# Combination toripalimab and bevacizumab for an elderly urothelial carcinoma patient with brain metastasis who failed rapidly after radiotherapy: a case report and literature review

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**Brain metastasis is a rare refractory event in patients with urothelial carcinoma. Platinum-based chemotherapy is the recommended first-line standard therapy for all metastasis urothelial carcinoma patients eligible for cisplatin or carboplatin. Patients ineligible for platinum may receive immunotherapy. No clear evidence exists that UC with brain metastasis is sensitive to immunotherapy, and the optimal treatment for patients with BM is uncertain. We evaluated the safety and efficacy of combined immunotherapy and antivascular therapy in an elderly patient with urothelial carcinoma with brain metastasis, and summarize the currently available evidence. First, she underwent a left nephrectomy and left ureterectomy and recovered well postoperatively. The postoperative pathologic findings were consistent with urothelial carcinoma. Approximately 2 years later, the patient developed impaired limb movement on the right side and underwent MRI, which revealed lesions in the left frontal lobe and suggested brain metastasis. The brain metastasis responded to local radiotherapy but progressed again in a short time. Then, the patient was administered toripalimab at 240 mg combined with bevacizumab at 300 mg every 3 weeks. After 1cycle of treatment, the patient achieved a quick response, and symptoms improved significantly. Repeat evaluation imaging demonstrated that the lesions in the brain and lung were significantly smaller and evaluation showed partial response. The treatment was well tolerated and the patient remained in partial response until the last follow-up by July 2022, 6 months after the initiation of treatment. This case suggests that immune checkpoint blockade combined with antivascular therapy might be a new possibility for patients with metastatic urothelial carcinoma, including brain metastases. *Anti-Cancer Drugs* 34: 317–324 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.**

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## Introduction

Brain metastasis is a rare refractory event in patients with urothelial carcinoma (UC). Currently, treatment of brain metastasis has no fixed therapeutic approach. Treatment strategies include neurosurgical resection, stereotactic radiosurgery, and whole brain radiotherapy [1]. Unfortunately, recurrence is often faced after surgery and radiotherapy. Immunotherapy represented by immune checkpoint inhibitors (ICIs) has achieved great success in recent years [2]. Platinum-based chemotherapy is the recommended first-line standard therapy for all metastasis urothelial carcinoma patients eligible for cisplatin or carboplatin [3]. Patients ineligible for platinum may receive immunotherapy, which provides a new treatment option [4,5]. Systemic therapies may achieve intracranial responses, however, high-level evidence is lacking, as patients with BM have routinely been excluded from phase III trials of new systemic treatment strategies [6,7]. Meanwhile, the efficacy of ICIs monotherapy is limited by primary and acquired drug resistance [4,5,8]. Immunotherapy combined with antiangiogenesis therapy has emerged as a new regimen in recent years. We herein evaluated the safety and efficacy of combined immunotherapy and antivascular therapy in an elderly patient with urothelial carcinoma brain metastasis, and summarize the currently available evidence.

## Case report

A 78-year-old woman was admitted with impaired limb movement on the right side in October 2021. About 2 years ago, a computed tomography examination was performed for gross hematuria: luminal lesions in the left renal pelvis and upper ureter. Urethral cystoscopy, left ureteroscopy and biopsy were performed on July 4 2019, and the biopsy pathology was considered urothelial carcinoma. She underwent a left nephrectomy and left ureterectomy and recovered well postoperatively. The postoperative pathologic findings were consistent with urothelial carcinoma. She did not search for further

treatment except for traditional Chinese medicine after the operation.

In September 2021, the patient had a sudden onset of right limb inactivity, accompanied by slow response and aphasia. CT was performed on 15 September 2021 (The Second Affiliated Hospital of Dalian Medical University): left frontal lobe occupation. Thereafter, the patient turned to our institute for further treatment on 8 October 2021. On admission, the patient was unresponsive, had aphasia, and impaired right limb movement, with a performance score of about 2. Further brain MRI showed a left frontal lobe mass, surrounded by a large area of cerebral edema, which was diagnosed as a brain metastatic tumor by radiologists in the hospital (Fig. 1a,b). A baseline chest computed tomography scan revealed multiple masses in the upper lobe of both lungs, with large nodules in the upper lobe of the left lung with a maximum diameter of 2.1 cm (Fig. 2a–c). Abdomen computed tomography showed no active findings. The patient was then diagnosed with left frontal lobe metastasis and multiple lung metastases after taking together all the information. The patient has no history of diabetes, hypertension or cardiovascular disease. Thus, one course of radiotherapy for brain metastasis was administered immediately, and local lesion-targeted radiation therapy (total dose of 50 Gy/25F for left frontal lesions) was administered from October 2021 to November 2021. Administration of mannitol and dexamethasone relieved symptoms and improved his status at the same time. All the symptoms were relieved after treatment and the tumor size in the head was reduced through MRI scan (Fig. 1c,d).

