Update on Urinary Bladder Pathology:

Recently described and unusual tumors of the urinary bladder

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Greater than 90% of bladder carcinomas are urothelial carcinomas. These have a great propensity to divergent differentiation. This occurs typically in high-grade disease resulting in a number of subtypes. These subtypes are morphologically unique and have significant diagnostic, prognostic and therapeutic differences. Squamous and glandular subtypes are the most common. These with a number of other well characterized morphological subtypes are described in the 2004 WHO classification. Some other subtypes have been described or more fully characterized only in the relatively recent past. Some of these have been listed in the 2004 WHO classification while others have not been included. In this article, recently described and selected unusual variants of urothelial carcinoma with significant new information are discussed. The following topics will be reviewed: Large nested and nested variants of urothelial carcinoma, Large cell undifferentiated carcinoma not otherwise specified, Lymphoepithelioma-like carcinoma, Osteoclast rich undifferentiated carcinoma, Pleomorphic giant cell carcinoma, urothelial carcinoma with syncitiotrophoblastic giant cells, Lipid cell variant of urothelial carcinoma, Micropapillary Urothelial Carcinoma, Urothelial carcinoma with abundant myxoid stroma and plasmacytoid variant of urothelial carcinoma.

LARGE NESTED VARIANT OF UROTHELIAL CARCINOMA

Epidemiology and Clinical features
An invasive urothelial carcinoma (UC) displaying deceptively bland cytological features and a large nested architecture, often mimicking low-grade urothelial carcinoma with an inverted growth pattern was first reported by Cox and Epstein in 2011. Twenty three cases in this series are the only reported of this entity to date. As with typical UC, these occurred more commonly in males and in an older age group with an age range of 39-89 years.

Pathological features
Histologically, the invasive component has medium to large-sized nests with rounded or irregular borders or both. These are typically spaced apart with abundant fibrous or muscular stroma in between. Rarely the invasive component shows a verruciform pushing growth front reminiscent of verrucous squamous cell carcinoma and these typically extend into the muscularis propria. Rarely cysts, necrosis, tubules and gland
formation are present. A fibro-inflammatory stromal reaction may or may not be present. A surface component of papillary UC is commonly present and this is often low-grade although rare cases can have associated high grade papillary UC. Invasion into muscularis propria is commonly present with occasional cases displaying invasion into perivesical tissues. Conventional invasive UC can also be seen in some cases although usually this is only a small component. Tumor cells are typically bland with uniform vesicular nuclei, only occasional hyperchromatic or enlarged nuclei and often only small or indistinct nucleoli. Mitotic figures are rare with 1.5 per 10 high power fields reported. Lymphovascular invasion has also been found rarely.

**Differential diagnosis**

Distinction of these tumors from low-grade papillary urothelial carcinoma with an inverted growth pattern is clearly difficult given the large nested architecture, bland cytology, absence of a stromal reaction in some cases and the presence of an accompanying low-grade exophytic papillary UC in most cases. Presence of large nests within the muscularis propria and an invasive appearance despite the large nested pattern are not features of papillary UC with an inverted growth pattern. In contrast to papillary UC with an inverted growth pattern which has rounded nests which are fairly uniform and evenly spaced, in large nested carcinoma the nests within the lamina propria and muscularis propria are variably sized and shaped, some with irregular borders and unevenly distributed, often separated by broad areas of fibrous tissue or smooth muscle with little or no back-to-back nests present. Inverted papilloma which is characterized by fairly uniform trabeculae and cords extending into the lamina propria and von Brunn nests can be distinguished from the large nested variant of UC due to the variably sized and shaped haphazardly infiltrating nests. Rarely, however these may pose a differential diagnostic problem. In contrast to these lesions, large nested carcinoma has mild cytologic atypia with mild pleomorphism and scattered hyperchromatic nuclei. Large nested carcinoma shares with the nested variant of UC, bland cytological features. However, the typical nested variant is composed of confluent small nests of varying shapes often lacking intervening stroma.

**Prognosis and treatment**

The large nested variant of UC appears to be an aggressive variant. Three of 17
patients with follow-up have developed metastatic disease with 2 patients dying of disease.

NESTED VARIANT OF UROTHELIAL CARCINOMA

Epidemiology and Clinical features
Nested urothelial carcinoma is an aggressive variant of urothelial carcinoma resembling von Brunn nests due to its small nested architecture and deceptively bland cytologic features. This is a rare tumor reported mostly as individual cases or small series. The largest series of this entity, of 30 cases was reported in 2010. Patients are aged between 41-83 years and there is a marked male predominance. Patients usually present with hematuria or urinary obstructive symptoms.

Pathological features
Most cases occur in the bladder, but cases have been also reported in the renal pelvis and ureter. In the recently reported series, pure nested carcinoma was seen in 37% and associated with <50% of conventional urothelial carcinoma in 63%. Most of the conventional urothelial carcinoma in these cases was high grade and rarely low-grade papillary. Urothelial carcinoma in situ was seen in some cases. Histologically, there are small nests resembling von Brunn nests displaying bland cytologic features. Some of these display variable size and disorderly proliferation with some confluence and focal cordlike areas. There can be focally prominent tubular growth pattern and areas resembling cystitis cystica. The deeper portion is invariability ragged and infiltrative. There are foci of high-grade cytologic atypia with enlarged nuclei and coarse chromatin, most prominent in the deep part of the tumor. A stromal reaction can be minimal but can be desmoplastic or myxoid and rarely there can be focal tissue retraction. Lymphovascular invasion is common.

