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Inflammatory Atrophy on Prostate Needle Biopsies: Is There Topographic Relationship to Cancer?

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ABSTRACT

Introduction: Chronic inflammation of longstanding duration has been linked to the development of carcinoma in several organ systems. It is controversial whether there is any relationship of inflammatory atrophy to prostate cancer. It has been suggested that the proliferative epithelium in inflammatory atrophy may progress to high-grade prostatic intraepithelial neoplasia and/or adenocarcinoma. The objective of our study is to compare on needle prostate biopsies of patients showing cancer the topographical relation of inflammatory atrophy and atrophy with no inflammation to adenocarcinoma.
Materials and Methods: The frequency and extent of the lesions were studied on 172 needle biopsies of patients with prostate cancer. In cores showing both lesions, the foci of atrophy were counted. Clinicopathological features were compared according to presence or absence of inflammation.
Results: Considering only cores showing adenocarcinoma, atrophy was seen in 116/172 (67.44%) biopsies; 70/116 (60.34%) biopsies showed atrophy and no inflammation and 46/116 (39.66%) biopsies showed inflammatory atrophy. From a total of 481 cores in 72 biopsies with inflammatory atrophy 184/481 (38.25%) cores showed no atrophy; 166/481 (34.51%) cores showed atrophy and no inflammation; 111/481 (23.08%) cores showed both lesions; and 20/481 (4.16%) showed only inflammatory atrophy. There was no statistically significant difference for the clinicopathological features studied.
Conclusion: The result of our study seems not to favor the model of prostatic carcinogenesis in which there is a topographical relation of inflammatory atrophy to adenocarcinoma.

***Key words**: prostate; inflammation; atrophy; carcinoma; needle biopsy*
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INTRODUCTION

Chronic inflammation of longstanding duration has been linked to the development of carcinoma in several organ systems (1-3). In the prostate, it is controversial whether there is any relationship of atrophy with inflammation (or inflammatory atrophy) to prostate cancer (4-10). De Marzo et al. (5) propose that there is a topographical relation with morphological transitions within the same acinar/duct unit, between high-grade prostatic intraepithelial neoplasia (HGPIN) and inflammatory atrophy which occur frequently (7). This finding supports a model whereby the proliferative epithelium in inflammatory atrophy may progress to HGPIN and subsequently to adenocarcinoma. The aim of this study is to compare in cores of needle biopsies of patients showing prostate cancer the topographic relation of inflammatory atro-

phy and atrophy with no inflammation to adenocarcinoma.

MATERIALS AND METHODS

The material of this retrospective study was obtained from 172 consecutive men with cancer on needle prostate biopsies and subsequently submitted to radical retropubic prostatectomy.

Both partial and complete prostatic atrophy were considered. Partial prostatic atrophy was diagnosed according to criteria described by Oppenheimer et al. (11) and complete atrophy by criteria described by Billis (4). Three histological subtypes were identified: simple atrophy, hyperplastic atrophy (or postatrophic hyperplasia) (Figure-1), and sclerotic atrophy. Elastosis of the stroma was a useful microscopic feature for the identification of prostatic atrophy of any subtype (12).

Inflammatory atrophy (prostatic atrophy with inflammation) - Both inactive and active inflammation were considered. Inflammatory infiltrate with lymphocytes, plasmacytes or macrophages was considered inactive. The infiltrate was considered active whenever neutrophils were seen in the stroma. All grades of inflammation were considered according to a modified consensus development of a histopathological classification system for chronic prostatic inflammation (13): mild (scattered individual inflammatory cells), moderate (clusters of inflammatory cells) and severe (confluent sheets of inflammatory cells) in areas of prostatic atrophy of any kind: simple, hyperplastic (Figure-2) or sclerotic.

According to the pathologic findings, patients were stratified into group A (biopsies with atrophy and no inflammation), and group B (biopsies with inflammatory atrophy).

