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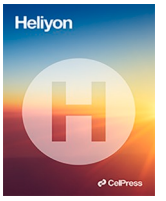

Case report

Case report: Successful treatment of advanced urothelial carcinoma with trophoblastic differentiation using Tislelizumab and Disitamab vedotin

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ABSTRACT

Background: Urothelial carcinoma with trophoblastic differentiation represents an uncommon and aggressive malignancy for which there is currently no established standard treatment. Systemic chemotherapy as the main treatment has limited efficacy. However, recent research has demonstrated significant improvements in patient survival with the use of immune checkpoint inhibitors and antibody–drug conjugates. To our knowledge, this case represents the first successful application of an immune checkpoint inhibitor (Tislelizumab) combined with human epidermal growth factor receptor 2-targeting antibody–drug conjugate (Disitamab vedotin) in the treatment of advanced urothelial carcinoma with trophoblastic differentiation.

Case report: We describe the case of a 36-year-old male patient diagnosed with urothelial carcinoma with trophoblastic differentiation, showing high expression of programmed death-ligand 1. Tumor progression occurred after six cycles of Tislelizumab combined with chemotherapy (gemcitabine and cisplatin) followed by five cycles of Tislelizumab monotherapy. Re-biopsy confirmed metastatic urothelial carcinoma with trophoblastic differentiation, now with epidermal growth factor receptor 2 overexpression. Treatment with Disitamab vedotin in combination with Tislelizumab resulted in a biochemical and imaging complete response, leading to an overall survival exceeding 24 months. Notably, no grade 3 or 4 adverse events were observed during treatment.

Discussion: The prognosis of advanced urothelial carcinoma with trophoblastic differentiation is unfavorable, and the available therapeutic options are limited. Combining Tislelizumab with Disitamab vedotin presents a promising anti-tumor strategy that warrants further investigation.

1. Introduction

Urothelial carcinoma (UC) is a prevalent malignant neoplasm originating from the urothelium, which includes cancers of the renal pelvis, ureter, bladder, and urethra [1]. UC often displays multidirectional differentiation, with squamous cell differentiation and adenoid cell differentiation being the most common [1]. Urothelial carcinoma with trophoblastic differentiation (UCTD) is a rare subtype of high-grade invasive UC that produces beta-human chorionic gonadotropin (β-HCG) [2]. Pathologically, trophoblastic components are present, and immunohistochemical (IHC) β-HCG staining shows positivity [2]. To date, fewer than 10 cases have been

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reported in the literature [3]. Platinum-based chemotherapy currently serves as the standard first-line treatment for advanced simple UC [4]. However, there is no established treatment regimen for advanced UCTD. Traditional chemotherapy has limited efficacy and poor prognosis, with extensive tumor metastasis accounting for most patient deaths [5]. The use of immune checkpoint inhibitors (ICIs) and anti-epidermal growth factor receptor 2 (HER2) antibody–drug conjugates (ADCs) have demonstrated promising potential in the therapeutic management of various malignancies [6]. We present a case of advanced UCTD with high programmed death-ligand 1 (PD-L1) expression and HER2 overexpression, which progressed despite treatment with gemcitabine and cisplatin (GP) chemotherapy combined with Tislelizumab. However, after undergoing combination treatment with Disitamab vedotin and Tislelizumab, the patient achieved a biochemical and imaging complete response (CR). To the best of our knowledge, this represents the first successful treatment of advanced UCTD using a combination therapy involving Tislelizumab and Disitamab vedotin. We aim to highlight the clinical characteristics, prognosis, and potential therapeutic strategies related to this rare disease. This case has been reported following the CARE guidelines.