Immunostaining is identical to that seen in conventional urothelial carcinoma with CK7, CK20, p63 and 34βE12 positivity.

Differential diagnosis
This entity can cause significant diagnostic problems with benign entities such as von Brunn nests, cystitis cystica and glandularis, nephrogenic metaplasia, carcinoid and paraganglioma. This is a particular problem in small biopsy specimens. It can also be under recognized as conventional urothelial carcinoma. This lesion is distinguished from benign urothelial lesions by its disorderly growth pattern, irregular jagged infiltrating deep portion of the tumor, foci of prominent cytologic atypia most marked in the deep infiltrating portion and in most cases and muscularis propria invasion which is not seen in benign urothelial perforations.

Nephrogenic metaplasia in contrast to this tumor, typically has a mixed pattern including, tubular, papillary, vascular-like dilated structures and only rarely has deep muscle invasion.

In contrast to this tumor, inverted papilloma has invaginated cords of cells and lacks a nested architecture and carcinoid has a monotonous pseudoglandular pattern with regular uniform nuclei containing stippled chromatin.

This tumor can mimic paraganglioma, however, the prominent vascular network of paraganglioma surrounding nests of cells is usually not present in nested carcinoma.

**Prognosis and treatment**

Most cases (85%) present at an advanced stage (≥pT2) and have a progressive clinical course with 70% dying of metastatic cancer 4-40 months after diagnosis despite therapy. In the recently reported large series, invasion of muscularis propria at TURBT, pT3 disease at cystectomy and metastatic disease at presentation were found in 70%, 83% and 67% compared with 31%, 33% and 19% with conventional urothelial carcinoma. There were no significant differences in clinical stage, pathologic stage or later development of metastases between the pure nested group and those with partially nested morphology associated with conventional urothelial carcinoma. For muscle invasive, nonmetastatic disease, radical cystectomy is the treatment of choice. The use of neoadjuvant or adjuvant chemotherapy might offer a survival advantage in some patients.

**LARGE CELL UNDIFFERENTIATED CARCINOMA OF THE URINARY BLADDER**
**Epidemiology and Clinical features**

Large cell undifferentiated carcinoma not otherwise specified (LCUC) is characterized by sheets of large polygonal or round cells with moderate to abundant cytoplasm and distinct cell borders. This has been previously included with other tumors such as pleomorphic giant cell carcinoma, osteoclast-rich undifferentiated carcinoma and lymphoepithelioma like carcinoma as undifferentiated carcinoma. The 2004 WHO classification has a brief section on undifferentiated carcinoma without describing features of this entity. LCUC has been suggested to occur in the recent literature, however, the only series of these cases to date was published only in 2010 by Lopez Beltran et al. This is a rare tumor of unknown incidence considering that it is likely to be reported as high-grade urothelial carcinoma by some pathologists. It occurs mostly in men and the reported age range was 61-87 years. Presenting features are usually hematuria sometimes with dysuria and frequency.

**Pathological features**

Histologically there are solid expansile sheets or infiltrating tumor composed of large polygonal or round cells with moderate to abundant eosinophilic cytoplasm, distinct cell borders and vesicular nuclei with prominent sometimes multiple nucleoli. A high mitotic count is typically seen. In the reported cases, a conventional urothelial carcinoma component was seen in a few cases, although this was small. These tumors are positive for cytokeratin AE1/AE3, and CK 7, sometimes for CAM 5.2, CK 20, thrombomodulin and uroplakin 111 and have a high proliferation index on Ki 67 immunohistochemistry. These are negative for neuroendocrine markers, beta-HCG, alpha-fetoprotein and PSA.

**Differential diagnosis**

An important differential diagnostic consideration in these cases is metastatic malignancy. The possibility of metastatic disease has to be ruled out clinically and radiologically before the diagnosis of LCUC. Immunostaining with positivity for cytokeratin, thrombomodulin and Uroplakin 111 can be of value. Presence of a typical urothelial carcinoma component is very useful in the diagnosis. Pattern 5 Prostatic adenocarcinoma typically has smaller, more monotonous cells which can be at least focally PSA positive. Anaplastic large cell lymphoma is also composed of
sheets of polygonal cells with a moderate amount of cytoplasm. However these tumor cells are not cohesive, are negative for cytokeratin and positive for lymphoid markers.

