

A case of isolated rectal recurrence of muscle invasive bladder cancer

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Abstract

We present the case of a 53-year-old man with a 25-pack/year smoking history and a 6-month history of gross hematuria, who presented with a pT3a, N0, M0, muscle invasive bladder cancer (MIBC). He declined neoadjuvant chemotherapy, but received post-cystectomy adjuvant chemotherapy. Six months post-adjuvant chemotherapy, he presented with abdominal pain and a large bowel obstruction, and was found to have an isolated rectal recurrence of MIBC. This case illustrates 2 important issues: (1) patients with a smoking history and symptoms of hematuria need to be carefully evaluated to rule out urothelial cancer; and (2) in patients with muscle invasive disease, local pelvic recurrence is common and close surveillance for recurrence needs to be implemented.

Case report

A 53-year-old previously healthy male presented to his family physician with painless, intermittent, gross hematuria for the preceding 6 months and was referred for urological workup. Cystoscopy on initial presentation was suspicious for intramural thickening and induration of the right lateral bladder wall, with questionable involvement of the right ureteric orifice. A transurethral resection of a bladder tumour (TURBT) was performed and confirmed poorly differentiated transitional cell (TCC) with extensive invasion of the fibrous lamina propria and muscularis mucosa, but questionable involvement of the muscularis propria. Due to the uncertainty of muscle invasion, a repeat TURBT was performed which confirmed high-grade TCC with extensive invasion into the muscularis propria. Subsequent staging investigations, including computed tomography (CT) and bone scan, showed thickening of the right lateral bladder wall with possible involvement of the distal right ureter, but no evidence of distant metastatic disease. Due to the invasive nature of his bladder cancer and the known survival

benefit with neoadjuvant chemotherapy,¹ the patient was seen at our tertiary cancer centre for consideration of neoadjuvant chemotherapy. The patient declined neoadjuvant chemotherapy and chose to proceed with cystectomy with adjuvant chemotherapy if required.

He underwent radical cystoprostatectomy and distal ureteric resection, pelvic lymph node dissection (distal to the external iliacs), and creation of an ileoconduit. Frozen sections at the time of surgery showed no involvement of the distal ureters. Final pathology revealed high-grade TCC with invasion of the muscularis propria and perivesical tissue both anteriorly and posteriorly (Fig. 1). The tumour also showed extensive lymphatic and perineural invasion with tumour in the lymphatics around the left seminal vesicle, but not involving the seminal vesicles, prostate or urethra; and 5 of the 17 lymph nodes were positive for TCC. The case was presented at our Multidisciplinary Cancer Conference (MCC) where it was agreed that the best course of action would be to proceed with 6 cycles of adjuvant gemcitabine and cisplatin chemotherapy and then consider pelvic radiation due to the extensive involvement of the disease. The patient completed 6 cycles of chemotherapy, but did not receive any radiation therapy following chemotherapy.

Unfortunately, 6 months after completing chemotherapy the patient presented to the emergency department with anorexia, diffuse abdominal pain and pencil thin stools. The patient was booked for urgent magnetic resonance imaging (MRI) of the abdomen and pelvis. This showed circumferential thickening of the rectum (Fig. 2), suspicious for metastatic TCC, but a metachronous primary rectal cancer could not be ruled out. Subsequent colonoscopy revealed a fixed pelvis with rectosigmoid mucosal induration and thickening. Rectal biopsies confirmed poorly differentiated carcinoma favouring high-grade TCC (Fig. 3). Given the rarity of isolated rectal recurrence, the patient was again presented at the MCC where it was suggested that given his poor performance status, symptom control with a rectal stent would be the best course of action, and that further invasive treatment would only impart risk and morbidity with

