Case Report

Rapid progression of recurrent disease in a patient with renal cell carcinoma with vaginal metastasis

Mizuki Hisano,[1] Renpei Kato,[1] Hiroaki Itamochi,[2] Tomohiko Matsuura,[1] Shigekatsu Maekawa,[1] Yoichiro Kato,[1] Mitsugu Kanehira,[1] Ryo Takata,[1] Tsukasa Baba[2] and Wataru Obara[1]

Departments of [1]Urology, and [2]Obstetrics and Gynecology, Iwate Medical University School of Medicine, Yahaba, Japan

Abbreviations & Acronyms
CT = computed tomography
ICI = immune checkpoint inhibitor
IHC = immunohistochemical
MTT = molecular targeted therapy
PD-L1 = programmed death ligand-1
PET = positron-emission tomography
RCC = renal cell carcinoma

Correspondence: Mizuki Hisano M.D., Department of Urology, Iwate Medical University School of Medicine, 2-1-1 Idaidori, Yahaba, Iwate 028-3695, Japan. Email: hisahisatf800@gmail.com

How to cite this article: Hisano M, Kato R, Itamochi H *et al*. Rapid progression of recurrent disease in a patient with renal cell carcinoma with vaginal metastasis. *IJU Case Rep*. 2020; **3**: 185–188.

Received 13 December 2019; accepted 25 May 2020.
Online publication 7 July 2020

Introduction: We report a rare case of renal cell carcinoma with vaginal metastasis that recurred with rapid progression and was resistant to sunitinib and nivolumab.
Case presentation: A 68-year-old woman presented with renal cell carcinoma and vaginal metastasis. Multiple lung metastasis appeared 3 months after simultaneous radical nephrectomy and hysterectomy with vaginal resection. Despite the treatment with sunitinib and nivolumab, the patient died 7 months after surgery. Immunohistochemical staining of primary and metastatic tumor specimens was CD8 and programmed death ligand-1 negative.
Conclusion: Although vaginal metastasis of renal cell carcinoma is rare, lack of CD8 and programmed death ligand-1 expression may cause nivolumab resistance and may be useful markers in patients with metastatic renal cell carcinoma.

Key words: CD8, PD-L1, immune checkpoint inhibitor, renal cell carcinoma, vaginal metastasis.

Keynote message

Vaginal metastasis of RCC is rare. There are no previous reports of the use of an ICI. The lack of CD8 and PD-L1 expressions in the tumor tissue was associated with resistance to ICI therapy.

Introduction

RCC often metastasizes to the lungs and bones but rarely to the vagina. A previous review of 85 cases of RCC with vaginal metastasis reported a median overall survival of patients with synchronous or metachronous metastasis of 19 months.[1] Previous reports describe treatment of RCC with vaginal metastasis with surgery and radiotherapy. However, there are no previous case reports of RCC with vaginal metastasis in a patient who received MTT and/or ICIs. In this patient, local and distant recurrence following surgery was resistant to ICIs and progressed rapidly.

Case presentation

A 68-year-old woman presented with left flank pain and genital bleeding. Contrast-enhanced CT revealed a 70 mm long left renal tumor and a 30 mm long mass in the vagina. PET-CT revealed accumulation by the vaginal mass (Fig. 1). A biopsy of the vaginal tumor revealed a clear cell carcinoma. The diagnosis was left RCC with vaginal metastasis (cT3aN0M1). Prognostic factors showed intermediate risk according to the International Metastatic Renal Cell Carcinoma Database Consortium risk model. We performed simultaneous radical nephrectomy, abdominal hysterectomy, and transperineal vaginectomy. The metastatic tumor was found in the anterior wall of vagina. Pathological evaluation following radical nephrectomy and simultaneous total vaginal hysterectomy found yellowish tumors in the kidney and vagina (Fig. 2). Histological findings showed clear cell carcinomas of the vagina and kidney with

