DIFFERENT TYPES OF ATROPHY IN PROSTATE WITH AND WITHOUT ADENOCARCINOMA

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"Take-home message" of the article: Different types of atrophy may be found in prostate with and without carcinoma. We showed that proliferative inflammatory atrophy (PIA) was significantly associated with carcinoma thus suggesting that PIA might play role in development of prostatic carcinoma.

ABSTRACT

OBJECTIVE: The purpose of this study is to evaluate the extent and type of atrophy lesions, according to classification proposed by Working group in radical prostatectomy specimens obtained from patients with prostatic carcinoma and benign prostatic hyperplasia (BPH) and compare prevalence and types of atrophy between two investigated groups.

METHODS: The total of 1096 slides from 50 patients with carcinoma and 277 slides from 31 patients with BPH were histologically analyzed to evaluate the number of foci and type of atrophic lesions according to the new prostatic atrophy classification.

RESULTS: Age, Gleason grade and TNM showed no significant correlation with the number of proliferative atrophy (PA) and proliferative inflammatory atrophy (PIA) foci ($p>0.05$). PIA was significantly more frequent in prostate with carcinoma (1.63 versus 1.27 atrophic lesions per slide) ($p<0.001$) while PA displayed an increased frequency in BPH (2.28 versus 0.76 atrophic lesions per slide) ($p<0.001$).

CONCLUSION: We confirmed that PA and PIA are common findings in prostate with and without carcinoma, but the question whether the inflammation produces tissue damage and proliferative atrophy or some other insult induces the tissue damage and atrophy directly, with inflammation occurring secondarily, is still unresolved.

1. INTRODUCTION

Approximately 20% to 30% of the world's cancer burden can be traced to infectious agents thought to act through the production of chronic infections and subsequent chronic inflammation [1-3]. In the prostate factors that determine the risk of developing clinical carcinoma are not well known; however it was clearly showed that chronic inflammation is associated with both postatrophic hyperplasia and focal simple atrophy [4,5]. The term proliferative inflammatory atrophy (PIA) was proposed to designate discrete foci of proliferative glandular epithelium with the morphologic appearance of simple atrophy or postatrophic hyperplasia occurring in association with inflammation. De Marzo et al. and Putzi and De Marzo suggested that PIA could be a precursor to prostatic adenocarcinoma directly, or may lead to carcinoma indirectly via development into high grade prostatic intraepithelial neoplasia (HGPIN) [5-9]. This finding supports a model whereby the proliferative epithelium in PIA may progress to HGPIN and subsequently to prostatic adenocarcinoma [8]. Investigations of frequency, distribution, proliferative state, molecular changes, and chromosome 8 gain in PIA also suggested connection between PIA, HGPIN and prostatic carcinoma [10-14]. This hypothesis is questioned by other authors, and its role as a precursor lesion has been controversial [15-21].

Recently, Working group for histological classification of prostate atrophy lesions proposed classification of focal prostate epithelial atrophy lesions in the two main groups. The major distinction between proposed groups was content of inflammatory cells. Focal atrophy lesions that contain an increase in inflammation above that found in normal tissue were classified as PIA and those without inflammation were considered as a proliferative atrophy (PA). Each group, whether it is considered PIA or PA was sub-classified into the following types: simple atrophy, simple atrophy with cyst formation, post-atrophic

hyperplasia, partial atrophy and mixed lesions. Working group also noted that vast majority of focal atrophy lesions contained at least some inflammation that was beyond that found in normal epithelium and, therefore, most atrophy lesions were considered PIA [22].

The purpose of this study is to evaluate the extent and type of atrophy lesions according to classification proposed by Working group, in radical prostatectomy specimens obtained from patients with prostatic carcinoma and benign prostatic hyperplasia (BPH) and compare prevalence and types of atrophy between two investigated groups.

