Letter to the Editor

A case of bladder urothelial carcinoma nested variant with invasion to the rectum treated with surgery and intraoperative radiotherapy

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Introduction

The most common histological type of urologic cancer is urothelial carcinoma (UC). Advanced UC can invade the surrounding organs or metastasize to distant organs such as the lungs, bone, and liver. The nested variant of urothelial carcinoma (NVUC) is a variant of UC that was added to the World Health Organization (WHO) classification in 2004 (1). NVUC is characterized by a bland histological appearance that has an aggressive behavior with a potential for deep invasion and metastases. The atypia of its surface-coated urothelial epithelial cells is not obvious whereas that of its intratumoral cells is obvious. Therefore, NVUC is often misdiagnosed as a benign lesion and its diagnosis is delayed when the tumors are collected in superficial biopsy specimens, contributing to stage migration and the resultant poor prognosis. The rectal metastases of bladder NVUC are extremely rare and easily missed or delayed in diagnosis. Herein, we present the case of a 64-year-old man diagnosed with rectal metastases of bladder NVUC who presented with rectal symptoms as the initial symptom. He underwent total pelvic exenteration (TPE) and intraoperative radiotherapy (IORT) as treatment.

Case presentation

A 64-year-old male patient was admitted to the hospital with a 2-month history of increased frequency of defecation (7–8 times per day) and decreased stool volume without an identifiable trigger. The digital rectal examination findings indicated the rigor of the rectal wall and stenosis of the rectal canal, with no palpable masses detected.

Colonoscopy released local hyperemia and edema of the rectal mucosa combined with a loss of vascular pattern and mucosal bleeding at 10 cm from the anus. The rectal canal was stenosed due to lesions. During the examination, four biopsy specimens were obtained for diagnostic purposes. While awaiting the biopsy results, we performed rectal magnetic resonance imaging (MRI) (*Figure 1A-1D*) which indicated that the rectal and bladder walls were thickened. The rectal biopsy findings revealed chronic hyperplasia of the rectal mucosa and glandular. The muscularis propria showed that the pigment granules were phagocytosed by the histiocytic cells.

A comprehensive examination of the bladder was performed next. Computed tomography urography (CTU) demonstrated irregular thickening of the urinary bladder

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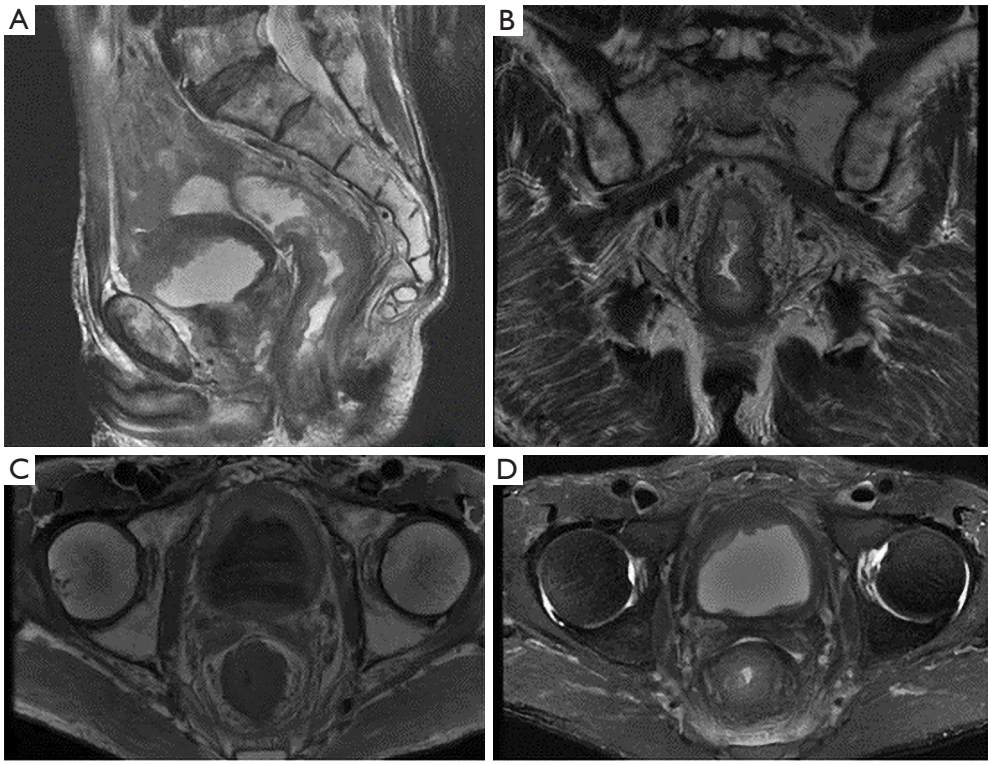

