los datos genéticos y epidemiológicos disponibles sugieren asociación con tumores poco agresivos.

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 PC[4,5]; 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.[3,5–7]

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.[3] 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.[10]

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).[4,5,11] 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.[5]

The lesions from prostatic atrophy and its anatomopathological variants were described in 1954.[12] 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.[11] 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.[13]

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.[14,15]

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).[3,16] Other studies have observed increased expression of the antiapoptotic Bcl-2 protein.[4]

The glutathione S-transferase 1 (GSTP1) gene encodes an enzyme responsible for eliminating DNA damaged by oxidative stress.[17] 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.[4] In contrast to these data, this hypermethylation has been found in 6% of PIA lesions.[18] Although we do not know the implication of this finding for clinical practice, the loss of GSTP1 functionality in PIA 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.[19]

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.[20] There are a number of studies that have verified the overexpression of AGR2 in HGPIN and PC lesions compared with benign tissue.[20,21] The overexpression of AGR2 has also been observed in PIA lesions.[22] 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
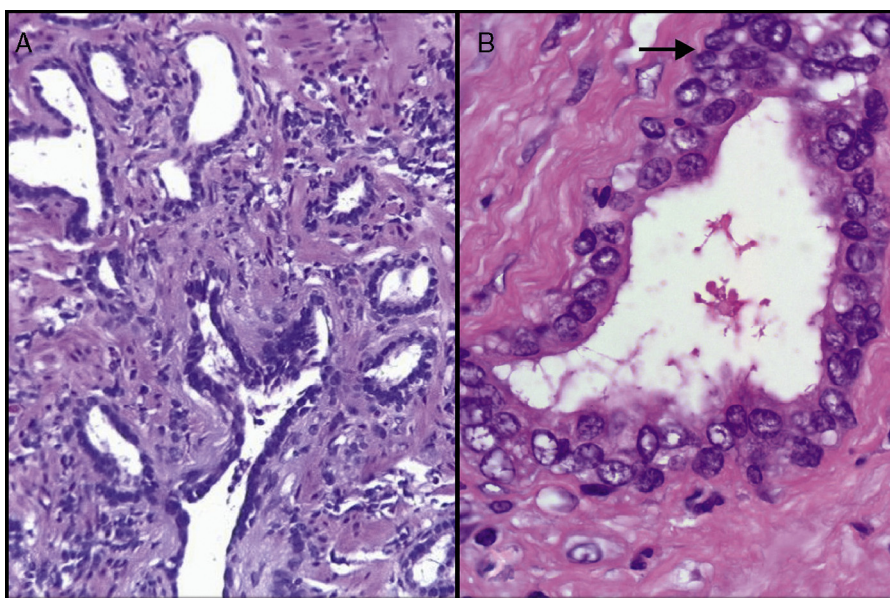

Figure 1 Pathology characteristics of the PIA lesion. (A) PIA lesion characterized by angulated atrophic glands with proliferative epithelium and surrounded by active chronic inflammatory cellularity (H–E 200×). (B) At considerable magnification (H–E 1000×), the glandular proliferative epithelium is observed with nuclear disorder, large nuclei and the presence of nucleoli (arrow).

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

	Function	PC	HGPIN[a]	PIA[a]	Normal epithelium[b]
Losses 8 p (%)		21.2	17.1	14.2	3.6
NKX3.1	Prostatic organogenesis				
MSR1 (Macrophage scavenger receptor 1)	Macrophage activity against infection				
Gains 8 q (%)		15.2	12.7	11.5	2.3
c-myconcogene	Various carcinogenic routes				

Source: Woenckhaus et al.[15]
[a] Samples obtained from patients with PC.
[b] Samples obtained from patients with no PC.

carcinogenesis.[20,21] 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.[21]

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.[22,23]

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.[6] 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.

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.[24]

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.

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Clinical Significance of Proliferative Inflammatory Atrophy Finding in Prostatic Biopsies

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BACKGROUND. Proliferative inflammatory atrophy (PIA) has been involved in prostatic carcinogenesis. However, little is known about the clinical significance of a PIA finding in prostatic biopsies (PBs). The aim of this study is to determine the incidence of prostate inflammatory atrophy (PIA) in prostate biopsies (PBs), its association to high-grade prostatic intraepithelial neoplasia (HGPIN), prostate cancer (PCa), and tumor aggressiveness.

METHODS. Prospective and observational study of PIA lesion in 528 extended PBs and 200 radical prostatectomy specimens (RPS). Outcome measurements: PIA, HGPIN, PCa incidence, Gleason score, clinical and pathologic tumor stage and insignificant tumor rate. Univariate and multivariate analysis.

RESULTS. Overall incidence of PIA and HGPIN was 30.3% and 54%. In RPS, the incidence was 30.5% and 72%, respectively. No significant association was found between PIA and HGPIN. Overall PCa detection rate in PBs was 38.1%. PCa was found in 27.5% PBs with PIA and 42.7% of those without PIA, $P < 0.001$. In contrast, PCa was detected in 50.9% of PBs with HGPIN and 23% of those without HGPIN, $P = 0.001$. Multivariate analysis revealed that PIA decreased the risk of PCa, OR:0.59 (95%CI:0.37–0.95), $P = 0.029$, while HGPIN increased OR:3.16 (95%CI:2.04–4.90), $P = 0.001$. PIA was not related to Gleason grade and clinical stage, however it was associated to an insignificant tumors increase, OR:3.08 (95%CI:1.09–8.7), $P = 0.033$. The information in RPS suggests that PIA is associated with less aggressive tumors and a higher probability of insignificant tumors.

CONCLUSIONS. PIA is present in one third of PBs, HGPIN in one half of them, and no association exists between both lesions. Contrary to HGPIN, PIA finding is associated to lower risk of PCa detection. Tumors accompanying PIA seem to be less aggressive and have a greater probability of being insignificant. *Prostate* © 2015 Wiley Periodicals, Inc.

KEY WORDS: prostate cancer; high-grade prostatic intraepithelial neoplasia; tumor aggressiveness; prostate biopsies; radical prostatectomies

INTRODUCTION

Prostate cancer (PCa) is the most frequent neoplasm in men and will be diagnosed in approximately 23 3000 US men in 2014. It is the second cause of cancer death among men, around 2 9480 men will die from this disease in 2014 [1]. Inflammation caused by chemical, physical, or biological agents are known [2,3] as important co-factors in the pathogenesis of many human cancers [4]. According to the injury and regeneration model, inflammatory cells infiltrating the prostate release reactive species in response to infections, uric acid, or dietary prostate carcinogens.

The term "proliferative inflammatory atrophy" (PIA) was proposed by De Marzo et al in 1999 [5] to designate focal simple or postatrophic hyperplasia occurring in association with inflammation. Only atrophy with hyperplasia of the basal cells shows a marked proliferative activity of the epithelia and a lower frequency of apoptosis in atrophic glands [6]. Morphologic transitions between PIA and high-grade prostatic intraepithelial neoplasia (HGPIN) occur frequently. The mere topographic relationship of the lesions is obviously not definitive proof of a continuum, but it is consistent with a model in which the proliferative epithelium in PIA may progress to HGPIN or adenocarcinoma or both [7]. Actually, there is some evidence that supports PIA involvement in prostatic carcinogenesis suggested initially by De Marzo [2,8]. Secretory cells in PIA lesions have a proliferative phenotype, increased expression of Ki67 and decreased expression of p27. Similarly, signals of stress-induced response such as expression of Bcl-2 and heterogeneous areas of GSTP1 and COX-2 expression are also present. Several molecular pathways involved in PCa have also been shown to be altered in PIA lesions. Three prostate tumor-suppressor genes, NKX3.1, CDKN1B, and PTEN, highly expressed in normal prostate tissue and often decreased or absent in HGPIN and PCa, are all down-regulated in PIA lesions [9]. Chromosomal abnormalities such as increases in chromosome eight centromere signals, loss of chromosome 8p and a gain of chromosome 8q24, similar to those found in HGPIN and PCa, also occur in PIA lesions [9].

