THE MORPHOLOGIC OVERLAP BETWEEN BENIGN AND MALIGNANT IN THE URINARY BLADDER: DIAGNOSTIC DILEMMAS

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This lecture will include a discussion of recently appreciated or re-emphasized aspects of bladder carcinoma and the overlap in the morphology of many of them with pseudoneoplastic lesions. Time will not permit in the lecture presentation of everything in this handout which is provided to aid in further study and literature review. A few things not necessarily part of the lecture subject matter are also considered.

PAPILLARY TRANSITIONAL CELL CARCINOMA

The recent flurry of activity concerning nomenclature in this area (1) dates largely from the paper of Jordan and colleagues in 1987 (2) in which they advocated use of the designation "papilloma" for lesion which in the preceding two decades had been diagnosed, at least by most, as grade 1 papillary urothelial carcinoma. Most authoritative publications in the previous two decades including the 1975 Armed Forces Institute of Pathology fascicle and the 1973 W.H.O. Classification (3,4) as well as other experienced writers in this area had a restrictive definition of papilloma as a papillary lesion covered by normal or nearly normal urothelium consisting of no more than six or seven layers of cells and generally lacking mitotic figures. All other papillary urothelial neoplasms, the vast majority, were considered carcinomas. In 1949 Dukes (7) had proposed a classification of bladder tumors in which "to preserve the time honored distinction between benign and malignant" he had suggested that papillary neoplasms in which the epithelial elements closely resemble normal and are non-invasive be diagnosed as "papilloma" and those in which there is "unmistakable evidence of malignancy shown by invasiveness or by irregularity in
the size and shape of neoplastic cells or atypical nuclear structures "be diagnosed as carcinoma". In 1968, Mostofi (8) recommended that the diagnosis of papilloma be restricted to non-invasive tumors with epithelium indistinguishable from normal and that any cytologic anaplasia that was not easily considered due to reactive change or regeneration be taken as evidence of malignancy. In 1965, Bergkvist (9) had proposed a five-grade system for classifying papillary urothelial neoplasms and considered tumors with cytologically normal urothelium of normal thickness grade 0. They thought that the line between a benign and malignant course fell between lesions that were grade 1 and 2 in their five-grade system. In contrast to the foregoing but in accordance with the approach of Jordan et al, the 1989 issue of Ackerman's Surgical Pathology recommended that grade 1 lesions in the WHO scheme not be considered carcinoma (10).

On this background, and perhaps influenced by the well-known usage in gynecologic pathology of the term "tumor of borderline malignancy (low malignant potential)", the Consensus Committee recommended that WHO grade 1 papillary carcinomas be considered papillary neoplasms of low malignant potential (1). I personally was not a strong advocate of this change although I have no serious issue with it. Some reluctance to the change was due to my concern that changes in classification have their own inherent problems, tending to lead to confusion, at least for a period of time. Also, at my own institution, I had not encountered what others apparently have, namely concern expressed by clinicians, apparently reflecting those of patients, with regard to the patients being given a diagnosis of "carcinoma" for such a generally innocuous lesion, and even an impact upon insurability in some cases. Reluctance was also caused by my own feeling that if "true papillomas" are excluded from the consideration, there is no clear dividing line between grade 1 and grade 2 or grade 2 and 3 papillary carcinomas, using the WHO approach of 1973, and knowledge that what on one month I might call grade 1 (low malignant potential of the new nomenclature) the next month I might call grade 2 of the old system (low
grade carcinoma of the new system), due to the inherent subjectivity in this area. Those reservations not withstanding, I think the current terminology is a reasonable compromise between calling lesion that overall can be handled conservatively assuming careful follow, carcinomas on the one hand and papillomas on the other. I was pleased that the consensus group acknowledged the existence of papillomas as a distinct benign lesion, albeit a rare one.

These tumors are characterized by papillae that are usually tall and often branch. The papillae are usually covered by hyperplastic urothelium. The cells covering the papillae vary from almost normal in appearance to highly atypical. They typically have moderate amounts of pale cytoplasm but rarely the cytoplasm is more abundant and densely eosinophilic, or, somewhat more often, is strikingly clear. Papillary carcinomas are graded using cytologic criteria, something with major prognostic significance (11). Grade 1 lesions show slight cytologic atypia and rare mitotic figures. Grade 2 lesions show areas of moderate cytologic atypia, and usually readily found mitotic figures. Grade 3 lesions show at least focal high-grade nuclear atypia and mitotic figures are typically frequent. Recently, "micropapillary transitional cell carcinomas" have been described in which numerous small cellular papillae are present, producing an appearance similar to that of ovarian serous carcinoma (12). Glandular and squamous differentiation are uncommon in non-invasive papillary carcinoma but are seen in about two percent of the cases. The cores of the papillae are usually slender and moderately vascular, composed of connective tissue with occasional inflammatory cells. They occasionally are edematous causing the lesion to appear polypoid rather than papillary. In some cases, the stroma or blood vessel walls within it are extensively hyalinized.

The features of the invasive tumor derived from papillary carcinoma are similar to those seen in non-papillary carcinoma described below. Because invasion is very rare in case of Grade 1 papillary carcinoma, it should not be diagnosed unless it is unequivocal. Assessment of
invasion in cases of papillary carcinoma may be difficult. They may be associated with non-invasive carcinoma in von Brunn's nests mimicking invasion. The well-circumscribed contour of these round to oval structures facilitates their distinction from true invasion. Occasionally, the bases of the papillae of papillary carcinoma are bulbous and protrude with a pushing border into the underlying stroma, occasionally approaching the muscularis propria. This is not generally considered to be invasion although it may be analogous to the pushing invasion that occurs in cases of verrucous carcinoma. A recent study described the features of 18 cases of transitional cell carcinoma with an endophytic growth pattern, with one exception, the lesions being from the urinary bladder. The broad pushing bulbous invaginations into the lamina propria led to the descriptive usage of the term "broad-front pattern" for one group of cases. In other cases there appeared to be true invasion but difficulty was caused by the relatively orderly endophytic growth of interanastomosing cords and columns often resulting in a striking resemblance to inverted papilloma but with focal deviations from the typical orderly pattern of that benign neoplasm and greater atypicality, in most instances, from that allowable for the benign lesion (12A). When invasion occurs in cases of papillary transitional cell carcinoma, it usually is seen at the bases of the papillae but rarely invasion of the cores of the papillae is seen.

