



# Early isolated bone metastases without local recurrence in non-muscle invasive bladder cancer



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## ABSTRACT

**INTRODUCTION:** Bladder cancer exhibits a broad spectrum of heterogenous clinical behavior. Conventionally used clinicopathological factors are associated with certain limitations regarding the accurate prediction of outcome. Recent studies have focused on the predictive role of cellular regulatory markers. **PRESENTATION:** The present case aimed to describe an extremely rare case of non-muscle invasive bladder cancer (NMIBC) patient with early isolated bone metastases following curative surgery. An assessment of the alterations of cellular regulatory biomarkers using immunohistochemistry was performed and a review of previous literatures is presented.

**DISCUSSION:** It is very unusual feature that the patients with NMIBC who developed bone metastases without regional lymph node metastasis or local invasion. The patient had a solitary, high-grade T1 tumor which was not associated with carcinoma *in situ* and microscopic lymphovascular invasion. However, it had rapidly metastasized to distant sites following definitive surgery and exclusively limited to bones. Of special interest appears that altered expressions of combined cellular biomarkers including p53, Ki-67, and epidermal growth factor receptor were not observed focally, but rather diffusely and intensively throughout the tumor tissue.

**CONCLUSION:** As an accurate prediction of outcome in patient with bladder cancer is currently limited, individual targeted approach based on pathological biomarkers may be helpful to determining what treatments are best or when the optimal time is.

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## 1. Introduction

Over 70% of patients with newly diagnosed bladder cancer have non-muscle invasive bladder cancer (NMIBC). The recurrence rate is high (50–70%) and a significant proportion (15–20%) will progress to muscle invasive disease [1]. As these tumors exhibits unpredictable clinical behavior regarding disease progression, standard prognostic characteristics are of limited predictive value for prognosis. Therefore, it is crucial to understand the complex molecular events that may explain the clinical heterogeneity. Molecular biomarkers have been investigated to improve the prediction of individual outcomes [2]. NMIBC metastasis to distant organs without local invasion or regional metastasis is a very rare occurrence. This is a case of unexpected isolated bone metastases in a patient with NMIBC following curative surgery. We also investigated the expression of cell cycle regulatory biomarkers, which has been extensively studied in bladder cancer for prognostication, and reviewed the related literatures.

