

INTERNATIONAL SOCIETY OF UROLOGICAL PATHOLOGY
COMPANION MEETING, SAN DIEGO, CALIFORNIA

MARCH 24, 2007

UNUSUAL TUMORS IN UROLOGICAL PATHOLOGY

Moderators:

Liang Cheng, Indiana University School of Medicine, Indianapolis, IN
Edward C. Jones, Vancouver Hospital and Health Science Center and the University of British Columbia, Vancouver, Canada

7:00-7:10 pm

President's Remark

Jonathan I. Epstein, Johns Hopkins Hospital, Baltimore, MD

7:10- 7:40 pm

Secondary Tumors Involving the Genitourinary Organs

George Netto, Johns Hopkins Hospital, Baltimore, MD

7:40-8:10 pm

Soft Tissue Lesions of the Genitourinary Organs

Andrew L. Folpe, Mayo Clinic and Mayo Foundation, Rochester, MN

8:10-8:40 pm

Neuroendocrine Lesions of the Genitourinary Organs

Samson W. Fine, Memorial Sloan Kettering Cancer Center, New York, NY

8:40 -9:10 pm

Hematologic Malignancies of the Genitourinary Organs

Lynne V. Abruzzo, The University of Texas M. D. Anderson Cancer Center, Houston, TX

INTERNATIONAL SOCIETY OF UROLOGICAL
PATHOLOGY (ISUP)

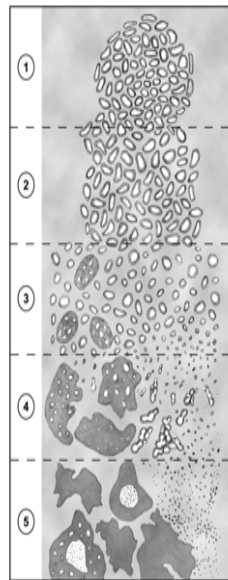
Website: <http://www.isuporg.org>

- **President**
Jonathan I. Epstein, M.D.
The Johns Hopkins Medical Institutions
Baltimore, Maryland, U.S.A.
- **President-Elect**
Brett Delahunt, M.D.
Wellington School of Medicine & Health Sciences
Newton, Wellington, NEW ZEALAND
- **Secretary**
Lars Egevad, M.D.
International Agency for Research on Cancer
Lyon, France
- **Treasurer**
Liang Cheng, M.D.
Indiana University Medical Center
Indianapolis, IN, USA

The 2005 ISUP Consensus Conference on Gleason
Grading of Prostatic Carcinoma

Epstein JI, Aallsbrook WC Jr., Amin MB, Egevad LL; ISUP Grading Committee
Am J Surg Pathol. Sep;29:1228-42, 2005.

- GENERAL APPLICATIONS OF THE GLEASON GRADING SYSTEM
- GRADING VARIANTS AND VARIATIONS OF ACINAR ADENOCARCINOMA OF THE PROSTATE
- REPORTING SECONDARY PATTERNS OF LOWER GRADE WHEN PRESENT TO A LIMITED EXTENT (Needle biopsy core that is entirely involved by cancer, with 98% Gleason pattern 4 and 2% Gleason pattern 3)
- REPORTING SECONDARY PATTERNS OF HIGHER GRADE WHEN PRESENT TO A LIMITED EXTENT (Needle biopsy which is entirely involved by cancer with 98% Gleason pattern 3 and 2% Gleason pattern 4)
- TERTIARY GLEASON PATTERNS
- RADICAL PROSTATECTOMY SPECIMENS WITH SEPARATE TUMOR NODULES
- NEEDLE BIOPSY WITH DIFFERENT CORES SHOWING DIFFERENT GRADES



Modified Gleason Grading System

Pattern 1:
Circumscribed nodule of closely-packed but separate, uniform, rounded to oval, medium-sized acini (larger glands than pattern 3).

Pattern 2:
Like Pattern 1, fairly circumscribed, yet at the edge of the tumor nodule there may be minimal infiltration. Glands are more loosely arranged and not quite as uniform as Gleason pattern 1.

Pattern 3:
Discrete glandular units. Typically smaller glands than seen in Gleason pattern 1 or 2. Infiltrates in and amongst non-neoplastic prostate acini. Marked variation in size and shape. Smoothly circumscribed small cribriform nodules of tumor.

Pattern 4:
Fused microacinar glands. Ill-defined glands with poorly formed glandular lumina. Large cribriform glands. Cribriform glands with an irregular border. Hypernephromatoid.

Pattern 5:
Essentially no glandular differentiation, composed of solid sheets, cords, or single cells. Comedocarcinoma with central necrosis surrounded by papillary, cribriform, or solid masses.

ISUP WEBSITE

ISUPORG.ORG

- History
- Society News
- Calendar/Meetings
- *Collaborations
- Board Members
- *Member Directory
- GU Fellowships
- Application
- Awards
- Other Links
- *Weekly Case

* Available to ISUP Members

ISUPORG.ORG: Weekly Case

- Clinical History
- 2-5 Color Images
- Diagnosis
- Histological Description
- Discussion
- Full spectrum of more common and unusual lesions of the Genitourinary Tract.

Membership at ISUPORG.ORG

- Yearly Membership: Only \$40
- Open to all Medical Practitioners: Residents, Fellows, General Pathologists, and Genitourinary Pathologists

International Society of Urological Pathology/

USCAP Companion Meeting

March 24, 2007

Secondary Tumors Involving The Genitourinary Organs

George Netto, MD, Johns Hopkins University, Baltimore, MD

Introduction:

Tumors of the genitourinary (GU) organs account for a significant portion of all malignancies in the US (1) . The overwhelming majority of GU tumors are primary epithelial neoplasms with only a minority representing a spread from a non-genitourinary site or other GU primary site. In surgical pathology specimens, secondary GU tumors account for 1.6-3 % of tumors.(2) . Not surprisingly, a higher incidence is reported in autopsy series (2) . Among non-genitourinary primary sites, colorectal, pulmonary, melanoma and breast are the most common contributors. Secondary spread from a GU primary tumor to another GU organ occur most frequently between the prostate and urinary bladder given the intimate topographic proximity of the two organs.

The following discussion will focus on secondary GU tumors that may pose differential diagnostic difficulties with primary lesions and highlight morphologic and ancillary features that could be helpful in reaching a proper primary origin assignment.

Secondary Tumors of Prostate Gland:

In surgical pathology specimens, metastases to prostate are extremely rare (0.2%) (3, 4) . Even in tumor related death autopsy series, the rate of prostatic involvement by metastasis is reported to be the low range of (1-6%). Primary tumor sites of origin include lung, melanoma and gastrointestinal tract (5) . Prostatic metastases from other GU primaries such as renal cell carcinoma and testicular germ cells have been rarely cited.

The more common occurrence of secondary involvement of prostate by a bladder urothelial carcinoma (UCa) can be diagnostically challenging in needle biopsy specimens. Attention to subtle histologic features such as the relatively higher degree of nuclear pleomorphism, brisk mitotic activity, the occasional squamoid cytoplasm should raise the possibility of such occurrence. Another helpful feature is the identification of preexisting prostatic duct/ acini distended by the malignant urothelial cells with

distinguish PCa recurrence from a second primary UCa on a TURP or needle biopsy. As mentioned under the discussion of secondary prostate tumors, poorly differentiated prostate cancers may have enlarged nuclei and prominent nucleoli, yet there is little variability in nuclear shape or size from one nucleus to another. High-grade URCa often reveal marked pleomorphism with tumor giant cells. Transitional cell cancer tends to grow in nests, even when poorly differentiated but usually lack the cribriforming and cord like architecture of PCa. The above immunohistochemistry approach will assure proper classification. (8) .

Among other rare sources of primary tumors metastasizing to bladder, mammary carcinoma deserves a cautionary note. The possibility of a breast metastasis should be raised when presented with an epithelial infiltration in the form of cords or individual, at times plasmacytoid to signet ring shaped, cells involving the lamia propria without associated overlying papillary urothelial proliferation or "flat" CIS. In such cases, the differential should also include a rare variant of urothelial carcinoma, namely plasmacytoid/signet ring variant. Obtaining a proper clinical history and the use of immunohistochemistry (ER, PR, Gross cystic disease fluid protein "GCDFFP", uroplakin and thrombomodulin) will help reach a proper diagnosis.

Secondary Tumors of Testis:

Compared to primary tumors, secondary testicular tumors are typically found in an older age group (over 50 years of age) . However, one third of the cases occur before age 40 (3, 22) . Prostate carcinoma (50%) dominates the list of primary sources, in large part due to the prior practice of bilateral orchiectomy as a part of hormone deprivation therapy for PCa. Other primary sources, in descending order, include kidney, melanoma and lung primaries. (3, 22-24) .

Metastatic carcinomas infiltrate the testicular interstitium while usually sparing seminiferous tubules. Rare intratubular growth pattern have been reported however. Extensive vascular involvement, and bilaterally are other features that are more likely to be encountered in metastatic tumors. The use of immunohistochemistry and ancillary techniques such as detection of isochromosome 12 (i12) by FISH are more likely resorted to in the differential of germ cell Vs somatic tumors in extratesticular locations. Germ cell markers such as C-kit, OCT3/4 can be rarely used in difficult testicular cases. EMA negativity and CD30 positivity can also be of help in the rare case where the differential diagnosis include Embryonal carcinoma vs a metastatic somatic carcinoma (25-28) .

occasional pagetoid or undermining pattern of spread. Some of the latter structures can be surrounded by concentric fibrosis even in the absence of stromal prostatic invasion. The differential diagnosis for the above intraductal pattern of spread of UCa into the prostate should include high grade prostatic intraepithelial neplasia (PIN), prostatic ductal adenocarcinoma and "intraductal" prostatic adenocarcinoma (6) . Unlike UCa, the latter lesions demonstrate positive reactivity for prostate tissue lineage specific markers (i.e. PSA, PSMA and P501s) and are negative for high molecular weight cytokeratins (HMWK). Furthermore, intraductal UCa spread into prostate is positive for uroplakin, thrombomodulin and or P63 (7-11)

intraductal UCa spread into prostate could be extensive and can involve the peripheral prostate zone and rarely the seminal vesicle through the ejaculatory duct. The latter should be distinguished from invasion into prostatic stroma which usually have a more infiltrative pattern, displaying irregular rather than smooth bordered urothelial nests and is associated with desmoplastic response. Prostatic stromal invasion carries a more ominous staging and prognostic implication. (12-15) .

In cases of advanced urinary bladder UCa, direct extension into prostate through transmural bladder wall penetration and or lymphovascular spread, the pathologist can be presented with a transurethral resection of prostate (TURP) containing a high grade carcinoma. The latter will raise the differential diagnosis of high grade UCa vs. high grade prostate carcinoma (PCa). Given the significant difference in management of the two diseases their distinction is crucial. Even in poorly differentiated PCa, there is relatively little pleomorphism or mitotic activity compared to poorly differentiated Uca. A subtler finding is that the cytoplasm of prostatic adenocarcinoma is often foamy and pale imparting a "soft" appearance. The findings of infiltrating cords of cells or focal cribriform glandular differentiation are other features more typical of prostatic adenocarcinoma than transitional cell carcinoma. As mentioned above, an immunohistochemistry panel including PSA, PSMA, P501s, PSAP, HMWCK, uroplakin and thrombomodulin will help resolve difficult cases. The addition of newer prostate lineage specific markers such as PSMA, P501s, proPSA and NKX3.1 have proven helpful in elucidating prostatic differentiation in some cases where PSA expression is not evident (8, 16) .

