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Original Article

Prostatic stromal tumor of uncertain malignant potential: a clinicopathologic study of two cases and review of the literature

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Abstract: Prostatic stromal tumor of uncertain malignant potential (STUMP) is rare tumor of the specialized prostatic stroma origin that encompasses a broad spectrum of histologic patterns and clinical behavior. Herein, we aimed to retrospectively review 2 cases of STUMP at our institution with a comprehensive discussion of its distinctive clinicopathologic features as well as the board spectrums of differential diagnosis. The first patient was a 49-year-old man who presented with lower urinary tract symptoms and the sensation of incomplete emptying of the bladder that had persisted for several months. The PSA value was 1.5 ng/ml. Transrectal ultrasound (TURS) of the prostate revealed an enlarged prostate with a mixed echogenic lesion in the peripheral zone. Laparoscopic radical prostatectomy with pelvic lymph node dissection was performed and pathologic examination showed a prostatic STUMP with moderate cellularity and marked pleomorphism, lack of mitotic figures, necrosis, and stromal overgrowth. The tumor involved the left lobe within the capsule, and the resection margin was clear. By immunohistochemistry, the atypical stromal cells displayed strong and diffuse immunoreactivity for CD34 and PR, focal immunoreactivity for SMA, and no significance all the other markers detected. At the 41-month postoperative follow-up, there was no evidence of tumor recurrence or metastasis. The second patient was a 60-year-old man who complained of dysuria and bladder outlet obstruction. PSA was 1.9 ng/ml. TURS revealed an increased prostate volume and cystoscopy demonstrated enlarged prostate adenoma which was subsequently resected. Histologic examination showed a prostatic stromal tumor with phyllodes tumor-like growth patterns. Immunostaining for PR and CD34 and negative for SMA, desmin, CD117, DOG-1 of the atypical stromal cells confirmed the diagnosis of phyllodes tumor of the prostate (STUMP). This patient denied radical surgery and he was in a good status without tumor recurrence after 39 months.

Keywords: Prostate, stromal tumor, STUMP, stromal sarcoma, phyllodes tumor, differential diagnosis

Introduction

Prostatic stromal tumor of uncertain malignant potential (STUMP) is an exceedingly rare tumor of the specialized prostatic stroma that encompasses a broad spectrum of histologic patterns and clinical behavior [1, 2]. Before the introduction of the term STUMP in 1998 by Gaudin et al [3], this entity has previously been classified under a variety of names including phyllodes tumor of the prostate, atypical stromal hyperplasia, cystosarcoma phyllodes, and cystic epithelial-stromal tumor. The histologic patterns of STUMP include (1) hyper-cellular stroma with degenerative atypia, (2) hyper-cellular spindle cells, (3) spindle cells in myxoid background, and (4) phyllodes-like pattern. The clinical course of STUMP is unpredictable, ranging from a focal incidental lesion on biopsy that never progresses, to an obstructing mass that recurs after resection, to a highly aggressive lesion leading to widespread metastases and death. In this study, we report on 2 cases of prostatic STUMP and a comprehensive review of its clinicopathologic features is discussed.

Materials and methods

Both cases were retrospectively collected from the archive file in our institution from 2005 to 2014 when electronic surgical pathology records can be available. The hematoxylin-and-eosin slides of all cases were reviewed and immunohistochemical studies using the avidin-

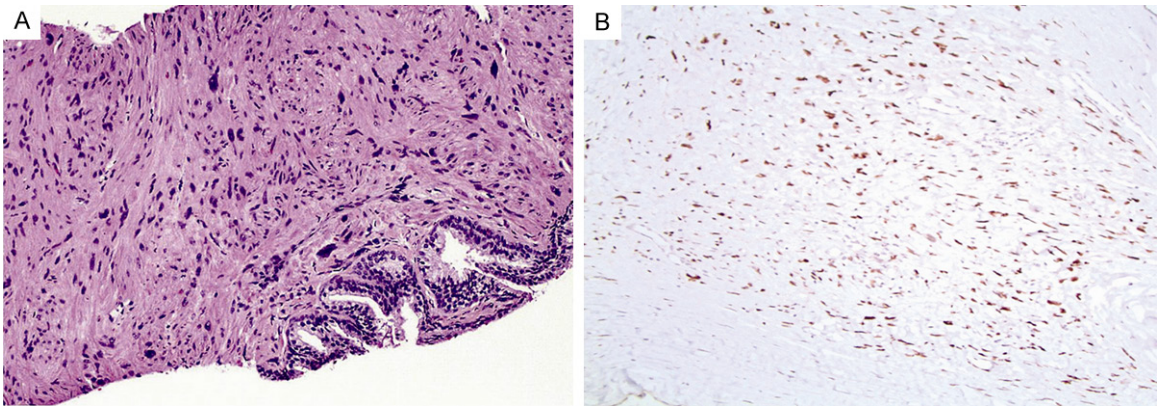

Figure 1. (A) Prostatic STUMP with moderate cellularity and marked pleomorphism (B) showing diffuse positivity for PR.

