Case Report

A case of marked rectal stenosis due to Douglas' pouch metastasis of renal pelvic carcinoma successfully treated with salvage enfortumab vedotin: correlation between serum KL-6 levels and tumor response

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Abbreviations & Acronyms
EV = enfortumab vedotin
KL-6 = Krebs von den Lungen-6
LDH = lactate dehydrogenase
MUC1 = polymorphic epithelial mucin
UC = urothelial carcinoma

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How to cite this article:
Akatsuka J, Kimura G, Katsu A *et al*. A case of marked rectal stenosis due to Douglas' pouch metastasis of renal pelvic carcinoma successfully treated with salvage enfortumab vedotin: correlation between serum KL-6 levels and tumor response. *IJU Case Rep*. 2023; 6: 449–453.

Received 23 June 2023; accepted 13 September 2023. Online publication 26 September 2023

Introduction: We report a rare case of marked rectal stenosis due to Douglas' pouch metastasis of renal pelvic urothelial carcinoma successfully treated with enfortumab vedotin.

Case presentation: A 77-year-old female presented with difficulty in defecation and abdominal distension. She had received two courses of cisplatin plus gemcitabine followed by four courses of maintenance avelumab for postoperative lymph node metastasis of renal pelvic urothelial carcinoma. KL-6 levels were elevated, and a computed tomography scan revealed an irregularly shaped large mass occupying Douglas' pouch, with marked rectal stenosis. Metastatic urothelial carcinoma was pathologically diagnosed, and enfortumab vedotin was initiated after colostomy. After 12 courses of enfortumab vedotin, metastatic lesions showed marked shrinkage and KL-6 levels decreased.

Conclusion: Enfortumab vedotin elicited a remarkable response in treating rectal stenosis due to metastasis of renal pelvic urothelial carcinoma in Douglas' pouch. Furthermore, serum KL-6 levels were correlated with the severity of metastatic urothelial carcinoma.

Key words: biomarker, KL-6, rectal stenosis, renal pelvic urothelial carcinoma.

Keynote message

We report a rare case with marked rectal stenosis due to postoperative metastasis of renal pelvic urothelial carcinoma. Furthermore, the serum KL-6 levels correlated well with the response following treatment with enfortumab vedotin.

Introduction

Upper tract UC is a relatively rare genitourinary malignancy, and <10% of patients progress to metastatic disease.[1] To the best of our knowledge, upper tract UC metastasis to Douglas' pouch, resulting in rectal constriction has not been reported.

EV is a nectin-4-directed antibody conjugated to monomethyl auristatin E.[2] EV is significantly more effective than standard chemotherapy, with an acceptable safety profile in patients with metastatic UC previously treated with platinum-based chemotherapy and immune checkpoint inhibitors.[3]

Biomarkers are measurable indicators of disease status or prognosis in clinical practice, and KL-6 level has been clinically applied as a biomarker for interstitial lung diseases and also some malignancies, such as lung, breast, and pancreatic cancer.[4,5] However, its clinical significance remains unclear in genitourinary cancer.

Here we report an extremely rare case of Douglas' pouch metastasis of renal pelvic UC that led to marked rectal stenosis, which was successfully treated with EV. Based on the clinical and pathological findings, KL-6 could be a useful biomarker for mUC.

Case presentation

A 77-year-old female presented to our emergency outpatient department with difficulty defecating and abdominal distension. The patient had undergone a right radical nephroureterectomy with a trans-retroperitoneal approach for right renal pelvic UC 3 years prior. The pathological findings were UC grade 3, LVI1, RM0, and pT3N0M0. Two years later, she had left supraclavicular and para-aortic lymph node metastases and received two courses of gemcitabine/cisplatin combination chemotherapy, followed by four courses of avelumab; this was performed according to our team's UC therapeutic protocol.

A computed tomography scan showed an irregularly shaped large mass centered on the uterus and rectal uterine fossa, with marked rectal stenosis and left supraclavicular (41 mm) and para-aortic lymph node metastases (19 mm) (Fig. 1a–c). Blood examination showed only mild inflammatory findings, with a white blood cell count of 9200/μL and serum C-reactive protein 0.24 mg/dL. The serum KL-6 level was extremely high at 12 893 U/mL (normal range: <500 U/mL). We consulted with the respiratory team to determine whether interstitial lung disease, potentially caused by avelumab, could explain the elevated KL-6 level. The patient did not exhibit any other indications of interstitial lung disease, including symptoms or abnormalities on chest computed tomography with 5 mm slice thickness, or abnormal biomarker levels (surfactant protein D was at 56.8 ng/mL [normal range: < 109.9 ng/mL]). Notably, the KL-6 level was markedly elevated at 2682 U/mL even prior to avelumab administration. Therefore, we ruled out drug-induced pneumonia as the cause of the patient's condition.

