Nephrogenic Adenoma

Report of a Case and Review of Morphologic Mimics

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Nephrogenic adenoma, also referred to as nephrogenic metaplasia, is an uncommon benign lesion of the urothelial tract, characterized by a circumscribed proliferation of tubules, cysts, and papillae lined by cells with low cuboidal to columnar epithelium. The diagnostic features that are useful in the recognition of this benign entity are the characteristic mixture of various architectural patterns, associated stromal edema and inflammation, hyaline sheath around tubules, eosinophilic colloidlike secretion within tubules, and lack of mitotic activity. Nephrogenic adenoma 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 with blue mucin simulating signet ring cells, and focal invasion into superficial muscle, when taken out of context, can mimic malignancy. Herein, I report a case of nephrogenic adenoma with some worrisome histologic features and review the diagnostic criteria as well as pertinent morphologic malignant mimics of nephrogenic adenoma.

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REPORT OF A CASE

The patient is a 71-year-old man with a previous history of urinary bladder cancer who underwent transurethral resections twice within the last 12 months. The current transurethral resection specimen showed a proliferation of numerous small tubular structures with attenuated hobnail cells, haphazard growth pattern, luminal blue mucin, and mild degenerative nuclear atypia, arranged in small groups and individually within the superficial lamina propria and muscle fibers. The mild nuclear atypia, presence of signet ring–like tubules, infiltrating pattern into the deep lamina propria, including focal involvement of muscularis mucosae and superficial muscularis propria, were unusual and prompted an immunohistochemical workup to rule out malignancy. This case is an example of a nephrogenic adenoma with some unusual morphologic features; however, given the patient’s history of previous resections, this is not an unexpected diagnosis. This case will be used to discuss diagnostic criteria of nephrogenic adenoma as well as its morphologic mimics.

COMMENT

Nephrogenic adenoma (NA) is a relatively uncommon lesion and in its most classic form is composed of small tubules resembling renal tubules that are confined to the lamina propria. The clinical association of this entity with injury to the urothelium and the histologic evidence of associated inflammation suggest that NA is a benign metaplastic response of the urothelium to injury or insult. Nephrogenic metaplasia is another term that is commonly used for this lesion.

Nephrogenic adenomas show a male predominance (male to female ratio, 2:1) and occur over a wide age range (4–81 years). Although most common in adults, approximately 10% of NAs have been observed in children. They commonly arise in the setting of prior urothelial injury, such as past surgery (60%), calculi (14%), or trauma (9%). Additionally, 8% of the patients have a previous history of renal transplantation or bacillus Calmette-Guérin therapy for urothelial carcinoma of the bladder. Nephrogenic adenomas are commonly seen in the urinary bladder (80%); however, urethra (12%) or ureter (8%) can also be involved. Nephrogenic adenomas are benign lesions that can recur.

Grossly, NAs appear as papillary (56%), polypoid (10%), fungating or sessile (10%) lesions. On cystoscopy, the sessile lesions appear friable and velvety, mimicking urothelial carcinoma in situ. Most NAs (62%) are small lesions (<1 cm) although, rarely, they may be as large as 7 cm. In about 18% of the cases, NA can be multifocal.

Histologically, NAs can show a variety of patterns including tubules, cysts, papillae, and focal solid growth pattern. The most common pattern consists of tubules often surrounded by a thickened hyalinized basement membrane and lacking a desmoplastic stromal response. Cystic tubules frequently show colloidlike eosinophilic secretions or blue-tinged mucin. The stroma is usually edematous and associated acute and chronic inflammation is common. Nephrogenic adenomas 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 cuboidal with scant pale cytoplasm (Figure I, A and B). 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. Small tubules with blue mucin lined by a single cell and resembling signet ring cells may be seen (Figure 1, C).

Figure 1. A, Nephrogenic adenoma with papillary architecture, lined by columnar cells with pink cytoplasm. B, Nephrogenic adenoma with tubular architecture composed of small tubules lined by low cuboidal to flattened epithelial cells containing blue mucin. Some nuclei show degenerative atypia with smudgy indistinct chromatin. C, Nephrogenic adenoma with small tubules simulating signet ring cells and degenerative nuclear atypia. D, Nephrogenic adenoma with invasion into superficial muscle. E, Nephrogenic adenoma with strong nuclear positivity with PAX2. F, Nephrogenic adenoma with cytoplasmic positivity with α-methylacyl-CoA racemase (AMACR) (hematoxylin-eosin, original magnifications ×200 [A through D]; PAX2, original magnification ×100 [E]; AMACR, original magnification ×100 [F]).

