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Role of Immunohistochemistry in the Differentiation between Low Grade Prostatic Adenocarcinoma (Small Acinar Pattern) and Some Benign Mimickers

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ABSTRACT

Background: prostatic adenocarcinoma is characterized by diverse architectural growth patterns and can be confused with some benign prostatic lesions. The most common pseudoneoplastic lesions in the prostate that can mimic low-grade prostatic adenocarcinoma are post-atrophic hyperplasia (PAH), atypical adenomatous hyperplasia (AAH) and sclerosing adenosis of the prostate (SAP). **Objective:** this study aimed to evaluate the histopathological and immunohistochemical features of some pseudoneoplastic lesions of the prostate that could potentially be confused with low-grade prostatic adenocarcinoma (small gland pattern). **Material and Methods**: 100 specimens of prostatic lesions were enrolled in this study and analyzed retrospectively (50 needle biopsy specimens and 50 transurethral resection of prostate (TURP) specimens). All cases had atypical foci that required further workup. Four slides per specimen were cut, one slide for hematoxylin and eosin stain (H&E) and the other 3 slides for immunohistochemical (IHC) staining by antibodies against 34βE12 cytokeratin, p63 and alpha methyl acyl coenzyme A racemase (AMACR). **Results:** histological examination (prior to IHC staining) revealed provisional histological diagnosis of 35 cases of PAH, 12 cases of AAH, 13 cases of SAP and 40 cases of low grade prostatic adenocarcinoma. Immunohistochemical results revealed immunopositivity to 34βE12 in a discontinuous pattern in 13 out of the 35 cases of PAH (13/35), immunopositivity to 34βE12 and p63 in a continuous basal pattern in 17 cases (17/35) and negativity for all markers in 5 cases (5/35). 29 cases out of the 40 prostatic carcinomas showed immunopositivity for AMACR and negativity for 34βE12 and p63 (29/40), 5 cases were negative for all markers (5/40) and 6 cases were positive to p63 and negative for AMACR and 34βE12 (6/40). 8 out of the 12 cases diagnosed as AAH showed immunopositivity to 34βE12 and p63 in a discontinuous pattern and negative to AMACR (8/12), 2 cases were positive to AMACR and negative to basal cell markers (2/12) and 2 cases were negative to all markers. All the 13 cases diagnosed histologically as SAP showed immunopositivity to 34βE12 and p63 and immunonegativity to AMACR. **Conclusion**: immunohistochemistry (IHC) can be contributive in the diagnosis of prostatic adenocarcinoma if used with care and experience. No single marker can establish a diagnosis on its own, but interpretation must always be in conjunction with H&E morphology.

Keywords: prostatic carcinoma, benign mimickers, immunohistochemistry

INTRODUCTION

Before making a diagnosis of prostatic carcinoma (PCA), it is prudent for the pathologist to consider the various benign patterns and processes that can simulate prostatic adenocarcinoma. Most mimickers fit within the small gland category and the most common ones giving rise to false-positive cancer diagnosis are atrophy, post-atrophic hyperplasia, atypical adenomatous hyperplasia, sclerosing adenosis and seminal vesicle-type tissue. Knowledge of these patterns on routine microscopy coupled with the prudent use of immunohistochemistry will lead to a correct diagnosis and avert a false-positive cancer interpretation [1]. Post-atrophic hyperplasia (PAH) is best known to the surgical pathologist as a mimic of prostatic adenocarcinoma because of its overlapping architectural and nuclear features. PAH is a proliferative, non-involuting lesion and distinguishing PAH from PCA is particularly important on prostate needle biopsy because of the therapeutic implications[2]. Atypical Adenomatous Hyperplasia (AAH) is another common mimicker of prostatic low-grade adenocarcinoma. AAH should be considered as a benign lesion and patients followed conservatively. The term should not be used as a 'wastebasket' for small glandular lesions that are difficult to classify, or for suspicious atypical small gland proliferations just below the threshold of adenocarcinoma [3]. Up to 2% of over diagnosis of prostatic adenocarcinoma in transurethral resection specimens might be due to sclerosing adenosis of the prostate (SAP). SAP is a transition zone lesion of the prostate that can simulate small acinar carcinoma [4].

