

Case Report

Pseudoangiomatous stromal hyperplasia of the prostate: report of an unprecedented entity in prostate pathology

Alexandra R Rapp, Elizabeth Jacobi, Min Jung Jung, Luan Truong, Alberto G Ayala, Jae Y Ro

Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Weill Medical College of Cornell University, Houston, Texas, America

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Abstract: Pseudoangiomatous stromal hyperplasia is a benign entity of the breast. It is histologically characterized by open, slit-like spaces lined by spindle cells of myofibroblast/fibroblast differentiation in a dense collagenous stroma. Although pseudoangiomatous stromal hyperplasia has been reported in ectopic breast tissue in anogenital mammary-like glands, it has not been previously reported in non-breast tissues. This includes prostatic tissue, which shares similar histology and pathology with the breast. Herein, we report the first case of prostatic pseudoangiomatous stromal hyperplasia based on histological, immunohistochemical, and electron microscopic findings. The patient was a 74-year-old man with a history of benign prostatic hyperplasia who presented with severe urinary retention and underwent transurethral resection of the prostate. In addition to benign prostatic hyperplasia, the prostate showed areas of irregular spaces lined occasionally by flattened spindle cells in a background of fibrocollagenous stroma. Immunohistochemically, these cells were diffusely positive for vimentin and negative for CD31, CD34, ERG, pancytokeratin, SMA, and D2-40. Electron microscopic findings also showed some cells with fibroblastic features lining these spaces. Given these findings, we postulated that pseudoangiomatous stromal hyperplasia of the prostate has some cells of fibroblastic lineage. Contrary to its breast counterpart where lining cells demonstrate diffusely and strongly positive staining for CD34 and PR, this prostate case showed negative staining for CD34 and PR. These findings indicate potential differences in the histogenesis of prostatic and breast pseudoangiomatous stromal hyperplasia.

Keywords: Pseudoangiomatous stromal hyperplasia, breast, prostate, immunohistochemical stains, electron microscopy

Introduction

Pseudoangiomatous stromal hyperplasia (PASH) is a well-known hyperplastic, benign, mesenchymal lesion of the breast, characterized histologically by open slit-like spaces lined by myofibroblasts/fibroblasts in a dense collagenous stroma. Previously, PASH had only been reported in the breast. In recent years, there have been case reports documenting PASH in anogenital mammary-like glands [1, 2]; yet they can still be classified as breast pathology cases due to the presence of ectopic breast tissue within the glands. While there are many shared pathological entities between breast and prostate, a case of PASH in the prostate has not been previously reported to the best of our knowledge. Herein, we report the first docu-

mented case of PASH of the prostate in the setting of significant benign prostatic stromal and glandular hyperplasia with supportive histologic, immunohistochemical, and electron microscopic findings.

Case report

A 74-year-old man with a history of significant benign prostatic hyperplasia (BPH) presented with severe urinary retention and inability to void, requiring clean intermittent catheterization (CIC) every 4 to 6 hours. Previously, he had been treated with finasteride and tamsulosin, but he did not respond to this medication regimen. The patient subsequently underwent transurethral resection of the prostate (TURP) to treat his urinary retention. Pathologic gross

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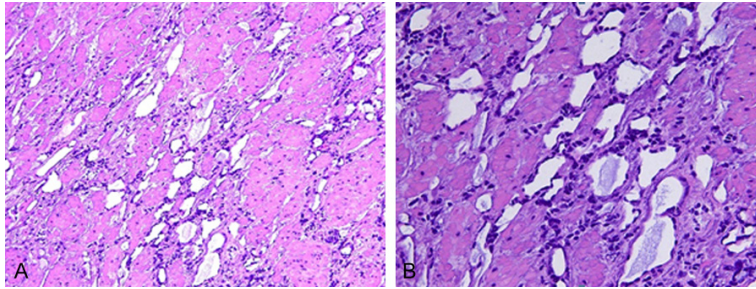


Figure 1. Microscopic views of prostatic stroma with areas of pseudoangiomatous stromal hyperplasia (H&E; A 40x; B 100x).

