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Review Article

Adenosis / Atypical adenomatous hyperplasia of Prostate Gland. Review and Update

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Abstract:

The diagnosis of carcinoma of prostate gland has tended to be challenging because of the existence of lesions that simulate adenocarcinoma of prostate gland. Such a type of prostate lesion is atypical adenomatous hyperplasia (AAH) or adenosis, which represents a proliferation of crowded, small to medium glands with basal cell layer invariably present, but often it has tended to inconspicuous upon routine histopathology of prostate gland examination staining. The importance of the lesion lies in its potential for being misdiagnosed as low-grade adenocarcinoma (Gleason 1 or 2). Atypical adenomatous hyperplasia (AAH) or adenosis of the prostate gland is terminology that is used for a pseudo-neoplastic lesion which can simulate adenocarcinoma of prostate gland in view of its cytological as well as its architectural features. It had previously been iterated that for many years, atypical epithelial lesions of the prostate gland had been known to occur, but much refining of this knowledge had eventually evolved over the last three and half decades. Previously two lesions, prostatic intraepithelial neoplasia (PIN) and AAH, were regarded to be precursors of adenocarcinoma of prostate gland. Nevertheless, PIN has now remained the only well-proven preneoplastic condition with clinical significance. It had been pointed out that AAH is no longer regarded to be a premalignant lesion but rather a benign small glandular process of the transition zone which does mimic acinar adenocarcinoma. In view of the fact that AAH occurs predominantly within the transition zone of prostate gland, which is only rarely sampled in needle biopsy of prostate gland, it has tended to be uncommon to visualise examples of this lesion in biopsy specimens. Nevertheless, as the sampling of the transition zone of the prostate gland had become more frequently undertaken over the past few decades with ultrasound-guided multiple segmental prostate biopsies, as well as radiology-mage guided- targeted prostate biopsies of suspicious lesion with utilisation of also computed tomography scan / magnetic resonance imaging scan, the practicing surgical pathologists needs to be aware of the histopathology examination features of AAH of the prostate in needle biopsy specimens, in order to avoid misinterpretation of AAH of the prostate, which is a benign lesion, as adenocarcinoma of prostate gland. Furthermore, because some patients manifesting with raised serum prostate specific antigen (PSA) levels and negative peripheral zone biopsy may manifest with transition zone adenocarcinoma of prostate gland, sampling of the transition zone of the prostate by needle biopsy and the identification of AAH are likely to increase. If an atypical adenosis hyperplasia (AAH) or adenosis is misdiagnosed as localised adenocarcinoma of the prostate gland, then the individual found to have AAH could be inadvertently treated as a treatment of curative intent of either radical prostatectomy or radical radiotherapy that would represent unnecessary treatment over-aggressive treatment associated with more significant side effects and complications. Nevertheless, if a correct diagnosis of AAH of the prostate gland is established then the patient would not need any surgical or radiotherapy. A number of cases of AAH of prostate gland also tend to diagnosed specimens of trans-urethral resection of prostate gland specimens and prostatectomy specimens. Diagnosis of AAH of prostate gland tends to be diagnosed based upon the histopathology and immunohistochemistry staining features of specimens of the prostate gland, The pathologist also needs to be aware of which antibody staining agents that need to be used in order to clearly confirm the diagnosis of AAH of prostate gland and this has been detailed out in the ensuing article.

Keywords: atypical adenomatous hyperplasia of prostate; adenosis of prostate; biopsy of prostate; transition zone of prostate; raised serum prostate specific antigen; ultrasound scan; computed tomography scan; magnetic resonance imaging scan; misdiagnosis; transition zone; repeat biopsy; follow-up assessment;high index of suspicion, pseudo-neoplastic lesion

Introduction

Atypical adenomatous hyperplasia (AAH) or adenosis of the prostate is a pseudo-neoplastic lesion that can mimic prostate adenocarcinoma because of its cytologic and architectural features [1-4]. For many years, atypical epithelial lesions of the prostate have been known to occur, but much refining of this knowledge has evolved over the last two decades. Initially two lesions, prostatic intraepithelial neoplasia, and AAH, were assumed to be precursors of prostatic adenocarcinoma [1-4]. Nevertheless, PIN now remains as the only well-proven preneoplastic condition with clinical significance. AAH is now, no longer regarded a premalignant lesion but instead a benign small glandular process of the transition zone which simulates acinar adenocarcinoma [1-4]. Since AAH occurs predominantly within the transition zone, which is only rarely sampled during the undertaking of needle biopsy of prostate gland, it is uncommon to see examples of this lesion in biopsy specimens. Nevertheless, as the sampling of the transition zone of the prostate has become more frequent recently with ultrasound-guided multiple segmental prostate biopsies [1,5] the practicing surgical pathologists needs to be aware of the histological features of AAH of the prostate in needle biopsy specimens, in order to avoid misinterpretation of AAH of the prostate gland, which is a benign lesion, rather than adenocarcinoma of prostate gland. Furthermore, because some patients who are found to have raised serum prostate specific antigen levels and negative peripheral zone biopsy may manifest with transition zone prostatic adenocarcinoma, sampling of the transition zone of the prostate by needle biopsy and the identification of AAH are likely to increase [1,5]. The ensuing article is divided into two parts (A) which has discussed general overview aspects of Adenosis / atypical adenomatous hyperplasia and (B) Miscellaneous narrations and discussions from some case reports, case series and studies related to Adenosis / atypical adenomatous hyperplasia.

Aim

To review and update the literature on Adenosis / atypical adenomato us hyperplasia.

Methods

Internet data bases were searched including: Google, Goggle scholar, Yahoo, and PubMed. The search words that were used included: Adenosis / atypical adenomatous hyperplasia.; Adenosis of prostate gland, atypical adenomatous hyperplasia of prostate gland, prostatic adenosis; and prostatic atypical hyperplasia. Thirty-five (35) references were identified which were used to write the article which has been divided into two parts: (A) which has discussed general overview aspects of Adenosis / atypical adenomatous hyperplasia and (B) Miscellaneous narrations and discussions from some case reports, case series and studies related to Adenosis / atypical adenomatous hyperplasia

Results

[A] OVERVIEW

Definition / general statement [6]

- It has been documented that a well circumscribed, microscopic nodular proliferation of crowded, small to medium glands with pale to clear cytoplasm, a fragmented and discontinuous basal cell layer and minimal atypia; may be mistaken for low grade adenocarcinoma [7-9]
- It has been iterated that Adenosis / atypical adenomatous hyperplasia.is found predominantly in the transition zone (1.6% of transurethral resection of the prostate [TURP], < 1% of core biopsies) of the prostate gland in association with nodular hyperplasia of the prostate gland [8,10]
- It has been pointed out that frequently Adenosis / atypical adenomatous hyperplasia.is found to be multifocal within the prostate gland [10]

Essential features [6]

- Benign lobular proliferation of small crowded glands
- Similar to prostatic adenocarcinoma; in adenosis, cells may show small or medium size nucleoli, crystalloids, intraluminal secretions, minimal infiltration and positive immunostaining for AMACR (racemase)
- In contrast to prostatic adenocarcinoma, in adenosis, glands have more pale cytoplasm, merge with adjacent benign glands, commonly have corpora amylacea [8,11]
- Basal cells can be identified on H&E slides or with immunohistochemistry for p63, cytokeratin 5/6 or HMWCK [12]
- AMACR (racemase) can be focally or diffusely expressed in up to 18% of cases of adenosis [13]
- Lack of ERG expression in adenosis supports the notion that it is not a precursor lesion of adenocarcinoma [14]