MATERIALS AND METHODS

Selection of the Studied Cases

100 specimens (50 needle biopsy specimens and 50 transurethral resection of prostate (TURP) specimens

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were selected during 2-years period from February 2015 to January 2017 at the Medical Hospitals of Al-Azhar University. All cases had atypical foci that required further workup. 40 cases were morphologically highly suggestive of prostate cancer and 60 cases were morphologically atypical but less likely suspicious for prostate cancer. In these latter cases, the differential diagnoses included AAH, PAH and sclerosing adenosis. Four slides per specimen with 2 levels on each slide were cut at 5-µm thicknesses. The first slide was stained with hematoxylin and eosin (H&E) and the remaining slides were used for immunohistochemical analysis. **The study was approved by the Ethics Board of Al-Azhar University.**

ImmunohistochemicalStaining Methods:

Following paraffin removal and hydration the slides were treated with a 0.1mol/L concentration of citrate, pH 6.0, in a pressure cooker and microwaved for 15 minutes for optimal antigen retrieval before immunostaining. Staining was performed on an autostainer (DAKO, Carpinteria, CA). Sections were incubated with a commercially available rabbit monoclonal antibody to AMACR (P504S) (monoclonal rabbit anti-AMACR, clone 13 H4, Dako, Glostrup, Denmark; dilution 1:100), 34βE12, (monoclonal mouse anti-human 34betaE12 antibody, dilution 1:100, code IR051, DakoCytomation, Denmark) and p63 (monoclonal mouse anti-human p63, clone 4A4, Dako; dilution 1:300) for 2 hours at room temperature. Sections later were washed and treated with diaminobenzidine and hydrogen peroxide for 5 minutes. Sections were counterstained with hematoxylin, dehydrated, and mounted with a cover slip. Internal positive controls included brown color reaction in the nuclei (for p63) and cytoplasm (for 34βE12) of basal cells of benign prostatic acini. External positive control for AMACR included colorectal adenocarcinoma. Positive staining for AMACR was identified as strong, circumferential, cytoplasmic and/or luminal, with a granular quality within epithelial cells. 34βE12 stained cytoplasm (brown cytoplasmic staining) and p63 stained nuclei (brown nuclear staining) of basal cells. The extent of staining was noted as absent, minimal (<5% of cells), focal (5%-50% of cells), or diffuse (>50% of cells). Staining intensity was graded as follows: 1, negative, 2, weak, 3, moderate, or 4, strong [5].

RESULTS

Histological Results:

In the current study, 35 out of the examined 100 cases showed lobular, well circumscribed growth pattern composed of small acini **(Figure1)** with uniformly enlarged nuclei and inconspicuous nucleoli, regular chromatin pattern, scant to moderate amounts of eosinophilic cytoplasm and pale fibrous stroma with periacinar collagen deposition. Scattered mononuclear inflammatory cells were also seen in some of these cases (12/35). The provisional histological diagnosis of these cases was PAH. 12 cases in the current study showed small uniform acini with minimal variation in size and shape **(Figure 3)** and lined by cuboidal to low columnar cells with moderate amount of clear to eosinophilic cytoplasm **(Figure 4)**. Individual glands were separated but closely packed with no evidence of fusion **(Figure 4)**. These lesions had a pushing border and were located adjacent to typical hyperplastic nodules with a prominent perinodular distribution of the abnormal glands. These cases were provisionally diagnosed as AAH. 13 out of the 100 investigated cases (13/100) showed a circumscribed proliferation of small glandular structures, with mild nuclear atypia, surrounded by a thick eosinophilic material and separated by cellular focally myxoid stroma and diagnosed provisionally as SAP **(Figures 6 and 7)**. Lastly, the remaining 40 cases showed closely packed small acini with enlarged nuclei, prominent nucleoli, moderate amount of basophilic cytoplasm and infiltrative margins with a provisional diagnosis of prostatic adenocarcinoma **(Figure 8)**.

Immunohistochemical Results:

Immunohistochemical results revealed immunopositivity to 34βE12 in a discontinuous pattern in 13 out of the 35 cases of PAH (13/35), immunopositivity to 34βE12 **(Figure 2)** and p63 in a continuous basal pattern in 17 cases (17/35) and negativity for all markers in 5 cases (5/35). 29 cases out of the 40 prostatic carcinomas showed immunopositivity for AMACR **(Figure 9)** and negativity for 34βE12 and p63 (29/40), 5 cases were negative for all markers (5/40) and 6 cases were positive to p63 and negative for AMACR and 34βE12 (6/40). 8 out of the 12 cases diagnosed as AAH showed immunopositivity to 34βE12 and p63 **(Figure 5)** in a discontinuous pattern and negative to AMACR (8/12), 2 cases were positive to AMACR and negative to basal cell markers (2/12) and 2 cases were negative to all markers. All the 13 cases diagnosed histologically as SAP showed immunopositivity to 34βE12 and p63 and immunonegativity to AMACR.