Another source of secondary tumor extension into prostate is the topographically adjacent colorectal tract. Here again, attention to some characteristic morphologic features should raise the possibility of a secondary spread on prostate needle biopsy

Secondary Tumors of Kidney:

Metastases to the kidney usually occur as part of a widespread dissemination. Renal involvement is frequently bilateral and in a multinodular fashion. Primary sources include lung, melanoma, contralateral kidney and GI tract (29-31) . Rarely, metastasis to kidney is the presenting manifestation. Therefore, such a possibility should be considered in needle biopsy specimens where the tumor lacks the typical morphologic features of the usual subtypes of renal cell carcinoma or those of URCa. Renal cell carcinoma markers such as RCC and CD10 and URCa markers such as uroplakin and thrombomodulin can be of some utility only when combined with other tissue lineage specific markers such as TTF-1 (lung and thyroid) and melanoma markers.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. CA Cancer J Clin 2006;56:106-30.
2. Bates AW, Baithun SI. The significance of secondary neoplasms of the urinary and male genital tract. Virchows Arch 2002;440:640-7.
3. Eble JN, Sauter G, Epstein JI, Sesterhenn IA. The World Health Organization Classification of Tumours of the Urinary System and Male Genital System. Lyon,France: IARC Press, 2004.
4. Bates AW, Baithun SI. Secondary solid neoplasms of the prostate: a clinicopathological series of 51 cases. Virchows Arch 2002;440:392-6.
5. Johnson DE, Chalbaud R, Ayala AG. Secondary tumors of the prostate. J Urol 1974;112:507-8.
6. Guo CC, Epstein JI. Intraductal carcinoma of the prostate on needle biopsy: Histologic features and clinical significance. Mod Pathol 2006;19:1528-35.
7. Varma M, Morgan M, Amin MB, Wozniak S, Jasani B. High molecular weight cytokeratin antibody (clone 34betaE12): a sensitive marker for differentiation of high-grade invasive urothelial carcinoma from prostate cancer. Histopathology 2003;42:167-72.
8. Chuang A-Y, DeMarzo AM, Veltri RW, Sharma RB, Bieberich CJ and Epstein JI. Immunohistochemical differentiation of high- grade prostate carcinoma from urothelial carcinoma. Am J Surg Pathol submitted;

specimen. The presence of goblet/columnar cell differentiation, pseudostartified basally located nuclei, and characteristic "dirty necrosis" are more likely encountered in colorectal carcinoma (CRCa) (16) . One should be cautioned that single infiltrating glands of prostatic duct adenocarcinoma can resemble infiltrating colonic adenocarcinoma. The differentiation between prostatic duct adenocarcinoma and secondary involvement of the prostate by CRCa can be facilitated by finding more typical prostatic duct adenocarcinoma elsewhere within the biopsy. An immunohistochemical profile of positive nuclear CDX2 staining, positive nuclear (cytoplasmic staining can occur in PCa) B catenin and positive staining for CK20 in the face of negative reactivity for PSA, PSMA, and p501s can be used to confirm the diagnosis of CRCa spread. (9, 16) .

Secondary Tumors of Urinary Bladder:

Urinary bladder involvement by a secondary tumor either as a metastasis or by direct extension, occur most commonly from colorectal (33%), prostatic (12%) and cervical (11%) sites (3, 17) . Less common sources include breast, stomach, lung and melanoma primaries.

Spread from colonic or rectal primary could represent a diagnostic challenge in Bladder transurethral resection (TUR) samples. In fact, such secondary involvement is a more common occurrence than a primary adenocarcinoma of the bladder. Differentiating a CRCa spread from "intestinal type" adenocarcinoma primary adenocarcinoma of bladder can not be made with certainty. The presence of a background of urothelial intestinal metaplasia with associated glandular dysplasia may favor a primary origin, however, one should be aware of the possibility of colonization of the bladder urothelial mucosa by a secondary well differentiated CRCa mimicking intestinal metaplasia/dysplasia background. (18, 19) . In general, a recommendation to rule out spread from a colorectal primary should be forwarded in order to avoid a potentially unjustifiable radical cystectomy procedure. Immunostains including CDX2, B-catenin, villin and CK7/CK20 have been shown to be helpful by some authors (20, 21) . However, some degree of overlap in staining patterns among primary "enteric type" bladder adenocarcinoma and secondary colorectal adenocarcinoma can still exist on an individual case basis. The second most common source of secondary tumor involvement of the bladder is prostate carcinoma. Even in cases where a prior known history of PCa is given, superimposed morphologic changes such as squamous differentiation due to prior hormonal or radiation treatment effect could pose additional difficulty in trying to

9. Hameed O, Humphrey PA. Immunohistochemistry in diagnostic surgical pathology of the prostate. Semin Diagn Pathol 2005;22:88-104.

10. Mai KT, Collins JP, Veinot JP. Prostatic adenocarcinoma with urothelial (transitional cell) carcinoma features. Appl Immunohistochem Mol Morphol 2002;10:231-6.

11. Oxley J, Abbott C. Thrombomodulin immunostaining and ductal carcinoma of the prostate. Histopathology 1998;33:391-2.

12. Esrig D, Freeman JA, Elmajian DA, et al. Transitional cell carcinoma involving the prostate with a proposed staging classification for stromal invasion. J Urol 1996;156:1071-6.

13. Wishnow KI, Ro JY. Importance of early treatment of transitional cell carcinoma of prostatic ducts. Urology 1988;32:11-2.

14. Shen SS, Lerner SP, Muezzinoglu B, Truong LD, Amiel G, Wheeler TM. Prostatic involvement by transitional cell carcinoma in patients with bladder cancer and its prognostic significance. Hum Pathol 2006;37:726-34.

15. Njinou Ngninkeu B, Lorge F, Moulin P, Jamart J, Van Cangh PJ. Transitional cell carcinoma involving the prostate: a clinicopathological retrospective study of 76 cases. J Urol 2003;169:149-52.

16. Owens C, Epstein J.I. and Netto G.J. Distinguishing prostatic from colorectal adenocarcinoma on biopsy samples: the role of morphology and immunohistochemistry. Arch Pathol Lab Med In Press;

17. Bates AW, Baithun SI. Secondary neoplasms of the bladder are histological mimics of nontransitional cell primary tumours: clinicopathological and histological features of 282 cases. Histopathology 2000;36:32-40.

18. Jacobs LB, Brooks JD, Epstein JI. Differentiation of colonic metaplasia from adenocarcinoma of urinary bladder. Hum Pathol 1997;28:1152-7.

19. Silver SA, Epstein JI. Adenocarcinoma of the colon simulating primary urinary bladder neoplasia. A report of nine cases. Am J Surg Pathol 1993;17:171-8.

20. Wang HL, Lu DW, Yerian LM, et al. Immunohistochemical distinction between primary adenocarcinoma of the bladder and secondary colorectal adenocarcinoma. Am J Surg Pathol 2001;25:1380-7.

21. Raspollini MR, Nesi G, Baroni G, Girardi LR, Taddei GL. Immunohistochemistry in the differential diagnosis between primary and secondary intestinal adenocarcinoma of the urinary bladder. Appl Immunohistochem Mol Morphol 2005;13:33-42.

22. Ulbright TM, Amin MB, Young RH. Tumors of The Testis, Adnexa, Spermatid Cord and Scrotum. Third Series ed. Washington: AFIP, 1999.

23. Damjanov I. Tumors of the testis and epididymis. In: Murphy WM, ed. Urological Pathology. Philadelphia, PA: WB Saunders, 1997;

24. Dutt N, Bates AW, Baithun SI. Secondary neoplasms of the male genital tract with different patterns of involvement in adults and children. Histopathology 2000;37:323-31.

25. Jones TD, Ulbright TM, Eble JN, Baldrige LA, Cheng L. OCT4 staining in testicular tumors: a sensitive and specific marker for seminoma and embryonal carcinoma. *Am J Surg Pathol* 2004;28:935-40.

26. Emerson RE, Ulbright TM. The use of immunohistochemistry in the differential diagnosis of tumors of the testis and paratestis. *Semin Diagn Pathol* 2005;22:33-50.

27. Ulbright TM. Germ cell tumors of the gonads: a selective review emphasizing problems in differential diagnosis, newly appreciated, and controversial issues. *Mod Pathol* 2005;18 Suppl 2:S61-79.

28. Kernek KM, Brunelli M, Ulbright TM, et al. Fluorescence in situ hybridization analysis of chromosome 12p in paraffin-embedded tissue is useful for establishing germ cell origin of metastatic tumors. *Mod Pathol* 2004;17:1309-13.

29. Petersen RO. Kidney: metastatic neoplasms. In: *Anonymous Urologic Pathology*, JB Lippincott, 1986:134-136.

30. Honda H, Coffman CE, Berbaum KS, Barloon TJ, Masuda K. CT analysis of metastatic neoplasms of the kidney. Comparison with primary renal cell carcinoma. *Acta Radiol* 1992;33:39-44.

31. Wagle DG, Moore RH, Murphy GP. Secondary carcinomas of the kidney. *J Urol* 1975;114:30-2.

Andrew L. Folpe, M.D.
Division of Anatomic Pathology
Mayo Clinic, Rochester, MN
folpe.andrew@mayo.edu

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 fibroxoid 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 neoplasms. 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 mucosae. 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 spindle cells with "cigar shaped" nuclei and perinuclear vacuoles, arranged in fascicles that intersect one another at right

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 40% 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 spindle 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

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 spindle 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 spindle cells, with lightly eosinophilic to clear cytoplasm and small nuclei. By definition, PEComas co-express actins and melanoeytic 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 spindle 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 three 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

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 spindle 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 amiotic, 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, and 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) (E1V6)(NTRK3). Sclerosing RMS may closely simulate osteosarcoma or chondrosarcoma, and require IHC for confident diagnosis.

Alveolar Rhabdomyosarcoma

Clinical Features

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/10HPF had an excellent outcome, whereas 2 of 5 tumors with >SMF/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, >SMF/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

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 fusion genes 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 (11;22) (EWS/WT1) gene fusion. Alveolar soft part sarcomas are composed of large, eosinophilic cells, rather than small, round cells.

Selected References

- Croes R, Debicq-Rychter M, Cokelaere K, et al. Adult sclerosing rhabdomyosarcoma: cytogenetic link with embryonal rhabdomyosarcoma. *Virchows Arch* 2005;446:64-67.
- Tobar A, Avigad S, Zoldan M, et al. Clinical relevance of molecular diagnosis in

childhood rhabdomyosarcoma. *Diagn Mol Pathol* 2000;9:9-13.

- Ruyman FB, Grovas AC. Progress in the diagnosis and treatment of rhabdomyosarcoma and related soft tissue sarcomas. *Cancer Invest* 2000;18:223-241.
- Dias P, Chen B, Dilday B, et al. Strong immunostaining for myogenin in rhabdomyosarcoma is significantly associated with tumors of the alveolar subclass. *American Journal of Pathology* 2000;156:399-408.
- Cavazzana AO, Schmidt D, Ninio V, et al. Spindle cell rhabdomyosarcoma. A prognostically favorable variant of rhabdomyosarcoma. *American Journal of Surgical Pathology* 1992;16:229-235.
- Caillaud JM, Gerard-Marchant R, Marsden HB, et al. Histopathological classification of childhood rhabdomyosarcoma: a report from the International Society of Pediatric Oncology pathology panel. *Med Pediatr Oncol* 1989;17:391-400.
- Nishio J, Altieri PA, Bailey JM, et al. Use of a novel FISH assay on paraffin-embedded tissues as an adjunct to diagnosis of alveolar rhabdomyosarcoma. *Lab Invest* 2006.
- Barr FG, Smith LM, Lynch JC, et al. Examination of Gene Fusion Status in Archival Samples of Alveolar Rhabdomyosarcoma Entered on the Intergroup Rhabdomyosarcoma Study-III Trial: A Report from the Children's Oncology Group. *J Mol Diagn* 2006;8:202-208.
- Parham DM. Pathologic classification of rhabdomyosarcomas and correlations with molecular studies. *Mod Pathol* 2001;14:506-514.
- Anderson J, Gordon T, McManus A, et al. Detection of the PAX3-FKHR fusion gene in paediatric rhabdomyosarcoma: a reproducible predictor of outcome? *Br J Cancer* 2001;85:831-835.
- Ardt CA, Hammond S, Rodeberg D, et al. Significance of persistent mature rhabdomyoblasts in bladder/prostate rhabdomyosarcoma: Results from IRS IV. *J Pediatr Hematol Oncol* 2006;28:563-567.
- Ferrer FA, Isakoff M, Koyle MA. Bladder/prostate rhabdomyosarcoma: past, present and future. *J Urol* 2006;176:1283-1291.
- Womer RB, Snyder HM. Bladder/prostate rhabdomyosarcoma: miles to go before we sleep. *J Urol* 2006;176:1278-1279.
- Godbole P, Outran A, Wilcox DT, et al. Myogenin and desmin immunohistochemistry in the assessment of post-chemotherapy genitourinary embryonal rhabdomyosarcoma: prognostic and management implications. *J Urol* 2006;176:1751-1754.
- Wong-You-Cheong JJ, Woodward PJ, Manning MA, et al. From the Archives of the AFIP: neoplasms of the urinary bladder: radiologic-pathologic correlation. *Radiographics* 2006;26:553-580.
- Canning DA. Rhabdomyosarcoma of the bladder, prostate or vagina: the role of surgery. *J Urol* 2005;173:982.
- Ardt C, Rodeberg D, Breitfeld PP, et al. Does bladder preservation (as a surgical principle) lead to retaining bladder function in bladder/prostate rhabdomyosarcoma? Results from intergroup rhabdomyosarcoma study iv. *J Urol* 2004;171:2396-2403.
- Filipas D, Fisch M, Stein R, et al. Rhabdomyosarcoma of the bladder, prostate or vagina: the role of surgery. *BJU Int* 2004;93:125-129.
- Coidre JM, Terri P, Guillou L, et al. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. *Cancer* 2001;91:1914-1926.
- Martin SA, Sears DL, Sebo TJ, et al. Smooth muscle neoplasms of the urinary bladder: a clinicopathologic comparison of leiomyoma and leiomyosarcoma. *Am J Surg Pathol* 2002;26:292-300.
- Montgomery EA, Shuster DD, Burkart AL, et al. Inflammatory myofibroblastic tumors of the urinary tract: a clinicopathologic study of 46 cases, including a malignant example inflammatory fibrosarcoma and a subset associated with high-grade urothelial carcinoma. *Am J Surg Pathol* 2006;30:1502-1512.