**Differential Diagnosis**

Cases occur in which it is debatable whether the diagnosis of urothelial hyperplasia or early papillary carcinoma is most appropriate (12B). These are usually seen in patients with a history of papillary carcinoma and this problem does not generally cause clinical difficulty in these patients who remain under observation. It is important to see unequivocal fibrovascular papillary cores before diagnosing papillary carcinoma. Sarma's elegant paper (12c) on the histogenesis of papillary carcinoma is worthy of review.

Papillary carcinoma must be distinguished from papillary or polypoid cystitis (13) a
reactive lesion in which papillae are covered by normal urothelium and often have a prominent layer of umbrella cells, a feature which is uncommon in papillary carcinoma. The frequent branching of small papillae from large papillae seen in papillary carcinoma is not a feature of either papillary or polypoid cystitis. The broad fronds of polypoid cystitis are much thicker than the thin papillae of most papillary carcinomas and the stromal cores of papillary and polypoid cystitis generally are more intensely inflamed and vascular than are those of carcinomas. The clinical setting such as the presence of an indwelling catheter or a vesical fistula, both of which may be associated with papillary or polypoid cystitis, may be helpful.

A controversial area concerns the existence, or otherwise, of papillomas of the bladder which can be reliably distinguished from low-grade papillary transitional cell carcinomas. I believe a distinction can be made (4), a small subset of papillary lesions having an appearance different from that of the typical papillary carcinoma. These lesions, which sometimes occur in younger patients than the usual papillary carcinoma, do not exhibit such prominent tall branching papillae as seen in papillary carcinoma, are covered by urothelium that is not hyperplastic, is not atypical, does not exhibit mitotic activity, and is generally covered by a relatively complete layer of umbrella cells. Most tumors reported as papillomas in the older literature (9) have more recently been considered grade I papillary carcinomas.

TRANSITIONAL CELL CARCINOMA (NON-PAPILLARY)

Transitional Cell Carcinoma-in-situ

A spectrum of atypical lesions occurs in non-papillary bladder urothelium, ranging from mild cytologic changes to cells with obviously malignant cytologic features characterizing transitional cell carcinoma-in-situ (1). Mild degrees of atypicality in which the cells have the cytologic features of grade 1 papillary transitional cell carcinoma are considered mild dysplasia, cells with the features of a grade 2 lesion are called moderate dysplasia and lesions with the
cytologic features of a grade 3 carcinoma are called severe dysplasia or transitional cell carcinoma in situ (1,14-20). In the latter cases the abnormal cells are usually, but not always, present throughout all layers and may show a marked loss of polarity. Mitotic figures are easily found in severe dysplasia and carcinoma in situ. As is the case with premalignant epithelial lesions elsewhere in the body, considerable subjectivity exists in the interpretation of these lesions (21), although this is less so for high-grade lesions. From the viewpoint of patient care the most important concern in this area is making sure that high-grade lesions falling in the category of severe dysplasia or transitional cell carcinoma-in-situ are not overlooked.

On gross inspection, bladder mucosa involved by transitional cell carcinoma-in-situ usually is erythematous, and may be slightly granular, or edematous due to the frequent associated edema of the lamina propria. Microscopically, the abnormal urothelium may vary in thickness from a single layer of cells, to normal, to hyperplastic. Loss of intercellular cohesion and adherence to the basement membrane with resultant urothelial denudation frequently occur. This frequently results in only a single layer of cells being present and in some cases considerable areas of the mucosa are denuded completely. When examining biopsies with denudation, one must be careful not to overlook even a small number of highly atypical cells. Even when only one layer of cells is present, the diagnosis of carcinoma-in-situ may be made on the basis of severe cytologic atypia. In the past, patients with carcinoma-in-situ and marked urothelial denudation have sometimes been followed for long periods of time with the diagnosis of nonspecific or interstitial cystitis (14). Deeper sections are often indicated in these cases, as is close correlation with the findings of urine cytology as malignant cells are often present in cytologic specimens from cases of carcinoma-in-situ. In many cases, a low-power clue to the diagnosis of transitional cell carcinoma-in-situ is a very edematous, inflamed, hypervascular lamina propria.

Invasive Transitional Cell Carcinoma
Several specific variants (22) will be described after the common forms of invasive transitional cell carcinoma are briefly reviewed. Most frequently there are nests, small clusters and single neoplastic cells irregularly dispersed in the lamina propria, and muscularis propria, if invasion of the latter is present. The tumor sometimes grows in a more diffuse pattern but even in these cases focal nests and clusters are generally present; rarely, the tumor is uniformly diffuse. Occasional carcinomas are associated with a pronounced chronic inflammatory cell infiltrate, which sometimes partially obscures the underlying tumor cells. Invasion usually occurs in the form of irregular infiltration but sometimes the nests of invasive tumors are well circumscribed.

The neoplastic cells in these patterns of transitional cell carcinoma are usually of moderate size and have modest amounts of pale to slightly eosinophilic cytoplasm. In some tumors the cytoplasm is more abundant and may be clear or strikingly eosinophilic. The presence of clear cells (22A) should not lead to a diagnosis of the very rare clear cell carcinoma unless the classic patterns of that tumor are present.