Due to the enlargement of intrapulmonary metastases (Fig. 2d–f), an interventional radiology-guided core biopsy of the lesion in the upper lobe of the left lung was performed on 7 January 2022, which demonstrated a poorly-differentiated carcinoma and hematoxylin and eosin staining of the lung lesion revealed that epithelioid tumor cells (Fig. 3a). Furthermore, immunohistochemistry (IHC) revealed CK7(+), CK20(+), GATA3(+), CK(+), HER2(–), P40 (+), TTF-1(focal +) (Fig. 3b–h), which considered metastatic urothelial carcinoma combined with the history and histological findings. A gene analysis of the new puncture sample showed a high tumor mutation burden (12.67 Muts/Mb). Immunohistochemistry indicated negative programmed death ligand-1 expression. Based on these results, this patient may be an ideal candidate for ICIs treatment. The patient did not receive immunotherapy at the time because of her age.

Unfortunately, the neurological symptoms worsened again after local radiotherapy and which performance for unresponsive, aphasia, and impaired movement of the right limb again. MRI on 10 February 2022 showed that the metastases in the left frontal lobe were larger than before (Fig. 1e,f).Subsequently, lacking standard treatment and with request to try immunotherapy by the patient, toripalimab (a PD-1 mAb) (day 1, 240 mg) plus bevacizumab (day 1, 400 mg) were administered from 18 February 2022.The treatment is given every three weeks. Surprisingly, she quickly achieved response after treatment of toripalimab plus bevacizumab. The clinical discomfort symptoms were quickly relieved a week later; Speech and action almost returned to normal three weeks later, with the retardation disappeared. Response to the therapy was also observed through MRI/CT scan, which showed that the tumor size in the head and both lungs were all reduced after three courses in 30 March 2022 (Fig. 4,5). After six courses on 1 July 2022, the imaging results showed that the patient exhibited continuous partial response (Fig. 4,5).In addition, the toxicities the patient experienced were mainly hypertension, which was well managed.

Although the patient regrettably developed brain metastases and was resistant to radiation therapy, Fortunately, she has a continuous survival benefit from treatment of toripalimab plus bevacizumab, with over 6 months of PFS benefit and over 10 months of OS benefit at the time of this article submission.

