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Relationship between Clinicohistomorphology Profile of Atypical Prostate Gland and Diagnosis Benign Lesion or Prostate Adenocarcinoma

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ABSTRACT

Background
Atypical prostate gland especially atypical small acinar proliferation (ASAP) is a histopathological diagnosis that requires a follow-up biopsy 3-6 months after the first biopsy, because 17-60% of cases potentially to be malignant. The varied clinical and histomorphological characteristics of the atypical prostate gland make it difficult to confirm the final diagnosis as a benign lesion or prostate adenocarcinoma. This study aims to describe clinicohistomorphological cases of atypical prostate gland at Anatomical Pathology Department FKUI/RSCM and to identify histomorphological features of the atypical prostate gland as benign lesions or prostate adenocarcinoma on immunohistochemistry diagnosis.
Methods
A histopathological investigation of prostate gland cases with atypical nuclei was carried out in 2011-2021 from archives of Anatomical Pathology Department FKUI/RSCM. Clinical and histomorphological characteristics were assessed and categorized into benign lesions or prostate adenocarcinoma based on immunohistochemistry appearance.
Results
There were 109 cases of atypical prostate gland, 49 of which met the inclusion and exclusion criteria and could be analyzed. Corpora amylacea was found in 11 cases (84.6%) in the benign lesion group, statistically significant (p-value 0.005). Intraluminal crystalloids were found in 4 cases (100%) in the prostate adenocarcinoma group with p-value 0.050, close to significant. Other clinicohistomorphological characteristics did not show a significant relationship both in benign lesions and prostate adenocarcinoma groups (p-value 0.05).
Conclusion
On histopathological examination of the atypical prostate gland that is difficult to re-biopsy, the discovery of corpora amylacea may lead to the diagnosis of a benign lesion, while the discovery of intraluminal crystalloids may lead to the diagnosis of prostate adenocarcinoma. The diagnosis must be supported by immunohistochemistry characteristics.

Keywords: Atypical prostate gland, atypical small acinar proliferation, prostate adenocarcinoma

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INTRODUCTION

Prostate carcinoma is the second most frequent malignancy and the fifth most common cause of death due to cancer in men worldwide in 2020. The incidence varies from 6.3 to 83.4 per 100.000 men worldwide, the highest in Europe and the lowest in Asia and North Africa.[1] According to GLOBOCAN, in 2020 the incidence of prostate carcinoma in Indonesia reached 13.563 (7.4%) new cases.[2]

Histopathological examination is a gold standard to diagnose prostate carcinoma, based on a morphological feature, such as growth pattern, atypical nuclei, and absence of basal cells.[3] However, histopathological diagnosis of prostate adenocarcinoma, especially in cases with a small volume or minimal lesion, can be biased by *pseudoneoplastic* lesions such as prostate atrophy and basal cell hyperplasia.[4]

The atypical prostate gland, especially *atypical small acinar proliferation* (ASAP), is a proliferation of acinar glands of the prostate with an atypical nuclei appearance suggestive of malignancy but not sufficient for a definitive diagnosis as a prostate adenocarcinoma.[5,6] ASAP is found in 1-5% of prostate biopsies and is most commonly found in the peripheral zone.[5] Data on cases of the atypical prostate gland and ASAP at Cipto Mangunkusumo Hospital (RSCM) Jakarta based on the results of histopathological examination recorded 109 cases (3.51%) of 3.099 cases from prostate biopsy/resection (2011 to July 2021).

ASAP carries a risk of developing carcinoma in 17-60% of cases, so a follow-up biopsy is required 3-6 months after the initial diagnosis.[5,6] Prostate biopsy is an invasive procedure and can be a burden to the patient and the healthcare system. Follow-up biopsies are usually disliked by clinicians due to various risk factors that are harmful to the patients and can increase the risk of infection.[6,7] Therefore, minimizing the histopathological diagnosis of the atypical prostate gland or ASAP during initial biopsy interpretation will reduce the requirement for repeat biopsies and the cost of other diagnostic procedures.[6]

