Two cases of aggressive sarcomatoid urothelial carcinoma reveal potential molecular targets

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ABSTRACT

Background: To detail two cases of sarcomatoid urothelial carcinoma (UC) with rapid progression, disseminated metastases, and early death, detailing the results of somatic tumor profiling using next-generation sequencing (NGS).

Case Series: The first case presented is a rare case of UC of the renal pelvis with osteosarcomatous differentiation and venous tumor thrombus in a 65-year-old man found to have a heterozygous germline variant of unknown significance in the neurofibromatosis-1 gene. The second case is a 72-year-old woman with sarcomatoid UC of the bladder. Herein, we discuss the presentation and clinical course, histology, immunohistochemical profiles, and somatic tumor testing results. We then review the literature regarding this rare and aggressive entity, detail options for optimal management, and address the role of molecular profiling in these cases.

Conclusion: Sarcomatoid UC is a rare and aggressive entity. NGS may be useful in these cases to guide systemic therapy.

Keywords: Sarcomatoid, urothelial carcinoma, bladder cancer, renal mass, next-generation sequencing.

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Background

Sarcomatoid urothelial carcinoma (UC) is a rare malignant neoplasm, representing less than 1% of urothelial tumors. To date, fewer than 30 cases of this entity have been described involving the renal pelvis, as it is more commonly identified in the urinary bladder [1,2]. Sarcomatoid UC is defined by features of both epithelial and mesenchymal differentiation [3]. The primary treatment modality of this neoplasm is surgical resection, with limited data and consensus regarding the utility of (neo) adjuvant chemotherapy and radiotherapy [4,5]. Renal vein and/or inferior vena cava involvement is exceedingly rare with only three previously reported cases [6-8]. In recent years, somatic genetic testing with next-generation sequencing (NGS) has been increasingly utilized to further characterize rare histologic variants, aiming to improve selection of targeted treatment options in clinical trials.

Herein, we present the case of a 65-year-old man with sarcomatoid UC of the renal pelvis with predominantly osteosarcomatous differentiation and an associated level 0 renal vein tumor thrombus with rapid progression to widespread metastasis following nephrectomy (patient A) and a 72-year-old woman who presented with sarcomatoid UC of the bladder with distant metastases at presentation (patient B). Using these cases, we highlight the aggressive clinical phenotype of sarcomatoid UC, with a focus on the histologic, immunohistochemical (IHC), and genomic profiles of these tumors.

Case Reports

Clinical presentation - patient A

The patient is a 65-year-old Korean man who presented with a 4-month history of intermittent gross hematuria. He was otherwise healthy with no associated symptoms. He was a lifetime non-smoker with no history of known chemical or environmental exposures. Four generations of family history was negative for cancer syndromes, including neurofibromatosis (NF) type 1. A computed tomography (CT) scan with intravenous contrast and excretory imaging demonstrated a central left renal mass measuring 3.6 × 3.3 cm and occupying the renal pelvis with delayed nephrogram in the upper third of the kidney concerning for urothelial versus renal cell carcinoma (Figure 1a). Staging imaging, including CT chest, was negative for metastases. Office cystoscopy was carried out in the clinic to complete the hematuria evaluation, and was negative

for urothelial abnormality. Voided cytology and bladder washings were negative for neoplastic cells.

To complete evaluation for upper tract UC given initial radiographic imaging, he underwent left ureteroscopy, biopsy, and upper tract barbotage. Ureteroscopy revealed a bulging mass into the renal pelvis without papillary features (Figure 2). Biopsy of the mass demonstrated necrotic tissue without definitive evidence of malignant cells. Intraoperative cytology was negative for abnormal urothelial cells.

Interval imaging was carried out 3 months after his original CT scan to ensure no evidence of metastatic disease before he was scheduled for surgery. This confirmed the absence of metastatic disease but was notable for the development of a venous tumor thrombus involving the posterior segment of the solitary left renal vein (Figure 1b). The patient consented for an open radical left nephrectomy with renal vein thrombectomy for the presumptive diagnosis of renal cell carcinoma. The patient's operative course and postoperative recovery were uncomplicated.

Pathologic review and molecular testing

As described, initial urine cytology demonstrated microscopic hematuria and pyuria, but there was no evidence of high-grade UC. Intra-operative renal pelvis biopsy consisted only of necrotic tissue without neoplastic cells and concurrent renal pelvis urine cytology was negative for high-grade UC.