The transitional character of the cells of transitional cell carcinoma, including the presence of focal longitudinal nuclear grooves, is often appreciable, at least focally, in low grade tumors and in some higher grade lesions. At least moderate, and frequently marked, cytologic atypia is present but occasional tumors are composed of cells with only mild cytologic atypia. Bizarre, hyperchromatic nuclei may be seen, particularly in patients whose tumors have been treated with radiation therapy. The mitotic rate is variable and related to the grade of the tumor. Lymphatic or vascular invasion is seen to varying degrees, occasionally being striking. In some tumors nests of cells lie in spaces that are artifactual and this should not be misdiagnosed as vascular invasion. These spaces, which have been described as a particular feature of "micropapillary" tumors (12), are not lined by endothelial cells.
Occasional transitional cell carcinomas have very small foci of early invasion, which it is possible to overlook. These have been referred to as “microinvasive” transitional cell carcinomas (23). When invasion of the lamina propria is present the pathologist then must assess whether there is invasion of the muscularis propria and if there is not, whether the muscularis propria is present in submitted tissue and if it is not, note this. Evaluation of muscularis propria invasion is difficult due to the artifact already referred to in some cases and fibrosis and inflammatory changes may sometimes make the interpretation even more difficult. It is best to be conservative when assessing muscularis propria invasion and require the presence of unequivocal involvement of well organized muscle bundles. This to prevent the misdiagnosis of invasion of the muscularis mucosae (24-27) as involvement of the muscularis propria. As the term muscle invasion is not in and of itself discriminatory between involvement of the muscularis mucosae and muscularis propria, it is probably better not just to say “muscle invasion” but rather "invasion of the muscularis propria" so that the clinician knows the pathologist is specifically referring to involvement of that muscle. The muscle of the latter tends to occur in smaller less well organized bundles than that of the muscularis propria.

Approximately 10 percent of transitional cell carcinomas contain foci of glandular or squamous differentiation (1). The glands are variable in appearance, occasionally being small and tubular, occasionally causing confusion with the benign nephrogenic adenoma (see below). Glandular differentiation is usually found in moderate to high grade, often deeply invasive tumors but it is occasionally seen in well differentiated, superficially invasive tumors. Since glandular and squamous differentiation have no clear-cut prognostic significance, by convention the primary diagnosis remains transitional cell carcinoma but squamous and/or glandular differentiation should be recorded. Rarely glands undergo cystic dilatation something that can lead to misdiagnosis as a benign process, usually cystitis cystica, on curettage material (28). This
problem is discussed further later.

Some high-grade transitional cell carcinomas contain areas composed of atypical spindle cells (29) meriting the descriptive designation "sarcomatoid carcinoma" (30). The neoplastic cells in these cases may grow in a variety of patterns. Most commonly fascicles impart a resemblance to leiomyosarcoma or there is a storiform pattern reminiscent of that seen in malignant fibrous histiocytoma (31). A resemblance to rhabdomyosarcoma results when pleomorphic, round or elongated cells with abundant eosinophilic cytoplasm are present. Usually there is moderate to severe nuclear atypia and mitotic figures are typically frequent. We reported a series of 25 sarcomatoid carcinomas that had myxoid or sclerosing areas occasionally causing diagnostic difficulty in their distinction from inflammatory pseudotumor (32A). The sarcomatoid areas usually merge with either invasive or in-situ transitional cell carcinoma (30,32). These carcinomas, on average, occur in an older, male, population than does the inflammatory pseudotumor. While generous sampling usually reveals the urothelial nature of these tumors, occasionally immunohistochemistry is helpful since the spindle cells may stain for cytokeratin and epithelial membrane antigen but are negative for mesenchymal markers (33).

Rare bladder carcinomas have areas resembling choriocarcinoma (34,35). Immunohistochemical studies have shown human chorionic gonadotropin (hCG) and its beta subunit in the cells of morphologically typical transitional cell carcinomas, invasive or in situ, in approximately 30% of the cases (36). The discovery that hCG production is common in high grade transitional cell carcinomas and well documented cases in which choriocarcinoma has evolved from or coexisted with high grade urothelial carcinoma suggests that most vesical tumors with trophoblastic elements are transitional cell carcinomas in which trophoblastic differentiation has occurred, rather than choriocarcinomas of germ cell origin.

The stroma in transitional cell carcinomas may exhibit some degree of desmoplasia but an
extremely desmoplastic reaction is unusual. The stroma occasionally contains significant numbers of atypical, but benign, mesenchymal cells, so-called transitional cell carcinomas with pseudosarcomatous stroma (37,38). The stroma of transitional cell carcinoma may also undergo osseous or cartilaginous metaplasia (39), and rarely contains osteoclast-type giant cells (40).

**Differential Diagnosis Emphasizing Problem of Deceptively Benign Patterns**

The usual invasive transitional cell carcinoma generally does not pose much diagnostic difficulty with regard to its distinction from a benign lesion but recent interest has forced attention on the small group of cases in which this is a problem. I have found it helpful in understanding this phenomenon to realize that what is seen in neoplasia recapitulates what is seen in various benign lesions and a listing of the features seen in carcinomas and the resultant benign lesion that they may mimic is presented in Table 2. The most common of the deceptively benign patterns is the nested pattern (41, 42) that suggests von Brunn's nests. It is helpful that in these so-called "nested carcinomas" the nests usually grow in more closely packed aggregates and are more irregular in size and shape than von Brunn's nests which are invariably round or oval and generally have an orderly distribution (43) which contrasts with the disorderly architecture of most carcinomas. This disorder of architecture is a crucial feature in recognizing all these deceptively benign patterns of neoplasia.

