

Review began 05/03/2026  
Review ended 05/17/2026  
Published 05/19/2026

© Copyright 2026  
Muro-Yu et al. This is an open access  
article distributed under the terms of the  
Creative Commons Attribution License CC-  
BY 4.0., which permits unrestricted use,  
distribution, and reproduction in any  
medium, provided the original author and  
source are credited.

DOI: 10.7759/cureus.109241

# Late-Onset Metastatic Signet Ring Cell Adenocarcinoma Following Bladder Exstrophy Reconstruction: Diagnostic Discordance and Uncertain Primary Origin

Lorena Muro-Yu <sup>1</sup>, Nivash Selvaraj <sup>1</sup>, David Lau <sup>1</sup>

<sup>1</sup>. Urology, Glangwili General Hospital, Carmarthen, GBR

**Corresponding author:** Lorena Muro-Yu, [lorenamuro94@live.co.uk](mailto:lorenamuro94@live.co.uk)

---

## Abstract

Bladder exstrophy is an uncommon congenital anomaly associated with a heightened lifetime risk of malignancy, particularly following reconstructive procedures incorporating intestinal segments. We describe a 60-year-old man with a history of bladder exstrophy repair who presented with flank pain and microscopic haematuria. Initial imaging suggested a bladder lesion; however, histological examination revealed a villous adenoma without evidence of malignancy. Subsequent investigations identified extensive skeletal metastases. Biopsy of a bony lesion demonstrated metastatic adenocarcinoma with signet ring cell morphology. Immunohistochemical analysis showed positivity for CK20 and CDX2 and negativity for CK7, suggesting a gastrointestinal origin. Despite a comprehensive evaluation, no primary tumour was identified. Following a multidisciplinary team discussion, the patient was commenced on systemic chemotherapy and bone-targeted therapy for presumed colorectal carcinoma. This case highlights the diagnostic complexity associated with malignancy in reconstructed urinary tracts and emphasises the need for long-term surveillance in this patient population.

---

**Categories:** Urology, Oncology

**Keywords:** bladder exstrophy, ileocystoplasty, metastatic adenocarcinoma, signet ring cell morphology, urothelial villous adenoma

## Introduction

Bladder exstrophy is an uncommon congenital abnormality resulting from failure of closure of the lower abdominal wall, with an estimated incidence of approximately one in 30,000-50,000 live births [1]. Surgical reconstruction is typically performed in early life and may involve augmentation using intestinal segments. While these procedures improve urinary continence and quality of life, they are associated with an increased long-term risk of malignancy, most commonly adenocarcinoma [2,3].

The development of malignancy in reconstructed urinary tracts is thought to be multifactorial, involving chronic inflammation, recurrent infection, and prolonged exposure of intestinal epithelium to urine [2,4]. Metastatic presentations arising several decades after reconstructive procedures remain uncommon but are increasingly recognised in the literature as important long-term complications, often posing diagnostic challenges due to altered anatomy and atypical histological features [2].

Signet ring cell adenocarcinoma is a rare and aggressive subtype most frequently associated with gastrointestinal primaries [5]. Signet ring cells are mucin-producing malignant cells that typically arise in the gastrointestinal tract and are characterised by intracytoplasmic mucin displacing the nucleus peripherally, giving the appearance of a signet ring. They are highly associated with early spread and poor prognosis. Its occurrence in patients with prior bladder reconstruction presents a particular diagnostic challenge, especially when the primary site cannot be identified.

## Case Presentation

A 60-year-old man with a history of bladder exstrophy repaired in childhood using ileocystoplasty presented with right-sided flank and back pain, along with recurrent urinary tract infections. Laboratory investigations demonstrated microscopic haematuria and mild proteinuria, while routine blood tests were otherwise unremarkable. A prostatic primary was considered during diagnostic evaluation; thus, prostatic-specific antigen and digital rectal examination were performed, but the findings were not suspicious for prostatic malignancy.

Ultrasound imaging revealed an abnormal bladder with a heterogeneous intravesical lesion, bilateral hydronephrosis, and non-visualisation of the right kidney, likely reflecting severe atrophy (Figure 1).

