

Differences in the Secretory Activity of the Atypical Adenomatous Hyperplasia and Low-Grade Prostatic Adenocarcinoma

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ABSTRACT

BACKGROUND

Atypical adenomatous hyperplasia (AAH) is a small, glandular proliferation that has histological similarities to Gleason grade 1 and 2 prostatic adenocarcinoma (PACG 1, 2). There are no distinct histomorphological criteria distinguishing these two lesions from each other and other small glandular proliferations. It is necessary to define histological criteria, as treatment approaches are different for these lesions.

OBJECTIVES

This study's aim was to evaluate the differences in the secretory properties of AAH and PACG 1, 2. We searched for intraluminal crystalloids, corpora amylacea, mucin, and eosinophilic material.

SUBJECTS AND METHODS

105 totally embedded radical prostatectomy specimens containing 11 AAH (22 foci) and 15 PACG 1, 2 (22 foci) lesions were evaluated. Basal cell specific antikeratin was applied. We accepted that PACG 1, 2 lesions do not contain basal cells, and we grouped lesions as AAH and

PACG 1, 2 based on this opinion. The luminal contents were evaluated by PASAB2, 5 and PTAH.

RESULTS

We found differences between the AAH and PACG 1, 2 lesions for some parameters, including crystalloids, corpora amylacea, and mucin. We found similar properties between the two lesions for eosinophilic material.

CONCLUSION

In a difficult case, evaluation of the luminal content features may be helpful, but the diagnosis must be supported by immunohistochemistry.

KEYWORDS

Adenosis, Small Glandular Proliferations, Low-Grade Cancer, Prostate, Crystalloids

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INTRODUCTION

Atypical adenomatous hyperplasia (AAH) of the prostate is a small, glandular proliferation that may be mistaken for adenocarcinoma. It has a frequency of 1.6-36.9% [1-7] and is more often seen in the transient zone [8-13]. It is also referred to as adenosis [14-16], AAH [1-7,17,18], atypical adenosis [19], small atypical acinar proliferation [20,21], and small gland hyperplasia [22]. The focus of the AAH is present around or in hyperplastic nodules [17]. Histologically, AAH displays a lobular pattern and has uniformly small glands [21,23]. The

border is usually distinct and orderly but may have a focal irregularity [10,24]. AAH consists of cells that have a clear or pale cytoplasm. The nucleus is round and is located at the basal section of the cell. The chromatin pattern is granular like a normal prostatic cell. The nucleolus is usually small, and the basal cells are inconspicuous [17,23].

Gleason grade 1 prostatic adenocarcinoma (PACG 1) is a round lesion that grows by pushing surrounding tissues and is composed of medium-sized monotonous glands. It displays

minimal stromal invasion, and the cytoplasmic features are like those of benign glands [25,26]. In addition to PACG 1 features, Gleason grade 2 prostatic adenocarcinoma (PACG 2) displays early infiltration findings and has mild variability in glandular size (25,26).

There are many studies on the diagnostic criteria for AAH and its differentiation from PACG 1, 2 (17,27-32). Additional data describing the lesion is needed when these criteria are inadequate.

We studied intraluminal crystalloids, corpora amylacea, mucin, and eosinophilic material in AAH and PACG 1, 2. The purpose of this study was to reveal the differences in secretory activity, which might be used for the differential diagnosis of these two lesions.

MATERIALS AND METHODS

We retrieved 105 consecutive radical prostatectomy specimens. All patients had clinically localized prostate cancer. The material was re-evaluated to search for AAH and PACG 1, 2 lesions. Lesions that were composed of small glandular proliferations and that usually had orderly margins were selected. Eleven (22 foci) AAH and 15 (22 foci) PACG 1, 2 lesions were included in the study. Four-micron thick sections were taken from the paraffin blocks with suspected diagnoses of AAH or PACG 1, 2, and an immunohistochemical study for the basal cell-specific antikeratin antibody 34 β E12 was performed. PASAB2, 5 and Phosphotungstic acid hematoxylin (PTAH) were applied to all AAH and PACG 1, 2 lesions. PTAH staining was used to identify intraluminal crystalloids, corpora amylacea, and eosinophilic material. With the PTAH dye, crystalloids are stained dark blue, corpora amylacea light brown, and eosinophilic material is not stained [9,33]. PASAB2, 5 staining was used to identify intraluminal mucin. With PASAB2, 5, acidic mucin is stained blue and neutral mucin is stained magenta [9].

