



Synchronous Urothelial Bladder and Renal Malignancies. Case Report and Review of Urologic Cancers in Patients With Familial Rb Mutations

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We present a urologic case report associated with retinoblastoma (RB1) mutation. A 65-year-old man, who has a history of bilateral retinoblastoma treated with primary radiation therapy at approximately 1 year of age. He presented with a 3-month history of gross hematuria and, on initial workup, was found to have synchronous renal and urothelial malignancies. The patient underwent complete transurethral resection of high grade Ta urothelial cancer and robotic-assisted partial nephrectomy for a pT3a leiomyosarcoma. He remains responsive to Bacillus Calmette-Guerin, and shows no recurrence of his renal malignancy. Through targeted sequencing, Rb mutations can predispose patients to several urologic malignancies. *UROLOGY* 131: 89–92, 2019. Published by Elsevier Inc.

Heritable retinoblastoma is seen with a germline mutation in the tumor suppressor gene *RB1*. Mutations in the *RB1* gene were the first demonstrated tumor suppressor gene in humans, leading to the development of the “two-hit hypothesis” by Knudsen.¹ Rb binds to transcription factors in the E2F family and inhibits the transition into S phase of cell division. Due to the altered or missing protein RB (pRB), second primary malignancies are commonly diagnosed in patients with germline or hereditary Rb1 mutations. Historically, the feared complication of this germline mutation was bilateral retinoblastoma. As the treatment for this improved, patients’ life expectancies approach that of the general population and secondary malignancies were identified.² We describe synchronous genitourinary malignancies identified in a patient with history of *RB1* mutation along with targeted next-generation sequencing of these lesions.

CASE

We report on a 65-year-old man with a history of intermittent gross hematuria for 3 months. He was referred for urologic evaluation of his gross hematuria. His medical history is significant for bilateral retinoblastoma as a child, for which he underwent external beam radiation at approximately 1 year of age. He had no occupational exposure to hazardous chemicals, no family history of

malignancy, and had been a lifelong nonsmoker. The patient had no family history of retinoblastoma and he and his partner elected not to have any genetic offspring.

The patient underwent complete hematuria workup with cystoscopy, demonstrating a 3 cm papillary urothelial tumor and, on computerized tomography imaging, we identified a 3.5 cm right lower pole renal lesion (Fig. 1). Metastatic workup was negative. He was taken to the operating room for a transurethral resection of bladder tumor and pathology reported a high-grade papillary urothelial carcinoma with glandular differentiation and focal microinvasion of superficial lamina propria. Repeated transurethral resection 2 weeks following initial procedure did not demonstrate any residual or invasive malignancy. One week following his repeat transurethral resection of bladder tumor, the patient underwent a right-sided, robotic-assisted partial nephrectomy. He had 100 mL estimated blood loss and 14 minutes of hilar clamp time and was discharged home the following morning without any change in estimated glomerular filtration rate. Pathology from his renal tumor was pT3a leiomyosarcoma with invasion into renal sinus adipose tissue, 4.1 cm in greatest dimension, with negative surgical margins. Microscopically, the tumor demonstrated spindle shaped cells with necrosis within the tumor as seen in Fig. 2. The specimen stained positively for Desmin, Ki-67, muscle-specific actin, and smooth muscle actin consistent with a leiomyosarcoma.

The patient had salivary based germline with an Invitae Multi-Cancer Panel testing of 83 genes. This demonstrated a c.191T>G (p.Leu64) mutation in *RB1* which is a known pathologic variant. His germline testing also identified a c.7040C>A (p.Pro2347Gln) in his *BRCA2* gene, although the importance of this specific variant has