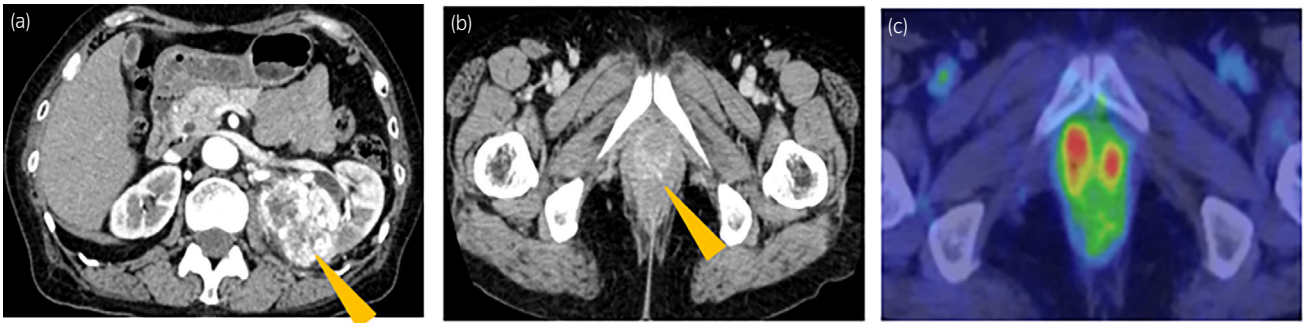

Fig. 1 The initial diagnosis on admission included (a) a contrast-enhanced abdominal CT showing a left renal tumor, (b) a contrast-enhanced pelvic CT showing a vaginal tumor, and (c) a PET-CT with accumulation at the vagina.

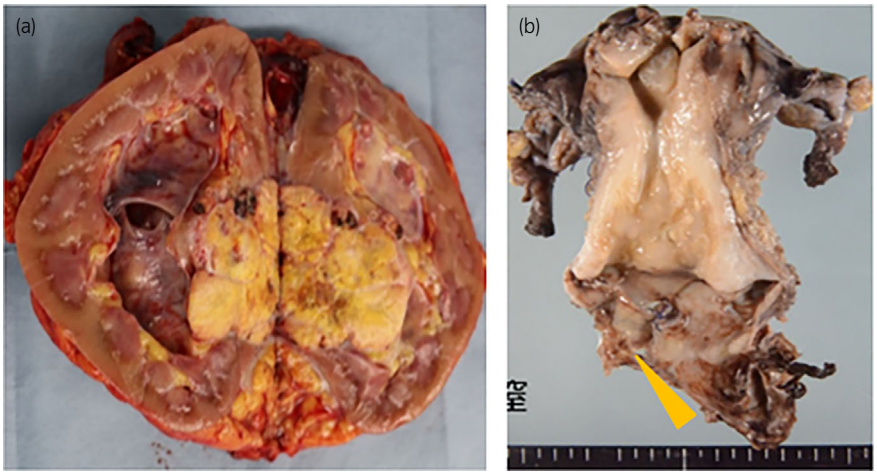

Fig. 2 Surgical specimen. (a) Gross specimen of the kidney showing a renal tumor in the middle pole with infiltration to the renal sinus fat. (b) Gross specimen of the vagina showing neoplastic cells with clear cytoplasm and arranged in sheets and nests. The arrow indicates the metastatic tumor in the anterior wall of the vagina.

necrosis, bleeding, and renal vein invasion (pathologic stage T3aN0M1) with Fuhrman grade 2 nuclei (Fig. 3). The perioperative course was uneventful. At three postoperative months, CT revealed multiple lung metastasis and vaginal recurrence. Sunitinib (37.5 mg/day) first-line therapy was initiated, but it was discontinued 14 days after administration because of severe fatigue, nausea, and vomiting. After 57 days of sunitinib discontinuation, CT revealed that multiple lung metastases and vaginal recurrence increased in size. Nivolumab was initiated as second-line therapy, but rapid growth of the lung metastases continued and a new liver metastasis appeared after two courses of treatment. The patient died 7 months after surgery because of disseminated disease. We performed IHC staining of the immune biomarkers PD-L1 (Abcam ab20592, Tokyo, Japan; 1:500) and CD8 (Dako IS623, Tokyo, Japan; prediluted) from the primary and cervix tumor tissue before MTT and autopsy tissue from cervix after ICI therapy. The percentage of positive staining was >1%. The PD-L1 positive cells primarily comprised infiltrating immune cells. IHC results of samples before MTT showed weak expression of PD-L1 in tumor cells, and CD8-positive T cells were absent in both primary tumor and

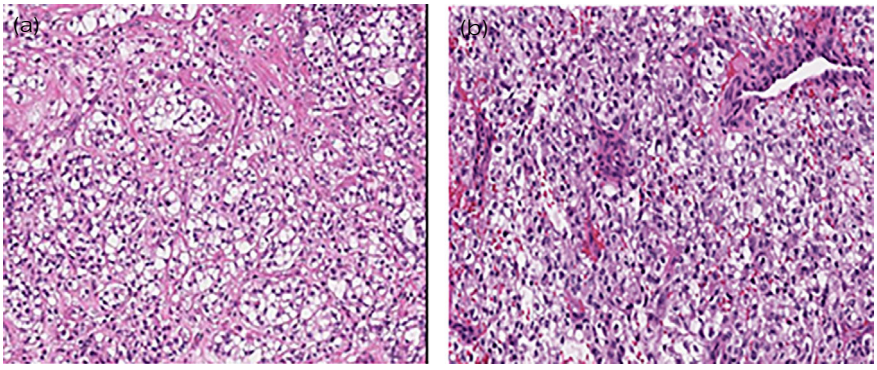

Fig. 3 Histopathological examination with hematoxylin and eosin staining. (a) Fuhrman grade 2 components in clear cell carcinoma of the kidney. Tumor thrombus develops in the renal vein. (b) Fuhrman grade 2 components in clear cell carcinoma of the vagina similar to the kidney.

