Case Report

Sarcomatoid High Grade Urothelial Carcinoma with Rhabdomyosarcomatous and Other Differentiation: A Case Report with Review of Literature

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It is not uncommon for high-grade urothelial carcinoma to show divergent differentiation with the most common being squamous followed by glandular. However, rhabdomyosarcomatous differentiation in urothelial carcinoma, which portends poor prognosis, is very rare. Here we described a case of bladder high grade urothelial carcinoma with rhabdomyosarcomatous as well as other histologic differentiation. The patient was a 91-year-old female with history of gross hematuria. She was found to have a large tumor protruding into the bladder lumen from the right lateral-posterior wall. The tumor was removed via transurethral resection. The tumor fragments measured 9.1 x 6.5 x 1 cm in aggregate and weighed 23.7 grams. Morphologically, the tumor demonstrated high grade urothelial carcinoma with an area showing abundant eosinophilic cytoplasm, large eccentric hyperchromatic nuclei, and prominent eosinophilic nucleoli, consistent with rhabdomyosarcomatous differentiation. Immunohistochemically, this area was positive for desmin and muscle-specific actin, supporting the above interpretation. There were also areas showing neuroendocrine, sarcomatoid, glandular and squamous differentiation. Scattered giant cells were also noted. Immunohistochemical stains for vimentin and synaptophysin/chromogranin were positive in the areas with sarcomatoid differentiation and neuroendocrine differentiation, respectively. Based on the overall morphological features and immunohistochemical patterns, this tumor was diagnosed as high grade urothelial carcinoma with rhabdomyosarcomatous, neuroendocrine, sarcomatoid, glandular and squamous differentiation. Similar cases in the literature were reviewed and compared with this case.
[N A J Med Sci. 2015;8(1):50-55. DOI: *10.7156/najms.2015.0801050]*

Key Words: *urothelial carcinoma, rhabdomyosarcomatous differentiation, malignant tumor of bladder*

INTRODUCTION

Urothelial carcinoma (UC) with rhabdomyosarcomatous differentiation is extremely rare and only a very limited number of cases have been reported in the literature. Here we present a case of urothelial carcinoma with rhabdomyosarcomatous differentiation. In the report, we describe its clinicopathological characteristics and summarize some clinical, prognostic, and genetic features of the tumor as well as some promising therapeutic agents based on the progress of molecular medicine.

CASE REPORT

The patient was a 91-year-old female with significant gross hematuria for an uncertain time. A cystoscopy was performed. It was noted there was a round large bladder tumor (about the size of a ping pong ball) protruding into the bladder lumen from the right lateral-posterior wall. She subsequently underwent a transurethral resection of the bladder tumor. The specimen consisted of multiple tan-pink fragments of soft tissue, measuring 9.1 x 6.5 x 1 cm and weighing 23.7 grams in aggregate. Morphologically, the tumor demonstrated high grade urothelial carcinoma with areas showing abundant eosinophilic cytoplasm, large eccentric hyperchromatic nuclei, and prominent nucleoli, morphologically consistent with rhabdomyosarcomatous differentiation. There were also areas showing neuroendocrine, sarcomatoid, glandular and squamous differentiation (**Figure 1**). An area with scattered giant cells was also noted. The malignant cells appeared to be invading as nests and sheets into the devitalized detrusor muscle. However, no lymphovascular invasion was identified. Immunohistochemical stains were performed, and the tumor was focally positive for desmin, muscle-specific actin, vimentin and synaptophysin/chromogranin (**Figure 1**). These immunohistochemical staining results supported the rhabdomyosarcomatous, sarcomatoid, and neuroendocrine differentiation. Based on the morphology and

Received: 06/05/2014; Revised: 12/30/2014; Accepted: 01/04/2014
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immunohistochemical stain patterns, a diagnosis of high grade urothelial carcinoma with rhabdomyosarcomatous, neuroendocrine, sarcomatoid, glandular and squamous differentiation was made. The patient was followed during the past 10 months and did relatively well.