NEUROENDOCRINE LESIONS OF THE GENITOURINARY TRACT

Samson W. Fine, MD

Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY

INTRODUCTION

Neuroendocrine [NE] lesions of the GU tract represent a spectrum of neoplasms with diverse incidence, clinicopathologic presentation, and outcome. An overview of their potential origins reveals three major theories. These include: 1) Derivation from NE cells of the diffuse neuroendocrine system – such as those identified in the normal urothelial tract and prostate and which may increase in number in reactive or metaplastic settings; 2) Derivation from a multipotent stem cell – a concept crucial to understanding the nature of NE tumors arising in conjunction with epithelial or germ cell malignancies, which may express markers of both components 3) Derivation from non-APUD cell neuroendocrine structures – encompassing lesions such as bladder paraganglioma, as well as its rare counterparts in other organs.

For each entity that follows, relevant epidemiologic, clinicopathologic, immunohistochemical, and prognostic data are surveyed, including a discussion of their proposed origins. Additionally, the most significant differential diagnostic considerations have been highlighted.

NEUROENDOCRINE LESIONS OF UROTHELIUM

High grade neuroendocrine carcinoma

The majority of previous reports of high grade neuroendocrine carcinoma [NEC] involve small cell carcinoma [SmCC] of bladder, which accounts for 0.5 to 1% of primary bladder malignancies (1-3). SmCC is comparable to high grade urothelial carcinoma [UC] with regard to median age in the seventh decade, gender [M:F ratio – 2:1 to 5:1] (4-5) and clinical presentation with hematuria >75% (1). Unlike SmCC in the lung (6) however, bladder SmCC is uncommonly associated with paraneoplastic syndromes (5).

Microscopically, high grade NEC represents a spectrum of findings. "Pure" SmCC cases are infrequent, with approximately 50% showing admixed carcinoma, including urothelial carcinoma, NOS, but also adenocarcinoma, squamous cell carcinoma, and/or sarcomatoid features (7-8). The co-existence of these epithelial components, as well as identification of overlying flat in situ UC, strongly suggest that the high grade NE phenotype reflects divergent differentiation of multipotent malignant urothelial cells (1, 9). Even within the NEC component, tumors exhibit a range of morphology, from "classic" SmCC features, as seen in the lung, i.e. diffuse sheets of round blue hyperchromatic cells exhibiting nuclear molding, granular chromatin, inconspicuous nucleoli, scant cytoplasm, and frequent mitoses/apoptotic debris and necrosis to lesions with better-defined organoid, palisaded, or trabecular architecture and large cells with abundant cytoplasm and macronucleoli (10). In areas, the latter may convey a "carcinoid-like" architecture at low-power, albeit with cytologic features better associated with high grade NEC.

- Harik LR, Merino C, Coidre JM, et al. Pseudosarcomatous myofibroblastic proliferations of the bladder: a clinicopathologic study of 42 cases. *Am J Surg Pathol* 2006;30:787-794.
- Leuschner I, Harms D, Matke A, et al. Rhabdomyosarcoma of the urinary bladder and vagina: a clinicopathologic study with emphasis on recurrent disease: a report from the Kiel Pediatric Tumor Registry and the German CWS Study. *Am J Surg Pathol* 2001;25:856-864.
- Mills SE, Bova GS, Wick MR, et al. Leiomyosarcoma of the urinary bladder: A clinicopathologic and immunohistochemical study of 15 cases. *Am J Surg Pathol* 1989;13:480-489.
- Rosser CJ, Slaton JW, Izawa JJ, Levy LB, Dinney CP. Clinical presentation and outcome of high-grade urinary bladder leiomyosarcoma in adults. *Urology* 2003; 61: 1151-55
- Farshid G, Pradhan M, Goldblum JR, Weiss SW. Leiomyosarcoma of somatic soft tissues: a tumor of vascular origin with multivariate analysis of outcome in 42 cases. *Am J Surg Pathol* 2002; 26: 14-24

A key differential diagnostic consideration is direct extension or metastasis from non-urothelial NEC. In addition to morphologic overlap, the difficulty in distinguishing primary from secondary lesions is compounded by immunohistochemical and ultrastructural similarities, including cytoplasmic chromogranin and synaptophysin positivity, "dot-like" cytokeratin positivity (4, 9), and sparse intracytoplasmic membrane-bound dense core granules (8-9). Although initially proposed as a specific marker for pulmonary SmCC (11-12), TTF-1 positivity has subsequently been demonstrated in 25% to 39% of bladder SmCC (13-14), limiting its utility in this differential diagnosis (15). Given these similarities, high grade pulmonary NEC secondarily involving urothelium must be excluded on clinical and radiologic grounds. As approximately half of prostatic SmCC have an associated conventional adenocarcinoma component, immunopositivity for prostate specific antigen [PSA] or prostatic acid phosphatase [PAP] in better differentiated areas may be helpful.

Bladder SmCC presents with high clinical stage and frequently displays rapid growth and metastasis at the time of or shortly after diagnosis to lymph nodes [LN], viscera, and vertebral bones (1-2, 4-5, 8, 16-17). Available outcome data suggests a poor prognosis for cases of bladder SmCC, correlating with advanced stage at presentation (2). Parallel clinicopathologic features and outcomes have been reported for exceedingly rare cases of SmCC of the ureters and renal pelvis, as well as large cell NEC [LCNEC] of lower or upper tract (3, 9-10, 18-21). Most modern series have highlighted therapeutic regimens containing cisplatin-based chemotherapy (22), in addition to surgical resection (4, 23) or radiotherapy (2, 24-25) as being beneficial. Given the propensity of SmCC for early systemic disease, some have further advocated neoadjuvant therapy with pulmonary SmCC dosages (26). However, the ideal timing and dosing of these treatments remains unknown due to the retrospective and sometimes limited nature of prior studies (27). Similarly, the low frequency of urothelial high grade NEC and its tendency to exhibit a range of morphologies has precluded clinically meaningful subclassification. Diagnostically therefore, it is reasonable to recommend reporting these cases as high grade UC with small cell/neuroendocrine differentiation, while noting explicitly the extent of the NE component, as it may affect therapeutic options.

NEUROENDOCRINE LESIONS OF BLADDER

Bladder Paraganglioma

Paragangliomas [PG] of the bladder represent 10% of extra-adrenal PG (28-29), with the classic clinical triad of sustained or paroxysmal hypertension, intermittent gross hematuria, and micturition "attacks", characterized by headache, palpitations, blurred vision, profuse sweating, tremulousness and occasional syncope, being observed in nearly 7% of patients (30-31). These usually well-circumscribed lesions are characterized by nests [Zellballen] of polyhedral cells with ampho- or basophilic cytoplasm and ovoid nuclei intertwined within a delicate vascular network. However, irregular growth, endocrine atypia, rare mitoses, dense fibrous septae, and focal ganglioneuromatous or neuroblast-like growth may also be seen (29). Immunohistochemical staining is identical to that seen in adrenal pheochromocytomas, with chromogranin and synaptophysin positive chromaffin cells, S-100 protein positive sustentacular cells, and negativity for keratins (32-33). While the true clinical behavior is unknown, approximately 80% of patients in small series have shown at least muscle invasive disease (33-34). This capacity to invade deeply, along with the Zellballen architecture of PG necessitate their distinction from nested patterns of UC, especially in small biopsies or those with thermal

Appendix 1: FNCLCC Grading System for Soft Tissue Sarcoma

FNCLCC Grading System: Definition of Parameters	FNCLCC Grading System: Tumor Differentiation Score According to Histologic Type																																																				
<p>Tumor differentiation score Table 2:</p> <p>Score 1: Sarcoma closely resembling normal adult mesenchymal tissue; eg, well-differentiated liposarcoma</p> <p>Score 2: Sarcoma for which histologic typing is certain; eg, myxoid liposarcoma</p> <p>Score 3: Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcoma, osteosarcoma, PNET</p> <p>Mitotic count</p> <p>Score 1: 0-9 mitoses per 10 HPF</p> <p>Score 2: 10-19 mitoses per 10 HPF</p> <p>Score 3: ≥20 mitoses per 10 HPF</p> <p>Tumor necrosis</p> <p>Score 0: No necrosis</p> <p>Score 1: <50% tumor necrosis</p> <p>Score 2: ≥50% tumor necrosis</p> <p>Histologic grade</p> <p>Grade 1: Total score 2, 3</p> <p>Grade 2: Total score 4, 5</p> <p>Grade 3: Total score 6, 7, 8</p> <p>* Modified from Trjampic et al¹ with permission from John Wiley and Sons, Inc. FNCLCC indicates Fédération Nationale des Centres de Lutte le Cancer; PNET, primitive neuroectodermal tumor.</p> <p>† A high-power field (HPF) measures 0.17-0.18 mm².</p>	<table border="1"> <thead> <tr> <th>Histologic Type</th> <th>Tumor Differentiation Score</th> </tr> </thead> <tbody> <tr><td>Well-differentiated liposarcoma</td><td>1</td></tr> <tr><td>Mixed liposarcoma</td><td>2</td></tr> <tr><td>Round cell liposarcoma</td><td>3</td></tr> <tr><td>Neuroepithelial liposarcoma</td><td>1</td></tr> <tr><td>Well-differentiated fibrosarcoma</td><td>2</td></tr> <tr><td>Conventional fibrosarcoma</td><td>3</td></tr> <tr><td>Poorly-differentiated fibrosarcoma</td><td>2</td></tr> <tr><td>Mixed fibrosarcoma</td><td>2</td></tr> <tr><td>Pleomorphic MFH with storiform pattern</td><td>2</td></tr> <tr><td>Pleomorphic MFH with no storiform pattern</td><td>3</td></tr> <tr><td>Giant cell MFH</td><td>3</td></tr> <tr><td>Well-differentiated leiomyosarcoma</td><td>1</td></tr> <tr><td>Conventional leiomyosarcoma</td><td>2</td></tr> <tr><td>Poorly-differentiated/pleomorphic epithelioid leiomyosarcoma</td><td>3</td></tr> <tr><td>Embryonal/blastoid/pleomorphic rhabdomyosarcoma</td><td>3</td></tr> <tr><td>Sarcoma</td><td>3</td></tr> <tr><td>Mesenchymal chondrosarcoma</td><td>3</td></tr> <tr><td>Osteosarcoma</td><td>3</td></tr> <tr><td>PNET</td><td>3</td></tr> <tr><td>Malignant triton tumor</td><td>3</td></tr> <tr><td>Synovial sarcoma</td><td>3</td></tr> <tr><td>Well-differentiated/embryonal angiosarcoma</td><td>2</td></tr> <tr><td>Poorly-differentiated/epithelioid angiosarcoma</td><td>3</td></tr> <tr><td>Epithelioid sarcoma</td><td>3</td></tr> <tr><td>Clear cell sarcoma</td><td>3</td></tr> </tbody> </table> <p>* Modified from Guillou et al² 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.</p>	Histologic Type	Tumor Differentiation Score	Well-differentiated liposarcoma	1	Mixed liposarcoma	2	Round cell liposarcoma	3	Neuroepithelial liposarcoma	1	Well-differentiated fibrosarcoma	2	Conventional fibrosarcoma	3	Poorly-differentiated fibrosarcoma	2	Mixed fibrosarcoma	2	Pleomorphic MFH with storiform pattern	2	Pleomorphic MFH with no storiform pattern	3	Giant cell MFH	3	Well-differentiated leiomyosarcoma	1	Conventional leiomyosarcoma	2	Poorly-differentiated/pleomorphic epithelioid leiomyosarcoma	3	Embryonal/blastoid/pleomorphic rhabdomyosarcoma	3	Sarcoma	3	Mesenchymal chondrosarcoma	3	Osteosarcoma	3	PNET	3	Malignant triton tumor	3	Synovial sarcoma	3	Well-differentiated/embryonal angiosarcoma	2	Poorly-differentiated/epithelioid angiosarcoma	3	Epithelioid sarcoma	3	Clear cell sarcoma	3
Histologic Type	Tumor Differentiation Score																																																				
Well-differentiated liposarcoma	1																																																				
Mixed liposarcoma	2																																																				
Round cell liposarcoma	3																																																				
Neuroepithelial liposarcoma	1																																																				
Well-differentiated fibrosarcoma	2																																																				
Conventional fibrosarcoma	3																																																				
Poorly-differentiated fibrosarcoma	2																																																				
Mixed fibrosarcoma	2																																																				
Pleomorphic MFH with storiform pattern	2																																																				
Pleomorphic MFH with no storiform pattern	3																																																				
Giant cell MFH	3																																																				
Well-differentiated leiomyosarcoma	1																																																				
Conventional leiomyosarcoma	2																																																				
Poorly-differentiated/pleomorphic epithelioid leiomyosarcoma	3																																																				
Embryonal/blastoid/pleomorphic rhabdomyosarcoma	3																																																				
Sarcoma	3																																																				
Mesenchymal chondrosarcoma	3																																																				
Osteosarcoma	3																																																				
PNET	3																																																				
Malignant triton tumor	3																																																				
Synovial sarcoma	3																																																				
Well-differentiated/embryonal angiosarcoma	2																																																				
Poorly-differentiated/epithelioid angiosarcoma	3																																																				
Epithelioid sarcoma	3																																																				
Clear cell sarcoma	3																																																				