Figure 1 Rectal MRI indicated that the rectal wall and bladder wall were thickened. (A) Preoperative sagittal MRI, T2WI; (B) coronal MRI, T2WI; (C) transverse MRI, T1WI; (D) transverse MRI, T2WI-FS. MRI, magnetic resonance imaging; T2WI-FS, T2-weighted imaging fat suppression.

wall and protrusion inside the bladder lumen, particularly on the anterior wall of the bladder (*Figure 2A*,*2B*). Cystoscopy and biopsy findings revealed that the neoplastic cells were arranged in nests or single file, with inconspicuous mitotic figures and little atypia. Immunohistochemical staining showed the urothelial markers. The samples were positive for Ki67 (positive rate was 5%), P53 (focal positive), CK (AE1/AE3), GATA3, CK7, and p63. The features were comparable to those of UC; however, the Ki67 expression was found to be low.

The patient also underwent positron emission tomography-computed tomography (PET-CT), which revealed thickening of the dome and focal anterior wall of the bladder, accompanied by slightly increased glucose metabolism. The possibility of a malignant tumor was considered. The diffuse rectal walls were thickened with slightly increased glucose metabolism. Thus, the possibility of a benign lesion was considered.

A multidisciplinary team meeting was held to discuss the patient's case, ultimately resulting in a diagnosis of UC but not typical UC. Accordingly, we decided to perform a second cystoscopy to confirm the diagnosis of UC. The cause of the rectal symptoms of the patient was not clear. The findings from the examinations were inconclusive in establishing a correlation between the bladder lesions and rectal lesions, necessitating further diagnosis of the rectal lesion. Although multiple-site rectal biopsies were taken for the diagnosis through colonoscopy, the pathological specimens did not include the submucosa and muscularis propria, rendering it uncertain whether they were invaded. Obtaining a deep biopsy that includes the muscularis propria is important for a definitive diagnosis. Additional examination of the rectal pathology was deemed necessary.

The patient underwent a second cystoscopy confirming the pathology as diffuse and invasive bladder UC (*Figure 3A-3C*). Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) of the thickened rectal wall was then performed, successfully diagnosing rectal metastasis of UC.

The patient's case was discussed at the second multidisciplinary team meeting. The patient's tumors were limited to the pelvic cavity, and he gradually showed symptoms of incomplete intestinal obstruction, including

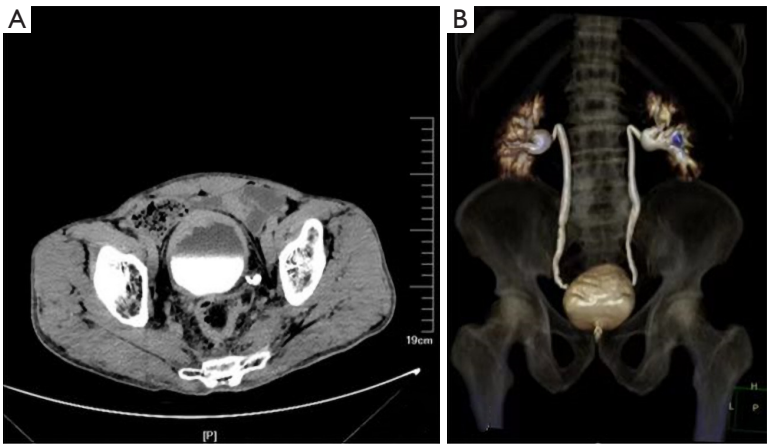

Figure 2 Imaging examination of the patient. (A) Computed tomography urography demonstrated irregular thickening of the urinary bladder wall and protrusion inside the bladder lumen, especially on the anterior wall of the bladder; (B) 3D reconstruction of the CT shows the lesion on the anterior wall of the bladder. CT, computed tomography.

