MESENCHYMAL TUMORS OF THE URINARY BLADDER:
A SELECTIVE UPDATE

Overview

Neoplasms of the urinary bladder are relatively common tumors, accounting in the United States for between 2-6% of all tumors. The overwhelming majority of bladder tumors are epithelial in origin, with mesenchymal tumors accounting for fewer than 5% of bladder tumors in adults. In pediatric patients, however, nearly all tumors of the bladder are mesenchymal in origin, with rhabdomyosarcoma (RMS) accounting for nearly all of such tumors.

Essentially any mesenchymal tumor can occur in the adult bladder. Smooth muscle neoplasms (leiomyoma, leiomyosarcoma) account for well over 75% of bladder mesenchymal tumors, with tumors of endothelial differentiation (hemangioma, hemangioendothelioma, angiosarcoma) probably forming the next largest group. Other tumors that have been reported in small series or as isolated case reports include paraganglioma, osteosarcoma, fibrosarcoma, solitary fibrous tumor, alveolar soft part sarcoma, perivascular epithelioid cell neoplasm (PEComa), granular cell tumor, neurofibroma, lipoma, liposarcoma, and undifferentiated pleomorphic sarcoma (“malignant fibrous histiocytoma”). In my experience, inflammatory myofibroblastic tumors (IMT, post-operative spindle cell nodule, inflammatory fibromyxoid pseudotumor, pseudosarcomatous myofibroblastic proliferation) are much more common than any other mesenchymal tumor of the bladder exclusive of leiomyoma (LM) and leiomyosarcoma (LMS), although the exact incidence of IMT is difficult to ascertain.

This handout and lecture will focus on smooth muscle tumors of the bladder and rhabdomyosarcoma.

Smooth muscle tumors of the bladder

Leiomyoma

Clinical Features

LM is the most common benign mesenchymal tumor of the bladder, accounting for less than 1% of all bladder neoplasm. It may occur in patients of any age, and is much more common in women than in men. Patients with bladder LM frequently present with urinary symptoms or urinary obstruction.

Pathologic and Immunohistochemical Features

Bladder LM most often arises within the muscularis propria, but may also occur within the muscularis mucosa. LM are radiographically and grossly well-circumscribed, and are usually fairly small at the time of diagnosis, although exceptional cases measuring up to 25 cm in greatest dimension have been reported. Microscopically, bladder LM are well-circumscribed and non-infiltrative tumors, which consist of distinctly eosinophilic spindled cells with “cigar shaped” nuclei and perinuclear vacuoles, arranged in fascicles that intersect one another at right
angles. Mitotic activity and nuclear atypia are by definition absent. Hyalinization and cystic degeneration may be present. “Degenerative” or “symplastic” nuclear atypia has not been described in bladder LM, and the finding of any cytologic atypia should prompt a careful search for other features of malignancy, such as infiltrative growth, mitotic activity, or necrosis. By immunohistochemistry (IHC) LM of the bladder usually show strong expression of smooth muscle actin and variable expression of desmin. Strong desmin expression is much more reliably present in LM of the bladder than in smooth muscle tumors of somatic soft tissue, and the absence of desmin expression should prompt consideration of IMT. Low-molecular weight cytokeratins may occasionally be positive in LM as well. High molecular weight cytokeratin expression is not seen in LM, in contrast to sarcomatoid carcinomas.

Differential Diagnosis

LMS display infiltrative growth, cytologic atypia, mitotic activity, and frequently necrosis, features not allowable in LM. It is generally accepted that the presence of infiltrative growth is probably the single most important factor to evaluate in attempting to distinguish leiomyoma from low-grade, well-differentiated leiomyosarcoma of the bladder. IMT are less well-circumscribed lesions that typically show significant myxoid change, numerous admixed inflammatory cells, and longer, less eosinophilic spindled cells with tapered nuclei. Schwannomas are extremely rare in the bladder, and display identical histologic features to those occurring in more common locations, with strong S100 protein immunoreactivity. Perivascular epithelioid cell neoplasms (PEComas) typically show an admixture of epithelioid and spindled cells, with lightly eosinophilic to clear cytoplasm and small nucleoli. By definition, PEComas co-express actins and melanocytic markers, such as HMB45 and Melan A.

Leiomyosarcoma

Clinical Features

LMS is the most common sarcoma of the bladder, occurring most often in middle aged to elderly adults, more often in men. Bladder LMS have been associated with prior radiation therapy to the pelvis, and in association with previous cyclophosphamide treatment for systemic malignancies. Most patients with bladder LMS present with hematuria.