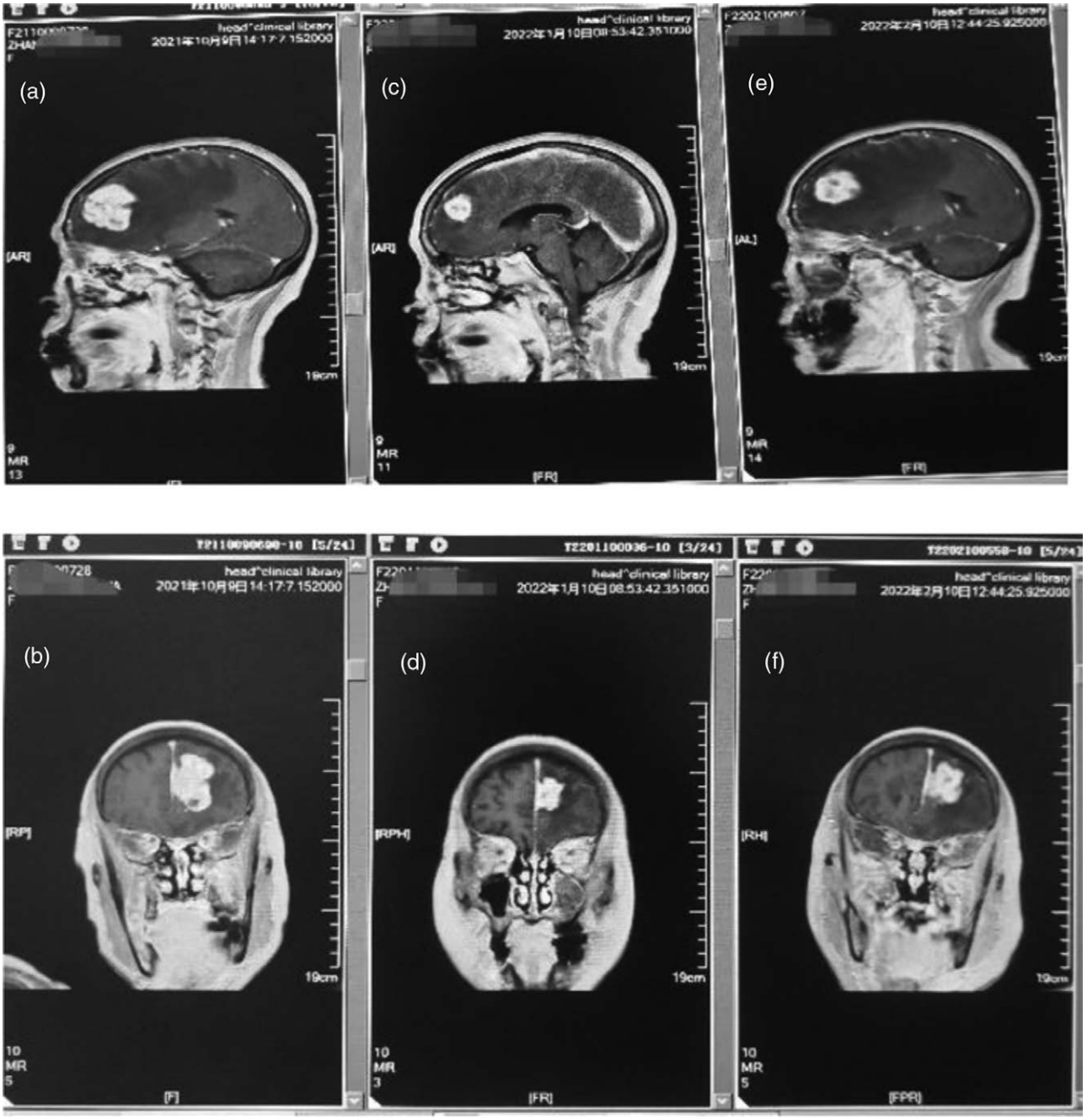
In this case report, informed consent was obtained before each treatment. The patients' responses to all drugs were according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and adverse events were as per the Common Terminology Criteria for Adverse Events criteria.

All procedures performed in studies involving human participants 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).The patient signed informed consent forms, which allowed for the publication of the relevant clinical and imaging data from her case.

## Discussion

Upper urinary tract urothelial carcinoma (UTUC) represents a rare and aggressive malignancy arising from the renal pelvis or ureter. Platinum-based chemotherapy is the recommended first-line standard therapy for all metastasis urothelial carcinoma patients eligible for cisplatin or carboplatin [3]. The elderly are often complicated with renal insufficiency and cannot tolerate cisplatin chemotherapy. In recent years, Immunotherapy represented by immune checkpoint inhibitors (ICIs) has been a great success and PD-1/PD-L1 checkpoint blockade immunotherapy has been rapidly undergoing a transition from clinical trials to routine clinical practice in multiple tumor types [2,9]. According to the results of IMvigor210, KEYNOTE 052, the United States of America (US) Food and Drug Administration (FDA) and European Association Of Urology (EAU) have approved Atezolizumab and Pembrolizumab for alternative immunotherapy in patients intolerant to platinum