2. Case report

A 36-year-old male patient presented to the hospital on August 20, 2022, with abdominal distension and pain. The Eastern Cooperative Oncology Group score was determined as 2 points. Physical examination revealed bilateral breast feminization, bilateral testicular atrophy, abdominal tenderness, and rebound pain. Serum tumor marker examination showed a β-HCG level of 36,364 mIU/mL, while levels of other tumor markers were within the normal range. A contrast-enhanced computed tomography (CT) scan revealed

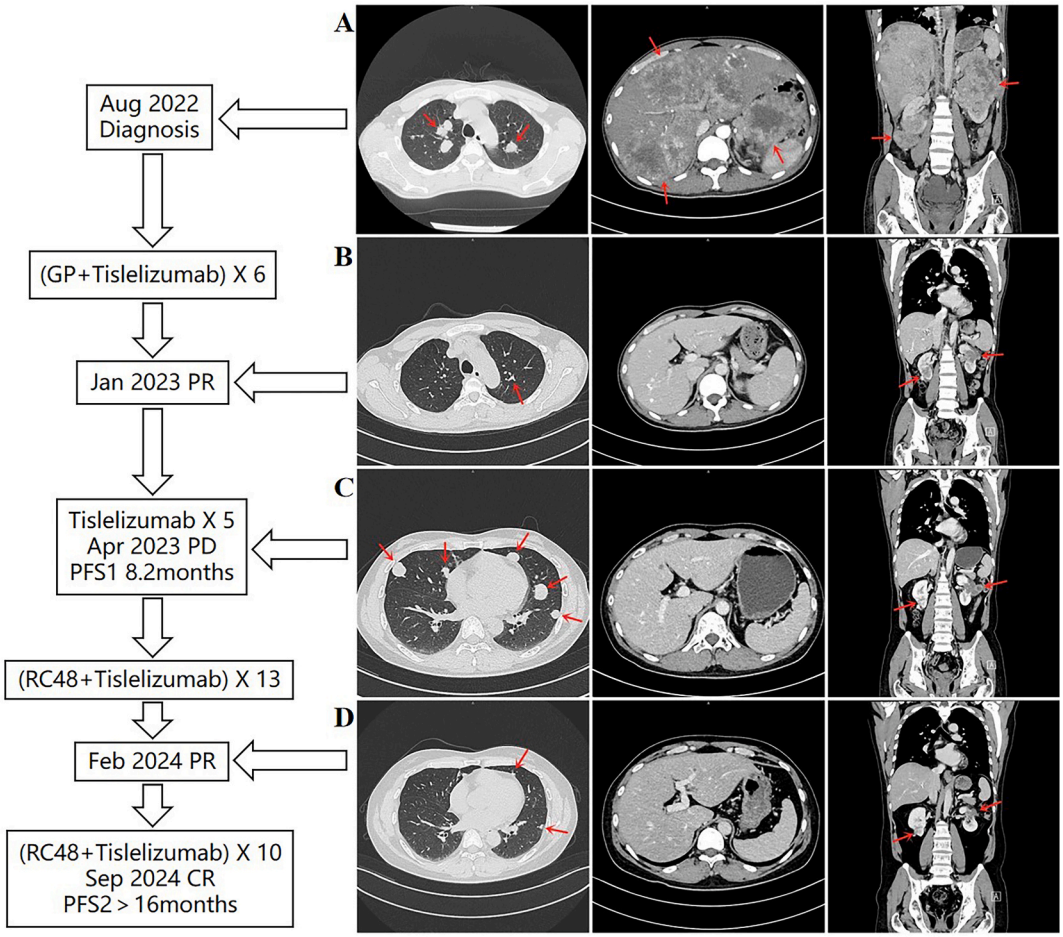

Fig. 1. The timeline of this patient's anti-tumor therapy and contrast-enhanced CT images during treatment. (**A**) Contrast-enhanced CT scan revealed bilateral kidney masses, multiple bilateral lung nodules, multiple intrahepatic masses, and most notably, liver tumors with rupture and hemorrhage. (**B**) Contrast-enhanced CT imaging revealed substantial reduction in both kidney masses and metastases within the liver and lungs compared to previous measurements. (**C**) Contrast-enhanced CT revealed enlarged pulmonary nodules with no significant changes in kidney and liver lesions. (**D**) Contrast-enhanced CT showed reduction in the size of the mass in the left kidney and multiple lung nodules compared to before treatment initiation (tumor indicated by red arrows). CT: computed tomography, GP: gemcitabine and cisplatin, RC48: Disitamab vedotin, PR: partial response, PD: progressive disease, CR: complete response, PFS: progression-free survival.

bilateral kidney masses, multiple lung nodules, multiple intrahepatic masses, and notably liver tumors with rupture and hemorrhage (Fig. 1A). The liver mass was managed through embolization and hemostasis after emergency intervention. Pathologic examination of the liver mass biopsy confirmed a diagnosis of metastatic high-grade UCTD. IHC revealed a high level of PD-L1 expression (tumor proportion score 50 %, combined positive score 53 %), as well as positive staining for β-HCG, MSH-2, MSH-6, MLH-1 and PMS-2. (Fig. 2A–C).