Nephrogenic adenomas typically are not large invasive tumors although rare cases of NA may focally involve the superficial muscularis propria (Figure 1, D). They are typically positive with cytokeratin 7 (CK7), α-methylacyl-CoA racemase (AMACR).
CoA racemase (AMACR) (P504S), PAX2, and epithelial membrane antigen are and are usually negative with p636,7 (Figure 1, E and F). PAX2, a key renal transcription factor, is commonly expressed in NA, which has been interpreted as evidence that NAs may be of renal tubular origin.8 Nephrogenic adenomas show patchy staining with high-molecular-weight cytokeratin (34bE12), although a subset of these (40%–45%) may be completely negative.1,7

The differential diagnosis of the surface lesions with papillary architecture includes urothelial papilloma, papillary urothelial neoplasm with low malignant potential, and low-grade papillary urothelial carcinomas. These neoplasms are lined by urothelium, unlike the cuboidal or columnar single cell lining the papillae in nephrogenic metaplasia, and are usually not difficult to distinguish from NA. Nephrogenic adenomas involving the deep lamina propria and/or superficial muscle can cause diagnostic difficulty and mimic malignancy, specifically prostatic adenocarcinoma, urothelial carcinoma with bland histology, and/or clear cell adenocarcinoma (Table).

When NA occurs in the prostatic urethra and involves the underlying prostatic stroma, its morphologic appearance may mimic prostatic adenocarcinoma.5,7 In this setting, NAs can have a pseudoinfiltrative pattern composed of small tubules lacking a basal cell layer; they occasionally demonstrate signet ring–like tubules, show mild to moderate cytologic atypia including occasional prominent nucleoli, and have intraluminal blue-tinged mucus. The histologic features that favor NA versus prostatic adenocarcinoma include a lack of significant cytologic atypia and mitosis, presence of adjacent urothelium with papillary architecture, and vascular-like cystic tubules lined by hobnail cells set in an edematous and inflammatory stroma (Figure 2, A). As NAs commonly express AMACR and may show complete lack of basal cell markers, they also represent a significant immunohistochemical mimic of prostatic adenocarcinoma. While most NAs are negative with prostate-specific antigen, a subset (approximately 30% of cases) show focal prostate-specific antigen positivity with cytoplasmic staining and/or within tubular secretions.1 Hence, one must be aware of this significant pitfall in the diagnosis of prostatic adenocarcinoma, as isolated features of NA (morphologic and immunohistochemical), when taken out of context, may mimic prostatic adenocarcinoma. Cytokeratin 7 and PAX2 positivity of NA (Figure 2, B) can be useful to distinguish it from prostatic adenocarcinoma, which is negative with these markers.

In general, the stroma of NA, which is commonly edematous and inflamed, receives scant attention. However, a recent study9 has described a series of NA cases with striking fibromyxoid change in the stroma. Most of the patients affected received various forms of therapy, which may have contributed to the appearance of NAs with prominent fibromyxoid change, compressed spindle cells (of epithelial origin), and distorted tubules, features that can easily be confused with adenocarcinoma.

Nephrogenic adenoma with focal solid and/or tubular pattern, especially with irregular borders and involving deep lamina propria/superficial muscularis propria,10 may mimic certain urothelial carcinomas with deceptively bland features, such as the nested variant of urothelial carcinoma, urothelial carcinoma with small tubules, and micropapillary urothelial carcinoma.11–16 Recognition and documentation of these variants in the pathology report is critical, as they have potential diagnostic and prognostic implications. Surgical pathologists must be cognizant of these variants of urothelial carcinoma as a malignant process, especially in small biopsy specimens, as these tumors frequently recapitulate benign entities.

The nested variant of urothelial carcinoma (Figure 2, C through F) has distinctive patterns in the superficial and deep portions of the tumor. In biopsies and transurethral resections, the superficial component is characterized by small, crowded, tightly packed nests with focal tubular differentiation that can be prominent in some cases. The tumor stroma can be variable, ranging from minimal stromal response, focally desmoplastic, and/or myxoid stroma. The nests commonly have central lumina resembling cystitis cystica.13–15 Most nests have a deceptively bland cytology in the superficial areas of the tumor, although random cytologic atypia within nests is commonly seen. Within the deeper portions, a prominent infiltrative base with frequent muscularis propria invasion and focal high-grade cytologic atypia is noted (Figure 2, E and F). Despite their deceptively bland histologic features, these tumors are associated with an aggressive clinical outcome characterized by high frequency of progression, with metastasis and death. Hence, the importance of recognizing this variant of urothelial carcinoma and distinguishing it from its benign mimics such as NA, especially in small biopsy specimens, cannot be overemphasized.

