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Original article

Nephrogenic adenoma of the urinary tract: A 6-year single center experience

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ABSTRACT

Background: Nephrogenic adenoma is an uncommon benign lesion that occurs at several sites in urinary tract, from the renal pelvis to urethra, with the highest frequency in urinary bladder. Nephrogenic adenoma displays a broad spectrum of architectural and cytological features. Hence, recognition of its characteristic histopathological features is needed to distinguish this lesion from its mimickers.
Materials and methods: A retrospective series of 21 cases of nephrogenic adenoma in 18 patients, which were diagnosed in our department between 2010 and 2016, were analyzed. All histological slides were reviewed by two pathologists and the diagnosis of each case was confirmed. Immunohistochemistry was performed for PAX-8 in all cases. CK7, PAX-2, PSA, p53, p63, GATA-3 and α-methylacyl-CoA racemase (AMACR) were applied in problematic cases.
Results: The most common location of the lesion was urinary bladder (14 patients) followed by renal pelvis (2 patients), ureter (1 patient) and urethra (1 patient). A history of urothelial carcinoma and repeated TUR procedures were observed in 12 patients. There were 2 pediatric patients aged 3 years. Both of them had undergone previous urosurgery because of megaureter in one and bladder exstrophy in the other. Other clinical antecedents included bladder diverticulum (1 patient), cystitis (1 patient) and nephrolithiasis (1 patient). Recurrence of lesion was seen in two patients (once in one case and twice in the other one). The median time to disease recurrence in these patients was 11 months (range, 2–20 months). Histologically, the lesions exhibited various morphological findings, with mixed (15 cases, 71.4%), pure tubular (3 cases, 14.3%), pure papillary (2 cases, 9.5%) and pure flat (1 case, 4.8%) growth patterns. Of the 15 cases with mixed patterns, 8 cases were tubulocystic and flat, 3 cases were tubular and flat, 2 cases were tubular, papillary and flat, 1 case was tubulocystic, papillary and flat, and 1 case was tubular and papillary. Flat pattern was observed in 15 cases (71.4%). It was seen in association with other patterns in 14 cases (mixed morphology) and purely in 1 case. Our findings suggested that the flat pattern is a frequent finding in nephrogenic adenomas. Notably one case in this series showed superficial extension into bladder muscularis propria.
Conclusions: Histologically nephrogenic adenoma may simulate a variety of malignancies. Awareness of characteristic morphologic features of nephrogenic adenoma is needed to diagnose this lesion correctly.

1. Introduction

Nephrogenic adenoma (NA) is an uncommon benign lesion that occurs due to seeding of exfoliated renal tubular cells to the urinary tract; mostly, to the urinary bladder [1,2]. Genitourinary trauma and chronic inflammation are predisposing factors [2,3]. Although it has a wide age range between two to ninety, it is mostly encountered in third or fourth decade of life. The incidence is higher in men compared to women [4]. Hematuria, dysuria, and frequency are common complaints in patients with NA [5–8]. Microscopically, NA consists of small to medium-sized tubules, cysts or papillae lined by cuboidal to low columnar epithelium with eosinophilic cytoplasm. Various growth patterns have been reported such as tubular, cystic, tubulocystic, papillary and flat. These patterns can be viewed as single or combined (mixed morphology). Although the diagnosis is straightforward in most cases, NA can mimic a variety of malignancies. Awareness of characteristic morphologic features of NA is needed to diagnose this lesion correctly.

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The aim of this study was to evaluate the clinicopathological features and differential diagnosis of NA in a series of 21 cases and review the literature.

2. Materials and methods

A retrospective series of 21 cases of NA from 18 patients, which were diagnosed in our department between 2010 and 2016, were analyzed. Age, sex, localization of the lesion, type of specimen, and recurrence status were obtained from clinical records. Coexisting lesions and previous biopsy findings were also obtained if available. All histological slides were reviewed by two pathologists and the diagnosis of each case was confirmed.

Immunohistochemistry was performed by using a Ventana Benchmark automated stainer (Ventana, Tucson, AZ) for PAX-8 (mouse monoclonal antibody, 1:100 dilution, Cell Marques, CA, USA) in all cases. CK7 (rabbit monoclonal antibody, ready-to-use [RTU], Ventana, AZ, USA), PAX-2 (rabbit monoclonal antibody, 1:20 dilution, Cell Marques, CA, USA), prostate specific antigen (PSA; rabbit polyclonal antibody, RTU, Ventana, AZ, USA), p53 (mouse monoclonal antibody, RTU, Ventana, AZ, USA), p63 (mouse monoclonal antibody, RTU, Ventana, AZ, USA), GATA-3 (mouse monoclonal antibody, 1:200 dilution, Cell Marques, CA, USA) and α-methylacyl-CoA racemase (AMACR; rabbit monoclonal antibody, 1:200 dilution, Cell Marques, CA, USA) were applied in problematic cases.

