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A unique case of sequential superficial bladder cancer with solitary pulmonary metastasis achieving long-term disease-free survival post-metastasectomy: A case report and literature review

Shatha Alhilaly, Ramy Elbaz, Israr Khan

ABSTRACT

Urothelial carcinoma of the bladder most commonly metastasizes to lymph nodes, liver, bone, and lung. Solitary pulmonary metastasis from superficial (non-muscle-invasive) bladder cancer (NMIBC) is exceptionally rare. Furthermore, the long-term sequelae and subsequent cancer risk in such patients remain poorly defined. We report a case of a 76-year-old male with a history of high-grade T1 NMIBC who was found to have a solitary pulmonary nodule 19 months after completing Bacillus Calmette-Guérin (BCG) intravesical therapy. The patient underwent a successful pulmonary metastasectomy, with histopathology confirming metastatic urothelial carcinoma. He remained disease-free for seven years. Surprisingly, he then presented with de novo muscle-invasive bladder cancer (MIBC) without evidence of distant recurrence. He was managed conservatively being of old age and poor performance. This case highlights two rare phenomena: (1) the potential for superficial bladder cancer to distant metastases, and (2) the development of a new, aggressive primary tumor in the bladder long time after the control of metastatic disease. It underscores the importance of long-term, multidisciplinary surveillance for bladder cancer survivors, the biological heterogeneity of urothelial carcinoma, and the curative potential of metastasectomy in selected patients.

Keywords: Distant metastasis, Metastasectomy, Non-muscle-invasive bladder cancer, Survival

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INTRODUCTION

Bladder cancer is the tenth most common cancer worldwide, with urothelial carcinoma representing over 90% of cases [1]. A critical distinction is made between non-muscle-invasive bladder cancer (NMIBC), which is confined to mucosa (Ta, Tis) or submucosa (T1), and muscle-invasive bladder cancer (MIBC), which invades the detrusor muscle (T2 or higher). Non-muscle-invasive bladder cancer accounts for approximately 75% of initial diagnoses and is characterized by a high rate of recurrence but a low rate of progression to MIBC and metastasis [2]. The metastatic pattern of urothelial carcinoma typically involves regional lymph nodes followed by distant sites such as lungs, bones and liver [3, 4]. The occurrence of distant metastasis from NMIBC is uncommon and is usually associated with high-grade

T1 disease, particularly with specific variant histology or lymphovascular invasion. A solitary pulmonary metastasis from NMIBC is an exceedingly rare event. Metastasectomy, the surgical removal of metastatic deposits, has been established as a curative-intent strategy in selecting cancers like colorectal carcinoma and sarcoma. Its role in metastatic urothelial carcinoma has been established to be associated with a long disease-free interval [5]. We present a highly unusual case of a patient with high-grade T1 NMIBC who developed solitary lung metastasis, was rendered disease-free for six years following metastasectomy, and then developed a subsequent, primary muscle-invasive bladder tumor. This case prompts a discussion on tumor biology, the role of local therapy for metastatic disease, and the long-term management of bladder cancer survivors.

CASE REPORT

A 76-year-old male with a significant smoking history of 40 pack-years presented with gross, painless hematuria. Cystoscopy revealed single, papillary tumor about 1 cm diameter at bladder trigone. Transurethral resection of the bladder tumor (TURBT) was performed. Histopathology showed high-grade urothelial carcinoma G3, stage pT1. There was no evidence of lymphovascular invasion. Associated carcinoma in situ (CIS) was present. A computed tomography (CT) urogram of the chest, abdomen, and pelvis at the time showed no evidence of lymphadenopathy or distant metastases, and the lungs were clear. Given the high-grade T1 disease, the patient received intravesical Bacillus Calmette-Guérin (BCG) therapy for a full induction course. 18 months following completing course of intravesical therapy, and during routine surveillance, a follow-up CT chest scan revealed a new, solitary 3 cm nodule in the left upper lobe (Figure 1). There was no evidence of local bladder recurrence or other metastatic sites by cystoscopy and CT scan. The patient was referred to cardiothoracic surgery. He underwent a video-assisted thoracoscopic surgery (VATS) wedge resection of the lung nodule. The resected nodule was confirmed to be metastatic high-grade urothelial carcinoma expressing CK7 and 20 and negative for CD56, TTF-1, chromogranin, and synaptophysin, known markers for lung cancer. The resection margins were negative. The case was discussed in a multidisciplinary tumor board. Given the solitary nature of metastasis and successful resection, the decision was made for close observation without immediate systemic chemotherapy.