Terminology [6]

- Atypical adenosis, atypical small acinar hyperplasia, atypical hyperplasia [10]

Epidemiology [6]

- AAH is found in 2% to 20% of transurethral resections of the prostate specimens, and in 1% of prostate needle biopsies

Sites [6]

- AAH is more commonly found within the transition zone of the prostate gland [8]

Pathophysiology [6]

- AAH is associated with benign prostatic hyperplasia

Clinical features [6]

- Morphologic variant of benign crowded glands, a mimicker of low-grade prostatic adenocarcinoma
- Does not have clinical implications

Diagnosis [6]

- AAH is detected on needle biopsy or transurethral resection

Radiology description [6]

- In cases of AAH, multiparametric magnetic resonance imaging (mpMRI) might be difficult to interpret because it shows overlapping features with low grade prostatic adenocarcinoma [15]

Prognostic factors [6]

- Not a precursor lesion of prostatic adenocarcinoma [14]
- Comparative genomic hybridization and multiplex PCR did not find common alterations between adenosis and accompanying cancer foci and concluded that adenosis should not be considered as an obligate premalignant lesion [16]
- Diffuse adenosis of the peripheral zone should be considered a risk factor for prostate cancer [1,17] as well as urinary obstruction as well as elevated serum PSA. [18]

Treatment [6]

- Treatment not needed

Microscopic (histologic) description [6]

- Relatively well circumscribed proliferation of small, crowded, closely spaced acini merging with surrounding benign glands
- Lobular proliferation of small disorderly glands with an expansile or minimally infiltrative growth pattern
- Budding of small glands from larger, more obvious benign glands
- Occasional single cells or poorly formed glands are common; may represent tangential section of small glands
- Resembles low grade (Gleason score 3 + 3 = 6) prostatic adenocarcinoma [18-22]
- Clear cytoplasm, usually normal sized nuclei, normochromasia and common corpora amylacea
- Occasionally, prominent nucleoli (13 - 15%) and mitotic figures (3 - 11%); rarely, blue tinged luminal mucinous secretions (3%) [11,23,24]
- Crystalloids can be present in 24 - 40% of cases [11,24]
- HMWCK labels the basal cells focally in a patchy fashion
- 3 dimensional renderings show network of interconnecting tubules with extensive branching, lacking obvious acinar organization [7]

Positive stains [6]

- Basal cell markers (**p63**, **CK5/6** and **HMWCK** are positive in a patchy fashion (discontinuous staining; mixture of glands with and without basal cell layer) [23]

Negative stains [6]

- **ERG** [14]
- **AMACR** (racemase) can be focally or diffusely expressed in up to 18% of cases of adenosis [13]

Molecular / cytogenetics description [6]

- It has been documented that there tends to be 12% allelic imbalance, with loss within chromosome 8p11-12 [25]

Differential diagnosis [6]

- Low grade (Gleason score 3 + 3 = 6, grade group 1) **adenocarcinoma of prostate gland:**
    - Cytologic atypia, including prominent nucleoli and lack of basal cells
- **Partial atrophy of prostate gland**:
    - Glands are partially atrophic with undulating luminal surface with papillary infolding; cytologic features are benign

[B} **MISCELLANEOUS NARRATIONS AND DISCUSIONS FROM SOME CASE REPORTS< CASE SERIES AND STUDIES RELATED TO**

Verhoef et al. [7] stated the following:

- Many glandular lesions of the prostate gland could simulate prostate cancer microscopically, including atrophic glands, adenosis and prostatic intraepithelial neoplasia.
- While the characteristic histopathological and immunohistochemical features of these lesions had been well established, little is known about their three-dimensional architecture.
- Their objective was to evaluate the three-dimensional organisation of common prostate epithelial lesions.

With regard to the materials and methods as well as the results of their study, Verhoef et al. [7] iterated the following:

- 500 μm-thick punches (n = 42) were taken from radical prostatectomy specimens, and they were stained with antibodies targeting keratin 8-18 and keratin 5 for the identification of luminal and basal cells, respectively.
- Tissue samples were optically cleared in benzyl alcohol/benzyl benzoate and imaged utilising a confocal laser scanning microscope.
- The three-dimensional architecture of peripheral and transition zone glands was acinar, composed of interconnecting and blind-ending saccular tubules.
- In simple atrophy, partial atrophy and post-atrophic hyperplasia, the acinar structure was attenuated with branching blind-ending tubules from parental tubular structures.
- Three-dimensional imaging demonstrated a novel variant of prostate atrophy characterised by large Golgi-like atrophic spaces parallel to the prostate surface, which were represented by thin, elongated tubular structures on haematoxylin and eosin (H&E) slides.

- Conversely, adenosis had lacked acinar organisation, so that it closely simulated low-grade prostate cancer.
- High-grade prostatic intraepithelial neoplasia had displayed prominent papillary intraluminal protrusions but had retained an acinar organisation, whereas intraductal carcinoma had predominantly consisted of cribriform proliferations with either spheroid, ellipsoid or complex interconnecting lumens.

Verhoef et al. [7] concluded that various prostate epithelial lesions might simulate malignancy on H&E slides, their three-dimensional architecture is acinar and clearly different from the tubular structure of prostate cancer, with adenosis as an exception.

Netto and Epstein. [8] stated that prostate needle biopsy currently is the gold standard method for the diagnosis, management, and prognosis of prostate cancer as well as that obtaining an accurate diagnosis is crucial for pursuing proper patient management. Netto and Epstein. [8] in their article summated the histology examination mimickers of prostate carcinoma by highlighting microscopic features that are helpful to reach a correct diagnosis and emphasizing potential diagnostic pitfalls. This article would provide additional educational material for readers.

Humphrey [9] stated the following:

- Atypical adenomatous hyperplasia (AAH) of the prostate gland is a microscopic proliferation of small glands which might be mistaken for adenocarcinoma.
- The extent and multicentricity of this histopathologic lesion had not been fully defined, and the spatial relationship with carcinoma had not been described in whole-mount surgical specimens.
- They sought to determine whether the extent and zonal location of AAH is related to prostate cancer by evaluating 217 totally embedded radical prostatectomy specimens with cancer.

