OPEN

Recurrent Cystitis Associated With 2 Programmed Death 1 Inhibitors

A Rare Case Report and Literature Review

Yong Fan, Juan Zhao,* Yue Mi,† Zhening Zhang,‡ Yan Geng,* Liqun Zhou,† Lin Shen,‡ and Zhuoli Zhang**

Summary: Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of advanced cancer, however, often with immune-related adverse events (irAEs). Adverse events involving the bladder were extremely rare with only few cases. Herein, we described a rare, recurrent cystitis associated with 2 programmed death 1 inhibitors (pembrolizumab and toripalimab) in 1 patient with advanced liver cancer. Cystitis associated with toripalimab, a novel humanized programmed death 1 monoclonal antibody, was first presented in our case. Cystitis is an extremely rare irAE associated with ICIs, especially anti–programmed death 1 antibodies. With widening indications of ICIs in clinical practice, physicians should be also aware of this rare irAE.

Key Words: immune checkpoint inhibitors, cystitis, immune-related adverse events, case report

(*J Immunother* 2023;46:341–345)

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of advanced cancer and currently been part of the frontline management in certain situations and, however, pose challenges due to a subset of immune toxicities, known as immune-related adverse events (irAEs). Theoretically, irAEs may occur in any organ at any time during ICI treatment or even after cessation of ICIs. Nevertheless, involvement of the bladder was extremely rare with few case reports. Herein, we described a rare, recurrent cystitis associated with 2 programmed death 1 (PD-1) inhibitors in 1 patient with advanced liver cancer. We present the following case in accordance with the CARE reporting checklist.

Received for publication October 23, 2022; accepted August 16, 2023.

From the *Department of Rheumatology and Clinical Immunology, Peking University First Hospital, Beijing, China; †Department of Urology, National Urological Cancer Center, Peking University First Hospital, Beijing, China; and ‡Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing, China.

Z.l.Z. participated in the design of the case report, acquired the data, took part in the interpretation of the data, and revised the manuscript. Y.F., J.Z., Y.M., and Z.n.Z. were involved in the literature search, acquired the data, and drafted the manuscript. Y.G., L.q.Z., and L.S. participated in the multidisciplinary discussion of this case report, interpretation of the data, and revised the manuscript. All authors read and approved the final manuscript.

The case report was approved and supervised by the Ethics Committee of the Peking University First Hospital. Informed consent was obtained from the patient's wife for publication of this case report and any accompanying images. The authors really appreciate her selfless dedication.

Reprints: Zhuoli Zhang, Department of Rheumatology and Clinical Immunology, Peking University First Hospital, 8 Xishiku Street, West District, Beijing 100034, China (e-mail: zhuoli.zhang@126.com).

CASE HISTORY

A 58-year-old man was diagnosed with intrahepatic cholangiocarcinoma with multiple intrahepatic and omental metastases at a routine annual check-up in November 2018. Partial hepatectomy was conducted very soon and histopathology confirmed cholangiocarcinoma with programmed death ligand 1 (PD-L1) tumor proportion score > 25%. Chemotherapy (fluorouracil and oxaliplatin) for 2 months in combination with targeted therapies of lenvatinib 12 mg q.d. and pembrolizumab 200 mg per 3 weeks for 18 months was subsequently applied. Unfortunately, multiple intrahepatic, lung, upper abdominal peritoneal, and vertebral bone metastases were detected. The patient received localized radiotherapy at the vertebra combined with continuous targeted therapies (lenvatinib plus olaparib) and immunotherapy (pembrolizumab) for 3 months (Fig. 1). However, positron emission tomography/computed tomography showed significantly increased metastases lesions in September 2020. The immunotherapy was then escalated to the combination of toripalimab and ipilimumab 2 times on September 30, 2020, and October 21, 2020.

About 8 days later, the patient started to suffer from urinary frequency, urinary urgency, urodynia, and gross hematuria. Urine routine tests showed a large amount of red blood cells (RBCs) with 90% isomorphic and white blood cells (WBCs) 100–120/HP. Multiple hypoechoic masses (maximum 2.65×0.66 cm) were found by ultrasound with no pathologic blood flow in the posterior wall of the bladder. Urinary tract infection was considered, and a serial of antibiotics including moxifloxacin, levofloxacin, and fosfomycin was successively administered, however, failed. Contrast-enhanced computed tomography scan showed localized thickening of the bilateral ureteral wall with the diffuse enhancement of bladder mucosal. *Prevotella bivia* was observed in mid-stream urine culture, and amoxicillin-clavulanate was chosen according to the antibiotic susceptibility test. Hematuria was partially improved after antibiotic treatment for 10 days, but irritative lower urinary tract symptoms persisted, and meanwhile, diarrhea and fatigue gradually occurred. Antibiotic treatment was then upgraded to meropenem and piperacillin/tazobactam, but the symptoms remained unimproved. Concurrently administered analgesic and anticholinergic drugs did not help either. Further cystoscopy showed that bladder mucosas were diffuse hyperemia and partially arranged in a trabecular architecture. Pathologies of bladder mucosa demonstrated active and chronic inflammation with granulation formation and visible epithelial shedding in some bladder epithelial cells. No evidence of malignancy or tuberculosis infection was obtained in all the biopsied tissues (Fig. 2). Repeated urine culture tests were also negative.

