Case Report

Distant recurrence of non-muscle invasive bladder cancer 8 years after initial treatment

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Abbreviations & Acronyms
BSC = best supportive care
Bmab = bevacizumab
CBDCA = carboplatin
CR = complete response
CT = computed tomography
EAU = European Association of Urology
GEM = gemcitabine
HG = high grade
ICI = immune checkpoint inhibitor
LG = low grade
LN = lymph node
mNMIBC = metastatic non-muscle invasive bladder cancer
N/A = not available
NMIBC = non-muscle invasive bladder cancer
PR = partial response
PTX = paclitaxel
TURBT = transurethral resection of bladder tumor

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Introduction: Distant recurrence of non-muscle invasive bladder cancer is a rare condition that is poorly understood and difficult to detect in follow-up protocols.
Case presentation: A 73-year-old female with a history of T1N0M0 bladder cancer 8 years ago suffered from a left axillary tumor, a left lung tumor, left mediastinal lymph node swelling, and bilateral adrenal gland tumors. Initially, she was diagnosed with metastatic left breast cancer of the left accessory mamma by needle biopsy of an axillary tumor. Subsequent bronchoscopic biopsy of the mediastinal lymph node revealed metastatic urothelial carcinoma, although no recurrence was detected in the urinary tract. She underwent systemic therapy, and all regions shrank without reprogression.
Conclusion: Non-muscle invasive bladder cancer should be managed considering distant metastasis. If the origin of the metastatic lesions is unknown, this disease should be considered as a possible origin, even in the absence of urinary tract recurrence.

Key words: distant recurrence, non-muscle invasive bladder cancer, urothelial carcinoma.

Keynote message

Distant recurrence of non-muscle invasive bladder cancer without local progression is rare. Diagnosis of this condition may be difficult when other tumor origins are clinically suspected or when the interval to recurrence is long. Although evaluation of the urinary tract is mainly recommended for follow-up of non-muscle invasive bladder cancer, the possibility of distant recurrence should be considered.

Introduction

Recurrence of NMIBC generally occurs in the urinary tract, but there are reports about rare metastatic recurrence of NMIBC without local progression.[1,2] Distant recurrence of NMIBC is poorly understood and sometimes difficult to detect in the current follow-up protocols.[2,3]

Here, we report a case in which the patient was treated for metastatic breast cancer, and the diagnosis was corrected to metastases of NMIBC 8 years after treatment of primary T1N0M0 bladder cancer.

Case presentation

A 73-year-old female presented to a nearby hospital with swollen left axilla. She had a medical history of diabetes mellitus, hypertension, and NMIBC, Stage I (pT1, cN0, cM0), which was diagnosed by TURBT 8 years ago (Fig. 1). On physical examination, she had a tumor around her left axilla and breast accompanied by diffuse erythema and skin edema. Mammography revealed axillary tumor, skin thickening, and trabecular thickening. However, mammography and ultrasonography revealed no tumor in the left breast. With core needle biopsy, the tumor was pathologically diagnosed as triple-negative breast cancer. Therefore, the tumor was

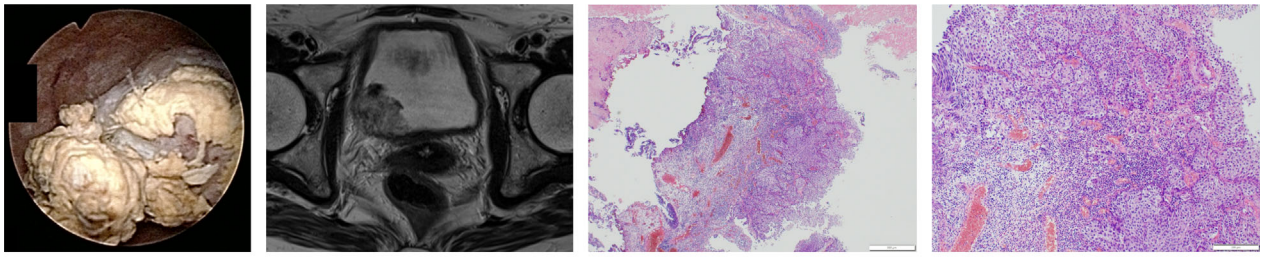

Fig. 1 Primary bladder tumor. Cystoscopy (a), MRI (b), and hematoxylin–eosin staining of the TURBT specimen at low (c) and high magnifications (d) are shown.

suspected to be an accessory breast cancer or a metastatic lymph node of an occult breast cancer. On CT, a left lung tumor, left mediastinal lymph node swelling, and bilateral adrenal gland tumors were found beside the left axillary tumor (Fig. 2).