The radical nephrectomy specimen contained a 4.8-cm, firm, white-tan mass in the left renal pelvis (Figure 3d). Histologically, the mass had almost complete sarcomatoid morphology contiguous with ~1% component of conventional high-grade papillary UC, strongly suggesting sarcomatoid differentiation of urothelial primary neoplasm (Figure 3a-c). The sarcomatoid component included many scattered areas of multi-nucleated giant cells and foci of osteoid formation consistent with osteosarcomatous differentiation. IHC revealed scattered GATA-3 positive cells, further supporting the urothelial origin of the tumor. IHC evaluation for epithelial-mesenchymal transition markers previously has been shown to be associated with sarcomatoid UC aggressiveness [9,10]. This staining was not carried out in this case given that it has limited clinical correlation. The tumor invaded both periureteric and peripelvic fat and had angiolymphatic invasion. All surgical margins were negative including the renal vein margin.

Somatic tumor mutational analysis (Foundation Medicine, Cambridge, MA) revealed a possible germline variant of unknown significance (VUS) in a conserved region of NF type 1 (*NF1*) (p.L2547S, NM_001042492.2:c.7640T>C, variant allele fraction [VAF] 0.49), which, to our knowledge, has not been previously described. Additional probable somatic mutations were identified in *NF1* (p.Q236E, NM_001042492.2:c.706C>G, VAF 0.14), *KRAS* (p.G12D) and multiple mutations in interconnected

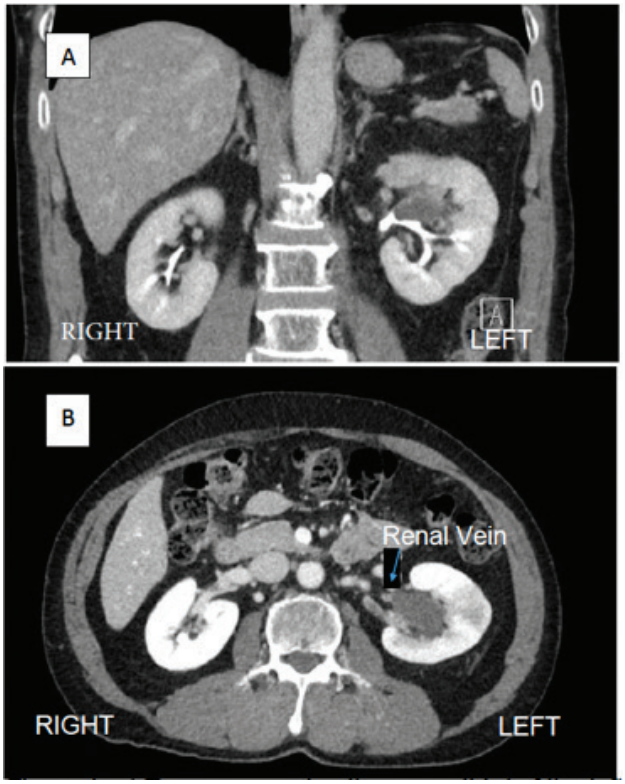

Figure 1. *(A) Tumor occupying the upper third of the left renal collecting system with delayed nephrogram in patient A. (B) Tumor invasion into the left renal vein in patient A.*

