Nephrogenic Adenoma: An Update on an Innocuous but Troublesome Entity

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Abstract: Nephrogenic adenoma (NA) is a rare benign lesion of the urothelial tract that is typically preceded by some form of genitourinary insult. 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. On light microscopy, NA shows a variety of patterns, including tubulocystic, papillary, and much less frequently solid, that often coexist. Recognition of its characteristic patterns, and awareness of its unusual architectural and cytologic features, is key to making the diagnosis of NA and distinguishing this lesion from malignant neoplasms occurring at the same sites, in particular, clear cell carcinoma, nested or microcystic variants of urothelial carcinoma and prostatic adenocarcinoma. Although straightforward in most cases, the correct diagnosis may be difficult to make on limited tissue samples. A number of immunohistochemical markers have been studied in an attempt to characterize NA; however, to date there is no specific immunohistochemical profile to distinguish this lesion from its malignant mimickers, although PAX2, a new marker, may prove to be helpful in this regard. Clinicopathologic correlation with careful attention to morphology remains the pillar in establishing the correct diagnosis.

Key Words: nephrogenic adenoma, urothelium, immunohistochemistry, pathogenesis, differential diagnosis, clear cell carcinoma, urothelial carcinoma, prostatic adenocarcinoma

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Nephrogenic adenoma (NA) is a rare benign lesion of the urothelium, first described by Davis in 1949,[1] but better characterized by Friedman and Kuhlenbeck in 1950.[2] They coined the term ''nephrogenic adenoma'' because of the morphologic similarity of NA to renal tubules. Some authors prefer the term ''nephrogenic metaplasia,'' as this lesion has been presumed over the years to represent one of multiple metaplasias involving the urothelium.

NA occurs mainly in adults and more commonly in males, while in children, females are more often affected.[3–5] Approximately 80% of NAs arise in the bladder, with the remainder involving the urethra (15%), ureter (5%) or rarely, the renal pelvis.[3,6–9] In a series of 80 NAs, 26% of cases involving the urethra were associated with a urethral diverticulum in females.[7] In most instances, NA is an incidental finding, but in one-third of cases, the lesions are sizable and may be seen on cystoscopic examination, causing concern for a malignancy.[10–12] NA can recur and recurrence rates have been reported to range from 28% to nearly 90%; however, there is no definitive proof that NA undergoes malignant transformation.[13–15]

Predisposing factors for the development of NA include genitourinary trauma, surgery, mechanical irritation, chronic inflammation, and renal calculi.[3,6,16] NA has been described after the administration of intravesical Bacille Calmette-Guerin for urothelial carcinoma and rare cases have also been reported in the mucosa of bowel conduits after cystectomy for urothelial carcinoma.[13,17–20] The lesion has been noted in immunosuppressed patients, particularly in those with a transplanted kidney,[13,21–23] and occasional such cases contain cytomegalovirus inclusions.[24–26]

PATHOGENESIS

Recently, it has been shown that NAs arising in renal transplant recipients derive from donor renal tubular cells that implant in the bladder mucosa. Mazal et al[27] analyzed tissue sections of NAs arising in such patients by fluorescence in situ hybridization using probes for the X and Y chromosomes. NAs in recipients of transplants from opposite-sex donors showed the sex-chromosome status of the donor kidney, and not the sex-chromosome status of the recipient's surrounding bladder tissue. In addition, the lesions showed strong immunostaining for aquaporin-1 (expressed in the proximal renal tubule and the descending thin limb of Henle's loop), PAX2 (a nuclear transcription factor expressed during mammalian kidney development), and for lectins, known to bind renal tubular cells.[27] The authors hypothesized, on the basis of their findings, that in renal diseases and hypoxic conditions there is an increased tendency for viable renal tubular cells to detach and secondarily seed, implant, and grow in the urothelium, particularly if the

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latter is injured by trauma or damaged due to a weakened host immune system.[27,28]