The frequency of atrophy was evaluated considering all cores of the biopsy as well as only the cores showing adenocarcinoma. Extent of inflammatory atrophy and atrophy with no inflammation was evaluated according to the number of cores showing the lesion. In group B, we counted the cores showing only inflammatory atrophy, cores showing atrophy and no inflammation, and cores showing both lesions. In cores showing both inflammatory atrophy and atrophy with no inflammation, the foci of each lesion were counted using an image analyzer (ImageLab-2000).

The clinicopathological features included age of the patients, preoperative PSA, and biopsy Gleason score.

The data were analyzed using the Mann-Whitney test for comparison of continuous variables

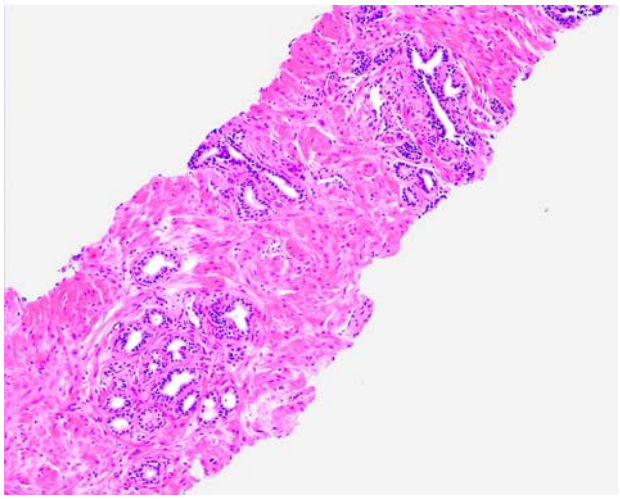

***Figure 1** – Atrophy with no inflammation, hyperplastic subtype (HE, X100).*

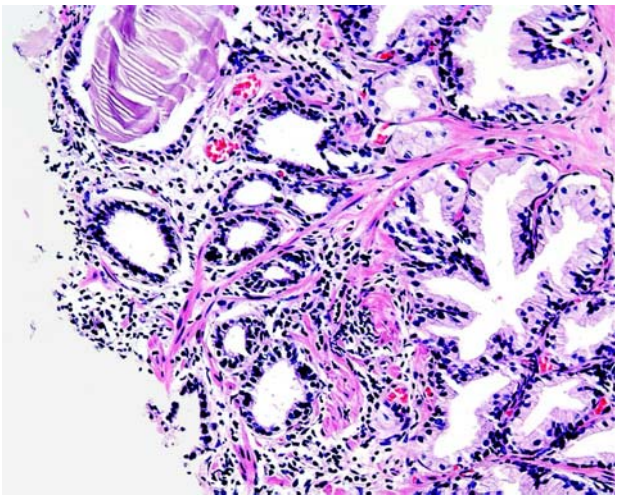

***Figure 2** – Inflammatory atrophy, hyperplastic subtype (HE, X200).*

with $P < 0.05$ being considered statistically significant. All statistical analyses were performed using Statistica 5.5 (StatSoft, Inc., Tulsa, OK, USA).

RESULTS

A total of 1,088 cores (mean, median and range 6.32, 6 and 1-13, respectively) were obtained from 172 needle biopsies of patients with prostate cancer. Considering all cores of the biopsy, atrophy was seen in 144/172 (83.72%) biopsies; 72/144 (50%) biopsies showed atrophy with no inflammation and 72/144 (50%) biopsies showed inflammatory atrophy. In 57/72 (79.16%) biopsies with inflammatory atrophy inflammation was inactive, and in 15/72 (20.83%) biopsies inflammation was active.

Considering only cores showing adenocarcinoma, atrophy was seen in 116/172 (67.44%) biopsies; 70/116 (60.34%) biopsies showed atrophy with no inflammation and 46/116 (39.66%) biopsies showed inflammatory atrophy (Table-1).

