Int J Clin Exp Pathol 2013;6(8):1665-1670
www.ijcep.com /ISSN:1936-2625/IJCEP1306007

Case Report

Urethral adenocarcinoma associated with intestinal-type metaplasia, case report and literature review

Christopher S Hale[1], Hongying Huang[1], Jonathan Melamed[1], Ruliang Xu[1], Larry Roberts[2], Rosemary Wieczorek[1], Zhiheng Pei[1], Peng Lee[1]

[1]*Department of Pathology, New York Harbor Healthcare System, New York University School of Medicine, New York, NY, USA;* [2]*Sound Shore Medical Center, New Rochelle, NY, USA*

Received June 6, 2013; Accepted July 8, 2013; Epub July 15, 2013; Published August 1, 2013

Abstract: The presence of glandular epithelium in urinary tract biopsies poses a diagnostic challenge. Intestinal metaplasia of the urethra may be seen in many congenital, iatrogenic, and reactive conditions, as well as in association with malignant conditions such as urethral adenocarcinoma. We present a case of a 61 year-old woman presenting with microscopic hematuria. Successive biopsies showed glandular epithelium with focal atypia in close association with inflammation, but no overt malignancy. Only on surgical resection was the associated high grade adenocarcinoma revealed. When intestinal-type mucosa is present within a urinary tract biopsy, associated malignancy may be present only focally. Thorough sampling and consideration of the differential diagnosis is imperative.

Keywords: Urethral adenocarcinoma, intestinal metaplasia

Introduction

Development of intestinal-type mucosa as a metaplastic response is a well-described phenomenon in sites such as the esophagus. Rarely, metaplastic intestinal-type mucosa may also be seen in the urinary tract. This is particularly true in the bladder, where glandular mucosa may be seen in the benign reactive condition cystitis glandularis [1]. Glandular cells may also represent a primary or metastatic malignancy, and merit careful inspection for atypical features. This diagnostic dilemma is even greater when intestinal-type epithelium is seen in less common locations, such as the urethra. We report the case of a urethral biopsy containing areas of intestinal-type glandular tissue, which on resection proved to be associated with high-grade urethral adenocarcinoma.

Clinical presentation

A 61 year-old woman was found to have microscopic hematuria on routine medical examination. Cystoscopic work-up revealed a ragged, red lesion on the anterior mid-urethra. Biopsies from this area were sent for histopathologic examination. After an unremarkable CT scan of the pelvis, a repeat biopsy was performed with similar findings. Transurethral resection six months later showed high grade urethral adenocarcinoma.

Histopathology

The first biopsy (**Figure 1**) was received in two parts. Hematoxylin and eosin stained, formalin-fixed, paraffin embedded sections of showed acute inflammatory exudate with mucin and rare clusters of benign glandular cells. The second part showed acutely inflamed benign urothelium with squamous and glandular metaplasia. Trichrome and smooth muscle actin stains demonstrated expected submucosal composition of fibro connective tissue without desmoplasia. An immunostain for PIN-4 (p63, 34βe12 and AMACR) demonstrated positivity for p63 and 34βe12 in an area of squamous metaplasia, as well as within a periurethral glandular remnant. The adjacent area of glandular metaplasia lacked PIN-4 immunoreactivity. An area of squamous metaplasia and an area of residu-