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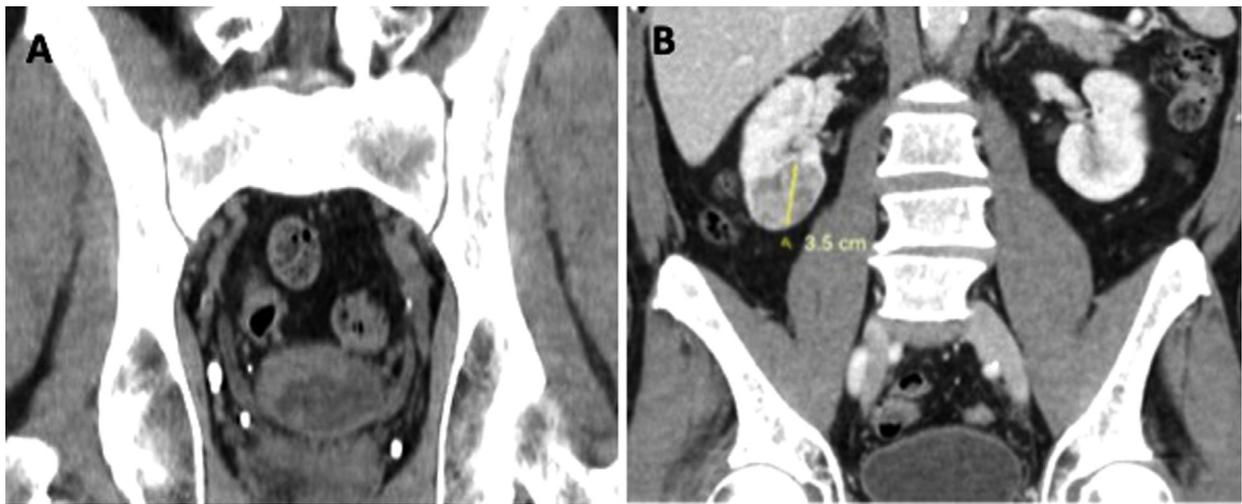


Figure 1. Computerized tomography image. (A) 3 cm papillary urothelial tumor. (B) 3.5 cm renal lesion located on the lower pole. (Color version available online.)

not been identified. Personal Genome Diagnostics Cancer SELECT-125” targeted sequencing of 125 cancer related genes. The tumor content was 80% of the bladder tumor and 90% for the renal cancer. The sections sent were independently reviewed by GU trained pathologist prior to sending for sequencing. Targeted exosomal mutations from both primary tumors are highlighted in [Tables 1](#) and [2](#). He demonstrated an FGFR1 deletion detected in his

urothelial cancer. Tumor mutational burden was not assessed in this platform. Microsatellite instability analysis was negative in both tumors.

The patient initiated an induction course of Bacillus Calmette-Guerin with continued maintenance therapy and has remained free of malignancy for 12 months. In addition, abdominopelvic imaging has not demonstrated concern for recurrence of his renal leiomyosarcoma.

