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Pseudohyperplastic Prostatic Adenocarcinoma: A Case Report and Review of the Literature+

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Pseudohyperplastic adenocarcinoma is a recently described rare type of prostatic adenocarcinoma with deceptively benign architectural features. Pseudohyperplastic pattern mimics benign glands owing to their papillary infoldings,luminal indulations, large size and occasional corpora amylacea. The main morphologic features helpful in establishing the malignancy are; nuclear enlargement, occasional to frequent nucleoli and total absence of basal cells. The diagnostic significance of this pattern lies in its potential to be misdiagnosed as benign prostate glands and adenosis. Herein we report a case of a pseudohyperplastic carcinoma and a brief review of the literature.

Key Words: Pseudohyperplastic prostatic adenocarcinoma, Gleason grade, Prostate cancer

Psödohiperplastik Prostat Adenokarsinomu: Olgu Sunumu

Psödohiperplastik prostat adenokarsinomu aldatıcı olarak benign arşitektürel özelliklere sahip bezlerle karakterize, prostat adenokarsinomunun son yıllarda tanımlanmış nadir bir varyantıdır. Psödohiperplastik patern, papiller katlantıları ve luminal düzensizlikleri olan geniş çaplı, arada corpora amylocea içeren bezler nedeniyle benign bezleri andırır. Nükleer irileşme, arada izlenebilen nükleol belirginliği ve bazal hücrelerin tamamen kaybı maligniteyi destekleyen morfolojik bulgulardır. Bu paternin bilinmesi ve tanınması, psödohiperplastik prostat adenokarsinomun, benign prostat bezleri ya da adenozis olarak yanlış tanı alma potansiyelinin bulunması nedeniyle önemlidir.

Anahtar Kelimeler: Psödohiperplastik prostat adenokarsinomu, Gleason grade, Prostat kanseri

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Pseudohyperplastic adenocarcinoma (PHPA) is a recently described type of adenocarcinoma which is characterized by back to-back arranged large glands with branching and papillary infoldings that simulate benign hyperplastic glands. The deceptively benign architectural features make this pattern of prostate cancer difficult to diagnose.[1] Nuclear enlargement with macronucleoli observed in some of these glands and complete lack of basal cells are the morphologic features that help to establish the malignant nature of the lesion. Therefore the diagnosis of PHPA is based upon a constellation of findings which include crowded glands, architectural hyperplastic pattern, atypical cytology and lack of basal cells by immunohistochemistry.[1,2] We report a case of a PHPA in transurethral (TUR) prostate specimen of a 55 year old man with initial clinical diagnoses of benign prostatic hyperplasia and review the literature.

CASE REPORT

76 year old man presented with dysuria, inconsistency and urgency of approximately one year duration. 6 months prior to this admission he had urinary catherization for 15 days because of urinary retention and then he was given alpha- adrenergic blocker (Flomax) which didn't stop his symptoms. On his second admission, digital rectal examination revealed grade1 benign prostate enlargement. Laboratory examinations revealed normal urine microscopy and culture and serum prostate- specific antigen measured 2.4 ng/ml. Transurethral resection (TUR) of the prostate was performed and sent to pathology department with initial diagnosis of benign glandular hyperplasia. All of the tissue samples underwent histological examination which was composed of a total of 190

chips. Microscopically at low power magnification, in 9 fragments, crowded glands, with papillary infoldings, branching and luminal indulations and occasional cystic glands associated with or without papillary infoldings were observed, comprising a length of between 2 to 5mm (figure 1,2,3). Some of the glands had corpora amylocea or pink amorphous secretions in their lumens. These foci of hyperplastic glands were partially well circumscribed resembling either benign glandular hyperplasia or adenosis at low magnification. In some foci, minimal extension of neoplastic glands into the nonneoplastic prostate was observed (figure 2). High power examination for nuclear features revealed rare to frequent prominent nucleoli, nucleomegali, hyperchromasia and scarce mitotic figures (figure 1). Basal cells of all these hyperplastic glands failed to show immunoreactivity for high molecular weight cytokeratin (figure 3). The case was reported as adenocarcinoma of prostate with Gleason grade 2+2 with a total Gleason score of 4. Because of his advanced age and poor general condition, instead of radical surgery it was decided that the patient should be followed up with serial PSA measurements at 6 months intervals. Antiandrogens and radiotherapy was not considered as a treatment option as it was an incidentally found tumor on TUR- prostate for BPH and it was a low clinical stage disease with low gleason score and low PSA levels. The patient's PSA levels were within normal limits at his first control.

