

THE DIFFICULT DIAGNOSIS IN THE URINARY BLADDER: A SELECTIVE CONSIDERATION, MULLERIAN AND MULLERIAN-LIKE CONDITIONS

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- Benign and malignant müllerian lesions
- Mullerian-like appearances in transitional-urothelial neoplasia
- Urachal lesions with müllerian-like features
- Secondary müllerian neoplasia.

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Not long after I accepted the invitation to speak on problematic bladder lesions, shortly after the US-CAP meeting last year, I realized that the comprehensive coverage of many aspects of non-neoplastic and neoplastic bladder disease at the Long Course last year made it difficult to come up with anything "fresh". That is even more so given that the supplement to Modern Pathology containing the short course proceedings will either have just appeared, or will be about to appear, by the time the spoken version of these words will be presented at the Boston meeting. I endeavored as one of course does for these occasions, to come up with something a little different and original and it struck me that given that I have interests in both gynecologic and urologic pathology a merging of these two with some comments on müllerian and müllerian-like lesions of the urinary bladder might be suitable. I think it is also timely inasmuch as there has been some focused interest in these lesions in recent years and the diversity of issues that may be encountered is quite remarkable. I will approach the topic by considering the following five categories: (1). Benign müllerian lesions; (2). Malignant müllerian lesions; (3). Mullerian-like appearances in transitional-urothelial neoplasia (4). Urachal lesions with müllerian-like features and (5). Secondary müllerian neoplasia.

Benign Müllerian Lesions

The bladder is involved in approximately one percent of women with endometriosis and is the commonest site of urinary tract involvement by this disease (1). Up to fifty percent of the patients have a history of a pelvic operation and in approximately 12 percent of them evidence of extra-vesical endometriosis is lacking. Vesical endometriosis is commonest in the fourth decade with the average age 35 years. The microscopic features of endometriosis are so distinctive that confusion with a neoplasm should not be an issue. This is in marked contrast to the other mullerian glandular lesions which are now considered. Potentially any of the common to rare

features of endometriosis seen elsewhere may be encountered in the bladder but are rarely reported.

Glandular lesions characterized by a prominent component of endocervical-type epithelium may involve the wall of the urinary bladder in women of reproductive age and have been designated “endocervicosis”(2). A mass that ranges up to 2.5 cm. is typically located in the posterior wall or posterior dome. Microscopic examination typically reveals extensive involvement of the involved bladder wall by irregularly disposed benign appearing or milding atypical endocervical-type glands some of which are cystically dilated. Occasionally one may find ciliated cells or a minor component of endometrioid glands and glands lined by non-specific cuboidal or flattened cells with eosinophilic cytoplasm. In some cases the glands are associated with fibrosis or edema in the adjacent stroma. Rarely there is some evidence of endometriotic stroma indicating a relationship of this lesion to endometriosis. This, and other features, such as an occasional association with a history of a cesarean section indicate that this is a unique müllerian lesion of the bladder and it is best considered the mucinous analogue of endometriosis. It is important because lack of awareness of it may lead to confusion with an adenocarcinoma, particularly one of urachal origin. Adenocarcinomas of the bladder, particularly of urachal origin, may have glands lined by tall mucin-rich epithelial cells and as these cancers and endocervicosis both occur at the dome one might think their distinction might be challenging. However, urachal adenocarcinomas broadly speaking fall in two groups, overtly infiltrating lesions with obvious malignant characteristics ruling out endocervicosis, or lower grade mucinous cystic lesions with differing gross characteristics. In some cases of benign müllerian lesions foci of endosalpingiosis are also present and when endometriosis and endocervicosis are present as well the designation “müllerianosis” has been suggested (3). Occasionally endosalpingiosis is seen in pure, or close to pure, form.

Malignant Müllerian Lesions

When we last explored the topic of clear cell carcinoma of the urinary bladder (4) we were able to collect together from our own material four cases of clear cell carcinoma morphologically typical of the usual müllerian form of this neoplasm (5) and almost certainly of müllerian origin because of an association in two cases with endometriosis and in two others with müllerian epithelium devoid of typical endometrial stroma but in two cases associated with elastosis, a subtle clue to a diagnosis of endometrial stroma in many cases. The literature on this topic is limited but it does appear that neoplastic transformation from endometriosis of the bladder usually is of clear cell type, something not surprising inasmuch as this carcinoma has the tightest association with endometriosis. There are no unique features to müllerian type clear cell carcinoma arising in the bladder to my knowledge. Potentially any form of müllerian neoplasia that may complicate endometriosis, as seen more commonly elsewhere, is a potential finding in the bladder and one could conjecture that it is perhaps surprising that there is not even more documentation of this in the literature. One wonders if some cases have not been correctly interpreted particularly when there is bulky disease with overgrowth of residual endometrial glands and stroma. At least one case of endometrioid carcinoma (6) and one case of müllerian adenosarcoma (7) are documented.