Table 1. Antibodies used for this study

Antibody	Clone	Dilution	Manufacturer
CD31	JC70	RTU (ready to use)	Ventana/Roche
CD34	QBEND/10	RTU	Ventana/Roche
ERG	EPR3864	RTU	Ventana/Roche
Cytokeratin	AE1/AE3	1:100	Dako/Agilent
Podoplanin	D2-40	RTU	Ventana/Roche
SMA	1A4	RTU	Ventana/Roche
ER	SP1	RTU	Ventana/Roche
PR	1E2	RTU	Ventana/Roche
AR	SP107	RTU	Ventana/Roche

SMA, smooth muscle actin; ER, estrogen receptor; PR, progesterone receptor; AR, androgen receptor.

examination of the TURP specimen showed a tan, rubbery, fibrous aggregate of tissue, which measured 5 × 5 × 1 cm and weighed 10 grams.

The entire TURP chips were submitted for histologic examination. Hematoxylin and eosin (H&E)-stained sections demonstrated a background of acute and chronic inflammation with stromal and glandular hyperplasia. There was no identifiable high-grade prostatic intraepithelial neoplasia (PIN) or malignancy.

The most dramatic histologic finding was the presence of multiple foci of slit-like, often anastomosing empty spaces in the fibromuscular stroma (**Figure 1**). These slit-like luminal spaces were either empty (they did not have lining cells) or were occasionally lined by flattened cells with no cytologic atypia or mitoses. These features resembled PASH of the breast.

Materials and methods

A representative block containing suspected PASH was selected for immunohistochemical stains and electron microscopic analysis. A

panel of immunohistochemical staining tests (**Table 1**) were performed to ascertain whether these spaces were vascular, epithelial, or artifact in nature. The CD31, CD34, ERG, pancytokeratin, podoplanin (D2-40), smooth muscle actin (SMA), estrogen receptor (ER), progesterone receptor (PR) and androgen receptor (AR) immunostains were performed to determine if these spaces were true vascular lumens or epithelial lined spaces, and to check any hormonal receptor activity.

Electron microscopic (EM) analysis was performed from paraffin embedded tissue blocks to demonstrate the lineage of differentiation of PASH lining cells. The EM preparation and procedure were followed by the routine EM analysis method [3].

Results

CD31, CD34, and ERG were positive in the lining of blood vessels, but negative in the linings of the corresponding slit-like spaces of interest in our case (**Figure 2**), thus ruling out a true vascular lesion. Pancytokeratin (AE1/AE3) was negative, ruling out an epithelial lesion (**Figure 3**). Smooth muscle actin (SMA) and D2-40 stains were also negative in the lining of the spaces (**Figure 3**). The lesion was diffusely positive for vimentin immunostain (**Figure 3**) in the lining cells of the slit-like spaces, suggesting absence of lining cells or lining cells that were fibroblasts. Thus, these areas were interpreted as “stromal hyperplasia with areas of benign pseudovascular changes”, which we currently believe to be consistent with prostatic PASH.

Immunostains for estrogen (ER) and progesterone (PR) were negative in prostate glandular cells, stromal cells, and PASH lining cells. Androgen receptor (AR) immunostaining was also negative in the PASH lining cells. Conversely, glandular and stromal positivity was detected for AR.