Following a suspicion of marked rectal stenosis due to Douglas' pouch metastasis, the patient was urgently hospitalized. Laparoscopic colostomy and biopsy of the pouch mass were performed for symptom relief and diagnosis. The pathological diagnosis was UC; immunohistochemical staining was positive for cytokeratin 19, carbohydrate antigen 19-9, and GATA binding protein 3 and negative for estrogen receptor, cytokeratin 20, and CDX2, consistent with the findings of the primary tumor (Figs 2a–d and 3a–c). In addition, immunohistochemistry was positive for MUC1, of which KL-6 is one of the surface antigens, and the same results were obtained in the nephroureterectomy specimen (Figs 2e,3d).

We chose EV therapy for metastatic lesions. Radiological findings showed a reduction in lymph node metastasis (partial response: 76%) and Douglas' pouch metastasis (near-complete response) after 12 courses of EV therapy (Fig. 1d). We also observed a marked decrease in serum KL-6 levels (Fig. 4), correlating with disease severity. The patient is currently on EV, and her disease is well-controlled with tolerability.

Discussion

Our patient developed obstructive ileus due to marked rectal stenosis caused by metastatic renal pelvic UC. EV administration after colostomy elicited a satisfactory response, and changes in serum KL-6 levels were well correlated with the clinical course.

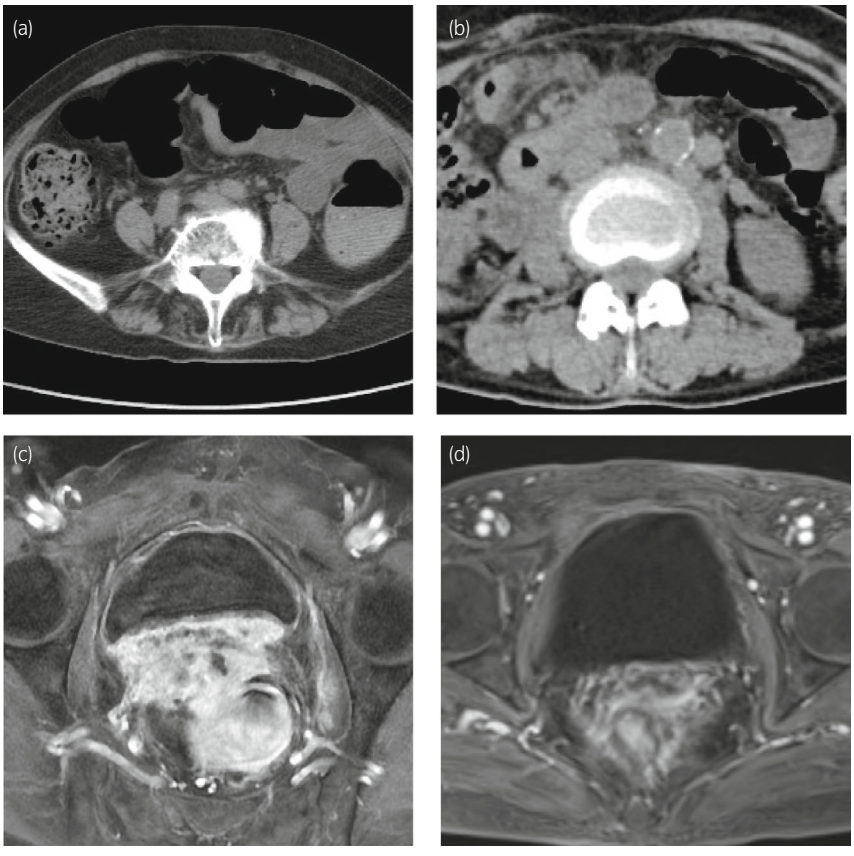

Fig. 1 Radiological imaging. (a,b) Computed tomography scans; (c,d) Magnetic resonance imaging. (a) Accumulation of intestinal gas due to obstructive ileus before EV therapy. (b) Para-aortic lymph node swelling before EV therapy. (c) An irregularly shaped mass centered on the uterus and rectal uterine pouch before EV therapy. (d) Reduction of metastatic lesion centered on the rectal uterine pouch after EV therapy.