Following the initial cycle of treatment with GP chemotherapy in combination with Tislelizumab (day 1: gemcitabine 1000 mg/m^2, cisplatin 75 mg/m^2, and Tislelizumab 200 mg; day 8: gemcitabine 1000 mg/m^2 Q3W) on August 29th, 2022, the patient reported significant relief in symptoms of abdominal distension and pain. Furthermore, there was a notable decrease in serum β-HCG levels to 124.50 mIU/mL after five cycles of GP chemotherapy combined with Tislelizumab (Fig. 4A). Reassessment through contrast-enhanced CT demonstrated a substantial reduction in both kidney masses and liver and lung metastases compared to previous measurements (Fig. 1B). As per the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 criteria, the patient achieved a PR.

Due to the remarkable efficacy observed during GP chemotherapy combined with Tislelizumab, the patient's therapy was subsequently switched to single-agent maintenance therapy, which consisted of Tislelizumab at a dosage of 200 mg Q3W. However, after five cycles of Tislelizumab monotherapy, the patient's serum β-HCG increased to 313.04 mIU/mL (Fig. 4B). Contrast-enhanced CT revealed enlarged pulmonary nodules with no significant changes in kidney and liver lesions (Fig. 1C). Subsequently, a re-biopsy of the pulmonary nodules was performed, and pathological examination confirmed metastatic high-grade UCTD with HER2 overexpression (IHC 2+, negative fluorescence in situ hybridization) (Fig. 3A–C). The treatment consisted of Disitamab vedotin at a dose of 120 mg every two weeks and Tislelizumab at a dose of 200 mg every three weeks starting from April 26th, 2023. After thirteen cycles of treatment, β-HCG decreased to within the normal range (<1.20 mIU/ml) (Fig. 4B), and contrast-enhanced CT showed a reduction in the size of the mass in the left kidney and multiple lung nodules compared to before treatment initiation (Fig. 1D). He then received another ten cycles, and 18F-fluorodeoxyglucose (FDG)-positron emission tomography-CT showed that the multiple pulmonary nodules disappeared and bilateral kidney mass were significantly reduced with no FDG uptake (Fig. 5). The patient achieved biochemical and imaging CR.

Currently, the patient has completed twenty-four cycles of Disitamab vedotin plus Tislelizumab therapy. Regular monitoring of serum β-HCG levels and contrast-enhanced CT scans has shown progression-free survival (PFS) exceeding 16 months during Disitamab vedotin plus Tislelizumab therapy. No recurrence has been observed thus far, resulting in an overall survival (OS) exceeding 24 months. The combination regimen was well-tolerated, with the patient experiencing grade 2 myelosuppression and mild nausea. No other adverse events were reported. The timeline depicted in Fig. 1 illustrates the course and outcome of this patient's treatment.

3. Discussion

The malignant trophoblastic tumor is a rare and highly aggressive neoplasm with an unfavorable prognosis [7]. It predominantly arises in the midline of the body, affecting areas such as the retroperitoneum, mediastinum, and pineal gland. Frequently, it coexists with other components of malignancy like teratoma, asthenoma, or seminoma [8]. Patients afflicted by this condition often exhibit significantly elevated serum β-HCG levels and may manifest specific signs including male mammary feminization, testicular atrophy, and decreased libido [9]. UC can manifest in all urothelial lining organs of the urinary system, including the bladder, renal pelvis, and ureter [1]. UCTD is an exceedingly rare condition, with fewer than 10 cases documented in the scientific literature [3]. The precise origin of choriocarcinoid cancer cells within UC remains elusive, giving rise to two hypotheses: one posits derivation from the ectopic genitourinary ridge, while the other suggests derivation from urothelial cancer cells—a notion predominantly supported by researchers [2]. Zettl et al. demonstrated through comparative genomic hybridization that choriocarcinoma and UC share clonal origin, suggesting that the activation of embryonic cell programs in tumor cells may contribute to the emergence of trophoblastic cell features [3]. UCTD exhibits pathological characteristics including the coexistence of urothelial cancer cells and trophoblastic differentiation components such as focal syncytiotrophoblastic cells and chorionic cancer cells [10]. Tumor tissue often presents extensive bleeding and necrosis, while IHC reveals positive β-HCG expression along with high levels of Ki-67 index [11]. UCTD displays a highly aggressive nature with a propensity for distant metastasis, most commonly observed in the lung and liver (90 %) [12]. Our case involved a young male presenting with acute abdominal pain, who was diagnosed with UCTD exhibiting multiple liver and lung