LCUC needs also to be differentiated from large cell neuroendocrine carcinoma. Large cell neuroendocrine carcinoma also has large cells with abundant eosinophilic cytoplasm, however appears different with coarsely granular chromatin, only occasional prominent nucleoli and a nesting pattern typical of neuroendocrine differentiation. These tumors are also uniformly reactive for synaptophysin or chromogranin. Lymphoepithelioma-like carcinoma is another undifferentiated carcinoma which in contrast to LCUC has a heavy inflammatory infiltrate almost obscuring the neoplastic cells. Plasmacytoid urothelial carcinoma typically has dyscohesive cells with small hyperchromatic eccentric nuclei with plasmacytoid features. Osteoclast-Rich undifferentiated carcinoma in contrast to LCUC has a biphasic appearance with numerous osteoclast-type giant cells. In contrast to the monotonous cells in LCUC, pleomorphic giant cell carcinoma has numerous highly pleomorphic tumor giant cells. Given the presence of focal vacuoles in LCUC, rarely signet ring cell adenocarcinoma and lipid cell variant of urothelial carcinoma may be considered in the differential diagnosis. However, in these cases vacuoles containing mucin or suggesting lipoblasts are numerous.

**Prognosis and treatment**

Given that there could be associated focal conventional urothelial carcinoma, LCUC may represent a poorly differentiated urothelial carcinoma. This tumour appears to have a dismal prognosis although reported number of cases is small. In the reported series all patients had advanced disease at presentation (≥pT3) and 87% had lymph node metastases. With follow up ranging from 6-26 months 75% of patients died of disease and 25% were alive with metastases. When compared with conventional urothelial carcinoma of similar stage, the survival was significantly worse in LCUC.

**LYMPHOEPITHELIOMA-LIKE CARCINOMA**

**Epidemiology and Clinical Features**

Lymphoepithelioma-like carcinoma is a rare entity characterised by syncytial masses
of undifferentiated carcinoma admixed with a prominent often obscuring inflammatory infiltrate resembling nasopharyngeal undifferentiated carcinoma or lymphoepithelioma. These tumours occur predominantly in the bladder with rare cases reported in the renal pelvis and the urethra. Males are much more commonly affected with the reported age range 44-90 years (mean age: 70 years).

**Pathological Features**

Lymphoepithelioma-like carcinoma can be pure, predominant or focal. Most cases are pure, while others are seen in association with other patterns of carcinoma, including invasive urothelial carcinoma, invasive adenocarcinoma and squamous cell carcinoma. Up to 50% of cases are associated with urothelial carcinoma in situ. Rarely, there can be surface high grade papillary urothelial carcinoma. Microscopically, there are nests, sheets cords and individual cells of undifferentiated carcinoma cells with large pleomorphic nuclei and prominent nucleoli. The cytoplasmic margins are poorly defined imparting a syncytial appearance. This is associated with a prominent inflammatory infiltrate which often obscures the carcinomatous component. Rarely, typical lymphoepithelioma-like carcinoma can have focal glandular differentiation or focal clear cell change. The inflammatory infiltrate consists predominantly of lymphocytes or a mixed inflammatory infiltrate composed of neutrophils, eosinophils, lymphocytes, histiocytes and plasma cells.

None of the cases have demonstrated Epstein Barr Virus infection in the form of EBV-encoded RNA by in situ hybridization or immunohistochemistry for Epstein Barr Virus latent membrane prostate. Tumour cells are positive for AE1/AE3, EMA, 34 beta E12, CK7 and p63 in most cases. CD30 and Thyroid Transcription Factor-1 are consistently negative. CK20 staining has been found to be negative or only weakly positive. A recent study has shown frequent chromosomal abnormalities on FISH similar to those of urothelial carcinoma. In this study, tumours with concurrent urothelial, squamous, sarcomatoid and glandular components displayed identical FISH abnormalities present in both areas.

**Differential Diagnosis**

Due to the presence of a heavy inflammatory infiltrate, Lymphoepithelioma-like carcinoma can be misdiagnosed as a reactive inflammatory lesion or lymphoma. This
can be a particular problem in small biopsy samples. Careful examination should reveal an epithelial component and it is important to perform keratin Immunostaining in any suspicious cases. A large cell undifferentiated carcinoma can have focal inflammatory cells, but not the prominent inflammatory infiltrate seen in these cases. Another differential diagnostic consideration is high grade urothelial carcinoma with abundant lymphocytes in the stroma. In contrast to these cases, lymphoepithelioma-like carcinoma has a syncytial arrangement of undifferentiated cells, often obscured by the inflammatory infiltrate.

**Prognosis and treatment**

About 70% of the patients present as stage ≥pT2. This tumour has been found to be responsive to chemotherapy. Some studies have shown that cases which are predominantly or entirely lymphoepithelioma-like carcinoma have a better prognosis than those with only a focal lymphoid lymphoepithelioma-like carcinoma component. However, a recent study has shows that lymphoepithelioma-like carcinoma whether in pure or mixed form had a similar prognosis to conventional urothelial carcinoma when treated with cystectomy.

**OSTEOCLAST-RICH UNDIFFERENTIATED CARCINOMA OF THE URINARY TRACT**

**Epidemiology and Clinical features**

Bladder cancers with an undifferentiated histological appearance and giant cells with features of osteoclasts were designated “osteoclast-Rich undifferentiated carcinoma of the urinary tract by Baydar et al in 2006. This is a rare tumor with less than 30 cases reported in the literature. This is the largest series of this entity with 6 cases whereas previous reports had only 1 or 2 cases describing it as osteoclast-like giant-cell tumor of the urothelial tract. These have occurred mostly in males in their seventh decade or older, but one case was reported in a 39-year-old male. The presenting symptoms are nonspecific and typical for urothelial tumors in general with gross hematuria as the most common manifestation. These occur both in the bladder and the renal pelvis. Reported cases
have been large at presentation, ranging from 5 to 11 cm.