An immunohistochemistry examination is part of the procedure to confirm a diagnosis of prostate adenocarcinoma and minimize a diagnosis of the atypical prostate gland or inconclusive answers that require further biopsies.[3,4,8] Immunohistochemistry examination can show the presence or absence of a basal cell layer in small/foci atypical prostate gland. Diagnosis of a benign lesion is established if foci still retaining the basal cell layer. Meanwhile, foci without a basal cell layer on immunohistochemistry examination can help guide the diagnosis of prostate adenocarcinoma, although correlation with morphological features is still needed.[4]

This retrospective review aims to determine the histomorphological clinical data of atypical prostate gland and ASAP cases on prostate biopsies at the Anatomical Pathology Department FKUI/RSCM. In addition, this study aims to identify types of histomorphological features of the atypical prostate gland that are more suggestive of a benign lesion/prostate adenocarcinoma compared to a final diagnosis that combines histomorphological and immunohistochemistry examination.

METHOD

This retrospective study is a descriptive-analytic study with a cross-sectional research design. The samples used were secondary data obtained from the archive of Anatomical Pathology Department FKUI/RSCM in the period of 10 years and 7 months, from January 2011 to July 2021, and then the immunohistochemistry preparations were traced.

The inclusion criteria were all preparations originating from the prostate and diagnosed as ASAP, prostatic hyperplasia with atypical cell foci, prostatic hyperplasia with acini of suspicious malignancy, and prostatic hyperplasia with foci of suspicious adenocarcinoma. Exclusion criteria were histopathological preparations without immunohistochemistry examination. *Dropout* criteria were cases with missing slides and incomplete immunohistochemistry panel staining (without basal cell or AMACR staining). Furthermore, cases were not categorized as atypical prostate gland at reassessment or from the expert consensus.

Samples that met inclusion and exclusion criteria and could be analyzed in this study were 49 cases. Sampling was carried out by *total sampling* in all cases. The histopathological preparations were stained with hematoxylin-eosin staining, while the immunohistochemistry preparations were stained with basal cell markers (p63, p40, and/or HMWCK) and AMACR.

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Two researchers (LIT, YDB) reassessed histopathological preparations into an atypical prostate gland, benign lesion, or prostate adenocarcinoma *blinded* without knowing the results of the immunohistochemistry examination. The histomorphological variables assessed were stromal infiltration, nuclei enlargement, nucleoli enlargement, nuclei chromatin, amphophilic cytoplasm, basophilic mucin, intraluminal crystalloid, mitosis, inflammation, and *corpora amylacea,* adapted from the approach of Sade et al.[6]

Samples with the histomorphological pattern as an atypical prostate gland will be categorized as benign lesion or prostate adenocarcinoma according to the pattern of immunohistochemistry staining. It is benign lesion if basal cell markers (p63, p40, and/or HMWCK) are positive (stained on basal cells) and negative AMACR (not stained on atypical cells). It is prostate adenocarcinoma if the basal cell marker (p63, p40, and/or HMWCK) is negative (not stained on basal cells) and positive AMACR (stained on atypical cells).

The results of the immunohistochemistry reassessment will be compared with the results of the immunohistochemistry profile that have been released by the Anatomical Pathology Department FKUI/RSCM. If there are different immunohistochemistry results, an expert consensus will be reached to determine the conclusion of the diagnosis. Data analysis in this study used SPSS 25.0 using the *Chi-Square* test and if the requirements for the *Chi-Square* test were not met, analysis was reached using *Fisher's exact test*. Data is considered significant if the *p-value* <0.05.

RESULTS

Based on archival data from the Department of Anatomic Pathology FKUI/RSCM for the period January 2011 to July 2021, 109 cases were found with a diagnosis of the atypical prostate gland. Forty-nine of these cases met the inclusion and exclusion criteria and were reassessed for their morphological characteristics and immunohistochemistry profile, then categorized as benign lesion or prostate adenocarcinoma. The distribution of age and clinical characteristics of atypical prostate gland patients in this retrospective review is presented in (Table 1).

After reassessment, all cases were grouped into two categories based on their immunohistochemistry profile, 25 cases in the benign lesion group and 24 cases in the prostate adenocarcinoma group (Table 2).

Table 1. Distribution of age and PSA levels in cases of atypical prostate gland in the Anatomical Pathology Department FKUI/RSCM 2011-2021.

Clinical characteristics	Frequency (%) (n=49)
Age	
40-59	7 (14,3)
60-79	40 (81,6)
≥80	2 (4,1)
PSA	
0-4	1 (2)
5-20	9 (18,4)
>20	2 (4,1)
Unknown	37 (75,5)

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Table 2. Association of clinical characteristics and histomorphology of atypical prostate gland on reassessment.