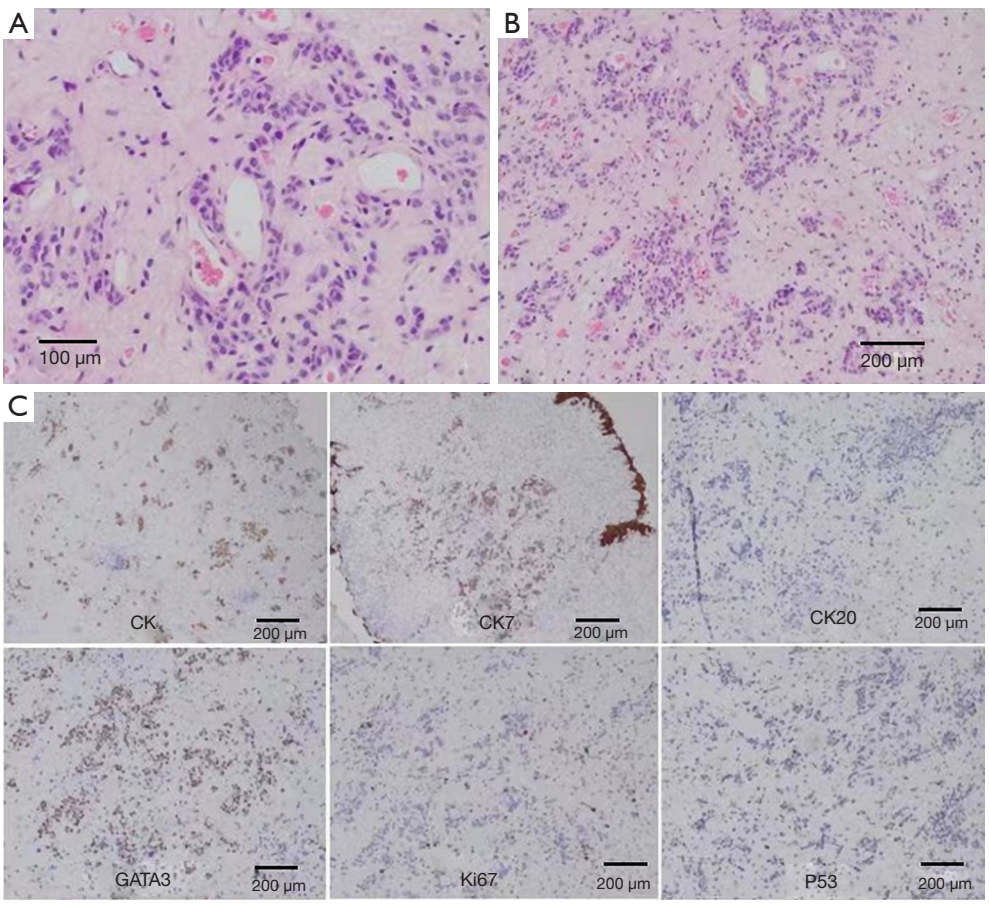

Figure 3 The pathology of the tumor showed bladder urothelial carcinoma. (A) Microscopic examination of urothelial carcinoma (HE, ×200); (B) microscopic examination of the urothelial carcinoma (HE, ×100); (C) immunohistopathological analysis of the puncture biopsy of the lesions. The samples were positive for Ki67 (positive rate was 5%), P53 (focal positive), CK (AE1/AE3), GATA3, and CK7. These features were consistent with diffuse and invasive urothelial carcinoma. HE, hematoxylin and eosin.

