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Case Report

Dramatic Response to Enfortumab Vedotin in Soft-tissue Metastases from Urothelial Carcinoma: A Case Report

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Abstract

Soft-tissue metastasis from urothelial carcinoma is a rare but advanced disease entity. We report a patient with muscle-invasive bladder cancer who experienced rapid disease recurrence following radical surgery and adjuvant platinum-based chemotherapy. Despite further treatment with taxane-based chemotherapy and immune checkpoint inhibitors, the patient developed diffuse soft-tissue metastases, including in the skin, muscles of the extraocular area, extremities, and trunk. Salvage treatment with enfortumab vedotin (EV) was administered along with local radiation therapy to the orbital metastasis for better symptom control. Unexpectedly, the soft-tissue metastases showed a dramatic response after the first cycle of EV. However, after two cycles of EV treatment, the skin and extremity muscular metastases progressed, while the extraocular metastasis remained controlled. Four months after EV treatment, the patient died due to systemic progression and infection.

Keywords: Enfortumab vedotin, soft-tissue metastasis, urothelial carcinoma

Introduction

Soft-tissue and skin metastases from bladder cancer are rare. Mueller *et al.* reported that only 38 (0.84%) of 4516 bladder cancer cases were diagnosed with cutaneous metastases, and Shinagare *et al.* reported that only 14 (9%) of 150 bladder cancer cases had soft-tissue metastases. The prognosis for patients with soft-tissue and skin metastases is generally poor.[1-3]

Enfortumab vedotin (EV), a nectin-4 targeting antibody–drug conjugate, has marked a paradigm shift in bladder cancer treatment.[4,5] We present a patient with metastatic urothelial carcinoma who failed both platinum-based chemotherapy and immunotherapy and exhibited diffuse soft-tissue metastases, including in the skin, muscles of the extraocular area, extremities, and trunk. Unexpectedly, these soft-tissue metastases showed a dramatic response after the first cycle of EV.

Case Report

A 72-year-old male presented with painless gross hematuria for 3 months. Urine cytology showed the presence of

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malignancy. Subsequent cystoscopy revealed bladder tumors, and transurethral resection of the bladder tumors confirmed the diagnosis of high-grade muscle-invasive urothelial carcinoma (pT2). Despite three transurethral resections of the bladder tumors, a follow-up computed tomography scan revealed disease progression, manifesting as obstructive uropathy.

After a thorough discussion regarding treatment options, the patient and his family opted for a laparoscopic radical cystectomy with ileal conduit reconstruction. The final pathological staging was pT4aN0. He received four cycles of adjuvant chemotherapy with gemcitabine and cisplatin (gemcitabine 850 mg/m^2 and cisplatin 32 mg/m^2 on day 1 and day 8, repeated every 3 weeks).

Six months after the completion of adjuvant chemotherapy, follow-up abdominal magnetic resonance imaging (MRI) disclosed a recurrent presacral tumor [Figure 1]. Two cycles of paclitaxel plus fluorouracil (paclitaxel: 65–85 mg/m^2 on day 1 and day 15; fluorouracil: 2150 mg/m^2 plus leucovorin 215 mg/m^2 infusion for 48 hours on day 1 and day 15, repeated every 4 weeks) were administered as salvage treatment. Less than 1 month after chemotherapy, a physical examination identified a growing tumor in his left arm, approximately 1.6 cm in diameter. Follow-up MRI showed soft-tissue metastases in the left biceps brachii muscle and left trunk [Figure 2].

The patient received pembrolizumab (200 mg every 3 weeks) for progressive disease. However, multiple palpable and firm skin and muscular masses developed after the second cycle of pembrolizumab. He also reported progressive swelling and blurred vision in the right eye for 1 month [Figure 3b]. Brain MRI revealed a right intraconal orbital tumor, partially encasing the optic nerve [Figure 3a]. Biopsies of both the left forearm tumor and orbital tumor confirmed the diagnosis of metastatic urothelial carcinoma.

As a salvage treatment, EV (1 mg/kg on day 1, day 8, day 15, repeated every 4 weeks) was initiated. In addition, palliative radiation therapy at a total dose of 30 Gy in 10 fractions was administered to the right orbital tumor. Unexpectedly, the soft-tissue metastases began to shrink 2 weeks after EV treatment, and the right eye swelling also subsided after EV and radiation therapy [Figure 4b]. Eight weeks after EV treatment, follow-up imaging confirmed a partial response [Figure 4a and c].