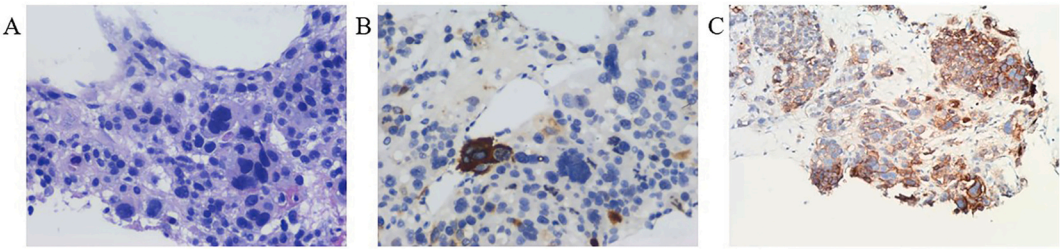

Fig. 2. Pathological and immunohistochemical pictures of the liver metastases (**A–C**). (**A**) High-grade urothelial carcinoma with scattered syncytiotrophoblasts, which are large multinucleated cells with abundant eosinophilic cytoplasm distributed throughout the urothelial carcinoma component (H&E, magnification × 200). (**B**) Immunohistochemistry found positivity for human chorionic gonadotropin (magnification × 200). (**C**) Immunohistochemistry found positivity (50 %) for programmed death-ligand 1 (magnification × 400).

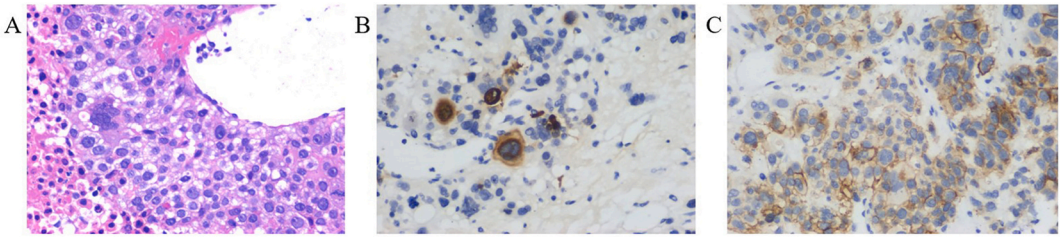

Fig. 3. Re-biopsy of a lung metastasis: pathological and immunohistochemical pictures (**A–C**). (**A**) The periphery of the tumor nest contains hyperchromatic syncytiotrophoblastic-like cells with deeply eosinophilic cytoplasm (H&E, magnification × 200). (**B**) Immunohistochemistry found positivity for human chorionic gonadotropin (magnification × 200). (**C**) Immunohistochemistry found positivity (2+) for human epidermal growth factor receptor 2 (magnification × 200).