Pathologic features

Radiographically and grossly, LMS of the bladder tend to be much larger than LM (>5cm) infiltrative, with poorly defined borders and infiltrative growth. LMS of the bladder are identical to their counterparts in somatic soft tissue elsewhere, with intersecting, hypercellular fascicles of pleomorphic, mitotically active, eosinophilic spindled cells, often with necrosis. Occasional leiomyosarcomas may be extensively hyalinized or anaplastic, requiring IHC for diagnosis. LMS show an identical immunophenotype as LM, with uniform expression of smooth muscle actins, variable desmin expression, and occasional low molecular weight cytokeratin expression. Caldesmon expression, absent in myofibroblastic tumors, may also be useful in confirming smooth muscle differentiation. Myogenin and MyoD1 expression is not seen in LMS, unlike RMS.

Criteria for Malignancy, Grading and Staging

One could argue that criteria for malignancy have not been well-established, although there seems to be a general consensus that benign smooth muscle tumors should show 1) a total absence of infiltrative growth, 2) no cytologic atypia, and 3) absent (or very low) mitotic activity. Owing to the rarity of such cases, no study to date appears to have evaluated the
malignant potential of smooth muscle tumors of the bladder showing only one of these features, i.e., infiltrative tumors devoid of atypia or mitotic activity, or non-infiltrative tumors with cytologic atypia and/or elevated mitotic activity.

There is no universally accepted grading or staging system for LMS of the urinary bladder. Mills and colleagues used mitotic activity alone to distinguish low and high grade leiomyosarcomas, noting that infiltrative tumors with <5 MF/10 HPF had an excellent outcome, whereas 2 of 5 tumors with >5MF/10 HPF metastasized. Martin and co-workers considered as “low-grade” tumors with mild to moderate nuclear atypia, <5MF/10HPF, and <25% tumor necrosis, whereas tumors showing moderate to severe nuclear atypia, >5MF/10HPF and >25% necrosis were considered “high grade”. By definition, all tumors classified as leiomyosarcoma were infiltrative. In this study, the metastatic rate for putative low and high grade leiomyosarcomas was 33% and 75%, respectively. A recent series of high-grade tumors (grading scheme not stated) from MD Anderson found a 5-year disease-specific survival of 62% for patients with LMS of the bladder, confirming the aggressive nature of this disease.

In somatic soft tissue, the French Federation of Cancer Centers (FNCLCC) grading scheme has been shown to be strongly predictive of behavior in LMS, in both univariate and multivariate analysis. This grading scheme is presented below, in Appendix 1. Similarly, for somatic soft tissue LMS, Farshid and colleagues have shown a strong association between adverse patient outcome and FNCLCC grade 3, large size, incomplete excision, and intravascular extension. Unlike the situation in uterine smooth muscle tumors, which clearly behave in a different fashion to their somatic soft tissue counterparts, I can see no clear reason why bladder LMS should not be graded using the FNCLCC system. At the very least, this would seem to be a reasonable hypothesis to test in a large, multicenter study of such tumors, and I very much hope that we as pathologists will undertake such a study in the immediate future.

There is no organ-specific staging system for bladder leiomyosarcoma. Recent series from MD Anderson and other cancer centers have utilized the AJCC/MSKCC staging system for soft tissue sarcomas generally, and this is probably the best system to use at the present time.

Differential Diagnosis

The distinction from LM is discussed above. Sarcomatoid carcinoma often are associated with high-grade papillary urothelial neoplasms or urothelial CIS, and typically show strong cytokeratin expression, including high molecular weight cytokeratins. Actin expression is uncommon in sarcomatoid carcinoma, and desmin expression is almost unheard of. IMT displays a more loosely textured, myxoid background with numerous inflammatory cells, and usually does not show well-defined fascicles of distinctly eosinophilic cells, intersecting at right angles. Most IMT are devoid of cytologic atypia. By IHC, desmin expression is typically absent in IMT. ALK-1 expression, although non-specific, may be helpful in distinguishing IMT from LMS; demonstration of ALK gene rearrangements by FISH is much more specific, in my experience.

Rhabdomyosarcoma

General comments

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in pediatric patients, and accounts for nearly 20% of soft tissue sarcomas overall. In children, close to 20% of rhabdomyosarcomas arise in the pelvic portion of the genitourinary tract. The most common locations for genitourinary RMS are the paratestis, urinary bladder, prostate and vagina. RMS of the bladder and prostate are typically treated as a single group, as it may be difficult if not impossible to distinguish RMS of the bladder from those of the prostate, and as these tumors
have a worse prognosis than do non-bladder/prostate RMS.

