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10-Year observation of a rare presentation of pure fibromyxoid nephrogenic adenoma in the renal pelvis

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ABSTRACT

Nephrogenic adenoma (NA) is an unusual benign epithelial tumor in the genitourinary tract. Here we report a fibromyxoid nephrogenic adenoma in a 37-year-old female presenting with over 10-year slow-growing renal pelvic mass that was diagnosed with bland spindle cell lesion in multiple previous biopsies. This is the first reported case of pure fibromyxoid NA in renal pelvis with close comparison and correlation of biopsy and resection findings over a 10-year span. This will enhance awareness of pathologists to consider this unusual entity when examining spindle cell lesions in this setting, and prevent misdiagnosis and overtreatment of a typically benign process.

1. Introduction

Nephrogenic adenoma (NA) is a rare, benign tumor that typically develops along the urinary tract, in which the urinary bladder is most commonly documented site followed by the urethra and ureter, and rarely the renal pelvis.[1–3] It is more common in males, with a male-to-female ratio of approximately 2:1 and a wide age range (4 years–81 years).[4] It predominantly occurs in adults (90 %) and rarely in children (10 %).[5] NA mainly presents with irritative bladder symptoms including urinary frequency and urgency, flank pain, and hematuria. Macroscopically, NA generally presents as a lesion with papillary architecture and measures 1–2 cm on average. It is microscopically composed of surface papillary structure with subepithelial entrapped small tubular components, and both the surface epithelium and submucosal tubules are usually lined by a single layer of mitotically inactive bland cuboidal or hobnail cells. Although rare, recurrences and malignant transformations of NA have been reported.[6]

Broad spectrum of morphologic patterns, including tubular, papillary, cystic, fibromyxoid, diffuse and flat pattern, has been reported in NA.[7] Histologically, fibromyxoid NA generally presents with a well-circumscribed bulbous, or tumefacient architecture, and is composed of mitotically inactive bland spindled cells within a myxoid or collagenized stroma, with only rare tubular structures. Notably, several architectural patterns are often admixed. So far, in the current literature, only 14 cases of fibromyxoid NA, including admixed classic/fibromyxoid NA and pure fibromyxoid NA, have been reported in the urinary tract. Interestingly, in the renal pelvis, only 3 pure fibromyxoid NA have been documented,[8,9] and no more than 20 cases (including all the variants of NA) have been reported.[10,11] Herein, we report a rare case of pure fibromyxoid NA involving the renal pelvis, with more than 10-year clinical observation and comparison and correlation of biopsy and resection findings.

2. Case presentation

A 37-year-old female presented to the urology department of University of California Irvine Medical Center with a right renal pelvis mass. Her history of urinary symptoms, dated back to a decade ago, and included recurrent urinary tract infection, gross hematuria, and intermittent chronic flank pain. CT imaging performed at her initial presentation revealed a nodular thickening at the right renal pelvis. Over the following years, she continued to remain symptomatic. Subsequently, she underwent cystoscopy a few years later, and the results were negative. In addition, repeat CT at this time showed progressive wall thickening of right proximal intra- and extra-renal collecting system with edema; this was regarded to be possibly associated with inflammation. A decade after her initial symptomatology, CT imaging reported a predominantly peripherally enhancing cystic-appearing

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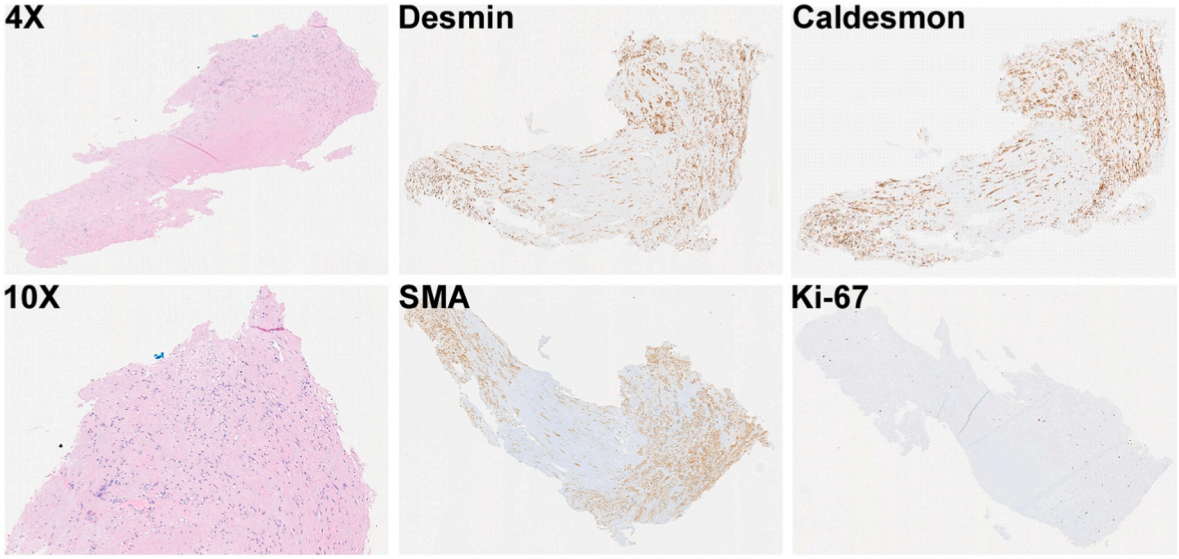