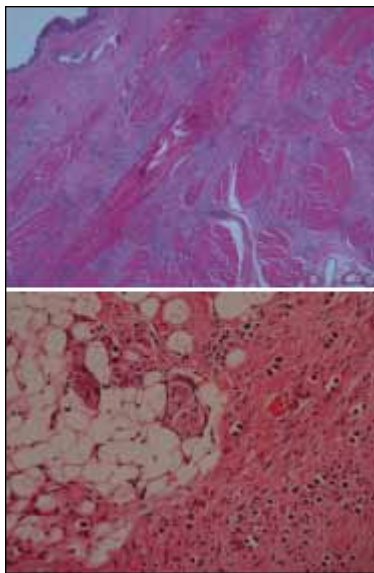


Fig. 1. Pathology sections showing small, hyperchromatic and mildly pleomorphic tumour cells (i) invading the bladder wall (2 \times) and (ii) present within the perivesical adipose tissue (20 \times).

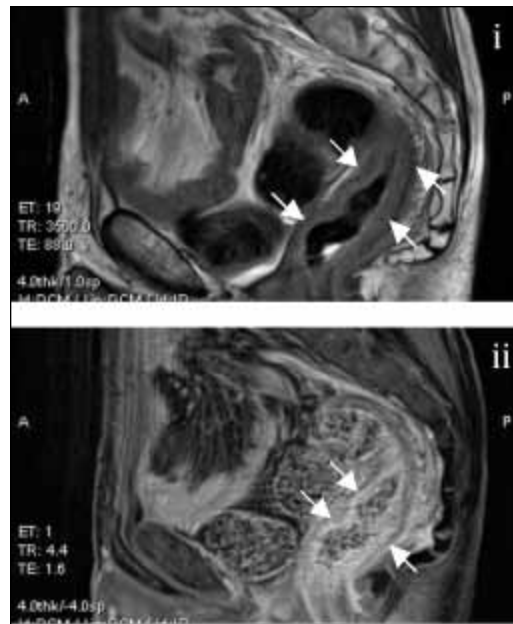


Fig. 2. Sagittal magnetic resonance images; (i) pre- and (ii) post-administration of gadolinium showing mild diffuse rectal wall thickening.

minimal benefit to the patient. With the patient's approval, outpatient palliative care was organized to maximize the patient's quality of life. Unfortunately, about 23 months after being diagnosed with pT3a bladder cancer, and 6 months after being diagnosed with rectal recurrence, the patient died from progressive disease and urosepsis.

Discussion

Gross hematuria, in addition to being alarming to the patient, can herald malignancy in up to 20% to 40% of cases,² and therefore requires prompt investigation under the appropriate clinical circumstances. The source of hematuria can originate from any point in the urinary system, extending from the kidney and upper tracts to the urethral meatus; therefore, this situation requires evaluation of the entire tract to determine the exact cause of bleeding. Fortunately, the differential diagnosis for hematuria is relatively narrow, with the most common causes in adults being urinary tract infections, neoplasms and urolithiasis.³ However, since the misdiagnosis of gross hematuria can have devastating consequences, it is important to identify and appropriately investigate those patients at high risk for a neoplastic cause of their hematuria (Table 1).⁴ Any individual with gross hematuria and risk factors for urological malignancy should be referred to a urologist for complete urinary tract evaluation.³ Current guidelines suggest that urinalysis with microscopy and urine cytology be the initial workup, followed by cystoscopy and triphasic CT urogram under the guidance of a urologist.³

As illustrated by this case, the traditional mainstay of treatment of MIBC is radical cystectomy with pelvic lymphadenectomy. However, there has been a recent treatment paradigm shift as there is now mounting long-term evidence that suggests cisplatin based neoadjuvant chemotherapy confers an overall survival advantage of between 5% to 8%.^{5,6} This change has been adopted in several guideline statements as grade A recommendations, where the inclusion of cisplatin based neoadjuvant chemotherapy for MIBC should, at the very least, be offered to patients.⁷ Unfortunately our patient, along with many others in his situation, are offered and decline neoadjuvant chemotherapy or are not even offered neoadjuvant chemotherapy possibly due to the stigma and concerns about toxicity associated with chemotherapy, or due to the potential delay in receiving definitive surgical treatment. In either case, better education about the controllable side effects of chemotherapy and the potential survival benefit of neoadjuvant chemotherapy needs to be conveyed to patients in an attempt to decrease the mortality and the recurrence rate of MIBC.