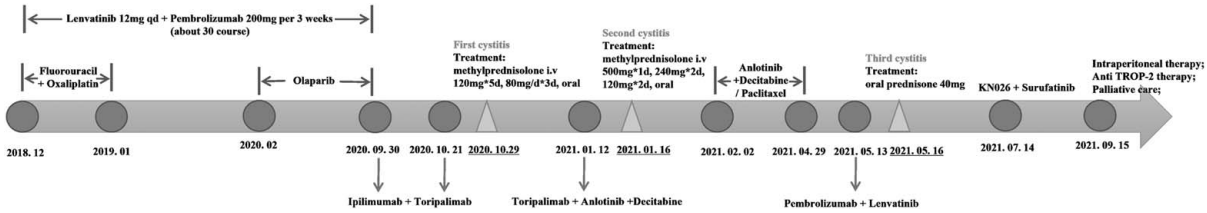

FIGURE 1. The course of antitumor treatment and the occurrence of cystitis. TROP-2 indicates trophoblast cell surface antigen 2.

Then, cystitis associated with ICIs was considered, and methylprednisolone (120 mg/d×5 d, 80 mg/d×3 d) was initiated intravenously on December 9, 2020. Interestingly, irritative symptoms of the lower urinary tract and gross hematuria were quickly improved. On day 5 after steroid therapy, the patient experienced complete resolution of symptoms with RBC 8–10/HP, WBC 1–3/HP on urine routine test. Oral prednisolone 40 mg/d was subsequently followed and tapered. The immunotherapy, both toripalimab and ipilimumab, was discontinued on October 21, 2020.

On January 4, 2021, a repeated ultrasound examination demonstrated a completely normal bladder (multiple masses disappeared). Considering the need for antitumor therapy, immunotherapy (toripalimab 240 mg) was restarted with targeted therapy (anlotinib) and chemotherapy (decitabine), concomitantly with prednisolone 28 mg/d. Notably, significant irritative lower urinary tract symptoms emerged again with a urine routine test showing RBC 100/HP, WBC 2–4/HP 4 days after the initiation of toripalimab. No causative microorganism was identified in the urine culture. Cystitis associated with ICIs was reconsidered, toripalimab was discontinued, and methylprednisolone was re-used (500 mg×1 d, 240 mg×2 d, 120 mg×2 d) followed by oral methylprednisolone 40 mg/d. Symptoms were improved quickly, and the urine routine test was back to normal 10 days later. Methylprednisolone was tapered quickly at 4 mg per 3–5 days. During the following 3 months, he did not suffer from cystitis at all. Anlotinib in combination with decitabine/paclitaxel was used for cancer; he unfortunately developed pneumocystis jiroveci pneumonia and lung aspergillosis infection but was promptly recovered with antimicrobial therapy.

Nevertheless, radiographic imaging remained indicating progression of metastatic carcinoma. After a multidisciplinary consultation on May 13, 2021, he rechallenged pembrolizumab, an anti-PD-1 inhibitor; he had ever used for a long time. Unfortunately, cystitis reoccurred after 3 days with elevated erythrocytes and WBC on a urine routine test. Prednisone 40 mg/d was restarted and fully effective in handling this irAE. Afterward, this patient was treated with concurrent chemotherapy (cisplatin+gemcitabine) and targeted therapy (lenvatinib) and presented with grade 3 chemotherapy-associated neutropenia. After discussion, the patient decided to receive an experimental antitumor medication KN026 (anti-HER2 bispecific antibody) plus surufatinib (novel tyrosine kinase inhibitor) from July 14, 2021. Unfortunately, the treatment response was poor and he withdrew from the study on September 15, 2021. Afterward, intraperitoneal therapy involving paclitaxel +cisplatin+bevacizumab was used for intractable ascites. In the meanwhile, sacituzumab govitecan (a novel antibody drug conjugate–targeting trophoblast cell surface antigen 2) was tried for the last opportunity (Fig. 1). However, the treatment is ineffective, and the patient started to receive palliative care and eventually lost his life on July 10, 2022.