The patient was admitted to our hospital for treatment. She had a high fever related to the tumor, and the general condition was as poor as Eastern Cooperative Oncology Group-Performance Status 3. Blood tests revealed anemia, inflammation, and renal dysfunction. Tumor marker levels showed no significant increase. The tumor burden depressed her general condition; therefore, early initiation of systemic therapy was planned. A bronchoscopic fine needle biopsy of the left mediastinal lymph node was performed, and Bmab + PTX therapy was synchronously started for metastatic breast cancer.

Pathological findings of the left mediastinal lymph node biopsy were not similar to breast cancer. Hematoxylin–eosin staining showed mild atypia compared with typical triple-negative breast cancer histology. Immunohistochemistry showed p40(+), TTF-1(−), GATA3(+), CK7(+), CK20(−), CK5/6(−), which did not suggest a particular diagnosis because these immunohistochemical features might be observed in both urothelial carcinoma and breast cancer. The same characteristics were observed in the left axillary tumor specimens: p40(+), TTF-1(−), CK7(+), and CK20(−). Immunohistochemistry was unavailable for the TURBT specimen, but the histological appearances in hematoxylin–eosin staining were similar in these three specimens (Fig. 3). Considering the history of bladder cancer, the histology was not contradictory to metastatic urothelial carcinoma. No urothelial recurrence was detected with cystoscopy, urine cytology, and CT urography. However considering the clinical history and histology, the clinical diagnosis was updated to the distant recurrence of bladder cancer.

After the first course of Bmab + PTX was completed in partial response, two courses of GEM + CBDCA therapy were subsequently administered for metastatic urothelial carcinoma. The general condition was improved and the effect was stable disease; however, she was intolerant to the GEM + CBDCA regimen because of severe myelosuppression and fatigue. The treatment was switched to pembrolizumab, and the effect was partial response after three courses (Supplementary 1). Subsequently, pembrolizumab was discontinued due to diarrhea and dehydration, and radiation was administered to the left lung tumor. Although systemic therapy was stopped for over 6 months, no progression was detected and a year of the progression-free period was achieved.

Discussion

After NMIBC treatment, follow-up with regular cystoscopy, cytology, and upper urinary tract imaging with ultrasound or CT urography is recommended in EAU guidelines.[3] Whole-body CT has no significance considering its cost and diagnostic benefit.[4] Although NMIBC sometimes progresses to invasive or metastatic carcinoma, less than 5% of NMIBC have metastasis without regional progression.[5] Matthews called this condition "metastatic NMIBC (mNMIBC)."[1] The mechanism of mNMIBC is not well known and some hypotheses are proposed: lymphatic drainage from bladder neck tumor, tumor cell contamination through bladder perforation in TURBT, and increased circulating tumor cells occurred from breaking bladder basal membrane during TURBT.[6–8] In our case, bloodborne metastasis related to the initial TURBT was considered because there were only distant regions and the bladder neck was not involved in the initial tumor.

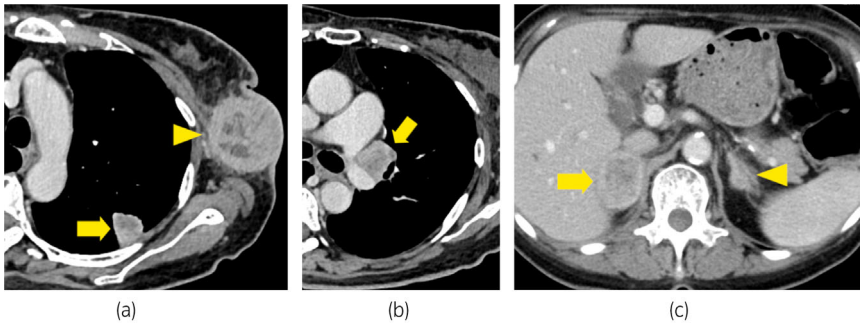

Fig. 2 CT showed a left axillary tumor (arrowhead) and a left lung tumor (arrow) (a), left mediastinal lymph node swelling (arrow) (b), right adrenal tumor (arrow), and left adrenal tumor (arrowhead) (c).

