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INDEXING/ABSTRACTING

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJCC* as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Lin-YuTong Wang*; Production Department Director: *Xiang Li*; Editorial Office Director: *Jin-Lai Wang*.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

January 7, 2022

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Successful response to camrelizumab in metastatic bladder cancer: A case report

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Author contributions: Zhong XM and Xie C conceived and designed the case report; Yuan X collected the data; Liu ZY, Chen SH, Xie C, and Chen ZQ performed the analysis; Lu DL performed the follow-up and recorded treatment-related side effects; Xu F and Zhong XM wrote the paper.

Informed consent statement:

Informed written consent was obtained from the patient for the publication of this case report and any accompanying images.

Conflict-of-interest statement:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CARE Checklist (2016) statement:

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Abstract

BACKGROUND

There has been no report to use camrelizumab with chemotherapy for advanced bladder cancer patients with positive programmed death-ligand 1 (PD-L1) expression and high tumor mutational burden (TMB). More effective predictors of bladder cancer immunotherapy have yet to be explored, and the combination of multiple factors may be more predictive than a single factor.

CASE SUMMARY

We report the case of a 74-year-old male patient with recurrent metastatic bladder cancer, which demonstrated positive PD-L1 expression and high TMB. The immune checkpoint inhibitor camrelizumab was administered to the patient in combination with gemcitabine and cisplatin. The patient achieved a partial response with a progression-free survival of 11 mo.

CONCLUSION

This is the first report to use camrelizumab with chemotherapy for advanced bladder cancer patients with positive PD-L1 expression and high TMB.

Key Words: Programmed death-ligand 1; Tumor mutational burden; Bladder cancer; Camrelizumab; Next-generation sequencing; Case report

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Country/Territory of origin: China

Specialty type: Medicine, research and experimental

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

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Received: March 11, 2021

Peer-review started: March 11, 2021

First decision: May 11, 2021

Revised: May 20, 2021

Accepted: July 12, 2021

Article in press: July 12, 2021

Published online: January 7, 2022

P-Reviewer: Bellini MI, Desai DJ, Sachdeva S

S-Editor: Gao CC

L-Editor: Wang TQ

P-Editor: Xing YX



Core Tip: Eighty percent of patients with positive programmed death-ligand 1 (PD-L1) expression are unable to benefit from immunotherapy. Herein, we report the case of a 74-year-old male patient with recurrent metastatic bladder cancer, which demonstrated positive PD-L1 expression and high tumor mutational burden. The immune checkpoint inhibitor camrelizumab was administered to the patient in combination with gemcitabine and cisplatin. The patient achieved a partial response with a progression-free survival of 11 mo. More effective predictors of bladder cancer immunotherapy have yet to be explored, and the combination of multiple factors may be more predictive than a single factor.

Citation: Xie C, Yuan X, Chen SH, Liu ZY, Lu DL, Xu F, Chen ZQ, Zhong XM. Successful response to camrelizumab in metastatic bladder cancer: A case report. *World J Clin Cases* 2022; 10(1): 254-259

URL: <https://www.wjgnet.com/2307-8960/full/v10/i1/254.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v10.i1.254>

INTRODUCTION

Multiple studies have demonstrated that blocking of programmed death 1 (PD-1) or its ligand programmed death-ligand 1 (PD-L1) improved anti-tumor activity in metastatic urothelial cancer patients with disease progression after standard chemotherapy[1-3]. However, only a subset of patients is sensitive to immunotherapy. In addition to microsatellite instability (MSI) status and PD-L1 expression, tumor mutational burden (TMB), the third approved biomarker for immunosuppressant, could be used to predict the efficacy of immunosuppressive agents. Recently, increasing studies have indicated that there were no overlapping effects of PD-L1 expression and TMB on the response rate to PD-1/PD-L1 inhibitors across distinct tumor types, therefore they can be broadly used to categorize the immunologic subtypes of cancer[4].

Camrelizumab, as an anti-PD-1 inhibitor, provided an improved objective response rate (ORR) and disease control rate (DCR) in pre-treated patients with dMMR/MSI-high (MSI-H) and advanced or metastatic solid tumor. Several clinical trials of camrelizumab for advanced urinary system tumors such as NCT03827837 have been launched. It brings more treatment options to patients with an advanced or metastatic solid tumor, including bladder cancer. Herein, we report the case of a recurrent bladder cancer patient with positive PD-L1 expression and high TMB. The patient received camrelizumab in combination with chemotherapy and achieved a partial response (PR).