### How to cite this article

Muro-Yu L, Selvaraj N, Lau D (May 19, 2026) Late-Onset Metastatic Signet Ring Cell Adenocarcinoma Following Bladder Exstrophy Reconstruction: Diagnostic Discordance and Uncertain Primary Origin. *Cureus* 18(5): e109241. DOI 10.7759/cureus.109241

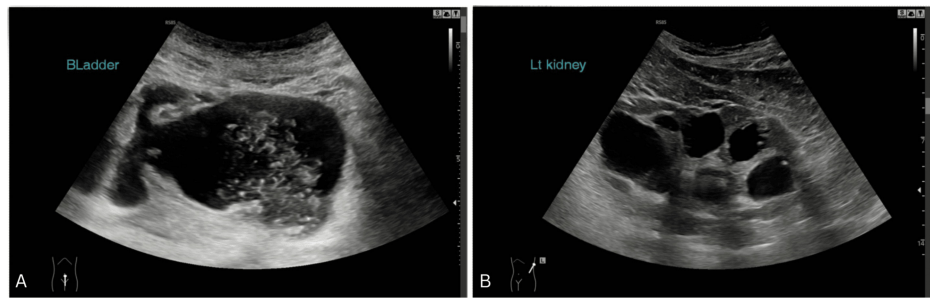


**FIGURE 1: Ultrasound KUB showing a large heterogeneous mass in the bladder and hydronephrosis in the left kidney with multiple cysts**

KUB: kidney, ureter, and bladder

Subsequent contrast-enhanced CT imaging confirmed right renal atrophy and a structurally irregular, diverticular bladder. However, it did not demonstrate a discrete mass, raising the possibility that the ultrasound findings reflected inflammatory or structural changes rather than a true neoplasm (Figure 2).

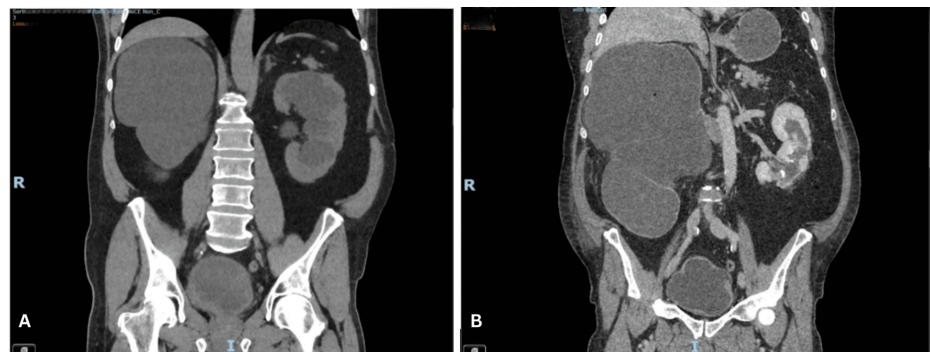


**FIGURE 2: Serial CT imaging showing right hydronephrosis with sclerotic lesions in the bone**

CT: computed tomography

Flexible cystoscopy identified an exophytic lesion suspicious for malignancy, and a biopsy was planned. Prior to this, the patient was admitted with sepsis and acute kidney injury. Nephrostomy placement for obstructive uropathy yielded purulent material consistent with pyonephrosis, and he was treated with targeted intravenous antibiotics. Three separate bladder biopsies were obtained during cystoscopy; the first two were from a papillary and solid lesion, respectively, and the third was a cold-cup biopsy.

Following clinical stabilisation, further imaging, including CT, MRI, and nuclear medicine bone scintigraphy, demonstrated widespread skeletal metastases (Figures 2-3). Histological examination of bladder biopsies revealed a villous adenoma with dysplastic glandular epithelium and associated hyperplastic urothelium, with no evidence of invasive malignancy (Figure 4).

