

# Metastatic signet ring cell adenocarcinoma of the bladder: responsive to treatment?

Jessica Singh, MD,\* Viktor Zhrebetskiy, MD;† David Grynspan, MD, FRCPC;‡ Piotr Marek Czaykowski, MD MSc FRCPC‡

\*Department of Internal Medicine, University of Manitoba, Winnipeg, MB; †Department of Pathology, University of Manitoba, Winnipeg, MB; ‡Children's Hospital of Eastern Ontario and Department of Pathology and Laboratory Medicine, University of Ottawa, Ottawa, ON; ‡Departments of Internal Medicine and Community Health Sciences, University of Manitoba, and Department of Medical Oncology and Haematology, CancerCare Manitoba, Winnipeg, MB

Cite as: *Can Urol Assoc J* 2012;6(1):e15-19. <http://dx.doi.org/10.5489/auaj.11019>

## Abstract

Signet ring cell variant of mucinous adenocarcinoma of the urinary bladder is an exceptionally rare urologic malignancy, generally felt to be resistant to chemotherapy and radiotherapy. We describe a case of this malignancy with unusual sites of metastasis and an unexpectedly good response to treatment.

## Introduction

Signet ring cell variant of mucinous adenocarcinoma (SRCC) of the urinary bladder is exceptionally rare, comprising 2% to 43% of primary bladder adenocarcinomas, which in turn represent 0.5% to 2% of all bladder neoplasms.<sup>1,2</sup> It is generally felt to be resistant to chemotherapy and radiotherapy, and has been associated with a poor prognosis.<sup>3</sup> We review the challenges in making a diagnosis of urinary bladder SRCC, and describe a case of this malignancy with an unexpectedly good response to fluoropyrimidine/oxaliplatin chemotherapy and localized radiotherapy.

## Case report

A 62-year-old male presented with 4 months of gross hematuria. Abdominal computed tomography (CT) revealed a 8.0 × 2.5 cm hypoechoic solid mass in the dome of the bladder extending into perivesical fat, without evidence of locoregional lymph nodes, metastases or a primary tumour in other abdominal or pelvic organs. Transurethral biopsy demonstrated mucinous adenocarcinoma with signet ring cell features. Partial cystectomy and bilateral lymph node dissection were undertaken.

Grossly, the primary tumour was covered by thick mucus (Fig. 1). Histological findings were consistent with poorly differentiated mixed mucinous and signet ring cell adeno-

carcinoma (Fig. 2, panel A), with high mitotic activity (>10 mitotic figures/10 high power fields) and areas of necrosis. The tumour was situated in the lamina propria beneath the intact urothelial epithelium of the bladder with a close surgical resection margin (1 to 3 mm) and microinvasion into the perivesical fat. Five lymph nodes were negative. An urachal remnant could not be identified.

Immunohistochemical studies demonstrated strong positivity for CK7, CK20, CDX-2, E-cadherin, CEA, EMA, p53,  $\beta$ -catenin (nuclear stain) and villin, and negativity for thrombomodulin, TTF-1, PSA and WT-1. Proliferation index (Ki67) was high. Electron microscopy revealed core filamentous rootlets and mucus vacuoles in signet ring cells (Fig. 2, panel D). Molecular testing was negative for microsatellite instability.

Gastroduodenoscopy failed to reveal an obvious upper gastrointestinal tract primary cancer. A colonoscopy was not performed; at no time were there symptoms or radiologic findings to suggest a colorectal primary tumour.

Several months after cystectomy, a fistula developed through an ulcerated lesion on the patient's lip under the vermilion line, resulting in pain and difficulty eating (Fig. 4, panels A and B). Biopsy of the lower lip confirmed similarity to the primary tumour (Fig. 2, panels B and C). Additionally, CT imaging demonstrated progressive disease in the region of the duodenal bulb, within the pancreas, anterior to the right kidney, and on both sides of the bladder (Fig. 3, panels A, B and C). An endoscopic ultrasound-guided fine needle aspiration biopsy of the pancreatic mass confirmed metastatic disease.