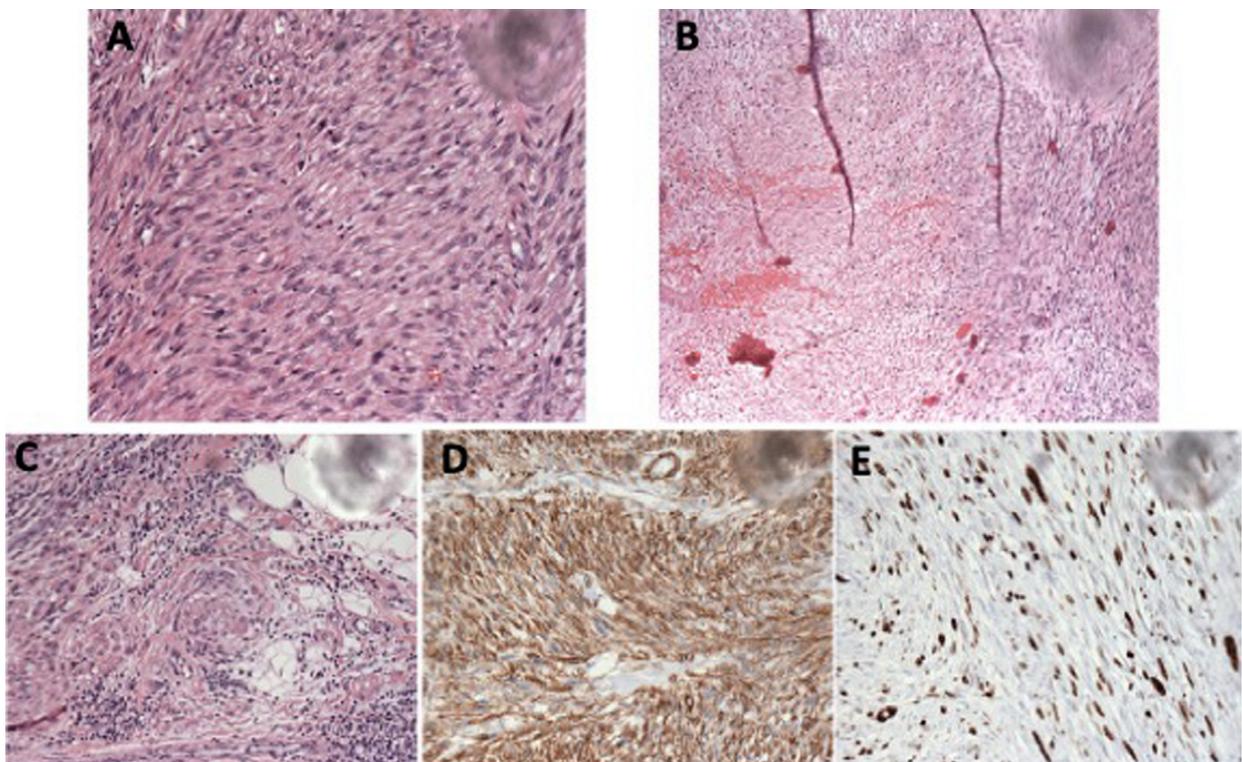


Figure 2. Histopathologic examination of case study renal tumor. (A) 100× magnification of malignant spindle cell lesion with prominent mitotic activity consistent with leiomyosarcoma. (B) 40× magnification leiomyosarcoma with necrosis. (C) 100× magnification with hilar adipose tissue invasion. (D) 100× magnification of leiomyosarcoma stained for Desmin. (E) 100× magnification of tumor stained for Ki-67. (Color version available online.)

Table 1. Bladder tumor targeted exosomal sequencing

Gene	Mutation	Consequence	Mutant fraction (%)	Exon	Percentage mutation in TCGA (%)
BRCA2	P2347Q	Missense	36	13	14
ERBB2	S310F	Missense	4	8	17
ERBB3	E150K	Missense	45	4	12
FBXW7	R505C	Missense	34	9	10
PMS2	E5K	Missense	39	1	7
PTPN11	S548C	Missense	4	14	3
TP53	R273C	Missense	46	7	50
TP53	E221X	Nonsense	32	5	50

Seven genes were found to be mutated including 2 separate *P53* mutations.

DISCUSSION

The cumulative incidence of secondary malignancies in patients with germline *RB1* gene mutations is substantially increased following radiation therapy. Researchers have found that incidence increases steadily with age, and reaches up to 60% at 50 years of age, although this high rate has been debated.² The majority of these secondary malignancies occur in the head and neck; however, almost every type of neoplasm has been reported. A 2010 study of 676 patients with a previously treated retinoblastoma found subsequent second primary tumor cancer types to be 55% sarcomas, 11% carcinomas, 11% midline primitive neuroectodermal tumor, 7% melanomas, 4% lipomas, 3% leukemia/lymphoma, 3% central nervous system tumors, and 2% embryonal or undifferentiated tumors.³

In hereditary retinoblastoma survivors, an 8% risk of leiomyosarcoma diagnosis has been reported. Primary leiomyosarcomas of nongenitourinary organs is established in the literature. In 525 patients with hereditary RB followed for 50 years, Abramson found women to have a higher incidence of uterine leiomyosarcoma.⁴ Wong et al confirmed this research with long-term follow-up of 906 hereditary Rb survivors. Patients receiving an alkylating agent containing chemotherapy were at increased risk of forming bone tumors and leiomyosarcoma, but no significance was found for incidence of melanomas or other malignancies. The risk of leiomyosarcoma was found to be significantly increased for those receiving chemotherapy when younger than 1 year old, but no increased risk for receiving the treatment at older ages.⁵ Primary leiomyosarcoma of renal origin has not been reported.

