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Histologic and Immunohistochemical Features of Pseudohyperplastic Prostatic Adenocarcinoma on Prostatectomy

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Abstract：Due to the limited availability of tissue, the diagnosis of prostate cancer on needle biopsies is often difficult. The pseudohyperplastic variant of prostatic carcinoma resembles benign hyperplastic glandular tissue in structure, and it can be misdiagnosed as benign. To better understand pseudohyperplastic adenocarcinoma, we reviewed all radical prostatectomy specimens at Fukuoka University Hospital, Japan taken from January 2006 to December 2010 and identified 14 cases. Data on the following clinical characteristics in these 14 cases of pseudohyperplastic adenocarcinoma were collected: age（mean = 64.6 years; range = 54-72 years)，prostate-specific antigen（PSA）level（mean = 9.30ng/ml; range = 3.17 -30.10ng/ml)，TNM classification（T2a, 1 case; T2b, 1 case; T2c, 11 cases; T3a, 1 case)，Gleason score（3+3=6, 3 cases; 3+4=7, 7 cases; 4+3=7, 4 cases)．The frequency of histologic features in pseudohyperplastic adenocarcinoma in the 14 cases included : papillary infolding, 100%; nuclear enlargement, 100%; prominent nucleoli, 92.9%; dense pink secretions, 78.6%; crystalloids, 71.4%; blue-tinged luminal mucin, 7.1%; mitosis, 7.1%. Immunohistochemical studies demonstrated negativity of p63 and 34 β E12（i.e., basal cell markers）in 14（100%）cases and positivity of α -methylacyl CoA racemase（p504s）in 12（85.7%）cases. We conclude that careful observation of intraluminal features and nuclear structures on hematoxylin and eosin stains aids diagnosis of pseudohyperplastic adenocarcinoma. Additional immunohistochemical staining for basal cell markers and p504s is helpful when establishing a definitive diagnosis from H&E slides is difficult.

Key words：**Prostate, Pseudohyperplastic adenocarcinoma, p63, 34 β E12, p504s**

Introduction

Pseudohyperplastic adenocarcinoma is a variant of prostatic adenocarcinoma structurally characterized by large branching glands with papillary infolding.[1)]

Because these glands resemble those in benign hyperplasia,[2)] the diagnosis of small atypical foci of prostatic cancer on needle biopsy can be challenging. The aim of this study was to clarify the histological and immunohistochemical features of pseudohyperplastic adenocarcinoma in radical prostatectomy specimens.

Materials And Methods

We identified 14 cases of pseudohyperplastic adenocarcinoma after examining routine hematoxylin and eosin（H&E）slides from radical prostatectomy performed at Fukuoka University Hospital between January 2006 and December 2010. The data concerning TNM classification,

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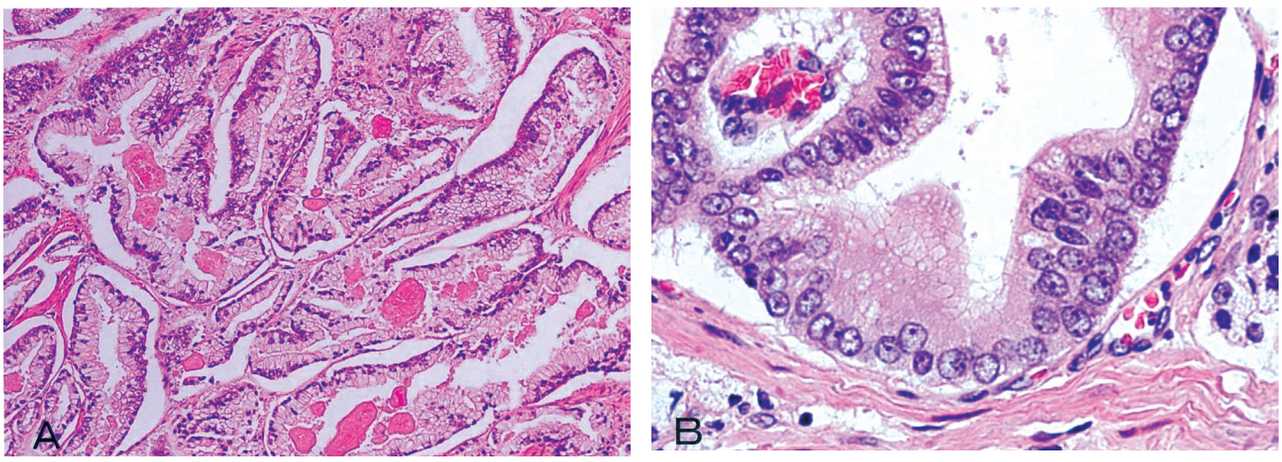