Unfortunately, multiple progressively enlarging soft-tissue tumors in the right arm, left thigh, shoulder, back, and chest wall were found 9 weeks after EV treatment. A follow-up image 16 weeks after EV treatment showed extensive progression in bilateral lungs, peritoneum, and soft tissues. Notably, the orbital metastasis remained stationary without evidence of progression. The patient died of cancer and superimposed pulmonary infection 17 weeks after EV treatment.

Immunohistochemistry for nectin-4 was performed on a series of specimens from the patient using the commercially available primary antinectin-4 antibody EPR15613-68. Nectin-4 expression was quantified using an H-score, determined by multiplying the staining intensity (scored from 0 to 3) by the percentage of cells stained at each intensity level (ranging from 0 to 100), and then summing these products. Based on the H-score, samples were categorized as negative (H-score: 0–14), weak (H-score: 15–99), moderate (H-score: 100–199), or strong (H-score 200–300). The H-score of the metastatic sites was 80 for the orbital metastasis and 100 for the left arm soft-tissue metastasis [Figure 5].

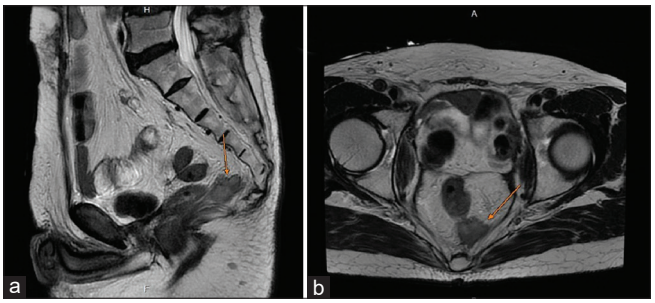

Figure 1: Abdominal magnetic resonance imaging (a: sagittal and b: axial view, T2) showing recurrent pelvic metastasis

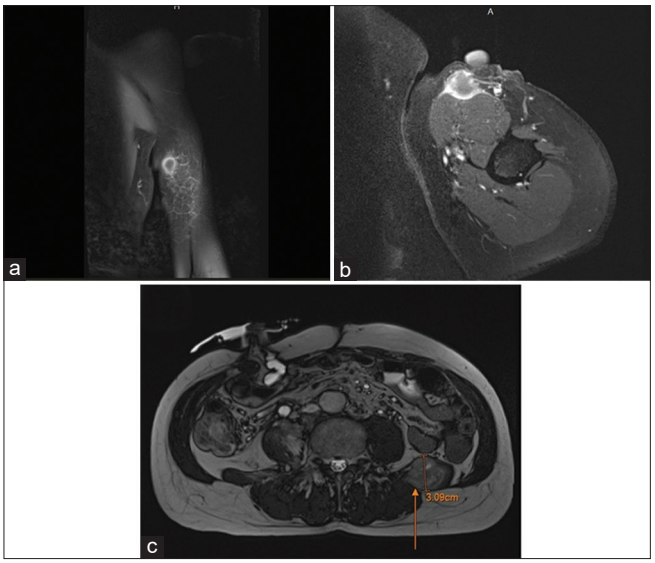

Figure 2: Left forearm magnetic resonance imaging (MRI) (a: coronal, and b: axial view, T1 with contrast) and abdominal MRI (c: axial view, T2) showing muscular metastases

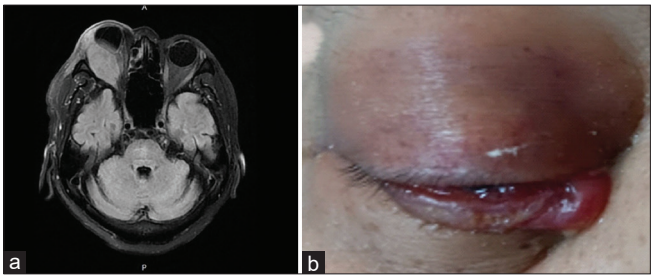

Figure 3: Brain magnetic resonance imaging (a: T2 FLAIR) and photo of the right eye (b) showing orbital metastases before enfortumab vedotin treatment