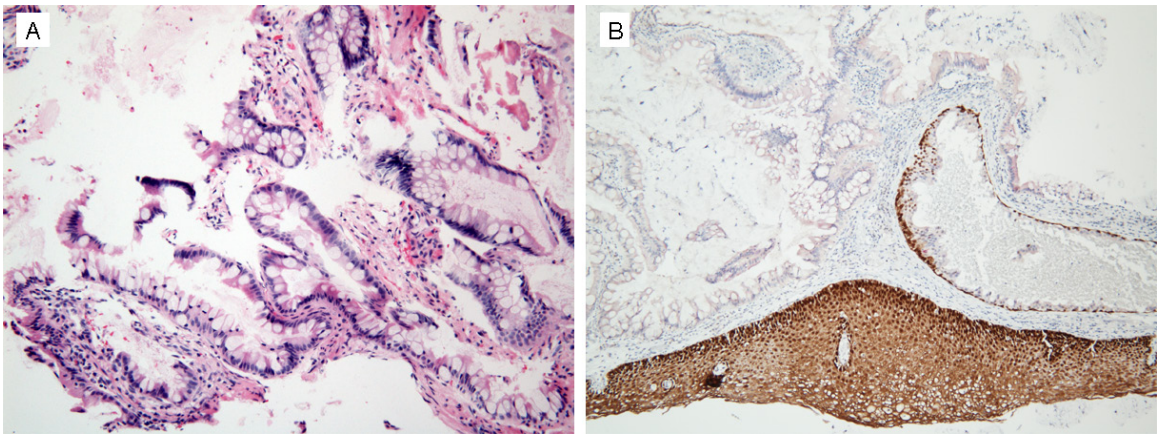

Figure 1. A: H&E shows predominately benign glandular cells; B: a periurethral Skene's gland and an area of squamous metaplasia are highlighted by p63 and 34βe12, but not AMACR (PIN-4 cocktail). Adjacent glandular metaplasia lacks immunoreactivity.

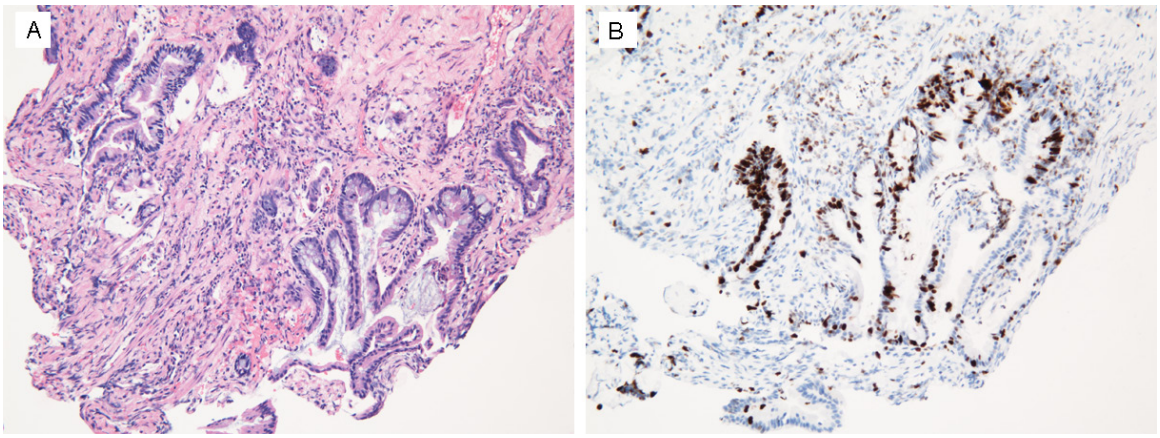

Figure 2. A: H&E shows an area of bland appearing intestinal-type metaplasia; B: Ki-67 immunostain shows focally increased proliferation.

al Skene's gland tissue both showed strong nuclear reactivity for p63. The metaplastic glandular cells lacked p63 immunoreactivity. Nuclear Ki-67 reactivity in the areas of squamous metaplasia showed 10% reactivity in a basal pattern, whereas Ki-67 positivity in the glandular areas was 5%.

After an unremarkable CT scan of the pelvis, a repeat biopsy was performed. The repeat biopsy (**Figure 2**) was processed as described above and showed glandular intestinal-type epithelium with clusters of highly atypical cells within the superficial lamina propria, as well as fragments of benign squamous epithelium. Significant chronic inflammation was present in most of the biopsy parts. An immunostain for Ki-67 showed 85% nuclear positivity in the atypical glandular cells. Trichrome and smooth muscle actin stains demonstrated expected submucosal composition without desmoplasia or invasion.