Chemotherapy, consisting of capecitabine 1000 mg/m<sup>2</sup> daily for 14 days and oxaliplatin 130 mg/m<sup>2</sup> once every three weeks, was initiated 8 months post-cystectomy. This regimen was chosen because of its efficacy against gastrointestinal malignancies, such as gastric carcinoma, which have histological analogy to this case. In addition, the tolerability and practicality were favoured because the patient had to travel from a remote locale for therapy. No "standard"



**Fig. 1.** This is an image of a well-circumscribed mass, 6.5 cm in diameter and 2.5 cm in thickness, occupying the dome of the bladder. There was an exophytic growth pattern, and the outer surface was covered in a thick gelatinous material.

chemotherapy exists for this very rare tumour.

Radiotherapy to the lip was administered at 9 months post-cystectomy at 50 Gray in 20 fractions with photon treatment. For the duration of radiotherapy, oxaliplatin was held, but concomitant capecitabine was administered at a reduced dose.

Chemotherapy was well-tolerated, and the patient was able to remain physically active throughout his treatment course. Seven months post-initiation of chemotherapy, imaging revealed stable disease at the area of thickening on the left lateral bladder, and regression of the low attenuation areas in the right renal pelvis region, neck of pancreas, and paraduodenal regions (Fig. 3, panels D, E and F). There was almost complete resolution of the lip lesion and fistula (Fig. 4, panels C and D), with significant improvement in symptoms.

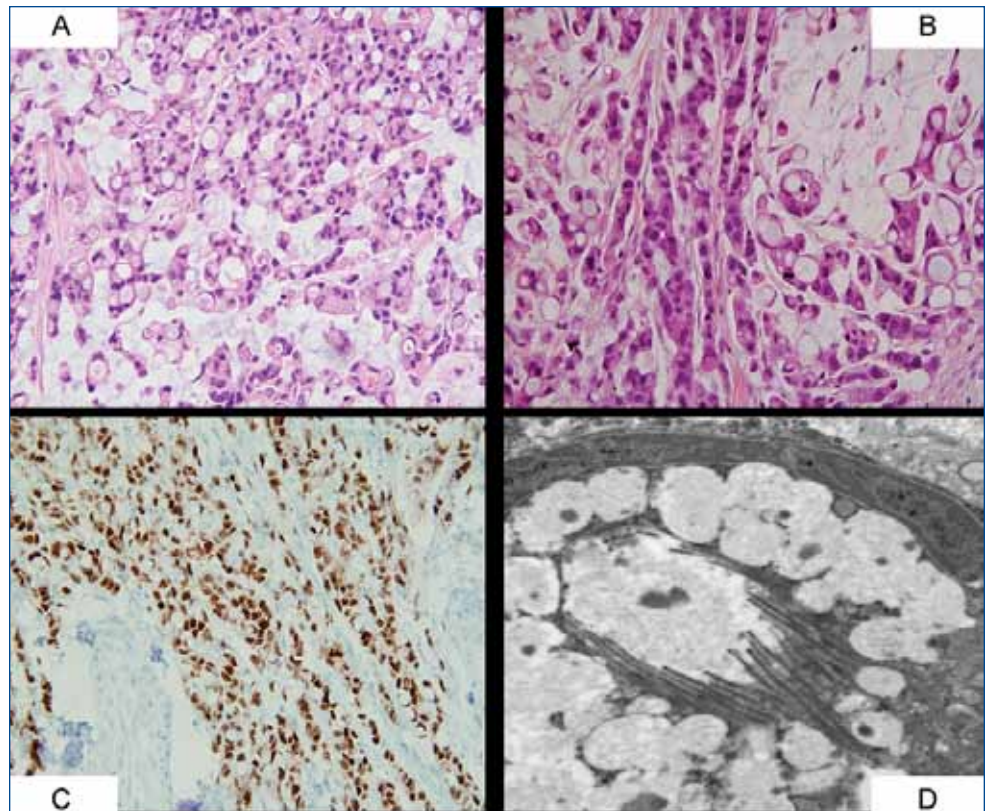
Stable disease persisted for 16 months before progression within the chest became apparent. There was no response to second-line chemotherapy with capecitabine and irinotecan. The patient subsequently died about 24 months after the start of chemotherapy.

