

·Original Article·

Associations among benign prostate hypertrophy, atypical adenomatous hyperplasia and latent carcinoma of the prostate

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Abstract

Aim: To investigate the frequency of atypical adenomatous hyperplasia (AAH) and its associations with benign prostate hypertrophy (BPH) and latent histological carcinoma of the prostate (LPC) in autopsy material. **Methods:** Two hundred and twelve prostate specimens obtained from autopsy material were subjected to whole mount analysis in an attempt to investigate the associations among BPH, AAH and LPC. **Results:** Most histological carcinomas and AAH lesions were found in enlarged prostates with intense hypertrophy. No statistically significant relation was found between BPH and the main characteristics of LPC, such as tumor volume, histological differentiation and biological behavior. Our data regarding multi-focal tumors showed a tendency for multi-focal carcinomas to develop in larger prostates, and a tendency of AAH lesions to develop in larger prostates. No statistically significant relation was found between AAH and LPC. **Conclusion:** There seems not any causative aetiopathogenetical or topographical relation between AAH lesions and prostate adenocarcinoma. AAH lesion seems to be a well-defined mimicker of prostatic adenocarcinoma, and the reported association of AAH with prostatic carcinoma could probably be an epiphenomenon. (*Asian J Androl* 2007 Mar; 9: 229–233)

Keywords: atypical adenomatous hyperplasia; histological prostate cancer; benign prostate hypertrophy

1 Introduction

Atypical adenomatous hyperplasia (AAH; also termed

adenosis), is a localized proliferative lesion consisting of small amounts of atypical epithelial cells arranged in irregular glandular patterns. AAH lesions usually appear as compact, well-circumscribed nodules, in which the basal cell layer is often indistinguishable or discontinued. Although being of uncertain biologic significance and easily mistaken for Gleason pattern 1 or 2 prostate cancer [1], AAH lesions can be easily distinguished from carcinomas by the degree of nucleolar enlargement [2]. The occurrence rate of AAH is not known,

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and its aetiopathological associations with benign prostate hypertrophy (BPH) and latent carcinoma of the prostate (LPC) have not been completely clarified. We performed 212 consecutive autopsies in an attempt to investigate the frequency of AAH and its associations with BPH and LPC. To our knowledge, there are few up-to-date published necropsy studies. Of those few studies, some described significant differences of the occurrence of AAH, histological BPH and LPC [3–7].

2 Materials and methods

2.1 Study population

The study included 212 men between 30 and 98 years of age who died between August 2002 and August 2004, of diseases other than clinically diagnosed carcinoma of the prostate. All of them were of Greek origin. Cases suspected with a history of prostate cancer, cases with abnormal digital rectal examination in the pre-necropsy examination and cases found with macroscopic foci of cancer in any organ were excluded.

2.2 Sample removal and processing

The whole prostate and seminal vesicles were removed with accuracy. The specimen was weighed and measured in three dimensions (width \times height \times length). The surface of the two lobes was colored in different colors and fixed in acetic acid. A 10% formalin solution was injected uniformly (per cm²) into the gland and the specimen was then immersed in formalin solution allowed to fix for 3 days. Seminal vesicles were removed and sectioned through the base. Base and apex were also removed by transversal sections and the slices were cut at 4-mm intervals. The rest of the two lobes were divided and sectioned at 4-mm intervals perpendicular to the long axis of the gland. Pieces were postfixed, resectioned, dehydrated, cleared in xylene and embedded in paraffin. Every piece was numbered and registered to record the exact size and dimensions of the pathologic findings.

2.3 Histological assessment

The presence of BPH was recorded. The diagnosis of prostate cancer was based on the criteria described in the World Health Organization (WHO) classification system [8]. Latent cancers were classified, by an expert pathologist, according to the Gleason scoring system [9]. Cases of multi-focal tumors were classified according

to the prevalent histological model of the larger tumor (index tumor). The diagnosis of AAH and the discrimination between AAH and cancer were based on a constellation of histological and cytological features [10, 11].

2.4 Classification

For statistical analysis purposes, AAH lesions were divided according to the overall volume into small (< 0.5 mL) and large (> 0.5 mL). According to the grade of the hypertrophy (BPH), prostates were studied in three distinct groups (large > 50 mL, medium 25–50 mL and small < 25 mL), and histological LPC were divided according to overall volume into small (< 1 mL) and large (> 1 mL).

2.5 Statistical analyses

The associations among AAH, BPH and LPC were assessed with paired *t*-test and Mann–Whitney *U*-test.