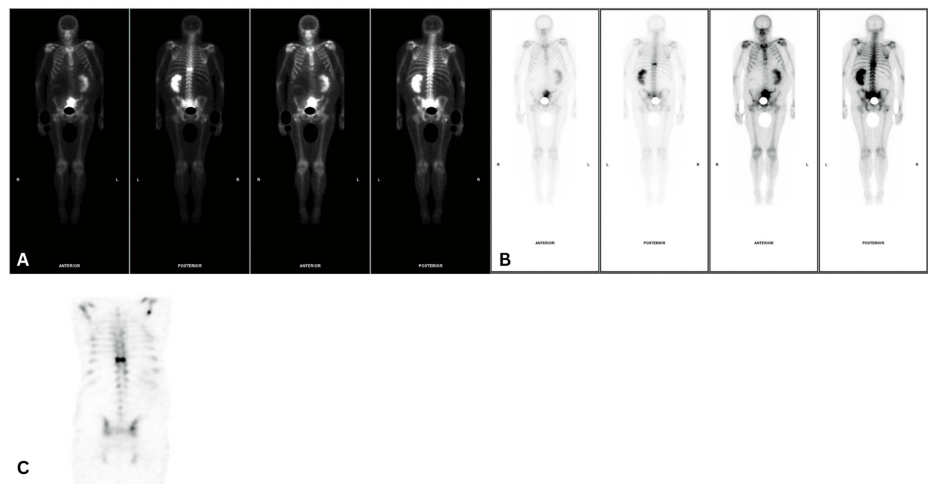


**FIGURE 3: Whole-body nuclear medicine bone scan with SPECT demonstrating increased radiotracer uptake in T6, the left scapula, left ilium, and the right proximal femur (femoral neck), consistent with metastatic disease**

SPECT: single photon emission computed tomography

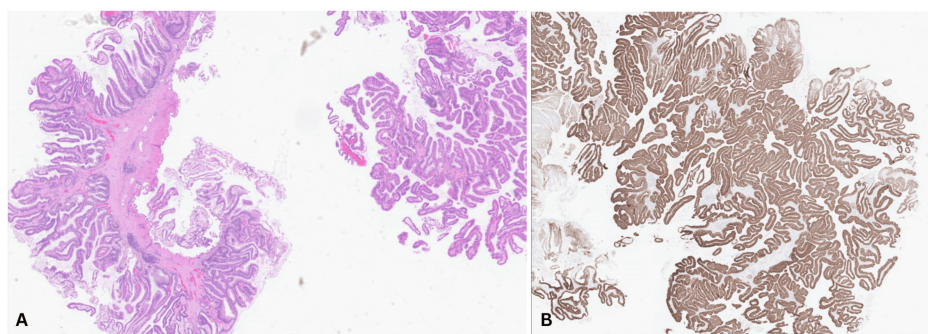


**FIGURE 4: Histology: bladder biopsy demonstrating villous adenoma with dysplastic glandular epithelium. No carcinoma in situ identified. Immunohistochemistry for CK20 showing diffuse cytoplasmic positivity within the glandular epithelium, supporting a colorectal-type phenotype**

Given the presence of metastatic disease, a CT-guided biopsy of a left iliac bone lesion was performed. Histopathological analysis demonstrated metastatic adenocarcinoma with signet ring cell morphology. Immunohistochemistry showed positivity for CK19, CK20 and CDX2, and negativity for CK7, GATA3, NKX3.1 and TTF1 (Figure 5). This immunoprofile is characteristic of colorectal-type adenocarcinoma and is atypical for primary urothelial malignancy [6,7].