There are 3 main subtypes of rhabdomyosarcoma: embryonal (including botryoid), alveolar and pleomorphic. Pleomorphic RMS is essentially unheard of in the bladder, and will not be covered in this handout. Based on the very small number of previously reported cases, the histologic features and clinical behavior of PRMS of the bladder are identical to those in other sites, and the reader is referred to standard soft tissue texts.

Embryonal rhabdomyosarcoma (ERMS) accounts for over 70% of rhabdomyosarcomas in children, with the alveolar rhabdomyosarcoma (ARMS) accounting for essentially all other pediatric cases. Older cases in the literature described as pleomorphic rhabdomyosarcoma (PRMS) in children very likely represent ERMS with anaplasia. It is not widely appreciated that ERMS remains the most common subtype of rhabdomyosarcoma in adults, with ARMS the next most common, and pleomorphic rhabdomyosarcoma (PRMS) the least common subtype. Essentially all PRMS, however, occur in adults. Prognosis in pediatric rhabdomyosarcoma is directly related to histologic subtype, with ERMS having a far better prognosis than ARMS. In contrast, histologic subtype does not appear to predict outcome in adult patients with rhabdomyosarcoma.

Overall Prognosis

The prognosis for bladder RMS has improved over the past few decades. In the first Intergroup RMS study, overall survival for bladder RMS was 78%, with bladder preservation in only 23% of patients. The rates of survival and bladder preservation were similar in IRS-II. Overall survival improved to 83% in IRS-III, with multiagent standardized chemotherapy, and bladder preservation was possible in 60% of patients. Results from IRS-IV, published by Arndt and colleagues in 2004, showed a 6-year disease free survival of 82%, with bladder preservation in 55% of event-free survivors, and relatively normal bladder function in 40% of all patients. The prognosis for patients with rare ARMS of the bladder remains grim, with up to 60% of patients dying from disease.

Embryonal Rhabdomyosarcoma

Clinical Features

Embryonal rhabdomyosarcoma is the most common type of rhabdomyosarcoma in the bladder, accounting for well over 75% of RMS in two recent large series of bladder RMS from the USA and Germany, respectively. The favorable prognosis botryoid variant of ERMS accounts for roughly 15% of ERMS in the USA (IRS-IV) and nearly 50% of cases in the German series. RMS of the bladder present with urinary symptoms, hematuria, or simply as a palpable mass. Botryoid tumors are by definition polypoid tumors, typically showing relatively minimal permeation of the bladder wall, whereas polypoid growth is less frequent and permeative growth much more extensive in non-botryoid ERMS and ARMS.

Pathologic Features

ERMS are characterized by primitive mesenchymal cells showing varying degrees of rhabdomyoblastic differentiation. In most cases a spectrum of differentiation is present, with primitive small round cells, undifferentiated-appearing spindled cells, strap cells with brightly eosinophilic cytoplasm and cross-striations, and larger, ganglion-like rhabdomyoblasts. Occasional tumors may be either extremely poorly differentiated, resembling an undifferentiated sarcoma, or very well-differentiated, mimicking rhabdomyoma. Mitotic activity is invariably present and necrosis is frequent. Myxoid change is frequent. Lesions occurring in a submucosal
location typically grow in a polypoid fashion (botryoid variant of ERMS) and show a cambium zone of increased cellularity immediately below the mucosa; such lesions are often extensively myxoid and may appear deceptively bland. The spindle cell variant of ERMS is characterized by well-differentiated, relatively bland-appearing spindled cells arranged in a fascicular or storiform pattern, reminiscent of a smooth muscle tumor or a fibrous histiocytoma. So-called “sclerosing rhabdomyosarcoma” most likely represents an additional variant of ERMS, based on its histologic, immunohistochemical and genetic similarities with conventional ERMS; these rare cases are characterized by the presence of a strikingly sclerotic, osteochondroid-like stroma, a microalveolar pattern, primitive round cells with only occasional rhabdomyoblastic differentiation in the form of strap cells, and diffuse MyoD1 expression despite only focal expression of myogenin and desmin. By IHC, ERMS typically show diffuse desmin immunoreactivity, with variable expression of myogenin, MyoD1 muscle-specific actin and smooth muscle actin. Expression of myoglobin is much less frequent, particularly in poorly differentiated ERMS. Synaptophysin, S100 protein and cytokeratins may also be expressed by some ERMS.