As we have just considered the problems posed by nested carcinomas of the bladder it is appropriate at this juncture to consider another issue in the differential diagnosis of nested tumors of the bladder, namely mimicry of transitional cell carcinoma by paraganglioma, a problem recently reemphasized (43a) in a paper in which 20 percent of the cases of paraganglioma reported were misdiagnosed as transitional cell carcinoma. There are four main reasons that account for this confusion. First of all, pathologists simply often fail to include paraganglioma in
the differential diagnosis when evaluating a bladder tumor forgetting that this tumor is commoner in the bladder than any other organ outside the adrenal gland. Secondly, as the lesion derives from deep seated paraganglia it is not surprising that there is frequent involvement of the muscularis propria and resultantty “infiltration” of the muscularis may be misconstrued as the muscle invasion of bladder cancer. Thirdly, the morphology of paraganglioma, particularly in a transurethral resection with the artifactual changes often induced by that procedure, can produce a picture quite reminiscent of conventional bladder cancer. Finally, only a minority of paragangliomas of the bladder are associated with symptoms that might bring the diagnosis to mind. Although the zellballen pattern of the paraganglioma may suggest a nested transitional cell neoplasm, the vascularity of paraganglioma should be a clue to the diagnosis although this may be subtle. Some paragangliomas show cytologic atypia, which may further mislead the pathologist. Some of them also have cells with abundant granular oxyphilic cytoplasm. Individual cases with this differential may be very difficult but our experience has led us to consider the diagnosis of paraganglioma when we see a putative invasive transitional cell carcinoma which for whatever reason is not perhaps a textbook example of usual bladder cancer and certainly this is an area in which immunostains to confirm the diagnosis, or otherwise, of paraganglioma are very justified.

Transitional cell carcinomas with squamous and/or glandular differentiation are usually grade 2 or 3 and their distinction from non-neoplastic lesions is rarely difficult. Rarely the glandular component takes the form of small, relatively regular, tubules suggesting the tubules of a nephrogenic adenoma (44). However, the association of the tubules with foci of transitional cell carcinoma usually facilitates the correct diagnosis, and there is often a peripheral layer of transitional cells, something absent in nephrogenic adenomas. This focal peripheral layer of transitional cells is also helpful in appreciating the neoplastic nature of microcystic carcinomas
(28), some of which appear to be transitional cell carcinomas with cystification, others of which appear to be tumors with gland differentiation with the same phenomenon. Intermediate between tumors with small tubules and tumors with cysts are tumors with medium sized glands which may be misconstrued as cystitis glandularis. The remaining deceptively benign features of transitional cell carcinoma are the inverted growth, one of the two unusual patterns of endophytic growth referred to earlier and the myxoid character of some sarcomatoid carcinomas as mentioned earlier.

Grade 3 transitional cell carcinomas often have a relatively nondescript appearance which, viewed in isolation, cannot be distinguished from poorly differentiated carcinomas of other types. A poorly differentiated bladder cancer is considered of transitional cell type unless there is good evidence to the contrary. The possibility of prostate carcinoma should be borne in mind with poorly differentiated tumors in males, particularly if the specimen is obtained from the trigone or bladder neck. Immunohistochemistry may be very helpful in these cases, as most prostate carcinomas will stain for prostate specific antigen and prostatic acid phosphatase. Occasional poorly differentiated transitional cell carcinomas without an obvious epithelial pattern may superficially resemble malignant lymphoma (45) or even plasmacytoma (45A), but small foci of epithelial differentiation and high power scrutiny of the neoplastic cells to recognize that their cytologic features are not typical of those of malignant lymphoma are usually helpful. Immunohistochemistry for epithelial and lymphoid markers may be of help in cases, which are difficult to distinguish on the basis of routine stains (45).

The tumors that enter into the differential diagnosis in cases of sarcomatoid carcinomas are sarcomas, mainly leiomyosarcoma (46,47), malignant fibrous histiocytoma and pleomorphic rhabdomyosarcoma, carcinosarcomas (48), and transitional cell carcinomas with pseudosarcomatous stroma. Although it is occasionally difficult, a distinction between
sarcomatoid carcinomas and sarcomas can usually be made by evaluating their features in routinely stained slides. The pathologic feature that is diagnostic of the former tumor is the presence of recognizable epithelial elements of various types that merge imperceptibly with the sarcomatoid areas. However, a small specimen may contain only the sarcomatoid component and immunohistochemistry may be helpful in disclosing the epithelial nature of the tumor cells in such cases. Carcinosarcomas often exhibit heterologous differentiation of the sarcomatous component, including skeletal muscle or chondro-osseous tissue, elements that exclude the diagnosis of sarcomatoid carcinoma (49). Distinction of myxoid sarcomatoid carcinoma from inflammatory pseudotumor is considered under the latter entity.

Another issue that comes up in the differential diagnosis of transitional cell carcinoma occurs in cases of so-called plasmacytoid carcinoma. We probably reported the first example of one of these when we focused on confusion with lymphoma (45) and in the same year another case was reported in which the mimicry of multiple myeloma was noteworthy (45A). A subsequent paper which likely was showing morphology of this fundamental nature emphasized the differential diagnosis with metastatic lobular carcinoma from the breast (45B). Other large studies of this pattern have appeared (45C,45D). In one case report CD138-positivity was obtained enhancing the potential confusion with myeloma (45E). This pattern of neoplasia can be problematic from the benign versus malignant viewpoint as the dispersed nature of the cells and their often uniform nature may make them somewhat hard to discern, particularly when there is artifact and inflammation and it is possible, particularly in a poorly-preserved specimen to misinterpret them as histiocytes or plasma cells or simply not recognize them.

