CASE REPORT

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Atypical adenomatous hyperplasia of the prostate mimicking adenocarcinoma lesion: case report and literature review

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Abstract

The diagnosis of prostate cancer is challenging because of the existence of lesions that mimic 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 being misdiagnosed as low-grade adenocarcinoma (Gleason 1 or 2). We present the case of a male patient, who suffered a transurethral prostatic resection surgery. Histopathological examination showed benign prostatic hyperplasia with a focus of crowded glands with a nodular appearance. The presence of basal cell was assessed using high molecular-weight cytokeratin (HMWCK), clone 34βE12 and p63 immunostaining, which revealed discontinuous positive immunostaining. In adenocarcinomas, the basal cell layer is absent. This case highlights the usefulness of 34βE12 antibodies, avoiding a false positive diagnosis of cancer, with negative consequences on the patient's psychological condition and treatment costs. We recommended the follow-up of the patient.

Keywords: atypical adenomatous hyperplasia, 34βE12, well-differentiated adenocarcinoma.

Introduction

The incidence of atypical adenomatous hyperplasia varies between 1.5 and 19.6% of transurethral resections and in up to 33% of radical prostatectomies. This lesion arises with predilection from transition zone of the prostate and is associated with typical hyperplasia. Low magnification shows a focus of small glands, with pushing borders, sometimes looking infiltrative, making more difficult the differentiation of cancer. Basal cells are seen at least focally. The luminal borders are irregular or serrated in contrast with straight borders observed in adenocarcinoma. The nuclei are round to oval. Nucleoli may be present, but they are small. The large nucleoli are rarely seen.

Patient, Methods and Results

We present the case of a male patient (VD), 73-year-old, who presented with signs of urinary obstruction. PSA has a value of 4 ng/dL. The material was excised by transurethral prostatic resection surgery in the Department of Urology of Emergency County Hospital of Constanta and identified prostatic tissue with a focus of small and medium glands with infiltrative edges and with no evidence of basal cells. The histopathological and immunohistochemical technique was performed in the Clinical Service of Pathology, Emergency County Hospital of Constanta. The specimen was fixed in 10% formalin and paraffin-embedded. The sections were stained with Hematoxylin–Eosin and monoclonal mouse anti-human high molecular weight cytokeratin, clone 34βE12, isotype IgG1, kappa (DAKO) and monoclonal mouse anti-human p63 protein, clone 4A4, isotype IgG2a, kappa (DAKO) were applied.

Microscopic images were taken with a Nikon camera using a Nikon Eclipse E600 Microscope.

Macroscopic examination revealed the presence of multiple fragments with variable diameters, which measures overall 5/2/0.5 cm, gray colored, and with low consistency. Histopathological examination revealed a nodule (Figure 1) composed of glands placed "back to back" (Figure 2), some of them separated by a minimal amount of stroma. The glands were small and medium size (Figure 3). The nuclei showed minimal atypia (Figure 4). The histological aspect on routine stains could not exclude a well-differentiated adenocarcinoma.

We considered that evaluation by immunohisto-chemical techniques was mandatory for evaluation of basal cells layer.

Immunohistochemical tests revealed the following features:

- discontinuous positive immunoreaction for high molecular weight cytokeratin (HMWCK) in basal cells layers, both in small and medium size glands (Figure 5);
- discontinuous reaction for p63 protein in basal cells of small and medium size glands (Figure 6).

The characteristic features of immunohistochemical reaction oriented for the final diagnosis of atypical adenomatous hyperplasia.