**Fig. 1**

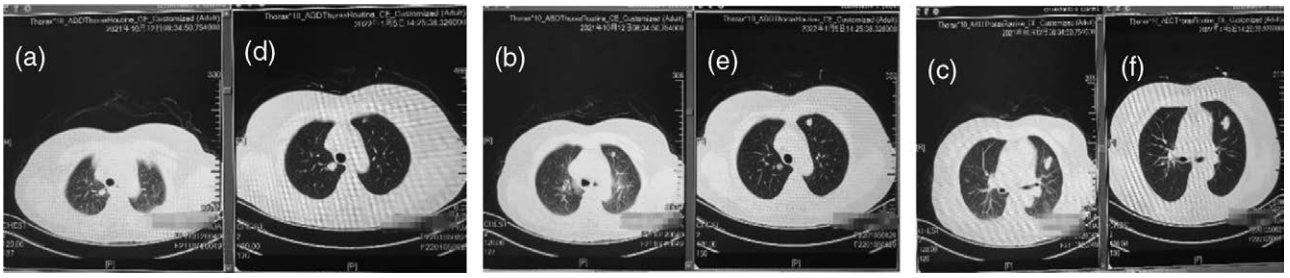



The brain MRI of different times showed a left frontal lobe mass. (a,d) (9 October 2021): A baseline brain MRI scan. (c,d) (10 January 2022) Radiotherapy for brain metastasis was completed more than 1 month. (e,f) (10 February 2022) Radiotherapy for brain metastasis was completed more than 2 months.

chemotherapy [4,5]. Immunotherapy targeting immune checkpoints has become a new therapeutic option for patients with metastatic urothelial carcinoma.

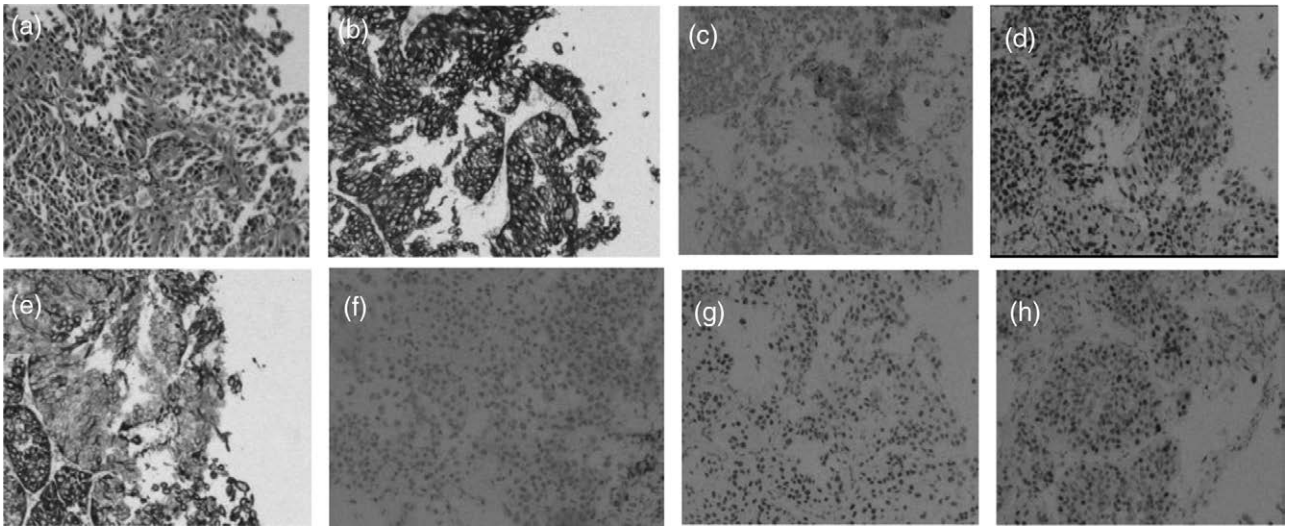
Brain metastasis is a rare refractory event in patients with urothelial carcinoma (UC). Incidence of BM differs between tumors, with the majority of brain metastases occurring in those with lung, breast and colorectal cancers, melanoma or renal cell carcinoma [10]. However, some cases of tumor types such gastro-oesophageal cancers, genitourinary cancers, head and neck cancers and sarcomas are rarely lead to BM. In 2700 cases from the Memorial Sloan-Kettering Cancer Center in New York,

**Fig. 2**




The pulmonary computed tomography (CT) of different times showed multiple metastases in both lungs. (a–c) (12 October 2021) A baseline chest computed tomography (CT) scan. (d–f) (5 January 2022) Radiotherapy for brain metastasis was completed more than 1 month.