Humphrey [9] summarised the results as follows:

- All but 17 patients had clinically localized prostate cancer, and none had received pre-operative treatment.
- The number of foci and volume of AAH were measured utilising a grid-counting method: proximity to cancer was recorded as either less than or equal to 2 mm from cancer or greater than 2 mm from cancer.
- AAH was identified in 23.0% of cases and was more frequent in the transition zone (19.8% of cases) in comparison with within the non-transition (peripheral and central) zone (6.0%).
- AAH was found within 2 mm of cancer in 34% of cases of AAH, including 30% of cases within the transition zone and 31% cases in the non-transition zone.
- The number of Ioci of AAH within the transition zone was always greater than that within the non-transition zone, regardless of whether it was within 2 mm of cancer or more than 2 mm from cancer.
- AAH was frequently multicentric (46% of cases), especially within the transition zone (47% of transition zone cases) compared with the non-transition zone (23% of non-transition zone cases).
- The mean volume of AAH was 0.029 cc and the volume of AAH had ranged between, 0 cc to 1.29 cc, and was much higher in the transition zone in comparison with in the non-transition zone, regardless of whether it was within 2 mm of cancer or more than 2 mm from cancer. In cases of AAH within 2 mm of cancer, the volume was lower than in cases more than 2 mm from cancer: this was true regardless of zonal location.
- AAH was more common in older patients and in those with greater prostatic weight, higher prostatic volume, greater percentage of nodular hyperplasia, greater volume of cancer, greater percent of Gleason patterns 4 and 5 cancer, higher volume of prostatic intraepithelial neoplasia, and higher serum prostate-specific antigen level.
- There was no correlation of number of foci of AAH or volume of AAH with pathology stage, seminal vesicle invasion.
- Gleason primary pattern or score, nuclear grade, perineural invasion by tumour, or DNA ploidy.

Humphrey [9] made the ensuing conclusions:

- Their results had indicated that AAH is usually found within the transition zone in association with nodular hyperplasia and is often multicentric.
- The extent and zonal distribution of AAH and carcinoma do show a weak but significant association.

Lopez Beltran et al. [10] stated the following:

- Atypical adenomatous hyperplasia (AAH) of the prostate gland is a microscopic proliferation of small acini that may be mistaken for adenocarcinoma of the prostate gland.
- Even though some data had suggested that AAH is associated with adenocarcinoma arising within the transition zone of the prostate gland, the clinical significance of this lesion was not certain.
- Therefore, they studied the DNA ploidy pattern and immunophenotype of AAH as compared with nodular hyperplasia and well-differentiated adenocarcinoma in 23 formalin-fixed, paraffin-embedded, whole-mounted retropubic prostatectomies.
- Representative sections were immunostained for keratin 34beta-E12, chromogranin, bcl-2, c-erbB-2, ki67-MIB1, and factor VIII (micro-vessel density).
- DNA ploidy was determined by image analysis and Feulgen-stained sections.

Lopez Beltran et al. [10] summarised the results as follows:

- There were rare scattered immunoreactive cells for chromogranin, bcl-2, and c-erbB-2 in nodular hyperplasia and AAH (mainly in the basal cell compartment) and in carcinoma.
- The ki67-MIB1 labelling index was different between nodular hyperplasia and AAH ($p<0.001$) and carcinoma ($p=0.003$) but not between AAH and carcinoma ($p=0.203$).
- Micro-vessel density was found to be different between AAH and carcinoma ($p=0.001$) but not between nodular hyperplasia and AAH ($p=0.105$) or carcinoma ($p=0.0820$).
- All foci of nodular hyperplasia, AAH, and carcinoma, were noted to be diploid.

Lopez-Beltran et al. [10] concluded that DNA Ploidy status and their selected panel of antibodies did not discriminate among these 3 entities reliably.

Gaudin et al. [11] stated the following:

- Adenosis (atypical adenomatous hyperplasia, small gland hyperplasia) of the prostate gland is typified by a relatively well-circumscribed proliferation of benign glands that frequently mimics low-grade adenocarcinoma.
- Even though general reviews of adenosis exist, relatively few specialized studies had characterized the histological features of adenosis.
- They undertook a study to review and better document the histology features of adenosis.

Gaudin et al. [11] evaluated forty-four trans-urethral-resection, (TUR) of prostate gland specimens containing a total of 145 foci of adenosis for the presence or absence of six histopathology examination features: mitotic figures, blue-tinged luminal mucinous secretions, intraluminal crystalloids, single cells, a focally infiltrative growth pattern, and prominent nucleoli. Gaudin et al. [11] performed immunohistochemical stains for high-molecular-weight cytokeratin on 66 (46%) of the foci to confirm the presence of a basal cell layer and thus the diagnosis of adenosis. Gaudin et al. [11] summarised the results as follows:

- Crystalloids were present in 58 foci (40%), an infiltrative growth pattern in 27 foci (19%), single cells in 23 foci (16%), prominent nucleoli in 22 foci (15%), mitotic figures in 16 foci (11%), and blue-tinged luminal mucinous secretions in 3 foci (2%).

Gaudin et al. [11] concluded that the diagnosis of adenosis was based upon a constellation of histological examination features and may be confirmed with the use of antibodies to high-molecular-weight cytokeratin.

Merrimen et al. [12] stated the following:

- There are a variety of morphology patterns and processes that had been implicated in the pathogenesis of prostate cancer.
- Prostatic intraepithelial neoplasia (PIN), inflammation with or without atrophy, and adenosis (atypical adenomatous hyperplasia) had all been given candidate status as precursor lesions of adenocarcinoma of prostate gland.
- Based upon decades of research, high grade prostatic intraepithelial neoplasia (HPIN), a proliferative lesion of prostatic secretory cells, had emerged as the most likely morphological pre-invasive lesion involved in the evolution of many but not all prostatic adenocarcinomas.

Merrimen et al. [12] briefly discussed other proposed precursors of prostatic adenocarcinoma and then focussed upon the history, diagnostic criteria and morphology of HPIN.

Yang et al. [13] stated the following:

- Atypical adenomatous hyperplasia (AAH) of the prostate gland, which also known as adenosis, is typified by a proliferation of prostatic glands with abnormal architectural patterns, but without significant cytologic atypia.
- In some cases, it may be difficult to differentiate AAH from prostatic carcinoma.
- Furthermore, it is not clear whether AAH is a precursor lesion of prostatic adenocarcinoma.
- P504S, which is a protein highly expressed in prostatic adenocarcinoma, had been recently demonstrated to be a marker of prostate cancer.

Yang et al. [13] undertook a study in order to examine the expression of P504S in AAH by immunohistochemistry. Yang et al. [13] summarised the results as follows:

- They had studied a total of 80 prostate specimens, including 40 cases of AAH (prostatectomy N = 30, biopsy N = 6, transurethral resection N = 4), 20 cases of prostatic adenocarcinomas, and 20 cases of benign prostatic hyperplasia.
- They had performed immunohistochemistry for a prostate cancer marker alpha-methyl acyl-CoA racemase (P504S) and a basal cell-specific marker 34betaE12 in all the cases.
- The 34betaE12 stain confirmed the presence of patchy basal cells in all 40 cases of AAH. P504S was undetectable in the majority of AAHs (33 of 40, 82.5%), focally expressed in four of 40 (10.0%), or diffusely positive only in three of 40 (7.5%) cases of AAH.
- Interestingly, two of seven P504S-positive AAHs were found adjacent to adenocarcinoma.
- In contrast, all benign prostatic hyperplasia cases, (20 of 20, 100%) were negative for P504S, and all 20 cases of prostatic carcinomas (100%) had exhibited a diffuse P504S staining pattern.

Yang et al. [13] made the following conclusions:

- These findings had suggested that AAH is a heterogenous entity.
- The biologic significance of P504S expression in a small subset of AAH has remained to be determined.
- Because most cases of AAH are negative for P504S, immunostaining of P504S is also of diagnostic value in differentiating the majority of AAHs from prostatic adenocarcinoma.