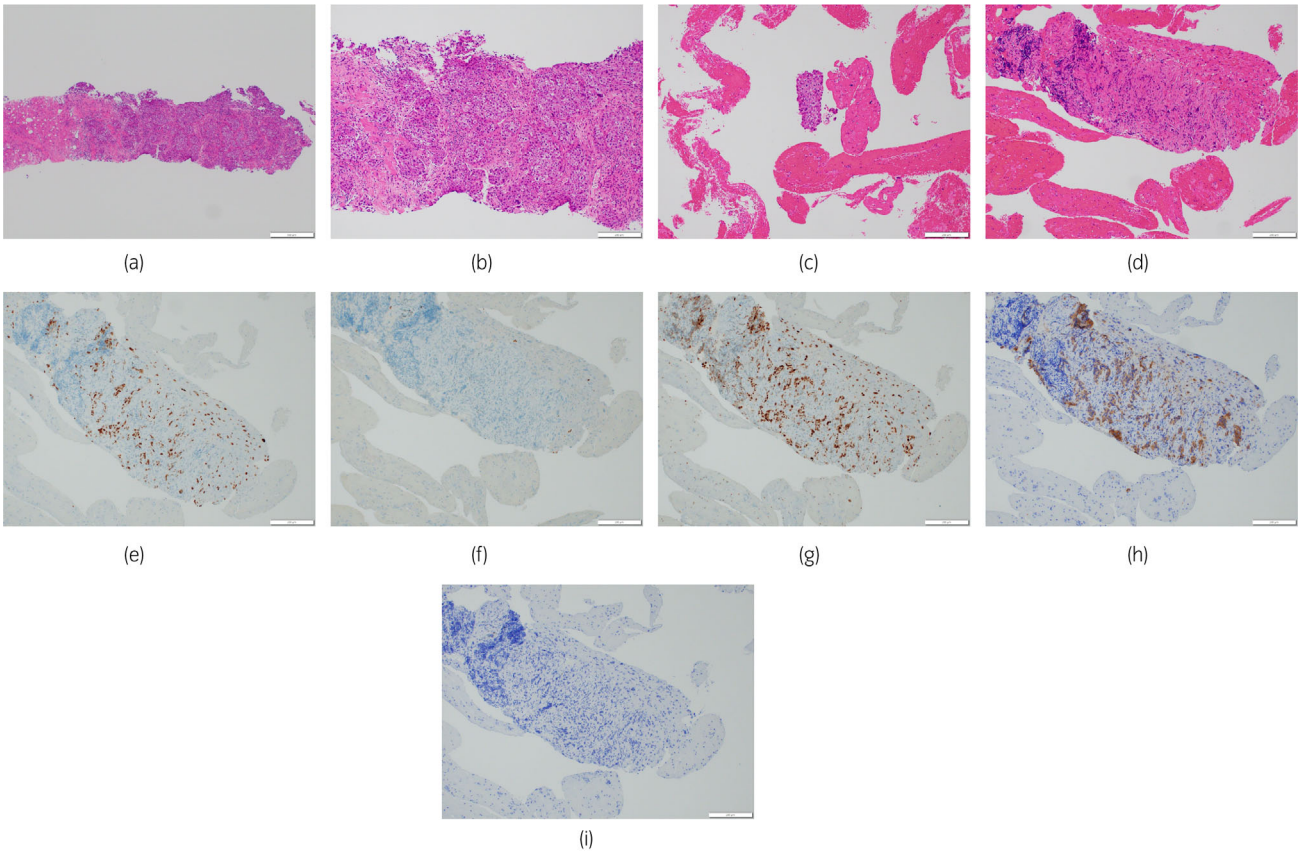

Fig. 3 Hematoxylin–eosin staining of the left axillary tumor biopsy specimen: low (a) and high magnification (b). Mediastinal lymph node biopsy specimen: low (c) and high (d) magnification in hematoxylin–eosin staining, p40 (e), TTF-1 (f), GATA3 (g), CK7 (h), and CK20 (i).

Based on our experience, some NMIBC cases require whole-body imaging to investigate metastatic recurrence, even in the absence of urothelial recurrence. Similarly, it is also important to consider metastatic recurrence of urothelial carcinoma when an unidentified tumor occurs in patients with a history of NMIBC. The table shows 50 cases of mNMIBC identified in the case studies (Table 1). Included reports are shown in Supplementary 2. The late appearance of mNMIBC is rare, but some reported NMIBC cases showed distant recurrence over 5 years after initial treatment, even in less malignant cases.[2,9,10] This suggests that mNMIBC tends to be concealed because of its low malignant potential.[2] Considering these facts, NMIBC cases might require long-term follow-up with whole-body CT to identify rare mNMIBC cases, but this will be challenging because of the economic burden and increased radiation exposure. At the beginning of treatment in our case, the diagnosis was breast cancer, but the histological appearance was non-specific. Immunohistochemistry showed GATA3 positivity, but this pattern suggests not only metastatic urothelial carcinoma but also breast cancer.[11] The critical information for the diagnosis was a history of bladder cancer.