Fig. 1 (A) Pseudohyperplastic adenocarcinoma shows large branching glands with papillary infolding (x100). (B) Enlarged nuclei and prominent nucleoli are observed in pseuohyperplastic adenocarcinoma (x400).

Gleason score, lymphatic invasion, venous invasion, and neural invasion were analyzed. Histologic features including tissue structure, nuclear structure, mitosis, and intraluminal materials were examined on H&E stains and immunohistochemical staining was performed. Paraffin-embedded formalin-fixed prostate tissues were cut into 3-μm sections and triple stained with anti-p63 monoclonal antibody, anti-34βE12 monoclonal antibody, and anti-α-methylacyl CoA racemase (anti-p504s) polyclonal antibody (all from Dako, Glostrup, Denmark).

Results

Pseudohyperplastic adenocarcinoma was detected in 14 (17.7%) of the 79 radical prostatectomies cases reviewed. From the data for these 14 cases, the following

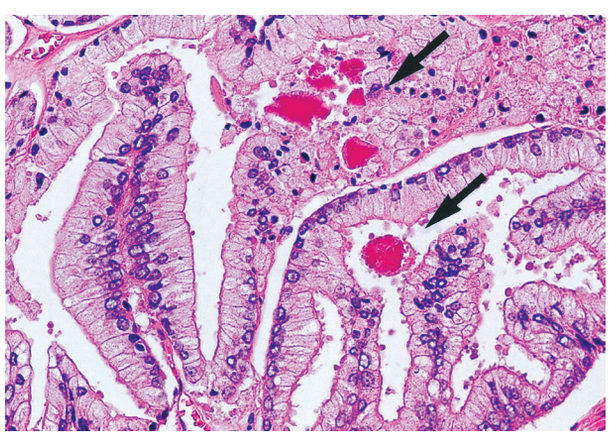

Fig. 3 Some crystalloids (arrow) are seen in the lumens of pseudohyperplastic adenocarcinoma (x200).

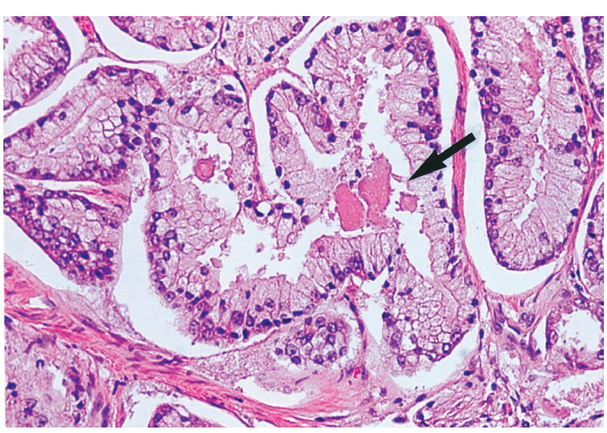

Fig. 2 Pink dense secretions (arrow) are seen in the lumens of peudohyperplastic adenocarcinoma (x200).