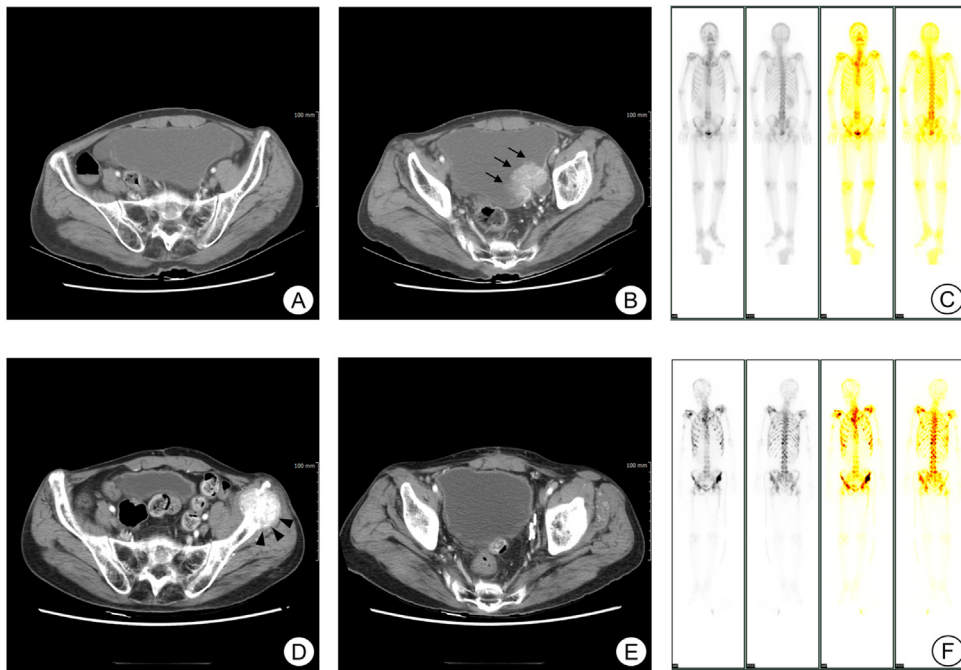
## 2. Presentation of case

A 60-year-old man presented with intermittent gross hematuria 1 year ago. A computed tomography (CT) scan of the abdomen revealed distended bladder with diverticulae and a 4.5 × 3.5 × 4.1 cm-sized bladder mass, approaching the ureterovesical junction (Fig. 1A and B). Severe hydronephrosis with parenchymal thinning of the affected kidney was identified. There was no evidence of lymph node or distant metastasis. Bone scintigraphy did not show any metastatic sites (Fig. 1C). The patient has suffered from paraplegia secondary to spinal infection of unknown origin since young adolescent and attempted voiding through manually compressing the bladder.

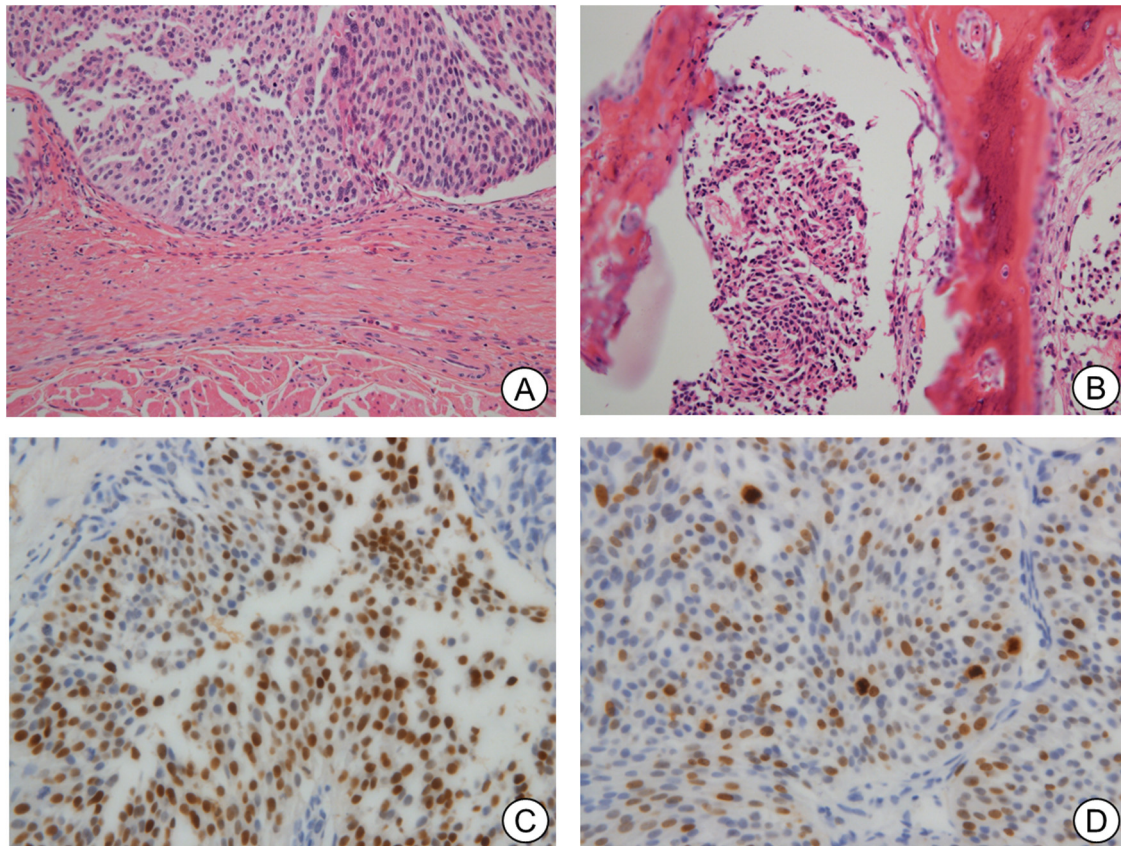
Since the initial transurethral resection (TUR) of the bladder tumor was incomplete and high-grade T1 urothelial carcinoma was diagnosed, the patient underwent a second TUR and random biopsies of the bladder wall and prostate gland. The pathological examination revealed that the tumor did not invade the muscularis propria and it was not associated with concomitant carcinoma *in situ* (CIS). As the patient belonged to high-risk group and the tumor was located at sites difficult to resect completely, a definitive extirpative surgery was considered; however, the patient insisted on a bladder preservation approach. A follow-up