Recurrence of MIBC can be distant recurrence (DR) and local recurrence (LR). Although MIBC can metastasize to any location, the most common sites of distant, non-lymph node recurrence is bone, liver and lung.⁸ Local recurrence of MIBC on the other hand, as defined in the literature, encompasses tumour recurrence in the pelvic soft-tissue and/or lymph nodes distal to the external iliac bifurcation, and in some studies, distal to the aortic bifurcation.¹⁸ LR of muscle invasive bladder cancer after radical cystectomy and pelvic

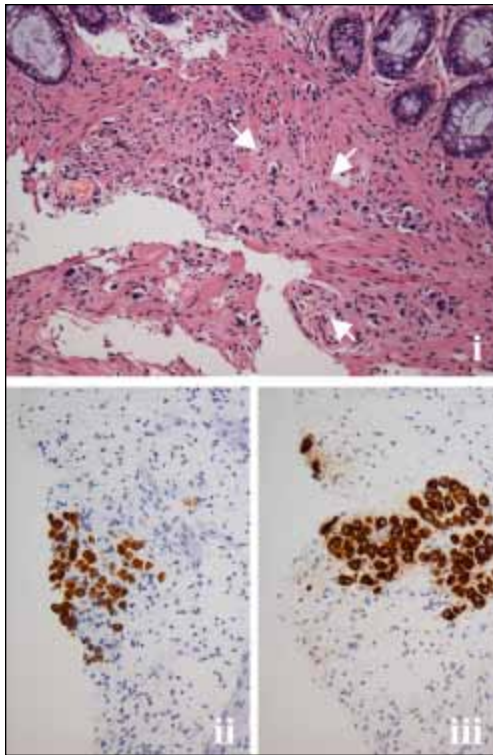


Fig. 3. Rectal biopsy sections showing (i) poorly differentiated tumour cells within the submucosa and sparing the mucosa; (ii) combined with CK7 positivity (iii) and CK 20 strongly suggests colorectal metastasis of urothelial origin, as opposed to primary colon cancer.

lymph node dissection was thought to be rare prior to the routine use of CT in cancer surveillance.^{8,10} Since then, the rates of LR involving the pelvis after cystectomy for bladder cancer are between 16% and 19% (Table 2, column A), with 63% of these associated with pathologically extravesical disease.¹⁰ Contemporary series, however, define LR as recurrence isolated to the pelvis or to exclude patients with pelvic recurrence with concurrent metastatic involvement outside of the pelvis.¹¹ In these cases, the isolated pelvic LR rate is reported between 5% and 7% (Table 1, column B). Although imaging has greatly enhanced the diagnosis of LR, most recurrences are only detected when the patient becomes symptomatic,^{5,11} which may suggest that current surveillance strategies do a poor job of detecting LR because LR after cystectomy tends to occur relatively early (Table 1, column C).

Although the rate of pelvic recurrence after radical cystectomy is relatively common (Table 1, column B), there is a paucity of information regarding the rate of isolated rectal recurrence post-cystectomy. In the study by Honma and colleagues, 55% of patients with isolated pelvic recurrence had recurrence within the pelvic soft tissue in front of the anterior rectal wall. The study did not comment on recurrence involving the rectum specifically.¹⁰ In another