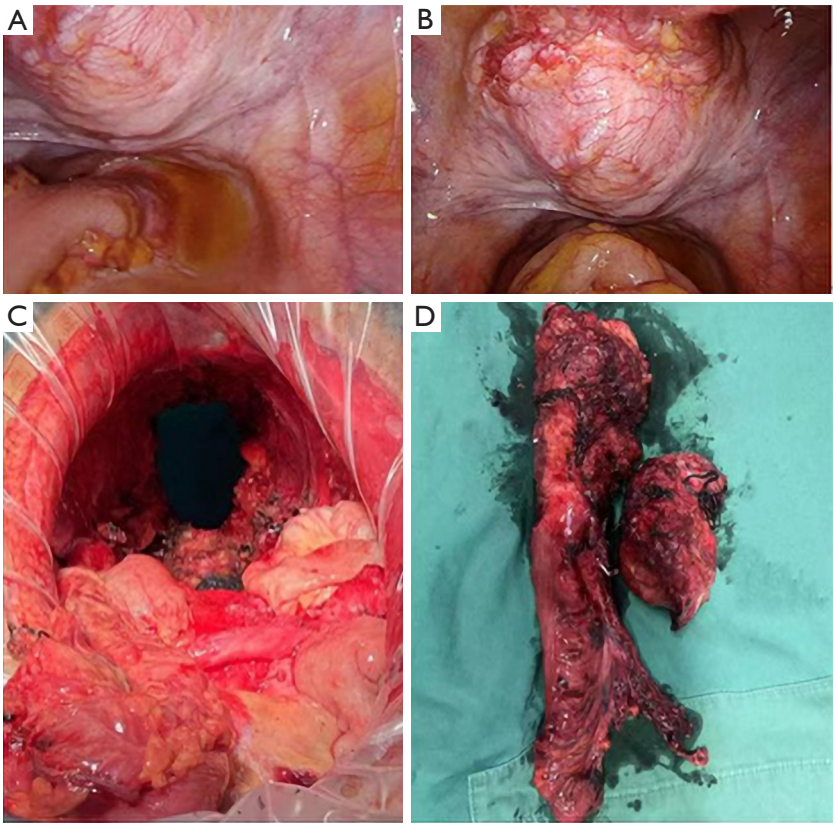

Figure 4 Intraoperative and specimen images. (A) The nested variant of bladder urothelial carcinoma metastasized to the rectum; (B) the picture showed the malignancy of the bladder; (C) the panel represented pelvic after total pelvic exenteration; (D) the surgical specimen, right bladder, left rectum.

abdominal distention, abdominal pain, and defecation difficulties during the examination. Therefore, surgery was required to relieve the obstruction as soon as possible. We considered resecting the bladder and surrounding organs where the tumors had invaded and performed TPE with IORT. Before the surgery, a thorough intraoperative surgical consultation was required. After obtaining the consent of the patient and his family, we decided to perform TPE combined with IORT.

The urology, colorectal Surgery and radiotherapy department performed the surgery including TPE, radical cystectomy, bilateral cutaneous ureterostomy, abdominoperineal resection for rectal carcinoma (Miles' resection), sigmoid colostomy, pelvic floor reconstruction, and IORT (*Figure 4A-4D*). During the surgery, the tumor was removed as much as possible. Two IORTs were performed at a dose of 25 Gy. The source applicator was placed at the abdominal incision to irradiate the wounds after rectal resection. Then, we continued to take the radiotherapy to the pelvic cavity via the perineal incision. After IORT, we placed a mesh in the pelvic cavity, sutured the mesh to the pelvic inlet, and reconstructed the pelvic floor. The operation lasted for 9.5 hours.