## Discussion

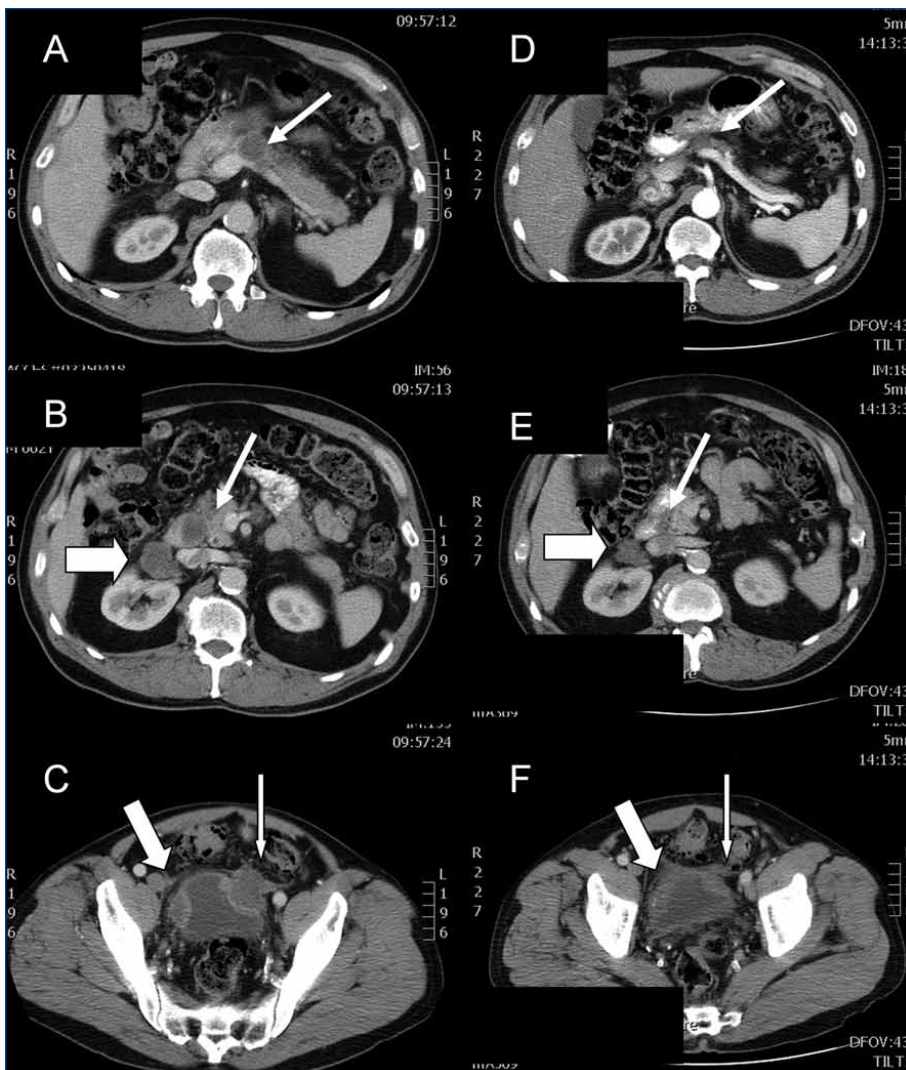
Signet ring variant of mucinous adenocarcinoma of the urinary bladder presents a challenge on two grounds: (1) ascertaining the correct diagnosis and (2) determining the most appropriate therapy.

A hallmark of SRCC is the presence of signet ring cells filled with cytoplasmic mucus-containing vacuoles, compressing and displacing the nucleus into a peripheral crescent alongside the cell wall. A pure SRCC can have subepithelial infiltration in a linitis plastica fashion without forming an exophytic mass,<sup>4</sup> a gross pattern found in less than a third of primary bladder SRCC cases.<sup>5</sup> More commonly, SRCC forms an exophytic intraluminal mass together with another subtype of adenocarcinoma.