CASE PRESENTATION

Chief complaints

A patient presented with recurrent metastatic bladder cancer (metastatic urothelial carcinoma, mUC), which demonstrated positive PD-L1 expression and high TMB.

History of present illness

A 74-year-old male patient, with a history of high-grade urothelial carcinoma of the bladder, was initially presented to our hospital in August 2017 due to gross hematuria and dysuria. Recurrence of bladder cancer was declared by computed tomography (CT) imaging. The patient was subjected to radical cystectomy and lysis of pelvic adhesions. The pathological evaluation of the tumor sample indicated infiltrating high-grade urothelial carcinoma of the bladder which invaded the entire layer and surrounding adipose tissue (Figure 1). Two months after surgery, the patient had pain in the right pubic bone while magnetic resonance imaging (MRI) revealed recurrence of stage IV bladder cancer with bone metastases.

History of past illness

The patient had a free previous medical history.

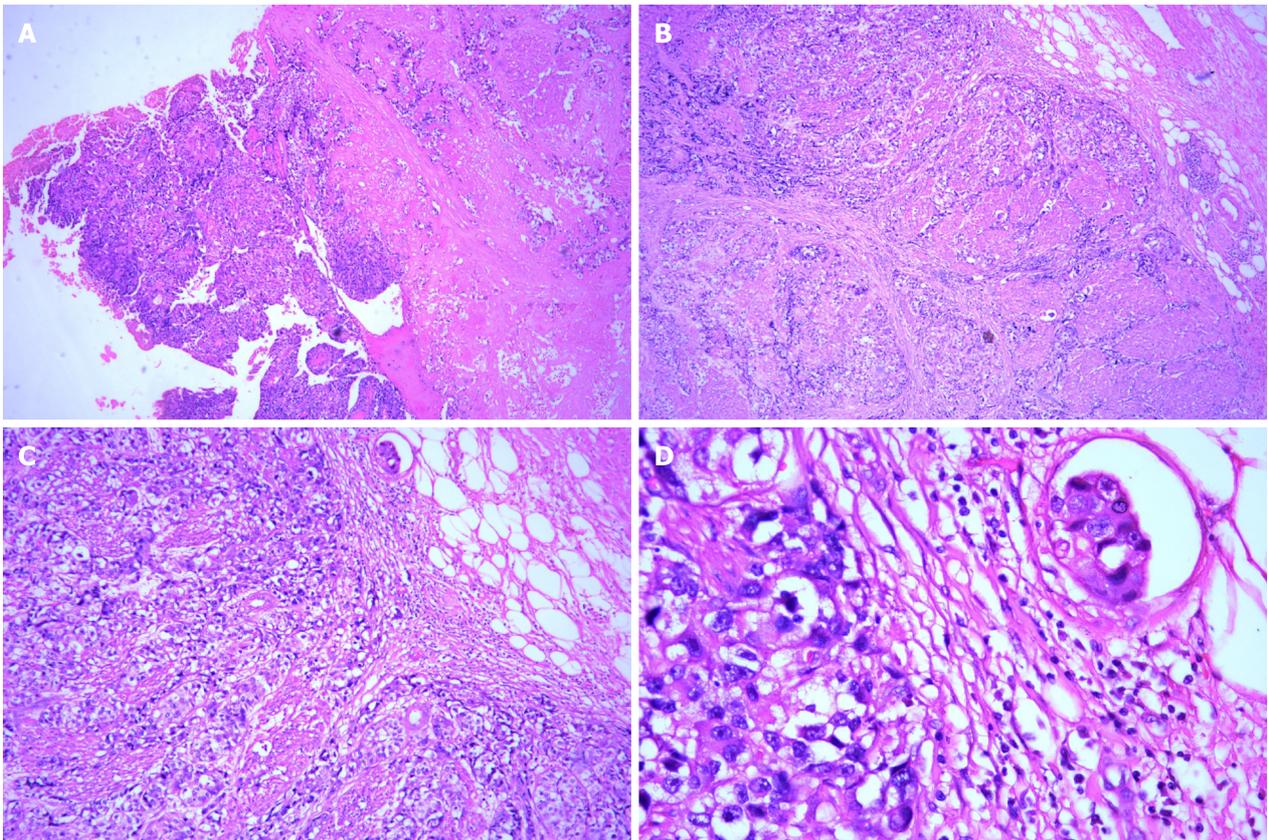


Figure 1 Pathological evaluation. A: High-grade urothelial carcinoma of the bladder (magnification, 40 ×); B-D: Invasion of the entire layer and surrounding adipose tissue by the high-grade urothelial carcinoma of the bladder [magnification, 40 × (B), 100 × (C), and 400 × (D)].