artifact (33). While infiltrative nests of UC, often without desmoplasia, may mimic PG, the latter should not exhibit superficial urothelial disease, true cytologic atypia, or significant mitotic rates. Furthermore, other than focally, nested variants of UC lack the fine vasculature characteristic of PG. In difficult cases, immunopositivity for CK7, 20, and HMW cytokeratin will resolve the dilemma (33).

Similar to other extra-adrenal PG, bladder PG are thought to arise by malignant transformation of paraganglia (29-30, 35-37). In an elegant autopsy study of over 400 patients, Honma has demonstrated paraganglia at all levels of the bladder wall, including within detrusor muscle, in > 50% of patients (38). Occasionally, in small specimens, these collections of clear to amphophilic cells may also cause diagnostic confusion with full-fledged PG (33). In this scenario, symptomatology and cystoscopic evidence of a mass, coupled with repeat biopsy documenting extent of disease, should clarify the issue.

Bladder Carcinoid

Less than ten true primary bladder carcinoids have been documented (39-44) with a usual presentation as small polypoid masses at the bladder neck/trigone in patients with hematuria. Tumors demonstrate classic carcinoid architectural patterns including glandular, acinar, cribriform, or trabecular arrangements of uniform cells with basally-oriented eosinophilic cytoplasm (43).

When considering a diagnosis of primary carcinoid tumor anywhere in the GU tract, it is essential to thoroughly exclude a metastatic lesion from more common sites such as lung or GI tract. In the bladder specifically, pathologists must also bear in mind that urothelial high grade NEC may also exhibit focal "carcinoid-like" morphology (8). Unlike SmCC of the urinary bladder, which may be considered divergent differentiation from UC, an association of bladder carcinoids and UC has not been observed. It is well known however, that cells with NE features may be situated against the basement membrane of normal urothelium, as well as in reactive lesions such as von Brunn nests and cystitis cystica et glandularis (44-46). Indeed, two cases of primary bladder carcinoid have developed in a background of proliferative cystitis of the overlying urothelium (41, 43), including one case with scattered argyrophil cell staining noted in this component (41). A proposed origin of primary bladder carcinoid from innate or metaplastic mucosal urothelial NE cells is consistent with these findings.

NEUROENDOCRINE LESIONS OF KIDNEY

Renal Carcinoid

Similar to patients with renal cell carcinoma (RCC), patients with carcinoid tumor of the kidney present with abdominal back or flank pain, accompanied by hematuria and fever (47-48). 25-30% of renal carcinoids are incidentally detected (49) and diagnosis may be complicated with small lesions, as neither CT nor MRI reliably distinguishes these tumors from RCC (50). Evidence of carcinoid syndrome with serotonin-related flushing, generalized edema, and diarrhea, and occasional elevation of urine 5-HIAA may occur in 10-15% of patients (51). In its presence, somatostatin receptor [SR] scintigraphy with octreotide has a high sensitivity for renal carcinoid detection, including small, clinically silent lesions (52).

Likewise, there is evidence that metastatic PCa contains a population of NE cells (97), which do not express the androgen receptor [AR] (98-100) and hence may not be suppressed by androgen ablation (97). It has therefore been conjectured that NE cells possess the ability to "escape" usual hormonal therapy in advanced PCa, with some reporting increased NE differentiation in androgen-insensitive PCa as well as possible prognostic significance (98, 101). However, others have argued that these relationships may depend on the agent used in androgen deprivation and have demonstrated no statistical correlation between amount of NE cells and disease specific survival (95). These varying results suggest that the often limited and focal distribution of NE cells in PCa makes it difficult to study their relevance, especially in limited specimens, such as needle biopsies (102). Nonetheless, a number of studies have shown potential roles for NE cells in PCa progression by paracrine growth stimulation of non-NE cells (97, 101, 103).

Occasionally NE cells with bland nuclei and cytoplasmic eosinophilic granules, superficially resembling Paneth cells of the GI tract (104-105) are seen in a patchy fashion in both normal and cancerous specimens. Unusually, these cells may be observed as single cells, cords, or nests of tumor cells, meeting architectural criteria for Gleason pattern 5, yet displaying bland cytology and frequent association with lower grade conventional PCa (106). A recent study found that among cases with Paneth cell-like rich areas resembling high grade PCa, none showed evidence of progression. Cases exhibiting progression reflected typical parameters such as high Gleason scores and/or extraprostatic extension/seminal vesicle invasion. Diagnostically therefore, it is suggested that one grade only the conventional carcinoma, as applying Gleason to such foci may inaccurately upgrade the tumor (105).

Prostatic Carcinoid

The literature contains a fair number of cases denoted as "prostatic carcinoid tumors" (106-111). However, as usual PCa may exhibit at least focal NE differentiation, distinguishing carcinoid-like adenocarcinomas from a true primary prostatic carcinoid is challenging (106). Especially in Gleason grade 4/5 tumors, these entities may share nested and microacinar/"rosette-like" patterns of growth with nuclear uniformity, PAP positivity, and immunohistochemical/ultrastructural evidence of NE differentiation (112-113). Most have argued therefore, that tumors with expression of both PSA and NE markers, as well as cases of histologically mixed prostatic "carcinoid" and PCa are best considered "carcinoid-like" adenocarcinomas (49, 114). This phenomenon may explain early reports of aggressive behavior for prostatic carcinoids (115), likely reflecting high Gleason score tumors with varying degrees of focal NE differentiation. Using these guidelines, only a handful of tumors exhibiting typical carcinoid architecture and features, PSA negativity and absence of admixed adenocarcinoma have been described (116-117).

High grade neuroendocrine carcinoma

First described by Wenk in 1977 (118), prostatic SmCC represents between 1 and 5% of all prostatic malignancies when mixed adenocarcinoma-SmCC are included (82). Conversely, in the constellation of extraprostatic SmCC, the prostate is a relatively common site (119). High grade NEC of prostate histologically resembles the spectrum of SmCC/LCNEC described at other sites (120-122), with approximately 1/2 of prostatic SmCC being composite tumors with conventional PCa (82). Diagnostically, high grade NEC should not be assigned a Gleason grade and may be differentiated from diffuse

Histologically, polygonal tumor cells with indistinct cell borders, rounded, regular nuclei, "salt and pepper" chromatin, and infrequent mitoses grow in trabeculae or nests set in a highly vascularized, yet thin fibroconnective tissue. Glandular, acinar, tubular, or rosette-like growth and densely fibrotic/clear stroma may also be observed (51, 53). Ultrastructural studies demonstrate abundant neurosecretory granules and diffuse labeling for cytokeratin, chromogranin, and synaptophysin is typical (47, 51). Interestingly, these tumors have demonstrated positivity for PAP, suggesting a rectal carcinoid-like hindgut origin (47-48, 51, 54). Approximately 15% of reported cases were initially diagnosed as RCC or Wilms tumor (52, 55), likely due to under-recognition of renal carcinoid, with uniformly negative WT-1 also ruling out the latter possibility (56). Finally, as in other sites, metastasis from a remote carcinoid tumor must be excluded.

Due to the vacuous nature of the retroperitoneal space, these slow-growing neoplasms are usually diagnosed at a large size, with ~ 75% being > 4 cm (50). A recent review found approximately 45% of patients with pT3 disease [tumor invading peri-renal or sinus/hilar fat or invading renal vein]. Metastases, seen in 50-60% of cases, are usually detected at initial evaluation, though they have been reported up to 7 years post-nephrectomy, emphasizing the need for long-term follow-up (51, 57-58). Metastatic lesions involve peri-aortic and peri-hilar LN, liver, and bone (50) and their presence may correlate with age > 40 years, tumors > 4 cm, pT3 tumors, and mitotic rates > 1 per 10 hpf. Surprisingly however, more than 90% of reported patients were without evidence of disease or alive with disease [median 34 months follow-up], while 47% of patients with LN metastases at the time of resection showed no evidence of disease [mean 43 months follow-up]. Hence, patients with renal carcinoids may experience a prolonged clinical course, even in the presence of widely metastatic disease (49-50, 57, 59).

Fascinating associations between primary renal carcinoid and horseshoe kidney [18-26%] or renal teratomas [~ 15% of patients] have been reported (58, 60-64). These findings have led some to postulate that hyperplasia of interspersed NE cells within metaplastic or teratomatous epithelium in horseshoe kidneys or nests of misplaced progenitor cells developing into teratomatous intestinal or respiratory epithelia in renal teratoma may serve as a nidus for renal carcinoids (63, 65). This view is supported by the common occurrence of renal carcinoids in the isthmus of horseshoe kidneys, a region formed by abnormal migration of posterior nephrogenic cells in utero (63). However, nearly 65% of reported lesions have not occurred in these settings. Other suggestions, including reactive NE metaplasia of the pyloro-caecal system and NE differentiation of multipotent renal stem cells have been fielded, yet neither pyelonephritis/renal calculi nor areas of renal carcinoid co-existent with UC or RCC have been observed (60, 63). While the presence of intrinsic NE cells in normal kidney may be debated, rare NE cells have been observed in urothelium of the upper tract (53, 66). It is possible therefore, that renal carcinoids bearing no relationship to congenital/acquired abnormalities arise directly from NE cells situated in the renal pelvic urothelium.

NEUROENDOCRINE LESIONS OF TESTIS

Testicular Carcinoid

Representing ~ 0.2% of all testicular neoplasms in a historical series from the AFIP (67), primary testicular carcinoids are infrequent, with reported patients ranging from 10 to 63 years (68) and, not unlike germ cell tumors, typically presenting with a mass or testicular

growth of Gleason pattern 5 PCa by the large cells with lower NC/ro ratio, prominent nucleoli, and absent nuclear molding seen in the latter (123). Conversely, due to its constellation of features, LCNEC may be easily mistaken for Gleason score 5+5=10 PCa and hence, the likelihood of its underdiagnosis is high (120).