Most adenocarcinomas of the urinary bladder result from direct extension from adjacent organs (e.g., colon, prostate).<sup>6</sup> Rarely, there can be metastatic spread to the bladder of SRCC originating in another organ (e.g., stomach or colon).<sup>7</sup> A carcinoma arising from an urachal remnant may also have a similar appearance. Differentiation of primary bladder adenocarcinoma from these other entities can be



**Fig. 2.** (A) Hematoxylin & Eosin stain: Roughly half of the tumour volume was occupied by mucin pools or lakes, and one third of the tumour cells had signet ring cell morphology. (B) metastasis to lower lip had similar morphology and immunohistochemical profile. (C) CDX-2 positivity of signet ring cells. (D) Presence of core filamentous rootlets and mucus vacuoles in signet ring cell shown by electron microscopy. Original magnification:  $\times 400$  on A, B and C, and  $\times 30000$  on D.



**Fig. 3.** Radiologic evidence of recurrence. Pre-treatment, Panel A demonstrates a low attenuation mass in the body of the pancreas (arrow), Panel B shows low attenuation lesions anterior to the kidney (thick arrow), and in para-duodenal location (thin arrow), and Panel C shows lesions on either side of the bladder. Panels D, E, and F are equivalent cuts after 7 months of chemotherapy with oxaliplatin and capecitabine.

challenging. Criteria favouring primary adenocarcinoma of the bladder versus secondary involvement of the bladder include location on the bladder base or lateral walls, and the presence of other elements, such as small cell carcinoma, transitional cell carcinoma or carcinoma in situ.<sup>3,6</sup> Clearly, a primary site, other than urinary bladder, should be ruled out clinically, and the tumour should not fulfill Wheeler-Hill criteria for urachal carcinoma.<sup>8</sup>

Immunoprofile of primary bladder SRCC and SRCC arising from the gastrointestinal tract overlaps, including positivity for CK7, CK20, CEA, EMA, CDX2, villin and E-cadherin. In this case, the immunoprofile was not definitive. Negativity for thrombomodulin favours a bladder origin, whereas a nuclear pattern of  $\beta$ -catenin staining favours a colorectal

primary. The presence of core filamentous rootlets on electron microscopy favours colorectal origin,<sup>9</sup> whereas a large percentage of colorectal mucinous adenocarcinomas displays microsatellite instability,<sup>10</sup> a feature absent in our case.

In the face of equivocal pathology clinical correlation helps arbitrate; we thus designated this tumour as a primary bladder adenocarcinoma based on the absence of an urachal remnant, lack of evidence of direct spread from another organ at the time of resection, and lack of imaging, endoscopic and clinical findings to suggest a gastrointestinal tract primary site.

### Management

Staging of these tumours usually employs the TNM system adopted for standard urothelial cancers. At the time of diagnosis, about 25% of patients have distant metastases,<sup>11,12</sup> and approximately 50% have Stage IV disease (i.e., including node positivity, T4b primary tumour, as well as distant metastases).<sup>11</sup> Unusual sites of metastasis have been reported,<sup>13</sup> as was the case with our patient.

Prognosis of bladder SRCC is poor due to high tumour grade and the typically late stage of presentation. Patients who receive no therapy have an average survival of 3.5 months.<sup>3</sup> An overall 1-year survival rate of 60% has been reported.<sup>12</sup> Fiter and colleagues reported 5-year survival rates of 75%, 38%

and 12% for the equivalent of stage II, III and IV tumours, respectively.<sup>7</sup> A recent large Japanese series (n = 54) reported 5-year survival for stages I-III as close to 50%, whereas no stage IV patients survived beyond 2 years, with a median time of about 8 months.<sup>11</sup> Non-urachal tumours, elevated carcinoembryonic antigen and tumours with a diffuse linitis plastica, like histology, are associated with particularly poor survival.<sup>1,11</sup>

For small, well-demarcated primary bladder or urachal tumours containing SRCC, partial cystectomy or transurethral resection may be indicated, and such patients can experience long-term survival.<sup>2,3</sup> Radical cystectomy is generally favoured over partial cystectomy, particularly for non-urachal tumours, because of the possibility of local invasion



**Fig. 4.** Histologically-proven metastasis to lower lip prior to (Panels A and B), and after chemo-radiotherapy (Panels C and D). Note that the centrally necrotic area (Panel B), which had actually fistulized into the oral cavity. This completely healed after treatment.

undetected by imaging.<sup>11</sup> In our patient, partial cystectomy was performed because the patient declined radical cystectomy.