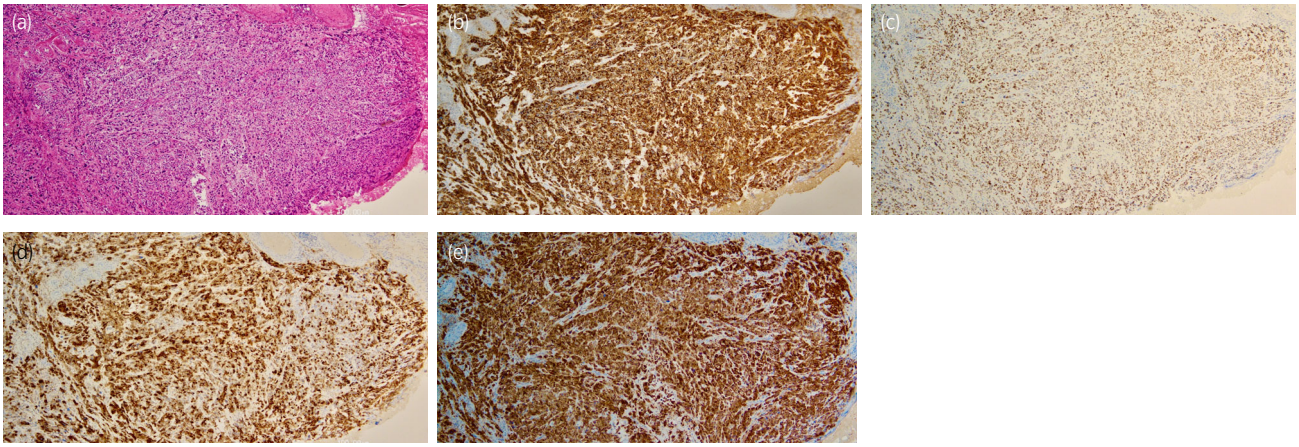

Fig. 2 Hematoxylin and eosin (HE) and immunohistochemical staining of Douglas' pouch metastasis. (a) HE staining (×40), (b) cytokeratin 19 (×20), (c) GATA binding protein 3 (×40), (d) carbohydrate antigen 19-9 (×20), (e) MUC1 (×40).

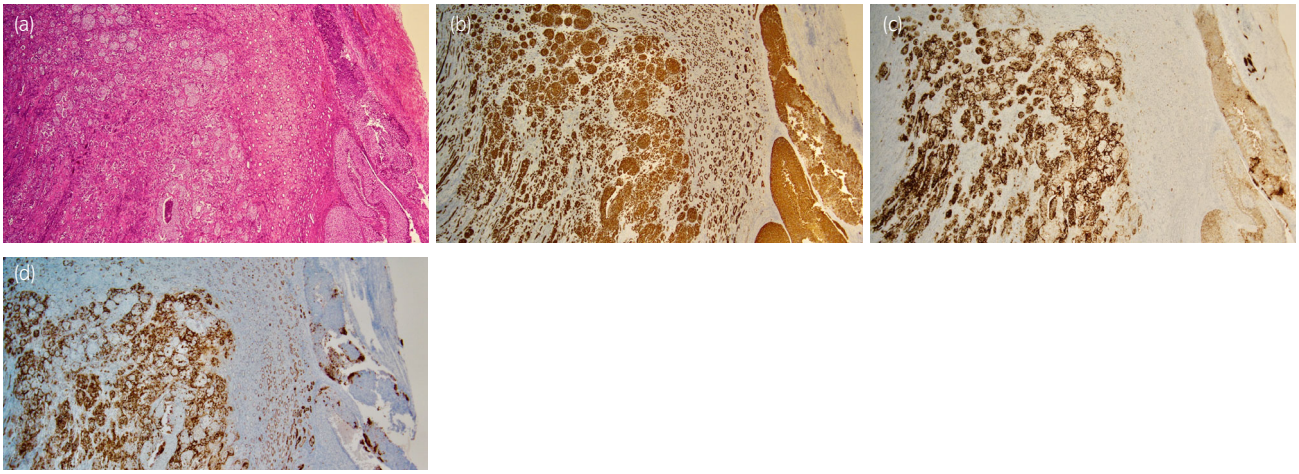

Fig. 3 Hematoxylin and eosin (HE) and immunohistochemical staining of the renal pelvic tumor. (a) HE staining (×20), (b) cytokeratin 19 (×20), (c) carbohydrate antigen 19-9 (×20), (d) MUC1 (×20).

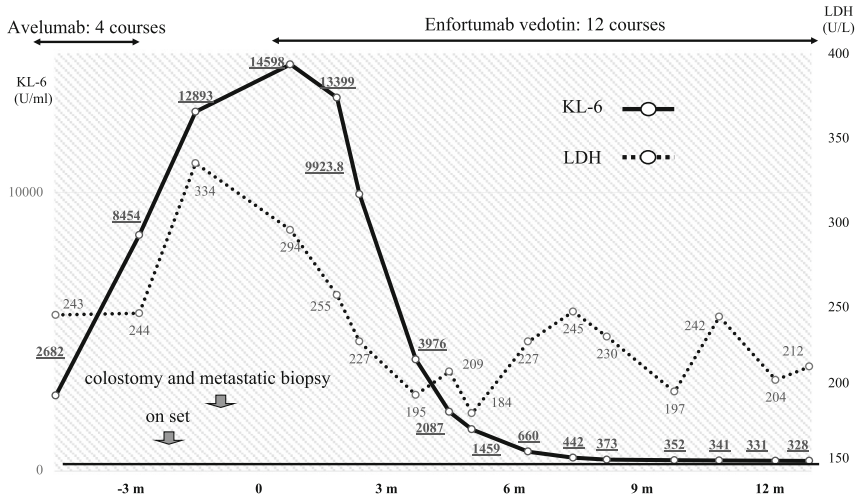

Fig. 4 Clinical course and sequential changes in KL-6 and LDH.