DISCUSSION

Cholangiocarcinoma is a rare malignancy with extremely limited options regarding systemic therapy. Historically, only chemotherapy with multiagents achieved favorable clinical efficacy; nevertheless, the prognosis remained very poor. The tremendous success of ICI treatment in cancer patients, with similar meaningful and durable responses, has been reported in a small subset of cholangiocarcinoma patients. Nevertheless, immune toxicities also known as irAEs have been also greatly noted since the commonplace of ICIs in cancer treatment. Although irAEs are widely considered to occur in any organ or tissue, urinary tract irAEs have been barely reported in either clinical trials or large-scale real-world studies. To date, 12 cases of ICIs associated with cystitis from 11 previous studies were reported (including the current case, Table 1).[1–10] All the patients came from East Asia (6 from China and 5 from Japan), except 1 from France. Among them, the age ranged from 47 to 78 years old, with 10 males (83.3%). Interestingly, the cystitis of all reported cases was associated with PD-(L)1, with Nivolumab in 7 patients, pembrolizumab in 3 patients, and sintilimab in 2 patients. There are 2 studies reporting additional drug-associated cystitis, that is, atezolizumab and toripalimab. With respect to cancer types, the majority (8/12, 66.7%) suffered from lung cancer, and 2 with liver cancer (intrahepatic cholangiocarcinoma). Most of these cases received steroid therapy as the symptoms seriously affected patients' quality of life, and the symptoms were all relieved.

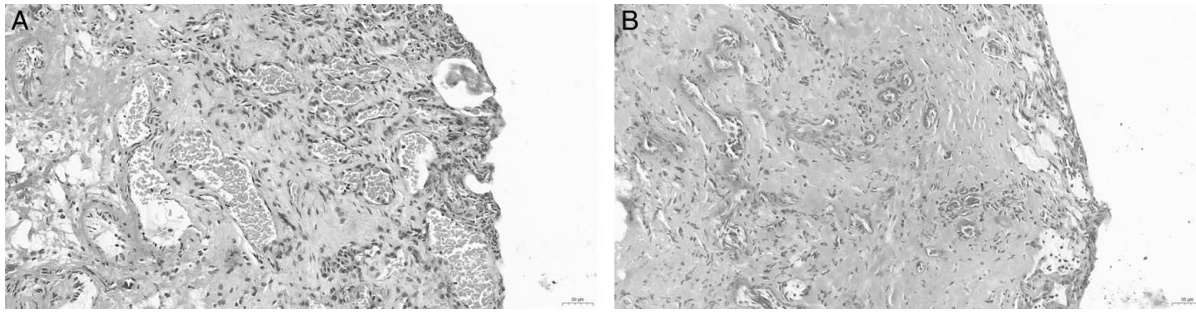

FIGURE 2. Histopathologic findings of bladder biopsy. A, Infiltration of massive inflammatory cells mainly composed of lymphocytes and neutrophils, with bladder epithelial desquamation. There was no evidence of malignancy. Scale bar = 50 μm. B, Negative acid-fast staining. Scale bar = 50 μm.

TABLE 1. Clinical Characteristics and Treatment of Case Reports From Previous Literature and Current Literature