Xu *et al*. analyzed 46 cases and reported that the median metastasis-free survival of mNMIBC was 42.5 months, in which the patients were treated with chemotherapy, radiation, and metastasectomy. While the responders showed more than 1 year of survival, untreated cases and non-responders showed poor prognoses.[2] In our case, platinum-based chemotherapy was aborted due to adverse effects, and after the transition to pembrolizumab monotherapy, no disease progression has been detected. Although surgical intervention was incapable because of the multisite regions, we achieved 1-year progression-free survival with systemic therapy and radiation. In some reported mNMIBC cases, metastasectomy provided relatively good prognoses, but further evaluation is required to establish the optimal approach for managing mNMIBC.[12]

Conclusion

We report a case of distant recurrence of T1 bladder cancer without regional recurrence 8 years after initial treatment. After NMIBC treatment, distant metastasis should be considered even without local recurrence. Similar, if the origin of metastatic lesions is unknown, NMIBC may be a candidate. Although systemic therapy, radiation, and surgery are available for mNMIBC, further studies are needed to establish optimal management strategies.

Acknowledgments

None.

Table 1 The list of mNMIBC cases from case studies and our center

Case	Study	Age (year)	Sex	Pathology	MFS (months)	Sites of metastases	Post-metastatic treatment	Outcomes
1	Seymour, 1972	33	Male	G2	117	Lung	Metastasectomy	No evidence of disease after 1 year
2	Matthews, 1984	35	Female	T1G2	86	Bone	N/A	Dead of disease after 6 months
3	Matthews, 1984	48	Female	TaG1	100	Lung	N/A	N/A
4	Matthews, 1984	76	Male	TaG2	14	Bone	N/A	Dead of disease after 1 month
5	Matthews, 1984	73	Male	T1G2	25	Lung	N/A	Dead of disease after 1 month
6	Matthews, 1984	57	Male	T1G3	70	Liver	N/A	Dead of disease after 2 months
7	Matthews, 1984	77	Male	T1G2	12	Lung	N/A	N/A
8	Andriole, 1985	60	Female	T1G1	31	Ovary, tube, uterus	Metastasectomy, chemotherapy	Local progression after 31 months
9	Francis, 1992	70	Female	TaG1	84	Ovary	Metastasectomy	N/A
10	Kakehi, 1992	63	Male	TaG2	46	Lung	N/A	N/A
11	Kakehi, 1992	55	Male	T1G2	26	Inguinal LN	N/A	N/A
12	Kakehi, 1992	48	Male	T1G3	12	Inguinal LN	N/A	N/A
13	Kakehi, 1992	51	Male	TaG2	38	Lung	Metastasectomy	N/A
14	Kawashima, 1993	67	Male	T1G3	N/A	Bone	Bone	Dead of disease
15	Koh, 1994	33	Male	TaG1	108	Lung	Metastasectomy, chemotherapy	No evidence of disease after 14 months
16	Kardar, 1998	60	Female	TaG2	48	Ovary	Metastasectomy	Dead of disease after 3 months
17	Saito, 1998	79	Male	T1G2	18	Skin	Metastasectomy, chemotherapy	No evidence of disease after 15 months
18	Davies, 2003	56	Male	T1HG	0	Cerebellum	Metastasectomy, chemotherapy, radiation	N/A
19	Shikishima, 2006	71	Male	T1G2	36	Orbit, bone	Chemotherapy, radiation	Dead of disease after 7 months
20	Hirayama, 2007	66	Female	T1G1	30	Lung	Metastasectomy	No evidence of disease after 12 months
21	Murakami, 2007	78	Female	T1G3	23	Uterus	Radiation	PR after 4 months
22	Haga, 2008	95	Male	T1G3	9	Lung	None	Dead of disease after 1 month
23	Zennami, 2008	65	Male	T1G3, CIS	34	Brain	Metastasectomy	Dead of disease after 2.5 months
24	Dougherty, 2009	66	Male	LG	120	Lung	Metastasectomy, chemotherapy	No evidence of disease after 1 year
25	Blasberg, 2009	83	Female	T1HG, sarcomatoid	3	Colon	Metastasectomy	N/A
26	D'Souza, 2011	69	Female	T1G3	11	Cerebellum	Metastasectomy, radiation	No evidence of disease after 21 months
27	Arai, 2012	52	Female	T1G3	19	Lung	Metastasectomy, chemotherapy	No evidence of disease after 53 months
28	Canter, 2012	76	Female	T1HG, CIS, micropapillary	0	Pancreas	N/A	N/A
29	Sano, 2013	66	Male	Ta, G1-2	72	Lung	Metastasectomy	No evidence of disease after 18 months
30	Sasaki, 2013	66	Male	T1G3	10	Bone	Chemotherapy	PR after 5 months
31	Tuncer, 2014	83	Male	T1HG	2	Bone, mediastinal LN, external iliac LN, thyroid, adrenal gland	Radiation	Dead of disease after 6 months
32	Hong, 2015	60	Male	T1HG	3	Bone	Chemotherapy	Dead of disease after 4 months