DISCUSSION

Prostatic adenocarcinoma mimicking benign processes has long been known, and article by Muir [3] was the first one to mention the diagnostic difficulty of prostatic adenocarcinoma resembling hyperplastic appearing benign glands. However it is claimed that the only illustration of his article related to this comment was of a typical adenocarcinoma with a Gleason score of 3+3=6. [1] Pseudohyperplastic change in prostate cancer was first described and illustrated by Epstein in1989 [4] but it has not been studied as a specific histologic variant. So far the main morphologic features and frequency of this neoplasm has been studied in limited number of reports.[1,2,5]

The term "Pseudohyperplastic prostatic adenocarcinoma " was first used by Humphrey et al.in1998.[2] They reviewed 302 cases of prostatic adenocarcinoma including 100 consecutive prostatic needle biopsies and 202 radical prostatectomy specimens. Pseudohyperplastic changes were present in 2 of 100 (2%) cases in needle biopsies and 22 of 202 (11%) cases in radical prostatectomy. In needle biopsies 5% and 24% of the total cancer length revealed pseuodohyperplastic foci and in radical prostatectomies pseudohyperplastic areas comprised 0,9-33% of total tumor size. They observed that hyperplastic alterations were in continuity with prostatic carcinomas and these carcinomas were of lower Gleason score (median Gleason score 5) in contrast to carcinomas without pseudohyperplastic change (median Gleason score 6). However, they failed to find pathologic stage differences in these two groups and concluded that the diagnostic significance of this pattern only lied in its potential to be misdiagnosed as benign, usual hyperplasia.[2]

Figure 1a. Crowded glands with papillary infoldings, luminal indulations and branching. The differential diagnosis is between pseudoyperplastic adenocarcinoma and adenosis.

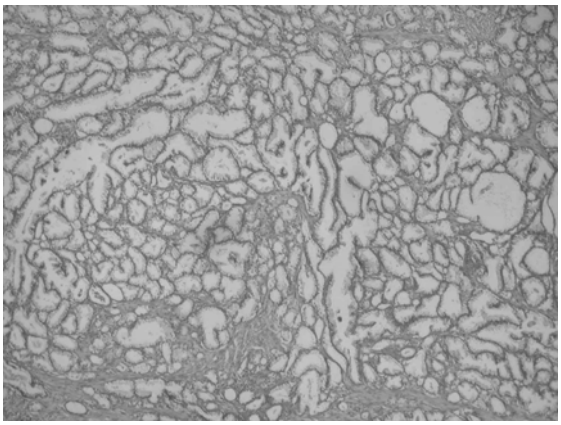


Figure 1b. High power magnification demonstrates columnar cells with basally located nucleus demonstrating marked cytologic atypia with nuclear enlargement and prominent macronucleoli consistent with adenocarcinoma

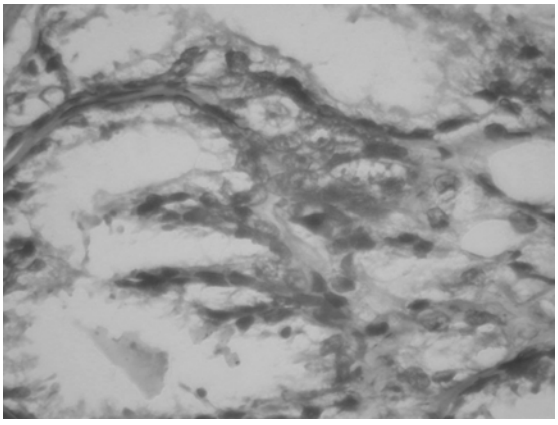


Figure 2a. Nodular growth pattern of neoplastic glands with cystic dilatation and papillary infoldings. Some contain corpora amyleocea and pink amourpous secretions. Transition to small aciner pattern of adenocarcinoma is present.

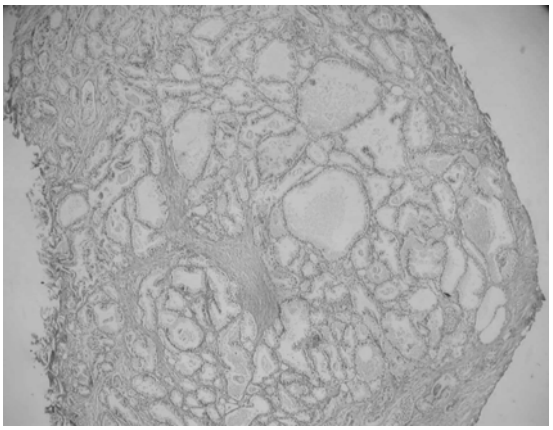


Figure 2b. Higher magnification shows that these glands lack prominent nucleoli but nuclear enlargement and scarce mitotic figures are present.