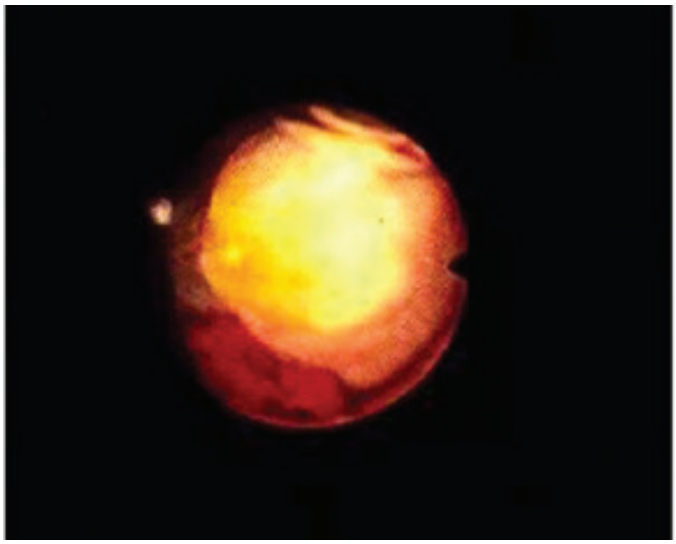

Figure 2. *Endoscopic view of tumor with no mucosal changes in patient A.*

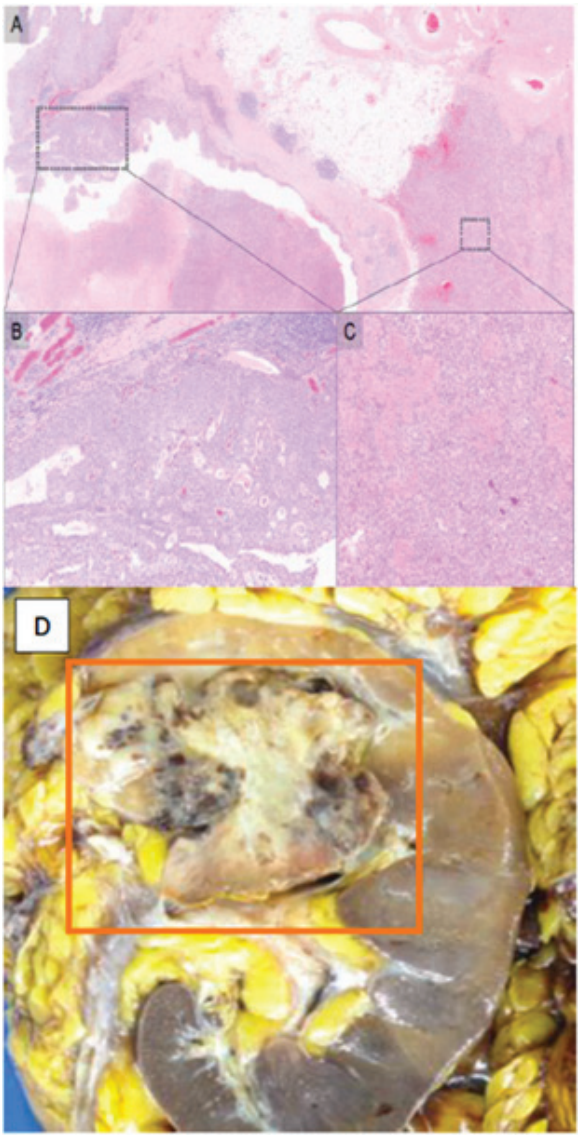

Figure 3. *(A) Low power view of left renal hilum involvement in patient A. (B) Focus of high-grade papillary UC. (C) Focus of carcinoma with osteosarcomatoid differentiation involving sinus fat. (D) Gross specimen of left kidney with renal vein invasion.*

tumor-suppressor pathways (probable biallelic losses of *PTEN0*, *CDKN2A*, and *CDKN2B*; *CDKN2C* p.E120*), and amplification of *MDM2* (also *MTAP* loss, *NFE2L2* p.E78K mutation, and *TERT* promoter mutation). The neoplasm was microsatellite stable (MSS) with a tumor mutational burden of 5 mutations per Mb [11].

Germline testing

This patient was referred for genetic counseling based on the somatic tumor findings and the diagnosis of upper tract UC. Paired analysis of peripheral blood and neoplastic tissue (ColoSeq Tumor, University of Washington, Seattle, WA) confirmed the *NF1* p.L2547S to be germline heterozygous in nature, and was classified as a variant of uncertain significance (VUS) [12]. No other germline variants were identified, including those associated with Lynch syndrome (*MLH1, MSH2, MSH6, PMS2*, and *EPCAM)*.

Follow-up

Following discharge from the hospital, the patient was referred to medical oncology for the evaluation for adjuvant systemic therapy. In the setting of initially localized disease, negative surgical margins, and in the absence of high-level evidence to support the efficacy of adjuvant systemic therapy in this setting in a tumor with predominately sarcomatoid histology, the multidisciplinary consensus plan was to proceed with close surveillance and initiation of systemic therapy in the event of recurrence. Four months following surgery, the patient underwent routine surveillance CT chest, abdomen, and pelvis, which demonstrated diffuse metastatic disease involving his lungs, liver, as well as extensive locoregional recurrence invading his flank musculature (Figure 4a-d). He became rapidly symptomatic with dyspnea, fatigue, weakness, weight loss, and subsequently was hospitalized for

palliative radiation therapy for left flank pain and palliative care evaluation. Given the diffuse symptomatic metastatic disease and his rapid clinical decline and deterioration in performance status, after multidisciplinary evaluation and discussion, the patient opted for hospice and subsequently expired approximately 2 weeks later.