To date no clinical study has supported the hypothesis that PIA is involved in prostate carcinogenesis. The objectives of this study were: (i) describe the incidence of PIA in actual extended prostate biopsies (PBs), (ii) analyse its relationship with HGPIN and PCa, and (iii) analyse the relationship between PIA and tumor aggressiveness.

MATERIAL AND METHODS

Study Design and Participants

Prospective and observational study carried out in 528 consecutive PBs done from January 2011 until December 2012 due to elevation of serum PSA (>4.0 ng/ml) and/or abnormal digital rectal examination (DRE). After analysing PBs we selected 200 consecutive radical prostatectomy specimens (RPS) done from January 2013 until December 2014 in order to verify the tumor aggressiveness findings in PBs. Patients receiving five alpha reductase inhibitors or any hormonal treatment before PB or RP were excluded from the study. Informed consent for both procedures and study participation was obtained. PCa was detected in 201 patients (38.1%) of PBs. Clinical characteristics of the patients subjected to PB are summarized in Table I..

Transrectal Ultrasound Guided PB Technique

PB was performed as an out patient procedure under local anesthesia. An end-fire ultrasound transducer (Falcon 2101, B–K Medical, Inc.) and a 16-gauge automated biopsy needle (Bard, Inc.) were used. A minimum of 10 cores were obtained, and two to eight additional cores were taken as determined by age and prostate volume according to a modified Viena nomogram [10].

Pathology Characterization of PBs and RPS

From 2007, an experienced pathologist (IT) always informs about the findings of PIA and HGPIN in all PBs and RPS. PIA is described as focal simple atrophy (SA) or postatrophic hyperplasia (PAH) occurring in association with inflammation. SA characteristics: little amount of cytoplasm compared with normal epithelium, acini of relatively normal caliber, number of acini per unit area similar to normal acini. Presence of chronic inflammatory cells and a variable fibrosis of stroma. Acute inflammatory cells may also be present, but in fewer proportion of cases. PAH characteristics: little amount of cytosplasm, small and mostly round glands situated very close to each other in a lobular distribution. Most of these lesions contain at least some chronic inflammatory cells in the stroma, epithelium, or lumen. Acute inflammatory cells may also be present [11]. Primary and secondary Gleason grade of tumor areas are assessed based on 2005 ISUP Modified Gleason System [12], number of affected cores and size and percentage of tumor core invasion. Primary and secondary Gleason grades, biggest tumor nodule

TABLE I. Characteristics of the patients subjected to PB

Patients, nº	528
Age*, years	67 ± 5.5 (43–84)
Serum PSA*, ng/ml	6.6 ± 2.1 (0.5–294.0)
Positive digital rectal exam, nº (%)	154 (29.2)
Prostatevolume*, cc	48 ± 14 (10–147)
PSA density*, ng/ml/cc	0.14 ± 0.6 (0.0–5.2)
Percent free PSA*, (%)	13.6 ± 4.9 (0.0–44.7)
Repeatedbiopsies, nº (%)	121 (22.9)
+ DRE** & PSA < 4.0, nº (%)	11 (2.1)
− DRE** & PSA 4.0 – 9.9, nº (%)	296 (56.0)
+ DRE** & PSA 4.0 – 9.9, nº (%)	93 (17.6)
− DRE** & PSA > 10, nº (%)	78 (14.8)
+ DRE** & PSA > 10, nº (%)	50 (9.5)
Proliferativeinflammatoryatrophy, nº (%)	160 (30.3)
High grade prostatic intraepithelial neoplasia, nº (%)	285 (54)
Prostatecancerdetection, nº (%)	201 (38.1)

PB: Prostate biopsy; PSA: Prostate specific antigen; DRE: digital rectal exam.

maximal diameter, multifocality and percentage of tumor to prostate volume were systematically informed in RPS.

PCa Clinical Staging

Patients with cancer were staged according to 2002 TNM classification. Multi-parametric magnetic resonance and bone scan were performed if Gleason score was higher than seven, serum PSA over than 20 ng/ml or suspected T3 by DRE.

Assessment of PCa Aggressiveness

Was done according to the Gleason grade and clinical stage. We also considered the diagnosis of insignificant cancer (IC) as cT1c, PSA density lower than 0.15 ng/ml/cc, less than three positive cores with less than 50% of cancer and no Gleason pattern four or five [13]. In RPS, insignificant tumor was considered for unifocal organ-confined tumors, maximal tumor diameter was less than 0.5 cm and Gleason score was six.

Statistical Analysis

Quantitative variables were expressed as medians $\pm$ semi-interquartile range (range). Qualitative variables were expressed as rates. Univariate analysis included χ^2 test to analyze the association between qualitative variables and Cochran test to evaluate their strength. Mann–Whitney U test was performed to compare quantitative variables. Multivariate analysis using binary logistic regression was carried out to examine independent predictors of PCa risk and tumor aggressiveness characteristics. Odds ratio (OR) and 95%CI were calculated. SPSS program V.20 was used to perform statistical analysis.

RESULTS

PIA was detected in 160 PBs (30.3%) and HGPIN in 285 (54%). No significant association between both lesions was observed, $P = 0.447$. PIA and HGPIN coexisted in 82 PBs (15.5%), none of these lesions were detected in 165 PBs (31.2%). In 117 PBs (14.7%) PIA without HGPIN was observed, and HGPIN without PIA was found in 203 (38.4%). In the subset of 201 PBs having PCa, PIA and HGPIN were present in 44 (21.9%) and 145 (72.1%), respectively, $P = 0.907$. In the subset of 327 PBs without PCa, PIA and HGPIN were present in 116 (35.5%) and 140 (42.8%) respectively, $P = 0.706$ (Fig. 1).

A significant but inverse association between PIA and HGPIN with the detection of PCa was observed. HGPIN was positively associated with PCa. HGPIN was detected in 145 of 201 PBs having PCa (72.1%), and 140 of 327 PBs without PCa (42.8%), OR: 3.459 (95%CI: 2.369–5.049), $P = 0.001$. On the contrary, PIA was negatively associated to PCa. PIA was found in 44 PBs having PCa (21.9%), and 116 without PCa (35.5%), OR: 0.510 (95%CI: 0.340–0.763), $P = 0.001$.

Table II summarizes clinical characteristics sorted by PIA finding in PB. It can be seen that age, serum PSA, percent free PSA, prostate volume, PSA density, rectal examination, repeated biopsies ratio and HGPIN finding ratio were similar in both groups. However, PCa detection rate was significantly lower
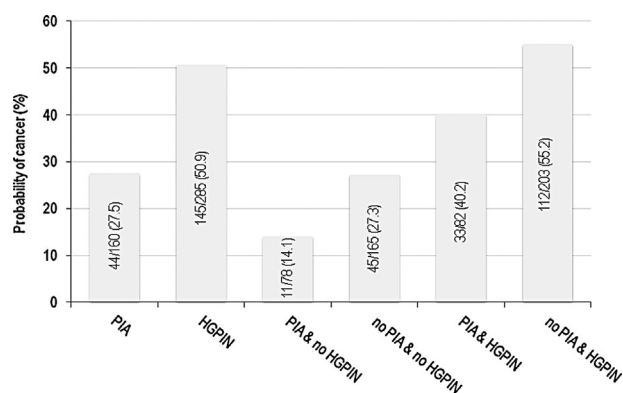
Fig. 1. Probability of PCa detection according to the finding of PIA or HGPIN and their combination in the PB.

in PBs containing PIA. PCa rate was 27.5% in PBs with PIA and 42.7% in PBs without PIA, $P < 0.001$.

