

ATYPICAL NEPHROGENIC METAPLASIA OF THE URINARY BLADDER: A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Nephrogenic metaplasia or nephrogenic adenoma of the urinary tract is an infrequent benign lesion that occurs in patients with a history of genitourinary surgery, stone disease, trauma, chronic urinary tract infection, or renal transplantation. The term “nephrogenic adenoma” was introduced by Friedman and Kuhlenbeck because the structure resembled that of renal collecting tubules. Nephrogenic metaplasia most frequently situated in the bladder; it demonstrates a variety of morphologic patterns including tubulocystic, papillary, and much less frequently solid, that often coexist. Nephrogenic metaplasia with cytologic atypia (atypical nephrogenic metaplasia) is occasionally encountered and displays substantial cytologic abnormalities of no apparent clinical significance. ANM may be confused with malignant neoplasms, especially clear cell carcinoma, some variants of urothelial and prostatic carcinoma. Although to date there is no specific immunohistochemical profile to distinguish this lesion from its malignant mimickers, clinicopathologic correlation with careful attention to morphology remains the milestones in establishing the correct diagnosis.

We describe a case of 54-year-old male that underwent a transurethral resection of the urinary bladder lesion due to hematuria. The diagnosis of atypical nephrogenic metaplasia was based on the histological patterns, the absence of p53 immunopositivity and low Ki-67 proliferative index (3.7 %). The clinical long-term follow-up demonstrated the proof for the diagnosis. We present this case because of its rarity and also to emphasize that analysis of immunohistochemical proliferative activity is helpful and leading to accurate identification of the lesion. Awareness of the spectrum of cytologic changes within this entity is critical to prevent overdiagnosis of cancer and avoid unnecessary treatment.

Key words: *nephrogenic metaplasia, histology, immunohistochemistry, differential diagnosis.*

INTRODUCTION

A rare benign lesion of the urothelium was first described by Davis in 1949 (3), but better characterized by Friedman and Kuhlenbeck in 1950, which introduced the term “nephrogenic adenoma” because of morphologic similarity to renal tubules (4). Some authors prefer the name “nephrogenic metaplasia” (NM) due to presumed metaplastic nature of the lesion. NM occurs mainly in adults and is typically preceded by different forms of genitourinary insult. Histologically, NM shows a variety of patterns, including tubular, tubulocystic, papillary to polypoid and, much less frequently solid, that often coexist (11). The term “atypical nephrogenic metaplasia” (ANM) was employed by Cheng et al. in 2000 for bladder lesions that revealed substantial cytologic abnormalities without apparent malignant potential (2). ANM may be confused with malignant neoplasms, especially urothelial and prostatic carcinoma, and from this point of view it is a diagnostic challenge for pathologists.

CASE PRESENTATION

A 54-year-old man was admitted to Urology Clinic with irritative urinary symptoms (dysuria and frequency) and medical history of nephrolithiasis. The patient's general physical examination was unremarkable. Except from hematuria in the urinalysis, urinary cultures, blood tests and abdominal ultrasonography were normal. At cystoscopic examination calculi and a small (2 mm in diameter) polypoid lesion in the posterior wall were found in a background of erythematous bladder mucosa. The lesion was resected and sent to Pathology Department for microscopic examination due to suspicion for malignancy. Hematoxylin&Eosin and PAS-stained slides showed tubules and microcysts, lined with inconspicuous cuboidal to flattened epithelium and contained scanty amount of PAS-positive eosinophilic material. In addition, papillary structures and small solid foci revealed large cells with abundant clear cytoplasm, apparent nuclear pleomorphism with hyperchromasia (Fig. 1A, B). Prominent nucleoli and mitotic figures were not encountered. Using formalin-fixed, paraffin-embedded sections ancillary immunohistochemical investigation with anti-Ki-67 and p53 antibodies (DAKO) was performed. The lesion was entirely p53-negative. In a computerized morphometrical analysis, percentage of Ki-67-positive cells was calculated as 3.7 % (Fig. 1C, D). Thus, the p53-negativity and low Ki-67 proliferative index supported the final histopathological diagnosis of ANM. The patient was followed-up for 10 years, at this point patient is alive with no evidence of disease.