Table 1. Risk factors for a neoplastic cause of hematuria

A smoking history
An occupational exposures to chemicals including benzenes and aromatic amines
Irritative voiding symptoms
Previous gross hematuria, previous genitourinary cancer
Previous pelvic irradiation
Patients who are 40 years of age or older

study, autopsies performed on (pT2-pT4) patients with MIBC treated with cystectomy showed that 12% to 13% of patients had some form of intestinal involvement, but again data on rectal recurrence was not reported.^{15,16} Most of the literature regarding rectal recurrence of muscle invasive bladder cancer comes from isolated case reports^{15,17} and autopsy-based studies, which describe rectal recurrence affecting about 10% of patients with LR post-cystectomy for muscle-invasive bladder cancer.¹⁸ Indeed this has been confirmed by a recent retrospective study using transrectal ultrasonography to detect local recurrence after cystectomy, which found the rates of rectal recurrence in patients with pelvic local recurrence of bladder cancer to be as high as 9.7%.¹¹

Despite these high rates of recurrence of MIBC, there is an absence of robust evidence to guide surveillance of these patients after surgical intervention. A recent retrospective study based on the recurrence patterns of 2287 patients across Canada advocates for a pathological stage based surveillance protocol, with higher stage disease being investigated earlier and more aggressively.¹² The subject of surveillance also identifies a unique issue illustrated by this case, namely that of cisplatin resistance. Data from the cisplatin sensitive Germ Cell Tumour (GCT) literature defines cisplatin resistance by the time to cancer relapse after completion of cisplatin based chemotherapy. Early relapse is defined by relapse within 2 years after completion of therapy, while cisplatin refractory disease is defined as relapse while on cisplatin treatment or within 4 weeks after its completion.¹³ The treatment options for cisplatin resistant MIBC are currently limited, and overall outcomes are poor.¹⁴ A case could be made for an aggressive surgical approach similar to that used in cisplatin resistant GCTs,¹³ unfortunately in this circumstance our patient was not a surgical candidate due to his poor functional status. Another question arising from this case is the role of adjuvant radiation in patients at high risk for local failure post-cystectomy. Patients post-neoadjuvant chemotherapy and surgery with residual disease could undergo additional radiation therapy to improve pelvic control and reduce morbidity associated with pelvic recurrences. Although not a standard approach, adjuvant radiotherapy in MIBC warrants further investigation.

Table 2. Rates of and median time to local recurrence after treatment of muscle invasive bladder cancer treated with cystectomy and lymphadenectomy without adjuvant treatment

Study	Date of data collection (sample size)	A	B	C
		Rate of local recurrence (with or without distant metastasis)	Rate of local pelvic recurrence (pelvic lymph nodes and soft tissue)	Median time to local recurrence
Greven et al. ²¹	1977-1986 (n=83)	15.7 %	n/a	9 months
Queck et al. ²² and Stein et al. ²³	1971-1997 (n=1054)	n/a	7.3%	18 months
Honma et al. ¹⁰	1990-2001 (n=145)	18.6%	5.5%	8 months
Hiroki Ide ²⁴	1987-2003 (n=146)	17.8 %	4.8%	10 months
Simon et al. ¹¹	1986-2003 (n=642)	18.3%	5.5%	13 months

Conclusion

We illustrated some of the diagnostic and treatment related issues related to MIBC, specifically the need to investigate hematuria in the right clinical context and to offer neoadjuvant cisplatin based chemotherapy to all patients with MIBC. We also demonstrated that isolated pelvic local recurrence after muscle invasive bladder cancer is relatively common, and that the rates of rectal recurrence may also be higher than once thought. Taken together, the literature suggests that about 0.5% of all patients with MIBC will have rectal recurrence, and that this recurrence will likely be diagnosed after the patient becomes symptomatic with symptoms of bowel obstruction.^{9,15,17} This signifies a large burden of morbidity in North America as 7100 patients in Canada and 70 530 in the United States were diagnosed with bladder cancer in 2010 alone.^{19,20} Given that the mean survival after diagnosis of rectal recurrence of MIBC is about 5 months, an evidence-based surveillance regimen is also required to mitigate the significant mortality associated with MIBC recurrence.

Competing interests: None declared.

This paper has been peer-reviewed.

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