**Fig. 3**



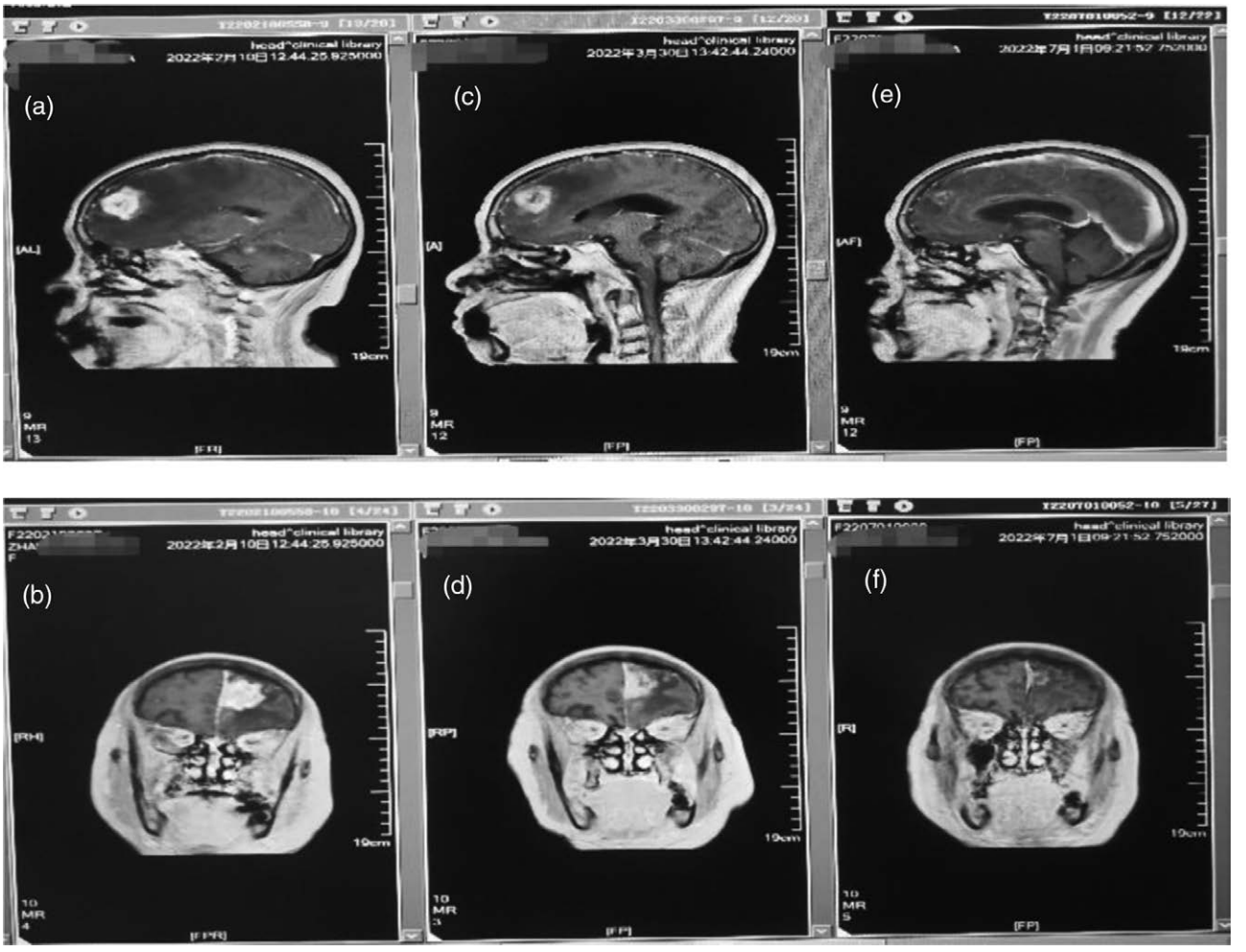

Histopathologic stains from the upper lobe of the left lung puncture biopsy. (a) Hematoxylin and eosin stain. Magnification: ×100; (b–h) Immunohistochemical stain: B, CK7(+); C,CK20(+); D,GATA3(+); E,CK(+); F, HER2(–); G,P40 (+); H,TTF-1(focal +);(200×).

Victor *et al*. reported that the distribution of primary cancers was as follows: 48% lung, 15% breast, 9% melanoma, 1% lymphoma, 3% gastrointestinal, 11% genitourinary, 10% osteosarcoma, 5% neuroblastoma and 6% head and neck cancer [11]. The prognosis of patients with brain metastases is generally poor, and survival is about 4 weeks, if untreated [12]. Development of brain metastases remains a substantial contributor to overall cancer mortality in patients with advanced-stage cancer [13]. Usually, metastatic brain tumors are diagnosed using imaging studies such as computed tomography and MRI [14]. Clinical symptoms or presentation of a patient with brain metastases have been described by Posner *et al*. In their series study, headache, vomiting and neurological symptoms were predominant clinical presentations in patients [15].