Table 1: immunohistochemical results for 34, p63 and AMACR

Histological diagnosis	IMMUNOHISTOCHEMICAL RESULTS					
	34βE12		p63		P504S	
PAH (35 cases)	+ve	13Discontinuous 17Continuous	+ve	17 Continuous	+ve	0
	-ve	5	-ve	18	-ve	35
AAH (12 cases)	+ve	8Discontinuous	+ve	8Discontinuous	+ve	2
	-ve	4	-ve	4	-ve	10
SA (13 cases)	+ve	13 Continuous	+ve	13 Discontinuous	+ve	-
	-ve	-	-ve	-	-ve	13
PCA (40 cases)	+ve	-	+ve	6	+ve	29
	-ve	40	-ve	34	-ve	11

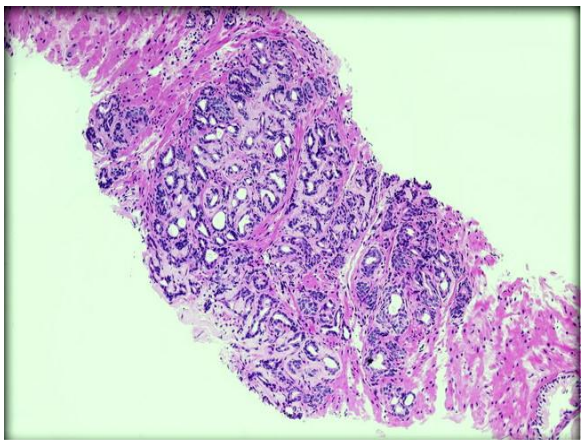

Figure 1: A case of post-atrophic hyperplasia showing well-demarcated clusters of basophilic acini arranged in lobular growth pattern (H&E x100).

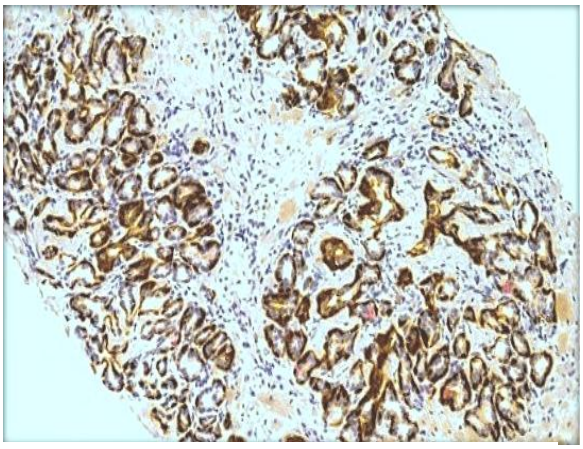

Figure 2: A case of post-atrophic hyperplasia showing strong and diffuse immunoreactivity to 34βE12 cytokeratin in continuous basal pattern (DAB x200).

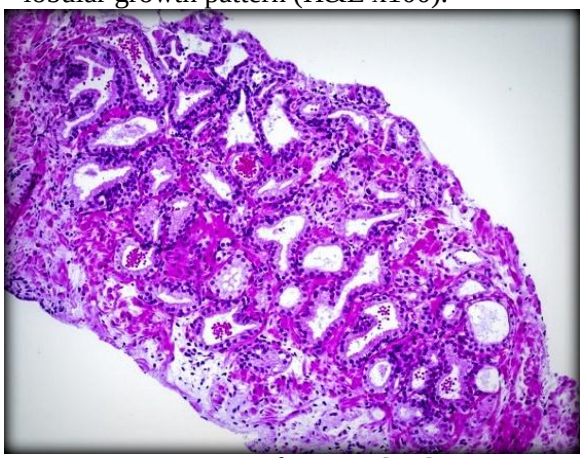

Figure 3: A case of atypical adenomatous hyperplasia showing crowded, irregular glands with pale cytoplasm (H&E x200).