The differential diagnosis of the clear cell carcinomas is with glandular morphology of very similar type occurring on the background of transitional cell neoplasia as considered below. Obviously the association with benign müllerian elements is crucial. A similar comment pertains to distinction of endometrioid carcinoma from a tubuloglandular pattern with endometrioid-like characteristics as a variant pattern of transitional cell carcinoma with gland differentiation. Perhaps enigmatically it is the rarest of all these neoplasms complicating endometriosis of the bladder, the müllerian adenocarcinoma, which is so distinctive that the diagnosis could be made with confidence even in the absence of associated endometriosis.

MULLERIAN-LIKE APPEARANCES IN TRANSITIONAL (UROTHELIAL) CELL CARCINOMA

The commonest variants of the regular carcinoma of the bladder which I still prefer to refer to as transitional (although many who read this doubtless call them urothelial) are those showing squamous or glandular differentiation. It is obviously those exhibiting gland differentiation that are the focus of our interest here. Gland differentiation may be seen in papillary non-invasive lesions, intramucosal neoplastic proliferations that are not papillary, and of course frank non-papillary carcinoma either projecting into the lumen or invasive of the bladder wall. Different problems arise with each and the extent to which they mimic müllerian lesions varies. The papillary carcinomas, when they show gland differentiation which is uncommon, typically show rather punched out pretty glands without any particular müllerian-like morphology. The intramucosal abnormalities that may be associated with invasive carcinoma elsewhere or a classic in-situ lesion cause their own problems, such as in some instances distinction from true glandular neoplasia, but they rarely mimic a müllerian lesion. Frank carcinomas may potentially mimic any of three common forms of müllerian carcinoma: serous, endometrioid and clear cell. These are considered in turn.

The best known of these is the micropapillary (serous-like) variant of transitional cell (urothelial) carcinoma first described by Amin and colleagues in 1994 (8). I refer the reader to Dr. Amin's outstanding summary of this entity in his recently (or about to be) published short course essay (9). I cannot improve on it but will make a few brief summary remarks. As he notes, a variety of patterns may be observed. Slender delicate filiform papillae, uncommonly having a fibrovascular core, dominate surface foci. When cut in cross section the papillae may appear glomeruloid. In invasive foci the tumor cells are typically arranged as small nests very reminiscent of the so-called "tight knots" of familiar serous carcinoma of the genital tract. However, unlike serous carcinoma psammoma bodies are rare but described (10). In many of the invasive cases just as may be seen with serous carcinoma, nests of cells are associated with retraction artifact and appear to be sitting in spaces which may be misconstrued as vascular invasion. Despite this particular aspect being artifactual mimicry of vessel space invasion, true vessel space invasion is common. An argument has been made that micropapillary variant of transitional cell (urothelial) carcinoma is an adenocarcinoma; however, transitional cell (urothelial) derivation is supported by frequent concurrence and/or transition with more typical areas of transitional cell (urothelial) carcinoma. Further, immunohistochemistry

including CK7, CK20, uroplakin 3 and high molecular weight cytokeratin (HMCK) are further supportive of transitional cell origin.

The second form of müllerian carcinoma that may be mimicked is endometrioid carcinoma. Some transitional cell carcinomas have a tubuloglandular pattern indistinguishable from endometrioid carcinoma. Obviously as in countless areas of diagnostic pathology everything must be put in context with the site of occurrence of the process and the associated findings. In other words, any co-existent carcinoma of usual type or even history thereof drives the diagnosis very much towards primary of bladder carcinoma of transitional-urothelial type with gland differentiation. That goes for invasive and intramucosal cases of glandular neoplasia in the urinary bladder in my opinion. Of course if associated endometriosis was present one would very quickly move to a diagnosis of a very rare true endometrioid carcinoma primary in the bladder. Parenthetically, in the differential diagnosis, one must also include an extension of a prostatic carcinoma with ductal morphology into the urinary bladder. The homology of this pattern with müllerian lesions is best exemplified by the initial use of the term “endometrioid carcinoma” of the prostate for these tumors. The immunoprofile of endometrioid carcinoma extending from the gynecologic tract into the bladder is Estrogen receptor+, CK7+, CK20-, vimentin +, p63+/-, HMCK+/- and uroplakin 3-; the immunoprofile of transitional cell (urothelial) carcinoma is CK7+, CK20+, vimentin-, p63+/-, HMCK+/-, Estrogen receptor- and uroplakin 3+; and immunoprofile of prostatic adenocarcinoma including ductal pattern is PSA and PSAP+, CK7-, CK20-, vimentin -, p63-, HMCK- and uroplakin 3-.