Although a prominent tubular histologic appearance may be noted in the nested variant of urothelial carcinoma, some urothelial carcinomas (urothelial carcinoma with small tubules) have an exclusive component of small to medium-sized tubules that mimic NA or cystitis glandularis. The biologic significance of this variant is as yet unclear owing to the paucity of cases, but cases that occur in conjunction with nested variant have an aggressive outcome.

Clinical implications. The nested variant of urothelial carcinoma is characterized by widespread cystic change within the nests of urothelial carcinoma or urothelial carcinoma with glandular differentiation.16 The most critical feature in distinguishing this rare (less than 20 cases reported in literature), deceptively
Figure 2. A, Nephrogenic adenoma (NA) involving prostate urethra. Note tubules and cysts lined by hobnail cells with a hyaline sheath surrounding some of the tubules, inflamed stroma, adjacent urothelium, and no significant cytologic atypia. B, Nephrogenic adenoma involving prostatic urethra shows nuclear positivity with PAX2. C through F, Nested variant of urothelial carcinoma. C, Irregular proliferation of discrete nests with bland cytology separated by edematous stroma. D, Frequent tubular differentiation is noted. E, Despite overall bland cytology, cells with random cytologic atypia can be seen (arrows). F, Nested variant of urothelial carcinoma invading into muscularis propria and showing focal high-grade cytologic atypia (arrows). G, Clear cell adenocarcinoma with prominent tubular architecture mimicking NA. H, Clear cell adenocarcinoma with solid growth pattern and obvious nuclear atypia (hematoxylin-eosin, original magnifications ×200 [A through F and H] and ×100 [G]).
bland urothelial carcinoma from benign conditions like cystitis cystica and NA is the often dramatic variation in size and shape of epithelial formations and haphazard infiltrative growth pattern.

The presence of nested, tubular, papillary, cystic, vascular-like, and sometimes solid architecture within the same lesion is very characteristic of NA and is a helpful feature in resolving this differential diagnosis. Also useful is the presence of edematous inflammatory stroma in NA, in contrast to the desmoplastic/myxoid stroma commonly seen in nested urothelial carcinoma. The tubules of NA are lined by a single layer of cuboidal, columnar, or hobnail cells in contrast to the nests of urothelial cells in nested variant of urothelial carcinoma and the attenuated urothelial cells lining the tubules in the nested variant as well as urothelial carcinoma with small tubules. Immunohistochemistry, especially p63 and PAX2, may be useful in resolving this differential diagnosis, as urothelial carcinomas with deceptively bland features (nested and/or urothelial carcinoma with small tubules) are strongly positive for CK7, p63, and 34βE12, while nephrogenic adenoma is positive with AMACR, PAX2, and CK7, variably positive with 34βE12, and negative with p63.6

Another rare entity that may mimic NA is clear cell adenocarcinoma (Figure 2, G and H): this tumor may show foci with tubular, cystic, and papillary architecture lacking significant cytologic atypia, focally resembling NA. Clear cell adenocarcinomas show a strong female predominance and is believed to arise through a process of metaplasia of the surface urothelium or from müllerian rests/müllerianosis.17 They are more common in the urethra than the urinary bladder and show multiple patterns including tubular, cystic, and papillary architecture with hobnail cells, and solid growth of cells with clear cytoplasm. These rare carcinomas are infiltrative, high grade, with frequent mitoses, obvious nuclear atypia and pleomorphism, necrosis, prominent areas of solid growth, and extensive muscle invasions, features which are absent in NA. A recent study18 of clear cell adenocarcinomas involving the urinary bladder and urethra, including a subset of clear cell adenocarcinomas that resembles NA, has shown that immunohistochemistry with p63, high-molecular-weight cytokeratin, and AMACR has limited utility in distinguishing NA-like clear cell adenocarcinoma from NA. PAX2 expression appears to be more useful, as it was more frequent in NA (89%) than clear cell adenocarcinoma (29%–32%).

CONCLUSIONS

Nephrogenic adenoma is a benign metaplastic response of urothelium to injury and has a broad histologic spectrum. Immunohistochemical profile of NA includes positive staining with CK7, AMACR, and PAX 2 (nuclear stain), negative staining with p63 (nuclear stain), and variable staining with prostate-specific antigen and high-molecular-weight cytokeratin (34βE12). Nephrogenic adenoma 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.

Nephrogenic adenoma of urothelial carcinoma has an aggressive clinical course and hence, it is critical to recognize this variant, especially in superficial biopsies with limited material. This variant is composed of discrete, small to variably sized nests, focal confluent nests, frequent tubular features, predominantly bland cytology with random cytologic atypia, and an infiltrative base. Immunohistochemical profile of the nested variant includes positivity for CK7, p63, and high-molecular-weight cytokeratin (34βE12).

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References