Green et al. [14] stated the following:

- Adenosis (atypical adenomatous hyperplasia) is a benign lesion, which morphologically simulates adenocarcinoma of prostate gland, even though the relationship between these 2 lesions was still debated.
- The TMPRSS2-ERG fusion is a common chromosomal rearrangement which occurs early in the development of invasive adenocarcinoma of the prostate and results in the expression of a truncated ERG protein.

- This fusion is present in 50% of adenocarcinomas and in 20% of high-grade prostate intraepithelial lesions.
- Until recently, fluorescent in situ hybridization was the only method available to detect these rearrangements.
- A specific anti-ERG antibody is now available for the detection of ERG protein expression and serves as a useful marker for ERG rearrangements.

Green et al. [14] analysed formalin-fixed, paraffin-embedded tissue sections of adenosis from cases of prostate biopsies (n = 30), transurethral resections of the prostate (n = 12), and radical prostatectomies (n = 3) via immunohistochemistry for ERG. Green et al. [14] summarised the results as follows:

- None (0%) of the foci of adenosis were positive for ERG protein expression.
- Out of 40 cases of Gleason score 6 adenocarcinoma on a tissue microarray, 22 (55%) were positive for ERG protein.
- Of the positive cases, 14 (63.6%) were moderate in intensity, with the remaining 36.4% being weak.

Green et al. [14] made the following conclusions:

- The lack of ERG expression in adenosis had supported the notion that it is not a precursor lesion of adenocarcinoma.
- Moreover, it had indicated that immunohistochemistry for ERG expression could be a useful tool to distinguish adenosis from adenocarcinoma.

De Visschere et al. [15] undertook a study to identify the multiparametric magnetic resonance imaging (mpMRI) characteristics of normal, benign and malignant conditions in the prostate. De Visschere et al. [15] reported the following:

- Fifty-six histopathological whole-mount radical prostatectomy specimens from ten randomly selected patients with prostate cancer (PC) were matched with corresponding transverse mpMRI slices.
- The mpMRI was undertaken preceding the biopsy and had consisted of T2-weighted imaging (T2-WI), diffusion-weighted imaging (DWI), dynamic contrast-enhanced imaging (DCE) and magnetic resonance spectroscopic imaging (MRSI).

De Visschere et al. [15] summarized the results as follows:

- In each prostate specimen, a wide range of histopathological conditions had been observed.
- They demonstrated consistent but overlapping characteristics on mpMRI.
- Normal glands within the transition zone had shown lower signal intensity (SI) on T2-WI, lower ADC values and lower citrate peaks upon MRSI as compared to the peripheral zone (PZ) due to sparser glandular elements and more prominent collagenous fibres.
- Within the PZ, normal glands were iso-intense on T2-WI, while high SI areas represented cystic atrophy.
- Mimickers of well-differentiated PC on mpMRI were inflammation, adenosis, HG-PIN and post-atrophic hyperplasia.

De Visschere et al. [15] made the following conclusions:

- Each prostate is a unique mixture of normal, benign and/or malignant areas that vary in extent and distribution resulting in very heterogeneous characteristics on mpMRI.
- Understanding the main concepts of this mpMRI-histopathology correlation might increase the diagnostic confidence in reporting mpMRI.

Bettendorf et al. [16] stated the following:

- High grade prostatic intraepithelial neoplasia (PIN) and atypical adenomatous hyperplasia (AAH) had been stated in a discussion to be precursors of prostate cancer (PC).
- Unlike high grade PIN the relation between AAH and PC is nevertheless, not clear.

Bettendorf et al. [16] undertook a study to analyse AAH, accompanying prostate carcinomas and carcinomas of the transitional zone after microdissection using comparative genomic hybridization (CGH) and multipelx-PCR with 10 microsatellite polymorphic markers. Bettendorf et al. [16] iterated that in every case non-neoplastic prostatic tissue was investigated for the same allelic imbalances. Bettendorf et al. [16] summarised the results as follows:

- Two AAH showed allelic imbalances in multiplex-PCR.
- These imbalances did not correlate with the corresponding tumours and furthermore were different to the LOH found in the investigated prostate tumours of the transitional zone.
- One AAH had demonstrated loss on chromosome 22q.
- They found allelic imbalances in over 50% of non-neoplastic tissue adjacent to prostatic carcinoma.

Bettendorf et al. [16] concluded that their findings had supported the idea that AAH does not seem to be linked closely to PC and should not be considered as an obligate premalignant lesion.

Lotan et al. [17] stated the following:

- They had observed a group of typically younger patients with multiple foci of small, non-lobular, crowded, but relatively bland acini on needle biopsy and in prostatectomy specimens.
- It is not clear whether this architectural pattern, which they had termed diffuse adenosis of the peripheral zone (DAPZ), is simply a crowded glandular variant of normal prostate morphology or whether it represents a risk factor for the development of prostatic carcinoma.

Lotan et al. [17] studied 60 cases of DAPZ on needle biopsy in their consult practice from 2001 to 2007. Lotan et al. [17] summarised their results as follows:

- Cases, on average, had shown 72% of cores involved by DAPZ.
- The average patient age was 49 years and the ages had ranged from 34 years to 73 years and the average serum prostate specific antigen (PSA) level at the time of biopsy was 5.2 ng/mL (in a total of 42 patients.
- Forty-three (72%) men had available clinical follow-up with 35 (81%) patients, having undergone re-biopsy and 8 (19%) followed with serial serum PSA measurements.
- Patients who were re-biopsied after DAPZ diagnosis had higher serum PSA levels than those who were followed by serum PSA levels alone (6.2 versus 3.1 ng/mL, P=0.04).
- Out of the re-biopsied cases, 20 (57%) were subsequently diagnosed with carcinoma, with an average of 15 months having elapsed between the initial biopsy and carcinoma diagnosis.
- Even though the majority of tissue sampled in a typical DAPZ case had no cytologic atypia, in 65% of cases there were admixed rare foci of atypical glands with prominent nucleoli comprising <1% of submitted tissue.
- Patients with a subsequent diagnosis of carcinoma were more likely to have had DAPZ with focal atypia, although this did not reach statistical significance (70% vs. 36%, P=0.08).
- They had histologically confirmed the carcinoma diagnosis in 18 out of 20 cases.
- In 12 out of 14 radical prostatectomies, they were able to review the slides. Eleven had Gleason score 3+3=6 adenocarcinoma in addition to background DAPZ; 9 had shown peripheral zone organ-confined cancer, and 2 had focal extra-prostatic extension. In one case of DAPZ misdiagnosed as cancer on biopsy, no carcinoma was found at prostatectomy.
- DAPZ is a newly described and diagnostically challenging mimicker of carcinoma of the prostate gland which is seen in prostate needle biopsies from typically younger patients.

Lotan et al. [17] concluded that their findings had suggest that DAPZ should be considered a risk factor for prostate cancer and that patients with this finding should be followed closely and re-biopsied.

Enciu et al. [18] stated the following:

- The diagnosis of prostate cancer is challenging because of the existence of lesions that simulate adenocarcinoma.
- Such a lesion is atypical adenomatous hyperplasia (AAH) or adenosis, which represents a proliferation of crowded, small to medium glands with basal cell layer invariably present, but often inconspicuous on routine stains.
- The importance of the lesion lies in the potential for it being misdiagnosed as low-grade adenocarcinoma (Gleason 1 or 2).