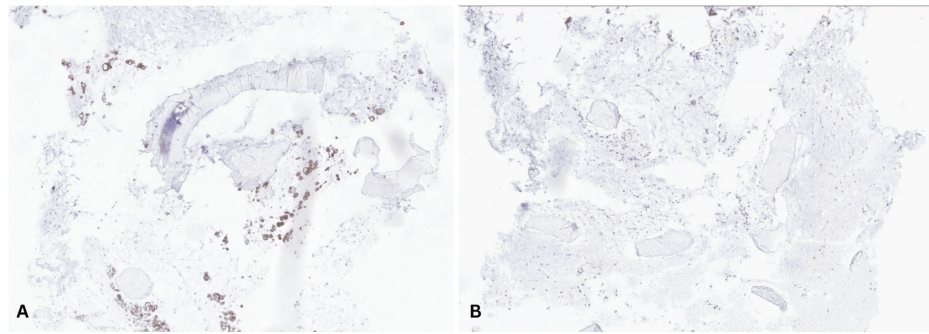


**FIGURE 5: Histology: bone biopsy demonstrating metastatic adenocarcinoma with signet ring cell morphology. Immunohistochemistry showing CK20 positivity (A) and GATA3 negativity (B)**

Despite a comprehensive evaluation, no primary tumour was identified. Following a multidisciplinary team discussion, the patient was commenced on systemic chemotherapy with a capecitabine and oxaliplatin (CAPOX) regimen, along with denosumab for the management of osseous metastases. He remains under ongoing oncological follow-up.

## Discussion

Patients with bladder exstrophy have a recognised increased lifetime risk of malignancy, particularly following reconstruction using bowel segments. The incorporation of intestinal mucosa into the urinary tract exposes epithelium to chronic inflammation, bacterial colonisation and prolonged contact with urinary metabolites, all of which are thought to promote dysplastic and neoplastic transformation over time [2]. Malignancies in this setting are most commonly adenocarcinomas and frequently arise several decades after the initial reconstructive procedure [5,7].

The presence of signet ring cell morphology in this case introduces additional diagnostic complexity. This histological subtype is most commonly associated with gastrointestinal malignancies, particularly colorectal carcinoma, and is often linked to aggressive clinical behaviour and early metastatic spread. Although primary signet ring cell carcinoma of the urinary bladder has been reported, it remains exceedingly rare [7,8].

Differentiating primary bladder adenocarcinoma arising within augmented bowel segments from metastatic gastrointestinal adenocarcinoma remains particularly difficult in patients with reconstructed urinary tract anatomy. Although the immunophenotype in this case, including CK20 and CDX2 positivity with absent CK7 expression, favoured a colorectal phenotype, significant immunohistochemical overlap between enteric-type bladder adenocarcinoma and metastatic colorectal adenocarcinoma has been reported [6,9]. CDX2 is a sensitive marker of intestinal differentiation but is not entirely specific for colorectal primary tumours, as it may also be expressed in primary bladder adenocarcinoma with enteric differentiation [9]. Similarly, CK20 positivity with reduced or absent CK7 expression may support gastrointestinal differentiation but cannot independently establish tumour origin.

Additional markers, including SATB2 and  $\beta$ -catenin, may provide further diagnostic support in selected cases. SATB2 expression has been shown to correlate strongly with colorectal differentiation. It may help distinguish metastatic colorectal adenocarcinoma from primary urinary tract adenocarcinoma when interpreted as part of a broader immunohistochemical panel [10]. Likewise, nuclear  $\beta$ -catenin staining is more commonly reported in colorectal adenocarcinoma, whereas primary bladder adenocarcinoma more frequently demonstrates membranous or cytoplasmic staining patterns [11]. Mucin profiling, including assessment of MUC1, MUC2, MUC5AC and MUC6 expression, has also been explored in enteric-type adenocarcinomas, although no single marker is entirely definitive in isolation [12]. Consequently, immunohistochemical findings alone may be insufficient to definitively distinguish between a primary tumour arising within the reconstructed bladder segment and metastatic gastrointestinal adenocarcinoma; therefore, correlation with additional markers and clinical investigations is essential.