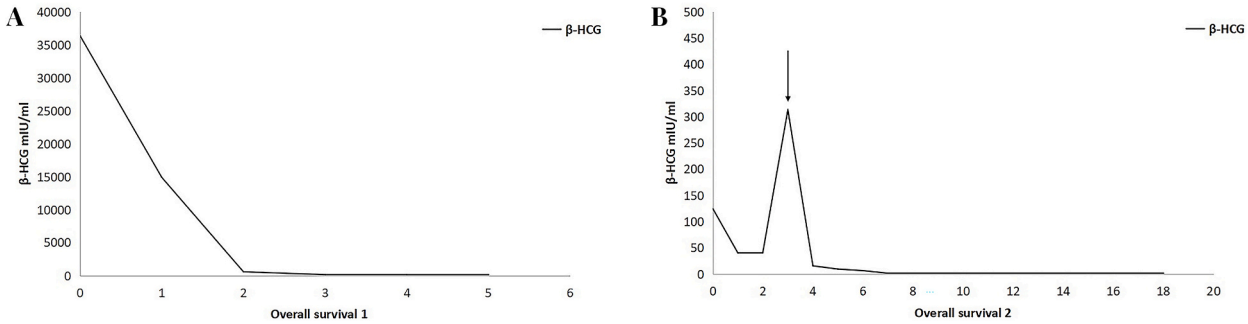

Fig. 4. Serum β-HCG trends during chemotherapy (**A**) and Tislelizumab combined with Disitamab vedotin (**B**). The arrow indicates the initiation of Disitamab vedotin.

metastases. The patient exhibited significantly elevated serum β-HCG levels, enhanced CT imaging revealed tumor necrosis, and physical examination indicated breast feminization and testicular atrophy—typical clinical features of trophoblastic tumors. Following treatment, the patient's serum β-HCG levels decrease to normal, suggesting that serum β-HCG can serve as a valuable indicator for disease diagnosis, prognosis evaluation, and therapeutic response monitoring.

Traditional platinum-based chemotherapy has limited efficacy as the primary treatment strategy for advanced UC due to the severe side effects and drug resistance associated with long-term treatment [5]. UCTD is an extremely rare condition with no standard treatment option. Studies have demonstrated that UCTD exhibits poor sensitivity to chemotherapy, and most patients are diagnosed at an advanced stage with a large tumor burden and compromised physical condition, rendering them unable to tolerate high-intensity chemotherapy [13]. Therefore, it is crucial to explore effective treatment strategies. In recent years, ICIs and anti-HER2 ADCs have significantly enhanced the therapeutic efficacy of advanced UC [14]. Tislelizumab, an ICI, is a potent and highly selective human monoclonal antibody specifically targeting the PD-1 receptor, effectively inhibiting the binding of its ligands PD-L1 and PD-L2, thereby eliminating the inhibition of T cell activation. Furthermore, modifying the Fc segment of Tislelizumab minimizes macrophage-mediated antibody-dependent phagocytosis and delays the development of drug resistance [15]. The clinical effectiveness of this treatment has been validated in various advanced malignancies, with the expression level of PD-L1 serving as a significant biomarker for predicting response [16,17].

A Phase II clinical trial presented at ESMO 2019 reported the efficacy of Tislelizumab monotherapy in Asian patients with advanced UC who were PD-L1-positive (≥25 %) and had previously failed first-line platinum-based chemotherapy. The study demonstrated an objective response rate (ORR) of 23.1 %, a median PFS of 2.1 months, and a median OS of 9.8 months [18]. Based on these compelling clinical findings, the National Medical Products Administration (NMPA) approved the use of Tislelizumab in April 2020 as a treatment option for locally advanced or metastatic UC characterized by high expression levels of PD-L1 that have shown resistance to platinum-based chemotherapy. Currently, the ongoing Phase III clinical trial in China is investigating the combination of Tislelizumab with cisplatin/carboplatin and gemcitabine as a first-line treatment for locally advanced or metastatic UC, providing a promising alternative for patients in need [19]. Despite favorable outcomes demonstrated by ICIs in the treatment of UC, their efficacy in UCTD remains uncertain [20–22]. Studies have indicated a high expression of PD-L1 in malignant trophoblastic tumors, which is significantly associated with a poor prognosis [23]. Therefore, it can be inferred that UCTD is likely to exhibit a higher incidence of elevated PD-L1 expression and may potentially benefit from ICIs. In our case, IHC revealed significantly increased expression of PD-L1, leading to a biochemical CR and an imaging PR following combination therapy with Tislelizumab. Notably, this represents the only reported case of advanced UCTD benefiting from ICIs, underscoring the significance of PD-L1 testing and demonstrating the efficacy of ICIs as a viable therapeutic option for advanced UCTD.

