Nephrogenic adenoma (NA) is an uncommon benign lesion of the urothelial tract, characterized by a proliferation of tubules, cysts, and papillae lined by cells with low cuboidal to columnar epithelium. NA can be a significant diagnostic pitfall as certain histologic features, such as the presence of enlarged nuclei with prominent nucleoli, degenerative nuclear atypia, tiny tubules simulating signet ring cells, and focal invasion into superficial muscle, when taken out of context can mimic malignancy. Here we report two cases of NA, a male and a female with some worrisome histologic features and review the diagnostic criteria as well as pertinent morphologic malignant mimics of NA.

Keywords: Nephrogenic adenoma, urinary bladder, Cytokeratin-7, Cytokeratin-20, P504S

Introduction

Nephrogenic adenomas (NA) are benign tumor-like lesions of the urothelium. It is a rare lesion of the urinary tract widely considered to be a metaplastic response to urothelial injury [1]. It shows proliferation of glands that can occur at several sites within the urogenital tract. Although it is benign, the histopathological appearance may sometimes be mistaken for a malignancy, particularly in biopsies around the prostatic urethra. NA is an infrequent lesion of the urinary tract, associated with a previous history of trauma or irritation of the urothelium. Predisposing factors include infections, calculi, surgery, trauma and kidney transplantation [2].

The diagnostic features that are useful in the recognition of this entity are the characteristic mixture of various architectural patterns, associated stromal edema and inflammation, hyaline sheath around tubules, eosinophilic colloid like secretion within tubules, and lack of mitotic activity [3]. Histologically they consists of tubules, cords, individual cells and/or signet ring cells within the urothelium, which can extend into the muscular wall and mimic adenocarcinoma [4]. NA may show papillae as well as a focal solid growth pattern; however, conspicuous diffuse solid growth pattern is extremely uncommon. The cells lining tubules, cysts, and papillae are cuboidal to low columnar with scant pale cytoplasm. Occasional clear cells can be seen especially in the solid areas. Although enlarged nuclei and prominent nucleoli may be observed in some cases, significant nuclear atypia, including
presence of mitosis, is extremely rare. Nuclear atypia, when present, appears degenerative with indistinct, smudgy chromatin [3, 5]. Many normal structures and pathologic lesions in the genitourinary system can resemble neoplastic processes histologically. Although some, such as NA, can be seen in different locations, most are identified in particular organs and, as such, have unique differential diagnostic considerations specific to that organ [6].

We report two cases of NA and review the literature, focusing on the pathological differential diagnosis and immunohistochemical studies.

Case reports

Case 1
A 61 years old male was admitted to the Urology Department for re-evaluation of bladder tumor. He was suffering from high grade transitional cell carcinoma stage T1 since 2003 and passed several courses of intravesical treatment with BCG following transurethral resection of bladder tumor (TURBT). No lesions were seen on cystoscopy. Random biopsies were taken. On microscopic examination in the lamina propria of the urinary bladder mucosa there was a focus of small tubules and glands, lined by cuboidal cells (Fig. 1).

The cells did not show any significant atypia, mitoses were not found. The tubules and glands were accompanied by chronic inflammatory infiltrate. Immunohistochemical stains for Pan Cytokeratin, Cytokeratin-7, EMA and P504S were positive in the small tubules. Cytokeratin-20, PSA and Prostatic Specific Acid Phosphatase (PSAP) were negative. Ki-67 was negative in the tubules and positive in some of the lymphocytes (Fig. 2). The differential diagnosis with prostatic adenocarcinoma, adenocarcinoma of the urinary bladder was taken into consideration, but they were ruled out with the help of the immunohistochemical stains, Table I.

These findings were compatible with the diagnosis of NA.

Case 2
A 68 years old female, suffering from cystinuria resulting in chronic renal failure treated on hemodialysis since 2008. In October 2006 was admitted to the urology department with complains of lower abdominal and flank pain, and hematuria. Cystoscopy was performed and revealed foci of ulcerated bladder mucosa with no space occupying lesion. Endoscopically these findings were consistent with the diagnosis of Hunner’s lesion. Hunner’s lesion is a distinctive inflammatory lesion presenting a characteristic deep rupture through the mucosa and submucosa provoked by bladder distension. Biopsies were taken from the ulcerated areas. On microscopic examination, infiltration of tubules lined by epithelial clear cells was seen in the lamina propria, (Fig. 3).