In diagnostically complex presentations such as the present case, establishing the origin of malignancy may remain challenging despite extensive investigation. This is particularly relevant in patients with reconstructed urinary tract anatomy, where structural distortion, chronic mucosal change and overlapping histopathologic features may complicate interpretation of isolated findings. Contemporary precision oncology literature increasingly emphasises the value of integrating multimodal data, including radiologic, histopathologic, molecular, immunohistochemical and clinical information, to improve diagnostic

interpretation and support personalised oncologic decision-making [13]. In this case, the discordance between local bladder biopsy findings and the extent of metastatic disease highlights the importance of synthesising clinical history, imaging evolution, pathology, immunophenotype, and overall disease distribution rather than relying on any single modality. Although such integrative approaches, including AI-supported multimodal frameworks, remain evolving and are not yet standardised for rare reconstructed urinary tract malignancies, they may provide a useful conceptual framework for interpreting diagnostically ambiguous oncologic presentations.

The choice of systemic therapy in this case also reflected the diagnostic uncertainty surrounding the tumour origin. The patient was treated with CAPOX, a regimen more commonly used in gastrointestinal malignancies, particularly colorectal adenocarcinoma. Although there is limited evidence guiding treatment of primary bladder adenocarcinoma due to its rarity, enteric-type bladder adenocarcinomas are often managed using colorectal chemotherapy protocols because of histologic and molecular similarities [14]. If the malignancy arose from the reconstructed ileal segment rather than the native bladder, this would further support the rationale for gastrointestinal-based systemic therapy. However, optimal management strategies for these rare tumours remain poorly defined, and treatment decisions frequently require individualised multidisciplinary discussion.

Although the immunophenotypic profile favoured gastrointestinal differentiation, definitive exclusion of an occult gastrointestinal primary remained challenging. Colonoscopy, PET-CT, and evaluation of serum tumour markers were not performed during the investigation, representing a limitation of the diagnostic evaluation. Appendiceal and mucinous gastrointestinal primaries were considered within the differential diagnosis, given the metastatic distribution and enteric immunophenotype. Consequently, the findings were considered suggestive of, rather than definitively diagnostic of, a colorectal primary.

This case also highlights the absence of universally accepted surveillance protocols for patients with bladder exstrophy following reconstructive surgery. Several reports have suggested that long-term monitoring strategies, including periodic cystoscopic evaluation, imaging and selective urine cytology, may help facilitate earlier detection of malignant transformation in high-risk patients [2,3]. Given the long latency period between reconstruction and malignancy development, lifelong surveillance may warrant consideration, particularly in patients with bowel-containing urinary reconstructions.

## Learning points

Patients with bladder exstrophy who undergo augmentation cystoplasty have an increased long-term risk of malignancy, particularly adenocarcinoma. The presence of signet ring cell morphology should prompt consideration of a gastrointestinal primary, although interpretation may be confounded by prior reconstruction using bowel segments. Immunohistochemical markers such as CK20 and CDX2 are helpful but not definitive in determining tumour origin in this setting. Discordance between local biopsy findings and metastatic disease should raise suspicion for sampling error or occult malignancy. Lifelong surveillance should therefore be considered in patients with reconstructed bladders due to the risk of delayed malignant transformation.

## Conclusions

Bladder exstrophy is associated with a substantial long-term risk of malignancy, particularly in patients who have undergone reconstructive procedures involving bowel segments. This case illustrates the diagnostic challenges posed by metastatic adenocarcinoma with discordant local findings and highlights the importance of considering both primary and secondary malignancies. Comprehensive evaluation, careful interpretation of immunohistochemical findings, and early multidisciplinary involvement are essential for accurate diagnosis and appropriate management. Lifelong surveillance should be considered in this high-risk population.

## Additional Information

### Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Concept and design:** Lorena Muro-Yu, David Lau