The patient was placed on a rigorous surveillance protocol involving cystoscopies and cross-sectional imaging (CT scans) every 3–6 months initially, then annually. He remained consistently free of disease, with no evidence of local recurrence in the bladder or distant metastasis for a period of 7 years. Surveillance cystoscopy revealed multiple papillary lesions at bladder neck, trigone, and left bladder wall each one was about 2 cm. A complete TURBT was performed, and histopathology was confirmed to be high-grade G3 urothelial carcinoma invading the muscularis propria of pT2 stage with associated CIS with no lymphovascular invasion. A repeat CT scan showed no evidence of distant metastasis with bilateral new moderate hydroureteronephrosis (Figure 2) down to circumferential bladder wall thickening (Figure 3) with large right common iliac artery aneurysm 4 cm (Figure 4). Glomerular filtration rate (GFR) at this time declined from 41 to 21 with baseline hemoglobin 9.8 g/dL. The patient has medical history of chronic kidney disease (CKD), hypertension (HTN), chronic obstructive pulmonary disease (COPD) with performance status 2 at this time. After multidisciplinary discussion, reviewing the patient fragility score, age and tumor status, vascular consultation, and aesthetic fitness, the decision was for bilateral nephrostomies fixation and referral for radiotherapy (Table 1).

Table 1: Summary of timelines and important events of the case

Time point	Clinical event	Key findings	Management/decision
Initial TURBT	TURBT performed	HG urothelial carcinoma G3, pT1, CIS present, no LVI	High-risk NMIBC
Post-TURBT	BCG therapy	Full induction course completed	Entered surveillance program
18 months post-BCG	Surveillance CT chest	Solitary 3 cm LUL pulmonary nodule & Complete resection of lung nodule	Curative metastasectomy
Post-metastasectomy	MDT decision	Solitary metastasis, R0 resection	Active surveillance
7 years later	Surveillance cystoscopy	Multiple papillary bladder tumors and TURBT	Diagnosed MIBC
At recurrence	CT imaging	Bilateral hydroureteronephrosis, bladder wall thickening, 4 cm CIA aneurysm	Complex local disease
At recurrence	Renal function	GFR declined from 41 to 21	Obstructive uropathy
Final MDT decision	Multidisciplinary review	Frail patient, CKD, COPD, PS 2	Bilateral nephrostomies + radiotherapy

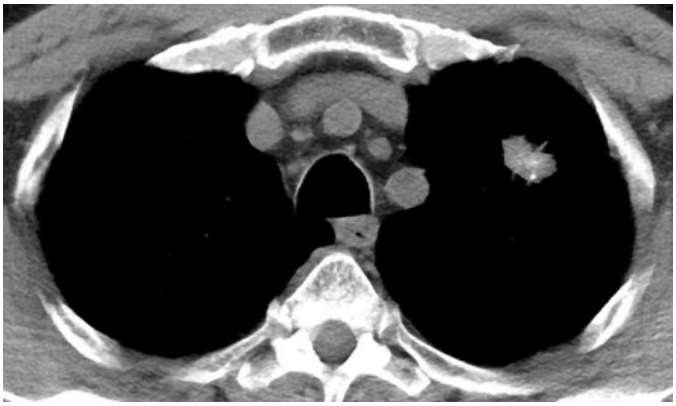

Figure 1: CT scan shows a 3 cm nodule in the left upper lobe with eccentric calcification.

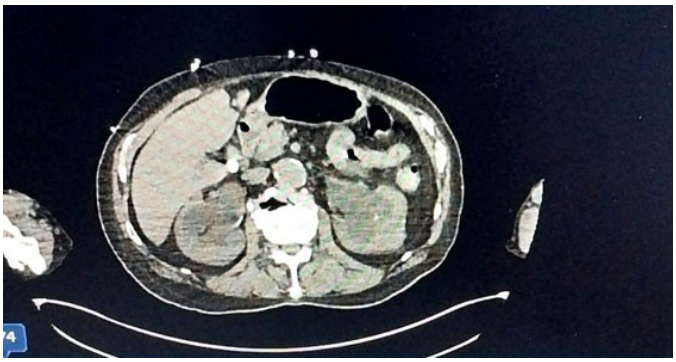

Figure 2: CT abdomen and pelvis showing bilateral hydronephrosis.