Enciu et al. [18] reported the case of a male patient, who had undergone a transurethral prostatic resection surgery. Histopathology examination of the specimen had shown benign prostatic hyperplasia with a focus of crowded glands with a nodular appearance. The presence of basal cell was assessed utilising high molecular-weight cytokeratin (HMWCK), clone 34βE12 and p63 immunostaining, which revealed discontinuous positive immunostaining. In adenocarcinomas, the basal cell layer was absent. Enciu et al. [18] concluded that their case had highlighted the usefulness of 34βE12 antibodies, avoiding a false positive diagnosis of cancer, with negative consequences on the patient's psychological condition and treatment costs. Enciu et al. [18] had recommended the follow-up of the patient.

Hameed et al. [19] stated that the differential diagnoses of prostatic carcinoma and bladder epithelial neoplasms include several histological mimics that should be known to avoid misdiagnosis. Hameed et al. [19] discussed pseudo-neoplastic lesions of the prostate gland and urinary bladder that could potentially be confused with carcinoma of the prostate gland and urinary bladder epithelial neoplasms, respectively, with specific focus on their distinguishing histopathologic features. Hameed et al. [19] utilised relevant literature and author's experience.

Hameed et al. [19] made the ensuing conclusions:

- Pseudo-neoplastic lesions within the prostate gland include those of prostatic epithelial origin, the most common being atrophy, adenosis (atypical adenomatous hyperplasia), basal cell hyperplasia, and crowded benign glands, as well as those of non-prostatic origin, such as seminal vesicle epithelium.
- Such lesions often mimic lower-grade prostatic adenocarcinoma, whereas others, such as clear cell cribriform hyperplasia and granulomatous prostatitis, for example, are in the differential diagnosis of Gleason adenocarcinoma, Gleason grade 4 or 5.
- Pseudo-neoplastic lesions of the urinary bladder include lesions that could potentially be confused with urothelial carcinoma in situ, such as reactive urothelial atypia, and others, such as polypoid/papillary cystitis, where papillary urothelial neoplasms are the main differential diagnostic concern.
- Many lesions could simulate invasive urothelial carcinoma, including pseudo-carcinomatous hyperplasia, von Brunn nests, and nephrogenic adenoma.
- Diagnostic awareness of the salient histomorphology and relevant immunohistochemical features of these prostatic and urinary bladder pseudo-neoplasms is critical to avoid rendering false-positive diagnoses of malignancy.

Beltran et al. [20] stated the following in 2019:

- There are few studies into the rate and causes of histopathologic false-positive diagnosis of prostate cancer.
- Only 2 of these, including a previous one from their group, had incorporated survival data.
- In addition, in none of the previous studies had immunohistochemistry (IHC) been originally requested on any of the misdiagnosed cases.

Lopez Beltran et al. [20] stated that diagnostic biopsies in 1080 cases and transurethral resection of prostate specimens in 314 cases from 1394 men

with clinically localized prostate cancer diagnosed within the United Kingdom but treated conservatively between 1990 and 2003 were reviewed by a panel of 3 genitourinary pathologists. Lopez Beltran et al. [20 also stated that thirty-five cases were excluded for being potentially incomplete. Out of the remaining 1359, 30 (2.2%) were reassigned to a non-malignant category (26 benign and 4 suspicious for malignancy). IHC had been originally performed on 7 of these. The reasons for the errors were recorded on each case as follows: adenosis (19), partial atrophy (3), prostatic intraepithelial neoplasia (2), seminal vesicle epithelium (1), and hyperplasia (1). Follow-up of these men had revealed only one prostate cancer-related death, possibly due to unsampled tumour. Lopez Beltran et al. [20] made the ensuing conclusions:

- A relatively small number of prostate cancer mimics were responsible for a large proportion of the false-positive prostate cancer diagnoses and the use of IHC did not prevent the overcall of benign entities as cancer in approximately a quarter of these cases.
- Targeting these mimics at educational events and raising awareness of the pitfalls in the interpretation of IHC in prostate cancer diagnosis, emphasizing that glands within a suspicious focus should be treated as a whole rather than individually, might be beneficial in lowering the rate of false-positive diagnosis.

Herawi et al. [21] undertook a study to determine the incidence of various benign mimickers of adenocarcinoma of prostate gland most commonly encountered in a busy consultation practice. Herawi et al. [21] reported that all prostate needle biopsies from the consult service of one of the authors were prospectively evaluated over a 7-month period. Only cases with foci where the contributor questioned malignancy and which upon expert review the entire case was determined to be benign were included in the study. Herawi et al. [21] summarised the results as follows:

- A total of 567 separate suspected atypical foci from 345 patients of a total of 4,046 patients (8.5%) received in consultation were identified.
- Out of these, 281 foci (49.5%) had immunohistochemical (IHC) studies undertaken by the outside institution, which included high molecular weight cytokeratin (HMWCK) (n = 280), alpha-methylacyl-CoA racemase (AMACR) (P504s) (n = 45), and p63 (n = 34).
- The most common mimicker was partial atrophy (203 of 567; 35.8%).
- Technically adequate IHC for basal cells was undertaken in 117 cases of partial atrophy with patchy or patchy/negative staining seen in 102 of 117 (87%), with the remaining 13% of cases completely negative.
- A total of 15 of 19 (79%) cases of partial atrophy were positive with AMACR.
- Crowded benign glands, insufficiently crowded or numerous to warrant a diagnosis of adenosis, was the second most common mimicker (146 of 567; 25.7%).
- Crowded benign glands had patchy or patchy/negative IHC for basal cells in 66 of 81 (81%) cases with the remaining 19% of cases completely negative.
- A total of 7 of 11 (64%) cases of crowded glands were positive for AMACR.

Herawi et al. [21] stated the following:

- In the past, complete atrophy, adenosis, seminal vesicle, and granulomatous prostatitis were considered common mimickers of prostate cancer on prostatic needle biopsies.
- Their study had shown that currently partial atrophy and crowded benign glands are the most common benign changes causing diagnostic difficulty and prompting consultation.
- Negative or patchy staining for basal cells and positive staining for AMACR might contribute to diagnostic difficulty in these entities.

Gaudin et al. [22] stated the following:

- Classically, adenosis had been described as occurring in the transition zone of the prostate gland, a region not routinely sampled with needle biopsies.
- Nevertheless, with urologists undertaking more needle biopsies, they had seen an increasing number of cases of adenosis in needle biopsies of the prostate gland.
- To better characterize the histology features of adenosis that are present in needle biopsy specimens, they reviewed 63 needle biopsies of the prostate containing a total of 75 foci of adenosis. Of the 63 cases, 51 (81%) were seen in consultation by one of the authors, and in approximately 80% of these cases, the differential diagnosis included low-grade adenocarcinoma.
- Crystalloids were present in 18 foci (24%), a minimally infiltrative growth pattern in 10 foci (13%), prominent nucleoli in 10 foci (13%), scattered single cells in eight foci (11%), mitoses in two foci (3%), and blue-tinged mucinous secretions in two foci (3%).
- Immunohistochemistry was undertaken on 29 (39%) foci to exclude adenocarcinoma.
- Intraluminal crystalloids, a minimally invasive growth pattern, and single cells occurred with sufficient frequency in adenosis, such that their presence was not useful in distinguishing low-grade adenocarcinoma from adenosis; 62 (83%) of the foci of adenosis were found to contain none of the remaining histologic features (mitoses, blue-tinged luminal secretions, prominent nucleoli), whereas 12 foci (16%) had one of the features and one focus (1%) had two features.

