



Pseudohyperplastic prostate carcinoma: histologic patterns and differential diagnosis



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ABSTRACT

The similarity between some carcinomas and many benign glandular proliferations has been mentioned in the literature for decades. The description of the main histologic features of pseudohyperplastic carcinoma has been very useful in avoiding errors of interpretation, particularly false-negative results. In recent years, we have found some histologic variants of this neoplasm that have not been mentioned previously. In order to classify the different histologic growth patterns and comment on their differential diagnosis, we reviewed the architectural and cytologic features of 34 cases of pseudohyperplastic adenocarcinoma in 2 radical prostatectomies, 4 transurethral resections, and 28 needle biopsies. Growth patterns most commonly observed included nodular, complex, and mixed (nodular and complex) patterns. Other less frequent histologic varieties included adenosis-like pattern, prostatic intraepithelial neoplasia-like pattern, pseudohyperplastic adenocarcinoma with xanthomatous features, and limited pseudohyperplastic adenocarcinoma. Frequent changes in neoplastic glands included papillary infoldings, large/cystic glands, and branching. Criteria associated with malignancy include nuclear enlargement (92%), apparent nucleoli (85%), pink amorphous secretions (78%), and transition to small acinar carcinoma (70%). However, in some biopsies, nuclear atypia was little apparent. Fifteen of the 34 cases were misdiagnosed as benign and 5 as other malignant neoplasms, and included the following diagnoses: hyperplastic nodules (11), prostatic adenosis (2), diffuse adenosis of the peripheral zone (1), benign cystic glands (1), and less frequently other malignant tumors including xanthomatous carcinoma (2), low-grade prostatic adenocarcinoma (2), and atrophic carcinoma (1). It is important to recognize the different growth patterns of this neoplasm in order to avoid an underdiagnosis of malignancy.

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1. Introduction

It has been known for many years that some prostate adenocarcinomas may resemble benign glandular proliferations [1–4]. The architectural and cytologic criteria for pseudohyperplastic adenocarcinoma (PHA) described by Humphrey et al [5] and by Levi and Epstein [6] have made it possible to interpret this neoplasm in prostate biopsies and products of prostatectomies. Although PHA is considered to be an infrequent neoplasm [5,6], in our population, it is the variety of prostate carcinoma most frequently seen, behind conventional acinar adenocarcinoma [7], and constitutes most prostate adenocarcinomas that we receive in consult. In the past 5 years, we have studied 34 cases of PHA, some of which had peculiar histologic characteristics that widen the morphologic spectrum of this neoplasm. The purpose of this review is to classify and illustrate the diverse histologic growth patterns of PHA and to comment on their differential diagnosis.

2. Materials and methods

During the period from 2008 to 2013, we studied 34 cases of PHA. Fourteen of them belonged to patients of our institute and 20 were received in consult. This study includes only those cases in which the diagnosis of PHA was a problem during the original study and/or when the neoplastic tissue was more than 90% of the neoplasm. Of the 34 cases, 28 were needle biopsies, 4 were the product of transurethral resection, and 2 were radical prostatectomies. The number of slides that showed PHA for each type of biopsy was written down and classified as follows: (a) 1 slide with PHA, (b) 2 to 4 slides with the tumor, and (c) more than 4 slides with PHA. In 30 cases, we performed immunohistochemical studies with high-molecular-weight cytokeratin (clone 34βE12; 1:100) and p63 (clone 4A4; 1:250). Antibodies were obtained from DAKO, Carpinteria, California. In 18 biopsies, additional levels were made to facilitate the histologic interpretation.

The following histologic criteria were evaluated: large/cystic glands, branching glands, straight luminal borders, columnar epithelium, clear cytoplasm, hyperchromatic nuclei, nuclear enlargement, apparent nucleoli, pink amorphous secretions, blue mucin, transition to small acinar carcinoma, infiltrative growth pattern, corpora amylacea, crystalloids,

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perineural invasion, collagenous micronodules, glomerations, associated prostatic intraepithelial neoplasia (PIN), and absent basal cells.

3. Results

The number of slides with PHA and the type of biopsy are shown in Table 1. The percentage of histologic findings in decreasing order of frequency is shown in Table 2. Pseudohyperplastic adenocarcinoma was found in only 1 slide in 15 of the 28 needle biopsies, and 2 of the 3 limited prostate adenocarcinomas were observed in these types of biopsies. In the products of transurethral resection, 1 case showed PHA in an isolated histologic field, and in the other 3, the neoplasm was associated with focal areas of conventional acinar carcinoma.

Criteria often associated with malignancy were found as follows: nuclear enlargement (92%), apparent nucleoli (85%), pink amorphous secretions (78%), and transition to small acinar carcinoma (70%; Table 2). The areas of transition between PHA and conventional acinar carcinoma were less apparent in the needle prostate biopsies. In 2 of the radical prostatectomies, the neoplasm was found in some cuts of the peripheral zone and the transition zone. One of these 2 cases showed areas of PHA mixed with xanthomatous carcinoma, as well as areas in which the glands shared histologic criteria for both types of tumor (PHA with xanthomatous features).

The histologic growth patterns and their corresponding illustrations are shown in Table 3. When there was more than 1 pattern, the neoplasm was classified according to the predominant (most extensive) pattern. Classification was relatively simple as these 34 cases of pseudohyperplastic carcinoma presented only 1 or 2 histologic patterns. In addition, in 16 of the 34 cases, the neoplasm was found only on one of the slides examined, facilitating evaluation.