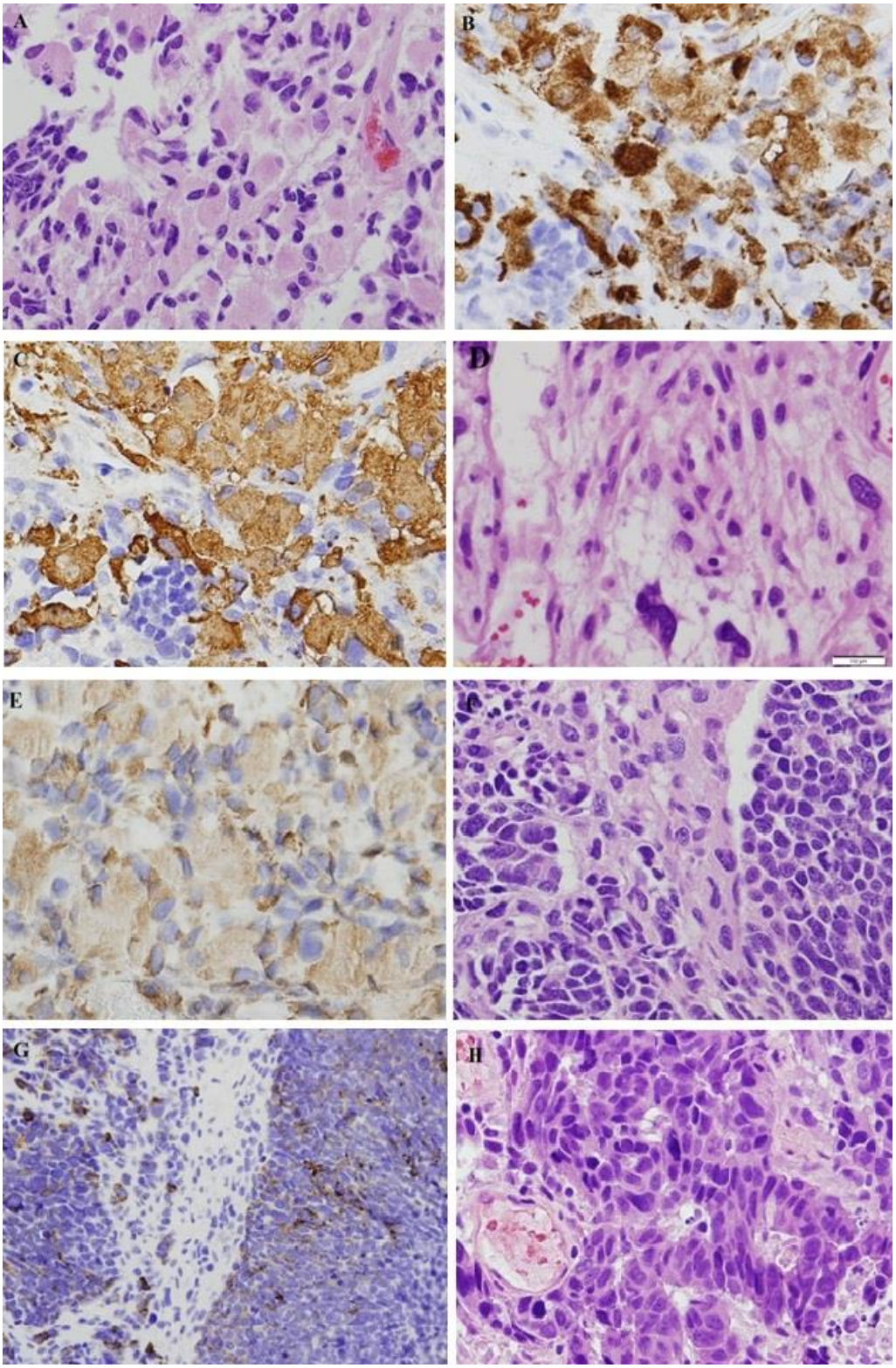

Figure 1. A. Rhabdomyosarcomatous differentiation. Round or oval cells show abundant cytoplasm and intracytoplasmic eosinophilic bodies, vesicular nuclei, and prominent nucleoli (HE stain, 400x); **B.** Immunohistochemical stain for desmin (400x); **C.** Immunohistochemical stain for muscle-specific actin (400x); **D.** Sarcomatoid component. Atypical spindled tumor cells show pleomorphic nuclei and coarse chromatin (HE stain, 400x); **E.** Immunohistochemical stain for vimentin (200x); **F.** Neuroendocrine component. Neoplastic cells show high nuclear–cytoplasmic ratio, inconspicuous nucleoli and typical nuclear molding (HE stain, 400x); **G.** Immunohistochemical stain for chromogranin (400x); **H.** Glandular differentiation (HE stain, 400x); **I.** Squamous differentiation (HE stain, 100x); **J.** High grade urothelial carcinoma component (HE stain, 100x).