Upper tract UC is a relatively rare malignancy; <10% of patients progress to metastatic disease. The most common sites are the lungs, liver, and bone.[6] To the best of our knowledge, this is the first report of a case of upper tract UC metastasizing to the pouch of Douglas, resulting in rectal constriction. The exact stage of progression remains unclear

owing to the rarity of such cases. In this case, the metastatic lesion occupied the pouch of Douglas, extending from the retroperitoneal region into the intraperitoneal cavity. Laparoscopic radical nephroureterectomy using a retroperitoneal approach could be performed without significant urinary leakage, peritoneal injury, or positive surgical margins. Therefore, we hypothesized that the pathogenesis in this case was likely due to minor urinary dissemination or hematogenous metastasis.

In the field of bladder cancer, only a few cases have reported metastasis to the perirectal tissues causing rectal constriction.[7,8] The common features are male sex, high pathological grade, and poor prognosis.[8] A Japanese report showed the efficacy of multidisciplinary treatment combining surgery and systemic chemotherapy for lesions that clinically metastasize to only the perirectal tissue.[8] Our patient developed rectal stenosis due to Douglas' pouch metastasis of renal pelvic carcinoma during avelumab maintenance therapy. Subsequently, colostomy management for rectal stenosis enabled EV therapy, resulting in beneficial outcomes.

KL-6 is a sialylated carbohydrate antigen of MUC1, produced from bronchial gland cells, bronchiolar epithelial cells, and type 2 alveolar epithelial cells.[4] KL-6 has been clinically applied as a biomarker in interstitial lung diseases.[4,9] In UC cases, MUC1 expression is higher than that in the normal non-neoplastic urothelium, and it is reported to be higher in the metastatic stage.[10] However, its clinical significance remains unclear. In the present case, immunohistochemical staining analysis showed MUC1 expression in both primary and metastatic specimens (Figs 2d,3e). Additionally, serum KL-6 levels correlated well with the patient's disease status during EV treatment, suggesting that it could be a biomarker for metastatic UC. Future research is needed to focus on examining the detailed correlation between MUC1 expression and KL-6 levels in UC and to assess its therapeutic implications.

A Phase III study has shown that EV is significantly more effective than chemotherapy with an acceptable safety profile in patients with metastatic UC previously treated with platinum-based chemotherapy and immune checkpoint inhibitors.[3] Based on these findings, EV was approved by Japanese health insurance in 2021. Due to the limited data in Japan, there is a need for real-world clinical practice data on EV therapy for mUC. In the present case, after colostomy for marked rectal stenosis caused by metastasis, EV was administered as salvage therapy for disease progression. Twelve courses of EV produced remarkable responses to metastatic lesions.

In conclusion, we encountered an extremely rare case of marked rectal stenosis caused by metastatic renal pelvic UC that was successfully treated with EV. Serum KL-6 levels correlated well with the clinical course, suggesting that it could be a biomarker for metastatic UC. However, further studies are warranted.

Acknowledgments

We thank Editage (www.editage.com) for the English language editing.

Author contributions

Jun Akatsuka: Conceptualization; methodology; project administration; writing – original draft; writing – review and editing. Go Kimura: Conceptualization; methodology; supervision; writing – review and editing. Akifumi Katsu: Data curation; writing – original draft. Hiroya Hasegawa: Data curation. Hikaru Mikami: Data curation. Masato Yanagi: Data curation. Yuki Endo: Data curation. Hayato Takeda: Data curation. Yuka Toyama: Data curation. Yukihiro Kondo: Supervision; writing – original draft; writing – review and editing.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

The protocol for this research project has been approved by a suitably constituted Ethics committee of Nippon Medical School Hospital and it conforms to the provisions of the Declaration of Helsinki. Ethics committee of Nippon Medical School Hospital, (#30-03-1100). Informed consent was obtained from the subject.

Informed consent

Written informed consent was obtained from the patient to publish this case report and accompanying images.

Registry and the Registration No. of the study/trial

Not applicable.

Data availability statement

The datasets analyzed in the current study are available from the corresponding author upon reasonable request.

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