HER2 plays a pivotal role in the pathogenesis and progression of UC [24]. Overexpression of HER2 is closely associated with

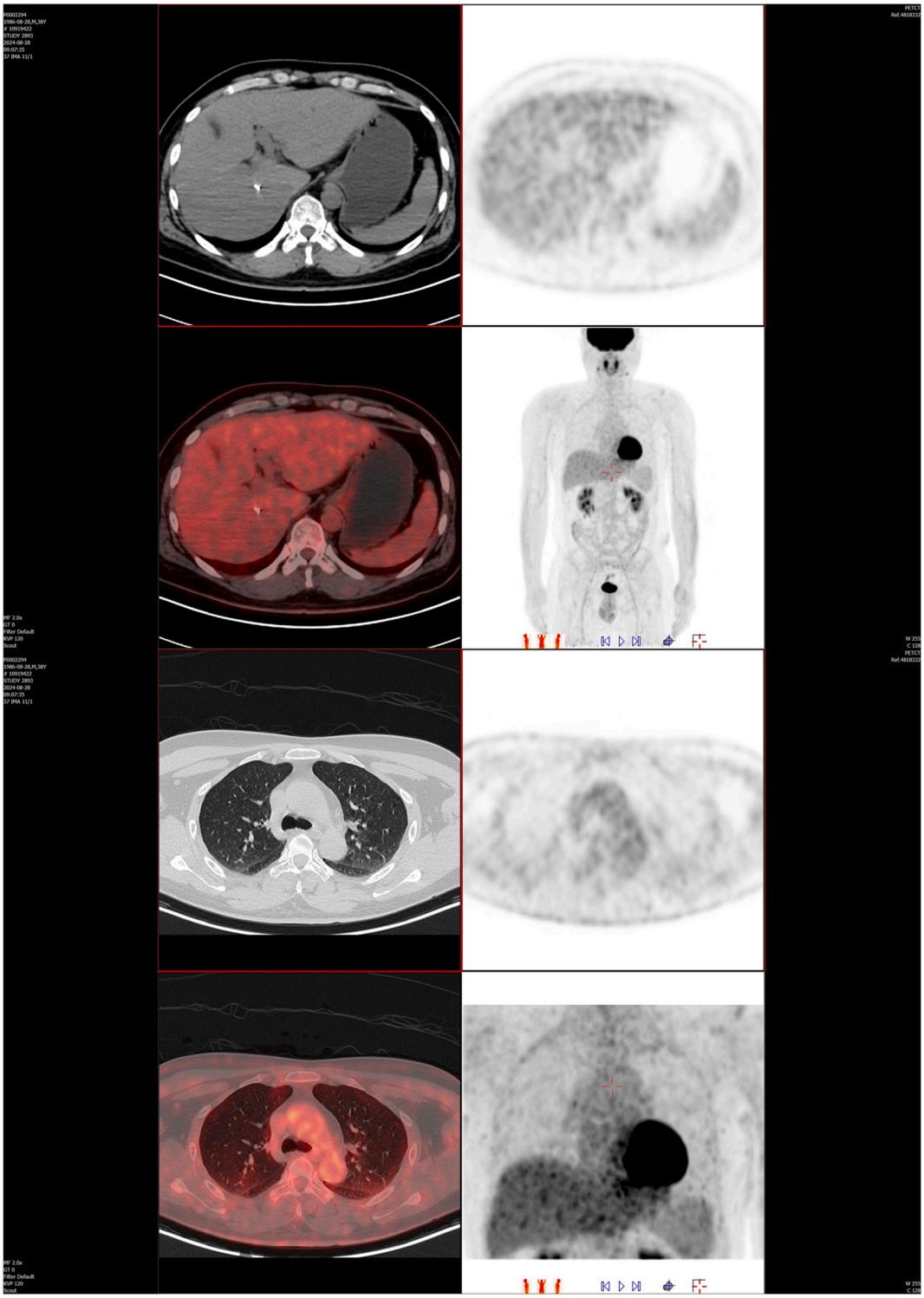

Fig. 5. 18F-fluorodeoxyglucose (FDG)-positron emission tomography-CT showed that the multiple pulmonary nodules disappeared and bilateral kidney mass were significantly reduced with no FDG uptake.