DISCUSSION

Urothelial carcinoma occasionally shows a broad spectrum of histological differentiation and has a variety of histopathological variants. According to 2004 WHO classification, invasive urothelial carcinoma includes many variants: urothelial carcinoma with rhabdomyosarcomatous differentiation, invasive urothelial carcinoma with squamous differentiation, invasive urothelial carcinoma with glandular differentiation, sarcomatoid variant, giant cell variant, etc. Among the variants, squamous and glandular differentiation are most common. Urothelial carcinoma with rhabdomyosarcomatous differentiation is an extremely rare variant. Only few cases have been reported in literatures (Summarized in **Table 1**).

Table 1. Clinicopathological Features.

Age (yrs)/sex	Location/size (cm)	Clinical presentation	Histopathology of rhabdomyosarcomatous component/ other components	Treatment	Outcome (months)	Reference
68/M	Posterior bladder wall /4 x 4 x 3	Hematuria	Round or oval abundant cytoplasm with an eosinophilic body, vesicular nuclei, and prominent nucleoli/small cell	RC	Died (4)	1
53/M	Left lateral bladder wall /3 x 2.5 x 0.3	Hematuria	Round or oval abundant cytoplasm with an eosinophilic body, vesicular nuclei, and prominent nucleoli/sarcomatoid and myxoid	RC	Alive (9)	1
68/M	Bladder and lower abdominal wall/10.6 x 10x8	Repeated UTIs	Round or oval abundant cytoplasm with an eosinophilic body, vesicular nuclei, and prominent nucleoli/myxoid	None	Died (1)	1
86/M	Trigone of bladder/NA	Hematuria	Round or oval abundant cytoplasm with an eosinophilic body, vesicular nuclei, and prominent nucleoli	Bilateral nephrostomy	Alive (3)	1
55/M	Posterior and right lateral bladder wall/3.5 x 2.5 x 1.5	Hematuria	Eccentric hyperchromatic nuclei, prominent eosinophilic nucleoli, and eosinophilic cytoplasm with round hyaline-like inclusions	RC	Alive (8)	2
4/F	Bladder dome/ 1.8 x 1.6 x 2.4	Hematuria	Monomorphous noncohesive large cells with peripherally displaced vesicular nuclei, prominent nucleoli and acidophilic cytoplasm containing typical cytoplasmic inclusion structures	Partial cystectomy	Alive (24)	3
2/F	Peri-trigone/3.4 x 2.0 x 1.8	Hematuria	Eccentric nuclei and abundant glassy eosinophilic cytoplasm with hyaline-like globular inclusions/sarcomatous	The tumor was resected	Alive (36)	4
46/F	Right-sided tumor of bladder/NA	Hematuria	Rounded or oval cells with abundant cytoplasm containing a brightly eosinophilic rounded slightly fibrillar body, vesicular nuclei with prominent nucleoli	The tumor was resected	Recurrence after 2 weeks, resected again; after 2nd resection, Died (13)	5
75/M	Right bladder wall/NA	Hematuria	Discohesive cells with a rich eosinophilic cytoplasm with bright eosinophilic bodies and large eccentrically located nuclei with coarse chromatin and conspicuous nucleoli.	Resection of bladder tumor	Alive (4)	6
59/M	A papillary and sessile tumor in bladder/NA	Hematuria	Discohesive and a high nuclear/cytoplasmic ratio, round to oval nuclei with conspicuous nucleoli, rich eosinophilic cytoplasm./LG papillary UC	Resection of bladder tumor	Alive (21)	6
91/F	Right lateral-posterior bladder wall/9.1 x 6.5 x 1 in aggregate	Hematuria	Abundant eosinophilic cytoplasm, large eccentric hyperchromatic nuclei, and prominent nucleoli/neuroendocrine, sarcomatoid, glandular and squamous features with scattered giant cells	Resection of bladder tumor	Alive (10)	Present case

RC: Radical cystoprostatectomy; UTI: Urinary tract infection; LG: Low grade; HG: High grade; NA: not available.

The differential diagnosis for urothelial carcinoma with rhabdomyosarcomatous differentiation of the upper urinary tract includes rhabdoid tumors of the kidney. The rhabdoid tumor of the kidney was first described in 1978 as a rare malignant renal tumor of childhood. A gene translocation [t(6;22)(p12;q11)] was found in rhabdoid tumor, but was not seen in UC with rhabdomyosarcomatous differentiation.1 Kagotani et al6 described urothelial carcinoma with rhabdomyosarcomatous differentiation as 1) commonly affects elderly men but can also occur in children; 2) can occur in the bladder or renal pelvis; 3) can have conventional papillary urothelial carcinoma or carcinoma in situ

components; 4) the eosinophilic inclusion body consists of intermediate filaments; 5) demonstrates an aggressive clinical behavior.

