



## Oncology

# A case of Avelumab response to multiple bone and lymph node metastases of plasmacytoid variant bladder cancer

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## ABSTRACT

A 74-year-old man was diagnosed with bladder cancer and referred to our department. For definitive diagnosis, transurethral resection of the bladder tumor (TURBT) was performed. The pathological result showed plasmacytoid variant of urothelial carcinoma. Subsequently, robot-assisted radical cystectomy, lymph node dissection and ileal conduit was performed, but multiple bone metastases and periaortic lymph node metastases newly appeared 30 days later. Gemcitabine and cisplatin (GC) was started, and after 4 courses, the patient became Partial Response (PR), and was switched to Avelumab as maintenance therapy. After about 1 year of maintenance therapy, the patient is still in PR.

## 1. Introduction

We report here a case of plasmacytoid variant bladder cancer that responded to initial chemotherapy and remained in PR after maintenance therapy with PD-L1 inhibitors, with some discussion of the literature.

## 2. Case presentation

A 74-year-old man visited his local doctor because of pain during urination for one week. He was referred to our department because his bladder tumor was detected between the left ureteral orifice and the left wall by cystoscopy and contrast-enhanced CT scan. An MRI scan performed to determine the depth of the tumor showed findings that suggested invasion into the surrounding fatty tissue. TURBT was performed to make a definitive diagnosis, and in addition to the usual high-grade papillary tumor, there were findings of invasion by plasmacytoid-like tumor cells with highly atypical nuclei and abundant acidophilic cytoplasm, which were unevenly distributed in the nucleus (Fig. 1). The diagnosis was cT3bN0M0. Thereafter, robot-assisted radical cystectomy, lymph node dissection and ileal conduit was performed, and the surgical specimen was confirmed to be pT3bN0 and negative for margins. The patient was scheduled to receive postoperative adjuvant chemotherapy. But 30 days after surgery, the patient complained of back pain and

underwent contrast-enhanced CT scan, which revealed the appearance of new metastatic lesions in the periaortic lymph nodes. Contrast-enhanced MRI, Bone scintigraphy, and PET-CT were performed for detailed metastatic examination, and multiple bone metastases were newly detected in the ribs, thoracolumbar spine, and pelvic bones (Fig. 2).

GC was started, and after 4 courses, imaging evaluation showed that both multiple bone metastases and lymph node metastases had shrunk significantly, and the patient was judged to be PR. The patient was switched to Avelumab for maintenance therapy. About one year has passed since the patient was shifted to maintenance therapy, and both multiple bone metastases and lymph node metastases are still in PR (Fig. 3).

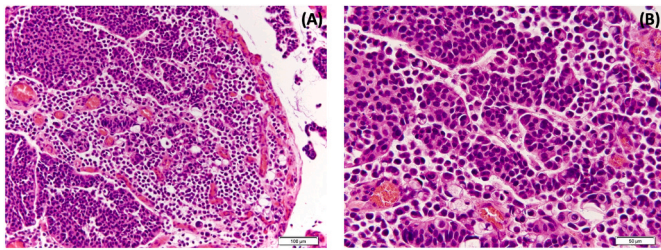
## 3. Discussion

The plasmacytoid variant is a relatively rare histology, accounting for 1–3% of all urothelial tumors. It is characterized by a high degree of invasiveness and a lack of hematuria. Histopathologically, the tumor cells have a plasmacytoid morphology with abundant acidophilic cytoplasm and an unevenly distributed nucleus. Loss of E-cadherin was also observed in the plasmacytoid variant component, which is thought to be one of the causes of the high invasiveness and metastatic potential of plasmacytoid variant.<sup>1</sup> Some reports have shown that the percentage of