2. MATERIAL AND METHODS

Our study group included randomly chosen radical prostatectomy specimens of 50 patients with prostatic adenocarcinoma diagnosed at the Department of Pathology, Leopold Franzens University Hospital Innsbruck, and simple open prostatectomy specimens of 31 patients with benign prostatic hyperplasia (BPH) diagnosed at the Ljudevit Jurak Department of Pathology, Sestre milosrdnice University Hospital Zagreb. At the time of diagnosis all patients were clinically without lymph node or distant metastases and patients were not previously treated for prostatic cancer or other primary tumour. Lymphadenectomy was performed in 13 patients.

The age range of the patients with carcinoma was between 43 and 79 years (median age 60.4), and age range of the patients with BPH was between 56 and 86 years (median age 69.7).

Specimens were fixed in 10% buffered formalin, embedded in paraffin, cut at 5 μm thickness, and routinely stained with hematoxylin and eosin. The diagnosis of adenocarcinoma and BPH was histologically confirmed in all cases. We evaluated each case as a whole, without regard to separate parts. Cases with carcinoma consisted from 16 to 42 slides, and cases with BPH consisted from 6 to 22 slides. All 1096 slides with carcinoma and 277 slides with BPH were microscopically sistematically analyzed to evaluate number of foci and type of atrophic lesions according the new atrophy classification proposed by Working group for histological classification of prostate atrophy lesions in two main types [22]. Following five subtypes are recognized. Simple atrophy is characterized by acini with relatively normal caliber that lack papillary fronds and were lined with atrophic cells. Simple atrophy with cyst formation is similar to simple atrophy but with some rounded and cyst-like glands. Post-atrophic hyperplasia is characterized with

smaller and round acini which appear in lobular distribution and often surrounding a somewhat dilated duct. In partial atrophy luminal cells contain less cytoplasm than normal, which is mostly clear. The architectural arrangement of glands can be similar to that of either simple atrophy or post-atrophic hyperplasia. Mixed atrophy contains admixed two or more above mentioned types [22]. Only atrophic lesions that contain an increase in inflammation above that found in adjacent tissue with normal appearing glands were classified as proliferative inflammatory atrophy. Atrophic lesions without inflammation or with inflammation which was sparse compared to adjacent tissue with normal appearing glands were considered as proliferative atrophy. Whole slides were screened under low magnification and type and quantity of inflammation were determined under high power field (400X). In cases of confluent areas of atrophy, foci were counted as separated only when intervening normal appearing glands or fibromuscular stroma without glands clearly made distinction between them.

The differences in the appearance, extent and type of atrophy lesions between carcinoma and BPH were tested using Spearman rank order correlation test, Mann-Whitney U test, Wilcoxon matched pairs test and χ^2 test. For all analyses type error of 5% was considered statistically significant ($p<0.05$).

3. RESULTS

Patients with benign prostatic hyperplasia (BPH) were significantly older compared to patients with prostatic adenocarcinoma ($p<0.05$). Statistical analysis revealed no significant correlation between age and appearance of proliferative atrophy (PA) and proliferative inflammatory atrophy (PIA) in cases with carcinoma and BPH ($p>0.05$).

The Gleason score and pTNM distribution are shown in Table 1 and 2. Eighteen tumors (36.0%) were moderately differentiated (Gleason score 5 and 6) and 32 (64.0%) were poorly differentiated (Gleason score 7 to 9). The most common Gleason grade was 3. In 45 (90.0%) tumors, one or both grades were three. Thirty-four tumors (68.0%) were confined to prostate and 16 (32.0%) were spread through prostatic capsule. Gleason grade and TNM showed no significant correlation with number of PA and PIA foci ($p>0.05$).

In all 81 prostates (50 with carcinoma and 31 with BPH) foci with PA and PIA were found. Proliferative atrophy in BPH was significantly more frequent compared to PIA (2.28 versus 1.27 focuses per slide) ($p<0.001$), whereas in cases with carcinoma PIA significantly outnumbered PA (1.63 versus 0.76 focuses per slide) ($p<0.001$) (Table 3).