Six months after the repeat biopsy, transurethral resection was performed. During the procedure, bimanual examination showed a fusiform mass surrounding the entire urethra and bladder neck. Cystoendoscopy showed a fusiform papillary-nodular tumor involving the bladder neck, proximal, mid and distal urethra, but not the urethral meatus. The tumor was resected and submitted in multiple specimens for histology (**Figure 3**). Tissue from the bladder neck showed intestinal metaplasia with severe atypia, similar to the earlier biopsies; however, tissue from the anterior urethra demonstrated

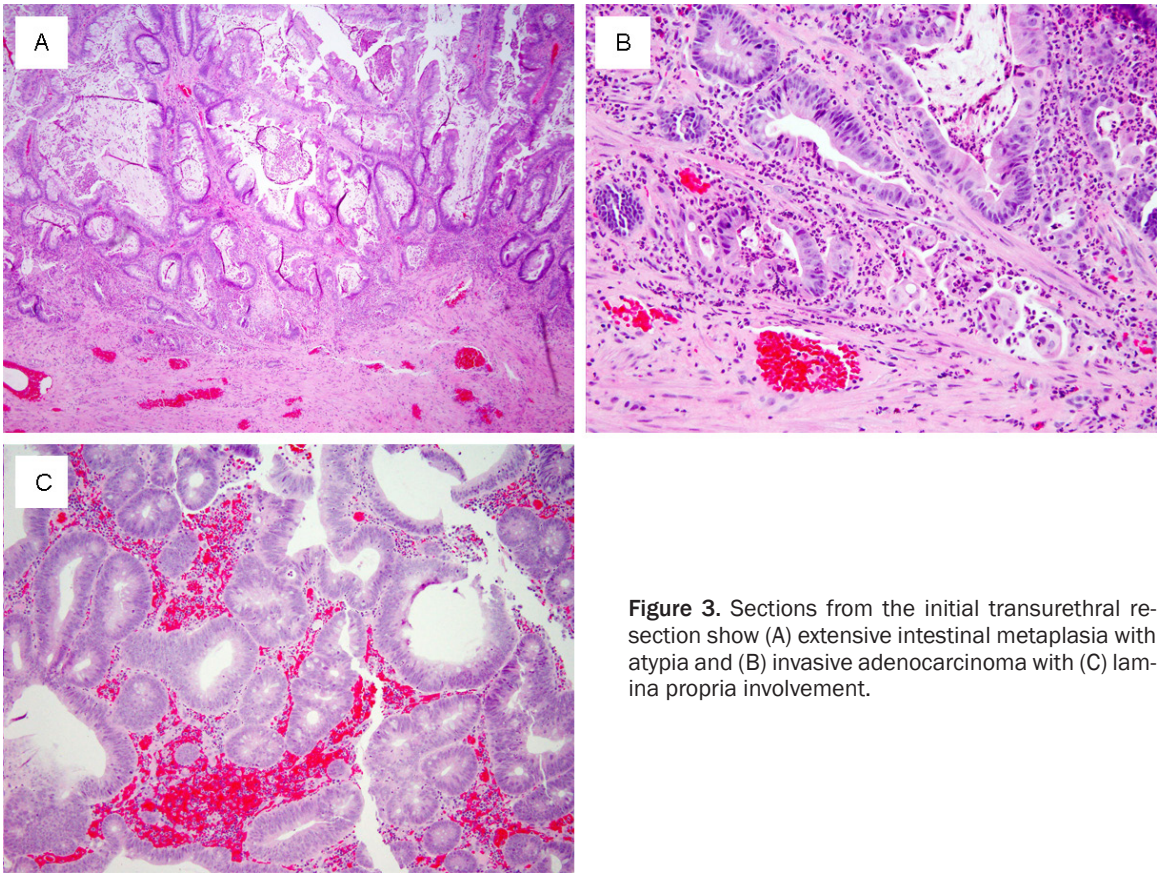

Figure 3. Sections from the initial transurethral resection show (A) extensive intestinal metaplasia with atypia and (B) invasive adenocarcinoma with (C) lamina propria involvement.

high grade invasive adenocarcinoma associated with extensive intestinal metaplasia with atypia. The tumor invaded the lamina propria, but did not involve the muscularis propria. Prominent proliferative cystitis was also present.