This study provides compelling evidence for a renal origin of NA in kidney transplant recipients; however, the origin of NA in other patients remains unclear. It can be hypothesized that since some type of injury to the bladder or urothelium precedes most NAs, the lesions could have a similar pathogenesis in nonimmunocompromised individuals. Tong and colleagues[29] explored this possibility in a recent study examining immunohistochemical expression of the renal-specific transcription factor PAX2 in 39 nonrenal transplant-related NAs. All 39 cases showed strong and distinct nuclear staining for PAX2, in contrast to invasive urothelial carcinoma and benign urothelial tissue, both PAX2 negative. The authors also reported focal positivity for CD10 and lack of expression of uroplakins (tested by 4 different antibodies) in a subset of NAs, further pointing to a renal rather than urothelial origin for this lesion.[29] Of note, NA is negative for p63, a marker of benign and neoplastic urothelium that is only rarely focally expressed in renal cell carcinoma, and distal convoluted renal tubular epithelial cells and NA both stain for α-methylacyl-coenzyme-A racemase (AMACR, P504S) and epithelial membrane antigen (EMA), findings that further support the relationship between NA and renal tubules.[30–34] Finally, additional support for a renal origin comes from earlier electron microscopy and immunofluorescence studies that showed ultrastructural features of proximal tubular epithelium in NA cells, and also absence of Tamm-Horsfall mucoprotein expression characteristic of urothelium.[35]

However, in contrast to these findings, a recent immunohistochemical study of 40 NAs not occurring in the renal transplant setting revealed that the majority of cases were strongly positive for cytokeratin 7 (CK7) and for antigens shown to be expressed by both neoplastic and benign urothelium but not typically expressed by renal tubular epithelium (CA-125 and CK20, although staining was often focal and moderate to weak for CK20).[36–38] Only one-quarter of these cases were positive for CD10 and RCC antibody, markers shown to be specific to proximal renal tubular epithelium.[31,36,38] None of the cases in this large series demonstrated membranous or luminal positivity for uroplakin characteristic of urothelial carcinoma, leading the authors to conclude that the results were equivocal in terms of defining a precise origin for this lesion.[38] We have also studied aquaporin-1 expression in NAs, and in our experience a large number of NAs in nonrenal transplant recipients are negative for this antibody by both immunohistochemistry and immunofluorescence (EO, personal observation). Finally, kidney-specific cadherin is a recently characterized calcium-dependent cell adhesion molecule that appears to be kidney-specific in its distribution, with expression localized primarily in the distal nephron.[39] We have stained 10 NAs with this antibody and all were negative (EO, personal observation).

Although these findings do not fully support a renal origin for NA, they do not exclude such a possibility either. Indeed, it seems that at least a subset of NAs is renally derived. Further studies of additional cases using a variety of markers are required before the histogenesis of these lesions, particularly those arising in nonimmunosuppressed patients, can be firmly established.

PATHOLOGIC FEATURES

Gross Findings

Although the majority of NAs are smaller than 1.0 cm and represent incidental microscopic findings, approximately one-third of lesions are sizable with 10% measuring 4 cm or more, and multifocal lesions may be found.[6] In large lesions the gross appearance of NA is typically described as papillary, polypoid, or sessile.[6] NAs occurring in the setting of end-stage renal disease are often large and multifocal (personal observation).

Microscopic Findings

Architecture

NAs may show tubular, tubulocystic, papillary to polypoid and, much less frequently, solid growth, and not infrequently a mixture thereof. The tubular pattern is the most common, present in 96% of cases in the largest published review (80 cases).[7] The tubules may grow in a bandlike pattern with a sharp demarcation from the underlying stroma and are medium to small in size (Figs. 1A, B). The majority are hollow, and may contain either basophilic or eosinophilic secretions, but they may be solid, and on rare occasions, the tubules are particularly tiny and closely packed, mimicking signet ring cells (Figs. 1C, D). Appreciable basement membrane may be seen surrounding some of the tubules and is quite a characteristic feature (Figs. 1D, E). The tubules are usually separated from one another by appreciable amounts of stroma, but focally may appear packed with little or no intervening stroma (Fig. 1F).

Cysts are frequently admixed with the tubules, present greater than 70% of the time, but conspicuous in only 7.5% of cases (Fig. 1G).[7] Occasionally the cysts contain eosinophilic colloidlike secretions and may bear a superficial resemblance to thyroid follicles (Fig. 1H). The papillary pattern is characterized by thin, generally nonbranching, papillae whereas polypoid structures exhibit greater stromal edema, a feature that may be striking in some cases (Fig. 1I). The papillary or polypoid growth is typically exophytic, but may be endophytic, projecting into adjacent cysts and tubules. Although minor degrees of branching may be observed coming off the main papillae, rare cases can exhibit florid complex branching with the formation of small papillary buds (Fig. 1J). Importantly, the various papillary or polypoid patterns are rarely seen in the absence of tubules. The final and least common pattern observed is the solid or diffuse pattern of growth (Figs. 1K, L). However, when present, it typically represents only a minor component of the lesion.