Immunohistochemical staining is a very useful tool that may be needed to distinguish rhabdomyosarcomatous differentiation from rhabdoid features because both could have the same morphological appearance under light microscopy.[7] Different authors employed different immunochemical reagents to characterize these components. Generally speaking, the UC with rhabdoid feature component does not harbor immunohistochemical or electron microscopic features of skeletal muscle differentiation while the UC with rhabdomyosarcomatous differentiation component does. These results were summarized in **Table 2** and **Table 3**.

Table 2. Immunohistochemical characteristics of the rhabdomyosarcomatous differentiation component.

Antibodies	Case# of positive stains/total case#	References
CK7	1/1	2
CK20	1/1	2
CD 34	8/16	8
EMA	6/16	8
Smooth muscle actin	6/16	8, present case
Desmin	11/17	8, present case
Vimentin	1/1	2
Carcinoembryonic antigen	1/10	8
HMB-45	3/13	8

Table 3. Immunohistochemical characteristics of the UC with rhabdoid features component.

Antibodies	Case# of positive stains/total case#	References
CAM 5.2	5/8	1, 6, 9
AE1/AE3	4/8	1, 6, 9
EMA	5/6	1
Smooth muscle actin	0/7	1, 6, 9
CK7	2/2	6
Vimentin	1/1	9
Desmin	0/1	9

The sarcomatous differentiation component was positive for vimentin from this case report and other studies.[4,7] The carcinomatous component was negagive for vimentin.[4] Interestingly, the transitional areas between sarcomatous and carcinomatous differentiation components demonstrated both vimentin and keratin positive stains.[4] Sarcomatous differentiation component was negative for desmin.[4]

The UC in this report has multiple differentiations including rhabdomyosarcomatous differentiation. It is not clear whether the different differentiation components stem from different clone cells within the tumor or from a same clone ancestor cell which subsequently underwent differentiation in different directions.[10]

The rhabdomyosarcomatous differentiation is almost always associated with poorly differentiated/high degree carcinomas. Study by Ma et al demonstrated a higher proliferative index with Ki-67 and epidermal growth factor receptor (EGFR) expression in the rhabdomyosarcomatous differentiation areas. The findings supported the rhabdomyosarcomatous differentiation cells have more aggressive biologic behavior, i.e. worse clinically aggressive course.[2,14] It has been reported that these patients with UC with rhabdomyosarcomatous differentiation died at a median period of 5 months (0.3 – 30 months).[15] On the other hand, a 5-year survival for patients with muscle invasive conventional UC is more than 40%.[16] In the present case, patient was still alive by 10-month follow up. However, we would like to emphasize that the rarity of these variants and short follow-up period made finding solid conclusions impossible in regards to the long term prognosis of these malignancies.

The prognostic significance of glandular or squamous differentiation is not well understood, although some reports demonstrated poor response to chemotherapy- or radio -therapy.[11] Molecular analyses have shown the carcinomatous and sarcomatous components have a common clonal origin.[12] However, a study indicated that carcinosarcoma and sarcomatoid carcinoma patients have worse prognosis than high-grade urothelial carcinoma.[13]

It has been extensively accepted that a cisplatin-based chemotherapy followed by surgery is for muscle invasive conventional UC, and gemcitabine + cisplatin and MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) for metastatic disease. But so far there are no standardized treatment regimens for various differentiation variants. Due to the rarity of UC differentiation, especially with only few reports of the rhabdomyosarcomatous differentiation, many aspects about these differentiation in UC remain unknown.

Some clinicopathological predictive factors for conventional UC have been investigated among different urothelial carcinomas (**Table 4**).

Table 4. Clinicopathological Predictive Prognosis Factors.[17,18]

Non-muscle IBC	**Muscle IBC**	**Upper urinary tract UC**
Number of tumors	T-stage	Lack of gross hematuria
Tumor size	Lymph node status	Tumor located at ureter
Prior recurrence rate	Variant history	Advanced stage
T-stage		Higher p53 expression
Presence of concurrent carcinoma in situ		
Tumor grade		