3 Results

According to our findings, histological BPH was the most common in our study population, accounting for 65.5% of prostates. Both AAH and LPC seemed less frequent, accounting for 15.5% (33 cases) and 18.8% (40 cases), respectively.

Age specific prevalence of BPH was similar to that of LPC but not identical: major prevalence of both diseases was observed in men of the eighth and ninth decade but BPH began to manifest in the male population earlier. Major prevalence of AAH was observed in men of the seventh and eighth decade (Table 1).

A possible relation between BPH, LCP and AAH has been identified: both AAH and LPC were found more in enlarged prostates than in small ones (< 25 mL). More precisely, almost 22% and 29% of the prostates with volume larger than 50 mL carried foci of AAH and LPC, respectively (Table 2). However, since benign hypertrophy existed in a greater percentage in specimens of all age groups examined without LPC and AAH, no statistical significant cross-correlation between BPH and LPC was obtained ($P > 0.05$, Mann–Whitney *U*-test). Interestingly, AAH and BPH were associated with larger prostate volume (statistical significant cross-correlation among BPH, AAH and prostate volume, $P < 0.01$).

Of the 40 LPC cases, 29 (72.5%) had an overall volume of less than 1 mL (average volume per focus less than 0.5 mL), whereas almost all AAH lesions (29 cases, [87.8%]) had an overall volume less than 0.5 mL. The

Table 1. Age specific prevalence of latent histological carcinoma of the prostate (LPC), benign prostate hypertrophy (BPH) and atypical adenomatous hyperplasia (AAH).

Age group (years)	Specimens	LPC (%)	BPH (%)	AAH (%)
> 90	16	9 (56.2)	13 (87.5)	3 (18.7)
80–89	30	12 (40.0)	29 (90.6)	6 (20.0)
70–79	36	11 (30.5)	31 (86.0)	9 (25.0)
60–69	36	5 (13.8)	25 (65.8)	7 (19.0)
50–59	38	2 (5.2)	20 (58.8)	4 (10.5)
40–49	38	1 (2.6)	18 (47.3)	3 (7.8)
30–39	18	0	5 (27.7)	1 (5.5)
Total	212	40	139	33

Table 2. Distribution of latent histological carcinoma of the prostate (LPC) and atypical adenomatous hyperplasia (AAH) lesions according to the volume of the prostate.

Prostate volume (mL)	Number	LPC (%)	AAH (%)	LPC & AAH
< 25	65	5 (7.7)	2 (3.0)	0 & 5 (0)
25–50	69	12 (17.4)	11 (15.9)	2 & 12 (16.7)
> 50	78	23 (29.5)	20 (25.6)	7 & 23 (30.4)
Total	212	40	33	9 & 40 (22.5)

small AAH lesions showed an increased frequency in enlarged prostates. Most LPCs of low volume showed an increased frequency in medium-sized prostates (Table 3). Parametric and non-parametric analysis did not confirm any statistically significant relation between the degree of BPH and the volume of latent carcinomas ($P > 0.05$). Similarly, no associations were obtained regarding the degree of BPH and the size of AAH lesions.

When presented with LPC (9 cases), AAH was found with rather small sized LPC (especially in younger subjects, Table 4), however, no statistically significant correlation was obtained between AAH and overall tumor volume ($P > 0.05$). No statistically significant correlation ($P > 0.05$) was obtained between AAH and histological differentiation of the concomitant tumors as well. Similarly, no statistical significant cross-correlation was found between BPH and histological differentiation of the coexistent LPC (t -test, $P = 0.907$; Mann-Whitney U -test 0.770).

Of cases of LPC, 87.5% (35 cases) were found to originate from the peripheral zone (PZ) and only 12.5% were found in the transition zone (TZ), where BPH also develops. In contrast, almost all AAH lesions were cen-

Table 3. Overall tumor volume and volume of the prostatic gland.

Prostate volume (mL)	Tumor volume (%)	
	< 1 mL	> 1 mL
< 25	5 (17.2)	0 (0)
25–50	10 (34.5)	2 (18.9)
> 50	14 (48.2)	9 (81.8)
Total	29	11

Table 4. Latent histological carcinoma of the prostate (LPC) with atypical adenomatous hyperplasia (AAH) and benign prostate hypertrophy (BPH) in different age groups. *Inadequate for statistical significance estimation, because of the small sample.