Fig. 1. Section of the first-time in house biopsy specimen shows bland spindle cell lesion with smooth muscle proliferation (4X and 10X); immunostains reveal that lesional cells are positive for Desmin, SMA, Caldesmon, and low ki-67 staining index as indicated in the images above.

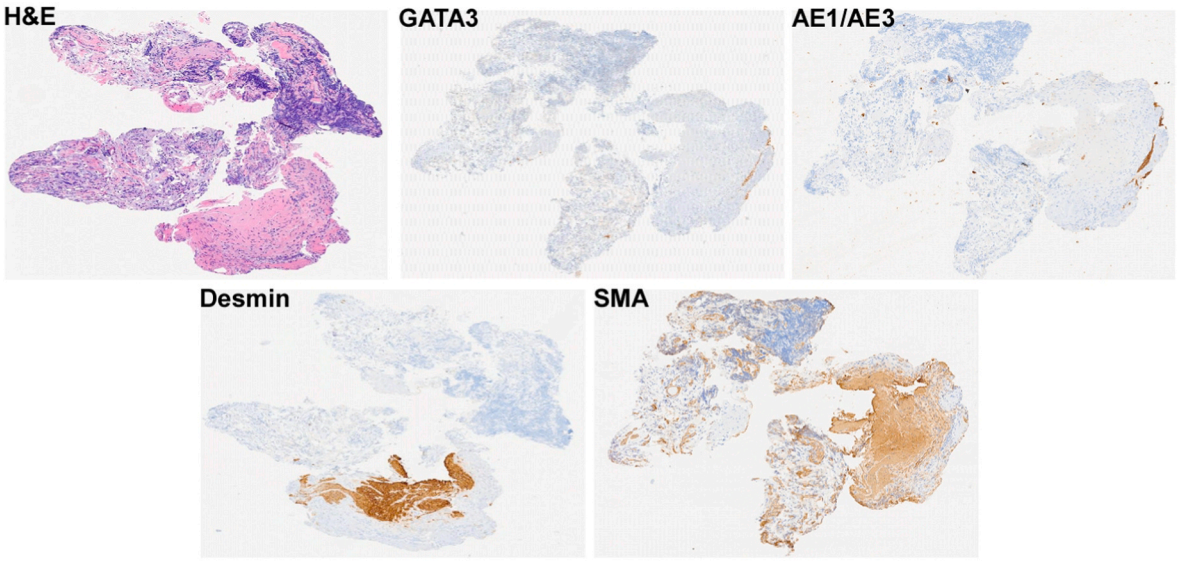

Fig. 2. Section of the second-time in house biopsy specimen shows similar morphological lesion with urothelial epithelial cells (H&E staining); immunostains reveal that urothelial epithelial cells are positive for GATA3 and AE1/AE3, and spindle-shaped cells are positive for Desmin and SMA as indicated in the images above.

structure in the right renal pelvis measuring 1.9 × 1.3 × 0.9 cm. She underwent multiple biopsies. The first biopsy revealed submucosal spindle cell lesions, while the subsequent one showed urothelial mucosa with acute and chronic inflammation and bland spindle cells. No malignancy was identified. Her two most recent biopsies showed spindle cell lesion with smooth muscle differentiation (positive for desmin, SMA and Caldesmon) and without cytologic atypia. Tubular structure or urothelial epithelial cells were identified and a low proliferative index (<1 %) as demonstrated by Ki-67 staining (Fig. 1) was noted. The urothelial components were labelled by GATA3(Fig. 2). Afterwards, the patient developed uncontrolled worsening right flank pain, despite non-surgical interventions. CT at this time showed a right renal pelvis mass measuring up to 2.1 cm (Fig. 3). She eventually elected for simple nephrectomy.