There was a total of 481 cores in the 72 biopsies with inflammatory atrophy; 184/481 (38.25%) cores showed no atrophy; 166/481 (34.51%) cores showed atrophy and no inflammation; 111/481 (23.08%) cores showed both lesions; and, 20/481 (4.16%) cores showed only inflammatory atrophy (Table-2). In the cores showing both lesions, inflammatory atrophy was seen in 193/398 (48.49%) foci, and atrophy with no inflammation was seen in 205/398 (51.51%) foci.

Table-3 shows the clinicopathologic features by groups A and B according to age, preoperative PSA and biopsy Gleason score. There was no statistically significant difference between patients showing atrophy and no inflammation (group A) and patients showing inflammatory atrophy (group B).

COMMENTS

Prostatic atrophy is one of the most frequent mimics of prostatic adenocarcinoma (14). It occurs most frequently in the posterior lobe or peripheral zone (15) and gained importance with the increasing use of needle biopsies for the detection of prostatic carcinoma (16). The frequency of the lesion in autopsies is 85% and increases with age (4). The etiopathogenesis of prostatic atrophy is unknown. Compression due to hyperplastic nodules, inflammation, hormones, nutritional deficiency, systemic or local ischemia, are all factors that may play a role in the pathogenesis of atrophy (4,14,15,17,18). The histologic subtypes of

Table 1 – *Frequency of atrophy in 172 biopsies considering only cores showing adenocarcinoma.*

Findings	N	%
Biopsies with atrophy (groups A + B)	116/172	67.44
Biopsies with atrophy and no inflammation (group A)	70/116	60.34
Biopsies with inflammatory atrophy (group B)	46/116	39.66

Table 2 – *Findings in 481 cores from 72 biopsies showing inflammatory atrophy.*

Findings	N	%
Cores without atrophy	184/481	38.25
Cores showing atrophy and no inflammation	166/481	34.51
Cores showing both lesions	111/481	23.08
Cores showing only inflammatory atrophy	20/481	4.16

Table 3 – *Clinicopathologic features of 172 patients with prostate cancer in the biopsy by groups A (with atrophy and no inflammation) and B (inflammatory atrophy).*

Characteristic	Group A	Group B	p Value
Age (years)			
Mean ± SD	63.70 ± 6.30	64.27 ± 5.60	0.7487 (§)
Median	64.50	65.00	
Preoperative PSA (ng/mL)			
Mean ± SD	10.05 ± 5.85	10.86 ± 7.70	0.9076 (§)
Median	9.12	8.90	
Gleason score	0		
Mean ± SD	6.34 ± 0.73	06.41 ± 0.66	0.5143 (§)
Median	6.00	6.00	

SD = standard deviation, § = Mann-Whitney test.

prostatic atrophy do not represent distinct entities but a morphologic continuum of acinar atrophy. Subtyping atrophy is useful not only for its recognition, and for distinguishing it from prostate cancer (4,16).

Chronic inflammation of longstanding duration has been linked to the development of carcinoma in several organ systems (1-3). In the prostate, it is controversial whether there is any relationship of inflammatory atrophy to prostate cancer (4-10). The term "proliferative inflammatory atrophy" was proposed by De Marzo et al. (5) to designate discrete foci of proliferative glandular epithelium with the morphological appearance of simple atrophy or postatrophic hyperplasia occurring in association with inflammation. According to these authors the morphology of proliferative inflammatory atrophy is consistent with McNeal's description of postinflammatory atrophy (19), with that of chronic prostatitis described by Bennett et al. (20), and with the lesion referred to previously as "lymphocytic prostatitis" by Blumenfeld et al. (21). De Marzo et al. (5) and Putzi and De Marzo (7) suggest that proliferative atrophy may indeed give rise to carcinoma directly or that proliferative atrophy may lead to carcinoma indirectly via development into HGPIN. This hypothesis by the authors is based on three separate findings providing supportive evidence: 1) A topographical relation with morphologic merging between proliferative inflammatory atrophy and HGPIN in 34% of the inflammatory atrophy lesions; 2) The phenotype of many of the cells in inflammatory atrophy is most consistent with that of an immature secretory-type cell, similar to that for the cells of HGPIN; and 3) proliferative inflammatory atrophy, HGPIN, and carcinoma all occur with high prevalence in the peripheral zone and low prevalence in the central zone of the human prostate.