Clinical and histomorphological characteristics	Benign lesion (n=25)	Prostate Adenocarcinoma (n=24)	P Value
Age[a]			
40-59	4 (57,1%)	3 (42,9%)	1,000
60-79	21 (52,5%)	19 (47,5%)	
>80	0 (0%)	2 (100%)	0,488
PSA			
0-4	1 (100%)	0 (0%)	NA
5-20	6 (66,7%)	3 (33,3%)	
>20	1 (50%)	1 (50%)	
Unknown	17 (45,9%)	20 (54,1%)	
Stromal infiltration[b]			0,628
No	10 (55,6%)	8 (44,4%)	
Yes	15 (48,4%)	16 (51,6%)	
Nuclei enlargement[b]			0,470
There is no nuclei enlargement	19 (54,3%)	16 (45,7%)	
There is a nuclei enlargement	6 (42,9%)	8 (57,1%)	
Nucleoli enlargement[b]			0,201
There is no nucleoli enlargement	9 (40,9%)	13 (59,1%)	
There is a nucleoli enlargement	16 (59,3%)	11 (40,7%)	
Nuclei chromatin			1,000
Normochromatic	7 (50%)	7 (50%)	
Hyperchromatic[a]	1 (50%)	1 (50%)	
Vesicular[b]	17 (51,5%)	16 (48,5%)	0,924
Amphophilic cytoplasm[b]			0,095
No	12 (66,7%)	6 (33,3%)	
Yes	13 (41,9%)	18 (58,1%)	
Basophilic mucin[a]			1,000
No	24 (51,1%)	23 (48,9%)	
Yes	1 (50,0%)	1 (50%)	
Intraluminal crystalloid[a]			0,050*
No	25 (55,6%	20 (44,4%)	
Yes	0 (0%)	4 (100%)	
Mitosis			NA
No	25 (51,0%)	24 (49%)	
Yes	0 (0%)	0 (0%)	
Inflammation[b]			0,675
Yes	5 (45,5%)	6 (54,5%)	
No	20 (52,6%)	18 (47,4%)	
Corpora amylacea[b]			0,005*
No	14 (38,9%)	22 (61,1%)	
Yes	11 (84,6%)	2 (15%)	

[a]*Fisher's* test
[b]*Chi-Square* Test
*p value is significant/close to significant

Based on the results of the study, there was no significant age difference between benign lesion group and prostate adenocarcinoma group with p>0.05, but 2 cases were found with age >80 in the prostate adenocarcinoma group. PSA serum levels could not be analyzed statistically because serum levels were unknown in 37 cases, that is 17 cases in the benign lesion group and 20 cases in the prostate adenocarcinoma group.

Data on histomorphological characteristics of stromal infiltration, nuclei enlargement, nucleoli enlargement, nuclei chromatin, amphophilic cytoplasm, basophilic mucin, and inflammation showed no statistically significant association with the diagnosis of benign lesion or prostate adenocarcinoma, p-value >0.05. Meanwhile, intraluminal crystalloid statistically showed a close to significant relationship with a p-value of 0.050, and *corpora amylacea* showed a significant relationship with a p-value <0.05. The mitosis variable could not be statistically assessed because it was not found in either group.

Stroma infiltration was found to be more prevalent in the prostate adenocarcinoma group, that is 16 cases (51.6%) compared to the benign lesion group. There were more enlarged nuclei in the prostate adenocarcinoma group, totaling 8 cases (57.1%) compared to the benign lesion group, which had 6 cases (42.9%). Enlargement of the nucleoli was found more in the benign lesion group, that is 16 cases (59.3%) compared to 11

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cases (40.7%) in the prostate adenocarcinoma group.