Gaudin et al. [22] made the following conclusions:

- Adenosis should always be in the differential diagnosis when one is considering low-grade carcinoma on needle biopsy.
- The key feature of adenosis is the merging of small crowded glands with surrounding benign glands; in contrast, the small glands of adenocarcinoma differ in their cytoplasm, nuclei, or luminal contents from adjacent benign glands.

Phillips et al. [23] stated the following:

- Arginine deprivation is a novel antimetabolite strategy for the treatment of arginine-dependent cancers that exploits differential expression and regulation of key urea cycle enzymes.
- Several studies had focused upon inactivation of arginine-succinate synthetase 1 (ASS1) in a range of malignancies, including melanoma, hepatocellular carcinoma (HCC), mesothelial and urological cancers, sarcomas, and lymphomas.
- Epigenetic silencing had been identified as a key mechanism for loss of the tumour suppressor role of ASS1 leading to tumoral dependence on exogenous arginine.
- More recently, dysregulation of arginosuccinate lyase had been documented in a subset of arginine auxotrophic glioblastoma multiforme, HCC and in fumarate hydratase-mutant renal cancers.
- Clinical trials of several arginine depletors were ongoing, including pegylated arginine deiminase (ADI-PEG20, Polaris Group) and bioengineered forms of human arginase.
- ADI-PEG20 is furthest along the path of clinical development from combinatorial phase 1 to phase 3 trials and is described in more detail.
- The challenge would be to identify tumours sensitive to drugs such as ADI-PEG20 and integrate these agents into multimodality drug regimens using imaging and tissue/fluid-based biomarkers as predictors of response.
- Lastly, resistance pathways to arginine deprivation require further study to optimize arginine-targeted therapies in the oncology clinic.

Gaudin et al. [24] stated that following:

- Classically, adenosis had been described as occurring in the transitional zone of the prostate gland, a region not routinely sampled with needle biopsies.
- Nevertheless. with urologists performing more needle biopsies, they had seen an increasing number of cases of adenosis in needle biopsies of the prostate.
- In order to better characterize the histology features of adenosis present within needle biopsy specimens, they had reviewed 63 needle biopsies of the prostate gland containing a total of 75 foci of adenosis.
- Out of the 63 cases, 51 (81%) were seen in consultation by one of the authors, and in approximately 80% of these cases, the differential diagnosis included low-grade adenocarcinoma.
- Crystalloids were present in 18 foci (24%), a minimally infiltrative growth pattern in 10 foci (13%), prominent nucleoli in 10 foci (13%), scattered single cells in eight foci (11%), mitoses in two foci (3%), and blue-tinged mucinous secretions in two foci (3%).
- Immunohistochemistry was undertaken on 29 (39%) foci to exclude adenocarcinoma.
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- Adenosis should always be in the differential diagnosis when one is considering low-grade carcinoma on needle biopsy.
- The key feature of adenosis is the merging of small crowded glands with surrounding benign glands; in contrast, the small glands of adenocarcinoma differ in their cytoplasm, nuclei, or luminal contents from adjacent benign glands.

Doll et al. [25] iterated the ensuing:

- Atypical adenomatous hyperplasia (AAH) of the prostate gland, a small glandular proliferation, is a putative precursor lesion to prostate cancer, in particular to the subset of well-differentiated carcinomas which arise within the transition zone, the same region where AAH lesions most often occur.
- Many morphology characteristics of AAH suggest a relationship to cancer; nevertheless, no definitive evidence had been reported.

Doll et al. [25] analysed DNA from 25 micro-dissected AAH lesions for allelic imbalance as compared to matched normal DNA, using one marker each from chromosome arms 1q, 6q, 7q, 10q, 13q, 16q, 17p, 17q, and 18q, and 19 markers from chromosome 8p. Doll et al. [25] observed 12% allelic imbalance, with loss only within chromosome 8p11–12. Doll et al. [25] stated the following:

- These results had indicated that genetic alterations in transition zone AAH lesions might be infrequent.
- This genotypic profile of AAH would allow for comparisons with well-differentiated carcinomas in the transition zone of the prostate.

Cheng et al. [26] stated the following:

- Atypical adenomatous hyperplasia (AAH) of the prostate gland is characterized by lobular proliferation of closely packed small acini.
- It has been postulated that AAH is a precursor lesion for low-grade prostate cancer arising from the transition zone of the prostate gland.
- Telomere dysfunction is common during malignant transformation of epithelia.

Cheng et al. [26] undertook a study, to investigate telomere shortening in AAH (in a total of 93 cases), high-grade prostatic intraepithelial neoplasia (HGPIN) (in 68 cases), and prostatic adenocarcinoma (PCA) (in 70 cases) using quantitative fluorescence in situ hybridization. Cheng et al. [26] summarised their results as follows:

- Twenty percent (19 of 93) of AAH specimens, 68% (46 of 68) of HGPIN, and 83% (58 of 70) of PCA had demonstrated significant telomere shortening.
- Thirty-two percent of AAH lesions had α-methylacyl-CoA racemase (AMACR) expression, a sensitive and specific marker for HGPIN and PCA.
- AMACR expression in AAH was seen more frequently in AAH foci with telomere shortening or coexisting PCA.

Cheng et al. [26] concluded that their findings had indicated that a subset of AAH lesions have telomere shortening and AMACR expression, suggesting that these foci may be precursors for PCA.

Zhang et al. [27] stated that they had analysed One hundred twenty-one AAH foci from 101 patients who had undergone transurethral prostatic resection or prostatectomy immunohistochemically for AMACR, high molecular weight cytokeratin 34βE12, and p63 expression by a triple antibody (PIN4) cocktail stain. Zhang et al. [27] summarised the results as follows:

- Sixty-eight foci (56%) of AAH had demonstrated no AMACR immunostaining.
- Fourteen cases (12%) had exhibited weak AMACR immunoreactivity in 1% to 9% of lesional cells.
- Sixteen cases (13%) had exhibited strong immunopositivity for AMACR in >50% of lesional cells.
- AMACR expression in AAH was found to be significantly higher in cases in which coexisting PCA was present, compared with its expression in AAH foci without coexisting PCA ($P = 0.03$).
- Strong diffuse AMACR positivity in over 50% of lesional cells was visualised almost exclusively in AAH foci with coexisting PCA ($P = 0.002$).
- AMACR expression in AAH demonstrated no correlation with patient age ($P = 0.38$), specimen type ($P = 0.35$), prostate weight ($P = 0.80$), zonal location ($P = 0.50$), distance to cancer ($P = 0.28$), Gleason score ($P = 0.06$), or pathologic stage ($P = 0.23$). Increased AMACR expression showed a negative correlation with the size of AAH foci ($P = 0.03$).
- All AAH lesions had demonstrated fragmented basal cell layers, which were highlighted by p63 and high molecular weight cytokeratin staining.

Zhang et al. [27] made the following conclusions:

- A significant percentage of AAH cases had exhibited stronger and more extensive AMACR expression when associated with prostatic adenocarcinoma, as compared to AAH foci found without coexisting prostate cancer.
- Their data had provided additional evidence linking AAH to adenocarcinoma of prostate gland.

