Urothelial carcinoma is a heterogeneous tumor with great propensity for divergent differentiation resulting in an urothelial carcinoma admixed with other morphologically recognizable components. [1] The most common mixed differentiation is squamous followed by glandular. [1-5] The whole spectrum of bladder carcinoma variants may be seen in variable proportion from an otherwise typical urothelial carcinoma, but most importantly, these variants may be relevant in clinical practice since they may simulate benign lesions, secondary tumors or necessitate a more complex therapeutic approach beyond surgery.[1, 6] Recent studies suggest an increasing likelihood of lymph node metastases associated with the finding of pathologic variants in the primary tumor.[7] Main pathologic variants of urothelial bladder carcinoma according to their suggested clinical and pathologic significance, follows:

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**UROTHELIAL CARCINOMA WITH DECEPTIVELY BENIGN APPEARANCE**

The nested variant of urothelial carcinoma is an aggressive neoplasm with less than 50 reported cases.[1, 8-10] There is a male predominance, and 70% of patients died 4-40 months after diagnosis, despite therapy.[9, 11] This pattern of urothelial carcinoma was first described as a tumor with a “deceptively benign” appearance that closely resembles Brunn’s nests infiltrating the lamina propria.[8, 12-14] Nuclei generally show little or no atypia, but the invariable presence of an infiltrative growth should facilitate accurate diagnosis. There is high p53 accumulation and tumor cell proliferation; findings that result useful in some cases. [1] In spite of the deceptively benign appearance of the tumor, recently, it has been proposed to grade this as high grade to assist the urologist in selecting the appropriated therapy.[1] A report based on 30 urothelial carcinoma cases with pure or predominant nested morphology [9] found patient’s age ranged from 41 to 83 years (average, 63 years) with a male-female ratio of 2.3:1. The architectural pattern ranged from a predominantly disorderly proliferation of discrete, small, variably sized nests to focal areas demonstrating confluent nests.
cordlike growth, and cystitis cystica-like areas to tubular growth pattern. The deep tumor-stroma interface was invariably jagged and infiltrative. Despite overall bland cytology, tumor nests demonstrated focal random cytologic atypia (90%) and focal high-grade cytologic atypia centered within the base of the tumor (40%). The tumor stroma ranged from having minimal stromal response to focally desmoplastic and myxoid. A component of usual urothelial carcinoma was present in 63% of cases. [9]

The nested component demonstrated an immunophenotype identical to usual urothelial carcinoma, with CK7, CK20, p63, and CK903 expression in 93%, 68%, 92%, and 92% of cases, respectively. At resection, 65% demonstrated invasion into perivesical fat, and 17% into adjacent organ(s). When compared with pure high-grade urothelial carcinoma, nested urothelial carcinoma was associated with muscle invasion at transurethral resection (31% vs. 70%), extravesical disease at cystectomy (33% vs. 83%), and metastatic disease (19% vs. 67%). [9]

Follow-up was available on 29 patients (97%) with a median of 12 months (range, 1-31 months); 3 (10%) died of disease, 16 (55%) were alive with persistent or recurrent disease, and 10 (34%) were alive without disease. Response to neoadjuvant chemotherapy was observed in 2 (13%) of 15 patients. Wasco et al [9] concluded that nested urothelial carcinoma seen either in pure form or with a component of usual UC had poor outcomes.

Urothelial carcinoma with endophytic growth (inverted papilloma-like carcinoma)

The recent interest in urothelial carcinoma with endophytic growth relays on the fact that may be misdiagnosed as the benign inverted papilloma.[1, 15-18] This is because inverted papilloma-like carcinoma may show variable-to- minimal cytologic and architectural abnormalities, but invariably has higher mitotic count and cell proliferation as seen by ki67, high p53 accumulation, aberrant cytokeratin 20 expression, and frequent polysomies at chromosome 3, 9 and 17.[19] This profile has been found very useful in differential diagnosis with inverted papilloma.[18, 19] In some instances, both inverted papilloma and inverted papilloma-like carcinoma are intimately mixed.[18] Other important feature in papillary tumours with endophytic growth is that they invade lamina propria with a pushing border.[20] Unless this pattern is accompanied by true destructive stromal invasion the likelihood of metastasis is minimal because the basement membrane is not truly breached.[15]