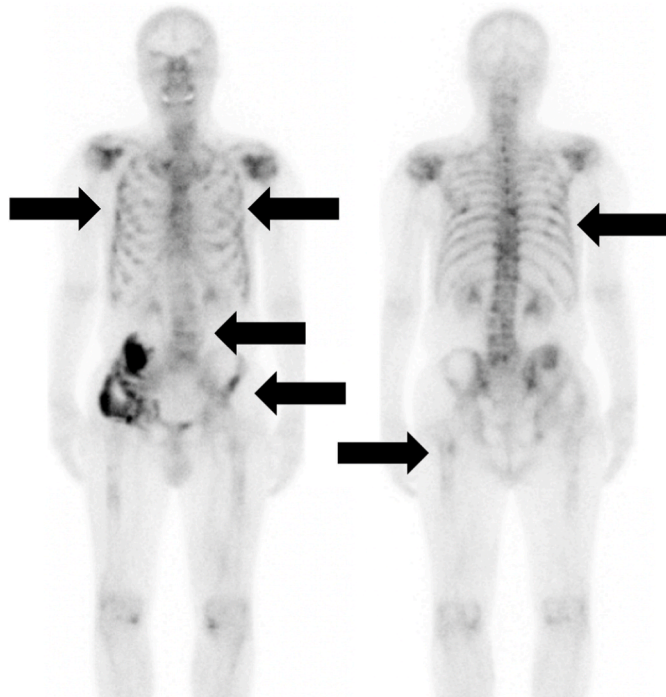
*Abbreviations:* CT, Computed tomography; HE, Hematoxylin and eosin; MRI, Magnetic Resonance Imaging.

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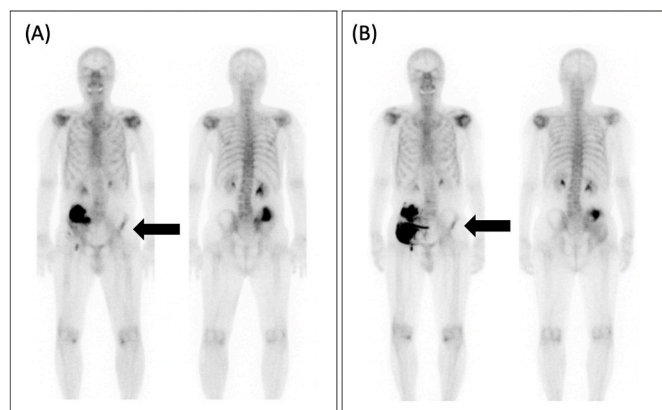
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**Fig. 1.** (A) HE staining(low power field): strong karyotypic plasmacytoid tumor cells infiltrate between normal papillary tumor tissue. (B) HE staining(high power field): Plasmacytoid cells were observed, with eosinophilic cytoplasm and small round nuclei that were unevenly distributed.



**Fig. 2.** Bone scintigraphy: Multiple bone metastases in ribs, thoracolumbar spine and pelvis.



**Fig. 3.** (A) After GC4 courses (B) One year has passed since the change to Avelumab.

positive margins and positive lymph nodes is also predominantly high.<sup>2</sup>

The treatment of plasmacytoid variant bladder cancer has been reported to be similar to that of conventional bladder cancer, including radical cystectomy and combination chemotherapy. In recent years, the pCR of preoperative chemotherapy for common bladder cancer is 25%, and prolonged survival has been reported.<sup>2</sup> On the other hand, regarding preoperative chemotherapy for plasmacytoid variant bladder cancer, Dayyani et al. showed a very high pCR (60%, 3 out of 5 cases) but recurrence was frequent, while Perrino et al. showed a pCR of only 7.1% (1 out of 14 cases).<sup>2</sup> Since the benefit of preoperative chemotherapy prior to radical cystectomy was unclear in this patient, we decided to schedule the patient on a waiting list for adjuvant chemotherapy in favor of radical cystectomy. As the patient responded well to chemotherapy, preoperative chemotherapy may have been effective.

Recently, Immune Checkpoint Inhibitors(ICIs) such as Pembrolizumab for 2nd line and Avelumab for maintenance therapy have been introduced in bladder cancer treatment, increasing treatment options. Reis et al. found that plasmacytoid variant antibodies differ in cut-off values and evaluation methods (tumor cells, immune cells). They found that the majority of bladder cancers express PD-L1.<sup>3</sup> The presence of plasmacytoid variant tissue in this case suggests that the tumor cells themselves express PD-L1 at a high frequency and that Avelumab administered as maintenance therapy may have responded due to high expression of PD-L1. At this time, however, there are no reports on the clear efficacy of ICI in plasmacytoid variant bladder cancer, and further therapeutic investigation is needed.

**4. Conclusion**

In this study, we experienced a case of plasmacytoid variant bladder cancer with multiple bone and lymph node metastases that responded to Avelumab. Plasmacytoid variant bladder cancer is a high-grade and rapidly progressing form of bladder cancer, but ICI is considered to be a possible treatment option. Further case series and studies are needed to increase the number of treatment options.

**Approval of the research protocol by an institutional reviewer board**

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**Informed consent**

N/A.

**Registry and the registration none of the study/trial**

N/A.

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**Declaration of competing interest**

N/A.

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