MZ [28] stated the following:

- Atypical prostate gland especially atypical small acinar proliferation (ASAP) is a histopathological diagnosis which requires a follow-up biopsy 3 months to 6 months after the first biopsy, because 17-60% of cases potentially to be malignant.
- The varied clinical and histomorphology characteristics of the atypical prostate gland make it difficult to confirm the final diagnosis as a benign lesion or adenocarcinoma of the prostate gland.
- They had undertaken a study to describe clinical-histomorphology cases of atypical prostate gland at Anatomical Pathology Department FKUI/RSCM and to identify histopathology-morphological features of the atypical prostate gland as benign lesions or prostate adenocarcinoma on immunohistochemistry diagnosis.
- MZ [28] undertook a histopathological investigation of prostate gland cases with atypical nuclei in from 2011 to 2021 from archives of Anatomical Pathology Department FKUI/RSCM. The clinical and histopathology-morphological characteristics were assessed and categorized into benign lesions or prostate adenocarcinoma based on immunohistochemistry appearance.

MZ [28] summarised the results as follows:

- There were 109 cases of atypical prostate gland, 49 of which had met the inclusion and exclusion criteria and could be analysed.
- Corpora amylacea was found in 11 cases (84.6%) within the benign lesion group, statistically significant (p-value 0.005).
- Intraluminal crystalloids were found in 4 cases (100%) in the adenocarcinoma of prostate gland group with p-value 0.050, close to significant.
- Other clinical-histomorphology characteristics did not demonstrate a significant relationship both in benign lesions and prostate adenocarcinoma groups (p-value 0.05).

MZ [28] made the ensuing conclusions:

- On histopathological examination of the atypical prostate gland which is difficult to re-biopsy, the discovery of corpora amylacea might lead to the diagnosis of a benign lesion, while the discovery of intraluminal crystalloids might lead to the diagnosis of adenocarcinoma of prostate gland.
- The diagnosis should be supported by immunohistochemistry characteristics.

Armah and Parwani [1] reported a 62-year-old man, who was referred to his urologist for symptoms of urinary tract obstruction and an elevated serum prostate-specific antigen (PSA) level of 3.61 ng/mL. He underwent digital rectal examination and ultrasound scan which demonstrated an ill-defined nodule within his prostate gland that was suggestive of malignancy. A needle biopsy of the prostate lesion was undertaken. The

histology section of one needle biopsy was typified at low-power examination by the replacement of normal prostatic tissue by a proliferation of haphazardly arranged glands, which were partially arranged in an ill-defined nodule. The lesions had an infiltrative aspect at their edge, but the glands were noted not to be admixed with normal prostatic acini. At medium power, the proliferating glands were found to be often slit-like, variably sized and shaped, alternating small and rounded acini with elongated and branching ones (see Figures 1A and 1B). Occasional solid nests and cords could be seen. The atypical acini were noted to be lined by epithelial secretory cells with clear eosinophilic cytoplasm (see Figure 1C). The nuclei were noted to be regular, rounded to oval, and slightly larger than those of the adjacent normal prostatic acini. There were inconspicuous nucleoli. There were a few focally prominent basally located cells with dense amphophilic cytoplasm. Eosinophilic crystalloids were present within some acinar lumina (see Figure 1C and 1D).

Figure 1

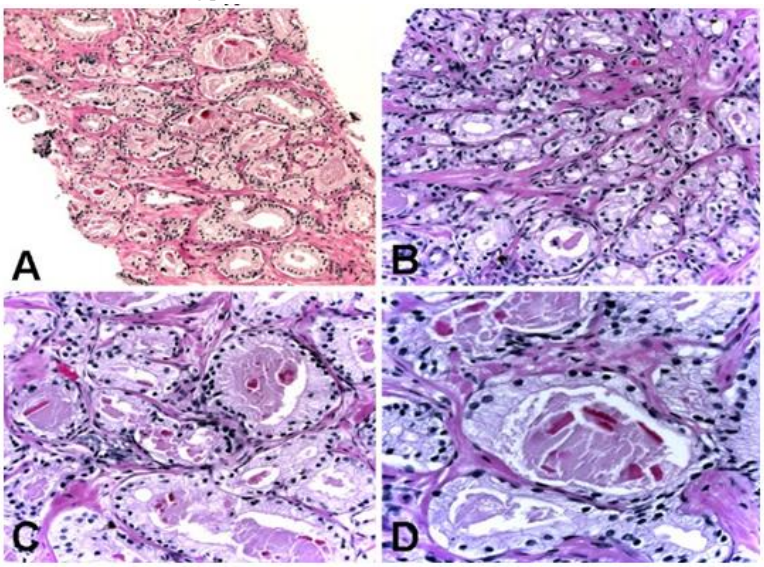

Figure 1: Histologic (hematoxylin-eosin) findings of atypical adenomatous hyperplasia of the prostate. (A) Crowded haphazardly arranged variably sized glands with infiltrative appearance of glands at the edges. Original magnification × 200. (B) Predominantly small glands lined by epithelial secretory cells with clear eosinophilic cytoplasm and minimal cytological atypia. Original magnification × 400. (C) Predominantly large glands lined by epithelial secretory cells with clear eosinophilic cytoplasm and minimal cytological atypia. Original magnification × 400. (D) Predominantly large glands lined by epithelial secretory cells with clear eosinophilic cytoplasm, minimal cytological atypia with inconspicuous nucleoli, few focally prominent basally located cells with dense amphophilic cytoplasm, and luminal eosinophilic crystalloids. Original magnification × 600. Reproduced from [1] Under the Creative Commons Attribution License.

Immunohistochemistry (IHC) staining studies revealed strong reactivity for alpha-methylacyl-coenzyme A-racemase (AMACR) in both small and large glands (see Figures 2A and 2B), patchy reactivity for p63 (see figure 2C) and patchy reactivity for high-molecular-weight cytokeratin CK903/34βE12 (see figure 2D).

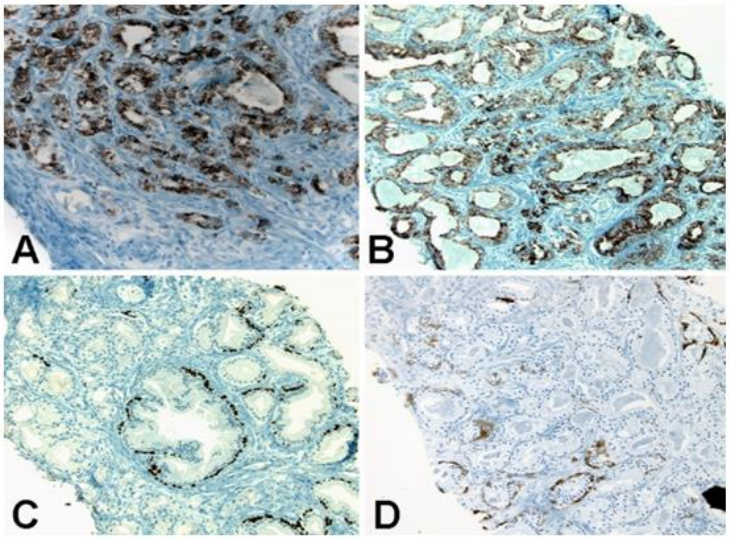

Figure 2: Immunohistochemical findings of atypical adenomatous hyperplasia of the prostate. (A) Strong reactivity for alpha-methylacyl-coenzyme A-racemase in predominantly small glands. Original magnification × 200. (B) Strong reactivity for alpha-methylacyl-coenzyme A-racemase in predominantly large glands. Original magnification × 200. (C) Patchy reactivity for p63 in both small and large glands. Original magnification × 200. (D) Patchy reactivity for high-molecular-weight cytokeratin CK903/34βE12 in both small and large glands. Original magnification × 200.