**SQUAMOUS CELL CARCINOMA**

Squamous cell carcinoma accounts for approximately 5 percent of bladder carcinomas in
areas where schistosomiasis is not endemic (49) but for approximately 75 percent of bladder carcinomas where schistosomiasis is endemic. The male-to-female ratio is lower than it is in cases of transitional cell carcinoma but the age distribution is similar. These tumors account for approximately 20% of cases arising within diverticula, 50% of cancers occurring in patients with non-functioning bladders and 15% of cancers in patients who have had renal transplants. They are usually large and deeply invasive tumors even when well differentiated. Their microscopic appearance is similar to that of squamous cell carcinomas arising elsewhere. Most are moderately or well differentiated and they often are abundantly keratinized. These tumors often are associated with keratinizing squamous metaplasia (so-called “leukoplakia”) (50,51) of the adjacent mucosa. In this area we have yet another potential for confusion of benign and malignant because prominent squamous metaplasia versus well-differentiated squamous cell carcinoma is not always easy. Luxuriant keratinizing tissue with an abnormal architecture obtained by curettage should always be viewed with suspicion. Features of well-differentiated squamous cell carcinomas seen elsewhere such as irregularity at the interface with the lamina propria and keratin pearl formation are obviously helpful in this situation.

**ADENOCARCINOMA**

Adenocarcinoma accounts for from 0.5 to 2 percent of bladder carcinomas (52-60). They may be of urachal origin (61), associated with exstrophy (62), or endometriosis (63), or unassociated with either of the aforementioned; the last is the commonest situation. In one large series one-third of the tumors were urachal and two-thirds, non-urachal (60). Adenocarcinomas account for approximately 90% of urachal cancers, the remaining tumors being divided, more or less equally, between those of transitional and squamous type.

The age distribution and male-to-female ratio of adenocarcinoma is similar to that of transitional cell carcinoma, the neoplasms usually arising in male patients over 50 years old. The
clinical presentation usually mimics that of transitional cell carcinoma but occasional patients present with mucinuria. Adenocarcinoma, like squamous cell carcinoma, accounts for a greater than normal percentage of bladder cancers in some clinical settings. They have accounted for approximately 15 percent of tumors arising in a patient with a non-functioning bladder and 85 percent of those associated with exstrophy. Adenocarcinoma of the bladder generally has a poor prognosis. The outlook for signet-ring cell carcinoma, which is typically high stage at presentation, is worse than for other types. Urachal tumors have a better prognosis than non-urachal tumors (60).

On gross examination these tumors vary considerably in appearance according in part to whether they are urachal, complicate exstrophy, or have neither association. Tumors of the last type may involve any part of the mucosa. They vary from papillary or polypoid, to nodular, to sessile and ulcerative. The neoplastic tissue is usually soft and often mucoid; foci of hemorrhage and necrosis are common. In cases of signet-ring cell adenocarcinoma, which account for from 3-5 percent of vesical adenocarcinomas (64), the mucosa often appears edematous and in most cases is ulcerated, but sometimes it is grossly normal. Some cases have the diffuse fibrosis and mural thickening typical of linitis plastica of the stomach.

Urachal tumors are typically submucosal masses at the bladder dome and often extensively infiltrate the surrounding muscle of the bladder wall and extend superiorly in the space of Retzius towards the umbilicus. There is usually some degree of overlying mucosal ulceration or abnormality of some type but this is variable. On sectioning, the tumors often have a gelatinous surface. Tumors that complicate exstrophy are remarkable primarily for their presence on the anterior abdominal wall. Biopsies of urachal adenocarcinoma may show features non-diagnostic of carcinoma so any mucinous proliferation from the dome should be evaluated cautiously unless it has typical features of endocervicosis. Urachal adenocarcinomas are typically cystic
intracavitary proliferations whereas endocervicosis is characterized by a pseudoinfiltrative picture of mucinous glands, sometimes cystic, but rarely markedly so, percolating between the bundles of the muscularis propria. Urachal adenocarcinomas of mucinous type represent a spectrum from lesions that can be categorized as mucinous cystadenoma to tumors that, according to ovarian guidelines, would be considered tumors of borderline malignancy, to low grade carcinomas, to frankly malignant and high grade invasive adenocarcinomas. In our experience with consultation cases, many are relatively low-grade mucinous cystic tumors and we recently proposed (65) that an argument could be made for classifying them in a manner analogous to the approach in the ovary.

Vesical adenocarcinomas are subclassified into the following microscopic groups whose frequency in one large series (60) was: adenocarcinoma, not otherwise specified (27.8 percent); mucinous (23.6 percent); enteric (19.4 percent); signet-ring cell (16.7 percent) and mixed (12.5 percent). Microscopic examination generally shows a predominantly glandular pattern although in poorly differentiated tumors areas of solid growth may be encountered. The glands frequently resemble those of intestinal adenocarcinoma of typical or colloid type. Their lining epithelium may have a prominent mucinous character. Urachal tumors tend to be more often mucinous than non-urachal tumors (60). Papillary tumors accounted for 8 percent of the tumors in one series (56).