Case/ references	Sex/age	Region	Primary cancer type	Drugs	Symptoms	Urinary tests	Histopathologic findings	Treatment for cystitis	Symptoms resolved	Rechallenge ICIs	Recurrent cystitis
1[1]	Male/62	Japan	Lung squamous cell carcinoma	Nivolumab	Pollakiuria, urodynia	Pyuria, hematuria, culture (−)	Epithelial desquamation and edematous changes in interstitium	MP 500 mg/d; tapered over several months	Yes	Yes, nivolumab 5 doses	No
2[2]	Male/50	Japan	Lung squamous cell carcinoma	Nivolumab	Pollakiuria, urodynia	Pyuria, culture (−)	NA	Prednisolone 1 mg/kg/d; then tapered	Yes	Yes, nivolumab 1 dose	Yes
3[2]	Male/60	Japan	Lung squamous cell carcinoma	Nivolumab	Pollakiuria, dysuria	Pyuria, culture (−)	NA	ICI discontinuation only	Yes	Yes, nivolumab 3 doses	Yes
4[3]	Female/78	Japan	Lung adenocarcinoma	Pembrolizumab	Pollakiuria, urodynia, dysuria, nocturia	Pyuria, hematuria, culture (−)	Numerous infiltrates of CD8 cells and/or TIA-1 and positive lymphocytes into urothelium	Prednisolone 25 mg/d; tapered over 2 mo; ICI discontinuation	Yes	No	No
5[4]	Male/51	China	Small cell lung cancer	Nivolumab	Urinary urgency, dysuria	Pyuria, culture (−)	Infiltrates of CD3 and CD8 lymphocytes into urothelium	MP 80 mg twice daily; tapered over 6 wk; ICI discontinuation	Yes	No	No
6[5]	Female/61	France	Melanoma	Nivolumab*	Pollakiuria, urinary urgency, urodynia, nocturia,	Pyuria, culture (−)	T lymphocytes infiltration in intraepithelial and subepithelial connective tissue	Prednisolone 0.5 mg/kg/d; tapered over 3 mo; ICI discontinuation	Yes	Yes	No
7[6]	Male/47	Japan	Lung adenocarcinoma	Nivolumab	Pollakiuria, urodynia	Pyuria, culture (−)	Slight eosinophils and plasma cells infiltration into urothelium, indicating allergy-related cystitis	ICI discontinuation only	Yes	Yes	No
8[7]	Male/56	China	Lung squamous cell carcinoma	Pembrolizumab	Pollakiuria, urinary urgency, urodynia	Pyuria, hematuria, culture (−)	Lymphocytes and neutrophils infiltration	methylprednisolone 40 mg × 3 d	Yes	Yes	Yes
9[8]	Male/53	China	Lung adenocarcinoma	Sintilimab	Pollakiuria, urodynia, low back pain	Pyuria, hematuria, culture (−)	Lymphocyte-dominant bladder inflammation and interstitial tissue hyperplasia	Methylprednisolone 80 mg	Yes	Yes	Yes
10[9]	Male/56	China	Gastric carcinoma	Sintilimab		NA		Sairei-To	Yes	Yes	No

TABLE 1. (*continued*)

Case/ references	Sex/age	Region	Primary cancer type	Drugs	Symptoms	Urinary tests	Histopathologic findings	Treatment for cystitis	Symptoms resolved	Rechallenge ICIs	Recurrent cystitis
11[10]	Male/48	China	Liver cancer (intrahepatic cholangiocarcinoma)	Nivolumab, atezolizumab	Pollakiuria, urodynia, urinary incontinence Bladder irritation symptoms	Pyuria, culture (−)	Infiltrates of CD3 and CD8 lymphocytes into urothelium chronic inflammation of mucosal tissue, and proliferation of granulation tissues and fibroblasts	Steroid 2 mg/kg, ICI discontinuation	Yes	No	No
12 current case	Male/58	China	Liver cancer (intrahepatic cholangiocarcinoma)	Pembrolizumab toripalimab	Urinary frequency, urinary urgency, urodynia, gross hematuria	Pyuria, hematuria, first culture positive and repeating tests negative	Massive lymphocytes and neutrophils infiltration into urothelium, and bladder epithelial desquamation	MP 120 mg/d; tapered to 28 mg/d over 2 mo for first time; MP 500 mg/d and tapered over 3 mo for second time; Prednisone 40 mg/d and tapered over 4 wk for third time; ICI discontinuation	Yes	Yes	Yes

*Although cystitis was just mentioned to be associated with ICI combination (ipilimumab and nivolumab) in the original article, it was more likely to be closely related to nivolumab.
ICI indicates immune checkpoint inhibitor; MP, methylprednisolone; NA, not available; TIA-1, cytotoxic granule-associated RNA binding protein 1.