**Pathological Features**

Morphologically, these tumors closely resemble giant cell tumor of bone with a biphasic appearance. There is a background of sheets and nodules of mononuclear cells and scattered evenly spaced osteoclast-like giant cells. Mononuclear cells are plump ovoid or elongated with abundant cytoplasm. Mononuclear cells can display variable atypia with mild to moderate pleomorphism but not severe pleomorphism. Mitotic figures are often frequent and atypical mitoses can be seen. Giant cells are cytologically bland and uniformly distributed through the tumor. These are identical to osteoclastic giant cells with up to 50 nuclei with bi- or trinucleated variants. Prominent vascularity, large hemorrhagic areas, blood-filled cysts, red cell extravasation and deposition of hemosiderin are also features in common with giant cell tumor. Large areas of necrosis, widespread invasion into surrounding tissues, tumor thrombi in large veins and atypical mitoses also common in these tumours are in keeping with their aggressive behavior. In most cases reported, there is an associated high grade papillary or in situ urothelial carcinoma. However, a merging of the undifferentiated component with invasive high-grade urothelial carcinoma has not been demonstrated.

The multinucleated cells have morphological and immunohistochemical properties of osteoclasts, positive for markers of monocytic/ macrophage lineage, CD68, LCA , CD 51 and CD 54 and negative for cytokeratins and EMA. Ultrastructural similarities to osteoclasts have also been shown. The mononuclear component has variable expression of smooth muscle actin, desmin, S100, LCA and CD 68 similar to those in skeletal osteoclastic giant cell tumors. However, mononuclear cells can also be positive for epithelial markers, cytokeratin AE1/ AE3, CAM 5.2, CK 7 and EMA unlike these tumours. P53 can be positive in the mononuclear cells and in these cases parallels the staining of the accompanying urothelial carcinoma whereas the osteoclastic cells are always negative. Ki 67 stains mononuclear tumor cells but not the osteoclast -like giant cells.

**Differential Diagnosis**

Other tumors of the bladder with giant cells including pleomorphic giant cell carcinoma, carcinosarcoma with malignant spindled giant cells, invasive high-grade
urothelial carcinoma with syncytiotrophoblastic giant cells or reactive stromal giant cells and tumors of classical morphology of osteoclastic giant cell tumors are morphologically distinct from osteoclast-rich undifferentiated carcinoma of the bladder.

**Prognosis and treatment**
The histogenesis of this tumor has been debated. However, given the immunoprofile with focal epithelial marker positivity in the undifferentiated component and the association with high-grade urothelial carcinoma in most cases, this is likely to be a variant of urothelial carcinoma. The osteoclastic-like giant cells appear to be a reactive component. The behavior of these tumors is unlike that of giant cell tumor of bone with most cases presenting at an advanced stage. In the largest series of these tumors, 4 of 5 patients with follow-up died of disease within 15 months of diagnosis. Of 8 previously reported cases with follow up 60% died of disease.

**PLEOMORPHIC GIANT CELL CARCINOMA**

**Epidemiology and Clinical features**
Although mentioned in the 2004 WHO classification as a type of urothelial carcinoma with giant cells, characteristics of pleomorphic giant cell carcinoma were described in the literature only in 2009 when Lopez Beltran et al. reported a series of 8 cases. This is a rare aggressive variant of urothelial carcinoma characterized by the presence of highly pleomorphic bizarre tumor giant cells similar to giant cell carcinoma of the lung. It occurs more commonly in males with ages ranging from 55-88 years. Patients present with hematuria with dysuria or frequency.

**Pathological features**
The pleomorphic giant cell component in the reported series varied from 20% to 100% of the tumor. There are variably cohesive expansile masses or infiltrating nests or single cells of pleomorphic epithelioid tumor with bizarre anaplastic multinucleated and mononucleated tumor giant cells. Extensive necrosis is common. Tumor cells have abundant cytoplasm, and have frequent typical or atypical mitotic figures. A hypocellular desmoplastic stromal response, intracytoplasmic vacuoles or
hyaline droplets are seen in some cases. A chronic inflammatory cell infiltrate can be present but is not prominent. Occasionally, osteoclastic-like giant cells can be present but these are in the minority compared with the number of pleomorphic giant cells.

A concurrent conventional invasive urothelial carcinoma is present in most cases and sometimes there are other variants such as micropapillary urothelial carcinoma. Immunohistochemically, both the pleomorphic giant cell carcinoma and associated conventional urothelial carcinoma are positive for CK7, CAM 5.2, AE1/AE3 and EMA. Some cases are positive for P63, thrombomodulin and Uroplakin111. CK 20, Melan-A, HMB-45, beta-HCG, PSA, vimentin, synaptophysin, MyoD1 and desmin are negative. Ki 67 labeling index is high (up to 90%, mean 71%) and P53 staining ranges from 50-90%. 