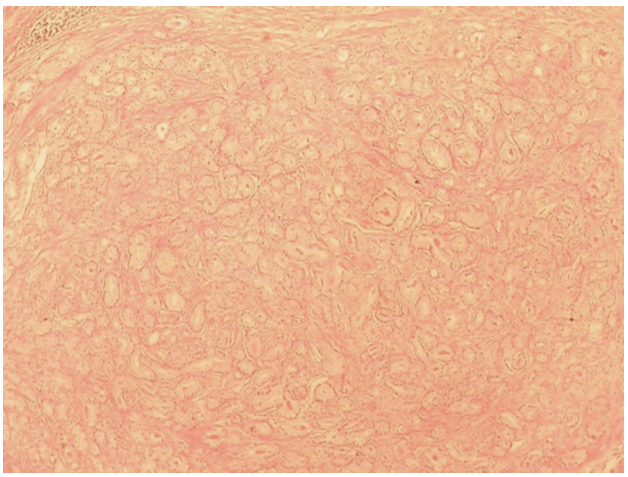

Figure 1 – ***A well-demarcated nodule containing small glands (HE stain, 50×).***

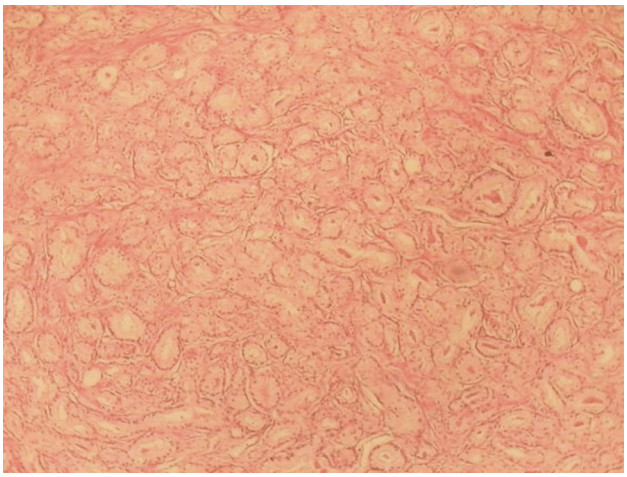

Figure 2 – ***Proliferation of small glands with back-to-back disposition (HE stain, 100×).***

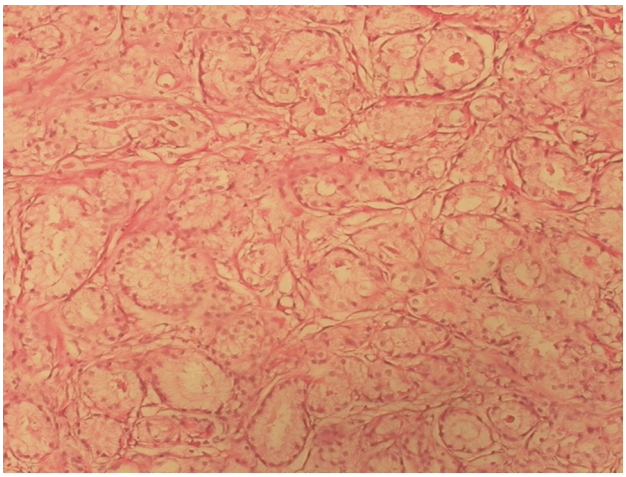

Figure 3 – ***Small and medium size glands with minimal intervening stroma (HE stain, 200×).***