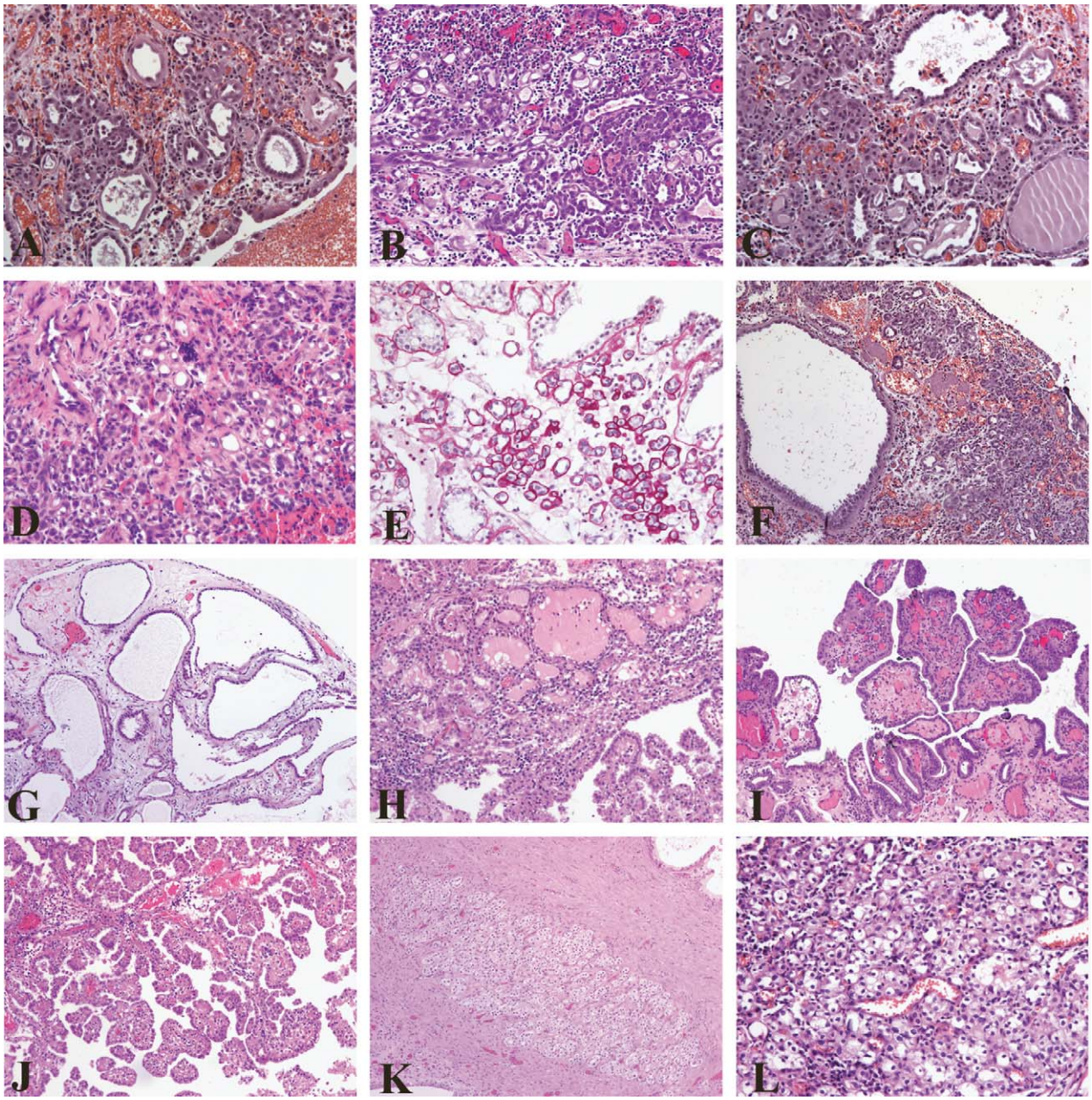

FIGURE 1. A, Typical tubular pattern with small to medium-sized hollow tubules; B, Irregularly shaped and compressed tubules are present in a background of chronic inflammation; C, Hollow tubules merge with a solid tubular growth; D, Tiny tubules, some simulating signet ring cells, are seen in association with elongated tubules surrounded by prominent basement membrane; E, Thickened basement membrane around tubules is highlighted by PAS stain; F, Back to back tubules with minimal intervening stroma are seen next to a cyst; G, Florid cystic pattern is present in an edematous stroma; H, Cysts containing eosinophilic colloid-like material resemble thyroid follicles; I, NA with thin to bulbous nonbranching papillae. Note the small tubules at the base of the lesion; J, Florid papillary pattern with complex branching including multiple small buds; K, Well-circumscribed solid pattern exclusively composed of clear cells; L, Solid arrangement of clear cells with minimal to absent cytologic atypia.