**Acquisition, analysis, or interpretation of data:** Lorena Muro-Yu, Nivash Selvaraj

**Drafting of the manuscript:** Lorena Muro-Yu, Nivash Selvaraj, David Lau

**Critical review of the manuscript for important intellectual content:** Lorena Muro-Yu, Nivash Selvaraj

**Supervision:** Lorena Muro-Yu, Nivash Selvaraj, David Lau

## Disclosures

**Human subjects:** Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

## References

1. Siffel C, Correa A, Amar E, et al.: Bladder exstrophy: an epidemiologic study from the International Clearinghouse for Birth Defects Surveillance and Research, and an overview of the literature. *Am J Med Genet C Semin Med Genet.* 2011, 157C:321-32. [10.1002/ajmg.c.30316](#)
2. Higuchi TT, Granberg CF, Fox JA, Husmann DA: Augmentation cystoplasty and risk of neoplasia: fact, fiction and controversy. *J Urol.* 2010, 184:2492-6. [10.1016/j.juro.2010.08.038](#)
3. Mehmood S, Alhazmi H, Al-Shayie M, et al.: Long-term outcomes of augmentation cystoplasty in a pediatric population with refractory bladder dysfunction: a 12-year follow-up experience at single center. *Int Neurourol J.* 2018, 22:287-94. [10.5213/inj.1836174.087](#)
4. Biardeau X, Chartier-Kastler E, Rouprêt M, Phé V: Risk of malignancy after augmentation cystoplasty: A systematic review. *Neurourol Urodyn.* 2016, 35:675-82. [10.1002/nau.22775](#)
5. Pernot S, Voron T, Perkins G, Lagorce-Pages C, Berger A, Taieb J: Signet-ring cell carcinoma of the stomach: Impact on prognosis and specific therapeutic challenge. *World J Gastroenterol.* 2015, 21:11428-38. [10.3748/wjg.v21.i40.11428](#)
6. Wang HL, Lu DW, Yerian LM, Alsikafi N, Steinberg G, Hart J, Yang XJ: Immunohistochemical distinction between primary adenocarcinoma of the bladder and secondary colorectal adenocarcinoma. *Am J Surg Pathol.* 2001, 25:1380-7. [10.1097/00000478-200111000-00005](#)
7. Bates AW, Baithun SI: Secondary neoplasms of the bladder are histological mimics of nontransitional cell primary tumours: clinicopathological and histological features of 282 cases. *Histopathology.* 2000, 36:32-40. [10.1046/j.1365-2559.2000.00797.x](#)
8. El Ammari JE, Ahsaini M, Riyach O, et al.: Primary signet-ring cell carcinoma of the urinary bladder successfully managed with cisplatin and gemcitabine: a case report. *J Med Case Rep.* 2013, 7:37. [10.1186/1752-1947-7-37](#)
9. Roy S, Smith MA, Cieply KM, Acquafondata MB, Parwani AV: Primary bladder adenocarcinoma versus metastatic colorectal adenocarcinoma: a persisting diagnostic challenge. *Diagn Pathol.* 2012, 7:151. [10.1186/1746-1596-7-151](#)
10. Giannico GA, Gown AM, Epstein JI, Revetta F, Bishop JA: Role of SATB2 in distinguishing the site of origin in glandular lesions of the bladder/urinary tract. *Hum Pathol.* 2017, 67:152-9. [10.1016/j.humpath.2017.07.002](#)
11. Rao Q, Williamson SR, Lopez-Beltran A, et al.: Distinguishing primary adenocarcinoma of the urinary bladder from secondary involvement by colorectal adenocarcinoma: extended immunohistochemical profiles emphasizing novel markers. *Mod Pathol.* 2013, 26:725-32. [10.1038/modpathol.2012.229](#)
12. Betge J, Schneider NI, Harbaum L, et al.: MUC1, MUC2, MUC5AC, and MUC6 in colorectal cancer: expression profiles and clinical significance. *Virchows Arch.* 2016, 469:255-65. [10.1007/s00428-016-1970-5](#)
13. Rajaei Rizi F, Jamadi MS, Rahimi S, Bighamian M, Paidar P, Taki MJ, Bahmaie N: Multimodal artificial intelligence in urologic precision oncology: from algorithm to translational medicine (a systemized narrative review). *Front Oncol.* 2026, 16:1763359. [10.3389/fonc.2026.1763359](#)
14. Gopalan A, Sharp DS, Fine SW, Tickoo SK, Herr HW, Reuter VE, Olgac S: Urachal carcinoma: a clinicopathologic analysis of 24 cases with outcome correlation. *Am J Surg Pathol.* 2009, 33:659-68. [10.1097/PAS.0b013e31819aa4ae](#)