INSPECTED PARAMETERS AND EVALUATION OF THE CRITERIA

The number of glands with intraluminal crystalloids, corpora amylacea, mucin, and eosinophilic material was evaluated, but the amount of luminal material was not taken into account. PASAB2.5 and PTAH were performed to demonstrate the kind of luminal material. Parameters were evaluated by assigning a numerical value from 1 to 4 with (1) signifying that none of the glands had luminal material, (2) that <5% of the

glands had luminal material, (3) that 5-50% of the glands had luminal material, and (4) that >50% of the glands had luminal material.

STATISTICAL EVALUATIONS

The findings were analyzed and transferred into a Statistical Package for Social Sciences for Windows, version 11.0 (SPSS) package program database. A chi-square related test was used to compare the data. Results were evaluated as significant if the p value was less than 0.05.

IMMUNOHISTOCHEMICAL STAINING METHOD

34 β E12

Keratin, HMW Ab-3 (1/50; Clone 34 β E12; MS-1447-S1; Neomarkers)

The streptavidine biotin/horseradish peroxidase (Str.AB/HRP) methods were used to show keratin immunoexpression. A drop of Ultra V Block (Ultra Vision Kit; TP-125-HL; Vision) was applied to the slide in order to block nonspecific dyeing.

The tissues were incubated for 10 seconds with biotinylated biotinized secondary antibody. Streptavidine Peroxidase was applied. DAB was used as a chromogen. Cytoplasmic brown painting in the basal cells was evaluated as positive.

Figure 1. A: PACG 1, 2 (H&Ex100); B: AAH (H&Ex100); C: PACG 1, 2 lesion do not contain basal cells (34 β E12 x100); D: AAH lesion focally contain basal cells (34 β E12 x100)

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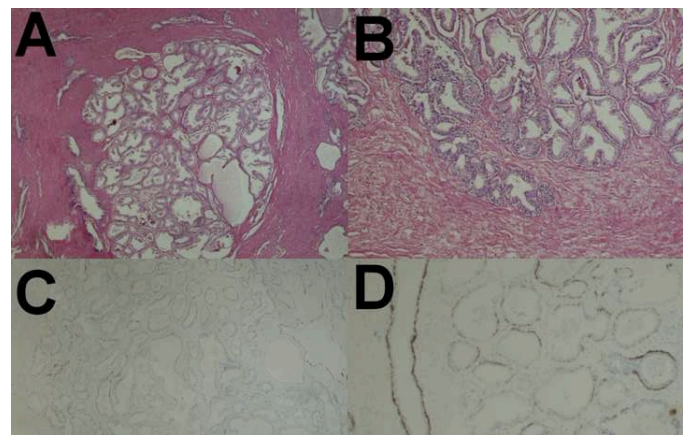


Table 1. Comparison of the AAH and PACG 1, 2 lesion in terms of luminal material parameters and the statistical results

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| Histological parameters | Evaluation | AAH number (%) | PACG 1, 2 number (%) | Applied test; P |
|-------------------------|------------|----------------|----------------------|--------------------------|
| Crystalloid | Absent | 19 (86.3) | 8 (36.4) | Chi-square test; p=0.007 |
| | <5% | 2 (9.1) | 7 (31.8) | |
| | %-50% | 1 (4.6) | 4 (18.1) | |
| | >50% | 0 (0) | 3 (13.7) | |
| Corpora amylacea | Absent | 6 (27.7) | 16 (72.7) | Chi-square test; p=0.01 |
| | <5% | 4 (18.1) | 3 (13.6) | |
| | 5-50% | 11 (50) | 2 (9.1) | |
| | >50% | 1 (4.6) | 1 (4.6) | |
| Eosinophilic material | Absent | 2 (9.1) | 1 (4.6) | Chi-square test; p>0.05 |
| | <5% | 7 (31.8) | 5 (22.7) | |
| | 5-50% | 11 (50) | 11 (50) | |
| | >50% | 2 (9.1) | 5 (22.7) | |
| Mucin | Absent | 22 (100) | 14 (63.6) | Chi-square test; p=0.02 |
| | <5% | 0 (0) | 4 (18.2) | |
| | 5-50% | 0 (0) | 2 (9.1) | |
| | >50% | 0 (0) | 2 (9.1) | |

RESULTS AND DISCUSSION

A comparison of the AAH and PACG 1, 2 lesions (Fig. 1) in terms of luminal material parameters and the statistical analysis of the results are shown in Table 1. Intraluminal crystalloids were present in 13.7% of AAH and 63.6% of PACG 1, 2 lesions (Fig. 2). Mucin was not detected in any AAH lesion but was present in 36.4% of PACG 1, 2 lesions (Fig. 3). Corpora amylacea were present in 72.3% of AAH and 27.3% of PACG 1, 2 lesions (Fig. 4). There was a statistically significant difference between the groups regarding the presence of corpora amylacea, intraluminal crystalloids, and mucin ($p < 0.05$). Eosinophilic material was present in 90.1% of AAH and 95.4% of PACG 1, 2 lesions, but the difference was not statistically significant ($p > 0.05$) (Fig. 5).