**Differential diagnosis**

In contrast to sarcomatoid carcinoma, this tumor does not have a malignant spindle cell component. If there is a component of malignant spindle cells associated with pleomorphic giant cell carcinoma, then it has to be considered a mixed pleomorphic giant cell carcinoma and sarcomatoid carcinoma.

The giant cells in these cases are highly pleomorphic tumor giant cells morphologically distinct from those in osteoclast-rich undifferentiated carcinoma in which giant cells resemble osteoclasts and urothelial carcinoma with syncytiotrophoblastic giant cells. In contrast to osteoclasts which stain positively with CD68 and syncytiotrophoblastic giant cells positive for beta-HCG these giant cells are positive for epithelial markers.

Presence of an associated invasive conventional urothelial carcinoma component is helpful in differentiating primary pleomorphic giant cell carcinoma from metastatic carcinoma or melanoma. In other cases, clinicopathological correlation and immunostaining need to be performed.

Pleomorphic giant cell carcinoma arising in the prostate can spread to the bladder and can be PSA negative or only focally positive. Presence of conventional urothelial carcinoma and other variants of urothelial carcinoma versus presence of other patterns of prostate cancer can help in the differentiation. In other cases a panel of immunostains including 34 β E12, P63, PSA, PSAP and uroplakin should be performed.
Prognosis and treatment
This tumor has a very poor prognosis. Patients have advanced stage cancer at presentation ( ≥pT3) and often have lymph node metastases. In the reported series, 2 90% died of disease or were alive with metastases up to 19 months later. Only 10% had no evidence of disease at 74 months.

UROTHELIAL CARCINOMA WITH SYNCYTIOTROPHOBLASTIC GIANT CELLS

Epidemiology and Clinical features
Trophoblastic differentiation is a very rare form of divergent differentiation in urothelial carcinoma. It may take the form of HCG production in an otherwise typical urothelial carcinoma, syncytiotrophoblastic giant cells within a urothelial carcinoma and exceptionally rarely, choriocarcinoma in association with urothelial carcinoma. 22-24 Patients usually present with macroscopic haematuria, a tumor mass on cystoscopy, elevation of serum and urinary HCG or Gynecomastia due to the HCG elevation

Pathological features
Microscopically, there is invasive high-grade urothelial carcinoma with scattered syncytiotrophoblastic giant cells. These have deeply eosinophilic cytoplasm and multiple large irregularly shaped hyperchromatic and often smudged appearing nuclei. These often have cytoplasmic lacunae. Invasive high-grade urothelial carcinoma with associated choriocarcinoma has an admixture of syncitiotrophoblastic, cytotrophoblastic and intermediate trophoblastic tissue in a haemorrhagic background. This tumor is highly vascular with prominent necrosis and frequent mitoses including atypical mitoses. Syncytiotrophoblastic cells are positive for Human chorionic gonadotrophin (HCG), placental alkaline phosphatase, human placental lactogen, alpha inhibin, epithelial membrane antigen and cytokeratin
Differential diagnosis
This tumor is morphologically distinct due to the presence of characteristic syncytiotrophoblastic cells with deeply eosinophilic cytoplasm and multiple irregularly shaped often smudged appearing nuclei, in a background of conventional high grade urothelial carcinoma in contrast to pleomorphic giant cell carcinoma in which the giant cells are bizarre anaplastic mononuclear or multinuclear tumor giant cells in a highly pleomorphic undifferentiated background and undifferentiated carcinoma with osteoclast-like giant cells in which the giant cells have features of osteoclasts.

Choriocarcinoma from a primary arising in the genital tract can spread to the bladder. Clinicopathological correlation is helpful in this diagnosis.

Prognosis and Treatment
Prognosis of urothelial carcinoma with syncytiotrophoblastic giant cells and choriocarcinoma appears to be much worse than that of typical high grade urothelial carcinoma, including those displaying HCG positivity. In most cases, survival has been less than 1 year. Treatment includes cystectomy and combination chemotherapy

LIPID CELL VARIANT OF UROTHELIAL CARCINOMA

Epidemiology and Clinical features
Lipid cell variant of urothelial carcinoma characterized by numerous lipoblast-like vacuoles was first described by Mostofi et al. in 1999. Since then, there have been a few case reports and a small series of 5 cases. Most recently, in 2010 Lopez Beltran et al. reported a series of 27 cases. This is a rare tumor occurring far more frequently in males than females. Age range reported has been 42-94 years with a mean age of 70 years. Patients usually present with hematuria with obstructive urinary symptoms, fever, anemia and urinary retention, occurring less commonly.

Pathological features
Histologically, there are solid expansile nests or infiltrating nests of large epithelioid cells containing abundant vacuolated cytoplasm indenting the nuclei imparting a lipoblast-like or signet ring cell like appearance to the cells. Nuclei can be
moderately to highly pleomorphic and sometimes nucleoli are prominent. High-grade conventional urothelial carcinoma is present in all cases (lipid cell component varying from 10-50%) and carcinoma in situ in some cases. Squamous or glandular differentiation or associated micropapillary or plasmacytoid urothelial carcinoma are present rarely.