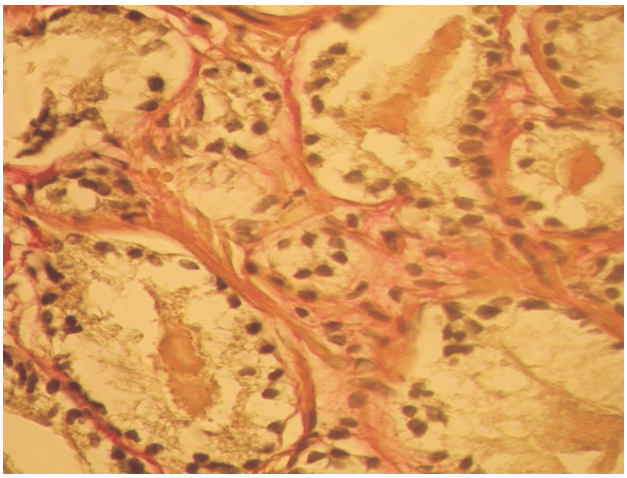

Figure 4 – ***Nuclei with minimal atypia (van Gieson stain, 400×).***

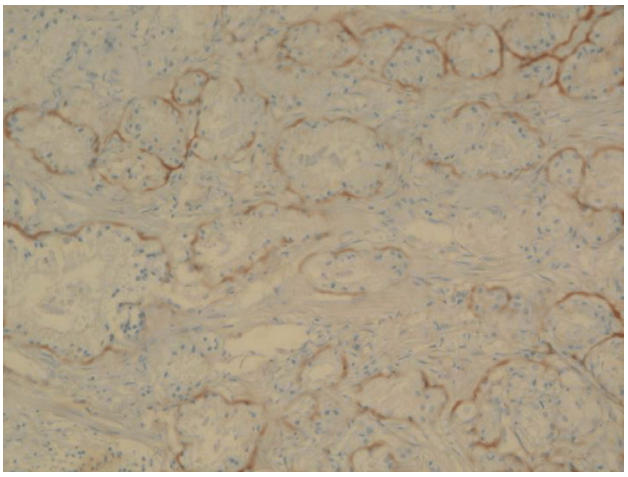

Figure 5 – ***Discontinuous positive immunoreaction for HMWCK in basal cells, 100×.***

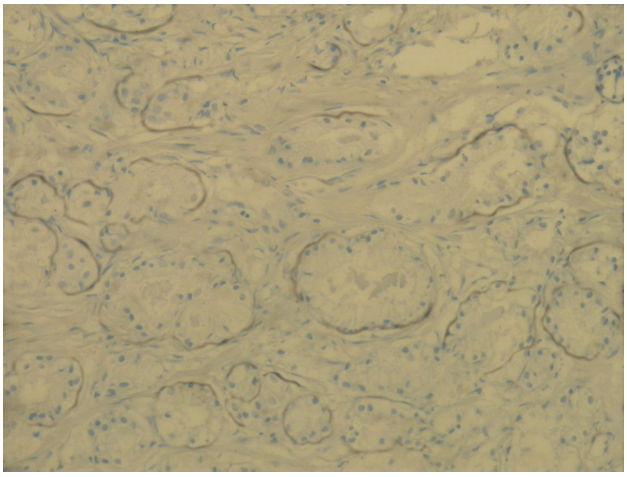

Figure 6 – ***Patchy immunostaining for p63 in basal cells, 100×.***

Discussion

AAH or adenosis represents a pseudoneoplasic lesion, which can simulate a low-grade adenocarcinoma because of its architectural and cytologic features [1, 2] (Table 1).

Adenosis, as a lesion that mimics adenocarcinoma, is found in 1.6% of benign transurethral prostatic resection surgery [3, 4]. However, the diagnosis of atypical adenomatous hyperplasia should be limited to cases with a sufficiently atypical pattern to simulate a prostate carcinoma. Although some authors consider this entity a preneoplasic lesion, there is insufficient evidence to prove the relationship with adenocarcinoma. Although McNeal described this entity as a preneoplasic lesion, this was not supported by most studies. Have been reported cases of prostatic adenocarcinomas arising in relationship with AAH. However, currently,

only high-grade prostatic intraepithelial neoplasia is considered a preneoplasic lesion with clinical significance while the role of AAH and atrophy remains uncertain [5].

Table 1 – ***Morphological aspects in AAH and well-differentiated adenocarcinoma****

	AAH	Adenocarcinoma (Gleason patterns 1 and 2)
Architectural features:		
▪ *The architecture of the focus at low power microscopic examination*	Circumscribed or limited infiltration	Circumscribed or limited infiltration
▪ *Lesion size*	Variable	Variable
▪ *Gland size*	Variable	Less variable
▪ *Gland shape*	Variable	
▪ *Crystalloids*	Infrequent	Frequent
▪ *Corpora amylacea*	Frequent	Infrequent
▪ *Basophilic mucin*	Infrequent	Frequent
Nuclear features:		
▪ *Nuclear size*	Less variable	Variable
▪ *Chromatin*	Uniform/granular	Uniform or variable
▪ *Nucleoli*	Inconspicuous	Prominent
Basal cell layer:		
▪ *Hematoxylin–Eosin stain*	Inconspicuous	Absent
▪ *HMWCK (34βE12)*	Fragmented	Virtually absent

*Modified from Bostwick DG and Dundore PA [6], and Srigley JR [7].