3. Results

3.1. Clinical findings

Study population consisted of 15 men and 3 women, aged between 3 and 80 years (mean 58.5). The most common location of the lesion was urinary bladder (14 patients) followed by renal pelvis (2 patients), ureter (1 patient) and urethra (1 patient) (Table 1). Surgical procedures were biopsy or transurethral resection (TUR) in 18 cases, cystoprostatectomy in 1 case, nephroureterectomy in 1 case and simple nephrectomy in 1 case. A history of urothelial carcinoma and repeated TUR procedures were observed in 12 patients (Table 2). There were 2 pediatric patients aged 3 years. Both of them had undergone previous urosurgery because of megaureter in one and bladder exstrophy in the other. Other clinical antecedents included bladder diverticulum (1 patient), cystitis (1 patient) and nephrolithiasis (1 patient). The patient, who had a nephrolithiasis history, had undergone simple nephrectomy because of an atrophic kidney and in the specimen, papillary renal cell carcinoma was also observed beside NA. Recurrence of lesion was seen in two patients (once in one patient and twice in the other one). The median time to disease recurrence in these patients was 11 months (range, 2–20 months).

Table 1
Clinicopathological characteristics of patients.

Characteristics	Value
Age	
Mean	58.5
Range	3–80
Sex	
Male	15/18 (83.3%)
Female	3/18 (16.7%)
Recurrence number	
0	16/18 (88.8%)
1	1/18 (5.6%)
2	1/18 (5.6%)
Location	
Urinary bladder	14/18 (77.8%)
Renal pelvis	2/18 (11.1%)
Ureter	1/18 (5.6%)
Urethra	1/18 (5.6%)
Histology[a]	
Mixed	15/21 (71.4%)
Pure papillary	2/21 (9.5%)
Pure tubular	3/21 (14.3%)
Pure flat	1/21 (4.8%)
Coexisting lesion	
Inflammation	9/18 (50%)
Urothelial carcinoma	4/18 (22.2%)
Papillary RCC[b]	1/18 (5.6%)
Chronic interstitial nephritis	1/18 (5.6%)
None	3/18 (16.7%)
Antecedent	
Urothelial carcinoma	12/18 (66.6%)
Previous urosurgery	2/18 (11.1%)
Inflammation	1/18 (5.6%)
Nephrolithiasis	1/18 (5.6%)
Bladder diverticulum	1/18 (5.6%)
None	1/18 (5.6%)

[a] 20 lesions in 17 patients.
[b] RCC, renal cell carcinoma.

3.2. Morphologic findings

Histologically, the lesions exhibited various morphological findings, with mixed (15 cases, 71.4%), pure tubular (3 cases, 14.3%), pure papillary (2 cases, 9.5%) and pure flat (1 case, 4.8%) growth patterns (Tables 1 and 2) (Fig. 1). Of the 15 cases with mixed patterns, 8 cases were tubulocystic and flat, 3 cases were tubular and flat, 2 cases were tubular, papillary and flat, 1 case was tubulocystic, papillary and flat, and 1 case was tubular and papillary. NA was usually located at the surface mucosa and in the underlying lamina propria. Notably one case in this series showed superficial extension into bladder muscularis propria (Fig. 2). Generally, papilla and/or tubules were lined by a single layer of cuboidal to low columnar cells with eosinophilic cytoplasm and small, round nuclei. Signet ring-like cells were seen in one case (4.7%), and hobnail appearance was seen in three cases (14.3%). The stroma was usually edematous and inflammatory, but recently described fibromyxoid features were not seen. In cases of NA with a cystic pattern, eosinophilic, colloid-like material was seen in the lumina. NA was observed in association with other lesions in most of the cases (Tables 1 and 2). The most common coexisting lesion was chronic inflammation (9 patients, 50%) followed by urothelial carcinoma (4 patients, 22.2%), papillary renal cell carcinoma (1 patient, 5.6%), chronic interstitial nephritis and hydronephrosis (1 patient, 5.6%) (Table 1). In three patients, no coexisting lesion was observed. All of these three patients were in clinical follow-up because of their previous urosurgery. In one of these patients, transurethral resection was performed due to the papillary lesion noted at cystoureteroscopy. In the other two patients microscopic hematuria was observed during the follow-up period. One patient showed a papillary lesion and the other had a velvety appearance on cystoscopy.

Immunohistochemically, all cases were positive for PAX-8 (21/21) (Fig. 3). PAX-2 and CK7 expressions were noted in all NA cases tested (5/5 and 8/8, respectively). AMACR expression was found in 5 of 6 cases (83%). Immunohistochemical analysis for PSA, p63, p53 and GATA-3 was performed only in one case, and all of these markers were negative.

4. Discussion

NA was first described by Davis [9] in 1949 as a benign hamartomatous lesion. In 1950, Friedman and Kuhlenbeck [10] used the term “nephrogenic adenoma” owing to the lesion’s similarity to renal tubules. There are different claims about the source of the pathogenesis of this lesion. One of these declare the origin of the