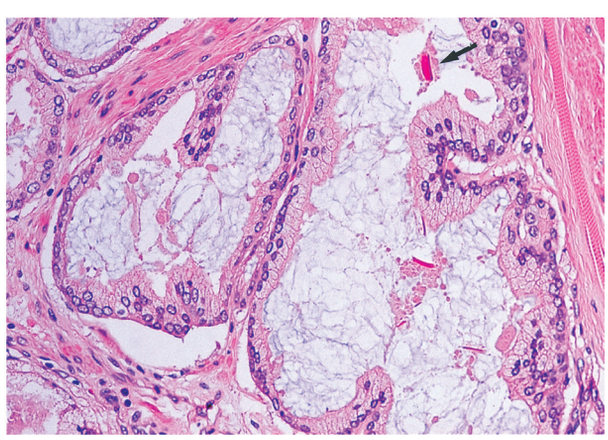

Fig. 4 Lumens of pseudohyperplastic adenocarcinoma are filled with blue-tinged mucin. Small crystalloids are also present (arrow) (x200).

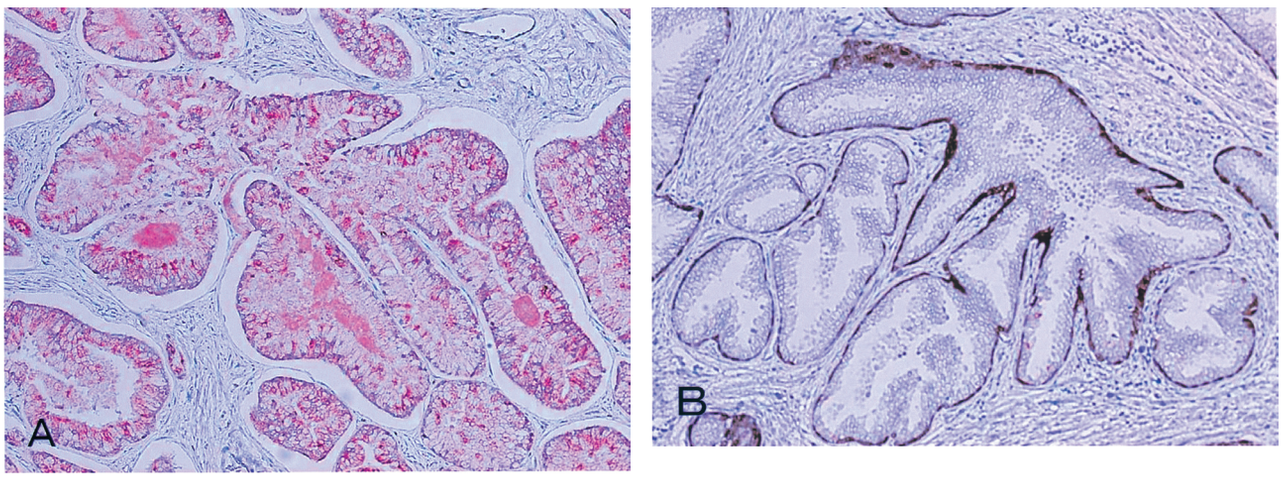

Fig. 5 Immunohistochemical antibody cocktail staining（p63/34 β E12/p504s）（A）Pseudohyperplastic adenocarcinoma is positive for p504s（red）, but negative for p63 and 34 β E12（x100）. (B) Benign hyperplastic glands are negative for p504s, but positive for p63 and 34 β E12（brown）（x100）.

clinical characteristics were observed: age（mean = 64.6 years; range = 54-72 years）, prostate-specific antigen level（mean = 9.30ng/ml; range = 3.17 -39.10ng/ml）, and TNM classification（T2a, 1 case; T2b, 1 case; T2c, 11 cases; T3a, extraprostatic extension, 1 case）. We identified one case of lymphatic invasion and five cases of neural invasion, but no case of venous invasion, lymph node metastasis, or seminal vesicle invasion. The Gleason scores were as follows: 3+3=6, 3 cases; 3+4=7, 7 cases; and 4+3=7, 4 cases. All cases manifested small-acinar adenocarcinoma. Findings of H&E stains were the following: papillary infolding, 14/14（100%）; nuclear enlargement, 14/14（100%）; prominent nucleoli, 13/14（92.9%）（Fig.1）; and mitosis, 1/14（7.1%）. The following intraluminal features were identified : dense pink secretions, 11/14（78.9%）（Fig.2）; crystalloids, 10/14（71.4%）（Fig.3）; blue-tinged luminal mucin, 1/14（7.1%）（Fig.4）; and corpora amylacea, 1/4（7.1%）. Immunohistochemical stainings showed that the basal cell markers p63 and 34 β E12 were negative in all cases, and p504s was positive in 12 cases（85.7%）（Fig.5）.