A number of studies have reported the immunophenotype of SmCC and conventional PCa (9, 124-125). Overall, they have found strong labeling for PSA/PAP in most PCa, and at least focal expression in ~ 25% of SmCC, as well as diffuse NE markers in a majority of SmCC with substantially less staining in PCa (124-125). Furthermore, while most have maintained that malignant NE cells do not express AR (98-99) a recent study has shown focal staining for AR in SmCC (125). The presence of mixed prostatic acinar adenocarcinoma in many high grade SmCC and LCNEC, coupled with evidence of cells that may co-express PSA/PAP/AR and NE markers (120-121, 124-125) suggests evolution of a subset of multipotent non-NE prostatic tumor cells as the derivation for prostatic high grade NEC (84-85, 120, 124, 126). As in high grade NEC of the urothelium, local extension or distant spread of NEC from other sites must be excluded clinically, as morphologic and immunohistochemical features may be identical.

Akin to SmCC at other sites, prostatic lesions present at advanced stage, are often unresectable, and display a high frequency of visceral metastases and a dismal survival (121, 127-128). Small series have suggested that prostatic SmCC with a combination of ADT with cisplatin-based regimens followed by consolidative surgery or radiotherapy (127-129). As in most SmCC however, even chemotherapy-treated patients tend to progress rapidly. As such, novel small molecule therapeutic approaches, developed for pulmonary high grade NEC (130), may have activity in prostatic SmCC. To this end, Yoo et al. have recently demonstrated high levels of labeling for CD56, bombesin/GRP, c-KIT, Bcl-2, and EGFR in a small series of prostatic SmCC, suggesting future therapeutic targets (125).

Few examples of distinct prostatic LCNEC have been reported (120, 131-133). Among these, the majority have been an incidental finding in palliative TURP specimens in patients with androgen-independent disease (120). As reported cases have been detected late in the disease course, widespread metastases to bone and viscera, uniformly poor responses to NE specific chemotherapy and limited survival have been observed (120).

swelling, accompanied by pain and tenderness (67). Clinical carcinoid syndrome may be seen in up to 10% of cases (68). Grossly, testicular carcinoids are solid, with an accompanying cystic component, when seen in conjunction with other teratomatous elements (67). Microscopically, they share characteristic features, immunoprofile, and ultrastructural polymorphous neurosecretory granules with carcinoids at other sites (67-70). Although most testicular carcinoids behave in an indolent manner, 10-15% metastasize, occasionally many years after orchiectomy (67-68, 71).

As with other GU tract carcinoids, metastasis from another site must be entertained, especially in the presence of bilateral tumors (72). Regarding primary lesions, early reports (67, 73-74) postulated that analogous to carcinoids arising in ovarian teratomas (75), primary testicular carcinoids may be derived from NE cells found in respiratory epithelial or enteric components of testicular teratomas (67). However, a teratomatous component has been associated with only 1/4 of reported cases and intratubular germ cell neoplasia [ITGCN], a precursor lesion indicating germ cell origin, has generally been absent (76). While overgrowth of a single teratomatous component may be observed, the finding of a pure testicular carcinoid without other demonstrable germ cell tumor on initial sampling should engender extensive testicular sampling to discover ITGCN, a minute teratoma, and/or evidence of a scar, representing a "burnt out"/regressed germ cell component (77). In the event of pure testicular carcinoid in association with OCT-4 labeling ITGCN, as recently reported (78), cytogenetic studies for 11p2 may still be warranted, to eliminate the possibility of concurrent metastatic carcinoid. Once these efforts are exhausted, one may entertain other proposed origins, including origin from yet undiscovered NE rests (71) or designation of the lesion as a monodermal teratoma with a pathogenesis different from that of usual postpubertal teratoma [i.e. no ITGCN] (79).

NEUROENDOCRINE LESIONS OF PROSTATE

Neuroendocrine cells in the prostate

First described in the prostate by Pretl in 1944 (80), focal NE cells are now known to be widely distributed in the prostate (81-82), are members of the diffuse APUD cell system (83), and along with prostatic serotonic cells, are thought to arise from endodermally-derived pluripotent prostatic stem cells (84-85). While their exact function is unknown, it is postulated that they are involved in both prostatic growth and differentiation, as well as in homeostatic regulation of the secretory process (86). NE differentiation in prostatic adenocarcinoma [PCa] has three major manifestations: 1. Focal NE differentiation in PCa; 2. Prostatic carcinoid tumor; 3. High grade NE carcinoma.

Focal neuroendocrine differentiation in prostate cancer

30 to 100% of conventional PCa contain scattered NE cells (46, 81, 87), with most resembling other prostatic secretory cells on light microscopy. NE cells may be detected immunohistochemically with markers such as chromogranin and/or bioactive hormones such as serotonin and somatostatin (88). Individual cells may express both PSA and PAP as well as NE markers (89). Whether focal NE differentiation in prostatic adenocarcinoma has prognostic import is controversial, as with a few studies suggesting correlation between increasing numbers of chromogranin-positive cells and worse prognosis (90-93). Most authors however, have shown a correlation of NE differentiation with tumor grade and failed to show an independent effect on survival (85, 88, 94-96).

REFERENCES

1. Blomjous CEM, Vos W, de Voogt HJ, et al. Small cell carcinoma of the urinary bladder: a clinicopathologic, morphometric, immunohistochemical, and ultrastructural study of 18 cases. *Cancer* 1989;64:1347-1357.
2. Holmberg S, Borghede G, Johansson SL. Primary small cell carcinoma of the bladder: a report of 25 cases. *J Urol* 1995;153:1820-1822.
3. Quek ML, Nichols PW, Yazmon J, et al. Radical cystectomy from primary neuroendocrine tumors of the bladder: the University of Southern California experience. *J Urol* 2005;174:93-96.
4. Grignon DJ, Ro JY, Ayala AG, et al. Small cell carcinoma of the urinary bladder: a clinicopathologic analysis of 22 cases. *Cancer* 1992;69:527-536.
5. Tines I, Algabli S, Gaudin E, et al. Small cell carcinoma of the urinary bladder: presentation of 23 cases and review of 134 published cases. *Eur Urol* 2001;39:85-90.
6. Jackman DM, Johnson BE. Small cell lung cancer. *Lancet* 2005;366:385-396.
7. Abrahams NA, Moran C, Reyes AO, et al. Small cell carcinoma of the bladder: a contemporary clinicopathological study of 51 cases. *Histopathology* 2005;46:57-63.
8. Mills SE, Wolfe III JT, Weiss MA, et al. Small cell undifferentiated carcinoma of the urinary bladder: a light-microscopic, immunocytochemical, and ultrastructural study of 12 cases. *Am J Surg Pathol* 1987;11:606-617.
9. Christl P, Miler, Saffer, Sprengel K, et al. Small cell carcinoma of the genitourinary tract: an immunohistochemical, electron microscopic, and clinicopathological study. *J Urol* 1991;146:382-388.
10. Hallemarian S, Gaspert A, Komminoth P, et al. Primary, pure, large-cell neuroendocrine carcinoma of the urinary bladder. *Mod Pathol* 1998;11:1016-1020.
11. Folpe AL, Gown AM, Lamps LW, et al. Thyroid transcription factor-1: immunohistochemical evaluation in pulmonary neuroendocrine tumors. *Mod Pathol* 1998;12:5-8.
12. Ordonez NG. Value of thyroid transcription factor-1 immunostaining in distinguishing small cell lung carcinomas from other small cell carcinomas. *Am J Surg Pathol* 2000;24:1217-1223.
13. Cheng L, Pan CX, Yang XJ, et al. Small cell carcinoma of the urinary bladder: a clinicopathologic analysis of 64 patients. *Cancer* 2004;101:957-962.
14. Olgab S, Koppie T, Saunders N, et al. Small cell carcinoma of the urinary bladder: a clinicopathologic study of 55 cases. *Mod Pathol* 2005;18:156A.
15. Agoff SN, Lamps LW, Philp AT, et al. Thyroid transcription factor-1 is expressed in extrapulmonary small cell carcinomas but not in other extrapulmonary neuroendocrine tumors. *Mod Pathol* 2000;13:238-242.
16. Angulo JC, Lopez JJ, Sanchez-Chapado M et al. Small cell carcinoma of the urinary bladder. *J Urol Pathol* 1996;5:1-19.
17. Swanson PE, Brooks R, Pearce H, et al. Small cell carcinoma of urinary bladder. *Urology* 1998;32:558-563.
18. Chuang CK, Liao SK. A retrospective immunohistochemical and clinicopathological study of small cell carcinomas of the urinary tract. *Chang Gung Med J* 2003;28:26-33.
19. Evans AJ, Al-Maghrabi J, Tshilias J, et al. Primary large cell neuroendocrine carcinoma of the urinary bladder. *Arch Pathol Lab Med* 2002;126:1229-1232.
20. Mackey JR, Au HJ, Hugh J, et al. Genitourinary small cell carcinoma: determination of clinical and therapeutic factors associated with survival. *J Urol* 1998;159:1624-1629.
21. Majhail NS, Elson P, Bukowski RM. Therapy and outcomes of small cell carcinoma of the kidney: report of two cases and a systematic review of the literature. *Cancer* 2003;97:1436-1444.