The final histopathology diagnosis was benign prostatic tissue with a focus of florid AAH. Two subsequent follow-up prostate needle biopsies were undertaken six months and 12 months later both showed benign prostatic tissue with atrophic changes.

Armah and Parwani [1] made the ensuing educative narrative discussions:

- AAH of the prostate is a microglandular lesion and a recognized mimicker of small acinar adenocarcinoma [2,3,4].
- AAH is typified by a proliferation of prostatic glands with abnormal architectural patterns, but without significant cytologic atypia.
- AAH of the prostate gland is usually an incidental finding in transurethral resections or simple prostatectomies undertaken in the clinical setting of benign prostatic hyperplasia.
- It has been documented that the prevalence of AAH in transurethral prostatectomy specimens without cancer ranges from 1.6% to 7.3% [11] compared to its prevalence of 0.8% in needle biopsy specimens [22].
- Their rarity in needle biopsies of the prostate is attributable to the fact that sampling of the transition zone is not common in needle biopsies. Although, AAH can be diagnosed throughout the prostate, it is most often located in the transition zone of the prostate in intimate association with benign nodular hyperplasia [29]. Since the frequency of needle biopsies, including tissue from the transition zone, is likely to increase due to the introduction of ultrasound-guided multiple segmental prostate biopsy [5], knowledge of the main diagnostic histologic features of AAH would represent an important issue in genitourinary surgical pathology. The diagnosis of AAH in needle biopsies, as seen in the case herein presented, relies on both histologic features in hematoxylin and eosin-stained slides and immunohistochemical features.

- Microscopically, AAH is a localized proliferative lesion consisting of small amounts of atypical epithelial cells arranged in irregular glandular patterns, often within or adjacent to typical hyperplastic nodules [30].
- At low magnification, it is usually partially circumscribed with a pushing rather than infiltrating border, although the small acini may show a limited degree of infiltrative features at the margins. The individual glands are closely packed but separate and show no evidence of fusion. The glands show some variation in size and shape and are lined by cuboidal to low columnar cells with moderate to abundant clear or lightly eosinophilic cytoplasm. [24,31]
- The basal cells are usually recognized at least focally. The luminal borders are often irregular and somewhat serrated in contrast to the rigid borders that typify small acinar carcinoma. The lumens are often empty but may contain corpora amylacea and in some instances luminal eosinophilic crystalloids [11,31]. The nuclei are round to oval, slightly enlarged, and with uniform fine chromatin and inconspicuous or small nucleoli [31]. AAH can be difficult to distinguish from low-grade prostatic adenocarcinoma (Gleason pattern 1 or 2) because both are located in the transition zone and show small acinar proliferation and intraluminal crystalloids [31]. The two distinguishing features of AAH are the lack of significant cytological atypia and the presence of patchy basal cells, which can be demonstrated by patchy immunostaining for high molecular-weight cytokeratin (CK903/34βE12) or p63 [29,30,31]
- In contrast, prostatic adenocarcinoma usually shows notable nuclear atypia, lacks basal cells, and rarely expresses high molecular weight cytokeratin. [32]
- Yang and colleagues [13] found that AMACR was focally expressed in 10% of cases and diffusely positive in only 7.5% of cases of AAH. The biological significance of AMACR expression in a small subset of AAH remains to be determined. AAH differs from sclerosing adenosis, another benign mimicker of prostate adenocarcinoma, since sclerosing adenosis displays myoepithelial features of the basal cells and an exuberant stroma of fibroblasts and loose-ground substance [33].

While circumstantial evidence exists, there is lack of proof of a relationship between AAH and adenocarcinoma. It has been suggested that AAH is a precursor of some low-grade transition zone carcinomas but the lack of an increased prevalence of AAH in prostate glands with transition zone carcinoma argues against this hypothesis. Clearly, there is less evidence linking AAH to carcinoma than there is for high-grade PIN and cancer. Therefore, the major importance of AAH is its potential for being misdiagnosed as adenocarcinoma. Biochemical and molecular analyses of AAH have generated inconclusive results. There is limited data that AAH has a proliferation rate higher than hyperplasia but lower than adenocarcinoma [2,29,30,34]. By the use of fluorescent *in situ* hybridization analysis, chromosomal anomalies were seen in only 9% of AAH cases, compared with 55% of prostatic adenocarcinoma cases. [34]. Two independent studies showed that AAH contains genetic alterations commonly found in early prostatic carcinoma, with changes being reported in 47% or 12% of AAH cases, respectively [25,30]. Recent cytogenetic analyses have detected abnormalities of chromosome 8 in a very small proportion (4–7%) of AAH cases [29,30]. The recent finding of molecular alterations in AAH including immunoreactivity for AMACR, a marker linked to prostate adenocarcinoma, suggests that at least a subset of AAH cases might be related to prostate carcinoma of the transition zone [13, 25,34].

The widespread use of PSA screening has led to an increase in prostate needle biopsies and, subsequently, an increase in earlier detection of prostate carcinoma. This trend has also led to an increase in the number of equivocal diagnoses on prostate biopsy specimens. Surgical pathologists must make critical decisions on an increasing number of prostate needle biopsy specimens with only small foci of atypical glands. In this setting, the mimics of prostate cancer must be distinguished from a small focus of adenocarcinoma. The distinction of benign small acinar proliferations (benign mimickers of cancer) from atypical acinar

proliferations suspicious for cancer is crucial, since the subsequent clinical approach is different. Biopsies harbouring a small focus of atypical glands frequently represent an under-sampled cancer and a subsequent biopsy will show cancer in up to 50% of cases [35]. In contrast, following a diagnosis of benign mimickers of cancer (such as atrophy or AAH), a re-biopsy is usually not indicated.

Armah and Parwani [1] made the following conclusions:

- AAH is a transition zone lesion of the prostate gland which could mimic small acinar carcinoma.
- By itself positive immunostaining for AMACR is not diagnostic for carcinoma because the latter is also positive in high-grade PIN and some benign mimickers of adenocarcinoma.
- The case they had reported had highlighted the utility of AMACR, p63 and CK903/34βE12 immunostaining in the accurate diagnosis of adenosis of the prostate, a benign mimicker of prostate adenocarcinoma.

Conclusions

- Atypical Adenomatous Hyperplasia (AAH) of Prostate Gland or adenosis of prostate gland **is** a terminology that refers transition zone lesion of the prostate which can mimic small acinar carcinoma of the prostate Gland.
- By itself positive immunohistochemistry staining for AMACR is not diagnostic for carcinoma because the latter is also positive in high-grade PIN and some benign mimickers of adenocarcinoma.
- There is the necessitation to utilize AMACR, p63 and CK903/34βE12 immunostaining in the accurate diagnosis of adenosis of the prostate, which is a benign mimicker of adenocarcinoma of prostate gland.

Conflict of Interest - Nil

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