Clear cell adenocarcinomas of the bladder (63) are much less common than those of the urethra (65A). Determining whether tumors with the appearance of a clear cell carcinoma as we would use that term in the female genital tract represent a peculiar pattern of differentiation of a neoplasm of transitional cell origin, represent a peculiar variant of adenocarcinoma of the bladder of non-mullerian nature, or represented malignant transformation of vesical endometriosis may be difficult. We recently investigated 13 tumors of the bladder that resembled clear cell
carcinoma. Eleven of the patients were female and two male. Their average age was 57 years. The clinical and gross features had no unique aspects. On microscopic examination the commonest pattern, present in all cases, was tubulocystic, with a papillary pattern in six tumors and a predominant solid growth in one. Cells with abundant clear cytoplasm were conspicuous in nine tumors and hobnail cells in eight. Four tumors showed focal recognizable patterns of transitional cell carcinoma in the available material. In five others, pseudostratified epithelium reminiscent of transitional epithelium was focally present. Endometriosis present in two cases and in two others benign cysts focally lined by ciliated epithelium and surrounded by elastosis were interpreted as most likely mullerian. Immunohistochemistry for CA-125, CK7 and CK20 and other markers were performed. This disclosed an immuno profile closer to transitional cell carcinoma and transitional cell carcinoma with gland differentiation than pure adenocarcinoma. We found CA125 expression in both our clear cell carcinomas and conventional adenocarcinoma of the bladder indicating a lack of specificity of CA-125 expression. We concluded that in the absence of endometriosis or conventional foci of transitional cell carcinoma it may be impossible to determine whether a tumor with the morphology of clear cell carcinoma is of mullerian or transitional cell lineage and at this time immunohistochemistry does not solve this problem.

UNDIFFERENTIATED CARCINOMA INCLUDING SMALL CELL CARCINOMA

Truly undifferentiated carcinomas of the bladder are relatively rare and often have the non-specific features of undifferentiated carcinomas of other sites. Only three specific subtypes are briefly discussed here. Small cell undifferentiated carcinomas that are similar histologically to pulmonary tumors of this type occur occasionally in the bladder (66-70). The tumors are typically large, often polypoid, and frequently ulcerated. Histologically they are composed of sheets of small, oat-shaped cells with hyperchromatic nuclei as well as slightly larger cells with
more variation in nuclear chromatin, comparable to the intermediate cell type of pulmonary small
cell carcinoma, or mixtures of the two cell types. Other forms of carcinoma, usually either in-
situ or invasive transitional cell carcinoma, but occasionally squamous cell carcinoma or
adenocarcinoma are often present. Small cell carcinomas may be confused with lymphoma,
particularly in a small biopsy specimen. Immunohistochemical stains for lymphoid and epithelial
markers may be helpful in these cases. Squeeze and cautery artifact may make the cells of some
conventional transitional cell carcinomas appear “small” and care should be taken not to confuse
such cases with small cell carcinoma. Primary small cell carcinomas of the bladder should be
distinguished from a metastasis from the lung, or rarely elsewhere. Occasional undifferentiated
carcinomas of the bladder are composed purely or predominantly of large pleomorphic cells with
abundant eosinophilic or amphophilic cytoplasm and have a conspicuous component of
malignant giant cells (71). Finally, rare bladder carcinomas have the features of a
lymphoepithelioma (45,72).
**TABLE 1**

**PRIMARY CARCINOMAS OF THE URINARY BLADDER**

1. **Transitional Cell Carcinoma**
   - Papillary
   - Non-papillary
     - (i) Transitional cell carcinoma-in-situ
     - (ii) Invasive transitional cell carcinoma

   **Variants**
   - i. With squamous and/or glandular differentiation
   - ii. Sarcomatoid carcinoma
   - iii. Micropapillary
   - iv. Plasmacytoid
   - v. Deceptively benign (nested, tubular, glandular, microcystic)
   - vi. With trophoblastic differentiation
   - vii. With pseudosarcomatous stroma, with osseous/cartilaginous metaplasia or with osteoclast-type giant cells.

2. **Squamous cell carcinoma**

3. **Adenocarcinoma**
   - A. Anatomic variants
     - i. From bladder mucosa
     - ii. Urachal
     - iii. From extrophy
     - iv. From endometriosis

   - B. Histologic Variants
     - i. Typical intestinal type
     - ii. Mucinous (including colloid)
     - iii. Signet-ring cell
     - iv. Clear cell
     - v. Not otherwise specified

4. **Undifferentiated carcinoma**

   **Variants**
   - i. Small cell carcinoma
   - ii. Lymphoepithelioma-like carcinoma
   - iii. Giant cell carcinoma
   - iv. Not otherwise specified
TABLE 2
DECEPTIVELY BENIGN FEATURES OF TRANSITIONAL CELL CARCINOMA

<table>
<thead>
<tr>
<th>Feature</th>
<th>Benign lesion they mimic</th>
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<tbody>
<tr>
<td>Nests</td>
<td>von Brunn's nests</td>
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<tr>
<td>Small tubules</td>
<td>Nephrogenic adenoma</td>
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<tr>
<td>Medium-sized glands</td>
<td>Cystitis glandularis</td>
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<tr>
<td>Cysts</td>
<td>Cystitis cystica</td>
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<tr>
<td>Inverted growth</td>
<td>Inverted papilloma</td>
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<tr>
<td>Myxoid appearance</td>
<td>Inflammatory pseudotumor</td>
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Selected Pseudoneoplastic Lesions

**Nephrogenic Adenoma**

This process (44) is generally accepted to be metaplastic, and the terms nephrogenic metaplasia or adenomatous metaplasia are preferred by some. Approximately 80 percent of the cases involve the bladder, but the urethra has been involved in 12 percent and the ureter in 8 percent. The lesion may be seen at any age and in either sex. The great majority of nephrogenic adenomas are associated with a history of an operative procedure on the genitourinary tract (61 percent of the cases), or one or more irritants including calculi (14 percent of the cases), trauma of various types (9 percent of the cases) and cystitis. Additionally, approximately 8 percent of the patients have been the recipients of a renal transplant.

At cystoscopy nephrogenic adenoma may simulate a papillary, sessile or in-situ carcinoma. Approximately fifty-six percent of the lesions are papillary, 10 percent polypoid, and 34 percent sessile. The lesions vary from incidentally discovered microscopic lesions (the majority) to
masses up to 7 cm in greatest dimension. Approximately 62 percent are 1 cm or less, 28 percent between 1 and 4 cm and 10 percent over 4 cm. They are typically single but approximately 18 percent are multiple.