advanced stage, strong aggressiveness, and poor prognosis of UC [24]. It is noteworthy that UCTD may exhibit a higher likelihood of HER2 overexpression, warranting attention. For advanced UC with HER2 overexpression, studies have demonstrated limited efficacy when combining chemotherapy with anti-HER2 targeting drugs such as trastuzumab or lapatinib; however, significant clinical benefits

can be achieved through the use of anti-HER2 ADCs [25,26]. Disitamab vedotin comprises a humanized anti-HER2 antibody, hertuzumab, with enhanced affinity for HER2. This antibody is conjugated to the tubulin inhibitor monomethyl auristatin E (MMAE) through a separable connector [27]. Disitamab vedotin exerts its anti-tumor effects by inducing cytotoxicity via MMAE [28]. Moreover, due to the high membrane permeability of enzyme-interpreted MMAE, Disitamab vedotin can infiltrate neighboring cells and elicit a bystander effect, thereby exhibiting therapeutic efficacy against tumor cells with low or no expression of HER2 [29–32]. In Phase II trials RC48-C005 (18) and RC48-C009 (19) conducted in 2021, Disitamab vedotin emerged as the first globally approved ADC drug targeting HER2 for treating advanced UC displaying HER2 IHC 2+/3+ staining patterns [33].

In addition to directly inducing cancer cell death, anti-HER2 ADCs also modulate the immune microenvironment by promoting immunogenic cell death, facilitating antibody-dependent cell-mediated cytotoxicity, activating dendritic cells, enhancing T cell activity, and upregulating PD-L1 expression [34–36]. Both in vitro and in vivo studies have reported synergistic antitumor effects of ICIs combined with anti-HER2 ADCs [37]. A Phase Ib/II study evaluating Disitamab vedotin in combination with an ICI (toripalimab) for locally advanced or metastatic UC demonstrated an overall ORR of 73.2 %. Subgroup analysis revealed an ORR of 83.3 % among patients with HER2 IHC 3+/2+, while patients with IHC 1+ and IHC 0 exhibited ORRs of 64.3 % and 33.3 %, respectively. Furthermore, the combined regimen was well-tolerated in terms of toxicity and side effects [26]. These findings suggest that combining Disitamab vedotin with ICIs yields favorable efficacy for treating UC across different HER2 expression statuses. Our case achieved promising outcomes when treated with a combination of Disitamab vedotin and Tislelizumab after chemotherapy failure, providing further evidence for the effectiveness of this combination regimen in advanced UCTD.

The tumor microenvironment consists of non-tumor stromal cells, including immune cells, fibroblasts, endothelial cells, and new capillary systems, which exert their influence on the occurrence and progression of tumors through interactions with tumor cells [38]. It is noteworthy that significant remission was observed in all lesions of this patient after receiving combination therapy with Tislelizumab and chemotherapy. However, lung metastases increased during Tislelizumab monotherapy maintenance, while liver and kidney lesions continued to show remission. We hypothesize that the tumor immune microenvironment exhibits heterogeneity. The dynamic changes in the tumor microenvironment during treatment have a profound impact on both tumor efficacy and drug resistance. In this case, tumor progression was attributed to the suppression of the local immune microenvironment in lung metastases during Tislelizumab monotherapy. We conducted a re-biopsy which revealed HER2 overexpression. Subsequently, we administered Disitamab vedotin in combination with Tislelizumab and achieved satisfactory results, indicating that Disitamab vedotin may possess the ability to modulate the immune microenvironment and overcome ICI resistance, while emphasizing the importance of re-biopsy following disease progression.

4. Conclusion

In summary, UCTD is a rare and aggressive malignancy with a poor prognosis. Due to the limited number of reported cases in the literature, there is currently a lack of standardized treatment strategies for advanced UCTD. However, our successful management of advanced UCTD using Tislelizumab in combination with Disitamab vedotin highlights the promising potential of this combination therapy approach for managing advanced UCTD, emphasizing the significance of assessing PD-L1 and HER2 status in this rare disease. However, further research is warranted to provide substantiating evidence for utilizing Tislelizmab in combination with Disitamab vedotin as a viable therapeutic option for this uncommon disease.

Ethics statement

Written informed consent was obtained from the patient for the publication of this case report.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

CRediT authorship contribution statement

Yaqian Han: Writing – original draft, Formal analysis, Conceptualization. **Yujuan Zhou:** Writing – review & editing, Data curation. **Zheng Wu:** Formal analysis, Data curation. **Lin Liu:** Data curation. **Chen Han:** Writing – original draft, Formal analysis, Conceptualization.

Declaration of competing interest

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.

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Not applicable.

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