Histopathologic findings revealed a solitary polypoid renal pelvis mass consisting of predominantly spindle cell and few entrapped tubules lined by a single layer of hobnail epithelial cells, sclerotic stroma, and calcification (Fig. 4). The pure tubular or tubular and papillary architecture of classic NA was not identified. Marked subepithelial lymphoid aggregate with germinal center formation and accompanying fibrosis was identified in the renal pelvis and adjacent ureter. A mild chronic inflammatory process extended into the pelvic fat. Akin to the immunohistochemical stain findings of her prior biopsies, the spindle cell component within the nodule were positive for desmin and SMA, and the urothelial epithelial cells strongly and diffusely labelled for GATA3 (Fig. 5). The tubules underlying the epithelium showed strong immunoreactivity for pan-cytokeratin AE1/AE3, as well as PAX8 and GATA3 (Fig. 5). Based on the patient's clinical presentation, imaging findings, histologic and immunoprofile, the pathologic diagnosis is consistent with fibromyxoid NA.

The patient is doing well after surgery with resolution of her symptoms.

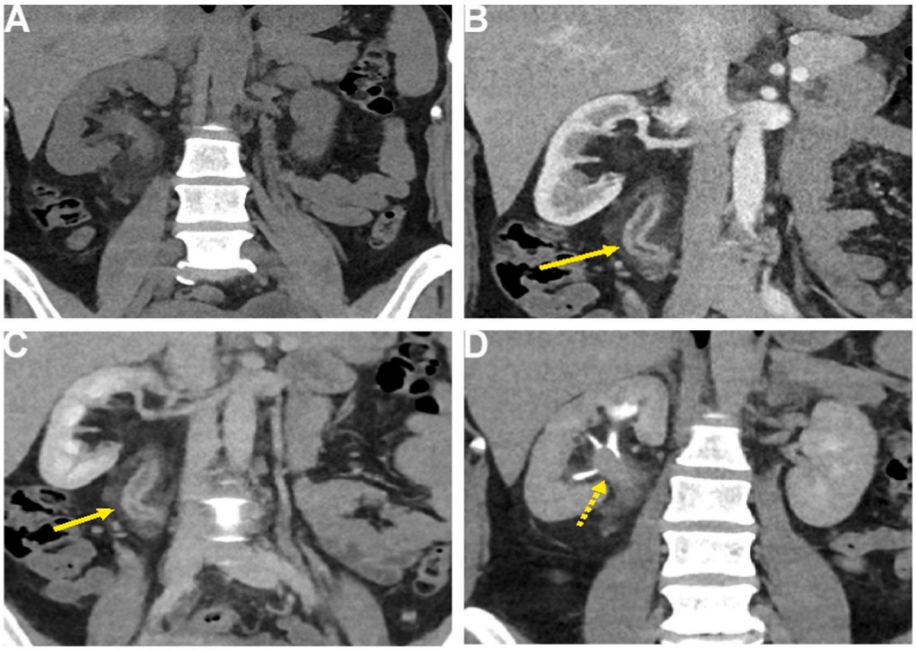

Fig. 3. Coronal images from contrast-enhanced CT urography including noncontrast (A), arterial phase (B), nephrographic phase (C), and 15-min delayed phase (D), which demonstrate an approximately 2.1 cm filling defect in the right renal pelvis, best appreciated on delayed phase (dotted yellow arrow). There is urothelial thickening and enhancement on the arterial and nephrographic phases, with adjacent inflammatory fat stranding from the proximal to mid right ureter (solid yellow arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