Immunohistochemical stain for Cytokeratin 7 was positive while Cytokeratin 20 was negative. Ki-67 was positive in only in the lymphocytes. These findings were suspicious for Clear Cell Carcinoma but not diagnostic. Other areas showed heavy infiltration of lymphocytes, plasma cells and histiocytes which were stained with CD68 immunostain. She was treated for interstitial cystitis with DMSO that was interrupted because of

Table I. The different immunohistochemical stains

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<thead>
<tr>
<th>Markers</th>
<th>Nephrogenic adenoma</th>
<th>Urinary bladder adenocarcinoma</th>
<th>Renal cell carcinoma</th>
<th>Prostate adenocarcinoma</th>
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<tbody>
<tr>
<td>CK 7</td>
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<td>P504S</td>
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Figure 1. Tubular structures are seen on the right side with prominent inflammatory infiltrate on the left side. H&E x20 (Sunt observate structuri tubulare in partea dreaptă, cu infiltrat proeminent inflamator in partea stângă. H&E x20)
severe irritative changes. On January 2010, six months after the treatment, while she was asymptomatic, a control cystoscopy was performed. A small lesion measuring 2-3mm found at posterior wall of the bladder was biopsied.

On microscopic examination the lesion was composed of small tubules and glands located in the lamina propria near an area of chronic inflammatory infiltrate. Neither atypia nor mitotic figures were seen. Immunohistochemical staining for Cytokeratin-7 and
P504S were positive, Cytokeratin-20 was negative. Ki-67 was positive in only few cells (Table I). These findings were compatible with the diagnosis of NA.

Discussion

The urinary bladder is the most common location for NA, usually the posterior wall. Occasionally it can be found in the renal pelvis, urethra, or urethra. It is found in young adults with a male predominance (2:1). About half of the cases are found after genitourinary surgery, including renal transplantation. NA is also associated with calculi, trauma, and cystitis. Usually the lesions are asymptomatic, although patients frequently present with hematuria or dysuria. It may present as a papillary or polyploidy exophytic mass or velvety lesion, which resembles cystoscopically, neoplasia. Sessile forms make up about 25% to 30% of cases. Papillary structures usually measure less than 1 cm, may rarely measure more than 5 cm.

Classic histologic pattern is that of small tubules resembling renal tubules. The tubules are lined by hobnail cells resembling endothelial-lined vascular spaces and are often surrounded by a layer of hyalinized basement membrane.

NA can resemble adenocarcinoma of the urinary bladder or of the prostate and also some urachal benign or malignant tumors [6]. The absence of epithelial stratification and the characteristic eosinophilic, cuboidal, low columnar, or hobnail cells should alert the pathologist to the correct diagnosis.

Immunohistochemical stains for EMA, cytokeratin-7, P504S and PAX-2 are positive. Ki-67 is positive in only few cells. Cytokeratin-20, PSA and Prostatic Specific Acid Phosphatase (PSAP) are negative.

P504S is also positive in NA and in prostatic carcinoma therefore it cannot differentiate between those two lesions [7], but it is negative in clear cell carcinoma of the bladder. PSA is usually positive in prostatic carcinoma and negative in NA, which is frequently negative for basal cell markers and PSAP as well. The characteristic histomorphologic and immunohistochemical features, possibly supplemented by positive PAX2 and/or PAX8 immunostains, which can be used to arrive at the correct diagnosis [8,9].

Careful examination of the H&E stained slides which do not show dysplasia together with PSA and PSAP negativity can exclude the diagnosis of prostatic carcinoma and support the diagnosis of NA [10].

Mazal et al. [11] showed that in renal transplant recipients the sex chromosome status of 46 NA was the same as that of the kidney donor. They suggested that NA is derived from tubular cells of the renal transplant and were not metaplastic proliferations of the recipient’s bladder urothelium. This was supported by the positive immunohistochemical studies for PAX-2 and other peanut agglutinin studies.

Conclusion

Nephrogenic adenoma is a benign lesion with a broad histologic spectrum. NA can sometimes cause diagnostic difficulty in some cases, as certain histologic features, when taken out of context, may simulate the appearance of prostate adenocarcinoma, nested variant of urothelial carcinoma and/or clear cell adenocarcinoma.

Immunohistochemical profile of NA includes positive staining with CK 7, P504S, and PAX-2; negative staining with p63, PSA, PSAP high-molecular-weight cytokeratin (34βE12) and Ki-67. Whenever in doubt, theses stains should be performed in order to arrive to the correct diagnosis.

References