Brain metastases are thought to occur via the seeding of circulating tumor cells into the brain microvasculature; within this unique microenvironment, tumor growth is promoted and the penetration of systemic medical therapies is limited. Currently, treatment of brain metastasis has no fixed therapeutic approach. All of the factors that follow should be taken into consideration: the patient's general condition, the site and the pathological type of primary disease, the number, size and localization of brain metastases. Treatment strategies include neurosurgical resection, stereotactic radiosurgery and whole brain radiotherapy[1]. WBRT has always been considered as the standard treatment of brain metastases [16].

Systemic therapies may achieve intracranial responses, however, high-level evidence is lacking, as patients with BM have routinely been excluded from phase III trials of new systemic treatment strategies [6,7]. The role of chemotherapy in the treatment of brain metastases is controversial because of the blood-brain barrier. Most authors maintain that most chemotherapeutic drugs cannot pass

**Fig. 4**



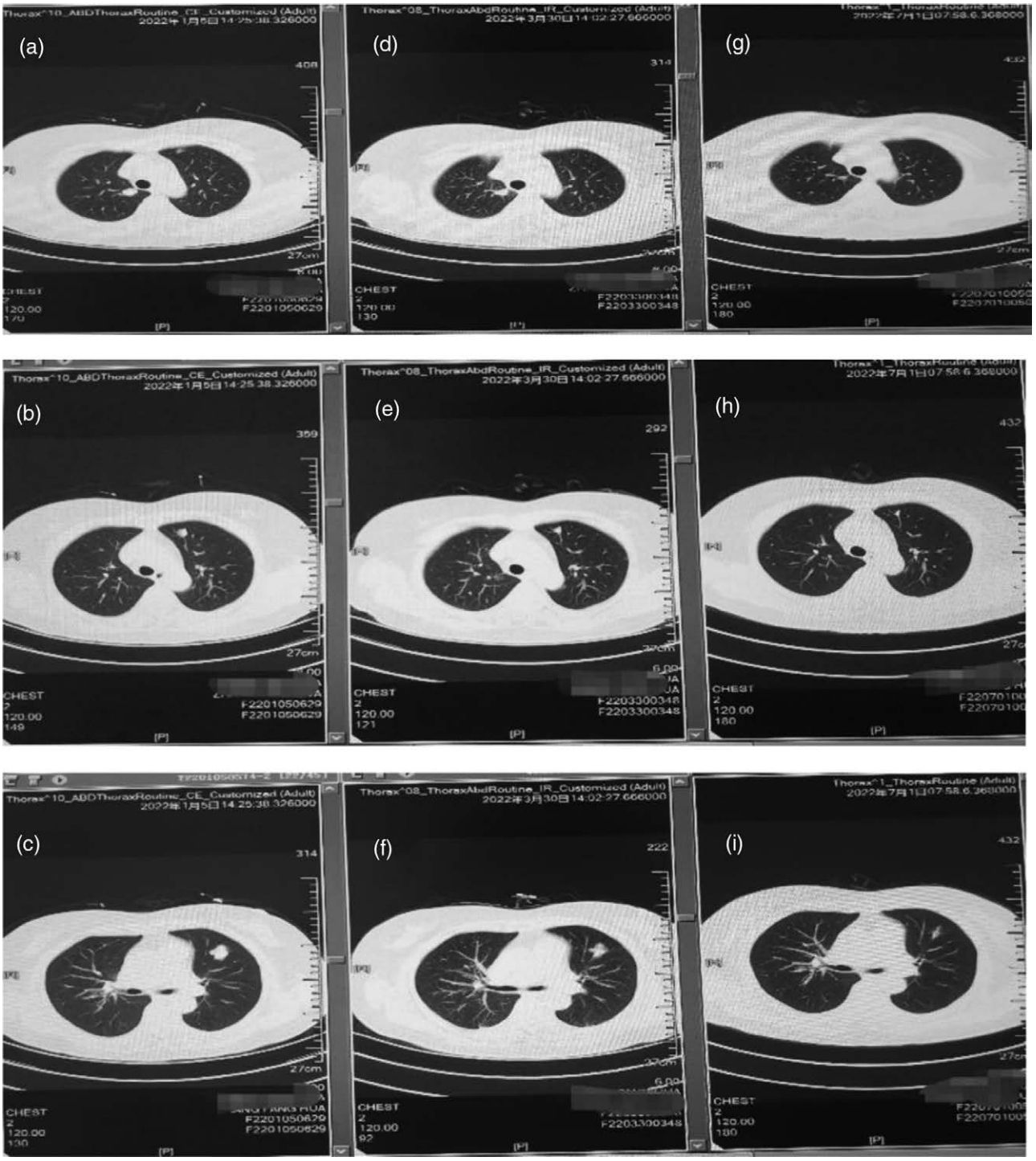

The brain MRI of different times showed a left frontal lobe mass. (a,c) (10 February 2022) Before 'toripalimab plus bevacizumab' treatment. (b,d) (30 March 2022) After 'toripalimab plus bevacizumab' treatment was administered for three cycles. (e,f) (1 July 2022) After 'toripalimab plus bevacizumab' treatment was administered for six cycles.

through the blood-brain barrier hence the chemotherapy efficacy in brain metastatic disease is low or absent [17]. Increased molecular understanding of brain metastases has driven continued development of novel immunotherapies and targeted therapies that have higher bioavailability beyond the blood–tumor barrier. Recently, some studies have shown clinically meaningful activity of systemic agents such as novel immunotherapies and tyrosine-kinase inhibitors in BM patient populations of melanoma, breast cancer and lung cancer, thus providing proof of concept for the efficacy of such approaches [18–21]. Immune checkpoint inhibitors work by activating the human immune system and have become an important method for treating brain metastases [22].