biotin-complex immunoperoxidase technique were performed. The following commercially available antibodies were used in all 3 cases: cytokeratin AE1/3, prostate-specific antigen (PSA), AMACR (P504S), 3, smooth muscle actin (SMA), desmin, CD10, S100, CD34, CD117, DOG-1, progesterone receptor (PR), estrogen receptor (ER), CD34, P53, p16 and Ki67. Appropriate positive and negative controls were run concurrently for all the markers tested. Clinical information was retrieved from the electronic medical records and follow-up information was obtained by clinical interviews.

Results

Case 1

The patient was a 49-year-old man who presented with lower urinary tract symptoms including nocturia, urinary frequency, and the sensation of incomplete emptying of the bladder that had persisted for several months. He had no specific medical or family history. In the digital rectal examination (DRE), a 3-cm, tender, well-demarcated nodule was palpated in the left lobe of the prostate. The PSA value was 1.5 ng/ml, and the urine culture showed no urinary tract infection. Transrectal ultrasound (TURS) of the prostate revealed a prostate volume of 28 ml with a mixed echogenic lesion (17 mm) in the left peripheral zone of the prostate. The prostate was biopsied under TRUS-guidance and Pathological examination showed a spindle cell proliferative lesion with focal hypercellularity and moderate cellular atypia interdigitating between benign prostatic glands in multiple cores of the left prostatic lobe, favoring a STUMP. Subsequently laparoscopic radical prostatectomy with standard pelvic lymph node dissection was performed. Grossly, the prostate lesion was a well circumscribed mass, of which the largest measured 40×35 mm, containing dilated spaces. The final pathologic results showed prostatic STUMP with moderate cellularity and marked pleomorphism, lack of mitotic figures, necrosis, and stromal overgrowth (**Figure 1A**). The tumor involved the left lobe within the capsule, and the resection margin was clear. On immunohistochemical study, the atypical stromal cells displayed strong and diffuse immunoreactivity for CD34 and PR (**Figure 1B**), focal immunoreactivity for SMA, and no significance for AE1/3, AMACR, desmin, S100, CD117, DOG-1, ER, P16, P53 and Ki-67. At the 41-month postoperative follow-up, there was no evidence of tumor recurrence or metastasis.

Case 2

The patient was a 60-year-old man who complained of dysuria and bladder outlet obstruction. DRE revealed a slightly enlarged benign-feeling prostate, PSA was 1.9 ng/ml. The urine culture showed no urinary tract infection. X-ray of the kidneys, ureters, and bladder was normal, as was renal ultrasound. TURS revealed an increased prostate volume (60 mL) without suspicious hypo-dense or hyper-dense areas. Cystoscopy demonstrated enlarged prostate adenoma causing bladder outlet obstruction, which was subsequently resected. Pathological examination showed a benign prostatic hyperplasia and features of complex glandular architecture with a prominent stromal component.

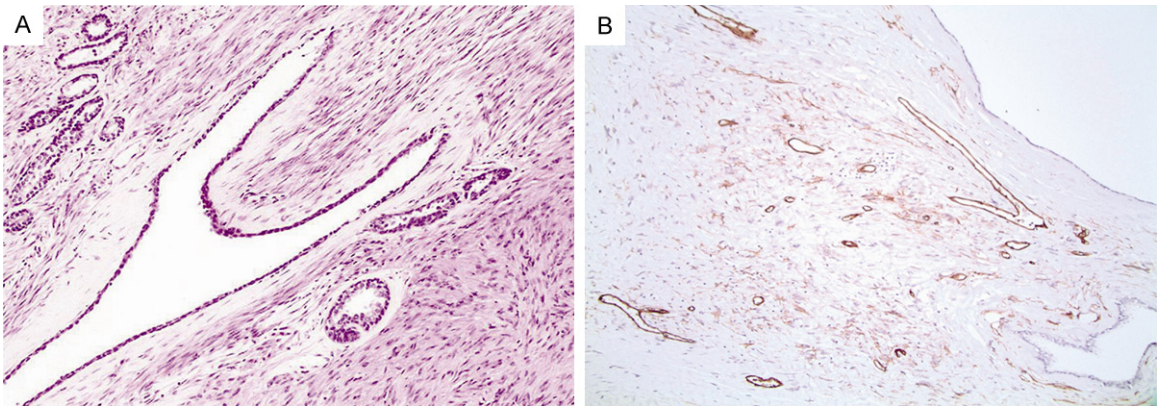

Figure 2. (A) Prostatic STUMP of phyllodes tumor-like growth pattern (B) with immunoreactivity for CD34.