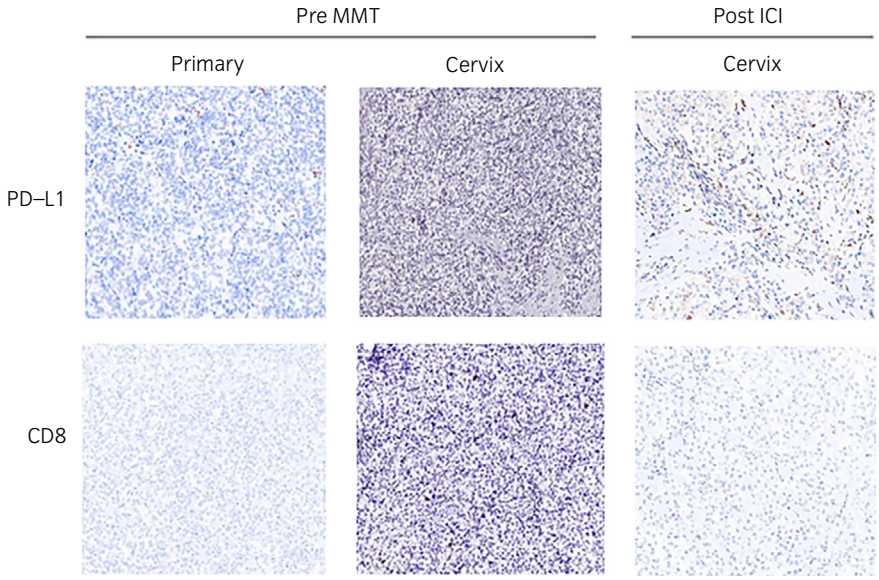

Fig. 4 IHC staining of primary and metastatic lesions shows weak expression of PD-L1 and absence of CD8 expression in the tumor specimen before the treatment with sunitinib and nivolumab.

metastatic tissue. These findings of IHC were also observed in the tissue with vaginal recurrence after ICI therapy (Fig. 4).

Discussion

Vaginal metastasis from RCC is rare. A review of 85 cases reported a median age at diagnosis of 57 (range 14–88) years, with vaginal leaking, hemorrhage, or mass effect seen on presentation in 65% of the patients. The vaginal lesions ranged from 0.5 to 8 cm and vaginal metastasis usually preceded and rarely appeared after the diagnosis of RCC. In 63% of the cases, the primary tumor was in the left kidney, usually with a solitary vaginal metastasis on the same side as primary tumor and usually located in the lower third of the anterior wall.[1,2] The most important prognostic factor in patients with vaginal metastasis is the presence or absence of other secondary tumors. Metachronous metastasis is associated with longer survival than synchronous metastasis, but overall median survival of all types combined is reported as 19 (range 1–96) months.[2–4] Vaginal metastasis of RCC could occur by urinary, lymphatic, or systemic dissemination, but the only route that has been demonstrated is retrograde venous spread. This case showed renal vein thrombosis and enlarged gonadal vein. Mulcahy and Furlow demonstrated retrograde flow of contrast medium from the renal vein to the genital vein at several patients with RCC and vaginal metastasis.[5] Because of this, we assumed that disseminated tumor cells might spread from the kidney to vagina through the gonadal vein.

Te expression in histiocytes related to tumor immunity was very weak. Abundant CD8-positive T cells in tumor tissue has been associated with decreased survival of RCC patients.[6,7] However, George *et al*. reported that increased abundance of CD8-positive T cells in tumor tissue was associated with increased disease-free survival of patients with sunitinib adjuvant therapy.[8] MTT increased the infiltration of CD4-positive and CD8-positive T lymphocytes. However, immune cell reactions were evident as tumor grade/biological malignancy progressed, possibly because of the increased antigenicity of the tumor cells. Therefore, MTT may both positively and negatively regulate the tumor immune microenvironment. Thus, the discrepancy between the short and long survival time among patients with abundant CD8-positive cells in the tumor may have been previously reported. The exposure of neoantigens in tumor tissue following vascular endothelial growth factor and vascular endothelial growth factor receptor inhibition and tumor hypoxia might promote recognition by CD8-positive T cells. The number of CD8-positive T cells in biopsy specimens may predict nivolumab treatment response in metastatic RCC.[9,10]