Cytology

The cells lining the tubules, cysts, and papillae are columnar to cuboidal to flattened, and contain eosinophilic to slightly clear and granular cytoplasm. Occasional cases show cells with greater amounts of clear cytoplasm (Figs. 1K, L).[6,7,40] Hobnail cells are typically present, most often lining cysts, but rarely are numerous (Fig. 2A).[7,41] Extreme attenuation of the epithelial lining of the tubules may result in an appearance that resembles small vessels as seen in granulation tissue.[42] Cells lining tiny

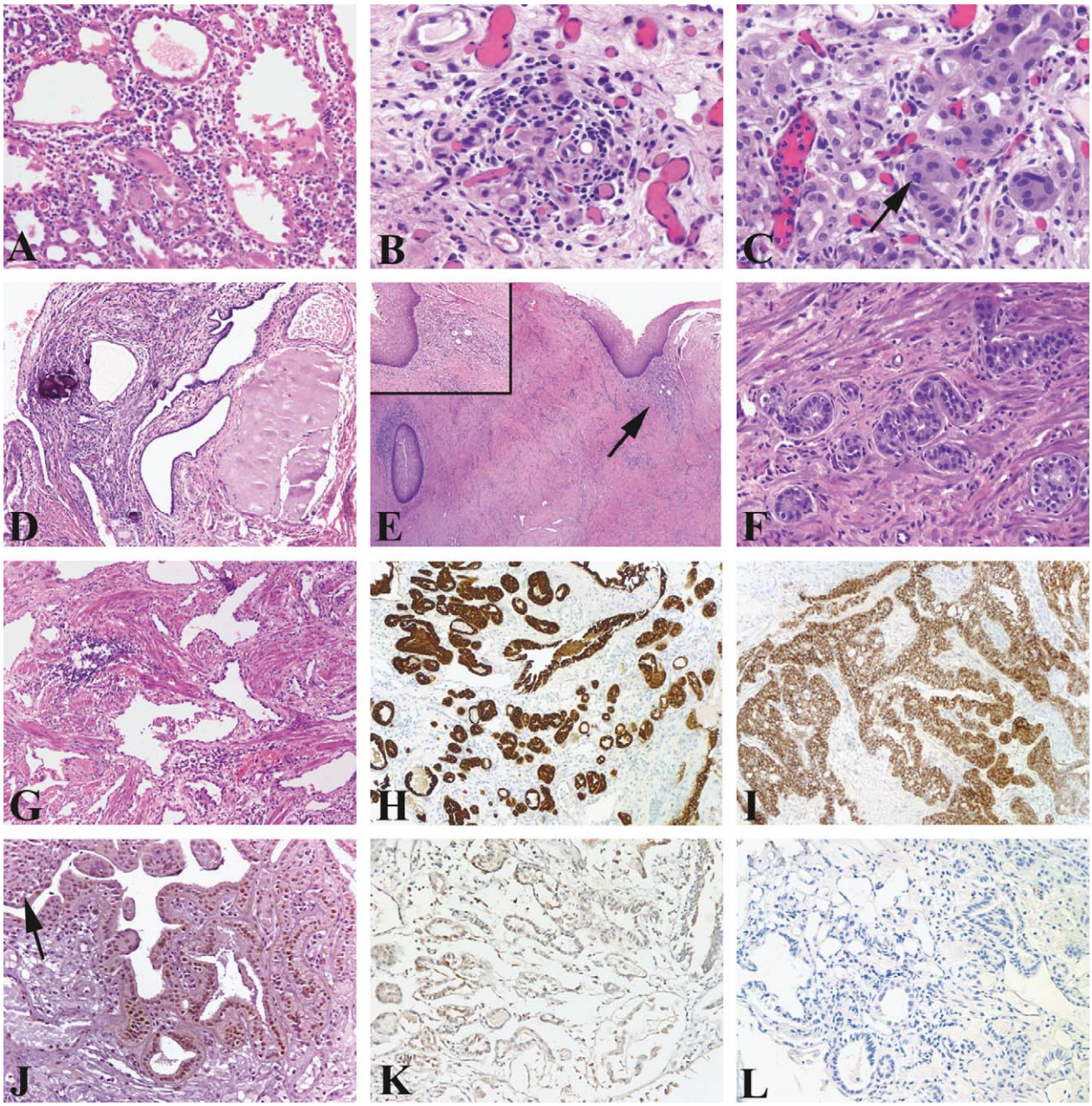

FIGURE 2. A, Hobnail cells line several tubules; B, Signet ring cell-like tubules with compressed solitary nuclei show intracytoplasmic vacuoles with basophilic secretion; C, Focal nuclear atypia consisting of prominent nucleoli and one mitotic figure (arrow) is present; D, Focal calcification and amyloidlike plaque are present in a inflammatory-rich stroma; E, Urethral diverticulum associated with NA (arrow). Note the superficial location and circumscription of the proliferation (inset); F, Small tubules infiltrating between muscle fibers simulate prostate carcinoma; G, Irregularly shaped cysts mimicking dilated vessels are diffusely present in between muscle fibers; H, Strong and diffuse CK7 staining; I, Papillary NA with extensive cytoplasmic AMACR positivity; J, Strong and distinct PAX2 nuclear positivity in NA. Note that the adjacent urothelium is negative for PAX2 (arrow); K, Negative nuclear p63 staining of NA; L, Negative cytoplasmic PSA staining.

tubules often have a compressed solitary nucleus with a single vacuole containing basophilic material, resembling signet ring cells (Figs. 1D, 2B). As a rule of thumb, there is minimal cytologic atypia with the nuclei being round to oval with small, inconspicuous nucleoli, and sparse mitotic activity (< 1 per 10 high power fields), but some cases may focally demonstrate some degree of atypia (Fig. 2C). In the largest series of 80 NAs reported in the literature, only 5% demonstrated a maximum of one mitosis per 20 high power fields.[7] When present, cytologic

atypia is often of the degenerative type, with a smudgy chromatin pattern.[42] However, the term "atypical NA" was coined by Cheng and colleagues[41] for NAs associated with prominent cytologic atypia encompassing nuclear enlargement, nuclear hyperchromasia, and enlarged nucleoli. Prominent nucleoli were observed at least focally in 16 NAs in the largest published series, and in 14 out of 26 NAs involving the prostatic urethra in another series.[7,42]