A multivariate analysis to detect independent predictors of PCa was done. Age, serum PSA, rectal examination, type of biopsy (first vs. repeated), prostate volume, PIA, and HGPIN findings were included as co-variables. This analysis confirmed that a PIA finding predicted a decreased risk of PCa detection, OR: 0.594 (95%CI: 0.372–0.949), $P = 0.029$. On the contrary, a HGPIN finding predicted a significant increase of PCa detection, OR: 3.163 (95%CI: 2.044–4.895), $P < 0.001$, Table III. PCa rate distribution according to the presence or absence of PIA and HGPIN, is represented in Figure 1.

It is noteworthy that men with HGPIN experienced a significant decrease in PCa detection when PIA was present (55.2% vs. 40.2%), $P < 0.001$. In PBs without HGPIN, the risk of PCa detection was also decreased when PIA was present (27.3% vs. 14.1%), $P < 0.001$.

After the results above, we analysed the relationship between PIA and HGPIN findings with

parameters of PCa aggressiveness, Table IV. We did not observe significant associations between Gleason grade (score six vs higher), clinical stage (localized vs advanced) and histologic findings. However, the finding of PIA was significantly associated with a greater rate of insignificant tumors, $P < 0.001$. Multivariate analysis was carried out to analyse predictors for PCa aggressiveness. PIA, age, serum PSA and prostate volume were independent predictors of insignificant cancer.

In order to complement and validate these results, we have analysed tumor aggressiveness according to PIA presence in 200 RPS. Table V summarizes the results. We want to emphasize that RPS having PIA were associated to a significant higher rate of Gleason score six tumors (37.5% vs 22.1, $P = 0.018$), lower tumor volume, lower rate of perineural invasion (59.4% vs 74.3%, $P = 0.025$), lower rate of multi-focal tumors (54.5% vs 80.9%, $P = 0.001$), lower rate of positive margins (10.9% vs 19.8%, $P = 0.015$), and higher rate of insignificant cancers (17.2% vs 6.6%). The rate of HGPIN was high independently of PIA presence. Finally, we found that PIA incidence was similar in PBs and RPS (30.3 vs 32%), whereas HGPIN was more frequently reported in RPS (54% vs 91%).

DISCUSSION

The present study first demonstrates that PIA can be found in around one third of extended PBs while HGPIN is detected in more than one half. PIA was detected in almost 36% of PBs were cancer was not found and 22% in those with cancer. In contrast, HGPIN was present in 42% of PBs without cancer and 72% in those with cancer. We did not find an association between PIA and HGPIN results. As expected, HGPIN was associated to an increased risk

TABLE II. Characteristics of the patients according to the PIA finding in the PB

Characteristic	With PIA	Without PIA	P-Value
No patients	160 (30.3)	368 (69.7)	-
Age*, years	66 ± 5.5 (50–83)	66 ± 5.5 (43–82)	0.932
Serum PSA*, ng/ml	6.4 ± 2.3 (2.9–49.2)	6.5 ± 2.0 (0.5–28.9)	0.620
Positive digital rectal exam, n° (%)	35/211 (16.6)	25/116 (21.6)	0.297
Prostatevolume*, cc	50 ± 15 (10–139)	53 ± 14 (10–147)	0.720
PSA density*, ng/ml/cc	0.13 ± 0.05 (0.05–0.76)	0.13 ± 0.04 (0.02–1.54)	0.509
Percent free PSA*, (%)	15.4 ± 4.8 (0.1–30.7)	14.4 ± 19.7 (1.4–41.3)	0.189
Repeatedbiopsies, n° (%)	43 (26.9)	78 (21.8)	0.176
High grade intraepithelial neoplasia, n° (%)	82 (51.2)	203 (55.2)	0.447
Prostatecancerdetection, n° (%)	44 (27.5)	157 (42.7)	0.001

PB: Prostate biopsy; PIA: Proliferative inflammatory atrophy, PSA: Prostate specific antigen.

TABLE III. Multivariate Analysis of Predictors of PCa

Variable	OR (95%CI)	P-Value
Age, years	1.039 (1.010–1.070)	0.009
Total PSA, ng/ml	1.064 (1.009–1.123)	0.022
Digital rectal exam, positive versus negative	2.667 (1.680–4.233)	0.001
Prostate volume, cc	0.982 (0.972–0.992)	0.001
Free PSA, ng/ml	0.947 (0.704–1.269)	0.707
Type of biopsy, first versus repeated	3.163 (2.044–4.895)	0.001
PIA, yes versus no	0.594 (0.372–0.949)	0.029
HGPIN, yes versus no	3.163 (2.044–4.895)	0.001

PCa: Prostate cancer; PSA: Prostatic specific antigen; PIA: Proliferative inflammatory atrophy; HGPIN: High-grade prostatic intraepithe.

of PCa detection. On the contrary, the finding of PIA was associated to a decreased risk of PCa. This was a surprising but interesting result. Furthermore, PBs with HGPIN had decreased PCa rate if PIA was also found. We can summarize that, in contrast to HGPIN, PIA detection in a PB would be associated to a lower risk of associated cancer.

It is difficult to contrast our results because there is limited information about this topic. There is some information about the hypothesis that PIA could precede HGPIN in the prostatic carcinogenesis [3,5,7,14], but only few studies analyse PIA incidence and its relationship with PCa [15–19]. Moreover, consensus on prostatic atrophy classification was established in 2006 [11] whereas the majority of studies are previous to this date.

In 1998, Hu et al [20] examined the relationship of various pathological features with PCa in 388 consecutive needle prostate biopsies of at least six cores. The results of the study showed a strong relationship between HGPIN and PCa on the same needle accession. Moreover, this group found chronic inflammation on 30% of PB, this finding was negatively associated with the presence of PCa. The authors affirm that this result may be related with the clinical indications for prostate biopsy, in patients with chronic inflammation DRE findings may show a

gland of firmer consistency than normal, or inflammation itself may elevate PSA.

In 2002 Bakshi et al [17] studied prostate atrophy in 79 consecutive sextant PBs, 54% of them were benign, 42% showed PCa and 4% had isolated HGPIN or atypia. Post-atrophic hyperplasia was seen in 17% of benign PBs, most of them were associated to some degree of inflammation. After a mean follow up of six years, no association was found between PCa diagnosis and previous finding of post-atrophic hyperplasia. The authors concluded that sub-categorization of atrophy did not appear to be associated with a significant increase in PCa detection. In 2005 Postma et al [15] analyzed 212 sextant PBs without PCa. On first PBs group, simple atrophy was present in 91%, sclerotic atrophy in 47% and post-atrophic hyperplasia in 9%. On repeated PBs group, no relation between any subtype of atrophy and PCa detection was found. Atrophy diagnosis was not predictive for HGPIN or PCa detection after eight years of follow-up. There is only one study published after prostatic focal atrophy classification consensus [11]. In 2007 Billis et al [18] analysed 172 sextant biopsies in which PCa was present and found atrophy in 67% of them. They also found that 41% of those PBs had atrophy without inflammation and 26% had inflammatory atrophy. We can compare this 26% rate of

TABLE IV. Characteristics of the Tumors Detected in PBs According to the PIA Finding

Characteristic	All tumors	With PIA	Without PIA	P-Value
Nº patients, (%)	201 (100)	44 (21.9)	157 (79.1)	-
Gleason score 6, (%)	112 (55.7)	27 (61.4)	85 (54.1)	0.249
Localized tumor, (%)	165 (82.0)	40 (90.1)	125 (79.6)	0.061
Low risk tumor, (%)	137 (68.2)	29 (65.9)	108 (68.8)	0.424
Insignificant tumor, (%)	27 (13.4)	13 (29.5)	14 (8.9)	0.001
HGPIN, (%)	145 (72.1)	33 (75.0)	112 (71.3)	0.392

PIA: Proliferative inflammatory atrophy, HGPIN: High grade prostatic intraepithelial neoplasia.