Following systemic chemotherapy (Ifex, Taxol, and Carboplatin), residual tumor remained on MRI. Examination under anesthesia showed abarely palpable mass extending from the proximal urethra to the meatus. Repeat transurethral resection was performed and submitted in several specimens for histology. Histology showed adenomatous changes with focal high grade dysplasia/focal carcinoma in situ, with no invasive carcinoma.

Discussion

The differential diagnosis for glandular lesions in the female urethra is challenging and includes developmental heterotopia, intestinal-type metaplasia, and adenocarcinoma. In this case, the etiology of the glandular epithelium was unclear despite two sets of biopsies. Significant atypia was present on each biopsy, but chronic inflammation and associated benign glandular tissue prevented an unequivocal diagnosis of adenocarcinoma. Only on resection was the patient's high grade adenocarcinoma definitively shown in association with the severely atypical glandular epithelium. This highlights the importance of adequate sampling in diagnosis of glandular urethral lesions.

The origin of female primary urethral adenocarcinomais not fully understood. Prostate-specific antigen (PSA) expression inprimary urethral adenocarcinoma supports an origin from female periurethral (Skene's) glands [2, 3]. More recently, PSA non-reactive, mAbDas1-reactive cases of primary urethral adenocarcinoma have been reported in association with intestinal metaplasia, leading to speculation that some cases of female primary urethral adenocarcinoma may arise from malignant transformation of urethritis glandularis, a condition histologically characterized by intestinal metaplasia [3, 4]. In this case, the lack of PSA

expression in the glandular tissue and lack of atypia in the adjacent periurethral glands point towards a non-periurethral gland origin (**Figure 1**).

The role of intestinal metaplasia in genitourinary tract carcinogenesis is not known. One retrospective study of 19 patients with intestinal metaplasia of the bladder did not find evidence that intestinal metaplasia represents a precursor to bladder adenocarcinoma [5]. Intestinal metaplasia could still be a precursor lesion to adenocarcinoma more distally in the urinary tract. A case report of a woman with an external urethral meatus tumor found mucinous adenocarcinoma in close association with both intestinal metaplasia and urethritis cystica, suggesting a connection [3]. In this case, a continuum of dysplastic changes is present: benign glandular mucosa, glandular mucosa with severe atypia, and high grade adenocarcinoma. The intimate association of these changes in our view points towards a connection.

Although extremely rare, intestinal-type epithelium has been found near the urethral meatus in females ranging from 2 to 78 years of age [6]. In younger patients, these rare cases of intestinal-type epithelium have been attributed to benign developmental malformation resulting from abnormal differentiation of the cloacal epithelium [6, 7]. In utero, the female urinary system is formed by division of the cloaca by the urorectal septum between 6 to 9 weeks of gestation [8]. If this division is perturbed, heterotopic rests of intestinal-type tissue could persist in the urinary tract.

In older women, intestinal-type metaplasiais believed to represent a metaplastic response to chronic injury [6, 9, 10]. This injury may be due to inflammation, as well as to mechanical or chemical irritation. In the bladder urothelium, it has been reported that intestinal metaplasiais accompanied by acquisition of CDX-2 immunopositivity, whereas cystitis cystica retains the CDX-2 negative immunophenotype of normal urothelium [11]. On the basis of these results, it has been suggested that intestinal metaplasia in the bladder may represent an alternative pathway of response to urothelial injury [11]. Whether this could be the case more distally in the urethral urothelium has not been explored.

Intestinal-type metaplasia has also been reported in association with posterior urethral polyps or “caruncles”. In addition to intestinal-type epithelium, metaplasia of urethral polyps may also exhibit squamous or rarely even gastric-type differentiation [12]. Paneth cell metaplasia was an unusual finding in another case [13]. Metaplastic change in urethral polyps could arise as the result of mechanical irritation, or as a reaction to the inflammation that gave rise to the polyp. Analogy has been made between this process, solitary rectal ulcer syndrome, and inflammatory cloacogenic polyps [7]. Stricture of the prostatic urethra in men has also been reported in association with intestinal metaplasia with dysplasia [14]. Similar mechanical obstruction or stricture in the female urethra could also lead to metaplastic response. Another study of over 300 prostatic urethra specimens has suggested that glandular metaplasia in the prostatic urethra may be a normal histologic finding [15].