Associated Findings

The stroma associated with NA is focally edematous and contains variable amounts of inflammatory cells (Figs. 1B, G). At times, the inflammatory infiltrate may be so prominent as to obscure the underlying NA. Occasionally, dilated vessels, focal stromal calcifications, amyloidlike plaques, and multinucleated giant cells may be present (Fig. 2D), but a cellular, desmoplastic stromal response has not been reported.[42] Because of its association with inflammation and prior trauma, it is not unusual to see other benign reactive lesions in the vicinity of NA, including cystitis glandularis or cystica, polypoid cystitis or squamous metaplasia.[6] In the largest series of 80 NAs, slightly more than one-quarter of the cases involving the urethra arose in association with a urethral diverticulum (Fig. 2E).[7] Of note, the tubules of NA may be intermixed with muscle fibers of the muscularis mucosae in the bladder, ureter, or more often, with the muscle fibers present in the wall of the prostatic urethra in transurethral resection specimens (Figs. 2F, G).[7,8,42]

Immunohistochemistry and Other Ancillary Studies

The immunohistochemical profile of NA is characterized by diffuse positivity for wide spectrum keratins, CK7 (Fig. 2H) and EMA.[29,31,42–44] Expression of various lectins that bind to renal tubular epithelium, such as peanut agglutinin, *Lotus tetragonolobus* agglutinin and *Sophora japonica* agglutinin has been reported.[27,45] It is important to be aware that AMACR, a mitochondrial enzyme normally present in distal renal tubular epithelium and expressed in prostatic adenocarcinoma, but absent or minimally expressed in benign prostatic glands and urothelium, is also positive in NA (Fig. 2I).[30,31,34] As discussed earlier, NA is positive for PAX2 (Fig. 2J) and CA-125, variably positive for CD10, RCC antibody, and CK20, and negative for uroplakin.[27,29,38] Variable staining for both monoclonal and polyclonal carcinoembryonic antigen, CA19-9, and S-100 has also been reported.[43] NA is typically negative for p53 and few or no cells express Ki-67 (MIB-1).[22,41,43]

Ploidy analyses have shown these lesions to be diploid,[14,22,46,47] whereas cytogenetic studies have shown that NA cells are characterized by monosomy 9.[22,41]

Differential Diagnosis

The salient features of entities that are most frequently entertained in the differential diagnosis of NA are summarized in Table 1.