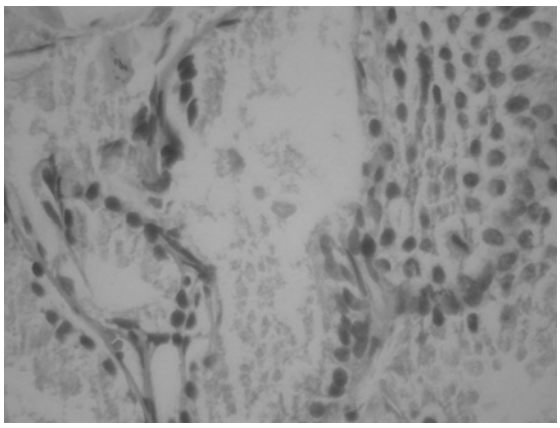


Figure 3a. Focus of crowded glands which resemble benign glandular hyperplasia with their large size and papillary infoldings.

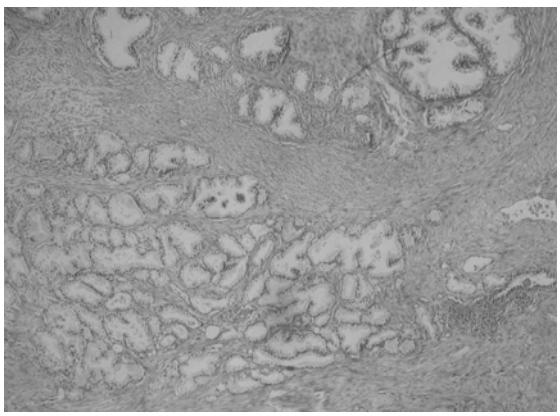
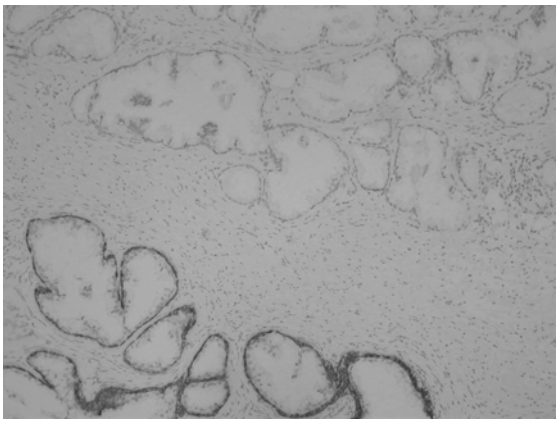


Figure3b. High-molecular cytokeratin stain shows total absence of basal cell layer in crowded glands whereas basal cell layer of benign glands is intensely positive.



Later on for defining better the histopathologic features of PHPA ; Levi and Epstein investigated 16 needle biopsy and 4 simple prostatectomy specimens in which the majority of the cancer (at least 60%- and in most cases, 90%) was pseudohyperplastic [1]. Within these pseudohyperplastic foci nuclear enlargement , pink amorphous secretions, occasional to frequent nucleoli, crystalloids and lack of basal cells were the important histopathologic features in establishing the malignant diagnosis [1](table 1). Arista-Nasr et al. examined histopathologic features (table1) and frequency of PHPA in transurethral resections.[5] They studied 150 specimens originally diagnosed as benign hyperplasia and 100 as conventional prostatic adenocarcinomas. Two (%1,3) of the benign TUR specimens were found to have PHPA in which the neoplasm was limited to two chips and measured 3 and 4 mm, respectively. Areas of PHPA was present in only three cases of the 100 biopsies with adenocarcinomas and found in two fragments in two cases, three fragments in one case and measured 3,4 and 6 mm respectively. Average of 115 fragments were analyzed in each biopsy.[5] In our case PHPA was present in 9 chips out of 190 fragments comprising a length between 2 to 5mm and was associated with transition to small aimer pattern of prostatic adenocarcinma in some foci**.** Main histologic findings in low power magnification were crowded glands with papillary infoldings, luminal indulations, branching and occasional cystic glands some of which contained corpora amylacea and pink amorphous secretions. Nuclear enlargement with rare to prominent macronucleoli and scarce mitotic figures detected in high power magnification helped to establish malignancy supported by the lack of basal cells with high molecular weight cytokeratin (hmwck).