The stroma, consisting of proliferations of elongated and spindle-shaped cells with only mild cytologic atypia, was covered by benign glands arranged in long, epithelial-lined clefts in a frond-like configuration, similar to that found in mammary phyllodes tumor (**Figure 2A**). No mitoses and necrosis was identified. Immunostaining for PR and CD34 (**Figure 2B**) and negative for SMA, desmin, CD117, DOG-1 of the atypical stromal cells confirmed the diagnosis of a phyllodes tumor of the prostate (STUMP). Luminal epithelial cells showed intense immunoreactivity for PSA. Additional staging investigations including X-ray of the lung and abdominal magnetic resonance imaging revealed no extra-capsular extension of the tumor with absence of lymph node involvement or metastasis. Sextant biopsies of the peripheral zone demonstrated normal prostatic tissue. The patient denied radical surgery and he was in a good status without tumor recurrence after 39 months.

Discussion

The clinical history of patients with STUMP is not well defined owing to the relative rarity of the tumor. Since 1998, there have been only a few published large case series that have summarized the major clinical features of patients with STUMP [3-5]. Patients in these studies range in age from 25 to 86 years, with men in their sixth or seventh decade of life most commonly affected. The clinical, laboratory, and imaging abnormalities associated with STUMPs are generally nonspecific. The most common presenting signs and symptoms were chronic lower urinary tract obstructive symptoms, abnormal DRE findings, hematuria, hematospermia, rectal dysfunction and/or sensation of fullness, acute urinary retention, and elevated prostate specific antigen levels. On rectal examination, the prostate may be diffusely enlarged, nodular, or soft, spongy, and cystic [4].

On gross examination, STUMP may be white, tan, or yellow and range from solid and firm to partially cystic and multiloculated. The lesions range in size from microscopic up to 15 cm with small or large smooth-walled cysts. The cyst contents may be serous, mucinous, or sanguinous [5, 6]. Both the peripheral and transitional zones of the prostate may be affected. In some cases, the tumor may extend out of the prostate and may be adherent to other organs of the pelvis [5].

While STUMPs have a variety of histologic appearances, all cases are characterized by expansion of the specialized prostatic stroma [2]. In all of the reported subtypes, mitotic activity is minimal and necrosis is not often seen. Gaudin et al [3] had classified STUMPs into 4 distinct histologic patterns by the degree of stromal cytologicatypia, and the presence and appearance of a non-neoplastic epithelial component, and patterns may coexist in the same specimen. The first pattern demonstrating marked cellular atypia akin to the so-called degenerative atypia seen in other spindle cell lesions is the most common and accounts for at least 50% of cases. It is composed of normal to slightly hyper-cellular stroma with scattered cytological atypical cells interdigitating between benign prostatic glands. Stromal cells vary from

plump to spindle with clear or lightly eosinophilic cytoplasm. Cytologic atypia is present and is manifested by degenerative-appearing cells with pronounced nuclear pleomorphism and enlargement; multinucleation; ground glass, vesicular, or smudged nuclei; prominent nucleoli; and occasional intra-nuclear inclusions. Squamous metaplasia is variably present [7]. The second, histologic pattern, "hyper-cellular", consists of hyper-cellular stroma composed of bland, fusiform cells with eosinophilic cytoplasm, resembling benign prostatic hyperplasia (BPH) but with more hyper-cellular stroma. The cytologic atypia characteristic of the first pattern is absent. The associated epithelial elements are non-neoplastic and look similar to those present in the first pattern. The third is composed of an expanded stroma and proliferating benign glandular elements reminiscent of the phyllodes tumor of the breast. The stroma is hypo-cellular, fibrotic, leaf-like in configuration, and devoid of mitotic figures. Cytologically atypical, degenerative-appearing stromal cells, similar to those seen in the first pattern, are variably present. The stroma is covered by benign glands arranged in long, epithelial-lined clefts in a frond-like configuration, similar to those found in mammary phyllodes tumors. Metaplastic and/or proliferative changes in the glands are often present, including basal cell hyperplasia, adenosis,sclerosingadenosis, and squamous metaplasia [7]. The fourth pattern, "myxoid" is composed of expansive overgrowth of bland stromal cells within a myxoid background. This pattern often lacks glandular epithelium and may also resemble the stromal nodules of benign prostatic hyperplasia; however, myxoid STUMP consists of sheets of stromal cells and lacks the nodularity of BPH. At last, a round cell pattern of prostatic STUMP, showing a new deceptively subtle pattern that may not be recognized as a neoplasm and may be misdiagnosed as BPH, has been documented most recently [8]. Some cases of STUMP have progressed to prostatic stromal sarcoma on subsequent biopsy, and some sarcomas are present in association with a concurrent STUMP, a feature that lends credibility to the hypothesis that STUMP has the ability to undergo malignant transformation [5]. No correlation with the histologic subtype of STUMP and the association with progression to sarcoma have yet been documented.