Clear Cell Carcinoma

This is probably the most common and difficult problem in the differential diagnosis of NA, particularly in limited biopsy specimens. Unlike NA which has a male predominance, clear cell carcinoma (CCC) is mostly seen in older women without a previous history of trauma.[6] Patients with these tumors frequently present with hematuria or other clinical symptoms, and the finding of a visible bladder mass.[43,48,49] On microscopic examination, the histologic patterns of CCC (tubular, tubulocystic, papillary, and solid) overlap with those seen in NA, although prominent solid growth is more common in CCC. The papillae of CCC are often complex and contain extensively hyalinized fibrovascular cores similar to CCC in the female genital tract. CCC and NA both contain hobnail cells, and NA may rarely contain significant numbers of cells with appreciable clear cytoplasm. However, CCC demonstrates a far greater degree of cytologic atypia and mitotic activity than NA, in which atypia is at the most mild or degenerative in nature and mitotic figures are rare to absent. Although CCC may have a subtle appearance focally, a diagnosis of NA should be made with caution if any degree of cytologic atypia or mitotic activity is present, particularly in the absence of a history of genitourinary surgery or trauma.[43,48,49] Furthermore, CCC frequently shows areas of hemorrhage and necrosis with deep infiltration of the bladder wall and may be associated with conventional urothelial carcinoma or endometriosis.[48]

A particular clinical scenario that merits further discussion is the observation that NA and CCC each have a propensity to arise within urethral diverticula.[3,6,40,48] In this setting, patients have been reported to present with vaginal complaints of a mass or lump in addition to urinary symptoms, thereby also raising the possibility of vaginal CCC of the Müllerian type.[40] It is helpful to keep in mind that NA involving a urethral diverticulum typically occupies a relatively superficial portion of the diverticular wall with a well-demarcated margin (Fig. 2E) in contrast to the irregular, infiltrative interface of CCC with the surrounding stroma.[40] Additionally, the absence of a diffuse growth of clear cells, significant nuclear atypia and mitotic activity, as discussed above, supports a diagnosis of NA.

Immunohistochemical stains are usually not helpful in distinguishing NA from CCC, as both are positive for low-molecular weight cytokeratins, CK7, CK20, monoclonal and polyclonal carcinoembryonic antigen, and CA-125, and negative for estrogen and progesterone receptors, prostate-specific antigen (PSA), and prostate-specific alkaline phosphatase (PSAP).[38,41,43,48] In one study comparing 13 NAs and 5 CCCs, all CCCs showed strong nuclear staining for p53 and high Ki-67 positivity, in contrast to the absence of p53 staining and low Ki-67 positivity seen in NAs.[43]

Although it has been postulated by some investigators that NA may be a precursor lesion of CCC,[50] this theory has never been proven conclusively, even by the use of molecular analysis.[51]

TABLE 1. NA: Differential Diagnosis

Malignant Mimicker	Confounding Features	Features Enabling Diagnosis of Carcinoma		
		Clinical	Histologic	IHC
CCC	• Tubules and cysts • Papillae • Hobnail cells • Clear cells	• Older females • No history of prior GU surgery or trauma • Visible bladder mass • Hematuria	• Prominent solid growth • Complex hyalinized papillae • Large numbers of clear cells • Significant cytologic atypia • Any mitotic activity • Bladder wall invasion • Necrosis	p53 + *, ↑ Ki-67 staining*
Nested/microcystic variants of urothelial carcinoma	• Small tubules • Solid nests • Microcysts	Not helpful	• Closely packed and irregularly shaped tubules and cysts • Two or more cell layers • Transitional morphology • Cytologic atypia, at least focal • Invasion of muscularis propria	P63 + *, ↑ Ki-67 staining*
Prostatic adenocarcinoma	• Small tubules • Solid nests and cords • Signet ring cell-like tubules • Blue mucinous secretions • Prominent nucleoli • Pseudoinfiltrative growth	Not helpful	• Absence of other distinctive NA patterns • Diffuse nucleolar prominence • Adjacent HG-PIN • Holmes crystals • Infiltration between normal prostatic glands • Lack of inflammatory infiltrate	PAX2 − CK7 − or focally + EMA − *, S-100 − *, CA19-9 − * PSA + /PSAP +, diffuse

↑Increased.
*Data based on a small number of cases.
GU indicates genitourinary tract; HG-PIN, high-grade prostatic intraepithelial neoplasia; IHC, immunohistochemistry.