Tumor cells are strongly positive for AE1/AE3 and CK7 and variably weakly staining for CK 20, CAM 5.2, EMA, thrombomodulin and 34 beta E12 and negative for vimentin and S100 protein. Mucin stains are negative in the vacuoles. Electromicroscopy supports the presence of lipid within tumor cells. Loss of heterozygosity (LOH) analysis using 4 polymorphic microsatellite markers (D9S171, D9S177, IFNA and TP53) revealed LOH for at least one marker in most cases with similar results in the lipid cell variant and conventional urothelial carcinoma. 

**Differential diagnosis**

Diagnosis can be difficult particularly in small biopsy samples. Given the presence of lipoblast-like cells, liposarcoma needs to be considered in the differential diagnosis. However, primary liposarcoma as a component of carcinosarcoma or secondary liposarcoma of the bladder is rare. Recognizing that the lipoblast-like cells are present within cohesive groups of epithelial cells and not within a liposarcomatous component is crucial in avoiding a misdiagnosis. Keratin staining and absence of S100 staining can help with the diagnosis.

Primary, signet ring cell adenocarcinoma can cause a diagnostic problem. Presence of many lipoblast-like cells and not single vacuoles and absence of cytoplasmic mucin can help in this differentiation. Metastatic signet ring cell carcinoma from other locations such as breast and stomach are also easily distinguished due to absence of single mucin containing vacuoles. Presence of an obvious urothelial carcinoma component in these cases can also help with the correct diagnosis.

**Prognosis and treatment**

These tumors have a poor prognosis with most cases advanced at presentation. In the series by Lopez Beltran et al., 45% had lymph node metastases at presentation, 60%
died of disease at 16-58 months and another 30% were alive with disease.

MICROPAPILLARY UROTHelial CARCINOMA

Epidemiology and Clinical features
Micropapillary Urothelial Carcinoma (MUC) is characterised by surface tumour of delicate papillary and filiform processes and invasive tumour of tight clusters of cells typically within tissue retraction spaces reminiscent of ovarian papillary serous carcinoma. MUC has morphological similarities to micropapillary carcinoma in other organs such as breast, lung and pancreas. This tumour was first described by Amin et al in 1994. Since then, there have been several case series reported with an incidence varying from 1-6%. Males are more commonly affected. The age range is 45-82 with a mean age of 66 years. Patients usually present with gross or microscopic haematuria but dysuria, recurrent UTI and urinary obstruction have been less common presenting symptoms.

Pathological features
MUC can occur anywhere in the urinary tract but most commonly involves the bladder. Grossly, tumours can be sessile, polypoid, ulcerative or infiltrative. Histologically, MUC is almost always associated with conventional Urothelial Carcinoma (UC). MUC has 2 distinct components. Surface MUC consists of small papillary tufts and delicate filiform processes, with or without central fibrovascular cores. Invasive MUC is characterised by small tight nests of cells, often seen within tissue retraction spaces. This pattern is often retained in metastatic sites. Cells often have a high nuclear cytoplasmic ratio and have small irregular nuclei with coarse uneven chromatin and prominent nucleoli. In some cases, there is more abundant clear or eosinophilic cytoplasm. Mitoses can be few to numerous and lymphovascular invasion is common. These are invariably high-grade given the coarse uneven chromatin, prominent nucleoli and often frequent mitoses, even though prominent pleomorphism may be difficult to appreciate due to a cell size smaller than that of conventional UC. In about 60% of cases there is associated urothelial CIS. Psammoma bodies are usually not found. MUC can rarely be associated with foci of
gland forming adenocarcinoma and even small cell carcinoma. A rare case with trophoblastic differentiation has been reported. Recently MUC has been reported in association with pleomorphic giant cell carcinoma and plasmacytoid UC indicating divergent differentiation. Metastases have been reported in lymph nodes, bone, peritoneum, lung, pleura, skin and the liver.

Immunohistochemical findings
Almost all cases are positive for epithelial membrane antigen (EMA), CK 7, CK 20 and Leu- M1, and many cases for carcinoembryonic antigen (CEA), 34beta E12 , PTEN, p53, Ki-67, Her2Neu, uroplakin , CA125, p16 and MUC1 and 2. A smaller number of cases show immunostaining for B72.3, BerEp4, placental alkaline phosphatase and S-100 protein. E-cadherin has also been shown to be diffusely positive in these tumors.

Differential diagnosis
MUC of the urinary tract needs to be differentiated from metastatic carcinoma with micropapillary histology from ovary, endometrium, lung, breast, GIT and salivary glands. Presence of urothelial carcinoma in situ, papillary or invasive conventional UC points to a urothelial primary cancer. In other cases, clinicopathological correlation is necessary demonstrating absence of a primary tumor elsewhere.

Immunohistochemical staining can be helpful, particularly with Uroplakin 111 and thrombomodulin, which are present in many MUC but not in ovarian, breast, lung or colonic tumours. 34 beta E12 present in most MUC, are only rarely present in other tumours. CK 7+/CK 20+ immunophenotype strongly suggests a urothelial primary, whereas MPC from lung, breast and ovary are most likely CK 7+/CK 20 −. A recent study found that uroplakin and CK 20 were most useful in identifying MUC whereas p63, high molecular weight cytokeratin, and thrombomodulin were less sensitive and specific. In this study, lung MPC was uniformly TTF-1 positive, breast MPC, ER and mammaglobin positive, and PAX8/WT-1 negative, while ovarian MPC was ER positive, mammaglobin negative, and PAX8/WT-1 positive.