SRCC of the bladder is generally not considered radiosensitive. In two cases in which SRCC was found in conjunction with transitional cell carcinoma, the signet-ring cells predominated after radiotherapy, suggesting a lack of response of that element.<sup>5,7</sup> Nonetheless, there is at least one case report of a sustained response to radiotherapy in a T2 tumour.<sup>6</sup> We are unaware of any published literature about combined chemoradiotherapy for this disease. Our experience suggests that it may be effective for metastatic lesions.

Studies evaluating chemotherapy for this rare neoplasm are limited due to the small number of cases per institution. No phase II or III chemotherapy clinical trials exist. A wide variety of agents and regimens have been used, generally in keeping with treatment used for gastric carcinoma, where signet-ring cell morphology is more common.<sup>11</sup> Chemotherapy appears to have been used in adjuvant fashion in some studies.<sup>1,2,11-15</sup> However, no comment can be made on its effectiveness in this setting without the benefit of a randomized controlled trial, although long-term survivors have been reported.

Patients with advanced/metastatic disease who undergo chemotherapy and/ or radiation have an average survival of 7 to 8 months,<sup>3,11</sup> with few patients surviving more than 16 months. Chemotherapy agents used in this setting

have included 5FU, methotrexate, cisplatin, mitomycin, doxocycline, tegafur, cyclophosphamide and carboplatin,<sup>1,2,5,11,16</sup> most commonly as part of a platinum-containing multi-agent regimen.

Our patient's impressive and sustained response to chemotherapy with a fluoropyrimidine (capecitabine) and a platinum derivative (oxaliplatin) may reflect an effective pairing of synergistic agents,<sup>17</sup> known to be active in gastrointestinal tract cancers of similar histology.<sup>18,19</sup> The excellent response to radiotherapy to a localized metastasis in conjunction with radiosensitizing capecitabine is also in keeping with what is expected for similar gastrointestinal tract cancers.

## Conclusions

We have described a case of a male with SRCC arising in the urinary bladder and metastasizing to unusual locations, including the duodenum, pancreas and lower lip.

An excellent, sustained response was achieved with chemotherapy comprised of a fluoropyrimidine and oxaliplatin, in conjunction with radiotherapy to the lip lesion. This combination appears to be safe, effective and well-tolerated for non-curative treatment of stage IV primary bladder SRCC, and should be explored further in this context.

Our case raises a number of salient points. First, SRCC of the urinary bladder is extremely rare, and it is important to rule out SRCC metastatic to the bladder, or invading into the bladder from an adjacent organ, particularly in apparently early stage disease when aggressive intervention is planned. Second, there does not appear to be a definitive immunoprofile that clearly distinguishes primary bladder SRCC from SRCC secondarily involving the bladder. Third, based on our case and on the literature, this is a cancer that has a tendency to metastasize widely and to unusual sites. Finally, our case does not support the contention that this is a treatment-resistant cancer; in otherwise fit patients with advanced disease wishing to undergo systemic therapy, a trial with a combination, such as oxaliplatin and a fluoropyrimidine, appears reasonable, and radiotherapy to symptomatic sites should be considered.

**Competing interests:** None declared.

This paper has been peer-reviewed.

**Acknowledgements:** We thank Dr. Douglas Horsman from the British Columbia Cancer Agency for performing microsatellite stability molecular testing.