Clinical presentation - case B

The second patient is a 72-year-old female never-smoker with no known family history of genitourinary malignancy, occupational or chemical exposures. She had a history of recurrent urinary tract infections and pelvic prolapse repair 19 years prior to presentation. She initially presented to the referring community hospital, where she was found to have multidrug resistant *Escherichia coli* septicemia and gross hematuria, which resolved with culture-directed antibiotic therapy. She subsequently re-presented reporting several months of gross hematuria and clot retention. Abdominal CT demonstrated a 10-cm bladder mass and retroperitoneal lymphadenopathy. She was taken to the operating room for transurethral resection of the bladder mass. During this evaluation, the tumor was noted to have completely replaced the bladder neck with extension into the sidewalls, anterior, and posterior walls of the bladder, with involvement of the proximal two-thirds of the urethra. Final pathology demonstrated high grade UC with predominantly sarcomatoid differentiation with invasion into the muscularis propria.

Approximately 2 months after her initial presentation, she was referred to our tertiary cancer center. Imaging at referral demonstrated diffuse retroperitoneal lymphadenopathy and osseous metastases including a lesion at T12-L1 with impending spinal cord compression (Figure 5a and c). Additionally, the primary tumor appeared to extend locally into the vagina, urethra, and peri-urethral fat consistent with clinical stage 4 disease (Figure 5b).

Upon referral, she was admitted and underwent posterior spinal fusion of T10-L3 fusion with L1 corpectomy for stabilization, followed by two courses of palliative radiation using 2400cGy to T11-L4 and to the symptomatic pelvic tumor. Repeat imaging immediately after radiation completion demonstrated continued disease progression including new abdominal, retroperitoneal, mediastinal and intrathoracic lymphadenopathy, and new bilateral pulmonary nodules. She was initially offered palliative systemic therapy but clinically declined rapidly, opted for hospice and died from her disease 5 months after initial presentation.

Pathologic review and molecular testing

The initial transurethral bladder tumor resection specimen contained multiple fragments of tissue. IHC staining was positive for pancytokeratin (variably), Epithelial Membrane Antigen (EMA) (variably), S100 (variably), and uroplakin (focal, weak), and negative for GATA-3, PAX-8, Cam5.2, desmin, SM actin, MyoD1, CDX-2, CD34, ERG, and ALK. This profile is consistent with UC with sarcomatoid differentiation.