When dealing with metastatic MPC of unknown primary, MUC should be considered a possibility. It is important to differentiate MUC from other MPC as treatment options are different. Clinicopathological findings and immunohistochemistry are again helpful in this setting.
**Genetics**

In 5 cases studied, MUC showed non-diploid indices with three cases displaying a higher DNA index than conventional non-invasive papillary UC. In another study of five cases, with sequencing used to identify point mutations in exons 5 to 9 of p53 and exons 1 and 2 of H-ras no significant abnormalities were found.

**Prognosis and treatment**

The overall prognosis for micropapillary urothelial carcinoma is poor with patients often presenting at an advanced stage and about 20% with metastases. The proportion of MUC appears to impact on the stage at presentation and survival. However, micropapillary morphology appears to worsen the outlook for UC irrespective of whether it is focal or diffuse, and therefore any amount of MUC should be reported. Recent studies suggest that early treatment with cystectomy could improve outcome, as these tumors are unlikely to respond to chemotherapy when used as a secondary treatment option. Given the immunoreactivity of these tumors to Her2Neu and PTEN, targeted therapy maybe a useful treatment option to be developed.

**UROTHELIAL CARCINOMA WITH ABUNDANT MYXOID STROMA**

**Epidemiology and Clinical features**

Although briefly mentioned in text books, urothelial carcinoma with abundant myxoid stroma was first described in detail only in 2009 when Tavora and Epstein reported a series of 13 cases involving the bladder. Shortly thereafter Cox et al. reported a series of 12 similar cases which were labeled invasive urothelial carcinoma with chordoid features, given the distinct cord like arrangement of tumour cells, at least focally resulting in patterns resembling myxoid chondrosarcoma, chordoma and yolk sac tumor. These tumours are striking due to the presence of abundant extracellular virtually acellular pools of mucin resembling mucinous adenocarcinoma, but in the absence of any glandular differentiation. These tumours were not listed in the 2004 WHO classification as a separate entity, although mentioned in the section of
infiltrating urothelial carcinoma with glandular differentiation. This is a rare tumour, although in the series by Cox et al at least 5% of extra cellular myxoid stroma was found in about 7% of invasive urothelial carcinoma cases. The histogenesis of this tumor is controversial with some suggestion that the extracellular mucin is secreted by the urothelial carcinoma. These occur more commonly in males than females with a mean age of 66 (range 45-85years).

Pathological features
In all cases, acellular myxoid stroma is seen in association with invasive urothelial carcinoma. The percentage of the tumour with myxoid stroma ranges from 5-95%. Tumour cells have sparse to moderate amounts of cytoplasm and are arranged in cords, small to medium sized nests, filigree patterns and microcysts with single cells and sheets of cells found rarely. Nuclear features are those of high grade carcinoma in most cases but lack prominent pleomorphism and the mitotic count is typically low. A few can have receptively bland cytologic features similar to the nested variant of UC. Some cases are associated with a papillary urothelial carcinoma which can be high grade or low grade. There can be associated other variants and urothelial carcinoma in situ. These tumours do not show gland formation, intra-cytoplasmic mucin or sarcomatoid differentiation.
The myxoid stroma stains positively with Alcian blue with and without hyaluronidase, PAS, colloidal iron and mucicarmine. Tumor cells are positive for CK7, 34βE12, p63 and variably positive for CK20, MUC2, MUC5 and polyclonal CEA. Tumor cells are negative for CDX2, calponin and GFAP.

Differential diagnosis
These tumors can be confused with adenocarcinoma either primary in the bladder or metastatic, particularly from the prostate or intestine. Mucinous prostatic adenocarcinoma can mimic these tumors given that there are pools of mucin and relatively bland cytology. In contrast to nests and cords of cells in these tumors, mucinous prostatic adenocarcinoma, typically has individual or cribriform glands floating in mucin. In bladder adenocarcinoma (including mixed urothelial carcinoma and adenocarcinoma) and intestinal adenocarcinoma, mucinous pools are lined by neoplastic epithelium displaying varying degrees of atypia.
In contrast to this tumor, micropapillary urothelial carcinoma shows prominent retraction artifact surrounding small tight nests of tumor cells reminiscent of papillary serous carcinoma.

Sarcomatoid carcinoma can mimic this tumor given the presence of myxoid stroma. In sarcomatoid carcinoma, there are malignant spindle cells embedded in myxoid stroma in contrast to these tumors in which hypocellular myxoid stroma surround urothelial carcinoma. Similarly, in urothelial carcinoma with pseudosarcomatous stroma, there are atypical spindle cells in the stroma.