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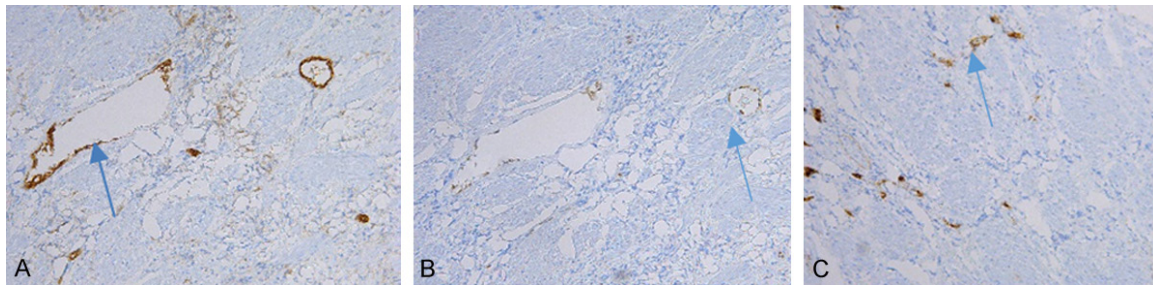


Figure 2. Microscopic views of immunohistochemical stains CD31 (A), ERG (B), and CD34 (C) show no staining for the lining of the areas of pseudoangiomatous stromal hyperplasia. See positive staining of true vascular endothelial cells (arrows) (100x).

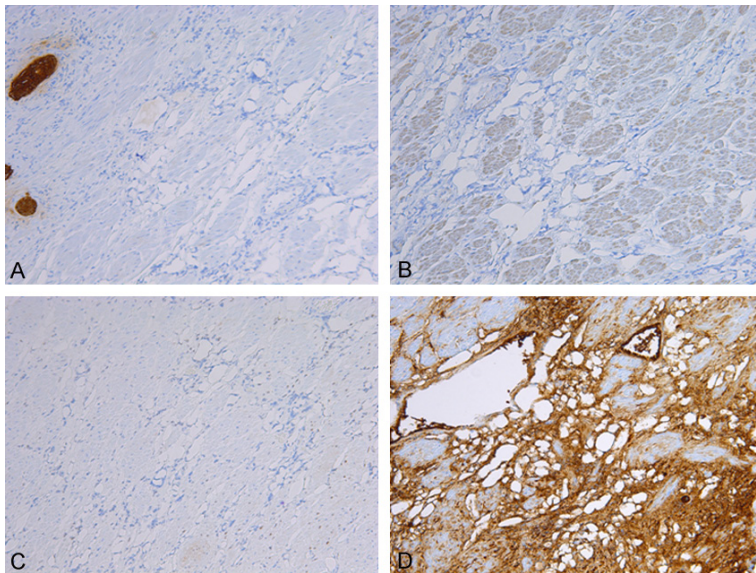


Figure 3. Microscopic views of negative immunohistochemical stains pancytokeratin (A), SMA (B), and D2-40 (C), and diffusely positive stain for vimentin (D) (100x).

By EM analysis, most spaces were empty, but some of the luminal spaces of interest were lined by cells showing well-developed granular endoplasmic reticulum with visible collagen and occasionally prominent Golgi apparatus. These findings were consistent with the electron microscopic features of fibroblasts (**Figure 4**), and further supported our diagnosis of PASH of the prostate.

Discussion

PASH refers to a well-known, frequently documented hyperplastic lesion in male and female breasts, recognized on histology as areas of open, slit-like spaces in a background of dense collagenous stroma. A few case reports of this entity in areas other than the breast involving anogenital mammary-like glands have been

reported [1, 2]. However, such lesions still involve breast tissue, even though it is ectopic. An extensive search of the literature revealed absence of documented PASH cases other than in breast. No reported cases of PASH were found in prostate, despite the fact that the breast and prostate share analogous histology and pathology: They both have duct and lobular systems, and many similar disease entities occur in both the breast and prostate. We therefore believe that this is the first documented case of prostatic PASH in the setting of significant BPH.