Exposure of the urothelium to irritants such bacterial colonization and retained urine, as occurs in urethral diverticula, may be associated with development of intestinal-type metaplasia, villous adenoma, or even adenocarcinoma [13, 16]. Metaplastic diverticular epithelium can undergo malignant transformation, with up to 6% of diverticula in one case series containing invasive adenocarcinoma [16]. Other premalignant glandular lesions were also reported in the same case series, including high grade dysplasia and villous adenoma [16]. Diverticula can also occur in children, usually as a complication of surgical correction of anorectal malformations. Intestinal-type metaplasia in pediatric urethral diverticula has not been reported, although a case of mucinous adenocarcinoma has been reported [17]. Conversely, removal of the urothelium from the normal flow of urine may also be associated with glandular urothelial lesions. A case of mucinous adenocarcinoma, not known to be associated with intestinal metaplasia, was reported in a patient with urinary diversion without cystectomy [18].

Evaluation of urethral adenocarcinomas should also include exclusion of metastatic origin. Local extension or metastasis of gastrointestinal or prostatic malignancies can be difficult to distinguish from primary urethral adenocarcinoma. Colonic adenocarcinoma metastatic to the urethra presents a particular diagnostic

dilemma [19]. Normal urothelium lacks immunoreactivity for CDX-2, but CDX-2 reactivity has been reported in urethral intestinal metaplasia and in urethral adenocarcinoma [20]. Absence CK7 immunoreactivity and the presence of villin immunoreactivity may be useful in distinguishing colonic from urothelial origin. In the male urethra, both CDX-2 and CK-20 immunoreactivity may also be seen in mucinous prostatic adenocarcinomas [21]. In exceptional cases, prostatic adenocarcinoma may spread to involve the urethra [22]. At least some cases of mucinous prostatic adenocarcinoma appear to arise from PSA-immunonegative, CEA immunopositive intestinal metaplasia of the prostatic urethra [23].

Acknowledgements

This material is based upon work supported in part by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development (Biomedical Laboratory Research and Development) and by grant UH3CA140233 from Human Microbiome Project of the NIH Roadmap Initiative and National Cancer Institute.

Disclosure of conflict of interest

No conflict of interest to declare.

Address correspondence to: Dr. Peng Lee, Departments of Pathology and Urology, New York Harbor Healthcare System, New York University School of Medicine, 423 E. 23rd Street, Room 6139N, New York, NY, USA. E-mail: peng.lee@nyumc.org

References

[1] Young RH and Bostwick DG. Florid cystitis glandularis of intestinal type with mucin extravasation: a mimic of adenocarcinoma. Am J Surg Pathol 1996; 20: 1462-1468.

[2] Kato H, Kobayashi S, Islam AM and Nishizawa O. Female para-urethral adenocarcinoma: histological and immunohistochemical study. Int J Urol 2005; 12: 117-119.

[3] Chan YM, Ka-Leung Cheng D, Nga-Yin Cheung A, Yuen-Sheung Ngan H, Wong LC. Female urethral adenocarcinoma arising from urethritis glandularis. Gynecol Oncol 2000; 79: 511-514.

[4] Murphy DP, Pantuck AJ, Amenta PS, Das KM, Cummings KB, Keeney GL and Weiss RE. Female urethral adenocarcinoma: immunohistochemical evidence of more than 1 tissue of origin. J Urol 1999; 161: 1881-1884.

[5] Smith AK, Hansel DE and Jones JS. Role of cystitis cystica et glandularis and intestinal metaplasia in development of bladder carcinoma. Urology 2008; 71: 915-918.

[6] Jarvi OH, Marin S and de Boer WG. Further studies of intestinal heterotopia in urethral caruncle. Acta Pathol Microbiol Immunol Scand A 1984; 92: 469-474.