TABLE V. Characteristics of the Tumors in RPS According to the PIA Finding

Characteristic	All tumors	With PIA	Without PIA	P-Value
No patients	200	64 (32.0)	136 (68.0)	-
Gleason score 6, (%)	54 (27.0)	24 (37.5)	30 (22.1)	0.018
Organ confined tumor (pT2a-b), (%)	170 (85)	57(89.1)	113 (83.1)	0.187
Percentage of tumor to prostate volume* (%)	13.4 ± 7.0 (0.1–70.0)	10.0 ± 5.0 (0.1–40.0)	15.0 ± 7.5 (1.0–70.0)	0.012
Maximal length of index lesion*, cm	1.5 ± 0.5 (0.1–5.0)	1.2 ± 0.5 (0.1–5.0)	1.6 ± 0.5 (0.2–5.0)	0.001
Perineural invasion, (%)	139 (69.5)	38 (59.4)	101 (74.3)	0.025
Multifocal tumor (%)	145 (72.5)	35 (54.7)	110 (80.9)	0.001
Insignificant tumor (%)	20 (10.0)	11 (17.2)	9 (6.6)	0.022
Positive margins, (%)	34 (17%)	7 (10.9)	27 (19.8)	0.015
HGPIN, (%)	182 (91.0)	59 (92.2)	123 (90.4)	0.456

PIA: Proliferative inflammatory atrophy, HGPIN: High grade prostatic intraepithelial neoplasia.

inflammatory atrophy with the 22% rate of PIA observed in our study.

In 1999, Anton et al [21] studied the topographical relationship of postatrophic hiperplasia (PAH) and PCa in 272 RP specimens and 44 cystoprostatectomy specimens. This group concluded that PAH is a common lesion present in one-third of prostates, either with or without PCa. They found no association between PAH detection and the probability of cancer and no topographic association between PAH and PCa foci.

In 2007, Tomas et al [19] evaluated the extent and type of atrophy lesions in 50 RPS and 31 open prostatectomy specimens with benign prostatic hyperplasia, according to the classification proposed by a working group [11]. Proliferative atrophy and/or PIA were present in all the specimens. No association between proliferative atrophy or PIA foci with age, Gleason grade or pathologic stage was found. Moreover, PIA was significantly more frequent in specimens with carcinoma, whereas proliferative atrophy displayed an increased frequency in benign hyperplastic tissue. In a series of 100 autopsies of men older than 40 years who died from other diseases, Billis and Magna in 2003 [22] selected prostate peripheral zone and detected atrophy with inflammation in 66 of them, HGPIN in 78 and incidental cancer in 24. The incidence of cancer was 24% in both glands, with and without inflammatory atrophy. HGPIN incidence was 80% and 74%, respectively. Prostatic inflammatory atrophy did not appear to be associated with incidental carcinoma or HGPIN.

In 2012 Vral et al point out an inverse relation between low-grade PIN and extent of PIA lesion, they suggested a low likelihood of concomitant present of these two lesions [23].

The second important finding of our study is the suspicion established in PBs that PIA is associated to a greater probability of insignificant cancer. In RPS we confirmed that PIA is associated to less aggressive tumors and the probability of insignificant cancer nearly triples. Tomas et al [19] in their study, carried out in RPS, observed that PIA was not related with Gleason score and pathological stage. Unfortunately, there are no other studies analyzing the aggressiveness of tumors accompanying PIA lesion. Our observation suggests that if PIA was involved in prostatic carcinogenesis, it would be in relation to insignificant tumors. It would be interesting to review in the future the type of PIA involved in each situation. The reason why PIA could be associated with a decrease in PCa incidence and an increase of insignificant PCa, could be explained by the effect of chronic inflammation on PSA levels. These levels could lead to perform more PB in those patients. However, our group described in 2000 that prostatic size was the only variable which significantly influenced total serum PSA and percent free PSA. These data was obtained from a cohort of 284 patients with PB negative for PCa. The presence of chronic or acute prostatitis with no clinical evidence of prostatitis did not significantly influence total and percent free serum PSA [24]. PIA lesion is considered as an extreme of the inflammatory process. Despite this, HGPIN has not been considered a part of this process. Moreover, HGPIN neither seems to contribute to total serum PSA nor to percent free serum PSA [25].

Our study has the limitation of not being designed to predict the probability of associated cancer in patients with negative biopsy according to the finding of PIA. We are involved in a prospective study analysing the finding of PIA and HGPIN in previous biopsies of men subjected to repeat biopsies. However, we have established that PIA is a lesion frequently detected in PBs that can provide information about the risk of associated PCa and its aggressiveness. Perhaps this information could be useful to

candidates undergoing active surveillance. Well-designed and prospective studies are needed to answer these questions.

CONCLUSIONS

PIA lesion is a frequent finding in PBs. It is related to a lower risk of associated PCa contrary to what happens with HGPIN. Moreover if PCa is present, the finding of PIA seems to be associated to less aggressive and insignificant tumors.

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1   **Clinical Significance of Proliferative Inflammatory Atrophy in Negative**

2   **Prostatic Biopsies**

3

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23   **MeSH:** High-grade prostatic intraepithelial neoplasia; Proliferative inflammatory

24   atrophy; Prostate cancer.

Abstract

Purpose: To analyze the association between prostatic Proliferative Inflammatory Atrophy finding in negative prostate biopsies and future detection of prostate cancer (PCa) and its aggressiveness in men subjected to repeat biopsies, due to persistent suspicion of PCa.

Materials and Methods: Prospective and observational study of 474 men scheduled to repeated PBs. Assessment of PIA and its extension in the previous biopsy.

PCa detection rate and tumor aggressiveness. Age, serum total PSA, free PSA, percent free PSA (%fPSA), digital rectal exam (DRE), prostate volume (PV), PSA density (PSAD), PSA kinetics (PSAV and PSADT) findings of PIA and HGPIN and number of affected cores in previous PBs were included in the univariate and multivariate analysis. Aggressive tumors were considered when any Gleason pattern 4 was found.

Results:

PCa was detected in 133 men (28.1%). Age, serum total PSA, %fPSA, PV, PSAD, PSAV, PSADT and PIA finding were significantly associated to PCa detection. However, only age, OR: 1.061(95%CI:1.025-1.098), p=0.001; DRE, OR: 1.755(95%CI:1.054-2.923), p=0.031; %fPSA, OR: 0.963(95%CI: 0.933-0.996), p=0.028; PV, OR: 0.983(95%CI:0.972-0.994) and PIA finding, OR: 0.491(95%CI:0.291-0.828), p=0.008, were independent predictors of PCa detection. PCa was found in 18% of 159 men with previous PIA finding while in 33% of 315 men without previous PIA (p=0.001).

None of the studied parameters including PIA in the previous biopsy were related with subsequent PCa aggressiveness.

50 **Conclusions:**

51 PIA finding in negative biopsies decreases the risk of PCa detection in men with

52 persistent suspicion of PCa. The aggressiveness of future detected tumors was

53 not associated with previous PIA finding.