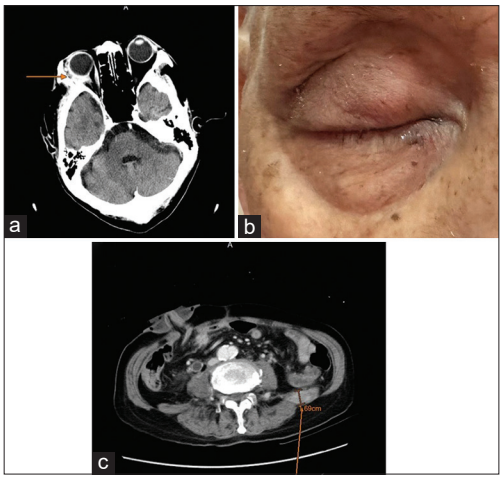

Figure 4: Brain computed tomography (CT) with contrast (a) and photo of the right eye (b) showing orbital tumor shrinkage after enfortumab vedotin (EV) and radiation therapy. Abdominal CT with contrast (c) showing partial response of muscular metastasis after EV

Discussion

Bladder cancer is the tenth most common cancer worldwide[6] and typically metastasizes through lymphatic and hematogenous routes. The 5-year survival rate of metastatic bladder cancer is <10%. The most frequent sites of metastasis include distant lymph nodes, bones, lungs, and liver.[7] Soft-tissue metastases, including skin involvement, are rare and signify a poor prognosis, with a median overall survival of less than 4 months in published cases.[2,3,8-10] Treatment options for these challenging cases remain unclear.

In recent years, the introduction of the antinectin-4 antibody–drug conjugate EV has transformed the therapeutic landscape for metastatic urothelial carcinoma. Nectin-4, a transmembrane polypeptide, plays a role in cell–cell adhesion in normal skin keratinocytes, bladder urothelium, salivary glands, esophagus, and breast tissue.[11] Overexpression of nectin-4 has been observed in various cancers, including breast, urothelial, and lung cancers.[12] Based on data from the phase I EV-101 trial, nectin-4 is highly expressed in most urothelial carcinoma patients (147/152; 96.7%). Consequently, EV is currently approved for urothelial carcinoma treatment without the need to evaluate nectin-4 expression.

However, the lack of nectin-4 expression has been associated with EV resistance in preclinical studies. Klümper *et al.* demonstrated significantly decreased nectin-4 expressions at metastatic sites compared to the primary sites. In their multicenter EV cohort, the absence or weak expression of nectin-4 was associated with a shorter progression-free survival on EV.[13] In our case, the metastatic sites exhibited weak nectin-4 expression (H-score: 80–100), which likely explains the excellent but not durable response to EV. Assessing nectin-4 expression levels may help evaluate the effectiveness of EV.

Of note, the orbital metastasis in our patient was treated not only with EV but also with radiation therapy for local control. The response was notably durable, even as the disease progressed extensively elsewhere. Zhou *et al.* suggested that EV or sacituzumab govitecan combined with radiation therapy may have had additive antitumor activity in preclinical models of bladder cancer.[14] Further investigations are needed to evaluate the efficacy of EV plus radiation therapy.

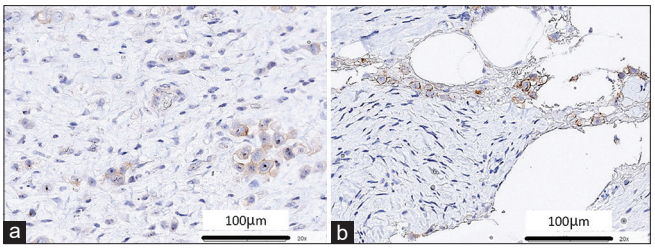

Figure 5: Immunohistochemical staining for nectin-4. (a) Orbital metastasis (H-score: 80) and (b) skin metastasis (H-score: 100)

In conclusion, we report a heavily pretreated metastatic urothelial carcinoma patient whose soft-tissue metastases had a remarkable initial response to EV treatment. The duration of response to EV was short, suggesting that nectin-4 expression may play a role in evaluating the effectiveness of EV. In addition, the exclusively durable response in the orbital metastasis underscores the potential effectiveness of combining EV with radiation therapy, which warrants further investigation.

Declaration of patient consent

This study was performed in accordance with and conforming to the Declaration of Helsinki. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Data availability statement

All data generated or analyzed during this study are included in this published article.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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