Nuclei chromatin between the benign lesion and prostate adenocarcinoma groups differed only in vesicular variables with 17 cases (51.5%) found in the benign lesion group and 16 cases (49%) found in the prostate adeno-carcinoma group. Amphophilic cytoplasm was found in more cases of prostate adenocarcinoma with 18 cases (58.1%) compared to the benign lesion group with 13 cases (41.9%). Basophilic mucins were difficult to find in this study, with only 2 cases with basophilic mucin characteristics, that is 1 case (50%) in the benign lesion group and 1 case (50%) in the prostate adenocarcinoma group. Intraluminal crystalloids were found in the prostate adenocarcinoma group in 4 cases (100%) and were not found in the benign lesion group. Mitosis was difficult to identify in this study and was not found in all cases. Inflammation was found in 11 cases, that is 5 cases (45.5%) in the benign lesion group and 6 cases (54.5%) in the prostate adenocarcinoma group.

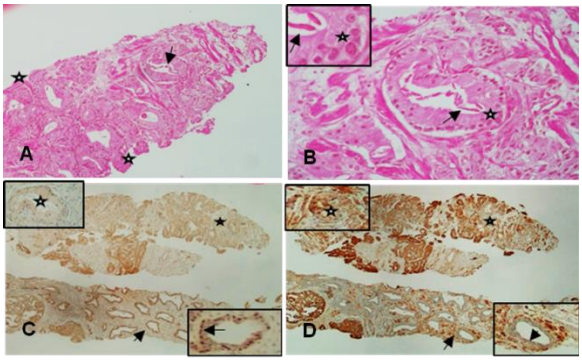

Figure 1. A. Atypical prostate gland with stromal infiltration (pattern between the two stars) and intraluminal crystalloid (arrows), immunohistochemistry diagnosis is adenocarcinoma, HE 100 times. B. Intraluminal crystalloid (arrow) with enlarged nuclei and enlarged nucleoli (star), HE 400 times C. Staining of p63 gave negative results in basal cells (star) and positive in the normal prostate gland (arrow), 100 times. D. AMACR staining was positive for tumor cells (stars) and negative for normal prostate glands (arrows), 100 times.

Corpora amylacea was found more frequently in the benign lesion group with 11 cases (84.6%) compared to the prostate adeno-carcinoma group, which was only found in 2 cases (15.4%) and showed a statistically significant relationship (p-value <0.05).

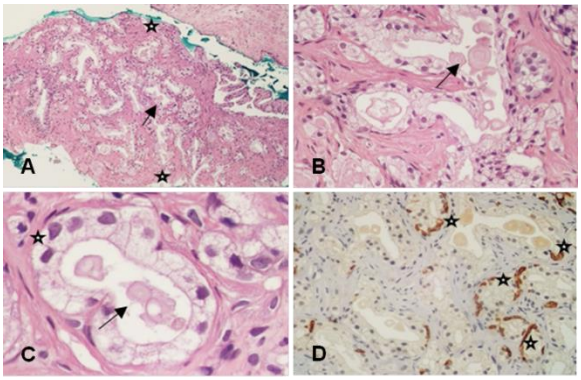

Figure 2. A. Atypical prostate gland with stromal infiltration (pattern between the two stars) with *corpora amylacea* (arrow), immunohistochemistry diagnosis is benign lesion, HE 100 times. B. Prostate gland with *corpora amylacea* (arrow), HE 400 times. C. Prostate gland with enlarged nuclei and nucleoli (asterisks) accompanied by *corpora amylacea* (arrow), HE 400 times. D. HMWCK stains gave positive results in basal cells (asterisks), 100 times.

DISCUSSION

The atypical prostate gland, especially ASAP, is a proliferative acinus of the atypical prostate gland suggestive of carcinoma but not sufficient for a definitive diagnosis as prostate adenocarcinoma.[5,6] Cases of the atypical prostate gland, especially ASAP, in this retrospective study were found to be more common in the range of age from 60-79 years, both in the benign lesion group and in the prostate adenocarcinoma group. According to Sade et al[6] study which stated that 60 years old, became the average age of ASAP cases in the second biopsy, with a median age of 62,65 years in the benign lesion group and 66,76 years in the malignant prostate group, the results were statistically significant. Likewise, the study of Engelman et al[4] stated that the average age of prostate cases, whether benign lesion, ASAP, or malignant prostate, was 66.75 ± 9 years.