54 **1.   Introduction**

55 Prostate cancer is the most frequent neoplasm in men and it was diagnosed in

56 233000 US men in 2014. PCa is the second cause of cancer death among men,

57 and around 29480 men died from this disease in 2014. [1] Inflammation caused by

58 chemical, physical or biological agents is known [2,3] as an important co-factor in

59 the pathogenesis of many human cancers.[4] According to the injury and

60 regeneration model, inflammatory cells infiltrating the prostate release reactive

61 species in response to infections, uric acid or dietary prostate carcinogens. [2-4]

62 The term "proliferative inflammatory atrophy" (PIA) was proposed by De Marzo et

63 al. in 1999 to designate focal simple or postatrophic hyperplasia occurring in

64 association with inflammation. [5] Only atrophy with hyperplasia of the basal cells

65 shows a marked proliferative activity of the epithelia and a lower frequency of

66 apoptosis in atrophic glands. [6] Morphologic transition between PIA and high-

67 grade prostatic intraepithelial neoplasia (HGPIN) occur frequently. The mere

68 topographic relationship of these lesions is obviously not definitive proof of a

69 continuum, but it is consistent with a model in which the proliferative epithelium of

70 PIA may progress to HGPIN or adenocarcinoma or both. [7] Actually, there is

71 some evidence that supports PIA involvement in prostatic carcinogenesis

72 suggested initially by De Marzo. [2,8] Secretory cells in PIA lesions have

73 proliferative phenotype, increased expression of Ki67 and decreased expression

74 of p27. Similarly, signals of stress-induced response such as expression of Bcl-2

75 and heterogeneous areas of GSTP1 and COX-2 expression are also present.

76 Several molecular pathways involved in PCa have been shown to be altered in

77 PIA lesions. Three prostate tumor-suppressor genes, NKX3.1, CDKN1B and

78 PTEN, highly expressed in normal prostate tissue and often decreased or absent

79   in HGPIN and PCa, are all down-regulated in PIA lesions. Chromosomal

80   abnormalities such as increases in chromosome 8 centromere signals, loss of

81   chromosome 8p and a gain of chromosome 8q24, similar to those found in HGPIN

82   and PCa, also occur in PIA lesions. [9]

83   To date no clinical study has supported the hypothesis that PIA is involved in

84   prostate carcinogenesis. [10] We have recently observed that PIA is present in

85   around one third of negative prostatic biopsies (PBs). Moreover, we have

86   observed that PCa incidence is lower in those PB specimens containing PIA, and

87   the presence of PIA tend to be associated with less aggressive tumors. [11] The

88   main objective of this study has been to confirm the hypothesis that PIA finding in

89   negative PBs predicts lower risk of PCa detection in those men scheduled to

90   repeat PBs due to persistent suspicion of PCa. A secondary objective was to verify

91   if previous PIA finding predicts tumor aggressiveness of future detected tumors.

92 **2.   Material and Methods**

93 ***2.1.   Study design, settings and participants:*** A reprospective study was

94 carried out in an academic institution between January 2010 and February 2014. A

95 group of 474 men with a previous negative biopsy men scheduled to repeat PB,

96 due to persistent suspicion of PCa based on PSA behaviour and digital rectal

97 exam (DRE), were selected. Men receiving 5 alpha reductase inhibitors and those

98 with ASAP (atypical small acinar proliferation) were excluded from the study.

99 Informed consent for repeated PB and study participation was obtained. The

100 median time between first and repeat PB was 10 to 44 months. PCa was detected

101 in 133 patients (28.1%). Clinical characteristics of men included in the study are

102 summarized in Table 1.

103 ***2.2.   Transrectal ultrasound guided PB technique****:* All PBs were performed as

104 an out patient procedure under local anaesthesia. Twelve systematic peripheral

105 cores scheme was used with an end-fire ultrasound transducer in a Falcon device

106 (B-K Medical, Inc.) and a 16-gauge automated biopsy needle (Bard, Inc.).

107 ***2.3.   Assessment of PIA in the previous PB:*** performed by an experienced

108 pathologist (I.dT). PIA was described as focal simple atrophy (SA) or postatrophic

109 hyperplasia (PAH) occurring in association with chronic inflammatory and fibrosis

110 of stroma. SA characteristics were little amount of cytoplasm compared with

111 normal epithelium, acini of relatively normal calibre and number of acini per unit

112 area similar to normal acini. PAH was defined by little amount of cytoplasm and

113 small and mostly round glands situated very close to each other in a lobular

114 distribution. Most of these lesions contain at least some chronic inflammatory cells

115 in the stroma, epithelium, or lumen, and acute inflammatory cells may also be

116 present. [12] The number of cores affected by PIA was also provided. Assessment

117 of HGPIN and its extension was also reviewed.

118 **2.4.** **Characterization of detected PCA:** Primary and secondary Gleason grade

119 of tumor in positive repeated PBs were assessed based on 2005 ISUP Modified

120 Gleason System. [13] The number of affected cores, size and percentage of tumor

121 core invasion were also provided. Patients with PCa were staged according to

122 2002 TNM classification. Abdominal CT and bone scan were performed if Gleason

123 score was higher than 7, serum PSA was over than 20 ng/mL, or cT3 was

124 suspected by DRE.

125 The aggressiveness of PCa was based on Gleason grade and D´Amico risk

126 classification. [14] We also considered the diagnosis of insignificant cancer (IC)

127 according to Epstein´s criteria: cT1c, PSA density lower than 0.15 ng/ml/cc, less

128 than 3 positive cores with less than 50% of cancer and no Gleason pattern 4 or 5.

129 [15]

130 **2.5.** **Statistical analysis:** Quantitative variables were expressed as medians ±

131 semi-interquartile range (range). Qualitative variables were expressed as rates.

132 Univariate analysis included the Chi-square test to analyze the association

133 between qualitative variables and Cochran test to evaluate their strength. The

134 median test and the Mann-Whitney U test were performed to compare quantitative

135 variables. Multivariate analysis using binary logistic regression was also carried

136 out to examine independent predictors of PCa detection and tumor

137 aggressiveness. Odds ratio (OR) and 95%CI were calculated. P-value <0.05 was

138 considered statistically significant. SPSS program V.20 was used to perform

139 statistical analysis.

140 **3.   Results**

141 In the previous PB, PIA was present in 159 patients (33.5.%) and HGPIN in 271

142 (57.6%). We found significant association between both lesions, p=0.001. PIA and

143 HGPIN coexisted in 108 patients (22.8%), while none of these lesions were

144 detected in 152 patients (32.1%). In 51 patients (10.8%) PIA without HGPIN was

145 observed, and HGPIN without PIA was found in 163 patients (34.4%)(Table 1).

146 When comparing the characteristics of the patients with PIA in the previous PB

147 and those with no PIA in the previous PB, we failed to find statistical significance

148 with age, serum PSA, PSA density, PSA kinetics and DRE. We found association

149 between HGPIN presence and PIA in the previous PB. Both lesions coexisted in

150 the previous PB in 67.9% (p=0.001), while only 51.7% of men without PIA had

151 HGPIN. A very important difference between these groups was PCa detection. In

152 the group of men without PIA 33% had PCa, compared to 18.2% men in the group

153 presenting PIA in previous PBs (p=0.001)(Table 2). The rate of high grade PCa

154 detected among both groups was similar.

155 We have analysed PCa detection rate regarding PIA and HGPIN presence in the

156 previous negative PB. PCa detection rate was around 30% in patients with PIA

157 alone and in patients with HGPIN alone (p=0.905). In the subset of men with

158 coexistence of both lesions PCa rate was 20.4%, which was slightly lower

159 compared to men with none of these lesions or HGPIN alone (p=0.006). Finally,

160 PCa rate of men with PIA alone was 13.7%, which was statistically similar to the

161 group with HGPIN and PIA (p=0.216) (Figure 1). In summary, the presence of PIA

162 was associated with lower PCa detection.

163 We have studied the relationship between the extension of PIA in the previous PB

164 and subsequent PCa detection rate. We have observed less tumor detection when

165　increasing the number of PIA affected cores. However, this aspect did not reach

166　statistic significance (Figure 2).