The bladder's pathological findings were in agreement with those of invasive UC, as evidenced by the infiltration of NVUC into the vasculature, nerves, and adipose tissue surrounding the bladder. Infiltration of carcinoma tissue was observed in the muscle layer of the cut margin of the bilateral ureters. The tumor cells in the rectal wall displayed a nest-like distribution and heteromorphism. Metastasis of UC was observed in the rectal muscularis mucosae, submucosa, surrounding fatty tissue, and external anal sphincter. The mucosal layer of the rectum did not have infiltrations. Metastases were observed in the lymph node along the right external iliac artery (1/1) and perivesical lymph node (1/1). The pTNM stage was pT3b, N2, M1b. The immunohistochemical staining findings were as follows: Ki67 (8%), P53 (30%), CK (AE1/AE3), S100P,

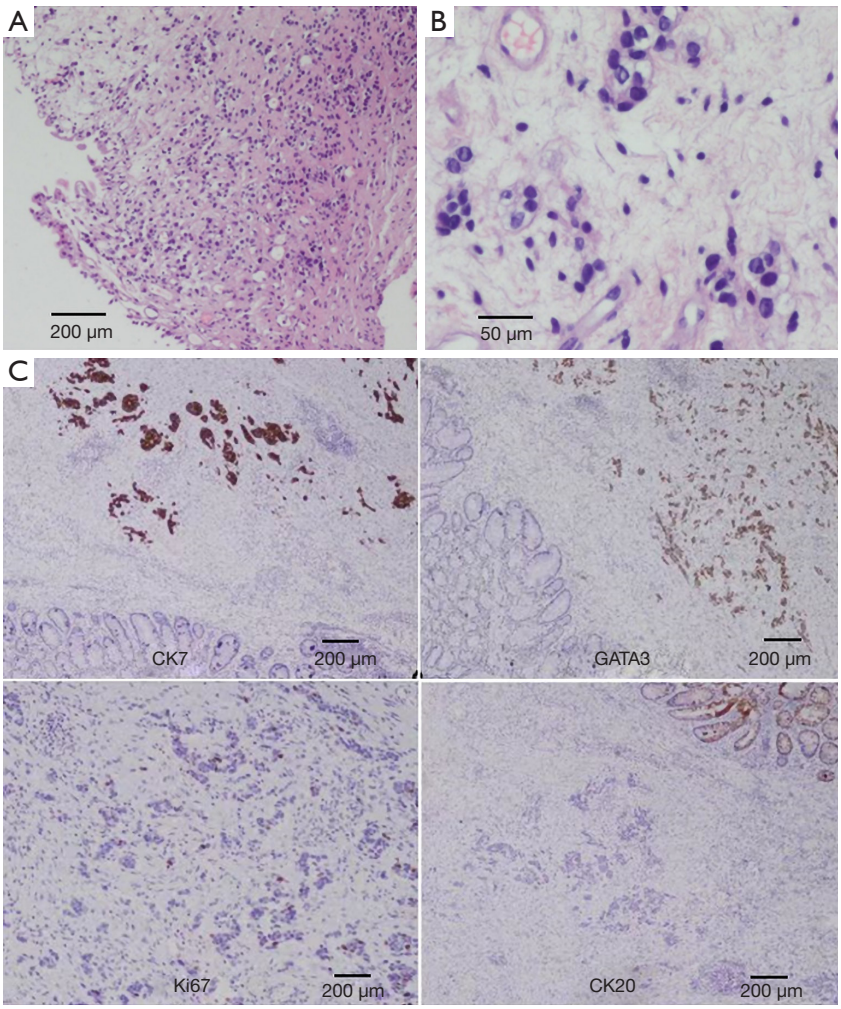

Figure 5 The pathology of the tumor showed the nested variant of urothelial carcinoma. (A) HE staining showed that the resected specimen revealed small nests and abortive tubules (×100); (B) HE staining showed that the nests are comprised of slightly atypical neoplastic cells with a slightly increased N/C ratio, little nuclear pleomorphism, and occasional prominent nucleoli (×400); (C) immunohistochemical staining showed the tumor cells were positive for Ki67 (positive rate was 8%), GATA3, CK7. HE, hematoxylin and eosin; N/C, nuclear/cytoplasmic.

GATA3, CK7, and p63 were positive (*Figure 5A-5C*).

After the surgery, the first cycle of chemotherapy with gemcitabine 1.7 g plus cisplatin 120 mg combined with PD-1 inhibitor—Sintilimab 200 mg was initiated on a postoperative day (POD) 21. Although Sintilimab has not been approved for metastatic UC in China, it has shown reliable efficacy and safety in clinical trials in solid tumors. Sintilimab is the only anti-PD1 antibody covered by national health insurance in China. The patient was aware of these medications' off-label use. With the patient's written consent, we treated the patient with Sintilimab.