The most common type of PA in slides with carcinoma and BPH was type 2 or simple atrophy with cyst formation, and 0.45 and 1.67 focus per slide of this atrophy type was found, respectively (Fig. 1A). Out of total number of PA in BPH and carcinoma, 461 (72.9%) and 489 (58.9%) were PA type 2 (Table 3).

Statistical analysis revealed that cases with BPH showed significantly higher frequency of PA than cases with carcinoma (2.28 versus 0.76 atrophic lesions per slide) ($p<0.001$).

On the contrary, PIA was significantly more frequent in prostate with carcinoma (1.63 versus 1.27 atrophic lesions per slide) ($p<0.05$). Increased PIA in prostate cancer in

comparison to BPH is mostly driven by type 1 ($p<0.001$) and type 5 ($p<0.001$) atrophic lesions (Table 3).

The most common type of PIA in both analyzed groups was type 1 (simple atrophy) (Fig. 1B). In slides with carcinoma 616 (34.4%) or 0.56 foci per slides of type 1 atrophy were found. The second most frequent type was mixed lesions (type 5) with 394 (22.0%) or 0.36 foci per slide. In BPH proliferative inflammatory atrophy type 1 was noted in 90 (25.5%) or 0.33 foci per slide. Slightly less common types of PIA in BPH were type 2 and 3 (0.31 and 0.32 foci per slide, respectively) (Table 3).

PA and PIA were most commonly observed in peripheral zone of prostate. Inflammatory infiltrate around atrophic glands in cases of PIA mainly consisted of lymphocytes with varying numbers of macrophages.

4. DISCUSSION

Chronic inflammation has been implicated in the development of tumors in wide range of organs including liver, stomach, pancreas and, urinary bladder [1-3]. Recent investigations also suggested connection between inflammation and prostatic carcinoma. Focal atrophy, which is often associated with chronic, and less frequently, acute inflammation has been especially suspicious [5-10]. De Marzo et al. proposed the term proliferative inflammatory atrophy (PIA) for this type of atrophy, and suggested its implication in prostatic carcinogenesis [5]. Unlike the type of prostatic atrophy associated with androgen depletion (hormonal atrophy), epithelial cells in PIA have low frequency of apoptosis, high proliferative index and share some molecular and genetics markers with prostatic carcinoma [11-14].

However, this hypothesis is not confirmed by some others, mostly morphological and epidemiological investigations, which found no connection between PIA and prostatic carcinoma [15-21].

In an autopsy study on 100 serially sectioned peripheral zone of the prostates from men older than 40 years, Billis found atrophic lesions in 85 of the 100 examined prostates, but did not confirm significant connection between the prevalence of atrophy and high grade prostatic intraepithelial neoplasia (HGPIN) or prostatic carcinoma [15].

Billis and Magna also denied the role of atrophy in prostatic carcinogenesis and suggested possible role of ischemia in etiopathogenesis of prostatic atrophy [16]. Same authors investigated inflammatory atrophy in an autopsy study and observed inflammatory atrophy in 66% and atrophy without inflammation in 22% of analyzed cases. The authors found no association between the presence of inflammatory atrophy and the likelihood of cancer and no topographic association between atrophy and prostate cancer foci and

concluded that possible cause of inflammatory infiltrate associated with prostatic atrophy might be due to extravasated prostatic secretion, which was commonly noted in areas of eroded epithelium [17].

Bakshi et al. studied 79 consecutive prostate biopsies: 54% of initial biopsies were benign, 42% of the cases showed cancer, and 4% HGPIN or atypia. Postatrophic hyperplasia (PAH) 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 [18].

Similar findings were reported by Postma et al. in their investigation about connection of appearance and extent of atrophy in sextant needle biopsy and subsequent risk for development of prostatic carcinoma [19]. They observed atrophy lesions in 94% of analyzed cases but patients with extensive atrophy were not exposed to increased risk for development of HGPIN or carcinoma [19].