Urothelial Carcinoma

Although the gross appearance of some sizable NAs may resemble that of papillary urothelial carcinoma by cystoscopy,[52] this distinction is usually not difficult to make under the microscope because the papillae of NA are not lined by multilayered urothelial cells but rather by a single layer of cells. However, the diagnosis of urothelial (transitional cell) carcinoma with prominent nested, microcystic or tubular growth patterns may be entertained in certain cases of NA due to overlapping morphologic features, especially in small samples.[53,54]

The nested variant of urothelial carcinoma is rare and characterized by confluent small nests or abortive tubules of urothelial cells present in the lamina propria and often infiltrating the muscularis propria of the bladder or ureter.[53,55] The nests and small tubules have a deceptively benign appearance, and may resemble the small tubules or solid nests seen in NA.[53] Cystic dilation of tubules may be present, resulting in a microcystic appearance that further mimics the appearance of NA.[54] Despite its bland appearance, the clinical course of the nested variant of urothelial carcinoma is typically aggressive, underscoring the importance of distinguishing it from a benign proliferation such as NA.[55,56]

Helpful features in this distinction include the presence of more than one cell layer lining the tubules of these unusual variants of urothelial carcinoma, appreciable cytologic atypia with prominent nucleoli seen at least focally in these neoplasms, and invasion of the muscularis propria.[7,53,55,57] The tubules in urothelial carcinoma are typically closely packed, the cells retain a transitional morphology, and frequently there is an associated stromal response. These variants of urothelial carcinoma may be associated with overlying flat urothelial carcinoma in situ; however, the absence of this feature should not be relied upon exclusively in ruling out a malignancy.[55] Importantly, the finding of an indolent epithelial proliferation in the muscularis propria of the bladder should always raise a very high suspicion for malignancy as NA is a benign lesion that does not invade the muscularis propria.[7] Furthermore, most NAs show a variety of distinctive architectural patterns in addition to

the solid and tubular components that facilitates its diagnosis. Finally, the finding of appreciable basement membrane surrounding the tubules and nests in some NAs, when present, may assist in making the diagnosis of NA.[7]

Immunohistochemically, the nested variant of urothelial carcinoma shares with conventional high-risk urothelial carcinoma the finding of a high proliferation index (> 15%) as assessed by Ki-67 staining that contrast with the near absence of Ki-67 expression in NA.[41,43,55] Although only very few cases have been studied, the nested variant of urothelial carcinoma shows nuclear positivity for p63 similar to conventional urothelial carcinoma, which is absent in NA.[31,34,58] PAX2 may also be helpful in this differential diagnosis. Tong et al[29] reported that 39 of 39 NAs were positive for this antibody in contrast to 0 of 47 invasive urothelial carcinomas tested; however, the study did not include any cases of the nested or microcystic variants of urothelial carcinoma. It should be noted that p53 immunoreactivity is not frequently seen in the nested variant of urothelial carcinoma and cannot be used in this differential diagnosis.[55,59]

Prostatic Adenocarcinoma

This challenging differential diagnosis typically arises in 2 settings. One is in transurethral resection specimens when NA involves the prostatic urethra, where it may demonstrate a pseudoinfiltrative growth pattern, with small tubules intercalating between muscle fibers as has been highlighted in the literature (Figs. 2F, G).[42,44,60,61] For example, Malpica and colleagues[44] reported that all 8 of their cases of NA involving the prostatic urethra showed extension into the fibromuscular stroma of the gland, raising the differential diagnosis of a benign or malignant small acinar proliferation. In Allan and Epstein[42] large series of 26 cases of NA involving the prostatic urethra, 20 cases (77%) demonstrated extension into muscle. Notably, in 15 of these 20 cases (75%), the lesion was identified underlying the urothelium, an unusual location for prostate cancer.[42] The second scenario involves prostate needle biopsies where the tiny tubules or solid architecture of NA may mimic a Gleason pattern 4 or 5 adenocarcinoma, especially when the cells show cords, nuclei with visible nucleoli, or luminal basophilic mucinous secretions, features present in 46%, 47%, and 32%, respectively, of 26 cases of NA involving the prostatic urethra reported by Allan and Epstein.[42] Another appearance that may imitate a single-cell pattern of prostatic adenocarcinoma arises when particularly tiny tubules of NA are lined by a single compressed peripheral nucleus resulting in an appearance reminiscent of signet ring cells, a feature present in 3 of 26 cases (12%) in Allan and Epstein series.[42] In such cases, it is important to keep in mind the possibility of NA before rendering a diagnosis of prostate cancer.