The patient was treated with two courses of combination chemotherapy. The patient was thrombocytopenic due to severe myelosuppression from the chemotherapy effect. Therefore, he was treated at a local hospital. Then, the patient was affected by the COVID-19 epidemic and did not go to the hospital for further treatment. We communicated with the patient's family over the phone and learned that the patient did not have new intestinal and urinary symptoms.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as

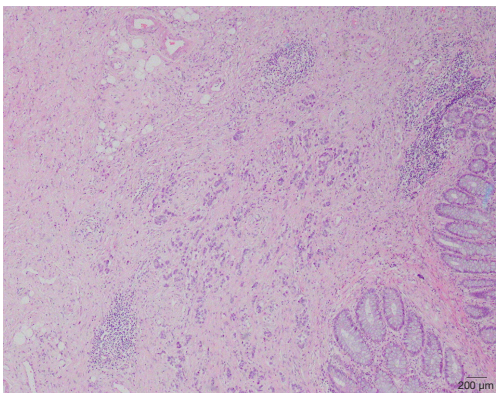

Figure 6 Pathological examination of the patient. HE staining showed that small nests of tumor cells are diffuse in the rectum (×100). HE, hematoxylin and eosin.

revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

UC has several variants, with the most common being squamous differentiation, followed by glandular differentiation, and the rare ones being the NVUC, microcapsule variant, plasmacytoid variant, sarcoma variant, etc. NVUC accounts for 0.3% of all invasive urinary bladder cancers (2).

NVUC is most common in older males (average age: 66 years; range: 48–83 years). The most common clinical presentation of NVUC is hematuria, with other symptoms being increased urinary frequency, dysuria, and nocturia (3). NVUC rarely metastasizes to the rectum, except for advanced or recurrent NVUC cases (4). Herein, we reported the case of a male patient who presented to our hospital with the symptoms of an increase in the frequency of defecation to 7–8 times per day and a decrease in the amount of defecation. The initial manifestation in this patient was rectal symptoms, while urinary symptoms were not evident. The patient did not complain of frequent urination or gross hematuria. Although the patient had dysuria, NVUC was difficult to detect; the symptoms of dysuria are similar to those of prostatic hyperplasia. In patients with UC presenting with gastrointestinal complaints, gastrointestinal metastases should be suspected even in the case of unremarkable imaging findings so that quick treatment for metastases can be offered.

Colonoscopy is a common procedure used in the diagnosis of various bowel disorders. Colonoscopy did not reveal the real disease in our patient as it has limitations in the diagnosis of tumors invading the submucosa and muscularis mucosa. NVUC has distinct patterns in the superficial and deep parts of the rectal wall. The deep lesions of NVUC have a greater degree of cytologic atypia. The tumors often infiltrated the muscularis propria. Therefore, it was easy to be misdiagnosed to distinguish benign lesions from malignant lesions by colonoscopy alone. A deep biopsy involving the muscularis propria is important for a definitive diagnosis. When patients present with digestive system symptoms and have no abnormalities detected by Colonoscopy, it is better to perform EUS-FNA which is an effective diagnostic method in cases wherein the cause of the thickened rectal wall is unknown.

UC most commonly metastasizes to the lungs, liver, and bone through the lymphogenous or hematogenous routes (5). NVUC rarely metastasizes to the rectum. Our patient showed rectal metastasis earlier than metastasis to those organs. For our patient, the most likely route is assumed to be that bladder cancer cells metastasize to the rectal wall using a lymphatic method. UC presents with metastasis to the rectal muscularis mucosae, submucosa, the surrounding fatty tissue, and the external anal sphincter. Tumors were observed in the vasculature and the patient had two lymph node metastases. Pathologic examination revealed the tumors are diffuse in the rectal wall (*Figure 6*).

