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Metastatic signet-ring cell carcinoma of the urinary bladder: A novel management approach to a rare tumour

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Abstract

Primary signet-ring cell carcinoma (SRCC) of the urinary bladder, a variant of adenocarcinoma, is exceedingly rare and as a result no gold standard exists for its management. We report a case of primary SRCC of the bladder with recurrent metastases; we utilized an innovative diagnostic approach and the patient exhibited a treatment response to palliative FOLFOX-6 chemotherapy.

Introduction

Most urinary bladder tumours are urothelial in origin; primary adenocarcinoma of the bladder represents only 0.5% to 2.0% of all bladder tumours.[1] Even rarer is signet-ring cell carcinoma (SRCC), a histologic subtype of adenocarcinoma, which often presents late in stage, with a poor prognosis, and is considered resistant to chemotherapy and radiation.[2-4] Due to its rarity, no standard treatment algorithm exists, especially for the management of metastatic disease after initial surgical intervention.[3,5] We report a case of primary bladder SRCC with recurrent metastases post-cystectomy; the patient exhibited response to palliative chemotherapy with a modified FOLFOX-6 regimen.

Case presentation

A 71-year-old man presented with gross hematuria and clot retention; cystoscopy and ureteroscopy revealed a friable bladder mass along the prostatic urethra, bladder neck, and encompassing the right ureteral orifice. Histopathology of the mass revealed a poorly differentiated adenocarcinoma with signet-ring features. Immunohistochemistry stained positively for CK7, CK20 and CDX2, consistent with primary bladder adenocarcinoma, and negatively for prostate-specific antigen (PSA), excluding a primary prostatic malignancy. Given the signet-ring histology, however, these staining patterns can be difficult to interpret and may have limited utility in diagnosis.[6] Initial positron emission tomography (PET) imaging revealed a mildly hypermetabolic paraesophageal lymph node, but no other findings consistent with advanced disease.

Metastasis from a primary gastrointestinal tumour was considered, but gastroduodenoscopy and colonoscopy did not reveal a primary malignancy and the patient was diagnosed with primary bladder cancer. Neoadjuvant chemotherapy was not recommended due to the tumour's aggressive nature and he instead opted for surgical management. Preoperative magnetic resonance imaging (MRI) of the abdomen and pelvis revealed that the mass invaded into the prostate gland but did not extend into the rectum (Fig. 1).

He subsequently underwent radical cystoprostatectomy with ileal conduit urinary diversion. Bilateral pelvic lymph node dissection was performed, which included lymphatics distal to the common iliac artery and veins bilaterally as well as pre-sacral and obturator nodes. The operation was without complication and his hospital course was uneventful.

Surgical pathology revealed metastatic mucinous adenocarcinoma, signet-ring cell variant (Fig. 2, A/B). Immunohistochemistry was reactive for CK7, CK20 and CDX2 and negative for PSA (Fig. 1, C/D). PAX2 and PAX8 staining were also negative which helped rule out a malignancy of kidney origin.[7] The patient was pathologically staged as T4aN2Mx; lymph nodes were positive in the external and internal iliac node packets bilaterally and margins were positive for carcinoma in the left apical prostate. Adjuvant chemotherapy was considered, but the decision was made to hold further treatment unless recurrence was seen on imaging.

Restaging MRI 3 months post-cystectomy revealed a 9-mm right iliac lymph node, 8-mm pericaval lymph node, and an 11-mm enhancing lesion in the L1 vertebral body,

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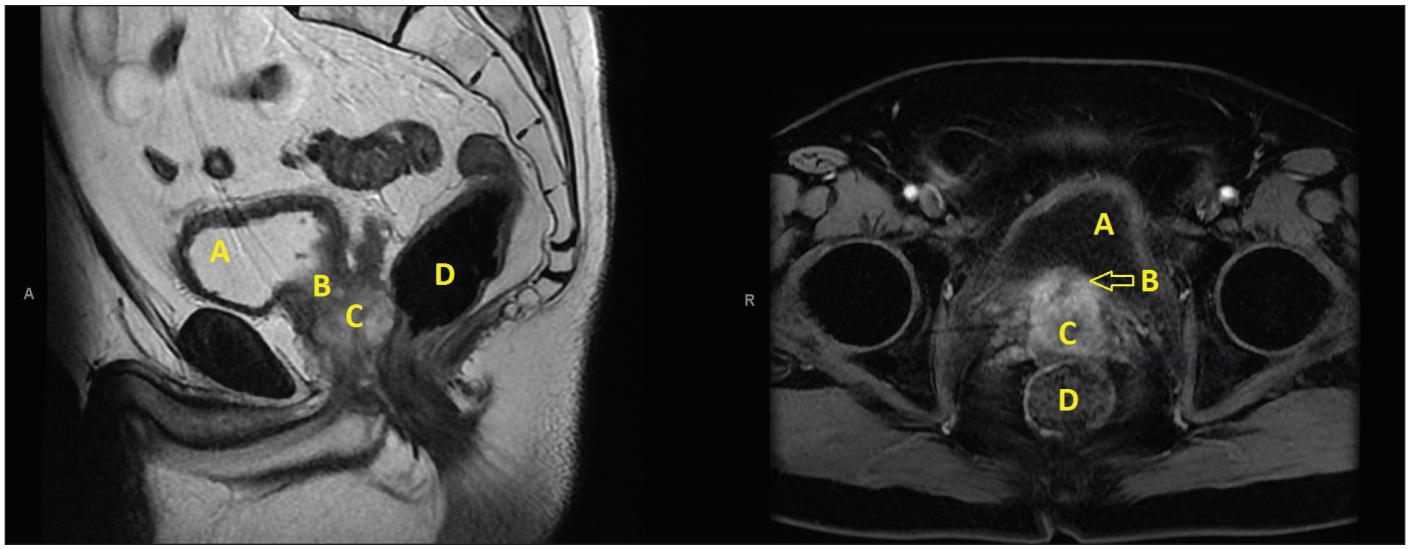