UROTHELIAL CARCINOMA WITH FEATURES SUGGESTING SECONDARY INVOLVEMENT TO THE BLADDER

Micropapillary urothelial carcinoma

This variant of urothelial carcinoma was initially described because it resembles papillary serous carcinoma of the ovary. [1, 21] This morphology has been further recognized in other organs such lung, colon, breast, renal pelvis or salivary glands.[1, 22] A recent report based on 100 consecutive cases treated by cystectomy, showed a mean age of the patients was 64.7 years, with a male: female ratio of 10:1. [22]Stage at the time of presentation was Ta in 5 patients, carcinoma in situ in 4 patients, T1 in 35 patients, T2 in 26 patients, T3 in 7 patients, T4 in 6 patients; N+ in 9 patients, and M+ in 8 patients. 5-year and 10-year overall survival rates were 51% and 24%, respectively. Intravesical bacillus Calmette-Guerin therapy was attempted in 27 of 44 patients with non-muscle-invasive disease; 67% (18 patients) developed disease progression (>\(=\)cT2), including 22% who developed metastatic disease.[22] Of 55 patients undergoing radical cystectomy for surgically resectable disease (<\(=\)cT4a), 23 received neoadjuvant chemotherapy and 32 were treated with initial cystectomy, with no significant difference noted in stage distribution between the 2 groups. For the 23
patients treated with neoadjuvant chemotherapy, the median overall survival was 43.2 months with 32% of patients still alive at 5 years. [22] For the 32 patients treated with initial cystectomy, 71% remained alive at 5 years. It was concluded that micropapillary bladder cancer is associated with a poor prognosis and that intravesical therapy appears to be ineffective in this disease and patients with surgically resectable disease should be offered early radical cystectomy. [22] Increased lymph node positivity was also associated with the presence of micropapillary carcinoma in a recent study. [7] [23]

At histology, the micropapillary component is found in association with non-invasive papillary or invasive urothelial carcinoma in 80% of reported cases. [1] Twenty-five percent of cases show glandular differentiation, and some authors consider it as a variant of adenocarcinoma. Vascular and lymphatic invasion is common, and most cases show invasion into muscularis propria or deeper, often with metastases at time of diagnosis. [24] Immunohistochemical studies show immunoreactivity for epithelial markers similar to conventional urothelial carcinoma in all and CA125 staining in 43% of cases. [25] The presence of a surface micropapillary component in bladder biopsy specimens is a useful clue for further investigation and an indication for deeper biopsies in order to determine the level of invasion. In addition to stage, the prognosis seems to be related to the proportion and location of the micropapillary component. [10, 25] Cases with a moderate or extensive micropapillary component are at high risk of having an advanced stage at presentation. Cases with <10% micropapillary component have a high chance of detection at an early stage.

A recent pathology report based on 13 cases of invasive micropapillary carcinoma [23] showed the micropapillary component varied from 50-100% of the tumor specimen with 5 cases showing pure micropapillary carcinoma. The architectural pattern of the tumor varied from solid expansile nests with slender papillae within tissue retraction spaces to pseudoglandular growth with prominent ring-like structures (2 cases, 15%), and invasive micropapillary carcinoma with squamous differentiation (2 cases, 15%); a streaking solid architectural pattern of micropapillary carcinoma was additionally present in 2 cases (15%). The individual tumor cells had abundant eosinophilic cytoplasm and nuclei with prominent nucleoli and irregular distribution of chromatin, and frequent mitotic figures. Most neoplastic cells had nuclei of low to intermediate nuclear grade with occasional nuclear pleomorphism. Eight mixed cases had concurrent conventional high-grade urothelial carcinoma with squamous or glandular differentiation in 3 and 1 cases, respectively. All patients had advanced stage cancer (>pT2); and 8 (62%) had lymph node metastases. [23] Some limitations still exists concerning the diagnostic reproducibility in invasive micropapillary carcinoma. [28]