The atypical stromal cells of STUMP arise from the specialized, hormonally responsive mesenchymal cells of the prostate and as such express similar immunohistochemical properties to normal prostate and stromal sarcoma [9]. STUMP, as well as prostatic stromal sarcoma, expresses PR but is negative for ER. In addition, STUMP is positive for CD34 and vimentin, with variable staining for SMA and desmin [5, 6].

Given the variety of histologic appearances of STUMP, other proliferations of the specialized prostatic stroma must be considered in the differential diagnosis. Cases that exhibit hypercellular or myxoid stromal patterns with admixed benign epithelial components are often confused with the stromal proliferations present in BPH, and the distinction may prove difficult in small specimens [10]. The presence of hypercellular stroma, eosinophilic cytoplasm, and lack of nodularity can assist in differentiating STUMP from BPH. STUMP is often difficult to distinguish from low-grade prostatic stromal sarcoma by morphology, especially in cases with a preponderance of large, bizarre, degenerative nuclei. While primary prostatic stromal sarcomas are rare, their differentiation is critical as the long-term survival in patients with stromal sarcoma is poor, with a 5-year disease-free survival of 38% [11]. The presence of necrosis, atypical mitotic figures, marked hypercellularity, and nuclear pleomorphism without degenerative features are features of sarcoma, rather than STUMP [5]. Sarcomatoid transformation of a high-grade prostatic adenocarcinoma may present with atypical spindle cells and may enter into consideration STUMPs with the common degenerative-atypia pattern. The presence of adjacent typical prostatic adenocarcinoma, combined with at least focal positivity for CKs, may be helpful in separating the two.

Other spindle cell lesions that rarely involve the prostate may enter the differential diagnosis, including inflammatory myofibroblastic tumor, solitary fibrous tumor, rhabdomyosarcoma, smooth muscle tumors, and direct extension of gastrointestinal stromal tumor from adjacent colon. These entities tend to occur as expansile masses without entrapped glandular elements, a finding that typically characterizes STUMP. Further, these other lesions tend to have proto-

typic architectural, cytologic, and immunohistochemical features that are noted in extra-prostatic sites, which aids in their distinction [6].

STUMP presents a significant challenge for patient management. While many will prove to be indolent in nature, their behavior is unpredictable. In cases where STUMP has behaved aggressively, dedifferentiated, or coexisted with sarcoma, no correlation with a specific histologic subtype or other risk factor has been identified. As such, close follow-up and consideration of surgical management, especially in younger patients, is warranted. The size and extent of the lesion, as well as patient age, comorbidities, and preferences, should be considered when determining a treatment plan. The prognosis of STUMP is equally variable [5]. One retrospective study [3] has found that in patients who did not undergo definitive resection, the tumor recurred in 46% of cases. In some cases, the tumor recurs several times, requiring multiple procedures over time. Several case reports have been published documenting patients diagnosed with STUMP who present with or develop distant metastasis, most commonly to the lung and lymph nodes [12, 13].

In summary, STUMP is a very rare tumor of the specialized prostatic stroma with an unpredictable clinical behavior, and considered by most as a neoplasm with 4 distinct histologic patterns, and more than one may be present within the same tumor [1, 2]. These lesions may locally invade surrounding tissues or recur after surgical intervention and be a potential precursor to prostatic stromal sarcoma. Owing to the rarity of this entity, the classification, clinical course, and recommended treatments are still under debate.

Disclosure of conflict of interest

None.

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