In the present study, we reported a case with advanced liver cancer experiencing recurrent cystitis associated with 2 PD-1 inhibitors (pembrolizumab and toripalimab). Notably, cystitis associated with toripalimab, a novel humanized monoclonal antibody with a high affinity for PD-1, was first presented in our case. Initially, it was extremely difficult to distinguish between bladder metastasis, urinary infection, and immune toxicity, based on multiple bladder masses and positive urinary culture. However, no response to variable antibiotics and negative further urine cultures allowed us to rule out the possibility of infection. The histopathologic examination showed massive inflammatory cell infiltration in the urothelium without any evidence of malignancy, which prompted us to consider the diagnosis of irAEs. Most importantly, recurrent cystitis, which was closely related to the administration of either pembrolizumab or toripalimab, made the causality more definitive. The precise pathophysiology of irAEs remains uncertain although preclinical, translational, and clinical studies have provided insights into their potential mechanisms. An attractive hypothesis, molecular mimicry, proposed that normal and cancer cells may share antigens targeted by enhanced cytotoxic T cells. In fact, PD-L1 expression in bladder tissue was previously identified in patients with interstitial cystitis. This may partly explain why all the reported immune-related cystitis were related to PD-(L)1 checkpoint blockades. However, it should be mentioned that both the current patient and a previous case[5] ever received combination therapy of ICIs [anti–cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) antibody+anti-PD-1 antibody]. Although both CTLA-4 and PD-1 are immune checkpoints, they have different mechanisms of action. In general, CTLA-4 controls the amplitude of immunologic response at the initial time of T-cell activation in lymph nodes, whereas PD-1/PD-L1 pathways act at later stages, limiting T-cell activity in the peripheral tissues. Therefore, it has been well acknowledged that ICI combination may lead to significantly higher rates and more severe irAEs than ICI monotherapy. Although cystitis in these 2 cases was more closely associated with anti-PD-1 antibodies from the timeline, the effects of anti-CTLA-4 antibodies in reinvigorating cytotoxic T cells were inevitable. We postulate that ICI combination led to overt activation of T cells, and afterward, even anti-PD-1 monotherapy triggered significant cystitis. This can also explain the current patient's good tolerability to anti-PD-1 monotherapy for 18 months before initiation of ICI combination. The hypothesis warrants further studies in cases receiving anti-CTLA-4 blockades.

It was noteworthy that, although the patient in our report did not achieve objective tumor response during the whole course of treatment, he had a prolonged survival (>3 y). This may be partially attributed to the multiple courses of immunotherapy. A recent meta-analysis has shown that the occurrence of any irAEs was significantly associated with prolonged survival in advanced cancer patients. It is thought to represent bystander effects of reactivated T cells.

CONCLUSIONS

Cystitis is an extremely rare irAE. Herein, we reported a case with recurrent cystitis definitely associated with ICIs, especially 2 PD-1 inhibitors (pembrolizumab and toripalimab). With widening indications and more application of ICIs in clinical practice, physicians should be also aware of the rare irAEs, such as immune-related cystitis.

CONFLICTS OF INTEREST/FINANCIAL DISCLOSURES

Supported by the National High-Level Hospital Clinical Research Funding ("Star of Outlook" Scientific Research Project of Peking University First Hospital, No. 2022XW05) and the National Natural Science Foundation of China (No. 82000060).

All authors have declared that there are no financial conflicts of interest with regard to this work.

REFERENCES

1. Ozaki K, Takahashi H, Murakami Y, et al. A case of cystitis after administration of nivolumab. *Int Cancer Conf J*. 2017;6:164–166.
2. Shimatani K, Yoshimoto T, Doi Y, et al. Two cases of nonbacterial cystitis associated with nivolumab, the anti-programmed-death-receptor-1 inhibitor. *Urol Case Rep*. 2018;17:97–99.
3. Ueki Y, Matsuki M, Kubo T, et al. Non-bacterial cystitis with increased expression of programmed death-ligand 1 in the urothelium: an unusual immune-related adverse event during treatment with pembrolizumab for lung adenocarcinoma. *IJU Case Rep*. 2020;3:266–269.
4. Zhu L, Wang Z, Stebbing J, et al. Immunotherapy-related cystitis: case report and review of the literature. *Onco Targets Ther*. 2021;14:4321–4328.
5. Schneider S, Alezra E, Yacoub M, et al. Aseptic cystitis induced by nivolumab and ipilimumab combination for metastatic melanoma. *Melanoma Res*. 2021;31:487–489.
6. Yajima S, Nakanishi Y, Matsumoto S, et al. Improvement of urinary symptoms after bladder biopsy: a case of pathologically proven allergy-related cystitis during administration of nivolumab. *IJU Case Rep*. 2021;4:213–215.
7. He X, Tu R, Zeng S, et al. Non-bacterial cystitis secondary to pembrolizumab: a case report and review of the literature. *Curr Probl Cancer*. 2022;46:100863.
8. Tu L, Ye Y, Tang X, et al. Case report: a case of sintilimab-induced cystitis/ureteritis and review of sintilimab-related adverse events. *Front Oncol*. 2021;11:757069.
9. Wang Z, Zhu L, Huang Y, et al. Successful treatment of immune-related cystitis by Chai-Ling-Tang (Sairei-To) in a gastric carcinoma patient: case report and literature review. *Explore (NY)*. 2023;19:458–462.
10. Zhu S, Bian L, Lv J, et al. A case report of non-bacterial cystitis caused by immune checkpoint inhibitors. *Front Immunol*. 2021;12:788629.