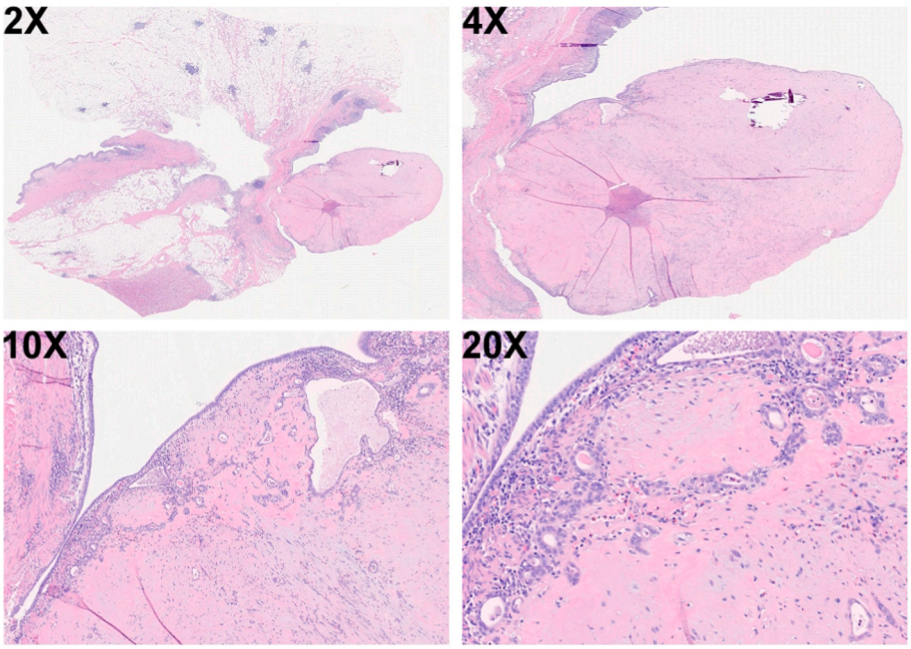

Fig. 4. Section of the final resection specimen shows a single solitary polypoid renal pelvis mass consisting of predominant spindle cell and few entrapped tubules lined by a single layer of hobnail epithelial cells, marked subepithelial lymphoid aggregate with germinal center formation, stromal fibrosis, and calcification.

3. Discussion

Histologically, a spectrum of differential diagnoses are recognized for the diagnosis of NA, mainly including clear cell adenocarcinoma, papillary urothelial carcinoma, metastatic prostatic adenocarcinoma, and nested variant of urothelial carcinoma.[12–14] Although several overlapping histopathological features of the entities above are shared by NA, fibromyxoid NA generally presents with a well circumscribed bulbous, or tumefacient architecture composed of compressed spindled cells and scattered tubular structures in a prominent fibromyxoid or collagenized background. Immunoreactivity for PAX2, PAX8, and GATA3 have been extensively reported in multiple independent studies,[12] however P504S and Napsin-A that are generally positive in classic NA have been reported to be negative in all the fibromyxoid NA.[9] In our case, histopathologic findings revealed a solitary urothelial-lined polypoid renal pelvis mass containing bland spindled cells with smooth muscle differentiation, and rare entrapped tubules lined by a single layer of hobnail epithelial cells within a collagenized stroma. No prominent