The evaluation of post-chemotherapy biopsies and/or resections from patients with ERMS may be challenging. It is important to distinguish residual viable ERMS from terminally differentiated rhabdomyoblasts, as the prognosis for patients whose post-treatment biopsies show only the latter appears to be improved, and as these patients may not require cystectomy. Mature rhabdomyoblasts are amitotic, and show a normal nuclear to cytoplasmic ratio, with small, dense nuclei. Expression of myogenin and MyoD1 is usually lost, while myoglobin is expressed. In contrast, residual viable ERMS cells have a higher N/C ratio, may show mitotic activity, and retain myogenin/ MyoD1 expression.

Genetic findings

At the cytogenetic level, ERMS are characterized by complex structural and numerical abnormalities, including trisomies of chromosomes 2, 8, and 13. Molecular analyses commonly show allelic loss at chromosome 11p15, a site containing a number of putative tumor suppressor genes, including IGF2, H19, and CDKN1C. A specific translocation has not been associated with ERMS, unlike ARMS.

Differential Diagnosis

Conventional ERMS may show a spectrum of differentiation, and may therefore be confused with both other primitive round cell tumors, when poorly differentiated, or with rhabdomyomas and leiomyomas, when well-differentiated. IHC for desmin, myogenin and MyoD1 are critical in the distinction of ERMS from other round cell tumors, and should be performed on any such tumor in a child. In general, RMS display greater pleomorphism than do the other common round cell malignancies in the head and neck of children, specifically Ewing sarcoma/ primitive neuroectodermal tumor and lymphoblastic lymphoma. Malignant peripheral nerve sheath tumors with rhabdomyoblastic differentiation (so-called “malignant Triton tumor”) may closely simulate ERMS histologically and immunohistochemically. In general, MPNST with rhabdomyoblastic differentiation occur in much older patients with a long history of NF1, and may arise from a pre-existing neurofibroma. Infantile fibrosarcoma occurs in slightly younger patients than does ERMS, lacks expression on myogenic markers, and harbors a diagnostic translocation, t(12;15) (ETV6/NTRK3). Sclerosing RMS may closely simulate osteosarcoma or chondrosarcoma, and require IHC for confident diagnosis.

Alveolar Rhabdomyosarcoma

Clinical Features
Alveolar rhabdomyosarcomas (ARMS) occur in older patients than do ERMS, with a median patient age of between 7 and 9 years reported in two large series of pediatric RMS. A considerable number of ARMS also arise in adolescents and young adults. Most ARMS arise in the soft tissues of the extremities. The prognosis for ARMS is considerably worse than for ERMS, irrespective of other clinical or pathological features, with many tumors presenting at a high clinical stage. The 5 year survival rate of ARMS is only approximately 50%. Recent data suggests a considerably improved prognosis for ARMS patients with metastatic disease if their tumor contains a PAX7-FKHR fusion gene, rather than a PAX3-FKHR fusion gene, although fusion subtype does not appear to be a prognostic factor for patients with localized disease.

Pathologic Features

In its classic form, ARMS is a highly malignant-appearing, diffusely infiltrative tumor comprised of distinctive nests of primitive-appearing round cells, which grow in a dyshesive fashion, producing a pseudoalveolar pattern. The surrounding fibrous septae are hyalinized and highly vascular. Multinucleated tumor giant cells with brightly eosinophilic cytoplasm are occasionally identified within these nests, are foci of clear cell change. Straps cells and cells with cross striations are seldom if ever identified. Solid forms of ARMS lack the prominent nested pattern and cellular dyshesion seen in classic ARMS. A nested pattern is usually at least focally present, however. Rare cases show foci identical to ERMS; these mixed ARMS/ERMS appear to behave as ARMS, with a poor prognosis. By IHC, ARMS express desmin, myogenin and MyoD1, similar to ERMS. Myogenin expression is often much stronger than is MyoD1, which may occasionally aid in the subclassification of a given tumor as ARMS. As in ERMS, cytokeratin, S100 protein and synaptophysin expression may occasionally be seen, with potential for the misclassification of ARMS as small cell carcinoma or melanoma.