The growth patterns most commonly observed included the following: nodular pattern with or without nuclear atypia (Figs. 1 and 2), complex pattern (Fig. 3A, B), and mixed pattern (nodular and complex patterns; Fig. 3C, D). The complex branching glands showed fibrovascular cores, papillary infoldings, small intraluminal papillary projections, and luminal undulations which were coated by tall cells with nucleomegaly and apparent nucleoli (Fig. 3B–D).

Then infiltrative pattern showed glands of highly variable form and size (medium to large), arranged irregularly and separated by scarce prostatic stroma (Fig. 4). Most of these glands had irregular borders, papillary infoldings, papillary projections, and, in some cases, corpus amyloaceous (Fig. 4). In some fields, the neoplastic glands were found located in between benign glands, confirming their infiltrative nature. In contrast with the benign adjacent cells, glands of PHA had either clear cytoplasm or pale and eosinophilic and nuclear atypia (Fig. 4B).

The adenosis-like pattern (Fig. 5) was made up of malign glands, predominantly medium sized, with eosinophilic and crystalloid luminal secretions with an expansive or infiltrative margin (Fig. 5A). In contrast with prostatic adenosis, most of the pseudohyperplastic glands had nuclear atypia characterized by nuclear enlargement, apparent nucleoli (Fig. 5C), and an absence of basal cells (Fig. 5B).

Others growth patterns include the following: PIN-like pattern (Fig. 6), PHA with xanthomatous changes (Figs. 7 and 8), and PHA in isolated histologic fields (limited prostate adenocarcinoma). The histologic criteria used to classify limited PHA were different from those for most acinar-type limited carcinomas. The latter are made up of small glands

Table 1
Number of slides with pseudohyperplastic carcinoma and type of biopsy

	1 slide	2–4 slides	>4 slides	Total
Needle biopsy	15	13		28
TURP	1	3		4
Prostatectomies			2	2
				34 cases

TURP, transurethral resection of the prostate.

Table 2

Architectural and cytologic features in 34 biopsies with pseudohyperplastic prostatic carcinoma

Absent basal cells	100%
Papillary infoldings	96%
Nuclear enlargement	92%
Columnar epithelium	92%
Clear epithelium	90%
Apparent nucleoli	85%
Pink amorphous secretions	78%
Transition to small acinar carcinoma	70%
Large/Cystic glands	64%
Branching glands	45%
Crystalloids	36%
Straight luminal borders	32%
Corpora amyloacea	27%
Nuclear hyperchromasia	24%
Infiltrative growth	23%
Mitotic figures	15%
Blue mucin	13%
Perineural invasion	6%
Collagenous micronodules	0%
Glomerulations	0%

in tight arrangement, occasionally between larger benign glands. Although there are no specific cytologic criteria to diagnose limited acinar adenocarcinoma, the presence of prominent nucleoli, nuclear enlargement, and nuclear hyperchromatism strongly support a diagnosis of malignancy. In contrast, limited PHA appears as large malignant glands with a diameter similar to or larger than that of the adjacent benign prostatic glands (Fig. 9A), papillary infoldings, undulations, straight luminal borders, nucleomegalia, apparent nucleoli, and eventually corpus amyloaceous (Fig. 9).

4. Discussion

Although pseudohyperplastic carcinoma was described more than 15 years ago [5,6], this neoplasm is still a diagnostic problem. We have noticed that the well-differentiated glands of PHA frequently are not recognized as malignant as they are analyzed under low magnifications and their cytologic characteristics are not often carefully analyzed. Another factor that may influence the erroneous interpretation of this neoplasm is that needle prostate biopsies frequently have scarce tumor tissue. In this series, 15 of the 28 needle biopsies had areas of PHA only in one of the biopsied cores (Table 1), and in 2 of them, it was limited to isolated histologic fields (limited prostate adenocarcinoma).

The morphology of PHA is variable and may be mistaken for several benign or malignant glandular proliferations. The original diagnosis for 20 of the cases received in consult included hyperplastic nodules, low-grade prostate adenocarcinoma [4,8], prostate adenosis [8–11], diffuse adenosis of the peripheral zone [12,13], benign cystic glands vs atrophic carcinoma [14–18], PIN [19,20], atypical small acinar proliferation [21,22], and xanthomatous carcinoma [23–26].

In the original description of this neoplasm [5], Humphrey et al [5] illustrated 2 frequent growth patterns: nodular and complex, formed

Table 3
Predominant growth patterns in pseudohyperplastic carcinoma

Growth pattern	No. of cases	Figures
(1) Nodular	8	
(A) With nuclear atypia	6	Fig. 1A, B
(B) Without nuclear atypia	2	Fig. 2A, B
(2) Complex	5	Fig. 3A–B
(3) Mixed (nodular and complex)	8	Fig. 3C, D
(4) Infiltrative	2	Fig. 4A, B
(5) Adenosis-like	4	Fig. 5A–C
(6) PIN-like	2	Fig. 6A–C
(7) With xanthomatous changes	3	Figs. 7A–C and 8A–C
(8) In isolated histologic fields	2	Fig. 9A–D
Total	34	

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