Vuitch *et al.* first described PASH of the breast in a group of nine pre-menopausal women in 1986 [4]. Since then, there have been multiple other case series documenting PASH in the breast [5]. PASH of the breast typically presents in women of childbearing age, although it can rarely occur in post-menopausal women, adolescents, children, and men with gynecomastia (<https://rarediseases.info.nih.gov/diseases/9410/pseudoangiomatous-stromal-hyperplasia>). It is usually discovered incidentally on breast biopsy, but it occasionally presents as a breast mass, termed nodular or tumorous PASH. Grossly, PASH is a non-encapsulated, well-circumscribed, rubbery mass with a solid, homogeneous, gray-white cut surface. As previously stated, histologically this lesion is characterized by open slit-like spaces that are lined with a discontinuous layer of flat, spindle-shaped cells with no nuclear features of malignancy.

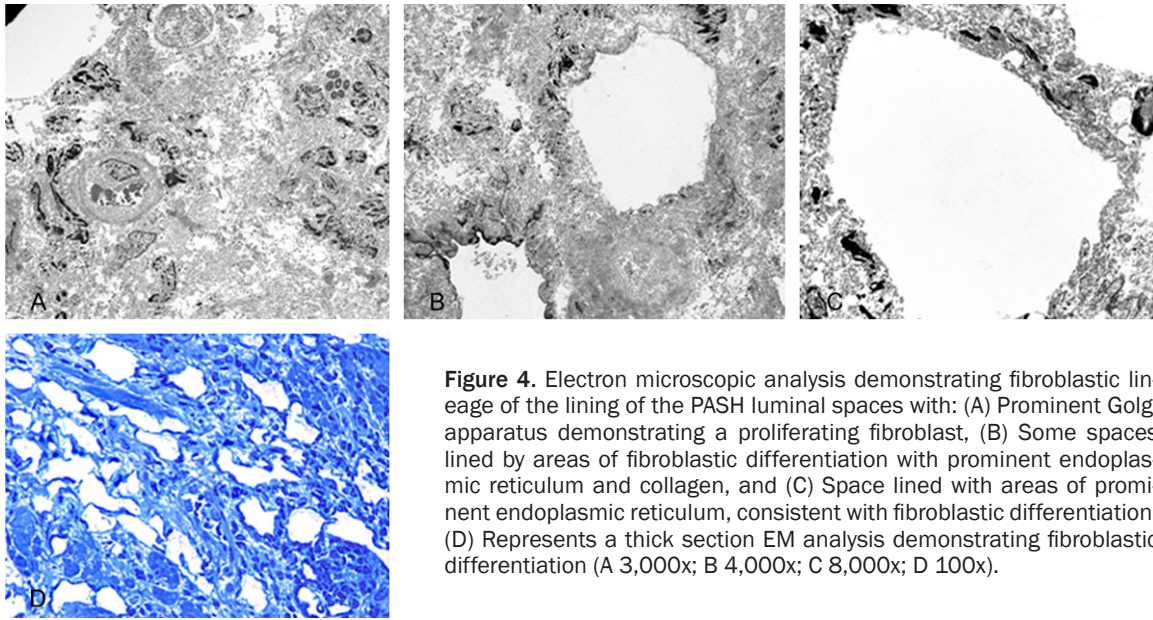


Figure 4. Electron microscopic analysis demonstrating fibroblastic lineage of the lining of the PASH luminal spaces with: (A) Prominent Golgi apparatus demonstrating a proliferating fibroblast, (B) Some spaces lined by areas of fibroblastic differentiation with prominent endoplasmic reticulum and collagen, and (C) Space lined with areas of prominent endoplasmic reticulum, consistent with fibroblastic differentiation; (D) Represents a thick section EM analysis demonstrating fibroblastic differentiation (A 3,000x; B 4,000x; C 8,000x; D 100x).

nancy [4]. The spaces are considered an artifact caused by induction of collagenous stroma retraction during the fixation process [6].