Immunohistochemical staining demonstrated that both micropapillary and associated conventional urothelial carcinoma were positive for MUC1 and 2; CK 7, PTEN, p53, and ki67; Her2Neu, Uroplakin, CK 20, 34ßE12, CA125 and p16 were positive in 4, 10, 8, 7, 3 and 3 cases, respectively. On follow up, 11 of the patients died of disease from 2 to 14 months. It was concluded that invasive micropapillary variant of urothelial carcinoma is an aggressive variant associated with poor prognosis that presents at an advanced clinical stage. The immunophenotype of invasive micropapillary carcinoma supports urothelial origin; the immunoreactivity to Her2Neu and PTEN might be relevant in terms of future targeting therapy. [23]

**Plasmacytoid urothelial carcinoma**

This is an unusual variant in which the tumour cells show eosinophilic cytoplasm and eccentric nuclei producing a plasmacytoid appearance, thus suggesting
multiple myeloma/lymphoma.\[1, 6, 10, 26] The epithelial nature of the malignancy is confirmed by positive immunohistochemistry of cytokeratin and negativity for lymphoma/plasmacytoma markers. This tumour is an aggressive neoplasm with stage-related outcome and frequent lymph node positivity at diagnosis. \[27\] A recent report based on 11 cases \[27\] showed that the plasmacytoid component varied from 30-100% of the tumor specimen; in 8 cases the plasmacytoid component composed greater than 50% of the tumor. The architectural pattern of the tumor varied from solid expansile nests with noncohesive cells to mixed solid and alveolar growth; a streaking discohesive architecture was additionally present in 2 cases (18%). Rarely, a myxoid pattern can be present. Histologically, the individual tumor cells had an eccentrically placed nucleus and abundant eosinophilic cytoplasm reminiscent of plasma cells. Most neoplastic cells had nuclei of low to intermediate nuclear grade with occasional nuclear pleomorphism. \[27\] Seven of 9 mixed cases had concurrent conventional high-grade urothelial carcinoma, and the remaining 2 cases presented features of nested or micropapillary urothelial carcinoma. All patients had advanced stage cancer (>pT3); and 8 (73%) had lymph node metastasis. \[27\]

Immunohistochemical staining demonstrated that both plasmacytoid and associated conventional urothelial carcinoma were positive for CKs7, 20 and AE1/AE3, and epithelial membrane antigen; CD138 was positive in 3 cases. On follow up 9 of patients died of disease from 2 to 11 months and 2 patients were alive with disease at 8 and 16 months. Lopez-Beltran et al \[27\] concluded that plasmacytoid variant of urothelial carcinoma is an aggressive variant associated with poor prognosis that presents at an advanced stage.

The differential diagnostic considerations include lymphoma (plasmacytoid type) and multiple myeloma. Identification of an epithelial component by immunohistochemistry confirms the diagnosis. Immunohistochemistry using CD45 (leucocyte common antigen) or cytokeratins is useful. \[27\] In limited samples, it may be misdiagnosed as chronic cystitis or plasmacytoma, a pitfall further compounded by CD138 (marker of plasma cells) expression in some cases. \[27\]

**Clear cell (glycogen-rich) urothelial carcinoma**

Up to two-thirds of cases of urothelial carcinoma have foci of clear cell change resulting from abundant glycogen, but the glycogen-rich clear cell “variant” of urothelial carcinoma, recently described,\[30\] appears to represent the extreme end of the morphologic spectrum, consisting predominantly or exclusively of cells with abundant clear cytoplasm that stains for CK 7, thus confirming urothelial origin.\[30, 31\] Recognition of this pattern avoids confusion with clear cell adenocarcinoma of the bladder and metastatic clear cell carcinoma of the kidney and other sites. Recent data relates this morphology with lymph node metastases.\[7\]