The role of PSA levels in cases with a risk of prostate malignancies after the diagnosis ASAP in the first biopsy is still controversial.[9] PSA levels in this retrospective study could not be analyzed statistically, because PSA levels were unknown in 37 cases, but there was no significant difference in the number of cases with PSA levels >20 ng/ml in the benign lesion and prostate adenocarcinoma groups. These results are similar to several other studies, which stated that serum PSA levels and their derivatives in the first biopsy of the ASAP case could not predict the possibility of malignancy

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in subsequent biopsies.[9] In contrast to the Sade et al[6] study which stated that there were significant differences in PSA levels in both the benign lesion group and the malignant prostate group with an average of 8.44 ng/ml and 16.42 ng/ml, respectively.

Stromal infiltration in this retrospective study was defined as the presence of either linear row suspicious cells or glands spanning the width of the biopsy or suspicious cells or glands on both sides of the normal gland.[10] Stroma infiltration is a major criteria for diagnosing prostate adenocarcinoma.[11] Study by Meiers and Sade et al.[6,12] stated that infiltrative growth patterns were often found in patients with ASAP (68-75%), although in that study no statistically significant differences were found between the benign lesion and malignant prostate groups. That study is similar to this retrospective study because 31 cases out of 49 atypical prostate glands including ASAP showed stromal infiltration, that is 16 cases (51.6%) among them in the prostate adenocarcinoma group.

Nuclei enlargement is an increase in ratio of the nuclei to the cytoplasm, this can be considered as one of the diagnostic signs of the atypical prostate gland or ASAP.[5,9] In this retrospective study, nuclei enlargement was more found slightly in the prostate adenocarcinoma group than in the benign lesion group, although this was not statistically significant. This is similar to Sade et al[6] study that showed nuclei enlargement can be found in 22% of benign lesion cases. While the study of Meiers and Iczowski et al[12,13] showed that mild nuclei enlargement can be found in ASAP and moderate nuclei enlargement is found in minimal carcinoma. Although nuclei enlargement is often associated with the diagnosis of prostate adenocarcinoma but the sensitivity is low and other diagnostic criteria must be considered.[14]

Nucleoli enlargement is a sign of malignancy, but there is no benchmark for the size of the normal nucleoli of the prostate gland. Previous studies suggest that nucleoli enlargement is the most common characteristic of prostate adenocarcinoma.[9] In this retrospective study, we used the criteria of the nucleoli with a microscope magnification of 100 times (*prominent*) and 400 times (*inconspicuous*) refers to the study of Cavalcanti et al.[15], which stated that the enlargement of the nucleoli could be the strongest variable for differentiating benign lesion from malignant prostate lesions. However, the results of our study found no difference in nucleoli enlargement between the two groups, and the nucleoli enlargement was more found in the benign lesion group. According to references, enlargement of the nucleoli in the prostate gland can also be found in conditions *mimicking* prostate adenocarcinomas, such as *atypical basal cell hyperplasia*, *post-atrophic hyperplasia,* and *reactive atypia.*[9,16,17]

Nuclei chromatin in ASAP from previous studies was shown to be hyperchromatic.[9,12] In this study, both the benign lesion and malignant prostate groups showed 1 case with hyperchromatic nuclei and no statistically significant results were obtained. Other studies state that hyperchromatic nuclei are more found in cases of the atypical prostate gland, including ASAP, compared to minimal carcinoma.[12,13]

In this retrospective study, amphophilic cytoplasm was found to be more abundant in the prostate adenocarcinoma group than in the benign lesion group, although this was not statistically significant. This is similar to other studies which show that amphophilic cytoplasm is more commonly found in malignant prostate glands than in benign lesion glands.[6,10,18] Research by Varma et al stated that the cytoplasm in prostate adenocarcinoma can vary in color, ranging from clear, amphophilic to eosinophilic and other characteristics are needed to strengthen the diagnosis of prostate adenocarcinoma.[18]

Basophilic mucin was very difficult to find in this retrospective study, only 2 cases showed basophilic mucin features, 1 case (50%) in the benign lesion group and 1 case (50%) in the prostate adenocarcinoma group. According to the reference, basophilic mucin was found in 18% to 34% of prostate biopsies and 70% of radical prostatectomies. Mucin is a carbohydrate-rich substance secreted by certain epithelial structures that functions as a lubricant or protector against injury.[19] Mucin in the prostate can be *neutral mucin* or *acidic mucin* which can be found in prostate adenocarcinoma or benign lesion lesions such as *mucinous metaplasia*, *atypical adenomatous hyperplasia, sclerosing adenosing,* and *basal cell hyperplasia*.[11,13,18] The study of Agrawal et al[20] demonstrated that the most common basophilic mucin found in prostate adenocarcinoma was *acidic mucin* that stained positively with *Alcian blue* staining on histochemical stains. Basophilic