IBC: invasive bladder cancer

Unlike many other epithelial cancers, the increasing data from clinical and molecular studies support a dual-pathway hypothesis of bladder carcinogenesis. It has been found that the development of low grade bladder UC and high grade/invasive bladder UC is driven by distinct molecular pathways.[11] Low grade non-muscle invasive tumors are genetically stable and are believed to develop from normal transitional epithelium through hyperplasia. These low grade tumors are characterized by alterations in the PI3K-Akt-mTOR and RAS-MAPK pathways with significant interaction between these pathways, causing overgrowth of urothelial cells. Genetic instability renders these tumors vulnerable to the accumulation of genetic alterations.[12,13] In addition, hyperactivity of HRAS, resulting from either alternative splicing or mutations in the HRAS gene, is reported in these low grade tumors.[14] It has been reported that 60–70% of these tumors harbor mutations in the fibroblast growth factor receptor 3 gene, a receptor tyrosine kinase.[15]

High grade non-muscle invasive and invasive cancers are believed to stem from carcinoma in situ or de novo. These high-grade invasive tumors are characterized by functional and structural defects in the p53 and retinoblastoma protein (RB) tumor-suppressor pathways.[11] Nuclear accumulation of p53 indeed was shown to be a poor outcome predictor in invasive bladder cancer.[16] pRb inactivation from pRb gene mutation or hyperphosphorylation was also identified in these tumors.[17]

More recently, the advance in molecular biology and high throughput genomic technologies has provided new insight into the bladder carcinogenesis. It has been realized that the epigenetic abnormalities, such as DNA methylation, microRNAs, chromatin remodeling, etc., play important roles in the bladder carcinogenesis, which hold promise for the development of new therapeutic agents and strategies for bladder cancer (**Table 5**).

Table 5. Strategic targets and corresponding therapeutic agents.[24]

Strategic targets	EGFR	HER2	EGFR + HER2	FGFR3 + VEGFR	IGF1R	PI3K	mTOR	VEGFR	VEGFR2 + c-MET	Hsp27
Agents on trial	Gemcitabine (Gemzar)	Trastuzumab (Herceptin)	Lapatinib (Tykerb)	Dovitinib (TKI258)	Cixutumumab (IMC-A12)	BKM120	GSK2126458	Sorafenib (Nexavar)	Cabozantinib (Cometriq)	OGX-427

EGFR: epidermal growth factor receptor (ErbB-1, HER1 in humans); HER2: receptor tyrosine-protein kinase erbB-2, a member of the epidermal growth factor receptor (EGFR/ERBB) family; FGFR3: Fibroblast growth factor receptor 3; IGF1R: insulin-like growth factor 1 receptor precursor; PI3K: Phosphatidylinositol-4,5-bisphosphate 3-kinase; mTOR: mammalian target of rapamycin. mTOR is a serine/threonine protein kinase and belongs to the phosphatidylinositol 3-kinase-related kinase protein family. It plays a role in regulating cell growth, proliferation, motility, survival, protein synthesis, and transcription. VEGFR: vascular endothelial growth factor receptor; c-Met: c-Met is a proto-oncogene. It encodes a protein known as hepatocyte growth factor receptor which has tyrosine-kinase activity; HSP27: a heat shock protein acting as a chaperone. It was found to be overexpressed in cancer cells after chemotherapy. Recent studies indicated that Hsp27 is expressed in UCs.

In summary, our report described a high grade urothelial carcinoma with rhabdomyosarcomatous, neuroendocrine, sarcomatoid, glandular and squamous differentiation as well as giant cells. Urothelial carcinoma of bladder with rhabdomyosarcomatous differentiation is extremely rare. In the report, we compared the clinicopathological features, treatments and prognoses of urothelial carcinomas with rhabdomyosarcomatous differentiation with the previously reported cases, and reviewed the genetic characteristics of the bladder carcinomas and some promising therapeutic agents that target the various molecular pathways in the urinary bladder carcinogenesis.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