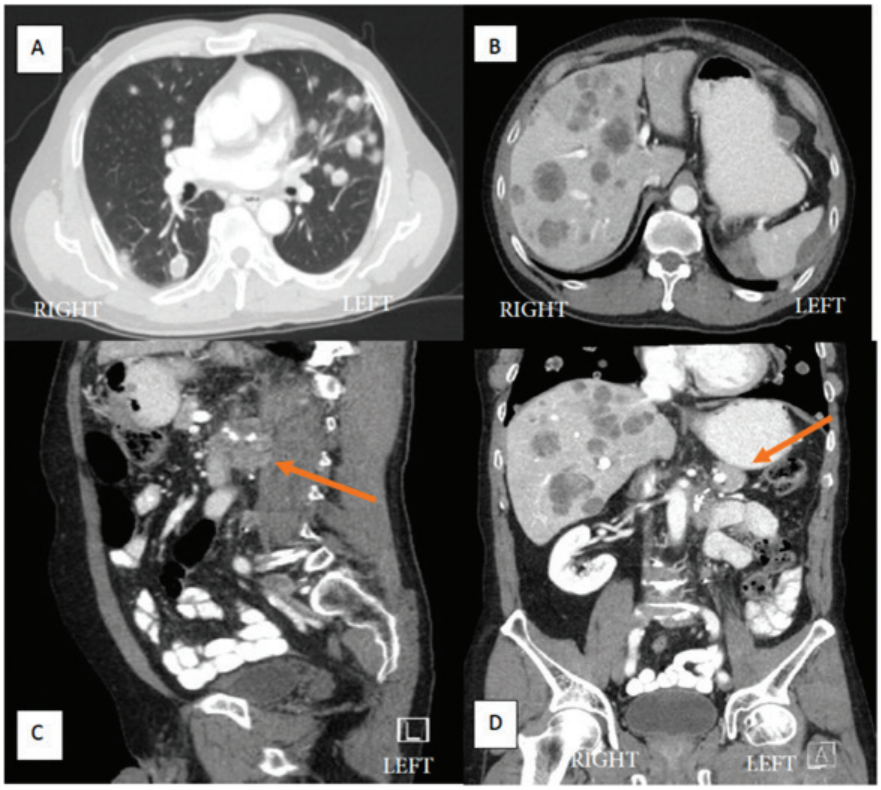

Figure 4. *(A) Pulmonary metastases in patient A. (B) Liver metastases and soft tissue recurrence medial and posterior to spleen with invasion of the diaphragm. (C and D) Local recurrence in resection bed on sagittal and axial imaging (orange arrows).*

Molecular testing (FoundationOne CDx) carried out on the TUR specimen demonstrated alterations in *PIK3CA* (p.H1047L and VAF 0.27), *MLL2* (p.E913* and p.E1594*, and VAF 0.23), *CREBBP* (p.Q1765* and VAF 0.27), *NFE2L2* (p.G81S and p.D29H, VAF 0.27, and 0.26, respectively), *TERT* (−124C->T and VAF 0.26), *AURKB* (p.S322L and VAF 0.23), and loss of CDKN2A, MTAP, and CDKN2B. Possible germline VUS in *NF1* (p.V1146I and VAF 0.50), *TNFRSF14* (p.V49L and VAF 0.51), *TSC2* (p.E75Kand VAF 0.51), and *ESR1* (p.H6Y and VAF 0.47) were identified. A likely somatic VUS was identified in SMARCB1 (p.R37Cand VAF 0.22). Tumor mutational burden was low (1 Muts/Mb) and the tumor was MSS. PD-L1 22c3 IHC (Dako, Carpinteria, CA) demonstrated a combined positive score of 10 (please see Table 1).

Discussion

Sarcomatoid carcinomas are rare and aggressive malignancies that feature histological and IHC findings of both epithelial and mesenchymal components, and have been variably described as pseudosarcoma and carcinosarcoma [13-15]. Sarcomatoid UC of the upper urinary tract represents a rare neoplasm with fewer than 30 cases reported in the literature. This entity primarily affects older individuals and carries a very poor prognosis [4,5,7,8,13]. Similar to previously reported cases, patient A was in his seventh decade of life. Although he presented with localized disease and successfully underwent extirpation with negative margins, he rapidly progressed to locoregional recurrence and diffuse terminal metastatic disease within 16 weeks of surgery. The presence of renal vein tumor thrombus, negative urine cytology and biopsy, lack of mucosal changes on endoscopy, and the osteosarcomatous differentiation of his tumor render his presentation relatively unique.

There are few cases of venous tumor thrombus involving the renal vein or inferior vena cava associated with sarcomatoid UC of the upper urinary tract [6-8]. As such, there is limited available information regarding optimal treatment strategies and outcomes in these patients. In each case, however, patients succumbed to their disease shortly after their initial presentation. Indeed, venous invasion by these tumors appears to be indicative of a highly aggressive phenotype. In the current case, the presence of renal vein thrombus, ureteroscopic findings which were

Table 1. *Summary of molecular testing findings.*

ALTERATIONS	*P*	VAF
NF1	L2547S	0.49
	Q236E	0.14
PIK3CA	H1047L	0.27
MLL2	E913	0.23
	E1594	0.23
CREBBP	Q1765	0.27
NFE2L2	G81S	0.27
	D29H	0.26
TERT	-124C>T (promoter)	0.26
AURKB	S322L	0.23
VUS		
NF1	V11461	0.5
TNFRSF14	V49L	0.51
TSC2	E75K	0.51
ESR1	H6Y	0.47
SMARCB1 (Somatic)	R37C	0.22