Favoring a link of inflammation to prostate adenocarcinoma, Cohen et al. (22) found a positive association between Propionibacterium acnes and prostatic inflammation, which may be implicated in the development of prostate cancer. However, the authors comment that it is possible that prostatic inflammation may also be caused by other microorganisms which could not be identified by the study, for example obligate anerobes or species which are difficult to culture under laboratory conditions. They also comment on a second important limitation of the study related to the lack of appropriate negative controls such as prostate tissue from patients without inflammation, atrophy and cancer.

Other studies are at odds with the findings of De Marzo et al. (5) and Putzi and De Marzo (7). In 100 consecutively autopsied men more than 40 years of age, Billis (4) studied the etiopathogenesis of atrophy and its possible potential as a precancerous lesion. There was no statistically significant relation of atrophy to histologic (incidental) carcinoma or HGPIN. The author concluded that prostatic atrophy probably is not a premalignant lesion. In this autopsy study, prevalence of atrophy increased with age and chronic

ischemia caused by local intense arteriosclerosis seemed to be a potential factor for its pathogenesis. In a subsequent study, Billis and Magna (9) stratified the 100 prostates into group A (atrophy without inflammation) and group B (inflammatory atrophy). The groups were correlated to age, race, histologic (incidental) carcinoma, HGPIN, and extent of both these latter lesions. There was no statistically significant difference between groups A and B for all the variables studied. Neither a topographical relation nor a morphologic transition was seen between prostatic atrophy and histologic carcinoma or HGPIN. The authors concluded that inflammatory atrophy does not appear to be associated with cancer or HGPIN.

Anton et al. (6) studying 272 radical prostatectomies and 44 cystoprostatectomies concluded that postatrophic hyperplasia is a relatively common lesion present in about one-third of prostates, either with or without prostate carcinoma. The authors found no association between the presence of postatrophic hyperplasia and the likelihood of cancer and no topographic association between postatrophic hyperplasia and prostate carcinoma foci.

Bakshi et al. (8) studied 79 consecutive prostate biopsies: 54% of initial biopsies were benign, 42% of the cases showed cancer, and 4% HGPIN or atypia. Postatrophic hyperplasia was seen in 17% of benign initial biopsies with available follow-up. Of these, 75% had associated inflammation. There was no significant difference in the subsequent diagnosis of prostate cancer for groups with postatrophic hyperplasia, partial atrophy, atrophy, or no specific abnormality. The authors concluded that the subcategories of atrophy do not appear to be associated with a significant increase in the risk of diagnosis of prostate cancer subsequently.

Postma et al. (10) evaluated whether the incidence of atrophy reported on sextant biopsies is associated with subsequent prostate cancer detection. The authors concluded that atrophy is a very common lesion in prostate biopsy cores (94%). Atrophy in an asymptomatic population undergoing screening was not associated with a greater prostate cancer or HGPIN incidence during subsequent screening rounds.

In the present study, from a total of 172 needle biopsies of men with prostate cancer, 144/172 showed atrophy; 72/144 (50%) biopsies showed atrophy and no inflammation and 72/144 (50%) biopsies showed inflammatory atrophy. However, considering only cores with cancer, atrophy was seen in 116/172 (67.44%) biopsies; 70/116 (60.34%) biopsies showed atrophy and no inflammation and 46/116 (39.66%) biopsies showed inflammatory atrophy. This finding seems to contradict the topographical model by De Marzo et al. (5) whereby inflammatory atrophy may progress directly to adenocarcinoma or indirectly via development to HGPIN. In cores with adenocarcinoma it would be expected a higher frequency of inflammatory atrophy. Another relevant finding in our study was the evaluation of the extension of inflammatory atrophy in the 481 cores of the 72 biopsies showing this lesion. In only 20/481 (4.16%) cores inflammatory atrophy was the only lesion present. Most frequently cores showed either atrophy with no inflammation (166/481, 34.51%) or both lesions (111/481, 23.08%). A criticism to our findings is that a thin prostate needle biopsy may not represent a real topographic relation between lesions if compared to findings in large specimens such as radical prostatectomy or autopsy prostates. In the study on autopsies with step-sectioning of the prostate, a topographic relation of inflammatory atrophy and HGPIN and/or histologic adenocarcinoma was also not found (9).