**Large cell undifferentiated carcinoma**

This is a poorly defined category that contains large cell type carcinoma that cannot be otherwise classified.\[1, 6, 33, 35\] They are extremely rare in the urinary tract, aggressive, and of high stage at presentation including frequent lymph node metastases.\[7\] One reported case showed increased α-fetoprotein production in patient’s serum and by immunohistochemistry in the tumour cells.\[32\] Some may contain abundant epithelial tumour giant cells resembling giant cell carcinoma of the lung (so called pleomorphic giant cell carcinoma of the bladder);\[1, 6, 33\] this is very infrequent and aggressive variant with poor prognosis, similar to that associated with giant cell carcinoma in the lung or prostate. The giant cells display cytokeratin immunoreactivity. We believe this should be considered in the spectrum of the large cell undifferentiated carcinoma of the bladder instead of a different pathologic variant until more experience
is made available. [1] The spectrum of neuroendocrine carcinomas of the urinary bladder may include rare examples of large cell neuroendocrine carcinomas, similar to the more common counterpart in the lung. The experience with these cases suggests they are at advanced stage at presentation. [34, 35]

**UROTHELIAL CARCINOMA WITH FEATURES SUGGESTING BENIGN PROLIFERATIVE LESIONS**

**Microcystic urothelial carcinoma**

This pathologic variant is characterized by the formation of cysts ranging from microscopic up to 1-2 cm in diameter.[13, 36, 37] The cysts or small tubules may be empty or contain necrotic debris or mucin. This variant of cancer may be confused with benign proliferations such as florid polypoid cystitis cystica and glandularis, nephrogenic adenoma and rarely with adenocarcinoma. [13, 36]

**UROTHELIAL CARCINOMA WITH A COMPLEX THERAPEUTIC APPROACH**

**Lymphoepithelioma-like urothelial carcinoma**

This tumour resembles lymphoepithelioma of the nasopharynx. [38, 39] The male-to-female ratio is 3:1, and occurs in late adulthood (range: 52-81 years; mean: 69 years). Most patients present with haematuria. [39-41] The tumour is solitary and usually involves the dome, posterior wall, or trigone, often with a sessile growth pattern. At histology, it may be pure or mixed with typical urothelial carcinoma. [42] The epithelial tumour cells show poorly defined cytoplasmic borders imparting a characteristic syncytial appearance. The background consists of a prominent lymphoid stroma that includes T- and B-lymphocytes, plasma cells, histiocytes, and occasional neutrophils or eosinophils. [39] Epstein-Barr virus infection has not been identified in lymphoepithelioma-like carcinoma of the bladder. [43] This tumour has been found to be responsive to chemotherapy when it is encountered in its pure form.

**Small cell carcinoma**

A recent molecular study indicated that small cell carcinoma and urothelial carcinoma are derived from the same clonal population and we consider small cell carcinoma of the urinary bladder as a variant of urothelial carcinoma with a dismal prognosis.[44, 45] In a recent series of 64 cases of small cell carcinoma of the urinary bladder, the mean age at diagnosis was 66 years and the male: female ratio was 3.3:1; 88% presented with haematuria.[44, 46, 47] All the patients except one had muscle-invasive disease at presentation. Thirty-eight patients (59%) underwent cystectomy and 66% of patients had lymph node metastasis at the time of cystectomy with regional lymph nodes, bone, liver and lung being the most common locations. Forty four cases (68%) cases consisted of small cell carcinoma with other histological types (urothelial carcinoma, 35 cases; adenocarcinoma, 4 cases; sarcomatoid urothelial carcinoma, 2 cases; and 3 cases with both adenocarcinoma and urothelial carcinoma).[44, 47] No clinico-pathologic parameters studied correlated with survival. No significant survival difference was found between patients who underwent cystectomy and those who did not receive cystectomy. Patients with organ-confined cancers had marginally better survival than those with non organ-confined cancer (P=0.06). [44] Overall, 1-year, 18-month, 3-year, and 5-year cancer-specific survivals were 56%, 41%, 23%, and 16%, respectively. The prognosis of small cell carcinoma of the urinary bladder remains poor irrespective of therapy. Hypercalcemia or hypophosphatemia, and ectopic secretion of ACTH have also been reported as part of the paraneoplastic syndrome associated with primary small cell carcinoma of the bladder.[46] On histological examination, they
mimic its pulmonary counterpart. The immunohistochemical profile reveals neuroendocrine markers at variable frequency, but the diagnosis of small cell carcinoma can be made on morphologic grounds alone, even if neuroendocrine differentiation cannot be demonstrated. The recent finding of c-kit and epidermal growth factor receptor expression by immunohistochemistry opens new possibilities for targeted therapy in small cell carcinoma of the bladder.[46, 48, 49]