In other case reports we found bladder cancer can invade the rectal wall through Denonvilliers' fascia. Advanced UC forms an annular constricting lesion and causes rectal obstruction via the Denonvilliers' fascia. Bladder carcinoma may break into the fascia of Denonvillier and could grow to encircle the rectum, leaving the normal bowel mucosa intact. Only normal rectal mucosa or reactive inflammatory tissue may be observed in proctoscopically obtained mucosal biopsy specimens (6). Bladder cancer can invade the rectal wall through four potential routes, including direct invasion into the rectum, invasion through Denonvilliers' fascia, lymphatic metastasis, and hematogenous metastasis.

NVUC should be clinically approached as a high-risk disease, with early cystectomy as an option for pT1 and pT2 tumors (7). Radical cystectomy is the standard treatment for muscle-invasive bladder cancer including NVUC (8). Radical cystectomy includes removing the bladder and surrounding organs where cancer can invade, followed by urinary diversion to control the disease and lymph node

staging. In Sten Holmäng's opinion, aggressive invasive growth and early metastases are factors that favor radical cystectomy combined with systemic chemotherapy (2). For an invasive NVUC with early metastases, we suggest that the invaded organ should be removed in combination with radical cystectomy. Although surgery is often used to remove macroscopic tumors, residual microscopic tumors can cause tumor recurrence or progression. Thus, treatment strategies that prevent or effectively treat NVUC recurrence are required. Single-modality approaches such as surgery, chemotherapy, or radiotherapy are highly unsuccessful in achieving long-term disease control. Surgery is often difficult due to tumor extension to the pelvic sidewall or adjacent organs. To overcome these limitations, we treated our patient with a multimodality approach including maximal surgical resection and IORT.

IORT is increasingly being used in the treatment of patients with cancer, particularly those with breast cancer and rectal cancer. IORT is less commonly used in the treatment of genitourinary cancers; however, it has attracted more attention in the treatment of UC including both operable and inoperable tumors. In conventional treatment, postoperative external beam radiation therapy is more often used. IORT has more benefits than postoperative external beam radiation therapy as it combines with surgery and radiation, avoids the repopulation of the tumor cells between the surgical removal of the tumor and external beam radiation therapy and accurate localization in the tumor bed with the delivery of high-dose radiation to the tumor bed which may decrease the damage of the normal tissues. The normal tissues are displaced away from the tumor bed to protect them from radiation (9).

IORT has been established as a reliable and superior method for the treatment of superficial bladder cancer due to the low recurrence rate and good preservation of vesical functions after treatment (10). Hallemeier *et al.* reported the use of intraoperative electron beam radiotherapy in 17 patients after maximal resection of the tumor (11). IORT allows precise delivery of radiation therapy directly to the tumor bed and is helpful to the accurate irradiation of the tumor lesion combined with postoperative systemic chemotherapy.

Since the late 1980s, cisplatin-containing combination chemotherapy has been the standard treatment for metastatic UC (12). Our patient was eligible for cisplatin chemotherapy and thus received cisplatin-based chemotherapy.

The prognosis of NVUC can be more influenced by the stage of the disease rather than the various histological types of the tumor. When stage matched to patients with pure UC, patients with NVUC did not display an increased rate of recurrence or adverse survival (13). The tumor invasion extent and lymph node status are critical for prognostic factors. Although NVUC has the possibility of rapid deterioration compared with usual UC, there might be no changes in the prognosis of NVUC after radical therapeutic intervention compared with that of usual UC.

In conclusion, we experienced a case of NVUC with symptoms of altered bowel habits due to metastasis to the rectum that presented before the appearance of hematuria, wherein EUS-FNA was useful for achieving a diagnosis. EUS-FNA can be an effective method for investigating unexplained thickening of the rectal wall in cases with negative endoscopic biopsy findings. The combination of TPE and IORT provides supplementary therapeutic options for NVUC metastasizing to the rectum. The combination of maximizing the extent of resection and providing a high radiation dose to the tumor bed offers a great treatment method for improving local tumor control and decreasing tumor burden. However, we studied only one such case, and further studies with a larger sample should be conducted to evaluate the efficacy of this combination.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-67/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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