Age group (years)	LPC	LPC & AAH	LPC volume < 1 mL (%)
> 90	9	2 (22.2)	2 (100)
80–89	12	2 (16.6)	1 (50)
70–79	11	3 (27.7)	2 (75)
60–69	5	2 (40.0)	2 (100)
50–59	2	0	—*
40–49	1	0	—*
30–39	0	0	—*

trally located in the transition zone (TZ) or in the bound between TZ and PZ. Although some AAH foci, especially those found on the boundaries between the transitional and the peripheral zone, had similar appearance with the well-differentiated LPC of TZ, no topographic relationship between AAH and prostate carcinoma of the TZ was found. Moreover, TZ and PZ LPC were nearly equivalent when compared for histological differentiation and tumor volume, respectively.

4 Discussion

AAH is a localized proliferative lesion whose occurrence, biological significance, pathogenesis and aetiopathological association with other prostatic conditions are controversial. AAH lesions consist of compact clusters of uniform small glands [1, 12]. Nuclei are slightly enlarged, the basal cell layer is often inconspicuous, and the nucleoli are commonly small [12]. Although reported in at least 20% of transurethral resection of the prostatic gland specimens [13], its occurrence in the general population is unknown. Differences in AAH frequency between necropsy (15.5%) and surgery material, could be explained by the relatively higher prevalence of AAH in age groups 3 and 4 (Table 1), who actually undergo surgery for BPH-related conditions. Moreover, as the age of observed peak-incidence of AAH is similar to that of BPH [14], differences in the overall prevalence of AAH worldwide could be related to the differences in BPH epidemiology [15]. Since the initial description of AAH by McNeal [16] in 1965, its biological significance remains controversial. AAH shares some common morphological characteristics with low-grade prostate cancer; therefore, the distinction between the two entities is often troublesome. Moreover, because Gleason pattern 1 and 2 carcinomas can sometimes closely resemble the appearance of AAH, AAH might be, like high-grade prostatic intraepithelial neoplasia, another precursor of prostate cancer [17]. In the present study, the age-specific prevalence of AAH showed a relative reduction after 70–79 years (age group 3), in contrast to the age-specific prevalence of both LPC and BPH (which actually sustained their increasing rates), a finding which could indicate that a percentage of AAH lesions in some patients could have probably been transformed in other lesions/entities (atrophy, neoplasm or otherwise) or gradually degenerated. Furthermore, there are several similarities between AAH and prostate cancer: AAH lesions are often

multi-focal, as is LPC, they display high-density architectural arrangement and contain prominent nucleoli and slightly enlarged nuclei. Several reports showed an increased incidence of prostate cancer in the presence of AAH [18]; according to Kastendieck, foci of atypical primary hyperplasia are commonly found with low volume high differentiated carcinomas [19]. Moreover, AAH lesions have been reported to be in close proximity to cancer lesions [13, 20]. In contrast, according to our findings, AAH was equally distributed in both samples with and without histological cancer, whereas, similarly to other reports, no topographic relationship between AAH and prostate carcinoma has been demonstrated [20]. Beyond the topographic relationships, the aetiopathological associations of AAH with other prostatic conditions are controversial. The fact that AAH arises always in prostates with concomitant BPH and exhibits several cancer-like features, places AAH as an intermediate lesion between BPH and the subset of well-differentiated cancers in a hypothetical pathway between BPH and LPC: according to Bostwick *et al.* [21], AAH could be related to the well-differentiated prostate cancers that arise in the transitional zone in combination with BPH. In addition to the numerical and topographical observations linking AAH with BPH, rather than with small-volume well-differentiated carcinomas, morphologic and histological features of cancers that arise from the TZ (which contain BPH nodules and AAH foci) and features of cancers that arise from the PZ, showed no significant differences in the present study [22]. Other studies provide further evidence that AAH is histologically closer to BPH: the AAH cell proliferation index was similar to those of BPH [23], nuclear volume was closer to the volume observed in BPH [19] and AAH cells had a normal DNA content similar to the BPH cells [25–27].

According to the results from the present study, there seems to be no causative aetiopathogenetical or topographical relation between AAH lesions and prostate adenocarcinoma. Although well-differentiated low volume carcinomas of the TZ have been previously correlated with AAH lesions, we did not observe such a relation in our relatively small sample of TZ carcinomas (12.5%). Despite the several morphological characteristics of AAH suggesting a relationship with prostate cancer, cellular changes observed in AAH are not necessarily an element of malignant transformation, while confounding atypical cellular features are occasionally seen in confirmed benign lesions [28]. In conclusion, we

confirm that the AAH lesion is a well defined mimicker of prostatic adenocarcinoma, whereas the reported association of AAH with carcinoma is probably an epiphenomenon. In addition, it seems that from the perspective of the practicing urologist, currently, there is no enough evidence to support the validity of a repeated biopsy protocol in patients with AAH lesions, although further studies are required to assess the need for such recommendations.

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