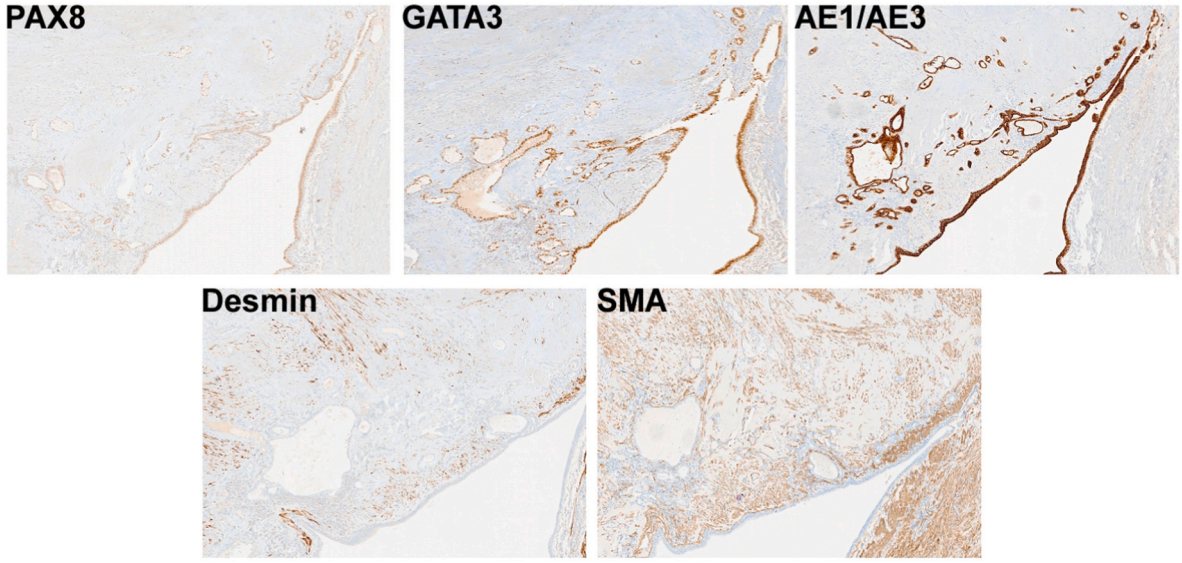

Fig. 5. Immunostains of the mass reveal that urothelial epithelial cells and epithelial cell-lining the tubules are positive for PAX8, GATA3 and AE1/AE3, and spindle-shaped cells are positive for Desmin and SMA as indicated in the images above.

mitosis, cytologic atypia, or necrosis is identified. IHC showed immunoreactivity for AE1/AE3, PAX8, GATA3, desmin and SMA with low proliferative index (<1 %). These morphological and immunohistochemical findings argued against clear cell adenocarcinoma and urothelial carcinoma, and are more supportive of the diagnosis of fibromyxoid NA.

NA is believed to occur secondary to urothelial injury due to chronic irritation or inflammation, including trauma, instrumentation, infections, lithiasis, diverticuli, intravesical BCG therapy, and surgery.[15] From a mechanistic point of view, two primary mechanisms regarding the pathogenesis of NA has been reported. One theory posits that NA may be a metaplastic lesion due to chronic irritation.[16] This is why NA is also named as nephrogenic metaplasia. The second theory postulates that seeding or implantation of sloughed renal tubular cells in the setting of an injured urothelial mucosa is significantly associated with the pathogenesis of NA.[17] Notably, NA has been demonstrated to be closely associated with chronic inflammation.[18] Chronic inflammation, on one hand, will contribute to the metaplastic process[19]; on the other hand, chronic inflammation can cause persistent tissue injury to further aggravate metaplasia,[19] as well as facilitate the seeding or implantation of incidental or procedure-induced sloughed renal tubular cells in setting of the injured urothelial mucosa.[17] Both the metaplastic process and implantation of renal tubular cells in the injured urothelial mucosa have been demonstrated to be involved in the pathogenesis of NA.[16,17]

The patient's clinical history is noteworthy for irritative urinary symptoms, including recurrent urinary tract infection and gross hematuria, that were intermittently present for over 10 years. Furthermore, multiple cystoscopies and biopsies may have further accelerated the disease process. Microscopically, marked subepithelial lymphoid aggregate with germinal center formation and accompanying fibrosis were identified in the stroma of renal pelvis, as well as mild chronic inflammatory infiltrate extending into the pelvic fat. Given this constellation of clinical and histologic findings, we speculate that her history of both long-term chronic urinary irritation and multiple surgical procedures may have cooperatively contributed to the progression of NA.

As mentioned above, NA can be easily misdiagnosed due to the nonspecific clinical manifestations or be confused with other malignant lesions due to significant overlapping histopathologic or immunohistochemical patterns. In this scenario, non- or minimally invasive tests, including urine cytology, as well as molecular techniques, such as single cell-RNA sequencing, might be promising tools for the early identification and diagnosis of NA. In fact, Zulfia and colleagues have investigated the diagnostic significance of urine cytology from patients with morphological and immunohistochemically diagnosed NA, and found that cytologic features of NA cannot be used as diagnostic criteria, since they are not characteristic for this entity.[20] Therefore, in-depth research and understanding of NA from molecular or genomic point of view may provide more detailed insights into the pathogenesis of NA, which will be helpful for the early diagnosis of NA, as well as the subclassification of NA.

4. Conclusion

To the best of our knowledge, this is a rare description of a pure fibromyxoid NA of the renal pelvis with more than 10-year clinical observation, as well as comparison and correlation of biopsy and resection findings. The patient's prior persistent urinary symptoms and multiple previous procedure cooperatively functioned as the underlying culprit of NA.