Fig. 1. Sagittal and transverse magnetic resonance imaging of the pelvis prior to radical cystectomy illustrates an ill-defined mass (B) at the base of the bladder (A) invading into the central prostate gland (C) without evidence of extension into the rectum (D).

consistent with recurrent metastatic disease. One month later, FDG PET/CT imaging again reported the osseous lesion in L1 (Fig. 3, A/B).The patient was discussed at interdisciplinary tumour board and he subsequently began palliative systemic chemotherapy.

At this time his tumour was assessed by next generation sequencing (NGS) to better classify its genomic profile. NGS identified genomic aberrations in AKT2, TP53, CCNE1, MYC, MCL1, and AXL. Sequencing was also significant for a mutation in KRAS, commonly found in both colorectal adenocarcinomas and a small subset of primary bladder adenocarcinomas, thus guiding the decision to pursue a systemic therapy typically used for colorectal malignancies.[8]

He then underwent chemotherapy with a modified FOLFOX-6 regimen (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and 5-FU 400 mg/m^2), which is commonly used to treat metastatic gastrointestinal cancers. CT imaging after 4 cycles revealed a sclerotic area in the L1 vertebra consistent with prior imaging but showed stable retroperitoneal and periportal lymphadenopathy (Fig. 3, part C). Follow-up CT imaging after 8 cycles of chemotherapy reported no osseous lesions in his lumbar spine and again stable lymphadenopathy, consistent with regression of his metastatic disease secondary to chemotherapy (Fig. 3, part D). He is about 12 months out from his

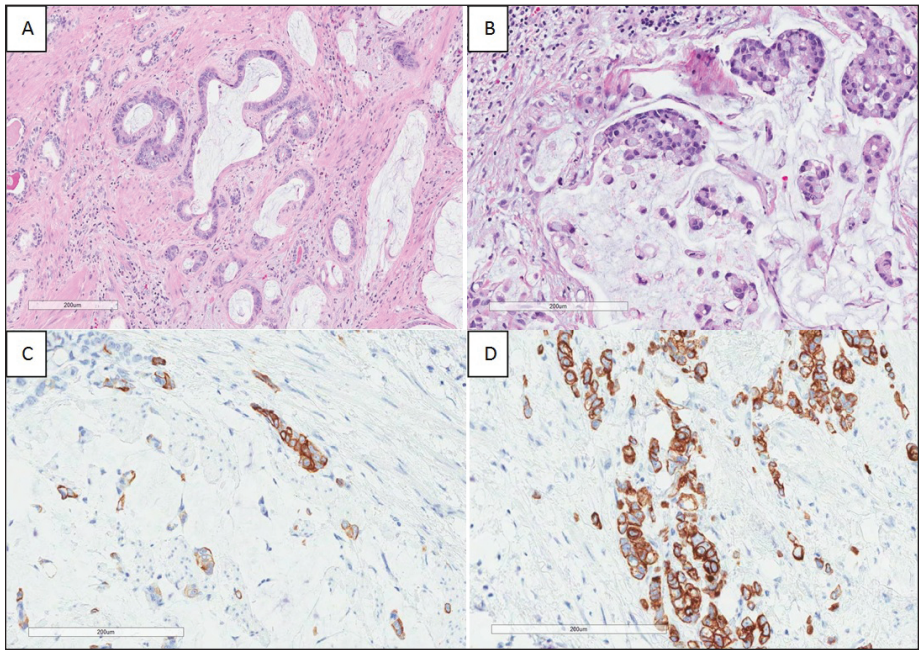

Fig. 2. Hematoxylin and eosin stain at 10× of resected bladder lesion with irregular glands (A) and lymph node metastasis displaying characteristic signet-ring cells in a mucinous background (B). Immunohistochemistry DAB chromagin marking CK7 (C) and CK20 (D) positivity which is characteristic of bladder carcinoma.

