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Original contribution

Primary mucinous adenocarcinoma of the female urethra: a contemporary clinicopathologic analysis☆

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Summary Primary mucinous adenocarcinoma of the female urethra is very rare and may lead to both diagnostic and therapeutic challenges. Although primary mucinous adenocarcinoma of the prostate and prostatic urethra has been well characterized in men, this is the largest clinicopathologic study to date of primary mucinous adenocarcinoma of the female urethra. A search was made through the files of 2 major academic institutions for cases of confirmed primary mucinous adenocarcinoma arising from the female urethra. Tumors arising from adjacent organs were excluded both clinically and pathologically in all cases. Five cases were identified. The mean patient age was 67 years (range, 54-74 years). All patients presented with a polypoid/papillary mass arising from the urethra. Pathologic stages were as follows: pT4 3 (60%) of 5 cases; pT3 1 (20%) of 5 cases, and pT2 1 (20%) of 5 cases. Immunohistochemical stains for GATA3, p63, CK7, CK20, CDX2, ER, PAX8, and β-catenin were performed on all cases. Immunohistochemical stains were positive in the tumor cells for CDX2 in 4/5 (80%) cases; focally positive for CK20 in 4/5 (80%) cases; focally positive for CK7 in 4/5 cases (80%); and negative for p63, GATA3, ER, PAX8 and β-catenin in all cases. In the 4 patients with available follow-up data, mean follow-up was 25 months (range, 4-54 months). It is critical for pathologists to be aware of this entity in light of potential diagnostic pitfalls and therapeutic implications.

1. Introduction

Cancer of the urethra is relatively uncommon, and those with glandular differentiation are exceedingly rare. Not surprisingly, the low incidence of primary urethral adenocarcinoma is reflected in the scant literature on this entity. Questions regarding clinical significance, prognostication and optimal treatment modalities remain largely unanswered.

One such subtype in male patients, mucin-producing urothelial-type adenocarcinoma of the prostate (mucinous

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adenocarcinoma of the prostatic urethra), was described relatively recently in a review of 15 cases arising from the prostatic urethra. In the publication, particular attention was given to the relationship, diagnostic challenges and implications of accurate diagnosis of mucinous urethral adenocarcinoma, especially vis-à-vis mucinous (colloid) adenocarcinoma of the prostate [1].

Although few case reports are in the literature, mucinous adenocarcinoma of the female urethra has not been adequately described as a unique morphologic entity with contemporary immunohistochemical analysis. The importance of the recognition of this entity in women lies in the negation of histologic mimickers, including mucinous tumors of similar microscopic appearance arising from adjacent anatomic sites such as the bladder and colorectum and mullerian structures, which may secondarily involve the urethra. This is all the more challenging in women, who in general have a shorter urethra and multiple diverse organ systems in close proximity to one another.

The aim of this contemporary case series (the largest to date) is to describe the clinicopathologic and immunohistochemical features of primary mucinous adenocarcinoma of the urethra in female patients.

2. Materials and methods

A search for mucinous adenocarcinoma of the female urethra was conducted through the surgical pathology and expert consultation files of two major academic centers in the United States. Cases considered for inclusion were required to have tumors originating from the urethra with mucinous features. All cases with evidence (clinical/radiological or pathological) of secondary spread via direct extension or metastasis from other sites were excluded. Only cases with available tissue blocks were selected. For those cases that met these criteria, formalin-fixed paraffin-embedded tissue blocks were obtained and cut at 4 μm to prepare hematoxylin and eosin–stained slides. In addition, immunohistochemical studies were performed utilizing antibodies specific for CK7, CK20, GATA3, CDX2, p63, ER, PAX8, and β-catenin. The medical record of each case was reviewed, and follow-up information was documented, when available.

This study was completed following the guidelines of and with approval from our institutional review board.

3. Results

After application of strict inclusion and exclusion criteria, a total of 5 cases were selected for review. The mean patient age at time of diagnosis was 67 years (range: 54–74 years). All patients presented with a polypoid/papillary mass arising from the urethra (confirmed on cystoscopy), with the mass protruding through the urethral meatus in one patient. In addition, three patients had urinary retention and two patients had hematuria. All patients had a comprehensive clinical/radiologic gynecologic work up, including a pelvic computed tomography (CT) scan and/or magnetic resonance imaging (MRI), which excluded a gynecologic primary. In addition, a female pelvic examination was also performed.

All patients eventually underwent major surgeries for tumor resection (radical cystectomy with urethrectomy and anterior vaginal wall resection, including resection of the inferior pubic ramus in one of the patients). In general, the carcinoma was locally advanced at time of resection as reflected by the pathologic T stage distribution, which was pT4 in 3 (60%) of 5 cases; pT3 in 1 (20%) of 5 cases, and pT2 in 1 (20%) of 5 cases.

All cases had significant mucinous features composed of pools of extracellular mucin (mucinous component of the tumor was at least 50% of the entire tumor), and emphasis was placed on ensuring that the tumor was of a primary urethral origin. Villoglandular and epithelial-lined microcystic spaces were often filled with mucin as well associated surrounding mucin pools, and the tumors were composed of 50% to 90% of extracellular mucin (Fig. 1). The invasive carcinomas in all five cases were also composed of cells with intracytoplasmic mucin, some exhibiting signet ring–like morphology (Fig. 2). Foci of adenocarcinoma in situ were identified in all cases, again serving as a surrogate indicator of primary origin. Interestingly, all 5 cases were closely associated with areas of overlying/adjacent glandular metaplasia (intestinal type) of the urothelium (Fig. 3). The intestinal (goblet cell) features were present in 20% to 30% of the overlying/adjacent glandular metaplasia in all cases. With regard to the immunohistochemical studies

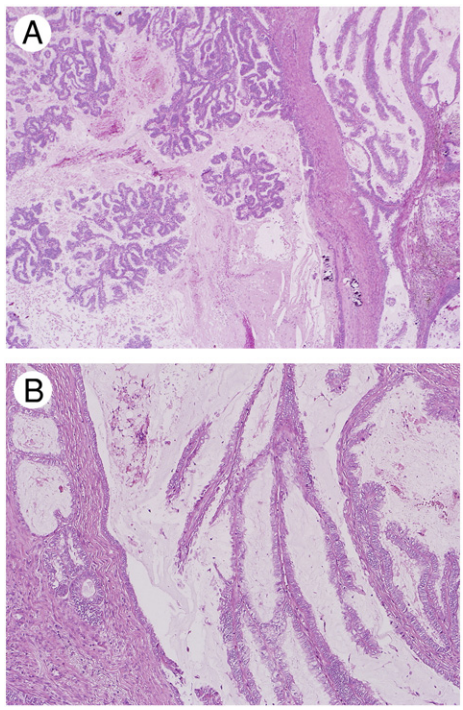

Fig. 1 Primary mucinous adenocarcinoma of the female urethra with villoglandular architecture and associated mucin pools. A, Low magnification (40×). B, High magnification (100×).