## References

1. Grignon DJ, Ro JY, Ayala AG, et al. Primary signet-ring cell carcinoma of the urinary bladder. *Am J Clin Pathol* 1991;95:13-20.
2. Holmang S, Borghede G, Johansson SL. Primary signet ring cell carcinoma of the bladder: a report on 10 cases. *Scand J Urol Nephrol* 1997;31:145-8. <http://dx.doi.org/10.3109/00365599709070320>
3. Erdogru, T., et al. Primary signet ring cell carcinoma of the urinary bladder. Review of the literature and report of two cases. *Urol Int* 55, 34-37 (1995).
4. Dahm, P. & Gschwend, J.E. Malignant non-urothelial neoplasms of the urinary bladder: a review. *Eur Urol* 44, 672-681 (2003). [http://dx.doi.org/10.1016/S0302-2838\(03\)00416-0](http://dx.doi.org/10.1016/S0302-2838(03)00416-0)
5. Blute, M.L., Engen, D.E., Travis, W.D. & Kvols, L.K. Primary signet ring cell adenocarcinoma of the bladder. *J Urol* 141, 17-21 (1989).
6. Torenbeek, R., et al. Primary signet-ring cell carcinoma of the urinary bladder. *Histopathology* 28, 33-40 (1996). <http://dx.doi.org/10.1046/j.1365-2559.1996.262303.x>
7. Fiter, L., Gimeno, F., Martin, L. & Gomez Tejada, L. Signet-ring cell adenocarcinoma of bladder. *Urology* 41, 30-33 (1993). [http://dx.doi.org/10.1016/0090-4295\(93\)90239-7](http://dx.doi.org/10.1016/0090-4295(93)90239-7)
8. Ayala, A.G. & Tamboli, P. Urachal carcinoma. in *Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs: World Health Organization Classification of Tumours* (eds. Eble, J.N., Sauter, G., Epstein, J.I. & Sesterhenn, I.A.) 131-132 (IARC Press, Lyon, France, 2004).
9. DeMay, R.M. & Grathwohl, M.A. Signet-ring-cell (colloid) carcinoma of the urinary bladder. Cytologic, histologic and ultrastructural findings in one case. *Acta Cytol* 29, 132-136 (1985).
10. Gopalan, V., Smith, R.A., Ho, Y.H. & Lam, A.K. Signet-ring cell carcinoma of colorectum-current perspectives and molecular biology. *Int J Colorectal Dis.* 26, 127-133, (2011). <http://dx.doi.org/10.1007/s00384-010-1037-z>
11. Akamatsu, S., Takahashi, A., Ito, M. & Ogura, K. Primary signet-ring cell carcinoma of the urinary bladder. *Urology* 75, 615-618 (2010). <http://dx.doi.org/10.1016/j.urolgy.2009.06.065>
12. Romics, I., Szekely, E. & Szendroi, A. Signet-ring cell carcinoma arising from the urinary bladder. *Can J Urol* 15, 4266-4268 (2008).
13. Morelli, O., et al. Colon and gastric metastases from a primary signet-ring cell carcinoma of the urinary bladder. *Dig Liver Dis* 38, 609-611 (2006). <http://dx.doi.org/10.1016/j.dld.2005.11.011>
14. Cobo Dols, M., et al. Secondary signet-ring cell tumour of the prostate derived from a primary gastric malignancy. *Clin Transl Oncol* 7, 409-412 (2005). <http://dx.doi.org/10.1007/BF02716587>
15. Hirano, Y., et al. Primary signet ring cell carcinoma of the urinary bladder successfully treated with intra-arterial chemotherapy alone. *Urology* 59, 601 (2002). [http://dx.doi.org/10.1016/S0090-4295\(01\)01676-4](http://dx.doi.org/10.1016/S0090-4295(01)01676-4)
16. Rosas-Uribe, A. & Luna, M.A. Primary signet ring cell carcinoma of the urinary bladder. Report of two cases. *Arch Pathol* 88, 294-297 (1969).
17. Schmall, H.J. & Cassidy, J. Integrating oxaliplatin into the management of colorectal cancer. *Oncologist* 6 Suppl 4, 24-28 (2001). [http://dx.doi.org/10.1634/theoncologist.6-suppl\\_4-24](http://dx.doi.org/10.1634/theoncologist.6-suppl_4-24)
18. De Vita, F., et al. A phase II study of biweekly oxaliplatin plus infusional 5-fluorouracil and folinic acid (FOLFOX-4) as first-line treatment of advanced gastric cancer patients. *Br J Cancer* 92, 1644-1649 (2005). <http://dx.doi.org/10.1038/sj.bjc.6602573>
19. Louvet, C., et al. Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. *J Clin Oncol* 20, 4543-4548 (2002). <http://dx.doi.org/10.1200/JCO.2002.02.021>

**Correspondence:** Dr. Piotr Czaykowski, Department of Medical Oncology and Haematology, CancerCare Manitoba, 675 McDermot Ave., Room ON2055, Winnipeg, MB R3E 0V9; fax: 204-786-0196; [piotr.czaykowski@cancercare.mb.ca](mailto:piotr.czaykowski@cancercare.mb.ca)