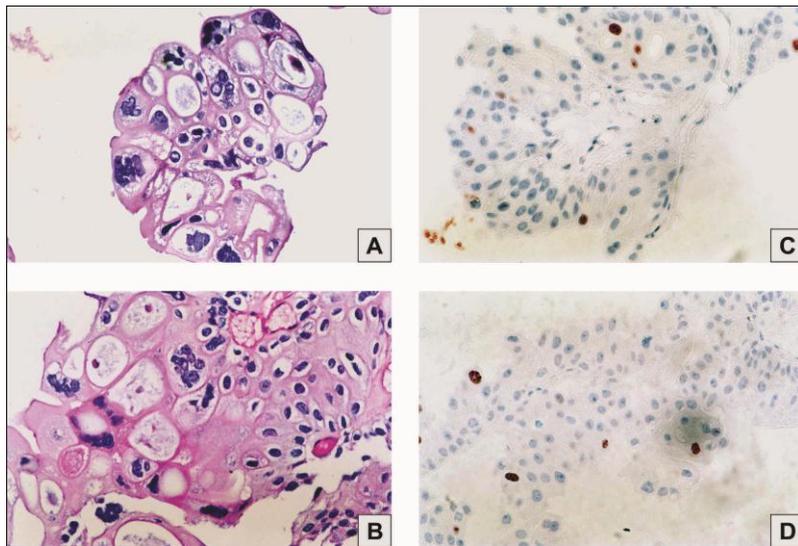


Fig. 1. A, B: PAS, small solid foci and papillary structures containing large cells with abundant clear cytoplasm and apparent nuclear pleomorphism with hyperchromasia.

C, D: Ki-67 labeling revealing single positive nuclei.

DISCUSSION

NM is a relatively uncommon urothelial lesion that occurs mainly in adults with male predilection (2:1 male: female ratio) (11). The typical clinical presentations are hematuria and/or voiding symptoms (12). The most affected organ is the urinary bladder, the rest include urethra, ureter and very rarely - renal pelvis (11). The majority of lesions is smaller than 1.0 cm and represent incidental microscopic finding. However, approximately in one-third of cases the lesions are sizable and may be seen in cystoscopic examination, causing concern for a malignancy; therefore, biopsies are recommended. The gross appearance is typically described as papillary, polypoid, or sessile (18). NM commonly arise in the setting of prior urothelial injury such as past genitourinary surgery, trauma, mechanical irritation, renal calculi, and chronic inflammation (12, 18). NM has also been described after BCG therapy for urothelial carcinoma of the bladder and in

patients with a transplanted kidney (16). The pathogenesis of NA is not entirely clear. Although generally presumed to be a metaplastic process of the urothelium, recent evidence suggests that NA may in fact be derived from detached renal tubular cells implanting along the urothelial tract in previously injured areas, at least in cases associated with a kidney transplant (10).

Histologically, NM can show a variety of patterns (11, 13). A common pattern consists of tubules lined by cuboidal to low columnar epithelium with eosinophilic to slightly clear cytoplasm, often surrounded by a thickened hyalinized basement membrane and lacking a desmoplastic stromal response. The stroma is usually edematous and associated acute and chronic inflammation is common finding. Cysts are frequently admixed with tubules and occasionally contain eosinophilic colloid-like secretion or blue tinged mucin. NM may also be papillary and occasionally show a focal solid growth pattern (conspicuous solid growth patterns is extremely rare). As a rule, there is minimal cytologic atypia with the nuclei being round to oval with small, inconspicuous nucleoli, and sparse mitotic activity (less than 1 per 10 high power fields). Some cases may focally demonstrate cytologic atypia, often of the degenerative type, with a smudgy chromatin pattern. Cheng et al. characterized ANM by a circumscribed proliferation of tubules, cysts, and papillae lined or covered by cells with enlarged hyperchromatic nuclei and prominent nucleoli (2). The authors postulated that ANM is not biologically different from typical NM and may be merely an unusual type of metaplastic transformation of urothelial cells without malignant potential. Despite single case reports that have described progression of NM to carcinoma (7, 8), the importance of recognizing of ANM is to avoid misinterpretation or overdiagnosis of malignancy.