The radiologic findings of primary renal leiomyosarcoma are similar to those of renal cell carcinoma. Primary

renal leiomyosarcomas most commonly present with flank pain, hematuria, and palpable tumor.⁶ In a recent review, the average size of a renal leiomyosarcoma was 9.4 cm. Of the cases in the literature, there were 9 reports of radical nephrectomy and 1 partial nephrectomy.⁷ The treatment of choice has been radical nephrectomy partially due to the large size at diagnosis. Robotic-assisted partial nephrectomy has not been reported in patients with a primary leiomyosarcoma; however, this is the primary treatment modality utilized at our institution and therefore the patient was amenable to this approach. With negative margins and short ischemia time, we believe this approach was successful in this individual, but encourage others to manage renal malignancies as they feel most comfortable.

While RB loss is seen in urothelial malignancies, the development of urothelial malignancy in childhood RB patients is not well documented. Several case reports detail treatment of leiomyosarcoma or alveolar soft part sarcoma of the bladder in younger patients with hereditary retinoblastoma treated with chemotherapy and radiation. We were unable to identify studies highlighting the development of primary urothelial malignancy in this subset of patients, despite a high prevalence of somatic RB loss in urothelial malignancies.

Importantly, for individuals with urothelial cancer, expression of RB and mutation of the *RB* gene can be linked to recurrence-free and overall survival.⁸⁻¹⁰ In patients receiving radical cystectomy following diagnosis of invasive urothelial cancer of the bladder, Cote et al found that patients with no pRB expression show a significantly lower survival and recurrence-free probability when compared to those with wild-type expression of pRB.¹¹ Similarly in breast cancer, Witkiewicz et al found a correlation between a lower relapse-free survival and an increased knockout of the RB pathway.¹² Further studies to determine chemotherapy response or role of neoadjuvant treatment based on RB status have been mixed. RB functional status can possibly be used to stratify patients into different surgical and clinical treatment options, allowing for improved outcomes.

On review of targeted sequencing in this individual, it was found that this patient has a pathogenic *RB1* variant c.191T>G (p.Leu64*), which is thought to result in absent or disrupted RB protein. Interestingly, we also

Table 2. Renal tumor targeted exosomal sequencing

Gene	Mutation	Consequence	Mutant fraction (%)	Exon
ATRX	W263C	Missense	42	9
BRCA2	P2347Q	Missense	47	13
PDGFRA	E750G	Missense	2	15
RB1	K154Nfs*21	Frameshift	19	4
TP53	R306X	Nonsense	30	7

Five genes were found to be mutated including RB1 and BRCA2.

identified at germline *BRCA2* mutation of unknown significance. In this patient, somatic sequencing did identify this *BRCA2* mutation in both the urothelial and renal malignancies. In this male patient with a *BRCA2* mutation of unknown significance, he has undergone screening for both breast and prostate cancer without any concerning findings. Interestingly the renal leiomyosarcoma appears to have acquired a second *RB1* mutation, which is likely associated with the development of this rare malignancy. The targeted sequencing in the urothelial malignancy did not identify a “second hit” *RB1* mutation, making *RB1* mutation less directly associated with developing his bladder tumor. Other mutations included are listed in Table 1, but the role of these in malignant transformation prognosis remains elusive.

In summary, this is an unusual case presentation identifying synchronous genitourinary malignancies occurring in a patient with a germline retinoblastoma mutation and history of radiation more than 60 years prior to evaluation.

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