There was no statistically significant difference for age (P = 0.7487), preoperative PSA (P = 0.7950), and Gleason score in the biopsy (P = 0.5143) between patients with atrophy and no inflammation and patients with inflammatory atrophy probably indicating no difference in temporal onset and aggressiveness of the tumor in this two groups.

CONCLUSION

The result of our study seems not to favor the model of prostatic carcinogenesis in which there is a topographical relation of inflammatory atrophy to adenocarcinoma. In cores with adenocarcinoma, atrophy with no inflammation was more frequently seen than inflammatory atrophy, and in biopsies with inflammatory atrophy, only 4.16% of the cores showed this lesion as the only finding.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

High-grade prostatic intraepithelial neoplasia (HGPIN) is the most likely precursor of prostatic adenocarcinoma, according to virtually all available evidence. There are other possible findings in the prostate that may be premalignant (Low-grade PIN, inflammatory atrophy, malignancy-associated foci, and atypical adenomatous hyperplasia), but the data for them are much less convincing than that for HGPIN (1).

The paper by Athanase Billis and collaborators entitled "Inflammatory Atrophy on Prostate Needle Biopsies: Is There Topographic Relationship to Cancer?" deals with the interesting topic of preneoplastic lesions and conditions of the prostate, in particular with proliferative inflammatory atrophy (2). The objective of their study was to compare on needle prostate biopsies of patients showing cancer the topographical relation of inflammatory atrophy and atrophy with no inflammation to adenocarcinoma. The result of their study did not favor the model of prostatic carcinogenesis in which there is a topographical relation of inflammatory atrophy to adenocarcinoma. Dr Billis' study does not exclude that inflammatory atrophy could be an early step in the development of prostate cancer and one of the possible preneoplastic conditions and lesions that precede the appearance of cancer.

Low-grade PIN (LGPIN) - Earlier morphometric and immunohistochemical studies showed that LGPIN has features that are intermediate between normal tissue and HGPIN (1). Little information on LGPIN has been accumulated in recent times. This is probably due to the fact, while HGPIN in needle biopsy tissue is a risk factor for the subsequent detection of carcinoma, LGPIN is not. Currently, LGPIN is not documented in pathology reports due a relatively low risk of cancer following re-biopsy.

In Bostwick's progression model of PIN to carcinoma, the transition between normal, low-grade PIN, high-grade PIN, and then carcinoma is continuous (3). Few epidemiologic, morphologic, or molecular genetic studies have examined the relation between low and high-grade PIN development. In part, this relates to the difficulty in distinguishing low-grade PIN from normal tissue on the one hand and high-grade PIN on the other. Nevertheless, Putzi and De Marzo (4) found that lesions that could be considered low-grade PIN often coexisted with high-grade PIN, suggesting either that high-grade PIN is derived from low-grade PIN or that high and low grade PIN arise concomitantly.

Focal Prostate Atrophy as a Morphological Manifestation of a "Field Effect" and a Potential Prostate Cancer Precursor - Pathologists have long recognized focal areas of epithelial atrophy in the prostate that appear more commonly in the peripheral zone of the prostate. These lesions may be associated with chronic inflammation, and less commonly with acute inflammation (5). The term proliferative inflammatory atrophy (PIA) has been proposed (5).