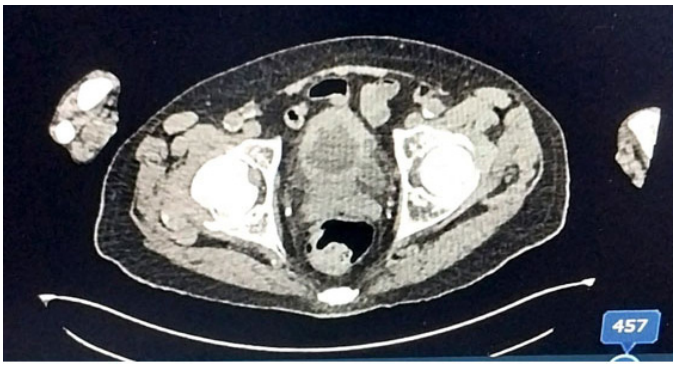

Figure 3: CT pelvis showing bilateral hydroureter and circumferential bladder mass.

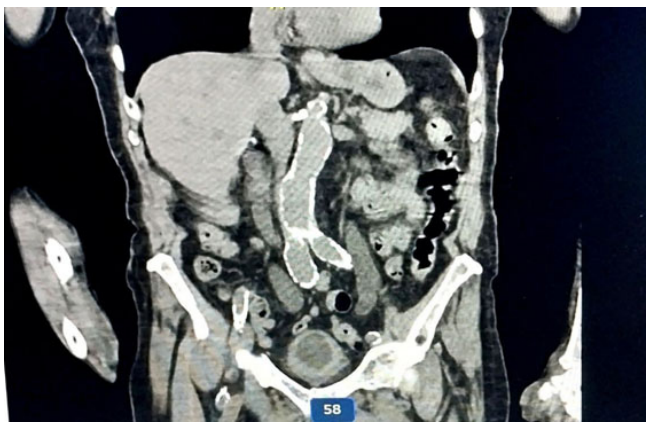

Figure 4: Coronal CT showing calcified atherosclerotic abdominal aorta with right common iliac artery aneurysm.

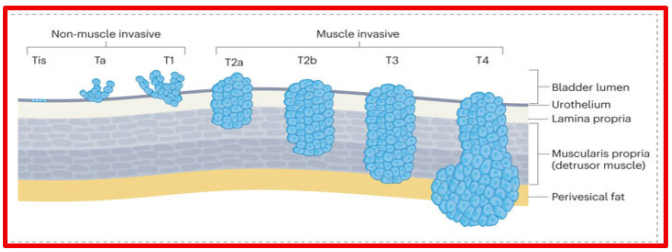

Figure 5: Bladder cancer categories.

DISCUSSION

This case presents a remarkable and clinically instructive sequence of events that challenges several conventional paradigms in urothelial carcinoma management while highlighting important biological concepts. This case is considered as a challenge to the dogma of "Superficial" bladder cancer. The term "superficial" bladder cancer is increasingly recognized as a misnomer, and this case exemplifies why. Urothelial cells are the primary cells of origin of bladder cancer, and urothelial cancer is the most common form of bladder cancer, affecting ~95% of patients. Other urothelial cell-derived bladder cancer types, occurring in <2% of patients, include small cell carcinoma, squamous cell carcinoma, and adenocarcinoma. At diagnosis, urothelial cancer is categorized as either non-muscle-invasive bladder cancer (NMIBC; stages Tis, Ta, and T1) or muscle-invasive bladder cancer (MIBC; stages T2–T4) when the disease has grown into the muscularis propria (Figure 5). The overall categorization of the disease into NMIBC or MIBC is used frequently as treatment modalities differ substantially between these entities. While the overall progression and metastatic potential of NMIBC is low (approximately 5–10% for T1 disease) according to European guidelines (EAU) [6], certain high-risk features can dramatically increase this risk. There are some key biological considerations. Of these considerations, there is microscopic invasion [7, 8]. What appears "superficial" macroscopically and even on standard histological examination may have microscopic extensions into lymphatic or vascular channels that escape detection. Our patient's initial T1 high-grade tumor, while reportedly without lymphovascular invasion (LVI) on standard staining, might have had undetected microvascular invasion. Another factor is tumor biology; this case emphasizes that tumor biology sometimes trumps clinical staging. Aggressive tumor clones with metastatic potential can emerge even from tumors confined to the lamina propria. Recent studies suggest that specialized staining for D2-40 (podoplanin) for lymphatic invasion and CD31 for blood vessel invasion might detect microinvasion missed by routine H&E staining [9]. Another point to be considered is risk stratification re-evaluation. The current risk stratification models (EORTC, CUETO) [10, 11] might need refinement for exceptional cases like this case because they may be missing risk factors like subtle

histological features (e.g., deep lamina propria invasion, tumor budding, or specific molecular markers) that could have predicted this aggressive behavior? Or not.