The final form of müllerian carcinoma (other than I suppose transitional cell carcinoma itself!) that may be mimicked is clear cell carcinoma. Although there is still limited information overall on this topic, appreciable knowledge has accrued over the past quarter century. In 1985 Dr. Robert E. Scully and I reported three clear cell adenocarcinomas of the bladder and urethra and reviewed the literature as of that time. One of our cases was in the bladder and two in the urethra. Since that time urethral clear cell adenocarcinoma has become well-established as a distinct variant of adenocarcinoma of that structure and is not the domain of our interest here. In retrospect our one bladder case was likely of müllerian origin because many years later a tiny focus of atrophic endometriosis that had originally been overlooked was noted. In the discussion of the paper being referred to we considered the various possible origins of clear cell adenocarcinoma of the bladder, müllerian, mesonephric, and urothelial-transitional. That has of course been one theme of the subsequent limited literature (4, 12, 13). The focus of the paper of Gilcrease et al. (12) was on the purported relation of nephrogenic adenoma and clear cell adenocarcinoma, a relation I have never favored. It can, however, be a significant problem in differential diagnosis as has been discussed in that paper and elsewhere. Gilcrease et al. found that two of their four bladder tumors had small foci of transitional cell carcinoma and favored a variant of transitional cell carcinoma with gland differentiation as the explanation, quite logically, for those two cases. Subsequently Drew et al. (13) reported another series of cases exploring primarily histogenesis of this neoplasm.

When we reported a larger series of clear cell carcinomas in 2002 we were able to collect together 13 cases, 4 of which are noted above in the section on true müllerian clear cell carcinoma. The remaining 9 tumors were considered by us to be of definite or

probable transitional cell nature because of an association of some with unequivocal transitional cell neoplasia, or, by exclusion, a lack of evidence directing to a müllerian origin. We did not see striking differences in the morphology of the clear cell tumors that were definitely of müllerian type, compared to the others. At this time immunohistochemical differences are not clear cut. There is, however, only limited information on this topic (4, 12, 13). An additional cause of confusion with clear cell carcinoma is based on cell morphology rather than patterns. Occasional transitional cell carcinomas have cells with striking clear cytoplasm (14) and that may reflexively make the pathologist think of a true clear cell carcinoma. The point should be made that the designation "clear cell carcinoma" both here and elsewhere is applied to a tumor with distinctive patterns rather than one that by definition has clear cells. The latter are certainly usually present but some clear cell carcinomas, enigmatically, do not even have clear cells and various other tumors, certainly transitional cell carcinoma, can have clear cells. In the latter tumors the overall patterns are generally typical of conventional transitional cell neoplasia.

Urachal Lesions with Müllerian-like Features

I include this category because the majority of urachal neoplasms have a mucinous nature and accordingly may resemble mucinous tumors as seen in the genital tract which, albeit many might actually be of teratomatous origin, are, pragmatically, for the most part considered in the müllerian family of neoplasms. Dr. Amin and colleagues are currently finishing up a study of 45 glandular neoplasms of the urachus which is focusing on their wide morphologic spectrum and similarity in many cases to mucinous cystic tumors of the ovary. 24 of the cases in his series resembled primary mucinous cystic neoplasms as seen more commonly in the ovary ranging from mucinous cystadenoma, to cystic tumors of borderline malignancy with or without intraepithelial carcinoma, and to cystadenocarcinomas. The remaining 21 cases in his total series of 45 were invasive non-cystic tumors ranging from pure mucinous to typical enteric to mixed in morphology. The immunoprofile of urachal carcinomas with enteric differentiation is similar to metastatic colonic carcinomas to the urinary bladder (CK7-, CK20+, CDX2+); nuclear beta catenin staining in metastatic colon cancers may be the only helpful differential stain, although it positive in only a small subset of cases. Dr. Amin and colleagues point out that the importance of subclassifying these tumors because of the great variation in behavior from benign to almost certainly benign, to in some cases of course having an ominous prognosis.

Secondary Müllerian Neoplasia

Obviously the consideration would be incomplete without noting that primary müllerian tumors of the female genital system may secondarily involve the urinary bladder. Although spread to the bladder in general has not received the attention that spread to certain other organs, the ovary perhaps being the most noteworthy, has received, a variety of problems in differential diagnosis may be encountered and representative examples, some of which have tricked this writer, will be presented at the meeting. One of these has been reported (15). Good reviews of the general topic of

secondary involvement of the urinary bladder are few, but some thankfully exist (16-19). In one large series (17) spread of gynecologic cancers were third (after colo-rectal and prostate primaries) most common but only in the category of ovarian primaries did antemortem cases exceed postmortem cases in number. In this as in so many other areas of diagnostic pathology the pathologist will do themselves a disservice if they do not pay appropriate attention to the clinical findings and even in the absence of any helpful clinical findings unusual morphologic features that could conceivably be related to a tumor spreading to the bladder from elsewhere, hopefully will be noted. In certain situations immunohistochemistry, of course, may be helpful as in the situation of secondary involvement from endocervical adenocarcinoma which may be supported by immunohistochemical staining for p16, and even HPV analysis, if indicated, as has been recently shown to be helpful in the more common issue of endocervical carcinoma spreading to the ovary.

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