Many of the atrophic cells are not quiescent and possess a phenotype that is intermediate between basal and luminal cells. Intermediate epithelial cells have been postulated to be the targets of neoplastic transformation in the prostate (6). Additionally, PIA cells show elevated levels of GSTP1, glutathione S transferase alpha (GSTA1) and COX-2 in many cells, suggesting that these cells are responding to increased oxidant/nitrosative/electrophilic stress. Many of the molecular and genetic changes seen in HGPIN and cancer have also been documented in PIA (7).

In morphological studies, it has been observed frequent merging of areas of focal atrophy directly with high grade PIN (7). It has been observed these atrophic lesions near early carcinoma lesions, at times with direct merging between atrophic epithelium in PIA and adenocarcinoma (7). Some of such changes could be called atrophic HGPIN.

Malignancy-associated changes (Putative preneoplastic markers with minimal or no morphological changes) - Malignancy-associated changes refer to molecular abnormalities in the epithelial cells that are not usually distinguishable by routine light microscopic examination.

Scant data are available in the prostate. Normal-looking epithelium in prostates with adenocarcinoma may show some molecular abnormalities in GSTP- I and telomerase that are similar to those in cancer (2). These observations are related to the so-

called "enzyme-altered foci" as putative preneoplastic markers (8,9). According to Dr TG Pretlow and coworkers, the most abundant of these lesions with molecular alterations show minimal or no morphological changes (8). Changes occur also in the stroma. Montironi et al (10) have shown that the degree of vascularization in normal-looking prostate tissue from total prostatectomies performed because of a preoperative diagnosis of PCa is close to that of LGPIN.

The transition from normal-looking epithelium to prostate cancer without an intermediate morphological stage identifiable as HGPIN was considered possible (8). This raises the question of the existence of PIN without morphological changes as a precursor of some well-differentiated adenocarcinomas of the transition zone.

Atypical adenomatous hyperplasia – AAH (Adenosis) - Is characterized by a circumscribed proliferation of closely packed small glands that tends to merge with the surrounding, histologically benign glands (11). AAH has been considered a premalignant lesion of the transition zone. A direct transition from AAH to cancer, as it has been observed between HGPIN and cancer, has not been documented. The link between cancer and AAH is probably an epiphenomenon and that the data are insufficient to conclude that AAH is a premalignant lesion.

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EDITORIAL COMMENT

A hypothesis for prostate carcinogenesis proposes that injury to the prostate from a variety of causes leads to chronic inflammation and proliferative inflammatory atrophy (PIA) which may be a risk factor for prostate cancer. Prostatic glandular atrophy can be diffuse or focal with diffuse atrophy resulting from androgen deprivation. PIA is a type of focal atrophy that occurs in the absence of androgen deprivation and occurs in small or large foci, most commonly in the peripheral zone. Recognized morphological types of PIA include simple atrophy and postatrophic hyperplasia in which chronic inflammation as well as increased proliferative activity has been demonstrated. It is unknown whether the other types of focal atrophy, including simple atrophy with cyst formation and partial atrophy have increased cellular proliferation. Therefore, these lesions are currently not considered PIA. A variety of other carcinomas including those in the liver, stomach, large bowel and urinary bladder appear to be related to long-standing chronic inflammation and proliferation. Prostate cancer and its precursor, high-grade prostatic intraepithelial neoplasia (HGPIN) have has been linked with PIA lesions through topographical and morphological associations. De Marzo et al. (1) have shown frequent morphological transitions between HGPIN and PIA suggesting that PIA may be a high-risk lesion for prostate cancer through HGPIN. Although topographical and morphological associations alone are not proofs of a cancer-causing role for PIA lesions, these support a model of prostatic carcinogenesis in proliferative epithelium in chronic inflammation. The authors studied needle core biopsies of patients with prostate cancer and did not show a topographical relationship of inflammatory atrophy to adenocarcinoma. Other studies have shown similar results with inflammatory atrophy found to be a very common lesion. These findings, while not supporting this model of prostate carcinogenesis, do not rule out this association and ultimately experimental animal studies, epidemiological studies and molecular pathological approaches are needed to clarify this hypothesis.

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