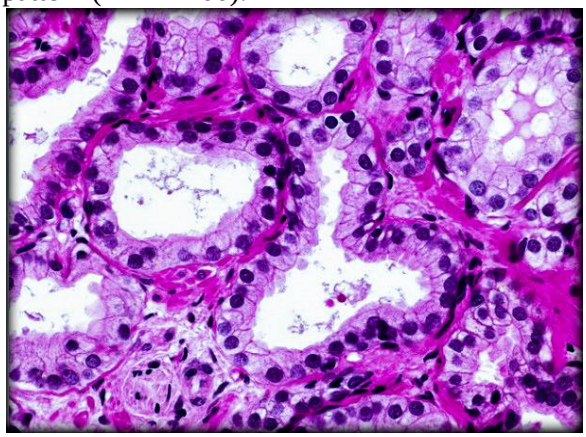

Figure 4: A case of atypical adenomatous hyperplasia showing enlarged uniform nuclei with pale to clear cytoplasm (H&E x400).

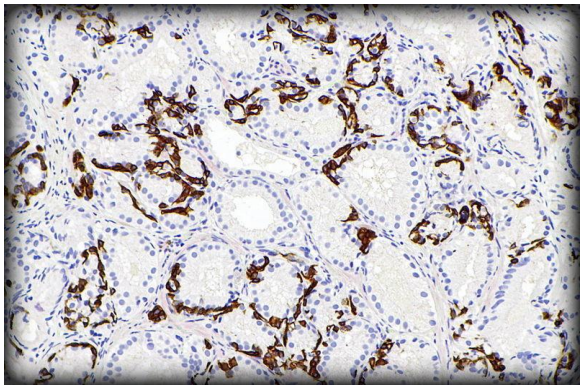

Figure 5: A case of atypical adenomatous hyperplasia showing strong and patchy p63 immunopositivity (DAB, x200).

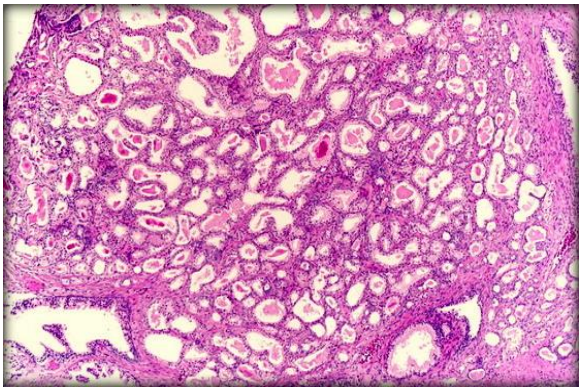

Figure 6: A case of sclerosing adenosis consists of variably sized glands in a cellular stroma and well-circumscribed growth pattern (H&E x100).

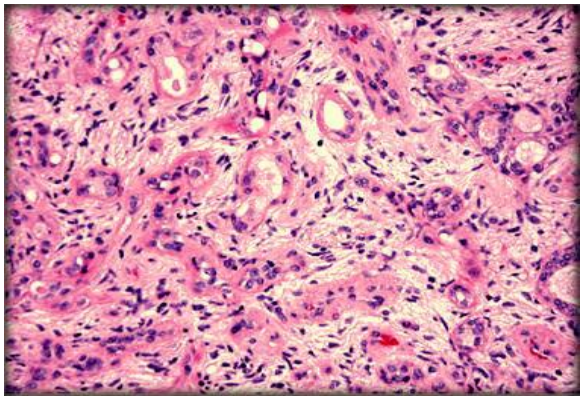

Figure 7: A case of sclerosing adenosis showing cellular focally myxoid stroma (H&E, x200).

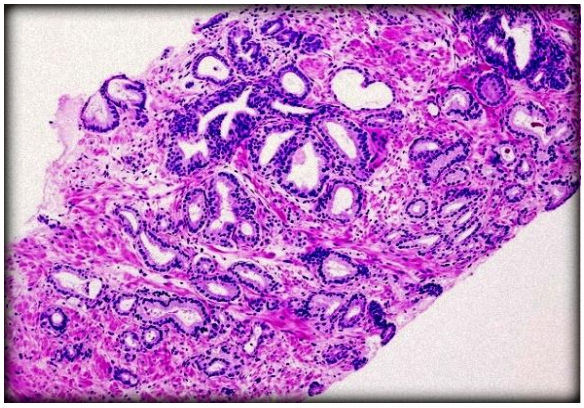

Figure 8: A case of low grade prostatic adenocarcinoma (H&E X200).