On microscopic examination the classic triad of patterns is tubular, cystic and polypoid to papillary. The tubules are usually small, round and hollow but are occasionally larger, elongated and solid. They are sometimes surrounded by a prominent basement membrane but this is less common in our experience than some of the literature might imply. The tubules frequently undergo varying degrees of cystic dilatation and cysts, which are present in most cases, sometimes predominate. The tubules and cysts may contain an eosinophilic or basophilic mucinous secretion. Papillae are less common than tubules and cysts but are not rare. Occasionally larger, broader, polypoid structures are present. The majority of the cells lining the tubules, cysts and papillae are cuboidal to low columnar with scant cytoplasm. Nuclear atypia is uncommon, and when present appears degenerative in nature. Nucleoli may be prominent. Mitoses are absent or rare.

Several features of nephrogenic adenoma may cause particular diagnostic difficulty and merit emphasis. Tiny tubules containing mucin and apparently lined by a single cell with a compressed nucleus may simulate signet ring cells and suggest a signet-ring cell adenocarcinoma. The haphazard distribution of the tubules may also simulate the appearance of an invasive adenocarcinoma, a resemblance that is enhanced when the tubules are admixed with the muscle fibers that may be found in the lamina propria. Hobnail cells may suggest the diagnosis of the rare clear cell carcinoma of the bladder, particularly because the latter, like nephrogenic adenoma, has tubular, cystic and papillary patterns. A solid growth of cells with clear cytoplasm may also raise the possibility of clear cell carcinoma. A variety of clinical and pathologic differences as outlined in Table 3 should enable these two lesions to be distinguished,
although this is occasionally difficult. Clear cell carcinoma is less common in the bladder than in the urethra and in our experience distinction between nephrogenic adenoma and clear cell carcinoma is more troublesome in the urethra particularly within urethral diverticula. A special problem associated with nephrogenic adenoma of the prostatic urethra is the occasional problem it causes when it involves the underlying prostatic tissue and may cause confusion with prostatic carcinoma. Although they persist and/or recur in about one-third of the cases, nephrogenic adenomas are benign. Evidence presented suggesting that nephrogenic adenoma is a precursor of clear cell carcinoma of the bladder is not convincing in our opinion. The fact that clear cell carcinoma is much more common in the urethra and in women whereas nephrogenic adenoma is more common in the bladder and in men also argues against such a relationship.

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<th>Nephrogenic Adenoma</th>
<th>Clear Cell Carcinoma</th>
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<tbody>
<tr>
<td><strong>Sex Distribution</strong></td>
<td>Male predominance</td>
<td>Female predominance</td>
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<tr>
<td><strong>Age Distribution</strong></td>
<td>One-third 30 yrs</td>
<td>None under 43</td>
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<tr>
<td><strong>Predisposing Factors</strong></td>
<td>Common</td>
<td>Absent</td>
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<tr>
<td><strong>Large Size</strong></td>
<td>Rare</td>
<td>Common</td>
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<tr>
<td><strong>Diffuse Pattern</strong></td>
<td>Rare</td>
<td>Common</td>
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<tr>
<td><strong>Clear Cells</strong></td>
<td>Rare</td>
<td>Common</td>
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<tr>
<td><strong>Cytoplasmic Glycogen</strong></td>
<td>Rare</td>
<td>Abundant</td>
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<td><strong>Atypia/Mitoses</strong></td>
<td>Rare</td>
<td>Common</td>
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Papillary-Polypoid Cystitis

This uncommon lesion arises when inflammation sometimes accompanied by edema, leads to the formation of papillae or polyps (13). The designation papillary cystitis is used when thin finger-like papillae are present, and polypoid cystitis when the lesions are edematous and broad based. In both papillary and polypoid cystitis there is typically prominent chronic inflammation in the stroma and blood vessels, some of them ectatic, may be conspicuous. As papillary and polypoid cystitis are associated with inflammation they may be associated with metaplastic changes in the urothelium covering them, or adjacent to them.

There are two particular clinical settings, which should suggest that an exophytic bladder lesion may be inflammatory. These are cases in which there is an indwelling catheter and cases of vesical fistula. Although a catheter is typically associated with polypoid cystitis, occasionally it is associated with papillary cystitis. The mucosal changes associated with a vesical fistula may have the characteristics of polypoid cystitis or papillary cystitis. The major causes of vesical fistula are intestinal and include diverticulitis, Crohn's disease, colorectal cancers, and appendiceal inflammations. However, symptoms indicative of extravesical disease are absent, at least initially in approximately half the cases, so diagnostic difficulty may be significant. Additionally, the appropriate history is not always furnished to the pathologist.

The most important differential diagnosis of papillary and polypoid cystitis is with papillary transitional cell carcinoma. Cases of papillary and polypoid cystitis without a history of catheterization are particularly likely to be considered carcinomas at cystoscopy. On gross inspection and microscopic examination, however, the fronds of polypoid cystitis are typically much broader than those of a papillary carcinoma. The thin papillae of papillary cystitis are more difficult to distinguish from carcinoma. In the former (as in polypoid cystitis) the urothelium may be hyperplastic, but usually is not as stratified as in a carcinoma; additionally, umbrella cells
are more often present. The fibrovascular cores of the papillae of a transitional cell carcinoma typically lack the prominent inflammation that characterizes both papillary and polypoid cystitis, and the edema seen in the latter. Large papillae of a transitional cell carcinoma also often give rise to smaller papillae, a feature not associated with papillary or polypoid cystitis. Finally, the urothelium adjacent to a papillary carcinoma is often hyperplastic and significant cytologic atypia within a papillary lesion or the adjacent urothelium favors a diagnosis of carcinoma.