Physical examination

Vital signs and general inspection included the head, neck, anterior torso, posterior torso, anterior chest, abdomen, male genitalia, gait, station, coordination. Our clinical consideration was the recurrence of bladder cancer.

Laboratory examinations

Routine blood tests, routine urine tests and urinary sediment examination, routine fecal tests and occult blood tests, blood biochemistry, immune indexes, infection indexes immunohistochemistry (IHC) test, routine blood test genetic mutation profiling, and TMB evaluation were performed.

The plasma sample of the patient was subjected to genetic mutation profiling and TMB evaluation through next-generation sequencing (NGS) with a panel consisting of 520 cancer-related genes (Burning Rock Biotech, Guangzhou, China). The sequencing identified a total of 19 somatic mutations, including PIK3CA (p.Glu545Lys) and ARID1A (p.Ser1948fs) mutations, and RAF1 amplification (CN = 3.6). The TMB level was 19.8 mutations per Mb. Furthermore, IHC on tissue samples indicated positive PD-L1 protein expression with a tumor proportion score (TPS) of 20%.

Imaging examinations

CT imaging and MRI were performed. In September 2019, the reexamination of abdominal CT identified multiple newly appeared swollen retroperitoneal lymph nodes in which the largest node had a diameter of about 1.7 cm (Figure 2A). After three treatment cycles, the patient achieved a PR as the repeated CT scan on December 20, 2019 showed a 53% decrease in the target lesion (Figure 2B). Then, the patient continued camrelizumab (200 mg, D0, q3w) and gemcitabine (1 g, D1, D8, q3w) and maintained the PR (Figure 2C and D).

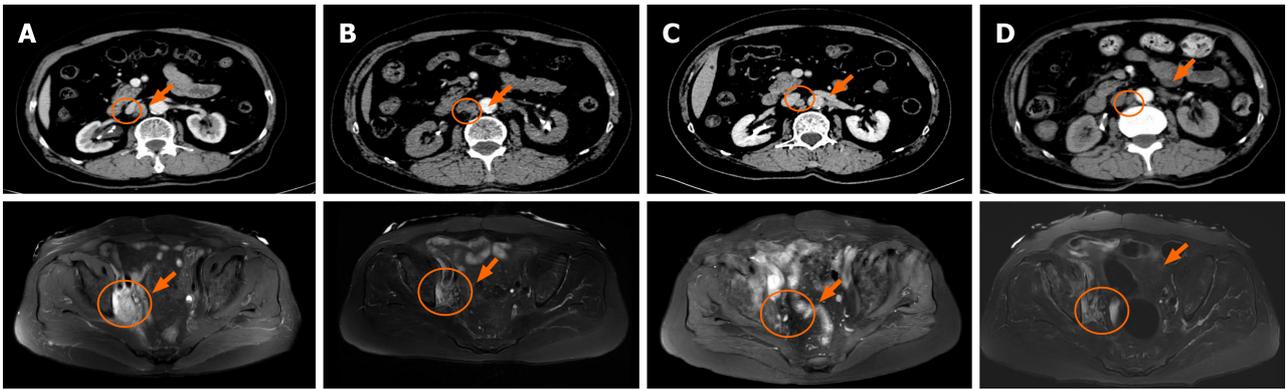


Figure 2 Computed tomography images. Computed tomography scans showed continuous shrinkage of lymph nodes in the retroperitoneum and right pelvic wall from September 2019 (A, 1.7 cm) to December 2019 (B, 0.8 cm), April 2020 (C, 0.8 cm), and July 2020 (D, 0.8 cm). Red arrows and circles indicate target lesions.

FINAL DIAGNOSIS

Recurrence of high-grade urothelial carcinoma of the bladder with bone metastases and multiple newly appearing swollen retroperitoneal lymph nodes.

TREATMENT

Palliative radiotherapy in the metastatic site was given to the patient. In May 2018, the patient had pain of the right ilium and the symphysis pubis and received palliative radiotherapy followed by four cycles of chemotherapy with paclitaxel liposome (210 mg Q3W) from July 10, 2018 to September 12, 2018. Based on the high TMB level and positive PD-L1 expression, the patient was administered with immunotherapy of camrelizumab (200 mg, D0, q3w) in combination with chemotherapy including gemcitabine (1 g, D1 and D8, q3w) and cisplatin (40 mg, D1-D3, q3w) since October 2019.