167　Using a logistic binary analysis we found that increased age, abnormal DRE,

168　increased %fPSA, decreased prostatic volume and absence of PIA were

169　independent predictors of PCa detection (Table 3). The presence of PIA

170　diminished to half the risk of PCa detection (OR 0.491 (0.291-0.818), p=0.008).

171　The other variables: PSA kinetics, HGPIN, PSAD and total PSA were not

172　statistically significant in this analysis.

173　Finally, presence or absence of PIA in previous PB was not associated with any

174　parameters of tumor aggressiveness at the univariate (Table 4) or multivariate

175　analysis not shown here.

176 **4.   Discussion**

177 PIA has been proposed to be involved in prostatic carcinogenesis and genetic

178 studies suggest that PIA share some characteristics with HGPIN and PCa. [16] We

179 have previously found that PIA is present in one third of negative PBs, its finding is

180 inversely associated to PCa detection, and maybe to less aggressive tumors.

181 In our present study, 474 men with previous negative PBs underwent a repeated

182 PB due to persistent PCa suspicion. As it can be seen the presence of PIA

183 decreases PCa detection in repeated biopsies. In 2005, Postma et al. [17]

184 analysed PCa incidence during eight years of follow-up of men with diagnosis of

185 atrophy in the first PB. They observed that atrophy was not associated with a

186 higher PCa rate in subsequent PBs. However, this study is not fully comparable to

187 our results because it was done before the classification system for focal atrophic

188 lesions of the prostate proposed in 2006. [12] A recent study has analysed atrophy

189 finding in a negative PB. The authors have concluded that atrophy in negative PB

190 is significantly associated with lower PCa detection in subsequent PBs. [18]

191 However, PIA was not evaluated in this large study and atrophy was subjectively

192 classified into mild, moderate or marked. These studies suggest that atrophy

193 presence decreases cancer risk. Our results are in agreement, however we have

194 focused specifically in PIA lesion and not in prostatic atrophy in general. PIA

195 incidence is less that atrophy incidence in general, which is around 70% at Moreira

196 et al. study. [18]

197 Another aspect that we have analysed in our study is the coexistence of HGPIN

198 and PIA in the same PB and its consequences. Among the subset of 271 men with

199 HGPIN in previous PB, those with PIA had a lower risk of PCa detection in

200 subsequent PBs. This is a paradoxical issue that has never been described in the

201   literature before. An explanation to this issue could be that HGPIN is a cancer

202   promoter while PIA is not, and the coexistence of both lesions decreases PCa risk.

203   In our previous study [11] there were some signs that PIA finding could be related

204   to less aggressive tumors. However, we have not been able to demonstrate that

205   PIA in a negative PB is associated with less aggressive tumors in subsequent PB.

206   These results are comparable to other studies like Moreira et al., [18] where they

207   found less low-grade and high-grade tumors in patients with prostate atrophy at

208   baseline PB compared to those without atrophy. However, they analysed atrophy

209   in general but not PIA.

210   As limitations in our study we emphasize that not all the patients with PIA finding

211   have undergone a repeat PB, we have only biopsied those with persistent

212   suspicion of PCa. Therefore, our results would not be totally comparable to PCa

213   detection in the general population. Moreover, there was not a protocol to decide

214   which men should undergo a repeat PB. The decision was based on clinical

215   judgement. In addition, tumor aggressiveness and the association between PIA

216   and PCa in the same prostate area are hardly assessed only by PB, the analysis

217   of radical prostatectomies could improve this bias. Unfortunately in our present

218   series of patients we did not have a sistematic MRI or other tumor markers. [19]

219   [20]

220   However, the clinical scenario that we have analyzed is real. Our objective was to

221   asses the meaning of finding PIA lesion in a negative PB and to asses its

222   coexistence with HGPIN. A study that includes this anatomopathological

223   information and other clinical variables could be used in a nomogram that would

224   avoid the performance of unnecessary PBs.

225 **5.   Conclusions**

226 PIA lesion can be identified in 30% of patients with a negative PB. We confirm that

227 PIA finding in negative PBs represents a decreased risk of PCa detection in future

228 rPBs due to persistent PCa suspicion. However, we did not find association

229 between PIA lesion and PCa aggressiveness.

230 Figure 1 – Prostate cancer detection according to the finding of PIA and HGPIN in the
231 previous biopsy.
232
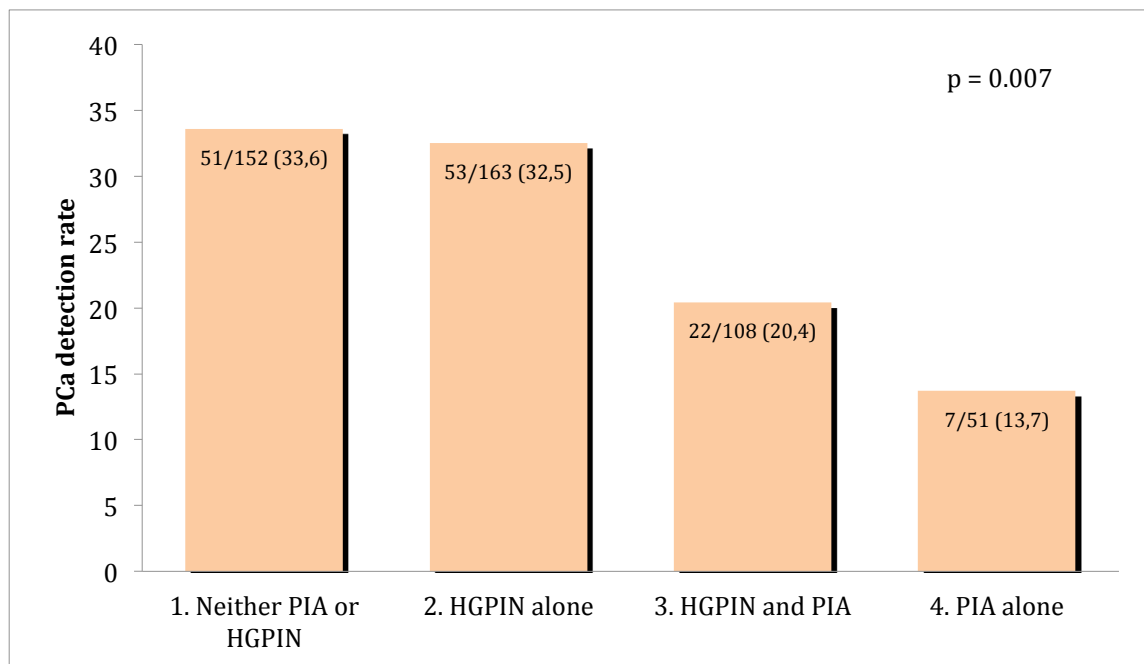
233
234 p Values between groups: 1 to 4: 0.001; 1 to 3: 0.006; 1 to 2: 0.905; 2 to 4: 0.014; 2 to 3: 0.019; 3 to 4:
235 0.216
236