Choueiri *et al*. reported that increased PD-L1 expression in tumor cells and increased number of CD8-positive T cells in the tumor were associated with decreased survival in patients receiving first-line endothelial growth factor receptor-targeting agents (i.e. pazopanib or sunitinib).[11] The degree of PD-L1 expression has not been shown to be useful as a biomarker of nivolumab response in RCC.[12] However, there were two reasons for the rapid progression of recurrent disease in this patient. First, effects of vascular endothelial growth factor receptor tyrosine kinase inhibitor might be attributed to the insufficient dose and duration of sunitinib because the patient had poor intolerance to sunitinib. Second, our findings of no CD8-positive T cells before and after systemic therapy suggested that the tumor immune microenvironment in this case is "immune desert."[13] Low PD-L1 expression in tumor cells and the absence of CD8-positive T cells infiltration in the tumor may prove useful as pretreatment indicators of the response to ICI treatment of metastatic RCC. A limitation of this case report is that statistical validation was not performed. Therefore, the association between CD8/PD-L1 staining and treatment resistance was speculation alone.

Conclusion

This is a rare case of vaginal metastasis with RCC. Immunohistochemistry using CD8 and PD-L1 in primary and

metastatic site might predict responsiveness to ICI treatment of metastatic RCC.

Acknowledgment

The authors would like to thank Enago (www.enago.jp) for the English language review.

Conflict of interest

The authors declare no conflict of interest.

References

1 Mendese GW, Ayvazian PJ, Li C. Renal cell carcinoma presenting as a perineal mass: case report and review of the literature. *Urology* 2006; **67**: 847.e1–2.
2 Benbrahim Z, Chouaib A, Mazeron R *et al*. Gynecologic bleeding revealing vaginal metastasis of renal cell carcinoma. *Pan. Afr. Med. J.* 2013; **14**: 62.
3 Saussine C, Delepaul B, Jacqmin D. Métastase vaginale du cancer du rein. *Prog. Urol.* 1994; **4**: 95–7.
4 Tarraza HM Jr, Meltzer SE, DeCain M, Jones MA. Vaginal metastases from renal cell carcinoma: report of four cases and review of the literature. *Eur. J. Gynaecol. Oncol.* 1998; **19**: 14–8.
5 Martínez JR, Ruiz RM, Carrión PL *et al*. Vaginal metastasis of a clear renal cell carcinoma. *Arch. Esp. Urol.* 2011; **64**: 380–3.
6 Liu XD, Hoang A, Zhou L *et al*. Resistance to antiangiogenic therapy is associated with an immunosuppressive tumor microenvironment in metastatic renal cell carcinoma. *Cancer Immunol. Res.* 2015; **3**: 1017–29.
7 Nakano O, Sato M, Naito Y *et al*. Proliferative activity of intratumoral CD8 (+) T-lymphocytes as a prognostic factor in human renal cell carcinoma: clinicopathologic demonstration of antitumor immunity. *Cancer Res.* 2001; **61**: 5132–6.
8 George DJ, Martini JF, Staehler M *et al*. Immune biomarkers predictive for disease-free survival with adjuvant sunitinib in high-risk locoregional renal cell carcinoma: from randomized phase III S-TRAC study. *Clin. Cancer Res.* 2018; **24**: 1554–61.
9 Shirotake S, Kaneko G, Nagata K, Oyama M, Nishimoto K. Histological complete response with nivolumab for renal cell carcinoma with multiple metastases: a case report. *Mol. Clin. Oncol.* 2019; **10**: 244–8.
10 Ikarashi D, Kato Y, Katagiri H *et al*. Case of complete response to neoadjuvant therapy using nivolumab in a patient with metastatic renal cell carcinoma. *Int. J. Urol.* 2018; **25**: 630–2.
11 Choueiri TK, Figueroa DJ, Fay AP *et al*. Correlation of PD-L1 tumor expression and treatment outcomes in patients with renal cell carcinoma receiving sunitinib or pazopanib: results from COMPARZ, a randomized controlled trial. *Clin. Cancer Res.* 2015; **21**: 1071–7.
12 Motzer RJ, Escudier B, McDermott DF *et al*. Nivolumab versus everolimus in advanced renal-cell-carcinoma. *N. Engl. J. Med.* 2015; **373**: 1803–13.
13 Galluzzi L, Chan TA, Kroemer G *et al*. The hallmarks of successful anticancer immunotherapy. *Sci. Transl. Med.* 2018; **10**: eaat7807.