In our investigation, atrophy was found in all analyzed prostatectomy specimens with and without carcinoma. De Marzo et al. found that 55 foci of atrophy in specimens consisted of portion of tissue dissected immediately after radical prostatectomy from 42 patients [5]. Similar frequency of atrophy is reported in two investigations of Billis (85% and 88%) and Postma (94%), who analyzed peripheral zone of prostate from autopsied men and sextant core needle biopsy from patients without diagnosed carcinoma [15,17,19].

Our patients with benign prostatic hyperplasia (BPH) were significantly older than patients with carcinoma, but age was not found as relevant factor, which could influence

the appearance of proliferative atrophy (PA) and PIA in cases with BPH and carcinoma. On the contrary, Billis and Di Silverio et al. reported increased number of atrophic foci in aged patients [15,20]. We also found that Gleason score and TNM were not correlated with the number of PA and PIA foci in cases with carcinoma.

The most common type of PA was type 2, and the most common type of PIA was simple atrophy (type 1) in both analyzed groups. In investigation of De Marzo et al. the most frequently observed atrophy types were simple atrophy and simple atrophy with cyst formation [5]. Postma et al. also recently reported that simple atrophy is very common lesion in a sextant needle core biopsy from population without carcinoma [19].

We found that postatrophic hyperplasia (type 3), which is histologically most commonly confused with prostatic carcinoma, was almost equally distributed in cases with and without carcinoma. Approximately one focus of this atrophy type was usually found in every third slide in both analyzed cases.

Anton et al. analyzed the presence, location and the number of foci of postatrophic hyperplasia. They found postatrophic hyperplasia in 32% of radical prostatectomy specimens and in 12% of cystoprostatectomy specimens and concluded that postatrophic hyperplasia is relatively common lesion but without any association with prostatic carcinoma [21].

In our study, PA was more frequent in benign cases compared to PIA and these patients had also significantly higher number of PA foci compared to patients with carcinoma. On the other hand, in patients with carcinoma PIA was more prevalent compared to PA and slides from these patients contained significantly higher number of PIA focuses compared to slides with BPH. However, slides with carcinoma contained peripheral and transitional zone while slides with BPH were mainly composed of

transitional zone. Thus obtained different prevalence of atrophy in malignant and benign cases could partially reflect the difference in distribution between various anatomic compartments of the prostate.

To our knowledge only two studies compared the appearance and frequency of inflammatory and non-inflammatory atrophy in patients with and without carcinoma. In these studies, no significant differences were found between the presence and types of atrophy in patients containing carcinoma with controls without carcinoma [15,17].

5. CONCLUSION

In conclusion, we confirmed that proliferative atrophy (PA) and proliferative inflammatory atrophy (PIA) are common findings in prostate with and without carcinoma, especially in the peripheral zone of prostate. Age, Gleason grade and TNM showed no significant connection with number of PA and PIA foci. PIA outnumbered PA in cases with carcinoma compared to benign prostatic hyperplasia (BPH), but the question whether the inflammation produce tissue damage and proliferative atrophy or some other insult induces the tissue damage and atrophy directly, with inflammation occurring secondarily, is still unresolved.

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Table 1. Distribution of Gleason grades and scores in 50 patients with prostatic adenocarcinoma.

Gleason grades with scores	Number of cases	%
5 (2+3)	3	6.0
5 (3+2)	4	8.0
6 (3+3)	11	22.0
7 (3+4)	20	40.0
7 (4+3)	3	6.0
8 (3+5)	3	6.0
8 (4+4)	3	6.0
8 (5+3)	1	2.0
9 (4+5)	2	4.0
Total	50	100

Table 2. Distribution of pTNM in 50 patients with prostatic adenocarcinoma.

pTNM	Number of cases	%
T2aNxMxR0	1	2.0
T2aNxMxR1	1	2.0
T2aN0MxR1	1	2.0
T2bNxMxR1	1	2.0
T2bN0MxR0	5	10.0
T2cNxMxR0	19	38.0
T2cNxMxR1	6	12.0
T3aNxMxR0	3	6.0
T3aNxMxR1	5	10.0
T3aN0MxR0	3	6.0
T3aN0MxR1	1	2.0
T3bNxMxR1	1	2.0
T3bN0MxR1	3	6.0
Total	50	100