237 Figure 2 – Prostate cancer detection according to the extension of PIA in the previous
238 biopsy.
239

240
241
242

243 Table 1 – Clinical and pathologic characteristics of the population included in the
244 study.
245

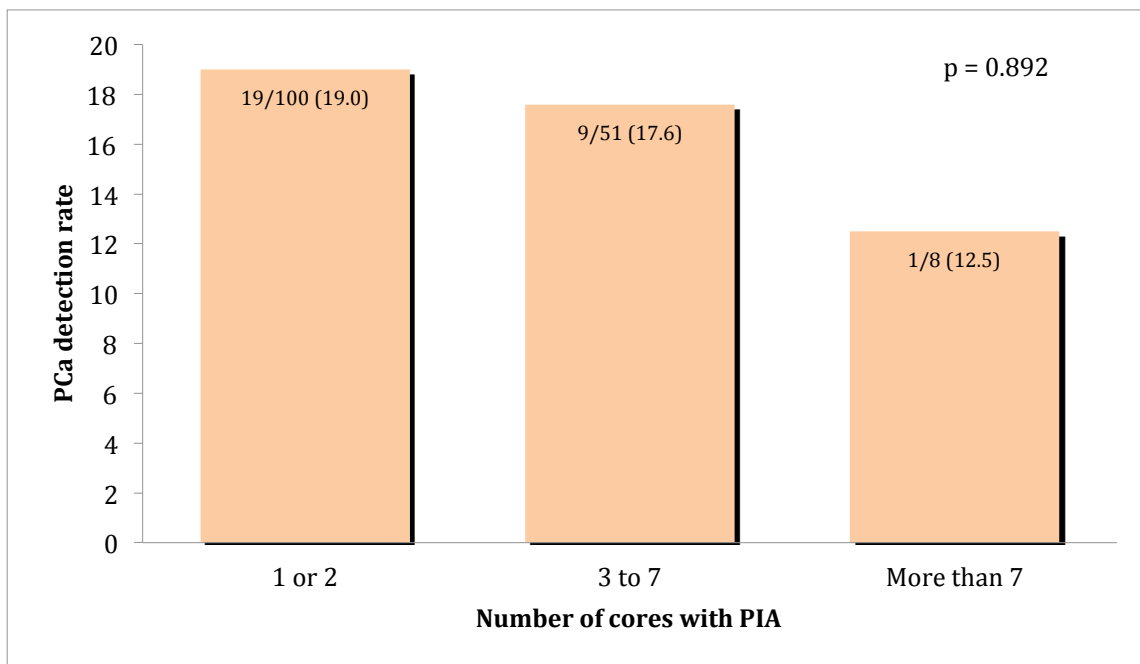|	
No patients	474
Age[1], years	67±5 (44-83)
Serum PSA[1], ng/mL	7.2±2.3 (0.9-98)
Prostate volume[1], cc	50±16 (13-290)
Percent free PSA[1]	16.7±4.6 (1.1-59)
PSA density[1]	0.14±0.6 (0.02-2.2)
Suspicious DRE[2] (%)	111 (23.4)
Time between biopsies[1]	17±3 (10-44)
PSA velocity[1], ng/mL/year	0.19±0.7 (-6 to +6)
PSA doubling time[1], months	15.9±26 (-416 to +329)
Number of previous biopsies	
One	375 (79.1)
Two	69 (14.6)
Three or more (3-6)	30 (6.3)
PIA and HGPIN in the previous biopsy	
PIA without HGPIN (%)	51 (10.8)
HGPIN without PIA (%)	163 (34.4)
PIA and HGPIN (%)	108 (22.8)
Without PIA or HGPIN (%)	152 (32.1)
PCa[3] detection (%)	133 (28.1)
High grade PCa[4] (%)	79 (59.4)

246 [1]Quantitative variables expressed as median±semi-interquartlile range (min-max). [2]DRE: Digital rectal
247 examination. [3]PCa: Prostate cancer. [4]High grade PCa, considered when Gleason ≥7.
248

249   Table 2 – Characteristics of the population included in the study according to the
250   finding of PIA in the previous biopsy.

Characteristic	Whitout PIA	With PIA	p Value
No patients (%)	315 (66.5)	159 (33.5)	-
Age[1], years	67±5 (44-82)	66±5 (49-83)	0.686
Serum PSA[1], ng/mL	7.1±2.4 (0.9-100)	7.3±2.7 (2.2-30)	0.584
Prostate volume[1], cc	50±15 (18-156)	54±16 (13-290)	0.070
Percent free PSA[1]	17.1±4.8 (1.1-59)	15.6±4.6 (1.5-42)	0.374
PSA density[1]	0.14±0.6 (0.02-2.2)	0.15±0.6 (0.03-1.5)	0.439
Suspicious DRE[2] (%)	76 (24.1)	35 (22.0)	0.347
Time between biopsies[1], months	17±17 (10-44)	17±13 (10-47)	0.799
PSA velocity[1], ng/mL/year	0.21±0.7 (-5 to +6)	0.19±0.7 (-6 to +4)	0.262
PSA doubling time[1], months	15.8±23 (-399 to +329)	16.0±31 (-416 to +245)	0.664
Number of previous biopsies[1]	1±0 (2-5)	1±0 (2-7)	0.629
HGPIN in the previous biopsy (%)	163 (51.7)	108 (67.9)	0.001
PCa[3] detection (%)	104 (33.0)	29 (18.2)	0.001
High grade PCa[4] (%)	60 (57.5)	19 (65.5)	0.295

251   [1]Quantitative variables expressed as median±semi-interquartlile range (min-max). [2]DRE: Digital rectal
252   examination. [3]PCa: Prostate cancer. [4]High grade PCa, considered when Gleason ≥7.
253

254 Table 3 - Binary logistic regression analysis to detect independent predictors of
255 prostate cancer detection.
256

Predictor	Odds Ratio (95%CI)	p Value
Age (years), continuous variable	1.061 (1.025-1.098)	0.001
DRE[1], suspicious versus normal	1.755 (1.054-2.923)	0.031
Percent free PSA (%), continuous variable	0.963 (0.933-0.996)	0.028
Prostate volume (cc), continuous variable	0.983 (0.972-0.994)	0.002
PIA[2] in previous biopsy, yes versus no	0.491 (0.291-0.828)	0.008

257 [1]DRE: digital rectal examination. [2]PIA: proliferative inflammatory atrophy.
258

259 Table 4 – Analysis of the aggressiveness of detected tumors according to the finding
260 of PIA in the previous biopsy.
261

Characteristic	All patients n = 474	Without PIA n = 315	With PIA n = 159	p Value
No of tumors	133 (28.1)	104 (33)	29 (18.2)	0.001
Insignificant tumors[1]	16 (12.0)	13 (12.5)	3 (10.3)	0.522
Low D´Amico risk	40 (30.1)	31 (29.8)	9 (31.0)	0.533
Gleason 3+3	54 (40.6)	44 (42.3)	10 (34.5)	0.295
Any Gleason 4	78 (58.6)	62 (59.6)	16 (55.2)	0.412
Gleason 8-10	34 (25.6)	27 (26.0)	7 (24.1)	0.526

262 [1] According to Epstein criteria
263

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DISCUSSION

PIA can be found in around one third of extended PBs while HGPIN is detected in more than one half. PIA was detected in almost 36% of PBs were cancer was not found and 22% in those with cancer. In contrast, HGPIN was present in 42% of PBs without cancer and 72% in those with cancer. We did not find an association between PIA and HGPIN results. As expected, HGPIN was associated to an increased risk of PCa detection. On the contrary, the finding of PIA was associated to a decreased risk of PCa. This was a surprising but interesting result. Furthermore, PBs with HGPIN had decreased PCa rate if PIA was also found. We can summarize that, in contrast to HGPIN, PIA detection in a PB would be related to a lower risk of associated cancer. It is difficult to contrast our results because there is limited information about this topic. There is some information about the hypothesis that PIA could precede HGPIN in the prostatic carcinogenesis [30,33,51,52], but only few studies analyse PIA incidence and its relationship with PCa[32,53-56]. Moreover, consensus on prostatic atrophy classification was established in 2006 [48] whereas the majority of studies are previous to this date.