**UROTHELIAL CARCINOMA THAT CAN BE MISDIAGNOSED AS CHORIOCARCINOMA EITHER PRIMARY OR SECONDARY**

**Urothelial carcinoma with syncytiotrophoblastic giant cells**

Up to 12% of cases of urothelial carcinoma show syncytiotrophoblastic giant cells producing substantial amounts of β-human chorionic gonadotropin (HCG). [50-53] Secretion of HCG into the serum may be associated with a poor response to radiation therapy.[53] The most important differential diagnostic consideration is choriocarcinoma; most but not all cases previously reported as primary choriocarcinoma of the bladder represent urothelial carcinoma with syncytiotrophoblasts rather than pure choriocarcinoma; a lesion that is very unusual in the bladder.[1] One reported primary choriocarcinoma of the bladder that occurred in a 19 year-old man showed high copy number of the isochromosome 12p supporting germ cell differentiation.[54]

**UROTHELIAL CARCINOMA WHICH CAN BE MISDIAGNOSED AS MYOFIBROBLASTIC PROLIFERATION OR SARCOMA**

**Sarcomatoid urothelial carcinoma (carinosarcoma, spindle cell carcinoma)**

The term sarcomatoid variant of urothelial carcinoma should be used for all biphasic malignant neoplasms exhibiting morphologic and/or immunohistochemical evidence of epithelial and mesenchymal differentiation (with the presence or absence of heterologous elements acknowledged in the pathology report).[55] Some patients have previous history of radiation or cyclophosphamide therapy.[56] The most frequent presenting signs and symptoms are hematuria, dysuria, nicturia, acute urinary retention, and lower abdominal pain.[56] The mean age is 66 years (range, 50-77 years). Pathological stage is the best predictor of survival in sarcomatoid carcinoma.[56] The tumours are often polypoid with large intraluminal masses. Microscopically, sarcomatoid carcinoma is composed of a urothelial, glandular or small cell component showing variable degrees of differentiation; carcinoma in situ is present in 30% of cases and occasionally is the only apparent epithelial component.[56] A small subset of sarcomatoid carcinoma of the bladder and the renal pelvis may have a prominent myxoid stroma, a finding that misguide the pathologist into inflammatory pseudotumour (inflammatory myofibroblastic tumour) but this is characteristically positive for anaplastic lymphoma kinase stains unlike sarcomatoid carcinoma which is negative.[56-61] The most common heterologous element in a large series is osteosarcoma followed by chondrosarcoma, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, or angiosarcoma, but multiple types may be present.[56] By immunohistochemistry, epithelial elements react with cytokeratins, whereas stromal elements react with specific markers corresponding to the type of mesenchymal differentiation. Recent molecular evidences strongly argue for a monoclonal origin of both components in sarcomatoid carcinoma. [62]

**MISDIAGNOSIS AS SQUAMOUS CELL CARCINOMA OR ADENOCARCINOMA EITHER PRIMARY OR SECONDARY**
Urothelial carcinoma with squamous and/or glandular differentiation (mixed differentiation carcinoma)