However, the efficacy of ICIs monotherapy is limited by primary and acquired drug resistance. Only 11% to 39% of UTUC patients respond to PD-1/PD-L1 inhibitors according to the current study results [4,5,8]. Immunotherapy combined with antiangiogenesis therapy has emerged as a new regimen in recent years. In terms of the mechanism [23], anti-angiogenic agents can not only reverse the immunosuppressive effects stimulated by vascular endothelial growth factor (VEGF) but also induce the normalization of tumor vascular system and promote the transition of T cells and other immune effector molecules. On the other hand, ICIs can activate effector T cells and increase the infiltration and cytotoxicity of effector T cells to normalize tumor vasculature. A series of clinical trials have also demonstrated that this combination strategy impressively improved the therapeutic efficacy of advanced renal carcinoma, hepatocellular carcinoma, non-small-cell lung carcinoma and other malignant tumors.

In addition, 90% of the patients with brain metastases had peritumoral brain edema (PTBE), which resulted in

**Fig. 5**




The pulmonary computed tomography of different times showed multiple metastases in both lungs. (a–c) (5 January 2022) Before 'toripalimab plus bevacizumab' treatment. (d–f) (30 March 2022) After 'toripalimab plus bevacizumab' treatment was administered for 3 cycles. (g–i) (1 July 2022) After 'toripalimab plus bevacizumab' treatment was administered for six cycles.

increased intracranial pressure and even secondary cerebral hernia in severe cases. It was an acute and critical disease of the tumor and a key factor affecting the life quality and duration of the patient [24]. Currently, the conventional treatment for PTBE is glucocorticoid and osmotic dehydrating agent, and the main drugs used in

clinical practice are dexamethasone and mannitol [25]. Previous studies [26] have confirmed that PTBE belongs to vasogenic edema, which is mainly caused by increased expression of vascular endothelial growth factor(VEGF), which is similar to the generation mechanism of brain edema associated with radioactive brain necrosis. In recent years, studies have found that the anti-VEGF drug bevacizumab has a significant effect on severe brain edema associated with radioactive brain necrosis [27,28]. Studies have reported that bevacizumab can also treat PTBE. Compared with conventional dehydration, clinical symptoms such as dizziness, headache, nausea and vomiting caused by PTBE can also be alleviated in a shorter time after using bevacizumab, and imaging results show that the range of PTBE is smaller than before [29,30].