Other features of malignancy such as blue mucin, cyrstalloids, adjacent prostatic intraepithelial neoplasia (PIN) or perineural invasion was not present.

As PHPA shares common features with benign glandular hyperplasia and is found in small and isolated areas, it wouldn't be unusual for this pattern of adenocarcinoma to be overlooked when analyzing TUR specimens. However percentage of false negative results (1,3%) appears to be infrequent according to the only study conducted on the frequency of PHPA in TUR specimens.[5] Considering the findings of Humphrey et al., who found that the pseudohyperplastic change consisted only 6% of tumor size in radical prostatectomies, it is not suprising to encounter PHPA in small amounts in TUR specimens.[2,5]

In low power magnification apart from a focus of crowded glands, only minority of the cases reported in the literature had diagnostically helpful features of malignancy such as crystalloids, blue mucin, intraluminal pink material and perineural invasion which urges high-magnification scrutiny for nuclear enlargement , prominent nucleoli and absence of basal cells (table 1). Therefore hyperplastic pattern must be suspected in low power microscopy [6] and due to difficulties in diagnosing these lesions on hematoxylin-and eosin stained sections, it is almost always helpful to confirm diagnosis with the use of immunohistochemistry to verify the absence of basal cells.[1,6-8]

Table 1. Frequency of histologic features, literature findings

Histologic feature	No.cases*	No.cases**	No.cases***
Papillary projections	22/22	20/20	5/5
Branching glands	11/22	9/20	1/5
Nuclear enlargement	22/22	19/20	5/5
Clear epithelium	19/22	N/A	5/5
Columnar epithelium	21/22	N/A	5/5
Macronucleoli	22/22	9/20	4/5
Large/Cystic glands	7/22	19/20	4/5
Straight luminal borders	N/A	4/20	4/5
Pink amorphous secretions	6/22	14/20	4/5
Nuclear hyperchromasia	N/A	3/20	3/5
Transition to small acinar ca	19/22	N/A	3/5
Infiltrative growth	6/22	5/20	0/5
Corpora amylacea	N/A	4/20	2/5
Mitotic figures	6/22	0/20	1/5
Blue mucin	3/22	3/20	0/5
Cyristaloids	8/22	9/20	0/5
Perineural invasion	2/22	1/20	0/5
Colleganeous micronodules	0/22	0/20	0/5
Glomerulations	N/A	0/20	0/5
Associated PIN	11/22	4/20	0/5
Absent basal cells	22/22	20/20	5/5

*Humprey et all ([2]), **Levi and Epstein ([1]), ***Arista-Nasr et al.([5])
N/A: not available

High grade PIN could resemble PHPA but PIN would not be as crowded or as infiltrative and maintains basal cells in varying proportions.[1,5] Although the Gleason scoring system did not account for this histologic pattern,[1,5] it was the consensus of the panel in the international consensus conference of Gleason grading system update that these tumors should be graded as Gleason score 3+3=6 as they were most often accompanied by the more typical 3+3=6 prostatic adenocarcinoma.[9] Without knowing this information, we graded our case as Gleason patern 2+2 (with a total Gleason score of 4) since neoplastic glands were partially well circumbsribed. We don't know whether gleason grade 3+3 adenocarcinoma was present in the rest of the prostat tissue, since radical prostatectomy was not performed in our patient.

The clinical course of PHPA is not well known due to insufficient literature regarding patient prognoses. Extraprostatic extension and seminal vesicle invasion was idendified in four cases by Levi and Epstein who suggested that this variant should not be considered as a low-grade cancer.[1] In the study of Arista- Nastr et al., two cases with small fragments of PHPA initially diagnosed as benign glandular hyperplasia had favorable clinical course of 2 and 4 years after diagnosis; but in the other two cases where PHPA represented a lower percentage of the neoplasm and was associated with moderately or poorly differentiated prostatic adenocarcinoma, unfavorable clinical course was detected with metastasis.[5]

Additional studies are needed not only to accurately grade the pseudoyperplastic pattern of prostatic adenocarcinoma but also to predict the patient prognosis. Limited data suggests that PHPA has potential to exhibit agressive behaviour. Nevertheless high degree of diagnostic awareness is required not to underdiagnose PHPA as a benign process due to the rarity of its presentation, deceptively benign architectural features and its potential to present unfavorable prognosis.

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