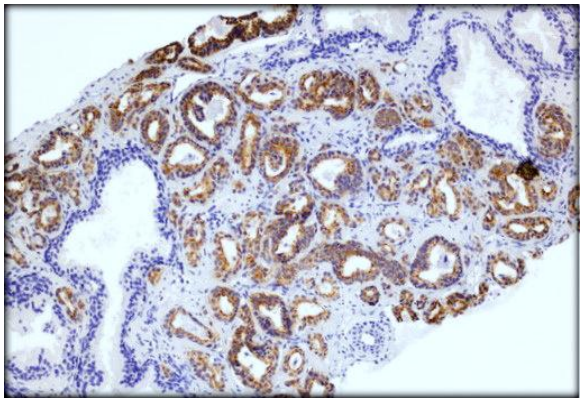

Figure 9:A case of prostatic adenocarcinoma showing strong and diffuse AMACR immunopositivity in the malignant acini and negativity in the intervening benign glands (x200).

DISCUSSION

In this study, the provisional histological diagnosis of pos-atrophic hyperplasia was based on lobular, well circumscribed growth pattern that composed of small acini with uniformly enlarged nuclei and inconspicuous nucleoli, regular chromatin pattern, scant to moderate amounts of pale to clear cytoplasm and fibrous stroma with periacinar collagen deposition. Similar features were reported by **Tsujimoto *et al.*** [6] who found that the hallmark of post-atrophic hyperplasia (PAH) was cytoplasmic volume loss, whereas most prostatic adenocarcinomas harbored a moderate amount of cytoplasm. Also, **Bakshi *et al.*** [7] reported that the lobular arrangement in PAH is usually maintained and there was often apparent budding of neoacini lined by cuboidal cells with clear cytoplasm. Some nuclear enlargement may be seen and rarely, enlarged nucleoli were identified. **Srigley** [8] stated that the busy architecture of post-atrophic hyperplasia may cause diagnostic confusion with adenocarcinoma, however there was generally maintenance of some degrees of lobular architecture and basal cells were usually recognized, even at the H&E level. Additionally, **Herawi *et al.*** [9] reported that the stroma in atrophy was altered by a pale fibrosis with periacinar collagen deposition, which can impart a sclerotic appearance. This sclerosis should not be confused with a desmoplastic response to invasive prostatic carcinoma, which is unusual. Lastly, **Farinola and Epstein** [10] demonstrated that one should be cognizant that atrophic-pattern adenocarcinoma exists and features favoring benign atrophy rather than atrophic-pattern adenocarcinoma include lack of infiltrative pattern of atrophic glands between larger benign glands, lack of coexisting usual acinar adenocarcinoma, with a moderate amount of cytoplasm, and lack of diffuse, significant cytological atypia in the glands of concern.

In the current study, 13 cases out of the 35 histologically diagnosed PAH (13/35) showed moderate positivity for (34βE12) in a discontinuous pattern and negativity for both AMACR and p63. 17 cases (17/35) showed continuous basal cell immunopositivity to both 34βE12 and p63 and immunonegativity to AMACR. Also **Hameed and Humphrey** [11] reported that prominent nucleoli in a significant number of cells were not typically found in post-atrophic hyperplasia and the prudent use of high molecular weight keratin (34βE12) immunostain was important in difficult cases because there was a continuous layer of basal cells in post-atrophic hyperplasia whereas in small acinar carcinoma, the basal cell layer was completely absent.

In this study, 5 out of 35 cases (14.3%) showed negativity for all markers and diagnosed PAH according to histological features. In a study performed by **Herawi *et al.*** [9] they found that the main diagnostic hindrance in post atrophic hyperplasia was patchy staining of basal cells seen in 102 (87%) of 117 cases and the remaining 13% of cases were completely negative. **Shah *et al.*** [12] reported that it is sometimes difficult to identify basal cells even with the use of immunohistochemistry (IHC) because up to 23% of atrophic glands can be completely negative for basal cell markers. Also **Paner *et al.*** [13] reported that the pitfalls in staining with basal cell–associated markers may be due to false negativity in benign mimics or false positivity in carcinoma and varies in the entities examined, in 5% to 23% of cases, scattered, obviously benign glands may show absent staining. Staining may be weak-reactive to non-reactive in some benign proliferations that mimic cancer, such as in up to 23% of glandular atrophy, up to 50% of atypical adenomatous hyperplasia and 23% of post-atrophic hyperplasia [11]. In addition, **Kumaresan *et al.*** [14] reported that atrophy and especially PAH, may be mistaken for prostatic adenocarcinoma because of its frequent (at least focal) expression of a-methyl acyl coenzyme A racemase (AMACR). This, along with basal cells often being difficult to discern in this form of atrophy as well, may also account, at least in part, for why it represented the most frequent lesion sent in for consultation. **Varma and Jasani** [15] suggested that prolonged formalin fixation has a negative effect on the detection of basal cell specific keratin and potentially giving rise to false negative staining.

