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Case Report

Organ-confined plasmacytoid urothelial carcinoma: implication of the lack of expression of the receptor tyrosine kinase MET

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Abstract: Plasmacytoid urothelial carcinoma (PUC), a morphological variant of urothelial carcinoma (UC), is composed of cancer cells that resemble plasma cells, monocytes, or both, and is clinicopathologically distinguished by its aggressive, non-organ-confined features. Here, we present a case of a patient with PUC with early invasion at diagnostic transurethral resection. Histopathologically, no residual cancer or lymph node metastasis was observed by total cystectomy. The patient remains disease-free after 18 months, without undergoing adjuvant chemotherapy. Interestingly, the immunoreactivity of MET, a receptor tyrosine kinase expressed in many invasive UCs, was minimal in the cancer cells. In contrast, archival pathological, non-organ-confined PUC cells exhibited strong MET immunoreactivity. The present case may imply a role for the MET protein in the aggressive behavior of PUCs. We propose the putative usefulness of MET inhibitors for the treatment of aggressive PUCs.

Keywords: Plasmacytoid urothelial carcinoma, urothelial carcinoma, MET

Introduction

Plasmacytoid urothelial carcinoma (PUC) is a histopathological variant of urothelial carcinoma (UC), defined by the presence of mononuclear tumor cells with plasmacytoid, lymphoid, signet-ring cell, or rhabdoid cell features [1, 2]. PUC is rare in occurrence, but is being increasingly reported, with an estimated incidence of 1-7% of all invasive UCs. Several large studies composed of more than 30 cases have demonstrated that most PUCs are aggressive, and are characterized as non-organ-confined cancers [3-5].

However, current studies have also documented some PUCs with favorable prognoses, namely pT1 PUCs, at early invasion stages of PUCs [3-6]. These PUCs have demonstrated favorable outcomes in follow-up studies spanning 3-47 months. Kawahara et al. have reported a case of pT1 PUC that was successfully treated by transurethral resection of the bladder tumor (TUR-BT) without cystectomy [7].

Here, we describe the case of a patient with organ-confined PUC, who was treated by TUR-BT, followed by cystectomy. Notably, no residual cancer cells were observed in cystectomy specimens. Without undergoing adjuvant chemotherapy, the patient is well, with no recurrences, since 18 months. Subsequent immunohistochemical staining unraveled that the PUC tissue from this patient exhibited minimal immunoreactivity, while archival pathological PUC tissue specimens showed strong MET immunoreactivity. As the MET protein promotes cancer invasions, its expression is related to poor prognoses in patients with UCs [8, 9]. We hypothesize that MET expression may be related to the aggressiveness of the PUC, and thus may be a potential candidate for molecular therapy. Additionally, to our knowledge, this is the first report that describes MET expression in PUC tissues.

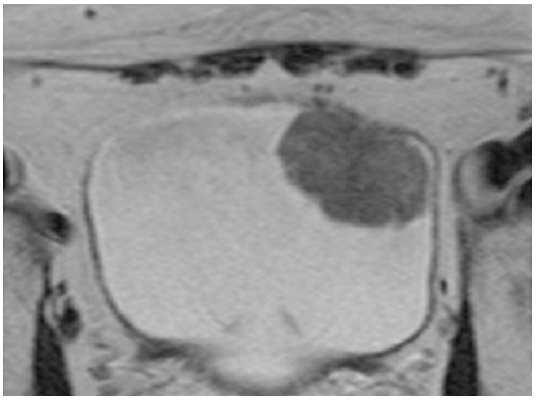

Figure 1. MRI imaging scan of the patient showing a tumor, measuring 43 mm in the bladder dome.

Materials and methods

Ethical statements

All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval to use archival pathological tissue specimens was obtained from the Institutional Review Board of the Gifu University Graduate School of Medicine (a specific approval number 24-256). Informed consent was obtained from individual participant with organ-confined PUC in the study.