A histologic feature more often seen in transurethral resections that would support a diagnosis of NA over prostatic adenocarcinoma is the presence of other distinctive patterns of NA, particularly the papillary/polypoid growth pattern and vascular and thyroid folliclelike structures, findings that are not characteristic of prostate cancer. In needle biopsies, the finding of a very circumscribed tubular proliferation would favor NA, in contrast to the infiltrative nature of the glands in prostate carcinoma. The absence of cytologic atypia that if present is frequently of a degenerative type without prominent nucleoli and the finding of associated acute or chronic inflammation and edematous stroma would also favor the diagnosis of NA in either specimen type.

In these cases, it is also important to be aware that NA and prostatic adenocarcinoma demonstrate overlapping immunohistochemical profiles. Although CK7 is reported to be positive in NA and usually negative in prostate cancer,[29,42] a large series of 225 prostatic adenocarcinomas with intermediate or high Gleason scores showed that CK7 was focally positive in nearly half of the cases, with higher Gleason score carcinomas showing a greater percentage of CK7-positive cells.[62] As mentioned previously, AMACR (P504S), a very sensitive marker of high-grade prostatic intraepithelial neoplasia and prostatic adenocarcinoma, is also positive in NA, including those cases involving the prostatic urethra (Fig. 2I).[30,34] In fact, it seems that urethral NAs express AMACR more often than NAs involving the urinary bladder.[34] As the tubules of NAs lack basal cells, they are negative for p63 and may not express 34βE12, thereby mimicking the staining pattern of prostatic adenocarcinoma (Fig. 2K).[30,31,34,42] Recently, Allan and Epstein[42] reported focal weak cytoplasmic positivity for PSA and PSAP in 9% and 30% of 11 cases of NA, respectively. However, PSA and PSAP are still helpful markers in most instances, as well to moderately differentiated prostatic adenocarcinoma typically shows diffuse and strong positivity for these markers, in contrast to the negativity or weak and focal positivity seen in some NAs (Fig. 2L).[42] Xiao et al[31] recently studied EMA expression in NA and prostate carcinoma, and found this marker to be positive in all 9 cases of NA, whereas all 9 cases of prostate carcinoma were negative for this antibody. Finally, in a series of 13 NAs, 11 showed at least weak positivity for S-100 protein and strong staining with CA19-9,[43] whereas prostate cancer has not been shown to stain with S-100 protein and only rare cases have been reported to be positive for CA19-9.[63,64]

PAX2 has been identified as a potentially useful marker to distinguish NA from prostatic adenocarcinoma (Fig. 2J). In a very recent study, Tong and colleagues[29] reported absence of PAX2 expression in 100 prostate cancers and 100 benign prostatic tissue samples using high throughput tissue microarrays, in contrast to the uniformly positive nuclear staining seen in all 39 NAs. The authors point out that all patterns of NA showed strong and distinct nuclear staining, including small tubules with blue-tinged mucinous secretions, and that this staining was preserved in rare cases with nuclear atypia and nucleolar prominence, underscoring the promising utility of this antibody in this differential

diagnosis.[29] However, further studies are required to ensure reproducibility of these findings before PAX2 is used in routine clinical practice.

The overlapping staining profile of NA and prostatic adenocarcinoma demonstrates the value of using a panel of antibodies in differentiating these lesions by immunohistochemistry and also highlights the importance of careful histologic examination.

Signet Ring Cell Carcinoma

Signet ring cell carcinoma arising primarily in the bladder or metastatic to the bladder very rarely may enter into the differential diagnosis, especially when the predominant pattern of NA is that of very small tubules containing basophilic secretions and compressed eccentric nuclei. However, the signet ring cell-like growth pattern of NA is almost always accompanied by larger tubules, cysts, and papillae, and shows neither diffuse involvement of the bladder wall nor the cytologic atypia seen in signet ring cell carcinoma.

CONCLUSIONS

In summary, NA should be a diagnostic consideration in the clinical setting of prior trauma or long-standing inflammation, particularly when a variety of architectural patterns are identified in the lesion being evaluated. As the immunoprofile of NA overlaps considerably with malignant entities in the differential diagnosis, clinicopathologic correlation, and careful histologic examination are paramount in avoiding a misdiagnosis of carcinoma.

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