The most common and difficult problem is the differential diagnosis between NM and clear cell carcinoma (CCC). Unlike NM, CCC is mostly seen in older women without a previous history of trauma (18). On microscopic examination, the histologic patterns of CCC (tubular, tubulocystic, papillary, and solid) overlap with those seen in NM. CCC and NM both contain hobnail cells, but in parallel with ANM, CCC demonstrates a far greater degree of cytologic atypia and mitotic activity and frequently shows areas of hemorrhage and necrosis with deep infiltrative growth. Immunohistochemical profiles of the two lesions are not distinguished significantly except for proliferative activity and p53-positivity. In all studies CCC showed strong nuclear staining for p53 and high Ki-67 positivity (above 15%) in contrast to the absence of p53 staining and low Ki-67 proliferative index (below 5%) in the cases with NM (2, 5).

NM with nested and/or tubular pattern, especially with irregular borders and present in deeper location may mimic certain urothelial carcinomas with deceptively bland features such as the nested variant of urothelial carcinoma, microcystic urothelial carcinoma and urothelial carcinoma with small tubules, especially in small samples (11). Helpful features in this distinction include the presence of more than one layer lining the tubules of these unusual variants, appreciable cytologic atypia with prominent nucleoli seen at least focally in these neoplasms, and invasion of the muscularis propria. Furthermore, most NMs show a variety of distinctive architectural patterns and appreciable basement membrane surrounding the tubules and nests (11). Immunohistochemistry may also be useful in resolving this differential diagnosis. The nested variant of urothelial carcinoma shares with conventional high-risk urothelial carcinoma the finding of a high proliferation Ki-67 index (above 15%), but p53 immunoreactivity is not frequently seen in this variant (2, 5, 9). The nested variant of urothelial carcinoma shows nuclear positivity for p63, which is absent in NM (17). All studied cases of NM were positive for PAX2 in contrast to tested invasive urothelial carcinomas (15).

There are some important clinical scenarios when NM can be mistaken for prostatic carcinoma (1). The first is in transurethral resection specimens when NM involves the prostatic urethra, where it may demonstrate a pseudoinfiltrative growth pattern, with small tubules intercalating between muscle fibers. The second scenario involves prostate needle biopsies where the tiny tubules or solid architecture of NM may mimic a Gleason pattern 4 or 5 adenocarcinoma. As NM commonly express AMACR and may show complete lack of basal cell markers (34βE12),

this also represents a significant immunohistochemical mimic of prostatic adenocarcinoma (14). While most NM are negative with PSA, a subset of NM (approximately 30% cases) show focal PSA positivity with cytoplasmic staining and/or within tubular secretions (1). Although CK7 is reported to be positive in NM and usually negative in prostate cancer, the study of Goldstain showed focal CK7 positivity in prostatic carcinomas and the higher the Gleason score the greater percentage of CK7-positive cells appear (6). PAX2 is a more helpful marker. Tong et al. reported absence of PAX2 expression in 100 prostate cancers and 100 benign prostatic tissue samples in contrast to the uniformly positive nuclear staining seen in all 39 examined NM (15). However, further studies are required before PAX2 is widely implemented in routine clinical practice.

IN CONCLUSION, to date there is no specific immunohistochemical profile to distinguish NM from its malignant mimickers and clinicopathologic correlation with careful attention to morphology remains the milestones in establishing the correct diagnosis. We present a case of ANM because of its rarity and also to emphasize that analysis of immunohistochemical proliferative activity is helpful and leading to accurate identification of the lesion. Awareness of the spectrum of cytologic changes within this entity is critical to prevent overdiagnosis of cancer and avoid unnecessary treatment.

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