Squamous differentiation, defined by the presence of intercellular bridges or keratinisation, occurs in 21% of urothelial carcinomas of the bladder. [1, 3, 6, 56] Its frequency increases with grade and stage. [3] The proportion of the squamous component varies considerably, with some cases having urothelial carcinoma in situ as the only urothelial component. These cases may have a less favorable response to therapy (surgical, radiation or systemic chemotherapy) than pure urothelial carcinoma. Of 91 patients with metastatic carcinoma, 83% with mixed adenocarcinoma and 46% with mixed squamous cell carcinoma experienced disease progression despite intense chemotherapy, whereas progression occurred in <30% of patients with pure urothelial carcinoma. [4, 5] Low-grade urothelial carcinoma with focal squamous differentiation also has a higher recurrence rate. Tumors with any identifiable urothelial element are classified as urothelial carcinoma with squamous differentiation. [3] Rare cases of squamous differentiation in the bladder with basaloid or clear cell features have been recognized. [3] The morphologic patterns of keratinizing and non-keratinizing squamous differentiation in a recent study by Lopez-Beltran et al. [3] were: i) wide nests and cords showing diskeratosis, intercellular bridges and corneous pearls; ii) small foci frequently overcome under conventional evaluation showing intercellular bridges but not diskeratosis or corneous pearls; iii) additional features suggestive of koilocytosis; iv) occasional but focally prominent intracytoplasmic lumina in nests of Squamous differentiation; and v) rare cases had rather clear cells forming nests of variable size well demarcated from concomitant urothelial carcinoma.

Glandular differentiation is less common than squamous differentiation and may be present in about 6% of urothelial carcinomas of the bladder. [2] Glandular differentiation is defined as the presence of true glandular spaces within the tumor. These may be tubular or enteric glands with mucin secretion. A colloid-mucinous pattern characterized by nests of cells “floating” in extracellular mucin, occasionally with signet ring cells, may be present. Cytoplasmic mucin-containing cells are present in 14-63% of typical urothelial carcinoma and are not considered to represent glandular differentiation. [1, 6] In rare cases, the glandular component has the morphology of hepatoid or clear cell adenocarcinoma. [63] A tumour with mixed glandular and urothelial differentiation is best classified as urothelial carcinoma with glandular differentiation.

A recent report by Scosyrev et al. [10] concluded that mixed histological features (presence of squamous and/or glandular differentiation) affect survival benefit from neoadjuvant platinum-based combination chemotherapy in patients with locally advanced bladder cancer, that this finding does not confer resistance to MVAC and in fact may be an indication for the use of neoadjuvant chemotherapy before radical cystectomy.

MISDIAGNOSIS AS OTHER TUMOR TYPES

Lipid-cell urothelial carcinoma

The lipoid cell variant is a rare neoplasm defined by the World Health Organization (1999, 2004) as a type of urothelial carcinoma that exhibits transition to cells resembling signet ring lipoblasts [1, 6]. It frequently presents with gross hematuria [64].

A recent report based on 27 cases [64] showed that the lipid-cell component varied from 10-50% of the tumor specimen; in 11 cases the lipid cell component composed greater than 30% of the tumor. The architectural pattern of the tumor varied
from solid expansile to infiltrative nests. The large epithelial tumor cells had an
eccentrically placed nucleus and abundant vacuolated cytoplasm resembling signet-ring
lipoblasts. Mucin stains were negative in all cases. Typical features of high grade
conventional urothelial carcinoma were present in all cases, with micropapillary or
plasmacytoid carcinoma in 2 and 1 cases, respectively; extensive squamous or glandular
differentiation was present in two additional cases. Most neoplastic cells had nuclei of
intermediate nuclear grade with occasional nuclear pleomorphism. [64]

Immunohistochemical staining demonstrated that the lipid cell component was
positive for CKs 7, 20, CAM 5.2, high molecular weight (34BE12) and AE1/AE3,
epithelial membrane antigen and thrombomodulin; vimentin and S100 protein were
negative. The LOH analysis was performed on 8 cases using 4 polymorphic
microsatellite markers (D9S171, D9S177, IFNA and TP 53); LOH at least in one
marker was present in 6 cases. The LOH results were the same for lipid variant and
conventional urothelial carcinoma. Electron microscopy analysis based on two cases,
supported lipid content in tumor cells. [64]