22. Sved P, Gomez P, Manoharan M, et al. Small cell carcinoma of the bladder. *BJU Int* 2004;94:12-17.
23. Osterling JE, Bredler CB, Burgers JK, et al. Advanced small cell carcinoma of the bladder: successful treatment with combined radical cystoprostatectomy and adjuvant methotrexate, vincristine, doxorubicin, and cisplatin chemotherapy. *Cancer* 1990;65:1928-1936.
24. Bastus R, Caballero JM, Gonzalez G, et al. Small cell carcinoma of the urinary bladder treated with chemotherapy and radiotherapy: results in five cases. *Eur Urol* 1999;35:323-326.
25. Bex A, Nieuwenhuijzen JA, Kerst M, et al. Small cell carcinoma of bladder: a single-center prospective study of 25 cases treated in analogy to small cell lung cancer. *Urology* 2005;65:295-299.
26. Siefker-Radtke AO, Dinney CP, Abrahams NA, et al. Evidence supporting preoperative chemotherapy for small cell carcinoma of the bladder: a retrospective review of the M.D. Anderson Cancer experience. *J Urol* 2004;172:481-484.
27. Abbas F, Civantos F, Benedetto P, et al. Small cell carcinoma of the bladder and prostate. *Urology* 1995;46:617-630.
28. Albores-Saavedra J, Maldonado ME, Ibarra J, et al. Pheochromocytoma of the urinary bladder. *Cancer* 1969;23:1110-1118.
29. Leesmaa JE, Price Jr, EB. Paraganglioma of the urinary bladder. *Cancer* 1971;28:1063-1073.
30. Das S, Bulusu NV, Lowe P. Primary vesical pheochromocytoma. *Urology* 1983;21:20-25.
31. Davaris P, Petraki K, Arvanitis D, et al. Urinary bladder paraganglioma. *Pathol Res Pract* 1986;181:101-106.
32. Grignon DJ, Ro JY, Mackay B, et al. Paraganglioma of the urinary bladder: immunohistochemical, ultrastructural, and DNA flow cytometric studies. *Hum Pathol* 1991;22:1162-1169.
33. Zhou M, Epstein JI, Young RH. Paraganglioma of the urinary bladder: a lesion that may be misdiagnosed as urothelial carcinoma in transurethral resection specimens. *Am J Surg Pathol* 2004;28:94-100.
34. Cheng L, Leibovich BC, Cheville JC, et al. Paraganglioma of the urinary bladder: can biologic potential be predicted? *Cancer* 2000;88:844-852.
35. Zimmerman I, Biron R, MacMahon H. Pheochromocytoma of the urinary bladder. *N Engl J Med* 1953;249:25-26.
36. Scott W, Eversole S. Pheochromocytoma of the urinary bladder. *J Urol* 1960;83:656-664.
37. Ostrowski ML, Wheeler TM. Paraganglia of the prostate: location, frequency, and differentiation from prostatic adenocarcinoma. *Am J Surg Pathol* 1994;18:412-420.
38. Honma K. Paraganglia of the urinary bladder: an autopsy study. *Zentralbl Pathol* 1993;139:465-469.
39. Colby TV. Carcinoid tumor of the bladder: a case report. *Arch Pathol Lab Med* 1980;104:199-200.
40. Burgess NA, Lewis DC, Matthews PN. Primary carcinoid of the bladder. *BJU* 1992;69:213-214.
41. Walker BF, Someren A, Kennedy JC, et al. Primary carcinoid tumor of the bladder. *Arch Pathol Lab Med* 1992;116:1217-1220.
42. Stanfield BL, Grimes MM, Kay S. Primary carcinoid tumor of the bladder arising beneath an inverted papilloma. *Arch Pathol Lab Med* 1994;118:666-667.
43. Martignoni G, Eble JN. Carcinoid tumor of the urinary bladder: immunohistochemical study of two cases and review of the literature. *Arch Pathol Lab Med* 2003;127:e22-e24.
44. Mascolo M, Altieri V, Mignogna C, et al. Calcitonin-producing well-differentiated neuroendocrine carcinoma (carcinoid tumor) of the urinary bladder: case report. *BMC Cancer* 2005;5:88.
45. Hoffman H, Gelbe (basegekornete) Zellen in der Schienhals einer ekstropierten Harnblase. *Virchows Arch A Pathol Anat* 1937;300:468-472.
46. Fetsioff F, Duboid WP, Arbellie-Brassart B, et al. Endocrine cells in the prostate gland, urothelium, and Brenner tumors. *Virchows Arch B Cell Pathol* 1983;42:53-64.
47. Goldblum JR, Lloyd RV. Primary renal carcinoid: case report and literature review. *Arch Pathol Lab Med* 1993;117:855-858.
48. Huettner P, Bird D, Chang Y, et al. Carcinoid tumor of the kidney with morphologic and immunohistochemical profile of a hindgut endocrine tumor: report of a case. *Ultrastruct Pathol* 1991;15:655-661.
49. Murali R, Kneale K, Laik N, et al. Carcinoid tumors of the urinary tract and prostate. *Arch Pathol Lab Med* 2006;130:1693-1706.
50. Romero FR, Rais-Bahrami S, Permpongkosol S, et al. Primary carcinoid tumors of the kidney. *J Urol* 2006;176:2359-2366.
51. Raslan WF, Ro JY, Ordonez NG, et al. Primary carcinoid of the kidney: immunohistochemical and ultrastructural studies of five patients. *Cancer* 1993;72:2660-2666.
52. McCaffrey J, Reuter VE, Herr H, et al. Carcinoid tumor of the kidney: the use of somatostatin receptor scintigraphy in diagnosis and management. *Urol Oncol* 2000;5:108-111.
53. Unger PD, Russell A, Thung SN, et al. Primary renal carcinoid. *Arch Pathol Lab Med* 1990;114:68-71.
54. Begin LR, Jamison BM. Renal carcinoid: a tumor of probable hindgut neuroendocrine phenotype. *J Urol Pathol* 1993;1:269-282.
55. Masera A, Ovcaik Z, Lamovec J, et al. Primary carcinoid of the kidney. *Int Urol Nephrol* 1993;25:129-131.
56. Hansel DE, Cheville JC, Berbesco E, et al. Renal carcinoid tumor: a clinicopathologic study of 21 cases. *Mod Pathol* 2007; in press.
57. Quinchon JF, Aubert S, Biserte J, et al. Primary atypical carcinoid of the kidney: a classification is needed. *Pathology* 2003;35:353-355.
58. Yoo J, Park S, Lee HJ, et al. Primary carcinoid tumor arising in a mature teratoma of the kidney: a case report and review of the literature. *Arch Pathol Lab Med* 2002;126:979-981.
59. Gunes A, Yilmaz U, Ugras M, et al. Primary renal carcinoid natural history of the disease for ten years: case report. *BMC Urology* 2002;2:1.
60. Begin LR, Guy L, Jacobson SA, et al. Renal carcinoid and horseshoe kidney: a frequent association of two rare entities: a case report and review of the literature. *J Surg Oncol* 1998;68:113-119.
61. Kim J, Suh K. Primary carcinoid tumor in a mature teratoma of the kidney: ultrasonographic and computed tomographic findings. *J Ultrasound Med* 2004;23:433-437.
62. Kojiro M, Ohishi H, Isobe H. Carcinoid tumor arising in cystic teratoma of the kidney. *Cancer* 1976;38:1636-1640.
63. Krishnan B, Truong LD, Saleh G, et al. Horseshoe kidney is associated with an increased relative risk of primary renal carcinoid tumor. *J Urol* 1997;157:2059-2066.
64. Kurzer E, Leveillee RJ, Morillo G. Rare case of carcinoid tumor arising within teratoma in kidney. *Urology* 2005;66:658.
65. Shibata R, Okita H, Shimoda M, et al. Primary carcinoid tumor in a polycystic kidney. *Pathol Int* 2003;53:317-322.
66. Guy L, Begin LR, Oigny LL, et al. Searching for an intrinsic neuroendocrine cell in the kidney: an immunohistochemical study of the fetal, infantile, and adult kidney. *Pathol Res Pract* 1999;195:25-30.
67. Berdjis CC, Mostofi FK. Carcinoid tumors of the testis. *J Urol* 1977;118:777-782.
68. Zavaia-Pompa A, Ro JY, El-Naggar B, et al. Primary carcinoid tumor of testis: immunohistochemical, ultrastructural, and DNA flow cytometric study of three cases and a review of the literature. *Cancer* 1993;72:1726-1732.
69. Kato N, Motoyama T, Kameda N, et al. Primary carcinoid tumor of the testis: immunohistochemical, ultrastructural and FISH analysis with review of the literature. *Pathol Int* 2003;53:680-685.
70. Taleman A, Gratama S, Miranda S, et al. Primary carcinoid tumor of the testis: case report, ultrastructure, and review of the literature. *Cancer* 1978;42:2696-2706.
71. Reyes A, Moran CA, Sustel S, et al. Neuroendocrine carcinomas (carcinoid tumor) of the testis: a clinicopathologic and immunohistochemical study of ten cases. *Am J Clin Pathol* 2003;120:182-187.
72. Haupt HM, Mann RB, Trump DL, et al. Metastatic carcinoma involving the testis: clinical and pathologic distinction from primary testicular neoplasms. *Cancer* 1984;54:709-714.
73. Berkheiser SW. Carcinoid tumor of the testis occurring in a cystic teratoma of the testis. *J Urol* 1959;82(3):352-355.
74. Simon HB, McDonald JR, Culp OS. Argentinin tumor (carcinoid) occurring in a benign cystic teratoma of the testicle. *J Urol* 1954;72:892-894.
75. Robboy SJ, Norris HJ, Scully RE. Insular carcinoid primary in the ovary: a clinicopathologic analysis of 48 cases. *Cancer* 1975;36:404-418.
76. Ulbright TM, Amin MB, Young RH. *Tumors of the Testis, Adnexa, Spermatic Cord, and Scrotum*. Washington, DC: Armed Forces Institute of Pathology; 1999:161. *Atlas of Tumor Pathology*, Third series, Fascicle 25.
77. Balzer BL, Ulbright TM. Spontaneous regression of testicular germ cell tumors: an analysis of 42 cases. *Am J Surg Pathol* 2006;30:858-865.
78. Merino J, Zuluaga A, Gutierrez-Tejero F, et al. Pure testicular carcinoid associated with intratubular germ cell neoplasia. *J Clin Pathol* 2005;58:1331-1333.
79. Ulbright TM, Young RH. Carcinoid tumor of the testis. *Am J Clin Pathol* 2004;121:297-298.
80. Pretl K, Zur frage der endocrine der menschlichen versterherdruse. *Virchows Arch* 1944;312:392-404.
81. Azzopardi JG, Evans DJ. Argentinin cells in prostatic carcinoma: differentiation from lipofuscin and melanin in prostatic epithelium. *J Pathol* 1971;104:247-251.
82. di Sant'Agnese PA. Neuroendocrine differentiation in carcinoma of the prostate: diagnostic, prognostic, and therapeutic implications. *Cancer* 1992;70(1 Suppl):254-268.
83. Pearse AGE. The cytochemistry and ultrastructure of polypeptide hormone-producing cells of the APUD series and the embryologic, physiologic, and pathologic implications of the concept. *J Histochem Cytochem* 1969;17:303-313.
84. Bonkhoff H, Stein U, Remberger K. Multidirectional differentiation in the normal, hyperplastic, and neoplastic human prostate: simultaneous demonstration of cell-specific epithelial markers. *Hum Pathol* 1994;25:42-46.
85. Noordzij MA, van der Kwast TH, van Steenbrugge GJ, et al. The prognostic influence of neuroendocrine cells in prostate cancer: results of a long-term follow-up study of patients treated by radical prostatectomy. *Int J Cancer* 1995;62:252-258.
86. Abrahamsson PA, di Sant'Agnese PA. Neuroendocrine cells in the human prostate gland. *J Androl* 1993;14:307-309.
87. di Sant'Agnese PA, de Mesy Jensen KL. Human prostatic endocrine-paracrine (APUD) cells: distributional analysis with a comparison of serotonin and neuron-specific enolase immunoreactivity and silver stains. *Arch Pathol Lab Med* 1985;109:607-612.
88. Abrahamsson PA. Neuroendocrine differentiation in prostatic carcinoma. *The Prostate* 1999;39:135-146.
89. di Sant'Agnese PA. Neuroendocrine differentiation and metastatic carcinoma: the concept "comes of age". *Arch Pathol Lab Med* 1988;112:1097-1099.
90. Abrahamsson PA, Falkmer S, Falt K, et al. The course of neuroendocrine differentiation in prostatic carcinomas: an immunohistochemical study testing chromogranin A as an "endocrine marker". *Pathol Res Pract* 1989;185:373-380.
91. Cohen RJ, Glezeron G, Haffajee Z. Neuro-endocrine cells: new prognostic parameter in prostate cancer. *Br J Urol* 1991;68:256-262.
92. Daige MC, Thomas V. APUD type endocrine tumor of the prostate: incidence and prognosis in association with adenocarcinoma. In: Murphy GP, Khoury S, Kuss R, et al, eds. *Progress in clinical and biological medicine*. New York: Alan R. Liss, 1986:529-531.
93. Weinstein MH, Partin AW, Veltri RW, et al. Neuroendocrine differentiation in prostate cancer: enhanced prediction of progression after radical prostatectomy. *Hum Pathol* 1996;27:683-687.
94. Abrahamsson PA, Cockett ATK, di Sant'Agnese PA. Prognostic significance of neuroendocrine differentiation in clinically localized prostatic carcinoma. *The Prostate (Suppl)* 1998;9:37-42.
95. Aprikian AG, Cordon-Cardo C, Fair WR, et al. Neuroendocrine differentiation in metastatic prostatic adenocarcinoma. *J Urol* 1994;151:914-919.
96. McWilliam LJ, Manson C, George NJR. Neuroendocrine differentiation and prognosis in prostatic adenocarcinomas. *Br J Urol* 1997;80:287-290.
97. Aprikian AG, Cordon-Cardo C, Fair WR, et al. Characterization of neuroendocrine differentiation in human benign prostate and prostatic adenocarcinoma. *Cancer* 1993;71:3952-3965.
98. Bonkhoff H, Stein U, Remberger K. Androgen receptor status in endocrine-paracrine cell types of normal, hyperplastic, and neoplastic human prostate. *Virchows Arch A Pathol Anat Histopathol* 1993;423:291-294.
99. Krijnen JL, Janssen PJ, Ruizeveld de Winter JA, et al. Do neuroendocrine cells in human prostate cancer express androgen receptor. *Histochemistry* 1993;100:393-398.
100. Huang J, Yao JL, di Sant'Agnese PA, et al. Immunohistochemical characterization of neuroendocrine cells in prostate cancer. *The Prostate* 2006;66:1399-1406.
101. Krijnen JL, Bogdanowicz JF, Seldentrik CA, et al. The prognostic value of neuroendocrine differentiation in adenocarcinoma of the prostate in relation to progression of disease after endocrine therapy. *J Urol* 1997;158:171-174.
102. Casella R, Bubendorf L, Sauter G, et al. Focal neuroendocrine differentiation lacks prognostic significance in prostate core needle biopsies. *J Urol* 1998;160:406-410.
103. Bonkhoff H. Neuroendocrine differentiation in human prostate cancer: morphogenesis, proliferation, and androgen receptor status. *Ann Oncol* 2001;12(Suppl 2):S141-S144.
104. Weaver MG, Abdul-Karim FW, Srigley J, et al. Paneth cell-like change of the prostate gland: a histological, immunohistochemical, and electron microscopic study. *Am J Surg Pathol* 1992;16:62-68.
105. Tamas EF, Epstein JI. Prognostic significance of Paneth cell-like neuroendocrine differentiation in adenocarcinoma of the prostate. *Am J Surg Pathol* 2006;30:980-985.
106. Almagro UA. Argrophilic prostatic carcinoma: case report with literature review on prostatic carcinoid and "carcinoid-like" prostatic carcinoma. *Cancer* 1985;55:608-614.
107. Ansari NA, Pintozzi RL, Choi YS, et al. Diagnosis of carcinoid-like metastatic prostatic carcinoma by an immunoperoxidase method. *Am J Clin Pathol* 1981;76:94-98.
108. Azumi N, Shibuya H, Ishikura M. Primary prostatic carcinoid tumor with intracytoplasmic prostatic acid phosphatase and prostate specific antigen. *Am J Surg Pathol* 1984;8:545-550.
109. Ghali VS, Garcia RL. Prostatic adenocarcinoma with carcinoid features producing adrenocorticotrophic syndrome: immunohistochemical study and review of the literature. *Cancer* 1984;54:1043-1048.
110. Ghannoum JE, DeLellis RA, Shin SJ. Primary carcinoid tumor of the prostate with concurrent adenocarcinoma: a case report. *Int J Surg Pathol* 2004;12:167-170.
111. Tash JA, Reuter VE, Russo P. Metastatic carcinoid tumor of the prostate. *J Urol* 2002;167:2526-2527.
112. Azumi N, Traweek ST, Battifora HA. Prostatic acid phosphatase in carcinoid tumors: immunohistochemical and immunoblot studies. *Am J Surg Pathol* 1991;15:785-790.
113. Sobin LH, Hjermstad BM, Sesterhenn IA, et al. Prostatic acid phosphatase activity in carcinoid tumors. *Cancer* 1986;58:136-138.
114. Srigley JR, Grignon DJ, Young RH. The distinction between pure carcinoid tumor and carcinoid-like adenocarcinoma of the prostate gland. *Mod Pathol* 2002;15:182A-183A.
115. Stratton M, Evans DJ, Lampert IA. Prostatic adenocarcinoma evolving into carcinoid: selective effect of hormonal treatment? *J Clin Pathol* 1986;39:750-756.
116. Wasserstein PW, Goldman RL. Primary carcinoid of the prostate. *Urology* 1979;8:318-320.
117. Reyes A, Moran CA. Low-grade neuroendocrine carcinoma (carcinoid tumor) of the prostate. *Arch Pathol Lab Med* 2004;128:e166-168.
118. Wenk RE, Bhagavan BS, Levy R, et al. Ectopic ACTH, prostatic oat cell carcinoma, and marked hypernatremia. *Cancer* 1977;40:773-778.
119. Galanis E, Frylak S, Lloyd RV. Extrapulmonary small cell carcinoma. *Cancer* 1997;79:1729-1730.
120. Evans AJ, Humphrey PA, Belani J, et al. Large cell neuroendocrine carcinoma of the prostate: a clinicopathologic summary of 7 cases of a rare manifestation of advanced prostate cancer. *Am J Surg Pathol* 2006;30:684-693.
121. Tetu B, Ro JY, Ayala AG, et al. Small cell carcinoma of the prostate. I. A clinicopathologic study of 20 cases.
122. Travis WD, Linnola RI, Tsokos MG, et al. Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma: an ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. *Am J Surg Pathol* 1991;15:529-553.
123. Epstein JI, Allsbrook WC, Amin MB, et al. The 2005 International Society of Urologic Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol* 2005;29:1228-1242.
124. Ro JY, Tetu B, Ayala AG, et al. Small cell carcinoma of the prostate. II. Immunohistochemical and electron microscopic studies of 18 cases. *Cancer* 1987;59:977-982.
125. Yao JL, Maded R, Bourne P, et al. Small cell carcinoma of the prostate: an immunohistochemical study. *Am J Surg Pathol* 2006;30:705-712.
126. Schron DS, Gipson T, Mendelsohn G. The histogenesis of small cell carcinoma of the prostate: an immunohistochemical study. *Cancer* 1984;53:2478-2480.
127. Amato RJ, Logothetis CJ, Hallinan R, et al. Chemotherapy for small cell carcinoma of prostatic origin. *J Urol* 1992;147:935-937.
128. Rubinstein JH, Katin MJ, Mangano MM, et al. Small cell anaplastic carcinoma of the prostate: seven new cases, review of the literature, and discussion of a therapeutic strategy. *Am J Clin Oncol* 1997;20:376-380.
129. Papanidreou CN, Daliani DD, Thall PF, et al. Results of a phase II study with doxorubicin, etoposide, and cisplatin in patients with fully characterized small-cell carcinoma of the prostate. *J Clin Oncol* 2002;20:3072-3080.
130. Murray N, Salgia R, Fossella FV. Targeted molecules in small cell lung cancer. *Semin Oncol* 2004;31:106-111.
131. Fernandes RC, Matushita MM, Mauad T, et al. Prostate carcinoma with neuroendocrine differentiation: case report and literature review. *Rev Hosp Clin Fac Med Sao Paulo* 2001;56:153-158.
132. Patel S, Rosenthal JT. Hypercalcaemia in carcinoma of the prostate: its cure by orchietomy. *Urology* 1985;25:627-629.
133. Wynn SS, Nagabandi S, Koo J, et al. Recurrent prostate carcinoma presenting as oriental large cell carcinoma with neuroendocrine differentiation and resulting in bowel obstruction. *Arch Pathol Lab Med* 2000;124:1074-1076.