Another issue that may cause spread of superficial tumor is tumor spillage. During surgery, concealed tumor leakage may also result in metastases. As a result of unintentional full-thickness bladder wall resection, bladder perforation is a TURBT complication. There were isolated instances of implantation metastases, even though the overall risk of extravesical tumor seeding might not have increased for the entire NMIBC cohort [12, 13]. Although there was no bladder perforation in our case, the procedure may cause tumor cells to migrate intravascularly, which could result in an unanticipated metastasis from a surface tumor.

In a pooled analysis of literature review of other metastatic NMIBC cases, 46 cases were evaluated and found that the most common site of distant metastasis was lung followed by bone, lymph nodes, and then central nervous system (CNS). Regarding the numbers of metastases, 6 patients had 2 or more metastases, and the other 40 patients had solitary metastasis. Regarding the median time between NMIBC detection and diagnosis of metastasis, it was found that it is around 1–2 years with lung metastases having the longest interval [14–16]. Our patient's presentation fits this model perfectly with a period of tumor dormancy about 18 months before metastasis detection where micro metastases remained quiescent before establishing a viable metastatic deposit.

The management option for metastases has been discussed in multiple studies and until now it is still a point of debate. In a large meta-analysis of 15,139 patient of bladder cancer with metastases, it has been showed that patients who underwent metastasectomy had better overall survivals (OS) than did those who only had non-surgical treatment [5]. However, in another meta-analysis in 2020, it was found that overall survival in metastatic urothelial carcinoma is associated with doing radical cystectomy not metastasectomy [17]. This discrepancy is probably because these researchers did not subdivide upper urothelial cancer and bladder cancer.

Another point to be discussed here is metastatic efficiency. The success of the pulmonary metastasectomy deserves careful analysis. Surgical factors contributing to success include complete resection or (R0). The negative margins were crucial for long-term control. Another important factor is surgical approach: The VATS approach provided adequate visualization while minimizing morbidity, facilitating recovery and potential future treatments.

The seven-year disease-free interval could be explained with the initial BCG therapy that might have primed a systemic immune response that controlled micro-metastatic disease elsewhere. The lung resection might have removed the source of immunosuppressive factors, allowing the host immune system to control residual disease. The absence of additional metastases during this period suggests either a limited metastatic cascade or effective host defense mechanisms.

Regarding the development of Muscle-Invasive Bladder Cancer (MIBC): A New Primary or Late Progression?

This represents the most intriguing aspect of the case, with profound biological implications. It could be explained with field cancerization or true progression. The rationale of that case may be related to field cancerization, as the seven-year interval without any bladder recurrence makes progression from a dormant focus unlikely, Molecular Evidence, if available, comparative genomic analysis would likely show significant molecular differences between the initial T1 tumor, the lung metastasis, and the subsequent MIBC [18]. Unfortunately, it could not be done in our case. The patient's significant smoking history created a "field defect" throughout the urothelium, predisposed to multiple independent tumor clones and field cancerization.

This extraordinary case serves as a living lesson in tumor biology and clinical management with important home messages: (1) Biology over stage: Tumor biology can override conventional staging predictions, (2) Oligometastasis is real: Selected patients with metastatic urothelial carcinoma can achieve durable remission with local therapies, (3) Field cancerization: The entire urothelial field remains at risk indefinitely in carcinogen-exposed patients, (4) Lifelong vigilance: Surveillance must be persistent and comprehensive. However, there are some unanswered questions: What molecular events distinguished the metastatic clone from the primary tumor? What host factors contributed to the seven-year disease control? Could targeted therapies based on molecular profiling have altered natural history? This case argues for a more personalized, biology-driven approach to bladder cancer management that considers individual tumor behavior beyond conventional risk stratification. It highlights the importance of multidisciplinary management and the potential value of metastasectomy in selected cases.

CONCLUSION

This report demonstrates two rare oncological events: the occurrence of distant metastases arising from superficially invasive bladder cancer, and the late development of a separate, biologically aggressive primary bladder tumor following long-term remission of metastatic disease. It highlights the marked heterogeneity of urothelial carcinoma, reinforces the need for lifelong, multidisciplinary follow-up, and supports the potential curative value of metastasectomy in highly selected cases.

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Author Contributions

Shatha Alhilaly – Conception of the work, Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Ramy Elbaz – Design of the work, Acquisition of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Israr Khan – Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

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Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.