Toripalimab (JS001) is a humanized immunoglobulin G4 mAb targeting programmed cell death-1 (PD-1) independently developed by China. Toripalimab received its first global conditional approval in China on 17 December 2018, for the treatment of unresectable or metastatic melanoma after the failure of previous systemic therapy [31]. It has a high binding affinity, which enables it to bind its specific antigen PD-1 receptor more firmly and compete better with PD-L1 and PD-L2 binding on tumor cells. After binding, it can induce strong endocytosis of PD-1 receptor, thus reducing the expression of PD-1 on the cell membrane surface. A study revealed the different binding orientation of toripalimab compared with other PD-1 blockades, which binds PD-1 mainly on a loop that contributes to multiple interactions with PDL1 [32]. Recently, increasing studies about various malignancies have proven the potential superiority of toripalimab, especially good tolerability, which may provide an opportunity to use concurrently with other anti-tumor drugs [33]. The results of the POLARIS-03 study showed that the median OS of patients with advanced urothelial carcinoma treated with toripalimab was 14.6 months, and the ORR was 27.2% [8].

The patient was an elderly woman with urothelial carcinoma diagnosed in gross hematuria 2 years ago and she underwent a left nephrectomy and left ureterectomy. Unfortunately, she recurred 2 years later, presenting as brain and lung metastasis, and worsened again soon after brain radiotherapy. The neurological symptoms performance as unresponsive, aphasia, and impaired movement of the right limb. Based on the above study results, we selected toripalimab immunotherapy combined with bevacizumab after thorough communication with patients. The neurological symptoms were quickly relieved after treatment and the evaluation 3 cycles later showed partial response according to RECIST. In addition, the toxicities the patient experienced were mainly hypertension, which was well managed.

In this case, we found that the TMB was high through genetic testing before treatment. Previous studies have shown that TMB can be used to predict the efficacy of immunotherapy, although it is not a perfect biomarker [34,35]. TMB has been reported to be highly correlated with the efficacy of PD-1/PD-L1 inhibitors in recent years, and high TMB, which represents genomic instability, is considered to have the potential to induce antigen production and further enhance immunogenicity [36]. Current studies have confirmed that TMB can be used as a clinical screening biomarker for the use of ICIs in melanoma, lung cancer and urothelial carcinoma [4,37,38]. However, the majority of patients are nonresponsive to PD-1/PD-L1 monotherapy in unselected populations. The optimization of combined treatment strategies and the search for effective biomarkers that predict the response to immunotherapy remains one of the major drawbacks in cancer management.

There are many kinds of antivascular targeted therapies and ICIs in clinical practice, and the choice of immune combination therapy in the treatment of urothelial carcinoma BM will indeed bring confusion to clinicians. CIs and antiangiogenic drugs have their own side effects, and the toxicity spectrum is more complex than if either therapy were used alone when they are combined. We applied toripalimab combined with bevacizumab in this patient, and achieved satisfactory results; however, when the patient is administered immunotherapy and antivascular targeted therapies, it should be noted that attention must be paid to common adverse reactions such as hypertension, rash, diarrhea and liver function injury; vigilance should also be raised for rare serious adverse reactions such as immune-associated pneumonia, immune-associated myocarditis and myasthenia gravis.

Although the patient regrettably developed brain metastases and was resistant to radiation therapy, Fortunately, she has a continuous survival benefit from treatment of toripalimab plus bevacizumab, with over 6 months of PFS benefit and over 10 months of OS benefit at the time of this article submission, which exceeds the average survival time of previously reported cases.

In conclusion, immunotherapy plus antivascular therapy may be a reasonable option for patients with metastatic urothelial carcinoma, including brain metastases, which is of great significance to prolong the survival period and improve the quality of life of patients.

Because only one patient with metastatic urothelial carcinoma was observed in this report, the clinical data are very limited and further observation and accumulation of more experience are needed, and further clinical studies will be conducted on the efficacy and safety of this combination regimen. We hope to encourage researchers to pay attention to patients with metastatic urothelial carcinoma, including brain metastases. Well-designed trials for better evidence are required to verify the findings in our report in the future.

## Acknowledgements

This study was approved by the institutional review board of Dalian Third People's Hospital. Written informed consent was obtained from all the patients. No funding was received for this study. Q.F., Y.X. and Y.W. were responsible for collecting data, sorting out data and writing the article; Y.W. was responsible for guiding the writing and participating in the revision of the article, and all authors read and approved the final manuscript.

### Conflicts of interest

The authors declare that there are no conflicts of interest.

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