Evaluating prostate lesions composed of small acini with a suspicion of malignity is a frequently encountered problem in pathology. Some cancers are diagnosed as benign, while some benign lesions are diagnosed as cancers. This is especially problematic with needle biopsies where the sample tissue can

be inadequate to characterize the tissue and evaluate histological criteria [34].

Current knowledge on the secretory activity of benign or malignant prostate lesions is still limited. Corpora amylacea are seen more commonly in the lumen of benign glands, while mucin and crystalloids in the lumen of malignant glands indicate alteration of the secretory activity of the cells. Crystalloids are more common in PACG 1, 2 than AAH. The frequency of corpora amylacea in PACG 1, 2 has been reported as 10-62% [1,6,23,35-44], while the frequency in AAH has been reported as 2-50% [17,29,36,45-48].

We found crystalloids, which are stained blue with PTAH, in 13.7% of the AAH and 63.6% of the PACG 1, 2 lesions. This is compatible with other reports and is statistically significant [33,46]. Furthermore, the presence of crystalloids has been shown in benign lesions, such as sclerosing adenosis [49] and prostatic hyperplasia [46].

Anton RC *et al.* found the frequency of cancer in benign prostate lesions containing crystalloids to be 38%, while the rate was 26% in controls that did not contain crystalloids in patients undergoing more than one biopsy [50]. Henneberry JM *et al.* found these ratios as 23% and 16%, and the difference was not significant in either study [51]. Furusato M *et al.* conducted a

Figure 2. A: Crystalloids in PACG 1, 2 (H&Ex400); B: Crystalloids in AAH (H&Ex400)

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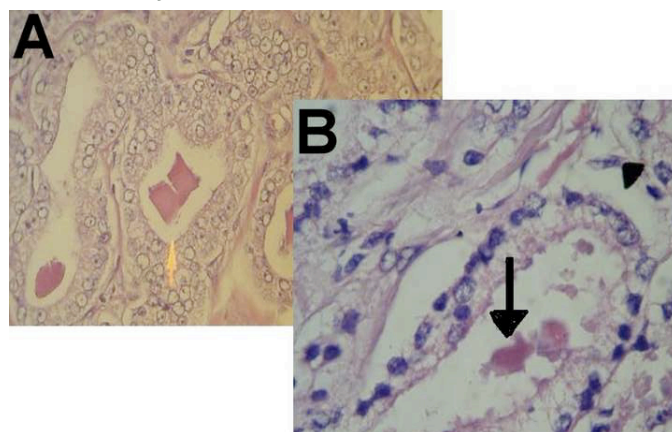
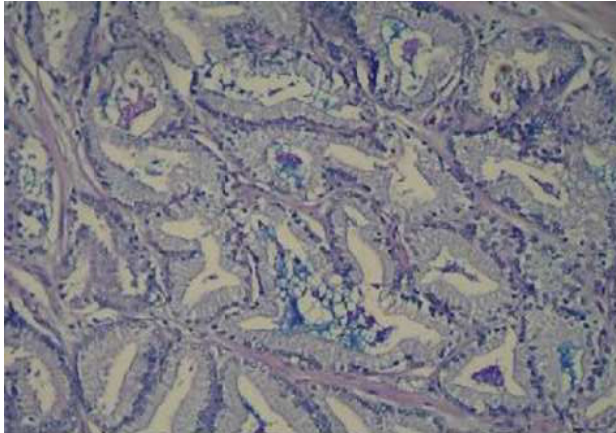


Figure 3. Mucin in PACG 1, 2 (PAS AB2.5x100)

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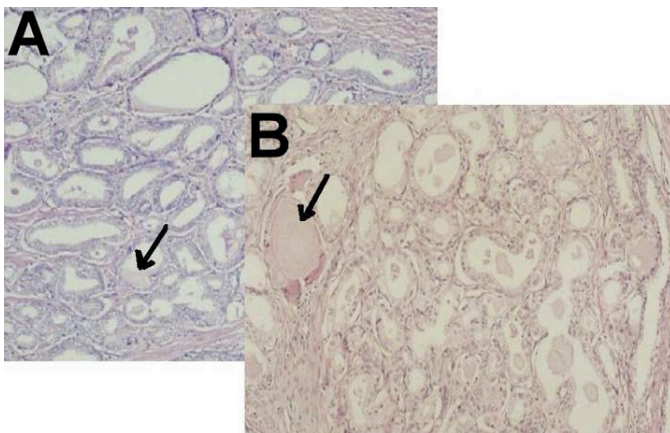
study consisting of an autopsy series with 108 latent prostate carcinomas and identified crystalloids in 62% of cases over 50 years old and 76% of those over 70 years old [43]. Interestingly in this study, when carcinoma focus was enlarged, the ratio of the malignant glands containing crystalloids to malignant glands not containing crystalloids was diminished.