Unusual Hematologic Tumors of the Genitourinary Organs

Lynne V. Abruzzo, M.D., Ph.D.
Department of Hematopathology
March 24, 2007

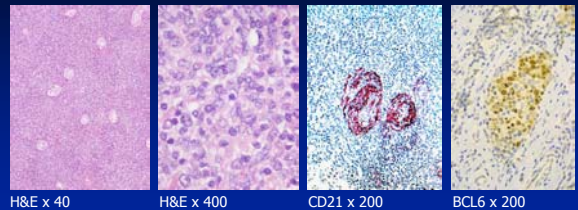


Case 1

Case History

- The patient was a 6 year old boy who presented with painless enlargement of the right testis. He was otherwise well. Physical examination was remarkable only for the enlarged testis. Laboratory tests, including a complete blood count and serum chemistries, and a bone marrow examination were within normal limits. Ultrasound of the scrotum showed an enlarged right testis with a focal hypoechoic mass. Chest radiograph, CT scans of the chest and abdomen, and bone scan were unremarkable.
- The patient underwent a right radical orchiectomy and right inguinal lymph node biopsy.

Histology and Immunophenotype



The immunohistochemical stains are reprinted with permission from Archives of Pathology & Laboratory Medicine. Copyright 2007. College of American Pathologists.

Diagnosis

Primary follicular lymphoma of the testis in childhood

Lymphoma of the Testis

- Lymphoma can involve the testis as
 - Disseminated nodal disease
 - Primary site of presentation of clinically occult nodal disease
 - True primary extranodal disease
- Presents as a hard, painless, usually unilateral scrotal mass
- Disseminated nodal lymphoma - common in adults and children
 - Adults
 - Most common testicular neoplasm in men older than 60 years
 - Usually diffuse large B-cell lymphoma
 - Follicular lymphoma rare

Lymphoma of the Testis

- Disseminated nodal NHL
 - Children
 - Usually precursor B or T lymphoblastic leukemia/lymphoma or Burkitt lymphoma
- Primary testicular lymphoma - rare in adults and children
 - Adults
 - Usually diffuse large B-cell lymphoma
 - Aggressive clinical course with propensity to spread to nasopharynx and central nervous system
 - Children
 - Usually follicular large cell lymphoma
 - Excellent prognosis

Follicular Lymphoma Comparison of Adults and Children

	Adults	Children
Occurrence	Common	Rare
Median age	59 years	11 years
M:F ratio	1:1.7	2.3:1
Stage	III/IV	I
Site	Widespread	Head and neck (esp. tonsil), testis
Grade	I/II	II/III
t(14;18)/BCL2	Positive	Negative
Course	Indolent, progressive	Usually curable

Follicular Lymphoma of Testis in Children

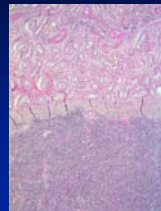
- Exceedingly rare
 - 11 reported cases
- Median age
 - 5 years (range 3-11 years)
- Stage IE
- Histology
 - Follicular, some cases with focal diffuse areas
 - Grade 3 (large cell) with no low-grade component
- Immunophenotype
 - CD20+, CD10 (5/8+), BCL6 (9/10+), BCL2-
- Excellent prognosis
 - All in complete remission (median 10 months, range 7-59 months)

Case 2

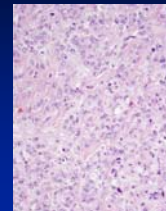
Case History

- The patient was a 35 year old man who presented with a painless 8 cm left scrotal mass that had been waxing and waning in size over the past 2 years. He was otherwise well. Physical examination was remarkable only for the mass. Laboratory tests, including a complete blood count and serum chemistries, and a bone marrow examination were within normal limits. Chest radiograph and CT scans of the chest and abdomen were unremarkable.
- The patient underwent a left orchiectomy.

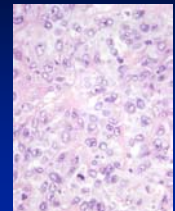
Histology



H&E x 40



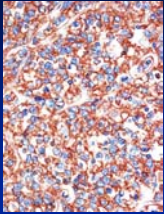
H&E x 200



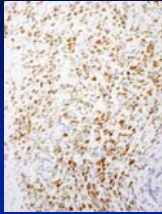
H&E x 400

The low-power image is reprinted with permission from Archives of Pathology & Laboratory Medicine. Copyright 2007, College of American Pathologists.

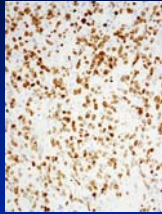
Immunophenotype



CD20 x 200



BCL6 x 200



Ki-67 x 200

Diagnosis

Primary diffuse large B-cell lymphoma of the epididymis

Primary Lymphoma of the Epididymis Clinical Features

Case	Age, y	Stage	Histology/ Immunophenotype	Therapy	Response	Follow-up, mos
1	35	IE	Diffuse large cell/B	O, CT, RT	CR	NED, 6
2	26	IE	"Histiocytic"/NA	O, RT	CR	NED, 12
3	73	IE	"Histiocytic"/NA	RT	CR	NED, 12
4	68	IE	Diffuse large cell/NA	O, CT	NR	DOD, 12
5	34	IE	Follicular lymphoma, grade 3/B	O, CT	CR	NED, 79
6	20	IE	MALT lymphoma/B	SR	CR	NED, 36
7	56	IE	Intravascular lymphoma/T	CT	NR	DOD, 11
8	25	IE	Diffuse large cell/NA	CT	CR	NED, 18

Primary Lymphoma of the Epididymis Clinical Features

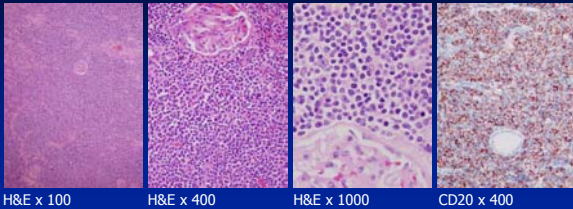
- Extremely rare
- Relatively young age
 - Range 20-73 years (median 34.5 years)
- Right side involved more often than left
 - 6 right, 1 left, 1 bilateral
- Low stage at presentation (IE)
- Intermediate to high-grade histology
- Difficult to determine behavior and survival due to small number of cases and short follow-up

Case 3

Case History

- The patient was a 76 year old woman who presented with right flank pain, anorexia, and weight loss for one month. Her past medical history was significant for essential hypertension, but she had been otherwise well. Physical examination was unremarkable. Laboratory tests, including a complete blood count and serum chemistries were remarkable only for an elevated serum creatinine of 127 $\mu\text{mol/L}$ (normal, 53-106 $\mu\text{mol/L}$). Urinalysis showed >30 leukocytes per high power field, but was negative for protein and glucose. Bone marrow examination was unremarkable. A CT scan of the abdomen showed a 5x3x3 cm mass in the anteroinferior aspect of the right kidney, with no evidence of lymphadenopathy.
- The patient underwent a right radical nephrectomy.