In 1998, Hu et al.[57] examined the relationship of various pathological features with PCa in 388 consecutive needle prostate biopsies of at least six cores. The results of the study showed a strong relationship between HGPIN and PCa on the same needle accession. Moreover, this group found chronic inflammation on 30% of PBs, this finding was negatively associated with the presence of PCa. The authors affirm that this result may be related with the clinical indications for prostate biopsy, in patients with chronic inflammation DRE findings may show a gland of firmer consistency than normal, or inflammation itself may elevate PSA.

In 2002 Bakshi et al.[54] studied prostate atrophy in 79 consecutive sextant PBs, 54% of them were benign, 42% showed PCa and 4% had isolated HGPIN or atypia. Postatrophic hyperplasia was seen in 17% of benign PBs, most of them were associated to some degree of inflammation. After a mean follow up of six years, no association was found between PCa diagnosis and previous finding of postatrophic hyperplasia. The authors concluded that subcategorization of atrophy did not appear to be associated with a significant increase in PCa detection.

In 2005 Postma et al.[53] analyzed 212 sextant PBs without PCa. On first PBs group, simple atrophy was present in 91%, sclerotic atrophy in 47% and postatrophic hyperplasia in 9%. On repeated PBs group, no relation between any subtype of atrophy and PCa detection was found. Atrophy diagnosis was not predictive for HGPIN or PCa detection after eight years of follow-up. There is only one study published after prostatic

focal atrophy classification consensus[48]. In 2007 Billis et al.[55] analysed 172 sextant biopsies in which PCa was present and found atrophy in 67% of them. They also found that 41% of those PBs had atrophy without inflammation and 26% had inflammatory atrophy. We can compare this 26% rate of inflammatory atrophy with the 22% rate of PIA observed in our study.

In 1999 Anton et al.[58] studied the topographical relationship of postatrophic hyperplasia and PCa in 272 RPs and 44 cystoprostatectomy specimens. This group concluded that postatrophic hyperplasia is a common lesion present in one-third of prostates, either with or without PCa. They found no association between postatrophic hyperplasia detection and the probability of cancer and no topographic association between postatrophic hyperplasia and PCa foci. In 2007, Tomas et al.[56] evaluated the extent and type of atrophy lesions in 50 RPs and 31 open prostatectomy specimens with benign prostatic hyperplasia, according to the classification proposed by a working group[48]. Proliferative atrophy and/or PIA were present in all the specimens. No association between proliferative atrophy or PIA foci with age, Gleason grade or pathologic stage was found. Moreover, PIA was significantly more frequent in specimens with carcinoma, whereas proliferative atrophy displayed an increased frequency in benign hyperplastic tissue. In a series of 100 autopsies of men older than 40 years who died from other diseases, Billis and Magna in 2003 [59] selected prostate peripheral zone and detected atrophy with inflammation in 66 of them, HGPIN in 78 and incidental cancer in 24. The incidence of cancer was 24% in both glands, with and without inflammatory atrophy. HGPIN incidence was 80% and 74%, respectively. Prostatic inflammatory atrophy did not appear to be associated with incidental carcinoma or HGPIN. In 2012 Vral et al. point out an inverse relation between low-grade PIN and extent of PIA lesion, they suggested a low likelihood of concomitant presentation of these two lesions[60].

The second important finding of our study is the suspicion established in PBs that PIA is associated to a greater probability of insignificant cancer. In RPs we confirmed that PIA is associated to less aggressive tumors and the probability of insignificant cancer nearly triples. Tomas et al.[56] in their study, carried out in RPs, observed that PIA was not related with Gleason score and pathological stage. Unfortunately, there are no other studies analyzing the aggressiveness of tumors accompanying PIA lesion. Our observation suggests that if PIA was involved in prostatic carcinogenesis, it would be in relation to insignificant tumors. It would be interesting to review in the future the type of PIA involved in each situation. The reason why PIA could be associated with a decrease in PCa incidence and an increase of insignificant PCa, could be explained by the effect of

chronic inflammation on PSA levels. These levels could lead to perform more PBs in those patients. However, our group described in 2000 that prostatic size was the only variable which significantly influenced total serum PSA and percent free PSA. These data was obtained from a cohort of 284 patients with PB negative for PCa. The presence of chronic or acute prostatitis with no clinical evidence of prostatitis did not significantly influence total and percent free serum PSA[61]. PIA lesion is considered as an extreme of the inflammatory process. Despite this, HGPIN has not been considered a part of this process. Moreover, HGPIN neither seems to contribute to total serum PSA nor to percent free serum PSA[62].

In the final part of our project we have evaluated 474 men with previous negative PBs that underwent a repeated PB due to persistent PCa suspicion. The presence of PIA decreases PCa detection in repeated biopsies. In 2005, Postma et al.[53] analysed PCa incidence during eight years of follow-up of men with diagnosis of atrophy in the first PB. They observed that atrophy was not associated with a higher PCa rate in subsequent PBs. However, this study is not fully comparable to our results because it was done before the classification system for focal atrophic lesions of the prostate proposed in 2006[48]. A recent study has analysed atrophy finding in a negative PB. The authors have concluded that atrophy in negative PB is significantly associated with lower PCa detection in subsequent PBs[63]. However, PIA was not evaluated in this large study and atrophy was subjectively classified into mild, moderate or marked. These studies suggest that atrophy presence decreases cancer risk. Our results are in agreement, however we have focused specifically in PIA lesion and not in prostatic atrophy in general. PIA incidence is less that atrophy incidence in general, which is around 70% at Moreira et al. study[63].

Another aspect that we have analysed in our study is the coexistence of HGPIN and PIA in the same PB and its consequences. Among the subset of 271 men with HGPIN in previous PB, those with PIA had a lower risk of PCa detection in subsequent PBs. This is a paradoxical issue that has never been described in the literature before. An explanation to this issue could be that HGPIN is a cancer promoter while PIA is not, and the coexistence of both lesions decreases PCa risk.

In our study carried out in PBs and RPs[64] there were some signs that PIA finding could be related to less aggressive tumors. However, we have not been able to demonstrate that PIA in a negative PB is associated with less aggressive tumors in subsequent PBs. These results are comparable to other studies like Moreira et al.[63], where they found less low-grade and high-grade tumors in patients with prostate atrophy

at baseline PB compared to those without atrophy. However, they analysed atrophy in general but not PIA.

As limitations in our study we emphasize that not all the patients with PIA finding have undergone a repeat PB, we have only biopsied those with persistent suspicion of PCa. Therefore, our results would not be totally comparable to PCa detection in the general population. Moreover, there was not a protocol to decide which men should undergo a repeat PB. The decision was based on clinical judgement. In addition, tumor aggressiveness and the association between PIA and PCa in the same prostate area are hardly assessed only by PB, the analysis of RPs could improve this bias. Unfortunately in our present series of patients we did not have a systematic multiparametric MRI or other tumor markers[65,66].

However, the clinical scenario that we have analyzed is real. Our objective was to asses the meaning of finding PIA lesion in a negative PB and to asses its coexistence with HGPIN. A study that includes PIA information and other anatomopathological and clinical variables could integrated in a nomogram that would avoid the performance of unnecessary PBs.

CONCLUSIONS

1. PIA lesion was found in 30% of extended PBs, only 27% of PBs with PIA had PCa. PIA incidence in RPs was 32%.

2. The finding of PIA in PBs is not related with HGPIN finding. PIA finding is related to a lower risk of associated PCa. If PCa is present in PBs, the finding of PIA is associated to less aggressive and insignificant tumors. Rate of HGPIN found in RPs was independent to PIA presence. The presence of PIA in RPs was associated to less aggressive and insignificant tumors

3. PIA lesion can be identified in 30% of patients with a negative PB. PIA finding in negative prostatic biopsies represents a decreased risk of PCa detection in future rPBs due to persistent PCa suspicion. There is no relation between PIA lesion in negative prostate biopsies and PCa aggressiveness in further biopsies.

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