Crystalloids may therefore be an early malignancy finding. We found crystalloids stained blue with PTAH in 13.7% of AAH and 63.6% of PACG 1, 2 lesions. Again, these results are compatible with other reports, and the difference was significant.

Corpora amylacea are a kind of crystalloid in benign prostate

Figure 4. A: Corpora amylacea in AAH (H&Ex100); B: Corpora amylacea in PACG 1, 2 (H&Ex100)

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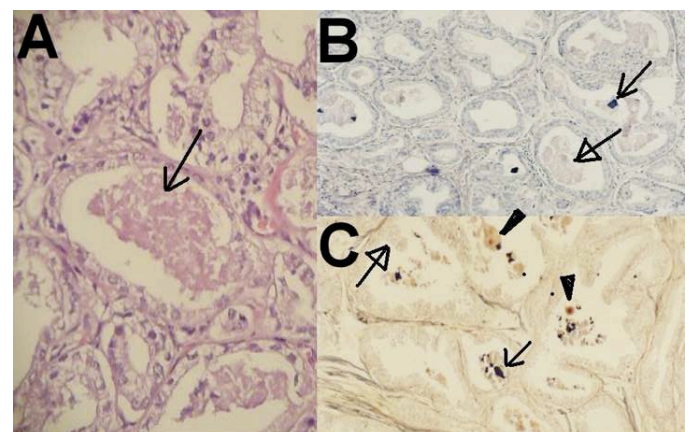
hyperplasia that is enhanced with aging and not correlated with neoplasia. Corpora amylacea are stained light brown with PTAH [9,33]. It is more frequent in benign acini, but it is seldom present in adenocarcinoma. Its frequency was shown to diminish with an increasing Gleason grade [48]. It is much more frequent in AAH than in PACG 1, 2, and it has been reported at a rate of 32-50% in AAH and 0-32% in cancer [4,6,17,23,36-38,52]. Our results indicate a 73% appearance rate for AAH and a 27.3% rate for PACG 1, 2. The fact that the reported frequency is considerably different in various studies is because of the different materials used in each and the range in number of cases studied.

Luminal eosinophilic material is more frequent in cancer than nodular hyperplasia and is pinker and has a more granular appearance in cancer [9,48]. PTAH does not stain eosinophilic material [33]. In our study, PTAH was used for all lesions, and we observed that eosinophilic material was not stained. In addition, light granular material consisting of the cell's cytoplasmic crumbs was excluded. Intraluminal eosinophilic material was found in 91% of AAH and 95.5% of PACG 1, 2 lesions. This difference was not statistically significant.

The presence of acidic mucin in AAH has been evaluated in a limited number of studies [53-56]. Its frequency has been reported as 2-54% in AAH and 23-80% in cancer

Figure 5. A: Eosinophilic material in AAH (H&Ex200); B: Eosinophilic material in PACG 1, 2 (pale); corpora amylacea (orange), crystalloid (dark blue) (PTAHx100);- C: PACG 1, 2 (PTAHx200)

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(1,16,17,23,36,57-59). Mucin is found in AAH and PACG 1, 2 and also in benign lesions such as mucinous metaplasia [55], PIN [31,60], sclerosing adenosis [29,37], and basal cell hyperplasia [28]. Some studies have accepted the presence of acidic mucin as an important criterion for the differentiation of AAH and PACG 1, 2 lesions [1,16,36]. Goldstein NS *et al.* found the same results in both kinds of lesions and reported that it was not useful for differentiating between these lesions, although it is useful to differentiate them from surrounding benign lesions [58]. Acidic mucin was found in none of the AAH lesions in our study, but it was present in 36.4% of PACG 1, 2 lesions, a significant difference.

In conclusion, the presence of intraluminal mucin and crystalloids in PACG 1, 2 and corpora amylacea in AAH were

significant parameters in our study. Although the presence of crystalloids and mucin is a significant parameter to differentiate between AAH and PACG 1, 2, differential diagnoses is still difficult in some cases, especially following needle biopsy. The concurrent evaluation of histological parameters in AAH shows that basal cells are fewer and focally, and this has been deemed to be important. The diagnosis should be mainly based on architectural, cytologic and immunohistochemical criteria that require a good expertise. Additionally, the consideration of secretory products is important when atypical suspicious lesions are evaluated.

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