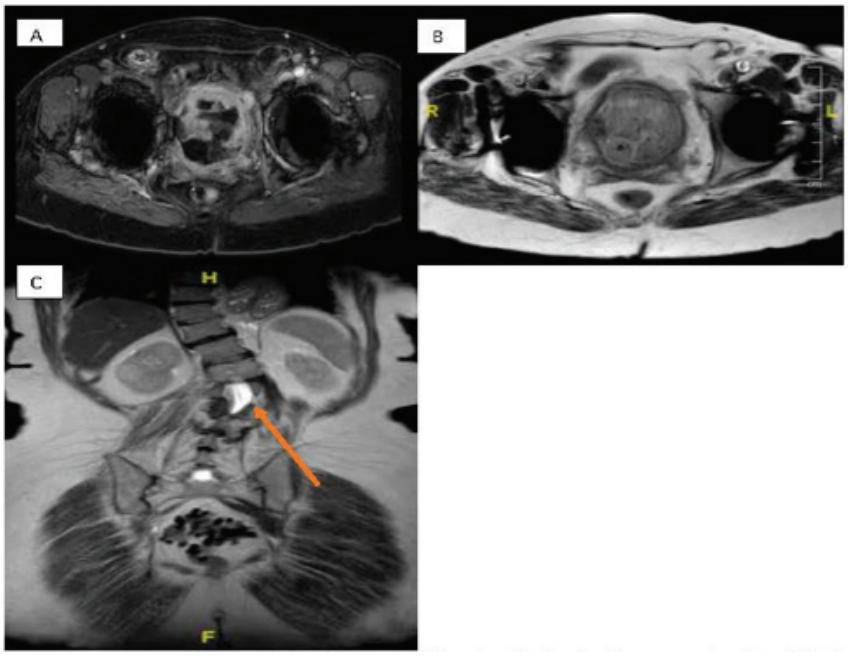

Figure 5. *(A) MRI axial T1-weighted image with spinal lesion in patient B. (B) MRI axial T2-weighted image of bladder. (C) MRI with coronal T2-weighted image demonstrating spinal metastases.*

not consistent with urothelial mucosal involvement and negative urothelial biopsies and cytology raised suspicion that tumor was an aggressive, centrally located renal cell carcinoma, thus prompting the decision to proceed with radical nephrectomy as opposed to a radical nephroureterectomy. Treatment with nephrectomy alone was similarly carried out in other case reports, with rapid progression of disease before ureterectomy could be carried out.

Our second patient represents a unique case of a patient with no traditional risk factors for UC and who presented with findings of infection and clot retention. Additionally, she had a very aggressive disease with widespread lymphadenopathy at presentation which quickly progressed to diffuse metastatic disease. This represents a treatment challenge with early consideration of a need for safe and effective systemic therapy. Unfortunately, this patient's cancer progressed too quickly to permit receipt of systemic treatment, thus she received palliative radiation for pain control and palliative care.

Regarding systemic therapy for sarcomatoid UC, reports of (neo) adjuvant therapies are limited and inconsistently reported, precluding definitive recommendations regarding optimal management strategies. Typically, cases with predominant sarcomatoid bladder tumors undergo upfront radical cystectomy and pelvic lymph node dissection [4,5]. For metastatic disease, there is limited data to guide whether these patients should receive systemic treatment regimens for UC or if the predominant sarcomatoid component would be more responsive to the "sarcoma type" of regimens. The cornerstone of systemic therapy for sarcomatoid UC has traditionally been cisplatin-based chemotherapy. More recently, however, a compelling role for immune checkpoint inhibitors has emerged, with several large trials reporting significant clinical benefit in advanced sarcomatoid renal cell carcinoma. The KEYNOTE-052 and IMvigor 210, cohort 1, both demonstrated the efficacy of the checkpoint inhibitors, pembrolizumab, and atezolizumab (monoclonal antibodies directed against PD-1 and PD-L1, respectively) in patients with advanced UC (especially. PD-L1 high tumors based on a companion diagnostic assay) who are cisplatin-ineligible as first-line therapy. However, patients with such extensive sarcomatoid histology are not well represented in those clinical trials. The recently reported Study of Atezolizumab in Locally Advanced or Metastatic Urothelial or Non-Urothelial Carcinoma of the Urinary Tract (SAUL) trial that included non-urothelial histology showed that atezolizumab safety and efficacy was similar to those reported in urothelial histology, but the predominant sarcomatoid variant was not represented.