Radiation Cystitis

Florid epithelial proliferations that may mimic carcinoma may complicate radiation therapy. We recently reported four cases of this type (73). They were characterized microscopically by irregularly shaped and arranged aggregates of epithelial cells in the upper and mid zones of the lamina propria. The cells typically showed at least mild, and sometimes severe pleomorphism and were typically of transitional cell type but squamous differentiation was seen focally in three cases. Crucial to suspicion of the diagnosis morphologically, was surface ulceration with prominent fibrin deposition and hemorrhage with associated edema and prominent vascular ectasia in all cases. Additionally, other changes characteristic of radiation injury such as atypical fibroblasts were present. In two of our cases the clinical history of radiation therapy was not available initially and only investigation of the clinical history uncovered this information and resulted in appropriate clinicopathologic correlation and establishment of the diagnosis of radiation induced pseudocarcinomatous proliferation.

A variety of abnormalities may be seen in the bladder as a result of radiation. The urothelial cells may show varying degrees of atypicality. Cytoplasmic and nuclear vacuolation, karyorrhexis and a normal nuclear-cytoplasmic ratio are features suggestive of radiation injury. Other characteristic changes of radiation injury include marked stromal edema and prominent telangiectatic vessels that explain the hematuria, which often occurs. Hyalinization and
thrombosis of the vessels is also seen. Atypical mesenchymal cells are typically present in the lamina propria.

Endocervicosis

Recently tumor-like glandular lesions characterized by a prominent component of endocervical type epithelium that have involved the wall of the urinary bladder in women of reproductive age have been reported (74). In each patient a mass that ranged from 2-5 cm. was typically located in the posterior wall or posterior dome. Microscopic examination typically revealed 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 mullerian lesion of the bladder and it is best considered the mucinous analogue of endometriosis.

Benign Mesenchymal Proliferations

i. Postoperative Spindle Cell Nodule

The unifying clinical feature of these cases is the development of an exuberant spindle cell proliferation 3 months or less after a transurethral resection of the bladder has been performed (75). Microscopic examination shows intersecting fascicles of spindle cells, which often show conspicuous mitotic activity. A marked resemblance to a sarcoma, particularly leiomyosarcoma, often results. Additional microscopic features, which are often present, include a delicate network of small blood vessels scattered acute and chronic inflammatory cells, small foci of
hemorrhage, mild to moderate edema and focal myxoid change in the stroma. Despite the generally numerous mitotic figures, the cells do not exhibit marked cytologic atypia. The clinical association with a recent operation is the major clue that these lesions represent an exuberant reactive proliferation.

The interpretation of spindle cell lesions of the urinary bladder and in particular the confident diagnosis of a postoperative spindle cell nodule is amongst the most difficult in urologic pathology. Although other sarcomas, such as Kaposi’s sarcoma, occasionally are suggested, leiomyosarcoma is usually the major consideration in differential diagnosis. Distinction from a moderate to poorly differentiated leiomyosarcoma is not difficult as the atypia in these cases exceeds that seen in a postoperative spindle cell nodule (PSCN). However, many well-differentiated leiomyosarcomas do not appear more atypical cytologically than a PSCN and may be less mitotically active than a PSCN. Although one might expect destructive growth to be helpful in this differential, the PSCN may invade the muscular wall of the bladder. Although leiomyosarcomas may be vascular, the often-prominent delicate network of small blood vessels that is seen in many PSCN is, in our opinion, more in keeping with a diagnosis of PSCN than sarcoma. Myxoid change may be seen in both the PSCN and leiomyosarcoma and is not particularly helpful diagnostically, although extensive and/or extremely prominent myxoid change is perhaps more in favor of a leiomyosarcoma.

Somewhat surprisingly, the PSCN has stained positively for cytokeratin in some cases whereas leiomyosarcomas of the bladder have been negative for cytokeratin in our experience. Ultrastructural studies of the PSCN are limited but the cells in the few cases studied have been more characteristic of myofibroblasts than smooth muscle cells. Therefore, features of unequivocal smooth muscle differentiation favor a diagnosis of sarcoma in this context. Ultimately, distinction between these two processes is very dependent on the clinical history of a
recent operative procedure. In occasional cases in our experience it has been impossible to make a confident distinction between them particularly when the interval between a prior operative procedure and the development of a spindle cell lesion is longer (over 3 months) than in most cases of PSCN. In these cases careful clinical follow-up with repeat cystoscopy and further biopsies is indicated. Conservative excision of a grossly visible lesion is also justified.

ii. Inflammatory Pseudotumor

Proliferative spindle cell lesions of the bladder which microscopically may suggest a sarcoma but which are benign, are also seen in patients without a recent history of an operation (76-78). This lesion may occur at any age but typically occurs in young adults with an average age of twenty-eight years. On gross examination the appearance may suggest a malignant tumor. On microscopic examination the characteristic microscopic appearance is that of spindle cells typically relatively widely separated in a vascular myxoid sometimes-basophilic stroma. Less commonly a more compact cellular less myxoid appearance reminiscent of a plasma cell granuloma variant of inflammatory pseudotumor is observed. Ultrastructural examination has typically shown the features of myofibroblasts and flow cytometric DNA analysis gave diploid results. The differential diagnosis of this lesion is similar to that of the post-operative spindle cell nodule both myxoid sarcomas and myxoid areas in sarcomatoid carcinoma (32A) occasionally being major considerations. With regard to the latter consideration, the age of the patient is also helpful in as much as most sarcomatoid carcinomas occur in an older age group. It should be mentioned that occasional inflammatory pseudotumors, like the post-operative spindle cell nodule, have been immunoreactive for keratin. The diagnosis of a reactive mesenchymal lesion in the bladder should be made with great caution in these cases in which there is no history of a recent operation, which is so helpful in cases of postoperative spindle cell nodule.
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