Table 1 (Continued)

Case	Study	Age (year)	Sex	Pathology	MFS (months)	Sites of metastases	Post-metastatic treatment	Outcomes
33	Vural, 2015	61	Male	TaLG	96	Lung	Metastasectomy, chemotherapy	PR after 4 months
34	Teyssonneau, 2017	63	Male	T1HG	36	Meninges, bone	Chemotherapy	CR after 4 years
35	Frydenlund, 2018	56	Male	TaHG	54	Mandible, lung	Radiation, chemotherapy	N/A
36	López, 2018	58	Male	TaLG	>60	Lung	Metastasectomy, chemotherapy	No evidence of disease after 8 months
37	Juri, 2018	63	Male	CIS, HG	60	Cervical LN	N/A	N/A
38	Juri, 2018	79	Male	CIS, HG	63	Mediastinal LN, bone	N/A	N/A
39	Kida, 2018	77	Male	T1HG	10	Bone, liver	Radiation	Dead of disease after 5 months
40	Kida, 2018	70	Male	T1HG	18	Common iliac LN, paraaortic LN	Chemotherapy	PR after 4 months
41	Garrido-Abad, 2019	72	Male	TaLG	60	Supraclavicular LN	Chemotherapy	Dead of disease after 5 months
42	Defant, 2020	64	Male	TaLG	0	Bone	Metastasectomy, chemotherapy, radiation	No evidence of disease after 10 years
43	Horibe, 2021	67	Male	T1G2	118	Paraaortic LN	Chemotherapy, ICI	Dead of disease after 21 months
44	Weiß, 2021	70	Male	TaLG	7	Liver, lung, bone, retroperitoneal LN, paraaortic LN	BSC	Dead of disease within 1 month
45	Nishiyama, 2021	68	Male	T1G2	51	Testis, paraaortic LN	Metastasectomy, chemotherapy	No evidence of disease after 1.3 years
46	Xu, 2022	70	Male	T1HG	41	Supraclavicular LN	Chemotherapy, ICI, radiation	PR after 1.6 years
47	Kim, 2023	48	Female	T1HG	9	Retroperitoneal LN, mediastinum LN, cervical LN	Chemotherapy, ICI	Dead of disease after 15 months
48	Kim, 2023	75	Female	T1HG	20	Cervical LN, supraclavicular LN, paraaortic LN	Chemotherapy	CR after 12 months
49	Kim, 2023	82	Male	T1HG	4	Lung	Chemotherapy, ICI	CR after 6 months
50	Watanabe, 2024	73	Female	T1HG	96	Mediastinal LN, axillary LN, lung, adrenal grand	Chemotherapy, ICI, radiation	PR after 6 months

Author contributions

Mahoro Watanabe: Writing – original draft. Naoki Kawamorita: Conceptualization; writing – review and editing. Tetsuro Shiraiwa: Data curation. Tomonori Sato: Data curation. Takuma Sato: Data curation. Yoshihide Kawasaki: Data curation. Shinichi Yamashita: Data curation. Akiko Ebata: Writing – review and editing. Satoko Sato: Writing – review and editing. Akihiro Ito: Supervision.

Conflict of interest

The authors declare no conflicts of interest.

Approval of the research protocol by an Institutional Reviewer Board

The study protocol was approved by the Ethics Committee of the Tohoku University Graduate School of Medicine (No. 34658).

Informed consent

Informed consent was obtained from the patient.

Registry and the Registration No. of the study/trial

Not applicable.

Funding information

Not applicable.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Supplementary 1. Longitudinal change of left axillary tumor. After one course of Bmab + PTX (arrowhead) (a), after two courses of GCarbo (arrowhead) (b), and after three courses of pembrolizumab (arrowhead) (c).

Supplementary 2. Identified studies of mNMIBC cases included in the table.