Discussion

With the recent introduction of PSA level measurement as an effective diagnostic assessment for prostate tissue, pathologists are now obtaining histological diagnosis through biopsy much more frequently than a decade ago. Prostatic adenocarcinoma is characterized by lack of basal cells, whereas benign glands contain basal cells in double layers. Furthermore, structural and cellular atypia are minimal in well-differentiated adenocarcinoma. In the Gleason grading system,[3] structures and invasive features are considered, rather than cellular atypia, in assigning the score between 1 and 5.

Establishing the correct diagnosis is often difficult for small foci of carcinoma with little structural or cellular atypia. Benign hyperplasia,[2] adenosis,[4,5] postatrophic hyperplasia,[6] partial atrophy,[7] basal cell hyperplasia,[8,9] benign crowded glands,[7] and prostatic intraepithelial neoplasia（PIN）[10,11,12] could potentially be confused with carcinoma. We identified 14 cases（17.7%）of pseudohyperplastic adenocarcinoma after reviewing 79 prostatectomy specimens. Humphrey et al.[13] reported pseudohyperplastic adenocarcinoma in 11% of cases in prostatectomy and 2% of cases in needle biopsies. The distribution of Gleason grading obtained by our study was as follows: 3+3=6, 3 cases（21%）; 3+4=7, 7 cases（50%）; and 4+3=7, 4 cases（29%）. The distribution of Gleason grading in another study by Angelique et al. [14] was: 3+2=5, 2 cases（29%）; 3+3 =6, 4 cases（57%）; and 4+3 =7, 1 case（14%）.

Consistent with previous reports[13,14] , we did not find any case with a Gleason sum of 8 or greater. Pseudohyperplastic adenocarcinoma, which is a variant of prostatic adenocarcinoma, is similar to benign hyperplastic glands in that the glands have papillary infolding. While, identifying basal cells in benign hyperplastic glands on H&E stains is often difficult. This raises the risk of misdiagnosing pseudohyperplastic

adenocarcinoma as benign on needle biopsy. Our review of pseudohyperplastic adenocarcinoma on H&E stains revealed papillary infolding and nuclear enlargement in all of the cases and prominent nucleoli in 92.9% of the cases. In addition, 7.1% of cases showed mitosis. Intraluminal features such as dense pink secretions, crystalloids, and blue-tinged luminal mucin are generally observed within the glands of adenocarcinoma.[1] In the present study, we found each of these features at the following frequencies: dense pink secretions, 78.6%; crystalloids, 71.4%; and blue-tinged luminal mucin, 7.1%. In contrast, Angelique et al.[14] found a much lower prevalence of crystalloids: dense pink secretions, 70%; crystalloids, 45%; and blue-tinged luminal mucin, 15%. In addition, we found one case (7.1%) with corpora amylacea. Although corpora amylacea are generally found in benign glands, they have been reported in adenocarcinoma [15,16]. In our study, immunohistochemical staining for p63 [17,18] in basal cell nuclei and 34 β E12 [18,19] in basal cell cytoplasm was negative in all 14 cases. However, staining for α -methylacyl-CoA recemase (p504s), [20,21] which is found in prostatic adenocarcinoma or high grade prostatic intraepithelial neoplasia, was positive in 12 cases (85.7%). Similarly, Ming et al. [22] reported positive staining of p504s in 13 of 17 cases (76.5%).

In summary, we reviewed specimens from 79 radical prostatectomies and identified pseudohyperplastic adenocarcinoma in 14 cases (17.7%). The presence of intraluminal materials, such as dense pink secretions and crystalloids, as well as nuclear enlargement and prominent nucleoli help identify pseudohyperplastic adenocarcinoma. Immunohistochemical stains that are negative for basal cell markers and positive for p504s may also help establish a definitive diagnosis when drawing a conclusion from H&E slides is difficult.

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