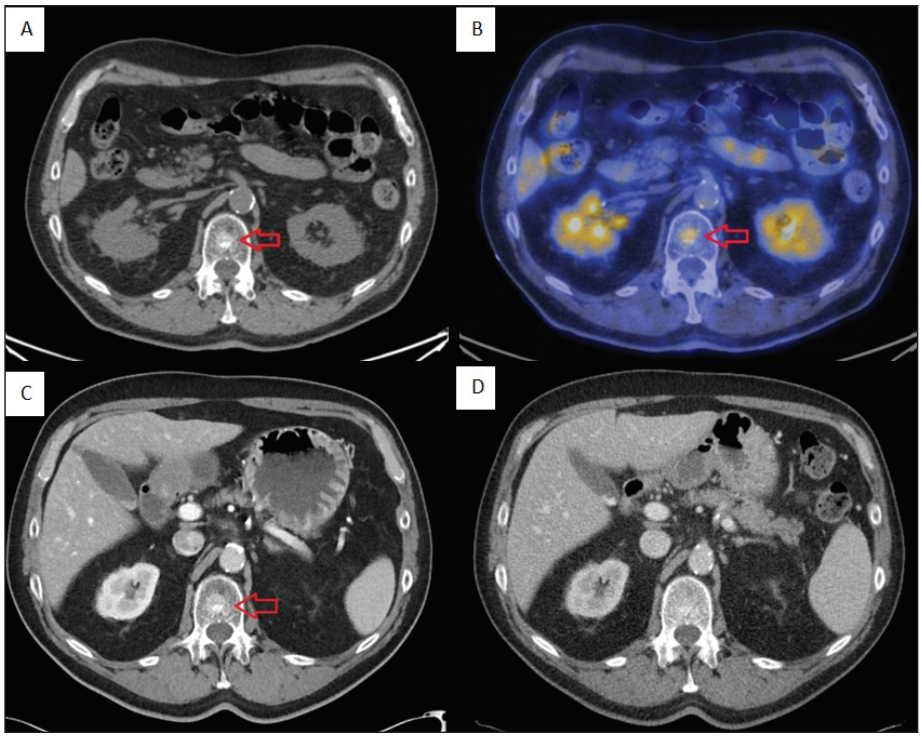

Fig. 3. Imaging prior to palliative FOLFOX-6 chemotherapy demonstrates a metastatic lesion in L1 on computed tomography (CT) without contrast (A) and the same image enhanced with positron emission tomography (B). Contrast CT demonstrates no interval change inL1 lesion after 4 cycles of FOLFOX-6 (C) but significant regression of L1 lesion after 8 cycles of chemotherapy (D).

initial imaging diagnosis and continues to follow-up at our institution with plans for additional chemotherapy.

Discussion

Primary adenocarcinoma accounts for less than 2% of tumours arising from the urinary bladder.[1,9] First described by Saphir, SRCC is a rare subtype characterized by early occlusion of ureteral orifices and invasion into adjacent structures, both of which occurred in the presenting case.[10] The tumour is aggressive; roughly half of patients are stage IV at diagnosis and carry a median survival time of approximately 8 months.[3]

Initial evaluation must include a workup for a possible gastrointestinal primary malignancy. Immunohistochemical staining using CK7 and CK20 can also be helpful in evaluating the cancer's primary origin, although a distinct immunohistochemical profile for primary SRCC has not been ascertained.[5,11] Our case provides a unique diagnostic approach by using NGS to understand the genetic characteristics of this unusual tumour and ultimately guide our choice of systemic therapy. NGS may be valuable in the management of these rare tumours by identifying specific molecular drivers that can be targeted pharmaceutically.

Currently, no clear consensus exists for management of this tumour. Surgery has been reported as a treatment modality in 70% of cases, and although not standardized, radical cystectomy is recommended as the surgical treatment of choice.[3] Similarly, medical management has not been standardized, although authors have reported that both systemic chemotherapy and radiotherapy provide little overall benefit, especially when patients present with metastatic disease.[4] Our case is unique in that treatment was initially focused on eliminating local disease, but due to early recurrent metastases, reliance on genomic profiling and rapid implementation of systemic therapy was necessary.

Our case also provides insight into specific management of metastatic SRCC, which currently has no therapeutic guidelines. Two cases of metastatic SRCC have shown sustained response to capecitabine-based chemotherapy, also used to treat advanced gastrointestinal cancers. Our case, however, highlights the use of the FOLFOX-6 regimen specifically and is the first to report treatment response of an osseous metastasis.[5,12] Similarly, one report describes response to palliative chemotherapy with the FOLFOX-6 regimen plus bevacizumab in the treatment of typical bladder adenocarcinoma, but ours is the first to describe response of the signet-ring cell variant specifically, and with the use of FOLFOX-6 alone.[13] Our patient's response to FOLFOX-6 supports the use of a therapy traditionally aimed at gastrointestinal malignancies for the treatment of metastatic SRCC of the bladder.[14]

Conclusion

Although cases of the signet-ring cell variant are exceedingly rare, our patient's meaningful treatment response highlights our unique diagnostic approach and challenges the notion that this cancer is resistant to chemotherapy.

Competing interests: The authors declare no competing financial or personal interests.

This paper has been peer-reviewed.

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