Pathologic stage at diagnosis was Ta (n=1), T1 (=2), T2, at least (n=7), T3a
(n=4), T3b (n=8), and T4a (n=5). Sixteen of patients died of disease from 16 to 58
months (mean, 33 mo) and 8 patients were alive with disease at 8 to 25 months (mean,
22 mo). Three additional patients died of other causes at 6 to 15 months (mean, 10 mo).
It was concluded that lipid cell urothelial bladder carcinoma is typically associated with
advanced stage high grade urothelial carcinoma, where the prognosis is poor; and is
clonally related to the concurrent conventional urothelial carcinoma. In limited samples,
it may be misdiagnosed as liposarcoma, sarcomatoid carcinoma (carcinosarcoma) with a
liposarcomatous component or signet-ring cell carcinoma. [64]

Urothelial carcinoma with stromal reactions (peudosarcomatous stroma;
stromal osseous or cartilaginous metaplasia; osteoclast-type giant cells; prominent
lymphoid infiltrate)

Infiltrating urothelial carcinoma may be associated with a variety of stromal
reactions, which are occasionally pronounced. The finding of a peudosarcomatous
stroma raises serious concern about sarcomatoid carcinoma or true sarcoma of the
bladder.[65] Tumor-associated stromal osseous and/or chondroid metaplasia is present
in some cases of urothelial carcinoma and its metastases, and this should be
differentiated from osteosarcoma, chondrosarcoma or heterologous type of sarcomatoid
carcinoma.[66] The presence of osteoclast-like giant cells in cases of invasive high-
grade urothelial carcinoma seems not to be related to tumor prognosis.[67] In fact,
‘Giant cell tumors’ or ‘osteoclastoma-like giant cell tumors’ of the pancreas, gall
bladder, liver, breast, salivary gland, thyroid, skin, lung, intestines, larynx and female
genital tract have been reported. [67] Less than 20 cases of a similar spectrum have been
reported in the bladder, most as case reports, with one series of 6 cases. The tumors are
composed of mononuclear cells (frequently positive for epithelial markers), osteoclast-
like giant cells (CD68-, CD51-, CD54-positive) and recognizable usual urothelial
neoplasia (carcinoma in situ, papillary or invasive carcinoma) in
varying proportions.[67]

An inflammatory cell response in the stroma adjacent to the invasive tumors is
relatively common. [69]This response usually takes the form of a lymphocytic infiltrate
with a variable admixture of plasma cells. Generally, this cellular reaction is mild to
moderate, but occasionally it may be dense. [69]

Other morphological variants of urothelial carcinoma

Baldwin et al. described a series of 10 cases of urothelial carcinoma with a
striking discohesive growth pattern which show morphological features that mimicked
infiltrating lobular carcinoma of the breast and diffuse carcinoma of the stomach.[70] The mean age was 67 years at presentation. All cases had advanced stage at time of diagnosis. This pattern is important to recognize in order to avoid misdiagnosis of metastatic lobular carcinoma of the breast or diffuse carcinoma of the stomach, especially in small biopsies; most authors currently believe this represent a form of plasmacytoid carcinoma [70] Gleason 3 prostate cancer with tubular pattern of growth which may be seen is the main differential consideration concerning bladder cancer with small tubules formation.[71] A rare case of urothelial carcinoma simulating endometrioid carcinoma of the endometrium has been reported.[1] Urothelial carcinoma with chordoid features is a recently described entity based on 12 invasive urothelial carcinomas with a unique chordoid morphology characterized by prominent cellular cording and associated myxoid stromal matrix, a pattern closely resembling extraskeletal myxoid chondrosarcoma.[68] The percentage of tumor with a chordoid appearance ranged from 5% to 95% (mean: 39%; median: 25%). No conventional sarcomatous differentiation, no intracytoplasmic mucin, and no glandular formation were present in any case. All 12 cases had foci of typical urothelial carcinoma present at least focally and a gradual transition to the chordoid pattern was commonly seen.[68] Rarely, bladder carcinomas may exhibit rhabdoid features.

Other important observation when dealing with urothelial carcinoma is that occasionally tumors with divergent differentiation show multiple histologic patterns within the same tumor such as sarcomatoid, small cell, micropapillary, squamous and glandular differentiation, and virtually all variants described above could be present. [1] When multiple histologies are encountered, it is recommended to report the relative percentage of each of the different components.

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