The recently described myxoid cystitis with “chordoid” lymphocytes can mimic this tumor due to the abundant myxoid stroma and cords of epithelioid cells with scanty cytoplasm and round nuclei. In this case the epithelioid cells are B lymphocytes, have bland nuclei and are admixed with other inflammatory cells. Immunostaining can sometimes be necessary to confirm the B-cell nature of these cells.

Another possible mimic is the fibromyxoid variant of nephrogenic adenoma which can have a corded pattern of growth. Nephrogenic adenoma often has other patterns typical of nephrogenic adenoma and hyaline basement membrane material around epithelium. This also expressed nuclear PAX-2 and PAX-8 which is not usually seen in urothelial carcinoma

**Prognosis and treatment**

It is difficult to ascertain how the prognosis of this tumor compares with that of conventional urothelial carcinoma. In one study, 69% presented with invasion of only lamina propria and only 31% had invasion of muscularis propria. 22% of patients in this series developed metastases and died of disease while a subset, although only with limited followup, had no evidence recurrence or metastases after TURB with or without BCG. In the other series, most cases were high stage at presentation (92% PT 2 or greater) and 6 of 9 patients with 1-10 months followup died of disease or were alive with metastases.

**PLASMACYTOID UROTHELIAL CARCINOMA**

**Epidemiology and Clinical features**
Plasmacytoid urothelial carcinoma is a unique variant of urothelial carcinoma in which tumor cells bear a strong resemblance to plasma cells. Since its first description in 1991, there have been several case reports and series published. With the largest series of 32 cases reported in 2011 by Kech et al., plasmacytoid differentiation has been reported in 2.7% of muscle invasive urothelial cancers. These tumors occur most commonly in males at an age range of 48–87. The median age of patients with muscle invasive plasmacytoid carcinoma was 56.9 years in one study, which was significantly lower than that of conventional urothelial carcinoma. Patients usually present with hematuria, dysuria, frequency or nocturia.

**Pathological features**

In reported cases the plasmacytoid component has varied from 10-100% of the tumor with the majority of cases displaying >50%. Histologically, tumor cells are present singly and in solid expansile non-cohesive nests. Sometimes there are alveolar patterns and strands of cells. The growth pattern is reminiscent of lobular carcinoma of the breast. Tumor cells are small to medium-sized, have eccentrically placed nuclei, abundant eosinophilic cytoplasm and sometimes an eosinophilic paranuclear hof reminiscent of plasma cells. Nuclei have mild to moderate pleomorphism. Nucleoli are indistinct. Intracytoplasmic vacuoles can be present. A large proportion of cases are associated with conventional invasive high-grade urothelial carcinoma. Rarely there can be urothelial carcinoma in situ or associated variants such as nested or micropapillary urothelial carcinoma.

Immunostaining reveals positivity for, cytokeratins 7, 20, AE1/AE3, epithelial membrane antigen, GATA-3 (endothelial transcription factor), CD15, p53 and p16. CD138 is strongly positive in some cases. Tumor cells stain negatively for Leukocyte common antigen, vimentin, multiple myeloma 1/interferon regulatory factor 4, and κ and λ light chains. The vast majority of cases display negative or strongly reduced membranous staining for E-cadherin. Multitarget fluorescence in situ hybridization has shown that these are highly aneuploid and polysomic with deletions on chromosome 9p 21 appearing to play an important role whereas FGFR3 and PIK3CA mutations are not found. TP53 mutations are found in about one third of cases. Ki-67 labeling index ranges form 20% to 60% (mean, 35.5%).

21
Differential diagnosis

Diagnosis can be difficult particularly on small biopsy. Plasmacytoid urothelial carcinoma can be mistaken for chronic cystitis with a predominant plasma cell infiltrate or plasmacytoma/multiple myeloma. CD138 positivity in some cases can further cause problems given its positivity in plasma cells. Diagnosis may not be problematic if there is an associated conventional urothelial carcinoma component which is present in nearly 90% of cases of plasmacytoid urothelial carcinoma. In other cases, a panel of immunostains including epithelial markers are necessary to make this distinction.

Presence of vacuolated cells can raise the possibility of signet ring cell adenocarcinoma. Primary signet ring cell carcinoma of the bladder is rare. In contrast to these cases in which signet ring cells are the predominant component, these are rare and focal in the plasmacytoid urothelial carcinoma.

Metastatic carcinoma from other primary sites especially breast, stomach and colon need to be always considered in the differential diagnosis. Again, presence of a conventional urothelial carcinoma component is very helpful in identifying plasmacytoid urothelial carcinoma. In other cases, clinicopathological correlation and immunostaining are necessary to make this distinction.

Carcinoma with rhabdoid morphology also should be considered in the differential diagnosis with plasmacytoid urothelial carcinoma. Unlike plasmacytoid carcinoma these tumors have dense eosinophilic cytoplasmic inclusions, large vesicular nuclei, prominent nucleoli and display vimentin immunostaining.

Prognosis and treatment

These tumors are often advanced at presentation. In the largest series of these cases 64% presented at pT3 and 23% at pT4 and 60% had metastases. The average survival of patients treated with radical cystectomy and adjuvant chemotherapy was also found to be lower than that for comparable conventional urothelial carcinomas.
REFERENCES


25. Burry AF, Munn SR, Arnold EP, McRae CU