Case presentation

A 71-year-old man presented with macroscopic hematuria, and was admitted to our hospital with a suspected bladder mass. Cystoscopy detected the presence of a tumor, measuring 43 mm in the bladder dome. The results of magnetic resonance imaging (MRI) imaging are shown in **Figure 1**. The patient underwent TUR-BT followed by total cystectomy

Antibodies and Immunohistochemical staining

We used anti-CK7 (clone name OV-TL 12/30; Invitrogen, Camarillo, CA), anti-CD138 (clone MI15; DAKO, Carpenteria, CA), anti-E-cadherin (clone EP700Y; Epitomics, Burlingame, CA), anti-MET (c-12, Santa Cruz Biotechnology, Inc., CA) antibodies. Archived pathological tissue specimens from four non-organ defined PUCs were also used in this study. All tissue specimens were obtained surgically, fixed in 10% buffered formalin, and embedded in paraffin. Tissues were immunostained with antibodies using the ImmPRESS™ polymerized reporter enzyme staining system (Vector laboratories, Inc. Burlingame, CA, USA) as previously reported [10].

Results

Pathology findings

Histopathological examination of the TUR-BT revealed that the mass was almost uniformly composed of plasmacytoid cells, characterized by loosely connected cells with eosinophilic, clear, or vacuolated cytoplasm (**Figure 2A**). Tumor invasion into the lamina propria was observed. Notably, Cytokeratin 7 (CK7) and CD138 immunoreactivity was observed in the cancer cells (**Figure 2B** and **2C**, respectively). Immunohistochemical staining was negative for E-cadherin (**Figure 2D**). Based on these results, we characterized this bladder tumor as a PUC.

Because of the aggressive pathobiological behavior of PUC and its invasion into the lamina propria, as visualized in TUR-BT tissue specimens, the patient further underwent total cystectomy and lymph node dissection. Subsequent histopathological examinations did not detect any residual cancer cells in the urinary bladder or lymph nodes. Post-surgically, the patient was discharged without further adjuvant chemotherapy or radiotherapy, and has been disease-free since 18 months.

MET expression in the present case and other PUCs

Many studies have shown the importance of the MET protein in the determination of the invasive phenotype of various cancers, including UCs [8, 9, 11]. In the present study, we have analyzed whether the MET protein was expressed in PUCs. Surprisingly, little or no MET expression was observed in the tissue specimen of the present case (**Figure 2E**), whereas we observed strong MET expression in all 4 archival pathological PUC tissue specimens (**Figure 2F**).

Discussion

Kaimakliotis et al. examined 30 PUC patients and documented that approximately 27% of PUCs were organ-confined [3]. Cockerill et al. reported 9 survivors among 46 patients with