The study of López-Beltrán A *et al.* [8] evaluated three-dimensional nuclear size in benign hyperplasia, AAH and well-differentiated adenocarcinomas. Have been identified differences between adenocarcinoma and the other entities, but the values were close for AAH and benign hyperplasia. This feature suggests that adenosis is a histologic variant of nodular hyperplasia. An immunohistochemical study for proliferation markers, such as Ki67 suggests that AAH has an intermediate proliferation rate between the malignant and benign lesions of the prostate [9, 10]. The molecular and phenotypic studies have shown a possible relationship between adenocarcinoma and adenosis in a small number of cases. Cytogenetic studies revealed abnormalities of chromosome 8 in 4–7% of cases [6, 7, 11, 12].

Most studies have found that age range in adenosis is 5–10 years less that in adenocarcinoma diagnosis. In the case we presented, the patient is in the specific age group of prostate carcinoma. The nodules measure less than 5 mm and accompanies nodules of benign hyperplasia.

The lesion is uncommon in needle biopsies because it originated in the transitional zone, which is rarely biopsied.

From architectural point of view, the low-power examination revealed a similar aspect with Gleason 1 or 2 adenocarcinoma. The glands were crowded, with minimal stroma interposed, well-defined edges, although 19% of cases revealed infiltrative aspects. The infiltrative pattern was more characteristic to malignant lesions. Also, the glands were both sizes: small and medium. In well-differentiated adenocarcinoma the glands are rather uniform [13].

The lobular pattern is considered the most important feature of the lesion. In contrast, well-differentiated adenocarcinoma presents this appearance in a smaller proportion.

Another feature considered characteristic to AAH is the presence of a main ductus like structure and this is due to this large glands benign-looking inside and on the periphery of the focus [14].

Glands vary in shape and size and are lined by low columnar to cuboidal epithelium with clear eosinophilic cytoplasm. The luminal contour is usually irregular. The lumens may contain corpora amylacea or may be empty. In some cases, we can identify eosinophilic crystalloids with various forms [15].

The nuclei are usually uniform. Most cases (60%) do not show nucleoli, or if present, they are rare prominent. In the other 40% cases was cited the presence of large nucleoli (larger than 1.6 μm), making the differential diagnosis more difficult. Another study revealed that 18% of cases showed nucleoli larger than 1 μm. In conclusion, only nucleoli measuring over 3 μm are incompatible with a diagnosis of adenosis [16].

According to the most studies, the most important feature of the lesion is the presence of a fragmented basal cell layer. In adenocarcinomas, the basal cell layer is absent or they are lined by a single row of epithelial cells. The antibodies used for highlighting the basal cell layer are high-molecular weight cytokeratin (clone 34βE12), p63 or cytokeratin 5/6. Although the immunoreaction shows a discontinuous or a fragmented basal layer, this is not indicative of malignancy. Usually, more than half of the glands react positively in the basal cells to high molecular weight keratin or p63. Only a few studies have showed the positive staining of neoplasic cells with 34βE12 [17]. Another study revealed that the basal cells staining positively with 34βE12 in adenocarcinoma did not morphologically resemble basal cell. On the other hand, basal cells of normal glands shows a continuous immunoreaction at this level, except when associated inflammation [18, 19].

A false negativity response in basal cells may be caused by formalin fixation [20].

Yang XJ *et al.* (2002) studied the expression of alpha-Methylacyl-CoA racemase (P504S) in 40 cases of AAH. He found that P504S was focally expressed in 10% of cases and diffusely positive in 7.5% of cases. In contrast, all cases of benign hyperplasia were negative while all cases of adenocarcinomas were diffuse positive. This finding revealed that adenosis represents a heterogeneous lesion [21].

From the clinical point of view, adenosis is a benign lesion and is recommended monitoring of the patient [22].

Conclusions

Before making a diagnosis of cancer, is advisable to exclude some benign lesions that can simulate a cancer. The combination of architectural appearance and immunohistochemical method proved extremely useful in the identification and recognition of AAH. Thus, was avoided a false positive diagnosis of cancer.

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