In this study, 6 cases showed patchy moderate positivity for p63 and negativity for both AMACR and 34βE12 but showed histologic features of prostatic adenocarcinoma. Aberrant diffuse nuclear expression of p63 in acinar prostate carcinoma had been reported in a study performed by **Osunkoya *et al.*** [16], and hence, they demonstrated that the use of a panel of tests is crucial to avoiding misdiagnosis from this rare phenomenon. In a study performed by **Paner *et al.*** [13] they reported that the pitfall in the use of immunohistochemistry for the diagnosis

of prostate adenocarcinoma was false positive staining for basal cell markers and this can occur in several patterns. A type of false positive staining with basal cell markers are uncommon cases of acinar adenocarcinoma that label focally with 34βE12 and less so with p63 in a non-basal cell distribution. This phenomenon can be seen in all grades of prostate cancer, although more commonly encountered in Gleason scores 8-10. **Parsons *et al.*** [17] reported that non-specific staining in prostatic carcinoma seems to depend on the antigen retrieval method used, with the hot plate method showing more non-specific reaction than the pepsin predigestion and microwave retrieval methods.

In the current study, 5 out of 40 cases (12.5%) were negative for all markers but showed histologic features of prostate adenocarcinoma. **Varma and Jasani** [15] reported that positive AMACR staining does not always indicate carcinoma, and negative staining does not rule out carcinoma and immunoreactivity to AMACR may be absent in 5% to 25% of typical prostate carcinomas. Staining with AMACR varies in patterns of prostate carcinoma and can be negative in 30% of atrophic carcinoma, 32% to 38% of foamy gland carcinoma, and 23% to 30% of pseudohyperplastic carcinoma variants. The expression can be substantially diminished or completely lost in up to 29% of prostate carcinoma after hormonal therapy [5]. **Zhou *et al.*** [18] reported that it is essential to interpret AMACR in the context of the entire lesion, using it to confirm a morphological impression of malignancy in a focus of suspicious glands. They also noted that a suspicious glandular focus that fulfills the histological criteria of carcinoma and that is negative for basal cell markers can still be diagnosed as adenocarcinoma even in the absence of AMACR reactivity

In the current study, 29 of the examined 100 cases showed strong circumferential immunoreactivity for AMACR and negativity for both basal cell markers, supporting the diagnosis of prostatic adenocarcinoma. Similar results were reported by **Jiang *et al.*** [19] who found that the prostate carcinoma–associated AMACR positivity complements the lack of basal cell–associated staining in prostate carcinoma and thus safeguards from false-negativity associated with basal cell–related markers. AMACR is more commonly applied to complement basal cell markers in an antibody cocktail [20]. **Paner *et al.*** [13] reported that malignancy in the prostate was strongly supported by the absolute absence of basal cell staining by IHC in a morphologically suspicious lesion and the lack of basal cell layer staining should be supported by the simultaneous demonstration of a positive basal cell layer in adjacent unequivocally benign glands (that serves as an internal quality control). In the current study and according to histological features, 12 cases were diagnosed as AAH and showed circumscribed growth pattern with pushing border and composed of small uniform acini with minimal variation in size and shape and lined by cuboidal to low columnar cells with moderate to abundant eosinophilic to clear cytoplasm. Individual glands were closely packed with no evidence of fusion. The abnormal glands were located adjacent to hyperplastic nodules with a prominent perinodular distribution. Similar features were also reported by **Lotan *et al.*** [21] who stated that foci of AAH were characterized by a proliferation of relatively small uniform acini, often within or adjacent to typical hyperplastic nodules, and sometimes, there is a prominent perinodular distribution of the abnormal glands. They also demonstrated that the low-power architecture is reminiscent of Gleason patterns 1 and 2 carcinoma. **Enciu *et al.*** [3] reported that AAH usually has a pushing rather than infiltrating border but may show a limited degree of infiltration. They also stated that individual glands are closely packed but separate and show no evidence of fusion but some variation in size and shape and were lined by cuboidal to low columnar cells with moderate to abundant clear or lightly eosinophilic cytoplasm. **Humphrey** [22] reported that the major importance of AAH is its potential for being misdiagnosed as adenocarcinoma and the most important features in separating AAH from adenocarcinoma were the lack of significantly enlarged nucleoli and the presence of a fragmented basal cell layer. Of the 12 cases diagnosed histologically as AAH in the current study, 8 cases showed strong immunoreactivity for both basal cell markers (p63 and 34βE12) in a discontinuous pattern and negativity for AMACR. Similar results were also reported by **Shah *et al.*** [12] who found that the basal cell-specific keratin stain in AAH showed a discontinuous pattern which is intermediate between the continuous pattern of normal prostate and the absence of basal cells in carcinoma. 2 out of the 12 cases of AAH showed focal, weak luminal,