OUTCOME AND FOLLOW-UP

Since the patient had pain in the right pubic bone with bone metastases, palliative radiotherapy in the metastatic site was given to the patient, followed by four cycles of chemotherapy with paclitaxel liposome (210 mg Q3W). Mild gastrointestinal reactions developed during paclitaxel liposome and immunotherapy of camrelizumab (200 mg, D0, q3w) in combination with chemotherapy with gemcitabine (1 g, D1, D8, q3w) and cisplatin (40 mg, D1-D3, q3w). Oppression in the chest, grade 1 myeloid suppression, and abnormal liver and kidney function occurred during the first gemcitabine and cisplatin chemotherapy, and gemcitabine dose was therefore reduced. In addition, abnormal liver function, moderate anemia, and mild gastrointestinal reactions occurred during the immunotherapy with camrelizumab and chemotherapy with gemcitabine and cisplatin. The patient maintained PR. The latest follow-up in October 2020 showed the progression of the tumor. The total progression-free survival (PFS) of the patient since camrelizumab therapy was 11 mo.

DISCUSSION

The application of immunotherapy has thoroughly promoted the progress of cancer treatment in recent years. However, 80% of patients with positive PD-L1 are unable to benefit from immunotherapy. Hitherto FDA has approved five drugs as immunotherapies for bladder cancer, but the ORRs of these drugs in bladder cancer are 13.4%-21.1% [5]. In clinical trials of camrelizumab in advanced solid tumors, some bladder carcinoma patients got a complete response [6]. Camrelizumab provided improved ORR and DCR in pre-treated patients with dMMR/MSI-H and advanced or metastatic solid tumor [7,8]. With the increase of approved immune checkpoint inhibitors, it is

urgent to define patient subgroups that are more likely to have treatment benefits. PD-L1, as the only effective biomarker for prediction, is far from being enough.

High tumor mutation may lead to high neoantigen load and increased immunogenicity, which could promote recognition and killing abilities of the immune system. Multiple studies have shown that TMB is associated with the efficacy of mUC immunotherapy. A study indicated that tumor mutational load predicts survival after immunotherapy in mUC by the TMB cutoff of 17.6% or the cutoff of 25% by quartering [9]. The updated result of the PURE-01 study revealed that TMB may predict the pathological response to pembrolizumab in patients with muscle-invasive bladder cancer while a pretreatment TMB of 15 mutations/Mb was predictive of pathological complete response [10]. Another study showed that higher TMB levels revealed improved overall survival (OS) and lowered tumor recurrence [11]. Based on many relevant clinical studies, On June 16, 2020, the Food and Drug Administration approved pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic TMB-high [≥ 10 mutations/megabase (mut/Mb)] solid tumors.

In addition, the NGS results of the patient revealed an inactivated nonsense mutation in ARID1A (p.Ser1948fs) which results in the loss of ARID1A protein expression and indicates potential treatment response to immunotherapy. ARID1A mutation has a high incidence in tumors, and it can increase the efficacy of tumor immunotherapy through multiple mechanisms of action, including MSI-H phenotype, high TMB, upregulation of PD-L1 expression, and immune activated tumor microenvironment. The largest study of 17486 patients with gastrointestinal tumors has demonstrated selective DNA damage repair (DDR) defects and ARID1A defects were associated with high TMB. In general, ARID1A was inactivated with increased TMB and low gene copy number, suggesting that it may be an indicator of immunotherapy [12]. Studies of immunotherapy for advanced urothelial carcinoma have shown that mutations in the *DDR* gene are associated with improved PFS and OS [13]. The *DDR* gene is an independent factor associated with the efficacy of immunosuppressive therapy in mUC. In addition to high TMB (19.8 mutations per Mb) and positive PD-L1 expression (TPS 20%), the treatment benefit of camrelizumab observed in our case may also be explained by the change of the *DDR* gene. Hence, the patient received immunotherapy in combination with chemotherapy and achieved a PR with a PFS of 11 mo.

More effective predictors of bladder cancer immunotherapy have yet to be explored, and the combination of multiple factors may be more predictive than a single factor.

CONCLUSION

Here, we report a Chinese patient with advanced bladder cancer showing effective treatment response to camrelizumab in combination with chemotherapy. This is the first case report on the treatment effect of camrelizumab for advanced bladder cancer with positive PD-L1 expression and high TMB. Our study suggested that TMB, PD-L1 expression, and *DDR* gene mutation can be used in combination to predict treatment effects of immunotherapy. More studies are needed to develop effective biomarkers and identify appropriate patient subgroups that are more likely to benefit from cancer immunotherapies.

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