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**Fig. 1.** Contrast-enhanced computed tomography (CT scan prior to surgery. (A) The preoperative CT scan shows multiple diverticula in the bladder. (B) Heterogeneously enhancing mass in the bladder (arrows) involving the ureterovesical junction. (C) Bone scintigraphy reveals no lesion exhibiting abnormal uptake. Contrast-enhanced CT scan following surgery. (D) The postoperative CT reveals a bulky osteoblastic lesion on the left iliac wing (arrowheads). (E) There was no evidence of local or regional relapse in the surgical field. (F) Bone scan shows multiple areas of abnormal uptake along the entire skeleton.



**Fig. 2.** Pathologic characteristics of specimens obtained following partial cystectomy and iliac bone biopsy. (A) The bladder tumor was diagnosed as non-muscle invasive, high-grade urothelial carcinoma (H&E,  $\times 200$ ). (B) The iliac bone specimen corresponded to metastatic urothelial carcinoma (H&E,  $\times 200$ ). Immunohistochemistry of the bladder tumor. (C) The tumor cells exhibit strong and diffuse immunoreactivity for p53 protein ( $\times 400$ ). (D) The Ki-67 labeling index was high with 60% positivity ( $\times 400$ ). H&E; hematoxylin-eosin.

**Table 1**  
Summary of immunohistochemical biomarkers used in the study.

| Biomarkers                           | Clinical status | No. of patients | Results   | Reference           |
|--------------------------------------|-----------------|-----------------|---|---------------------|
| Combination of p53, p27 and Ki-67    | pT1/RC          | 80              | Combination of biomarkers improves the prediction of RFS and CSS.                                     | Shariat et al. [6]  |
| Ki-67                                | All stages/RC   | 713             | High Ki-67 index is inversely associated with RFS and CSS.  | Margulis et al. [7] |
| Combination of p53, pRB, p21 and p16 | pT1-2/RC        | 324             | The increased number of altered cell cycle regulatory markers improves the prediction of RFS and CSS. | Shariat et al. [8]  |
| EGFR                                 | pT1/TUR         | 212             | EGFR status is independently associated with stage progression and survival.                          | Mellon et al. [9]   |

RC, radical cystectomy; RFS, recurrence-free survival; CSS, cancer-specific survival; EGFR, epidermal growth factor receptor; TUR, transurethral resection.

CT scan demonstrated no regional or distant metastasis. Laparoscopic nephroureterectomy was performed, followed by open partial cystectomy with bladder cuffing and ipsilateral pelvic lymphadenectomy. On microscopic examination, the residual tumor was only identified around the ureterovesical junction. The tumor focally infiltrated suburothelial connective tissue, without detrusor muscle invasion (Fig. 2A). There was no tumor invasion of the intravesical portion of the distal ureter. Microscopic lymphovascular invasion was not observed. All the surgical margins were free of tumor. There was no metastasis in the regional lymph nodes. The pathologic findings were the same as those of the TUR specimens.

Postoperatively, the patient was followed up regularly and remained well for 3 months. Subsequently, the patient developed generalized malaise. A follow-up CT scan revealed a 5.5 × 5.0 × 4.2 cm bulky osteoblastic lesion on the left iliac wing. There was no local or regional relapse in the previous surgical fields (Figs. 1D and E). A bone scan revealed multiple new areas exhibiting abnormal uptake in the vertebrae, pelvic bone, femoral head, left iliac bone and proximal metaphysis of femur (Fig. 1F). No other lesions were identified during further investigation, including positron emission tomography-CT scan and magnetic resonance imaging. Ultrasound-guided needle biopsy of a left iliac bone lesion was performed and the bone lesion was diagnosed as high-grade urothelial carcinoma, metastatic from the bladder (Fig. 2B).

It has been demonstrated that cellular regulatory markers improve the accuracy of prediction of clinical outcome in patient with bladder cancer [2]. Therefore, we investigated the expression of established cellular markers using immunohistochemistry. Diffuse co-expression of cytokeratin 7 and 20 in the bladder as well as the bone lesions definitely identified primary and metastatic urothelial carcinoma. The tumor cells exhibited strong and diffuse nuclear positivity for p53 protein (60–70%). The Ki-67 labeling index was also high (50–70%) positivity (Fig. 2C and D). In addition, the tumor cells were diffusely positive for epidermal growth factor receptor (EGFR) (data not shown). Of note, there was high intensity expression of p53, Ki-67, and EGFR in all the pathology specimens. The patient received combination chemotherapy, including gemcitabine and cisplatin; however, he developed grade 3, non-hematologic toxicity. The patient refused further chemotherapy and succumbed to the disease 4 months later.