[7] Willett GD and Lack EE. Periurethral colonic-type polyp simulating urethral caruncle. A case report. J Reprod Med 1990; 35: 1017-1018.

[8] Acien P. Embryological observations on the female genital tract. Hum Reprod 1992; 7: 437-445.

[9] Jarvi OH and Marin S. Intestinal mucosal heterotopia of an urethral caruncle. Acta Pathol Microbiol Immunol Scand A 1982; 90: 213-219.

[10] Urakami S, Igawa M, Shiina H and Ishibe T. Urethral caruncle with coexistence of intestinal heterotopia. A case report. Int Urol Nephrol 1997; 29: 341-344.

[11] Sung MT, Lopez-Beltran A, Eble JN, MacLennan GT, Tan PH, Montironi R, Jones TD, Ulbright TM, Blair JE and Cheng L. Divergent pathway of intestinal metaplasia and cystitis glandularis of the urinary bladder. Mod Pathol 2006; 19: 1395-1401.

[12] Jaidane M, Hidoussi A, Slama A, Hmida W, Ben Sorba N and Mosbah F. Gastric metaplasia of posterior urethral polyp: a case report. Cases J 2009; 2: 9119.

[13] Niemiec TR, Mercer LJ, Stephens JK and Hajj SN. Unusual urethral diverticulum lined by colonic epithelium with Paneth cell metaplasia. Am J Obstet Gynecol 1989; 160: 186-188.

[14] Maung R, Kelly JK and Grace DA. Intestinal metaplasia and dysplasia of prostatic urethra secondary to stricture. Urology 1988; 32: 361-363.

[15] Kiernan M and Gaffney EF. Brunn's nests and glandular metaplasia: normal urothelial variants in the supramontanal prostatic urethra. J Urol 1987; 137: 877-879.

[16] Thomas AA, Rackley RR, Lee U, Goldman HB, Vasavada SP and Hansel DE. Urethral diverticula in 90 female patients: a study with emphasis on neoplastic alterations. J Urol 2008; 180: 2463-2467.

[17] Alam S, Lawal TA, Pena A, Sheldon C and Levitt MA. Acquired posterior urethral diverticulum following surgery for anorectal malformations. J Pediatr Surg 2011; 46: 1231-1235.

[18] Taneous M, Ramalingam P, Mode DG, Heiner JG, Terris MK and Lee JR. Primary mucinous adenocarcinoma in a defunctionalized urinary

bladder: a case report. J Med Case Rep 2009; 3: 9306.
[19] Tamboli P, Mohsin SK, Hailemariam S and Amin MB. Colonic adenocarcinoma metastatic to the urinary tract versus primary tumors of the urinary tract with glandular differentiation: a report of 7 cases and investigation using a limited immunohistochemical panel. Arch Pathol Lab Med 2002; 126: 1057-1063.
[20] Ortiz-Rey JA, Anton Badiola I, San Miguel Fraile P, Alvarez Alvarez C, Iglesias Rodriguez B and Zungri-Telo E. [Expression of CDX2 in urinary bladder and urethra lesions]. Actas Urol Esp 2004; 28: 101-105.
[21] Leite KR, Mitteldorf CA, Srougi M, Dall'oglio MF, Antunes AA, Pontes J Jr and Camara-Lopes LH. Cdx2, cytokeratin 20, thyroid transcription factor 1, and prostate-specific antigen expression in unusual subtypes of prostate cancer. Ann Diagn Pathol 2008; 12: 260-266.
[22] Bubendorf L, Schopfer A, Wagner U, Sauter G, Moch H, Willi N, Gasser TC and Mihatsch MJ. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. Hum Pathol 2000; 31: 578-583.
[23] Furuta A, Naruoka T, Hasegawa N, Suzuki Y, Ikemoto I and Oishi Y. [Mucinous adenocarcinoma of the prostate: a case report and review of 32 cases on immunohistochemical study of both PSA and CEA]. Nihon Hinyokika Gakkai Zasshi 2003; 94: 570-573.