Genetic features

ARMS are characterized in nearly all cases by one of two specific translocations, t(2;13)(q35;q14), found in approximately 80% of cases, or t(1;13) (p36;q14), found in approximately 20% of cases. The t(2;13) results in fusion of the PAX3 gene on chromosome 2 to the FKR gene on chromosome 13, whereas the t(1;13) results in fusion of the PAX3 gene of chromosome 1 to the FKHR gene. Both fusion genes function as potent transcriptional regulators and produce high levels of their respective fusion proteins. These gene fusions may be demonstrated by traditional cytogenetics, RT-PCR or FISH, and are specific for ARMS, allowing its distinction from other round cell sarcomas.

ARMS differ from ERMS by virtue of its occurrence in older patients, distinctive pseudoalveolar pattern, usual absence of strap cells, and strong myogenin, rather than MyoD1 expression. Identification of a PAX3 or PAX7/FKHR fusion gene may be necessary for the confident distinction of ARMS from the most primitive forms of ERMS. IHC for myogenic markers is critical in the distinction of ARMS from other small round cell tumors, such as Ewing sarcoma, lymphoblastic lymphoma, small cell carcinoma, and melanoma. Desmoplastic round cell tumor may display a nested pattern reminiscent of ARMS and frequently expresses desmin, but lacks expression of myogenin or MyoD1, and contains a diagnostic t(11;22) (EWS/WT1) gene fusion. Alveolar soft part sarcomas are composed of large, eosinophilic cells, rather than small, round cells.

Selected References

# Appendix 1: FNCLCC Grading System for Soft Tissue Sarcomas

## FNCLCC Grading System: Definition of Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor differentiation</td>
<td>Sarcomas closely resembling normal adult mesenchymal tissue (e.g., well-differentiated liposarcoma)</td>
<td>Sarcomas for which histologic typing is certain (e.g., myxoid liposarcoma)</td>
<td>Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, osteosarcomas, PNET</td>
</tr>
<tr>
<td>Mitotic count</td>
<td>0–9 mitoses per 10 HPF+</td>
<td>10–19 mitoses per 10 HPF</td>
<td>≥20 mitoses per 10 HPF</td>
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<tr>
<td>Tumor necrosis</td>
<td>No necrosis</td>
<td>&lt;50% tumor necrosis</td>
<td>≥50% tumor necrosis</td>
</tr>
<tr>
<td>Histologic grade</td>
<td>Total score 2, 3</td>
<td>Total score 4, 5</td>
<td>Total score 6, 7, 8</td>
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</tbody>
</table>

* Modified from Troiani et al. with permission from John Wiley and Sons, Inc. FNCLCC indicates Fédération Nationale des Centres de Lutte le Cancer; PNET, primitive neuroectodermal tumor.  
+ A high-power field (HPF) measures 0.1734 mm².

## FNCLCC Grading System: Tumor Differentiation Score According to Histologic Type

<table>
<thead>
<tr>
<th>Histologic Type</th>
<th>Tumor Differentiation Score</th>
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<tbody>
<tr>
<td>Well-differentiated liposarcoma</td>
<td>1</td>
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<tr>
<td>Myxoid liposarcoma</td>
<td>2</td>
</tr>
<tr>
<td>Round cell liposarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Pleomorphic liposarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Well-differentiated fibrosarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Conventional fibrosarcoma</td>
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<tr>
<td>Poorly-differentiated fibrosarcoma</td>
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<td>Myxofibrosarcoma</td>
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<td>Pleomorphic MFH with storiform pattern</td>
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<tr>
<td>Pleomorphic MFH with no storiform pattern</td>
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<tr>
<td>Giant cell MFH</td>
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<tr>
<td>Well-differentiated leiomyosarcoma</td>
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</tr>
<tr>
<td>Conventional leiomyosarcoma</td>
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</tr>
<tr>
<td>Poorly-differentiated/pleomorphic/epithelioid leiomyosarcoma</td>
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</tr>
<tr>
<td>Embryonal/alveolar/pleomorphic rhabdomyosarcoma</td>
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</tr>
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<td>Mesenchymal chondrosarcoma</td>
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</tr>
<tr>
<td>Osteosarcoma</td>
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<tr>
<td>PNET</td>
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<td>Synovial sarcoma</td>
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<td>Well-differentiated/conventional angiosarcoma</td>
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<td>Epithelioid sarcoma</td>
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<tr>
<td>Clear cell sarcoma</td>
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</table>

* Modified from Guillou et al. with permission from the American Society of Clinical Oncology. FNCLCC indicates Fédération Nationale des Centres de Lutte le Cancer; MFH, malignant fibrous histiocytoma; PNET, primitive neuroectodermal tumor.