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mucin can be a supporting criteria for cases of prostate adenocarcinoma.[20,21]

Intraluminal crystalloids were first discovered in 1977 as intraluminal eosinophilic structures with varying sizes and geometric shapes such as needles, triangles, and hexagonal. The mechanism of intraluminal crystalloid formation is unknown, but references state that intraluminal crystalloid is the result of abnormal protein and mineral metabolism in both benign lesions and malignant prostate acini. Ultrastructurally, crystalloids consist of solid materials that do not contain crystal elements. Microanalysis has shown that crystalloids contain sulfur, calcium, phosphorus, and small amounts of sodium. Protein secretion always occurs in prostate acini and may be a source of intraluminal crystalloid formation.[22] The presence of intraluminal crystalloids in the prostate gland may indicate a risk of developing prostate adenocarcinoma on subsequent prostate biopsies. Intraluminal crystalloids are more common in prostate adenocarcinomas with lower *Gleason scores*. However, research to support this statement is still very limited.[10,23] In this retrospective study, intraluminal crystalloid was found only in the prostate adenocarcinoma group with a total of 4 cases (100%) and a p-value of 0.050 which means it is close to statistical significance. This is similar to the study of Calvacanti and Bostwick et al[15,24] which showed that intraluminal crystalloids were more frequently found in cases of prostate adenocarcinoma. Another study stated that intraluminal crystalloid could be a specific but not sensitive marker for prostate adenocarcinoma.[25] Whereas several previous studies concluded that intraluminal crystalloid is an uncommon feature found in ASAP cases and is not associated with the incidence of prostate adenocarcinoma.[6,12]

Mitotic features were not found in all cases in this retrospective study. According to references, mitosis can be found in benign lesion, especially those adjacent to infarction. The finding of atypical mitosis is very difficult in prostate adenocarcinoma except for prostate adenocarcinoma with a high *Gleason score*, therefore the use of mitotic criteria to support the diagnosis of prostate adenocarcinoma is still to be considered.[11] Previous studies show that mitoses were only found in 10% of prostate adenocarcinoma and not in benign lesion or biopsy prostate cases.[11,12]

Inflammation was found in 5 cases (45.5%) of the benign lesion group and 6 cases (54.5%) of the prostate adenocarcinoma group. Similar to the study of Meiers et al[12] which states that 30% of prostate glands with atypical nuclei are associated with inflammation. In 20% of cases, minimal carcinoma is also associated with acute and chronic inflammation. Other studies suggest that inflammation in the atypical prostate gland or ASAP that becomes malignant is less than in the atypical prostate gland or ASAP that becomes benign, which statistically shows a significant relationship. Inflammation can also increase serum levels of PSA and is more often found in benign lesion conditions.[6]

Corpora amylacea is a round-oval, well-defined, flat ring-shaped concentric structure, generally *pink* with varying sizes, found in the prostate gland and will be found more often with age. Microscopically, *corpora amylacea* are more frequently associated with damaged, atrophic, occlusive prostate gland epithelium and in prostate gland surrounded by inflammation. Pathologists found *corpora amylacea* as a clue for benign lesion glands because they are very rarely found in malignant prostate glands.[26,27] *Corpora amylacea* in this retrospective study was more found in the benign lesion group with a total of 11 cases (84.6%), while in the prostate adenocarcinoma group there were 2 cases (15.4%) with a p-value of 0.005 and was statistically significant. This is in accordance with the study of Christian et al[27] who found *corpora amylacea* in a few cases of prostate adenocarcinoma with a *Gleason score 3*, but these findings are very rare and are more often found in benign lesion cases such as *atypical adenomatous hyperplasia* and *postatrophic hyperplasia*.

CONCLUSION

In the diagnosis of the atypical prostate gland and advanced biopsy difficult to perform, supported by immunohistochemistry characteristics, finding of c*orpora amylacea* can help direct diagnosis to a benign lesion, while finding of intraluminal crystalloid leads to a diagnosis of prostate adenocarcinoma. So that it can minimize a diagnosis of the atypical prostate gland including ASAP and can accelerate to the next treatment.

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