Declaration of competing interest

The authors declare no conflict of interest.

References

1. Oliva E, Young RH. Nephrogenic adenoma of the urinary tract: a review of the microscopic appearance of 80 cases with emphasis on unusual features. *Mod Pathol.* 1995;8(7):722–730.
2. Gordetsky J, Gennaro KH, Selph JP, Rais-Bahrami S. Nephrogenic adenoma: clinical features, management, and diagnostic pitfalls. *Urology.* 2016;95:29–33.
3. Turcan D, Acikalin MF, Yilmaz E, Canaz F, Arik D. Nephrogenic adenoma of the urinary tract: a 6-year single center experience. *Pathol Res Pract.* 2017;213(7):831–835.
4. Kunju LP. Nephrogenic adenoma: report of a case and review of morphologic mimics. *Arch Pathol Lab Med.* 2010;134(10):1455–1459.
5. Crook TJ, Mead Z, Vadgama B, Malone PS. A case series of nephrogenic adenoma of the urethra and bladder in children: review of this rare diagnosis, its natural history and management, with reference to the literature. *J Pediatr Urol.* 2006;2(4):323–328.
6. Hartmann A, Junker K, Dietmaier W, et al. Molecular evidence for progression of nephrogenic metaplasia of the urinary bladder to clear cell adenocarcinoma. *Hum Pathol.* 2006;37(1):117–120.
7. Lopez JI, Schiavo-Lena M, Corominas-Cishek A, et al. Nephrogenic adenoma of the urinary tract: clinical, histological, and immunohistochemical characteristics. *Virchows Arch.* 2013;463(6):819–825.

8. Dropkin BM, Giannico GA, Reisz PA, Penson DF, Hsi RS. Fibromyxoid nephrogenic adenoma in the ureter. *J Endourol Case Rep*. 2018;4(1):97–99.
9. Li L, Williamson SR, Castillo RP, et al. Fibromyxoid nephrogenic adenoma: a series of 43 cases reassessing predisposing conditions, clinical presentation, and morphology. *Am J Surg Pathol*. 2023;47(1):37–46.
10. Khedaoui R, Encabo B, Tardio JC. Fibromyxoid nephrogenic adenoma protruding in a renal cortical cyst. A rare morphological variant in an outstanding location. *Pathol Res Pract*. 2016;212(2):135–138.
11. Zhang F, Wu J, Sun Z, Xie D, Yang X, Wang W. Nephrogenic adenoma of the renal pelvis: a rare case report and review of the literature. *Medicine (Baltim)*. 2021;100 (34), e27025.
12. Venyo AK. Nephrogenic adenoma of the urinary bladder: a review of the literature. *Int Sch Res Notices*. 2015;2015, 704982.
13. Porcaro AB, D'Amico A, Ficarra V, et al. Nephrogenic adenoma of the urinary bladder: our experience and review of the literature. *Urol Int*. 2001;66(3):152–155.
14. Chen CS, Cheng CL. Nephrogenic adenoma of the urinary bladder: clinical experience and review of the literature. *J Chin Med Assoc*. 2006;69(4):166–168.
15. Mostofi FK. Potentialities of bladder epithelium. *J Urol*. 1954;71(6):705–714.
16. Franke EI, Misseri R, Cain MP, et al. Nephrogenic adenoma in the augmented bladder. *J Urol*. 2011;186(4 Suppl):1586–1589.
17. Mazal PR, Schaufler R, Altenhuber-Muller R, et al. Derivation of nephrogenic adenomas from renal tubular cells in kidney-transplant recipients. *N Engl J Med*. 2002;347(9):653–659.
18. Kaswick JA, Waisman J, Goodwin WE. Nephrogenic metaplasia (adenomatoid tumors) of bladder. *Urology*. 1976;8(3):283–286.
19. Bockerstett KA, Lewis SA, Wolf KJ, et al. Single-cell transcriptional analyses of spasmolytic polypeptide-expressing metaplasia arising from acute drug injury and chronic inflammation in the stomach. *Gut*. 2020;69(6):1027–1038.
20. McCroskey Z, Pambuccian SE, Wojcik EM, Barkan GA. Can we identify nephrogenic adenoma in urine cytology specimens? A study evaluating previously described cytomorphologic features in correlation with PAX8 immunohistochemical staining results. *Am J Clin Pathol*. 2016;145(3):373–378.