non-circumferential immunoreactivity for AMACR and negativity for basal cell markers while 2 cases showed immunonegativity for all markers. In a study performed by **Paner *et al*** [13] they found that the basal cell layer in AAH was fragmented, with some small acini completely lacking basal cells. The same authors reported that the immunohistochemical staining with antibody 34βE12 demonstrates the absence of basal cells in about one-half of all glands (with a range of 10%–90%) and up to 18% of cases express AMACR, all features that may lead to diagnostic confusion with adenocarcinoma. Occasionally, reactivity with AMACR can be seen in benign entities, such as in 35% to 58% of nephrogenic adenoma, 18% of AAH and 2% to 36% of typical benign glands [23]**.** The frequency of positive AMACR staining in foci of AAH was specifically assessed by **Browne *et al*** [5] in 40 examples identified in prostatectomies, needle biopsies, and TURP specimens. They demonstrated that basal cell specific staining for 34BE12 confirmed the presence of patchy basal cells in all 40 cases. In 33 of 40 examples of AAH, there was no detectable staining for AMACR-P504S, although there was focal staining in four of 40 and diffusely positive staining in three of 40, prostatic carcinoma and benign prostatic hyperplasia served as positive and negative controls and showed the predicted staining patterns. As such, these authors concluded that AMACR-P504S immunostaing distinguishes most, but not all, cases of AAH from adenocarcinoma. In the current study, histological features supported the diagnosis of sclerosing adenosis which were seen in 13 cases and included a circumscribed lesion composed of small glandular structures surrounded by a thick, eosinophilic structure and separated by cellular stroma composed of bland spindled cell. Also, similar histologic features were reported by **luque *et al*** [24] who stated that the glands of sclerosing adenosis are surrounded by a thick, eosinophilic, basement membrane–like structure in most cases and basal cells are also present. They also reported that the spindled stroma and lack of appreciable nuclear atypia are useful in distinguishing sclerosing adenosis from adenocarcinoma. **Kuroda *et al.*** [4] reported that the characteristic feature of sclerosing adenosis was the presence of a thick eosinophilic basement membrane around at least some glands. **Paner *et al.*** [13] reported that the key features distinguished sclerosing adenosis from adenocarcinoma include the variation in gland size and shape, thickened basement membranes and cellular stroma, but immunohistochemistry for high molecular weight keratin (34βE12) can be used in problematic cases.

In the current study, all the 13 cases diagnosed histologically as SAP showed immunoreactivity for 34βE12 in basal cell layer and spindled stroma, patchy moderate p63 in the basal layer and negativity for AMACR. **Srigley** [8] reported that the characteristic expression of 34βE12 cytokeratin was diagnostic and demonstrates the presence of an intact basal cell layer in the acini and in plump fusiform cells infiltrating the stroma as solid nests and cords.

CONCLUSION

Although immunohistochemistry in prostatic lesions provided discriminatory staining patterns between the benign and malignant conditions, the final interpretation must be morphological by using appropriate staining with internal and external controls. AMACR staining and other supportive studies, such as a basal cell specific markers like 34βE12 or p63, must be interpreted in the context of basic hematoxylin and eosin criteria for malignancy. Increased diagnostic certainty achieved by immunohistochemistry also opens up the possibility of new pitfalls that the pathologist must be aware of.

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