Histology and Immunophenotype



H&E x 100

H&E x 400

H&E x 1000

CD20 x 400

Courtesy of Dr. L. Jeffrey Medeiros

Diagnosis

Primary low-grade MALT lymphoma of the kidney

Low-Grade MALT Lymphoma Clinical Features

- Median age 61 years
- Slight female preponderance (M:F = 1:1.2)
- Low stage at presentation (I/II)
- Sites of involvement
 - Stomach (85%)
 - Other common sites are lung, small intestine and colon (IPSID), salivary glands, ocular adnexae, skin, thyroid, breast
- Association with chronic inflammation
 - Stomach - *H. pylori*
 - Thyroid - Hashimoto thyroiditis
 - Salivary glands - Sjögren syndrome
- Indolent clinical course

Low-Grade MALT Lymphoma Morphologic and Immunophenotypic Features

- Morphology
 - Characteristic marginal zone B cells
 - Small to medium-sized cells with slightly irregular nuclear contours, dispersed chromatin, inconspicuous nucleoli, relatively abundant pale cytoplasm
 - Plasmacytic differentiation is common
 - Reactive germinal centers
 - Lymphoepithelial lesions
- Immunophenotype
 - CD20+, CD5-, CD10-
 - Monotypic immunoglobulin light chain

Low-Grade MALT Lymphoma Specific Chromosomal Translocations

- **t(11;18)(q21;q21)** - *API2* and *MALT1*
 - Fusion transcript
 - ~15% of MALT lymphomas - 30% gastric, 40% lung
- **t(14;18)(q32;q21)** - IgH and *MALT1*
 - Overexpression of *MALT1*
 - ~10% of MALT lymphomas - liver, lung, ocular adnexae
- **t(1;14)(p22;q32)** - *BCL10* and IgH
 - Overexpression of *BCL10*
 - <5% of MALT lymphomas - often advanced stage
- **t(3;14)(p14.1;q32)** - *FOXP1* and IgH
 - Recently described (2005)
 - <10% of MALT lymphomas - thyroid, ocular adnexae, skin

Primary Low-Grade MALT Lymphoma of Kidney Clinical Features

- Rare
 - 16 reported cases
- Median age
 - 65 years (range 43-83 years)
- Slight male preponderance
 - M:F = 1.3:1
- No apparent side preference
 - 7 left, 6 right, 3 not specified
- No known predisposing inflammatory condition
- No association with a specific chromosomal translocation
- Most patients achieve clinical remission

Primary Low-Grade MALT Lymphoma of Kidney Differential Diagnosis

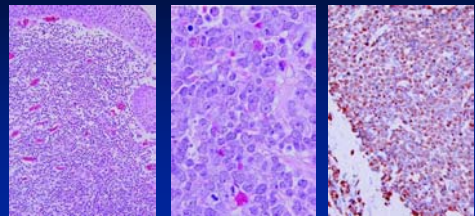
- Reactive processes
- Low-grade MALT lymphoma secondarily involving kidney
 - Also rare
- Small lymphocytic lymphoma/Chronic lymphocytic leukemia
 - Proliferation centers
 - CD5+
- Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia
 - IgM monoclonal gammopathy
- Mantle cell lymphoma
 - Cytologically monotonous without plasmacytoid differentiation
 - Positive for CD5 and cyclinD1

Case 4

Case History

- The patient was a 47 year old man who presented with intermittent hematuria, slight swelling of the right testis, and flank pain. He was otherwise well. Physical examination was remarkable only for a 4 cm hard painless mass in the right epididymis. Laboratory tests, including a complete blood count and serum chemistries, were within normal limits. Bone marrow examination showed only a slight monocytosis. CT scan of the abdomen and pelvis showed a 4x2x3 cm mass in the right posterior wall of the urinary bladder and right hydroureter.
- Cystoscopic examination demonstrated a sessile bladder mass in the trigone that obstructed the right ureteral orifice. The patient underwent an excisional biopsy and placement of a right ureteral stent.

Histology



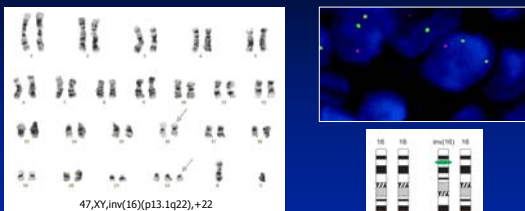
H&E x 200

H&E x 1000

MPO x 400

Reprinted with permission from Archives of Pathology & Laboratory Medicine. Copyright 2007. College of American Pathologists.

Cytogenetics inv(16)(p13.1q22)



47,XY,inv(16)(p13.1q22),+22

Diagnosis

Myeloid sarcoma of the urinary bladder with inv(16)

Myeloid Sarcoma

- Definition: a tumor mass of myeloblasts, immature myeloid cells, or monoblasts in an extramedullary site or in bone
- Synonyms: chloroma, granulocytic sarcoma, extramedullary myeloid cell tumors

Myeloid Sarcoma Clinical Features

- May occur *de novo* or concurrently with AML, CML, MPD, or MDS
- May precede AML by months to years
- May be the initial manifestation of relapse in a patient previously treated for AML
- Myeloid sarcoma is more commonly found in patients with
 - AML with maturation and t(8;21)(q22;q22)
 - Myeloid leukemias with monocytic differentiation
 - acute myelomonocytic leukemia with eosinophilia with inv(16)(p13q22) or t(16;16)(p13;q22)
 - acute monocytic leukemia
 - chronic myelomonocytic leukemia

Myeloid Sarcoma Histologic Features

- Most MS are composed of myeloid precursors and can be divided into three subtypes based on the degree of differentiation
 - Well-differentiated
 - Neoplastic cells at all stages of differentiation
 - Admixed eosinophilic myelocytes common
 - Poorly-differentiated
 - Large cells with irregular nuclear contours, vesicular chromatin, distinct nucleoli
 - Admixed eosinophilic myelocytes infrequent
 - Blastic
 - Medium or large cells with blastic chromatin and inconspicuous nucleoli
 - Eosinophilic myelocytes usually absent

Myeloid Sarcoma Prognosis

- In patients with a previous history of MPD (including CML) or MDS, MS is equivalent to blast transformation
- In patients with AML, the prognosis is equivalent to that of the underlying AML
- Isolated MS may respond to localized radiation therapy

Myeloid Sarcoma Cytochemical and Immunohistochemical Features

- Cytochemical reactions (touch preparations)
 - Myeloperoxidase
 - Naphthol ASD chloroacetate esterase
 - Non-specific esterase
- Immunohistochemical stains
 - CD43
 - Myeloperoxidase
 - Chloroacetate esterase
 - Lysozyme
 - CD68

Myeloid Sarcoma Differential Diagnosis

- Poorly-differentiated carcinoma
- Non-Hodgkin lymphoma
 - Lymphoblastic lymphoma
 - Burkitt lymphoma
 - Large cell lymphoma
- Small round cell tumors
 - Neuroblastoma
 - Ewing's sarcoma/PNET
 - Rhabdomyosarcoma

References

Follicular Lymphoma of the Testis in Childhood

- Moertel CL, et al. Follicular large cell lymphoma of the testis in a child. *Cancer*. 1995;75:1182-1186.
- Finn LS, et al. Primary follicular lymphoma of the testis in childhood. *Cancer*. 1999;85:1626-1635.
- Lu D, et al. Primary follicular large cell lymphoma of the testis in a child. *Arch. Pathol. Lab. Med.* 2001;125:551-554.
- Pileri SA, et al. Primary follicular lymphoma of the testis in childhood: an entity with peculiar clinical and molecular characteristics. *J. Clin. Pathol.* 2002;55:684-688.
- Pakzad K, et al. Follicular large cell lymphoma localized to the testis in children. *J. Urol.* 2002;168:225-228.
- Lorschech RB, et al. Clinicopathologic analysis of follicular lymphoma occurring in children. *Blood*. 2002;99:1959-1964.
- Heller KN, et al. Primary follicular lymphoma of the testis: excellent outcome following surgical resection without adjuvant chemotherapy. *J. Pediatr. Hematol. Oncol.* 2004;26:104-107.

References

Primary Lymphoma of the Epididymis

- Schned AR, et al. Primary histiocytic lymphoma of the epididymis. *Cancer*. 1979;43:1156-1163.
- Heaton JP and Morales A. Epididymal lymphoma: an unusual scrotal mass. *J. Urol.* 1984;131:353-354.
- Ginaldy L, et al. Epididymal lymphoma: a case report. *Tumori*. 1993;79:147-149.
- Ferry JA, et al. Malignant lymphoma of the testis, epididymis, and spermatic cord: a clinicopathologic study of 69 cases with immunophenotypic analysis. *Am J. Surg. Pathol.* 1994;18:376-390.
- McDermott MB, et al. Malignant lymphoma of the epididymis: a case report of bilateral involvement by a follicular large cell lymphoma. *Cancer*. 1995;75:2174-2179.
- Kausch I, et al. Primary lymphoma of the epididymis. *J. Urol.* 1998;160:1801-1802.
- Au WY, et al. T-cell intravascular lymphomatosis (angiotropic large cell lymphoma): association with Epstein-Barr viral infection. *Histopathology*. 1997;31:563-567.
- Novella G, et al. Primary lymphoma of the epididymis. *Urol. Int.* 2001;67:97-99.
- Vega F, et al. Primary paratesticular lymphoma: a report of two cases and review of the literature. *Arch. Pathol. Lab. Med.* 2001;125:428-432.

References

Primary Low-Grade MALT Lymphoma of Kidney

- Parveen T, et al. Low-grade B-cell lymphoma of mucosa-associated lymphoid tissue arising in the kidney. *Arch. Pathol. Lab. Med.* 1993;117:780-783.
- Jindal B, et al. Indolent behaviour of low-grade B cell lymphoma of mucosa-associated lymphoid tissue arising in the kidney. *Urol. Int.* 2001;67:91-93.
- Qiu L, et al. Low-grade mucosa-associated lymphoid tissue lymphoma involving the kidney: report of three cases and review of the literature. *Arch. Pathol. Lab. Med.* 2006;130:86-89.
- Colovic M, et al. Primary MALT lymphoma of the kidney. *Hematol Cell. Ther.* 1999;41:229-232.
- Mita K, et al. Primary mucosa-associated lymphoid tissue lymphoma in the renal pelvis. *Urol. Int.* 2002;69:241-243.
- Stokes MB, et al. Membranoproliferative glomerulonephritis associated with low-grade B-cell lymphoma presenting in the kidney. *Clin. Nephrol.* 2002;57:303-309.
- Tuzel E., et al. Primary renal lymphoma of mucosa-associated lymphoid tissue. *Urology*. 2003;61:463.
- Mhawech P, et al. Pathologic case quiz: a unilateral renal mass in an elderly woman. *Arch. Pathol. Lab. Med.* 2000;124:919-920.
- Garcia M, et al. Low-grade AMLT lymphoma involving kidney: a report of 9 cases and review of the literature. (submitted).

References

Myeloid Sarcoma of the Urinary Bladder

- Liu PI, et al. Autopsy study of granulocytic sarcoma (chloroma) in patients with myelogenous leukemia, Hiroshima-Nagasaki 1949-1969. *Cancer*. 1973;31:948-955.
- Chaitin BA, et al. Hematologic neoplasms with initial manifestations in lower urinary tract. *Urology*. 1984;23:35-42.
- Cartwright PC, et al. Leukemic relapse presenting with ureteral obstruction caused by granulocytic sarcoma. *J. Urol.* 1991;146:1354-1355.
- Bekassy AN, et al. Granulocytic sarcoma after allogeneic bone marrow transplantation: a retrospective multicenter survey. *Bone Marrow Transplant.* 1996;17:801-808.
- Aki H, et al. Primary granulocytic sarcoma of the urinary bladder: case report and review of the literature. *Urology*. 2002;60:345-347.
- Kerr P, et al. Bladder chloroma complicating refractory anemia with excess blasts. *Br. J. Haematol.* 2002;118:688.
- Uner A, et al. Granulocytic sarcoma of the urinary bladder. *Am J. Hematol.* 2004;75:262-263.
- Al-Quran A, et al. Myeloid sarcoma of the urinary bladder and epididymis as a primary manifestation of acute myeloid leukemia with inv(16). *Arch. Pathol. Lab. Med.* 2006; 130:862-866.



Courtesy of K. Coombes, Ph.D.