Table 3. The number and type of atrophy lesions in 1096 slides of 50 patients with prostatic adenocarcinoma and in 277 slides of 31 patients with benign prostatic hyperplasia

	Prostatic adenocarcinoma (n=1096)				Benign prostatic hyperplasia (n=277)			
	PA*		PIA**		PA*		PIA**	
	Number (%)	Number per slide	Number (%)	Number per slide	Number (%)	Number per slide	Number (%)	Number per slide
Type 1	117 (14.1%)	0.11	616 (34.4%)	0.56	70 (11.1%)	0.25	90 (25.5%)	0.33
§Type 2	489 (58.9%)	0.45	339 (18.9%)	0.31	461 (72.9%)	1.67	86 (24.4%)	0.31
Type 3	37 (4.5%)	0.03	332 (18.5%)	0.30	6 (0.9%)	0.02	88 (24.9%)	0.32
§Type 4	58 (7.0%)	0.05	110 (6.2%)	0.10	22 (3.5%)	0.08	24 (6.8%)	0.09
Type 5	129 (15.5%)	0.12	394 (22.0%)	0.36	73 (11.6%)	0.26	65 (18.4%)	0.22
Total	830 (100%)	0.76	1791 (100%)	1.63	632 (100%)	2.28	353	1.27

*PA – proliferative atrophy; **PIA – proliferative inflammatory atrophy

[§]type 2 and [§]type 4 atrophy are not yet formally considered proliferative inflammatory atrophy or proliferative atrophy since studies of these lesion looking at proliferation have not been published [22]

Legend:

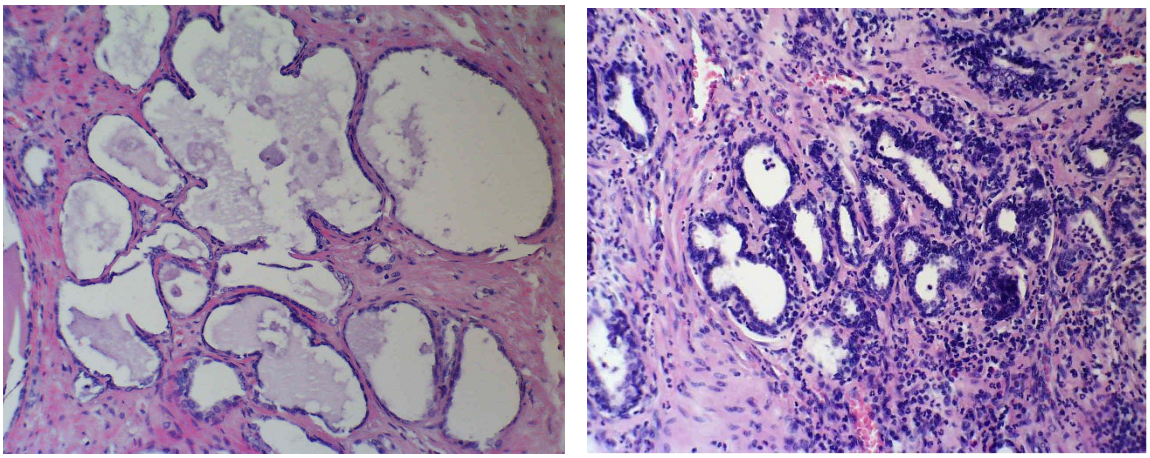
Type 1 – simple atrophy

Type 2 – simple atrophy with cyst formation

Type 3 – post-atrophic hyperplasia

Type 4 – partial atrophy

Type 5 – mixed lesions



A B

Figure 1. The most common type of proliferative atrophy in slides with benign prostatic hyperplasia and prostatic adenocarcinoma was simple atrophy with cyst formation (A), while simple atrophy was most frequent type of proliferative inflammatory atrophy in both analyzed groups (B). (Both microphotographs made under magnification of 200x.)