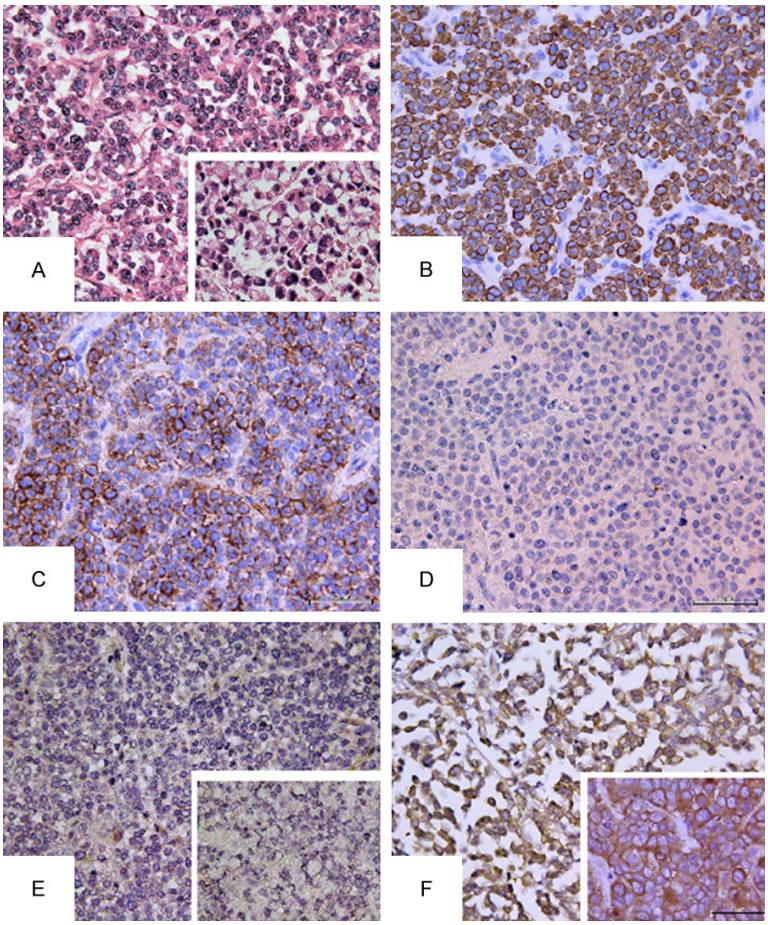

Figure 2. Representative results of histopathological examinations are shown. (A) Transurethral resection of the tumor revealed that it was composed of plasmacytoid or monocytoid cells. Signet-ring cell carcinoma-like cells were also focally observed (inserted figure), consistent with previous cases. (B-D) CK7 and CD138 immunoreactivity was observed (B and C, respectively), whereas little or no E-cadherin immunoreactivity was observed (D), in cancer cells. These results are compatible with those of previously reported PUC cases. We used anti-CK7 (clone name OV-TL 12/30; Invitrogen, Camarillo, CA), anti-CD138 (clone MI15; DAKO, Carpenteria, CA), and anti-E-cadherin (clone EP700Y; Epitomics, Burlingame, CA) antibodies. (E) Little or no immunoreactivity with an anti-MET antibody (c-12, Santa Cruz Biotechnology, Inc., CA) was observed in the PUC cells. Signet-ring cell carcinoma-like cells also showed minimal immunoreactivity (inserted figure). (F) By contrast, strong immunoreactivity with anti-MET antibody was observed in archival pathological non-organ-confined PUC cells. Note the surface membrane immunoreactivity (inserted figure).

PUC; these were mostly pT1 or pT2 PUCs without lymph node metastasis [4]. Li et al. examined the outcomes of 1312 patients with UCs, and 98 with PUCs, of which, 11 were pT1, and 35 were pT2 [5]. They also demonstrated significantly higher odds of the presence of a pT3 or pT4 stage in PUCs than in UCs. However, they concluded that plasmacytoid histology was not significantly associated with an increased risk of mortality, after adjusting for pathological stage or more [5].

These results raised the debate of whether the histopathological features of PUC warrant aggressive total cyste ctomy and adjuvant chemoradiotherapy at TUR-BT. The histopathological diagnosis of PUC is dependent on its cancer cell morphology, thus heterogenous biological behavior in PUCs may be unavoidable. Moreover, confirmed diagnostic criteria concerning about the percentage of plasmacytoid or monocytoid cancer cells necessary for histopathological diagnosis remain unestablished.

In this report, we have described the case of a patient with an organ-confined PUC with favorable pathobiological behavior. Notably, the PUC cells here did not show MET expression, unlike in our previous PUC cases. Aberrant HGF or MET signaling leads to increased cancer cell invasion [8]. We speculate that the lack of a MET signaling cascade might be related to the organ-confined feature of the PUC in our present case.

In conclusion, the present case may imply that MET expression is related to aggressive phenotypes in PUCs and may lead to molecular therapies using MET inhibitors [12] for patients with PUC.

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Disclosure of conflict of interest

None.

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