REFERENCES

1. Parwani AV, Herawi M, Volmar K, Tsay SH, Epstein JI. Urothelial carcinoma with rhabdoid features: report of 6 cases. Hum Pathol. 2006;37:168-172.
2. Pasricha S, Hafiz A, Gandhi JS, Mehta A. Urothelial carcinoma of bladder having rhabdoid differentiation with isolated scapular metastasis. J Cancer Res Ther. 2011;7:486-488.
3. Duvdevani M, Nass D, Neumann Y, Leibovitch I, Ramon J, Mor Y. Pure rhabdoidtumor of the bladder. J Urol. 2001;166:2337.
4. Inagaki T, Nagata M, Kaneko M, Amagai T, Iwakawa M, Watanabe T. Carcinosarcomawith rhabdoid features of the urinary bladder in a 2-year-old girl: possible histogenesis of stem cell origin. Pathol Int. 2000;50:973-978.
5. Harris M, Eyden BP, Joglekar VM. Rhabdoid tumour of the bladder: a histological, ultrastructural and immunohistochemical study. Histopathology. 1987;11:1083-1092.
6. Kagotani A, Ishida M, Yoshida K, Iwai M, Okabe H. High-grade urothelial carcinoma of the bladder with rhabdoid features: cytological and histological report of two cases. Cytopathology. 2014;19:1-3.
7. Perez-Montiel D, Wakely PE, Hes O, Michal M, Suster S. High-grade urothelial carcinoma of the renal pelvis: clinicopathologic study of 108 cases with emphasis on unusual morphologic variants. Mod Pathol. 2006;19:494-503.
8. Guillou L1, Wadden C, Coindre JM, Krausz T, Fletcher CD. "Proximal-type" epithelioid sarcoma, a distinctive aggressive neoplasm showing rhabdoid features. Clinicopathologic, immunohistochemical, and ultrastructural study of a series. Am J Surg Pathol. 1997;21:130-146.
9. Fukumura Y1, Fujii H, Mitani K, et al. Urothelial carcinoma of the renal pelvis with rhabdoid features. Pathol Int. 2009;59:322-325.
10. Mahul B Amin. Histological variants of urothelial carcinoma: diagnostic, therapeutic and prognostic implications. Modern Pathology. 2009;22:S96-S118.
11. Black PC, Brown GA, Dinney CP. The impact of variant histology on the outcome of bladder cancer treated with curative intent. Urol Oncol. 2009;27:3-7.
12. Sung MT, Wang M, MacLennan GT, et al. Histogenesis of sarcomatoid urothelial carcinoma of the urinary bladder: evidence for a common clonal origin with divergent differentiation. J Pathol. 2007;211:420-430.
13. Wright JL, Black PC, Brown GA, et al. Differences in survival among patients with sarcomatoid carcinoma, carcinosarcoma and urothelial carcinoma of the bladder. J Urol 2007;178:2302-2306; discussion 2307.
14. Hoot AC, Russo P, Judkins AR, et al. Immunohistochemical analysis of hSNF5/INI1 distinguishes renal and extra-renal malignant rhabdoid tumors from other pediatric soft tissue tumors. Am J Surg Pathol. 2004;28:1485–1491.
15. Gururangan S1, Bowman LC, Parham DM, et al. Primary extracranial rhabdoid tumors. Clinicopathologic features and response to ifosfamide. Cancer. 1993;71:2653-2659.

16. Nadal R, Bellmunt J. New treatments for bladder cancer: when will we make progress? Curr Treat Options Oncol. 2014;15:99-114.
17. Feng C, Wang L, Ding G, et al. Predictive value of 265clinicopathological markers for the metachronous bladder cancer and prognosis of upper tract urothelial carcinoma. Sci Rep. 2014;4:1-6.
18. Sapre N, Herle P, Anderson PD, Corcoran NM, Hovens CM. Molecular biomarkers for predicting outcomes in urothelial carcinoma of the bladder. Pathology. 2014;46:274-282.
19. Wu XR. Urothelial tumorigenesis: a tale of divergent pathways. Nat Rev Cancer. 2005;5:713-725.
20. Mitra AP, Cote RJ. Molecular screening for bladder cancer: progress and potential. Nat Rev Urol. 2010;7:11-20.
21. Liu S, Liu W, Jakubczak JL, et al. Genetic instability favoring transversions associated with ErbB2-induced mammary tumorigenesis. Proc Natl Acad Sci U S A. 2002;99:3770-3775.
22. Czerniak B, Cohen GL, Etkind P, et al. Concurrent mutations of coding and regulatory sequences of the Ha-ras gene in urinary bladder carcinomas. Hum Pathol. 1992;23:1199-1204.
23. van Rhijn BW, Lurkin I, Radvanyi F, et al. The fibroblast growth factor receptor 3 (FGFR3) mutation is a strongindicator of superficial bladder cancer with low recurrence rate. Cancer Res. 2001;15:1265-1268.
24. Egger G, Liang G, Aparicio A, Jones PA. Epigenetics in human disease and prospects for epigenetic therapy. Nature. 2004;429:457-463.
25. Gschwind A, Fischer OM, Ullrich A. The discovery of receptor tyrosine kinases: targets for cancer therapy. Nature Rev Cancer. 2004;4:361-370.