### 3. Discussion

In general, bladder cancer staged Ta, T1, and CIS are collectively referred to as NMIBC. The prognosis is based on the pathologic findings regarding tumor grade, multiplicity, size, concomitant CIS, depth of invasion, and early recurrence [3–5]. However, these factors are not adequately accurate in predicting the individual clinical behavior. Moreover, patients with high-grade, T1 NMIBC should be aware of their potentially worse prognosis [4,5]. It is important to determine whether the bladder may be preserved without progression or should be removed in a timely manner.

The identification of prognostic biomarker in bladder cancer has progressed over the last few years [2]. Those associated with the cell cycle and cell proliferation/apoptosis are the most extensively

investigated biomarkers. Of note, the combination of these cellular biomarkers provided more accurate prognostic information compared to any individual marker [2,6–8]. (Table 1). Therefore, we assessed whether the tissue expression of established cellular biomarkers, such as p53 and Ki-67, exhibits meaningful alterations in the specimens. These biomarkers are well studied prognosticator that were found to be correlated with progression in bladder cancer [2]. Nuclear p53 immunoreactivity is generally considered to be altered when the samples show at least 10% nuclear reactivity [8]. The Ki-67 labeling index is considered high when it is 20% or greater [7]. All the specimens exhibited p53 and Ki-67 positivity in more than 50% of the tumor cells. These alterations were not observed focally, but rather diffusely throughout the tumor tissue. Additionally, we assessed positivity for EGFR, a receptor tyrosine kinase of the ErbB family. Overexpression of EGFR was found to be associated with progression of high-grade T1 bladder cancer and decreased cancer-specific survival [9]. Together with p53 and Ki-67, overexpression of EGFR was widely identified.

This is a case of initially diagnosed NMIBC that developed early, multiple and isolated bone metastasis. It is very unusual for patient with NMIBC to develop bone metastases without regional lymph node metastasis or local invasion. The patient had a solitary, high-grade T1 tumor, which was not associated with CIS. In addition, there was no evidence of microscopic lymphovascular invasion of residual tumor at the specimens from TURs and partial cystectomy. However, the disease rapidly spread to distant organs following surgical excision and was exclusively limited to the bones. It is unlikely that bone metastasis was caused by direct invasion or tumor spillage during the operation. First, partial cystectomy with bladder cuffing was performed using an open technique, with extra care taken not to contaminate the surgical field with tumor. Second, the residual tumor was only confined to the lamina propria in the partial cystectomy specimen. Third, there was no evidence of local recurrence or regional lymph node metastasis on the follow-up CT scan. Therefore, it appears that the tumor metastasized to the adjacent iliac bone through the hematogenous route and then extensively spread to other distant bones.

It is reasonable to assume to hypothesize that long-standing, high-grade T1 tumor with extensive alterations of cellular regulating markers may be considered as aggressive disease, even in patients without muscle invasion. In addition, partial cystectomy may offer control of localized invasive bladder cancer in patients with a unifocal tumor that can be safely resected. However, about 20% of patients develop recurrence with locally advanced diseases or distant metastasis [10]. Although the high-grade, T1 tumors are suitable candidate for partial cystectomy, patients with marked alterations of combined biomarker expression may be benefit more from immediate cystectomy.

### 4. Conclusion

The therapeutic options for T1 NMIBC patients with high-grade tumors are currently limited. Personalized targeted therapy based on pathological biomarkers may prove to be helpful in determining the optimal treatment and timing. Therefore, earlier aggressive



and comprehensive systemic therapy, along with definitive local therapy is recommended for NMIBC patients with a high risk of progression or metastasis.

#### Conflicts of interest

The author declares that they have no competing interests.

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#### Ethical approval

Ethical approval not required.

#### Consent

Written informed consent was obtained from the legal guardian of the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

#### Author contribution

All work including study design, acquisition of clinical data and drafting the manuscript was done by the corresponding author.

#### Guarantor

Dr. Jeong Hee Hong, the contributing author, is the guarantor.

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