Both patients discussed in this series have several interesting molecular findings which warrant discussion. Unique to these patients were the presence of variants of the tumor suppressor gene, *NF1*. In the first patient, the observed *NF1* heterozygous germline variant is of uncertain significance, while the observation of likely inactivating somatic mutation initially raised the possibility that the germline variant may have a functional consequence in this neoplasm. However, this patient did not have physical findings or family history consistent with *NF1*, suggesting against impaired neurofibromin function. Patients with NF1 syndrome are at risk of development of tumors of the nervous system. Although patients with NF1 pathogenic mutations rarely have tumors outside the nervous system, increased utilization of genomic sequencing may lead to the identification of *NF1* gene mutations in neoplasms beyond the nervous system, including several sarcoma subtypes. There has been reported an increased risk of benign tumor formation, but a lower likelihood of progression or malignant transformation in patients with heterozygous variants in *NF1*. The authors also observed that patients with malignant transformation generally demonstrated a more indolent disease course. Moreover, Aaltonen et al. correlated a decrease in *NF1* expression with an increase in grade, although this study was limited to papillary UC. Although the exact role of neurofibromin is incompletely delineated in this setting and specific cases, the aggressive course in our patients may more strongly reflect the sarcomatoid differentiation observed in both tumors discussed herein, rather than this molecular finding. To our knowledge, to date, no known driving role of *NF1* mutations in the setting of sarcomatoid UC of the upper tract or urinary bladder has been described.

Interestingly, there are reports of *NF2* mutations in patients with sarcomatoid UC of the urinary tract. *NF2*, similar to *NF1*, is a tumor suppressor gene that codes for the protein merlin, which is specifically associated with regulation of the mammalian target of rapamycin (mTOR) complex. Tumors associated with *NF2* mutations have been reported to respond favorably to mTOR inhibitors, specifically everolimus, in the setting of metastatic disease. Very few UC cases with these particular molecular findings have been reported to date, thus, no generalized recommendation regarding the use of mTOR inhibitors or systemic platinum-based chemotherapy can be made at this time. Thus, the above findings must be considered as hypothesis-generating and require further mechanistic studies and prospective evaluation in the context of clinical trials. However, this work adds to a growing body of recent data regarding germline mutations in UC, which further supports the incorporation of genetic counseling in these patients.

In the case of our first patient, the findings of an activating *KRAS* oncogenic driver, in combination with multiple tumor suppressor mutations in interrelated pathways related to proliferation and cell-cycle regulation are suggestive of a neoplasm that is capable of rapid growth. When the genomic findings are considered in the context of the clinical presentation, with an initial biopsy of necrotic tissue, which may have represented a neoplasm rapidly outgrowing or compromising its blood supply, followed by a rapid and progressive clinical course, the

findings are intriguing. Additional work is needed to resolve the relationship between the molecular findings in this rare neoplasm and its clinical behavior. Integration of somatic NGS into the evaluation of patients with UC offers the potential to further characterize and understand the molecular drivers behind variable oncologic potential of tumors. Last, but not least, a detailed review of somatic NGS testing reports by experienced practitioners, such as genetic counselors, may uncover germline mutations with implications for patients and their family members. While somatic testing of tumor tissue cannot replace dedicated germline testing, it has been demonstrated to add clinical rationale for requesting such an evaluation.

Conclusion

Both our patients demonstrated a highly aggressive sarcomatoid UC with very poor prognosis, and rapid progression to metastatic disease and death within a few months of presentation. Further work is needed to define the optimal multimodal management of this entity in an effort to optimize outcomes for patients with this rare and aggressive malignancy.

What is new?

Sarcomatoid urothelial carcinoma is a rare malignancy with few reported cases. This manuscript contains two cases of this with new delineation of mutational changes which could help guide future therapy and evaluation.

List of Abbreviations

CT	computed tomography
IHC	immunohistochemical
MSS	Microsatellite stable
NF	Neurofibromatosis
NGS	next-generation sequencing
TUR	transurethral resection
UC	urothelial carcinoma
VAF	variant allele fraction
VUS	variant of unknown significance

Conflict of interest

None.

Funding

None.

Consent for publication

Written consent was obtained from the patients for publication.

Ethical approval

Ethical approval is not required from our institutions for publication of anonymous case reports.

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Summary of the case

1	**Patient (gender, age)**	Male, 65-year-old; Female, 72-year-old
2	**Final diagnosis**	Sarcomatoid UC
3	**Symptoms**	Gross hematuria
4	**Medications**	NA
5	**Clinical procedure**	Radical nephrectomy and transurethral resection of bladder tumor
6	**Specialty**	Urology