The linings of the slit-like spaces are typically positive for the immunohistochemical stains vimentin, CD34, and SMA (focally), findings leading to the accepted hypothesis that these spindle-shaped cells are of stromal myofibroblastic origin [6-8]. Additionally, these cells can be positive for desmin and bcl-2. They are negative for endothelial markers such as CD31 and Factor VIII, which can be helpful to distinguish PASH from hemangioma or angiosarcoma, which are positive for both markers [7, 8]. These lesions are also negative for S-100 and epithelial markers such as cytokeratin [7]. The spindle-shaped cells can also express PR [5], supporting the hypothesis that this lesion is hormonally driven by an exaggerated response of the spindle-shaped cells to progesterone. PASH of the breast used to be historically classified as a mammary hamartoma, but it is considered a distinct entity under current WHO guidelines [9].

To the best of our knowledge, herein we report the first recognized case of PASH in the prostate. Regular H&E stained microscopic slides demonstrated the classic open, slit-like luminal spaces, displaying frequent, irregular spacing without cells or lined by spindle cells that did not show nuclear atypia, mitoses, or other

nuclear features indicating malignancy. The negative AE1/AE3 stain ruled out any epithelial or glandular lesion from the differential diagnosis. Additionally, the negative ERG, CD34, and CD31 stains differentiated our case from a vascular lesion. The negative D2-40 stain was useful to eliminate lymphatic or mesothelial etiology from the differential diagnosis. The diffusely positive vimentin stain without other positive immunostains further supports our diagnosis of PASH. Occasionally, SMA can be focally positive in PASH; SMA was negative in our case, a finding that can be attributed to tissue sampling. Our case was negative for CD34; however, most cases of breast PASH are positive for CD34. Based on negative stains for CD34 and SMA and the positive stain for vimentin, the spindle cells in our case of PASH of the prostate have probable fibroblastic lineage. Our electron microscopic analysis further supported the fibroblastic nature of the cells, given the observed features of a well-developed granular endoplasmic reticulum with visible collagen and occasionally prominent Golgi apparatus. Positive PR staining can be a useful confirmatory test as the spindle cells in PASH of the breast frequently are positive for PR, but PR staining is also positive in a variety of stromal tumors and lesions without any specificity (<https://emedicine.medscape.com/article/161-1918-overview#al>). In our case, PR and the other hormone receptors were all negative in PASH lining cells. However, it is likely that hor-

mones do not influence PASH of the prostate as that of the breast. This can be explained by the fact that, in our case of prostatic PASH, the predominant lining cells were fibroblasts as opposed to myofibroblasts, the latter having been postulated to respond abnormally to progesterone in the breast. Our case is notable, but more detailed clinicopathological findings from other documented cases of PASH of the prostate are necessary to fully determine its characteristics.

Conclusion

This study describes the first reported case of PASH in the prostate, based on combined histological, immunohistochemical, and electron microscopic findings. Previously, this benign mesenchymal lesion had been described only in breast or ectopic breast tissue. It is well accepted that PASH is hormonally driven in the breast, presumably due to an exaggerated response to progesterone. Our case of PASH of the prostate may not be hormonally driven to the same extent as the breast given the negative PR, ER, and AR stains of the lining cells. PASH of the breast, presenting as a mass, is excised, and there is minimal risk of recurrence. Therefore, the patient's TURP procedure may have essentially treated both PASH and BPH.

It should be noted that it is not certain if PASH of the prostate behaves in exactly the same way as the breast because PASH of the prostate has never been documented heretofore. This difference in behavior can be seen in other shared entities between breast and prostate, and the discrepancies in CD34 staining (myofibroblasts versus fibroblasts) and hormonal staining (PR positivity versus negativity) could be indicators of a possible difference. Additional studies and case reports will further elucidate the etiology of PASH in prostate and non-breast tissue.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jae Y Ro, Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Weill Medical College of Cornell University, 6565 Fannin Street, Houston 77030, Texas, America. Tel: 713-441-2263; Fax: 713-793-1603; E-mail: jaero@houstonmethodist.org

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