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Thrombotic Thrombocytopenic Purpura Induced by Combined Toripalimab and Pazopanib Therapy in a Patient with Renal Cell Carcinoma and Vertebral Metastasis: A Case Report

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Abstract: Thrombotic thrombocytopenic purpura (TTP) is a rare and life-threatening form of thrombotic microangiopathy, primarily caused by a deficiency of ADAMTS-13 activity. Immune-related adverse events (irAEs) are autoimmune toxicities mediated by the use of immune checkpoint inhibitors (ICIs). Here, the study reports a case of thrombotic thrombocytopenic purpura that developed in a patient with renal cell carcinoma and vertebral metastasis following combined treatment with Toripalimab and Pazopanib. The patient received Toripalimab in combination with Pazopanib after undergoing radical nephrectomy for right renal cell carcinoma. Five days later, a generalized erythematous rash appeared, partly confluent, accompanied by congestion and swelling of both palpebral and bulbar conjunctiva. Based on the clinical presentation and laboratory results showing thrombocytopenia and hemolytic anemia, the diagnosis of TTP was established. The condition was considered an adverse effect associated with the combination therapy of Toripalimab and Pazopanib. Plasma exchange and high-dose intravenous immunoglobulin therapy were promptly initiated. The treatment regimen was subsequently modified to Axitinib combined with radiotherapy, leading to a gradual recovery of platelet counts. This report highlights the potential risk of TTP associated with combined ICI and TKI therapy, and underscores the importance of early recognition and timely management of this potentially fatal complication.

Keywords: Toripalimab; Pazopanib; Thrombotic Thrombocytopenic Purpura (TTP); Immune Checkpoint Inhibitors (ICIs); Renal Cell Carcinoma (RCC); Immune-related Adverse Events (irAEs)

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1. Introduction

Toripalimab is a humanized monoclonal antibody belonging to the class of immune checkpoint inhibitors (ICIs). It is the first programmed cell death 1 (PD-1) inhibitor approved in China. By blocking the interaction between PD-1

on T cells and its ligand PD-L1 on tumor cells, Toripalimab restores T-cell-mediated cytotoxicity against malignant cells. It has been approved for the treatment of advanced melanoma, nasopharyngeal carcinoma, and urothelial carcinoma [1]. However, the clinical use of ICIs can lead to immune-related adverse events (irAEs), including thrombotic thrombocytopenic purpura (TTP) [2]. Pazopanib is a small-molecule tyrosine kinase inhibitor (TKI), and TTP is listed among its potential adverse events. TTP is characterized by microangiopathic hemolytic anemia, thrombocytopenia, neurologic abnormalities, fever, and renal involvement. It may occur as either a hereditary or an immune-mediated disorder. We report a case of TTP occurring after combination therapy with Toripalimab and Pazopanib in a patient with renal cell carcinoma and vertebral metastasis.

2. Case presentation

A 50-year-old male was admitted to the Department of Oncology, Gansu Provincial Central Hospital, on January 31, 2024, with a 3-day history of fever. He had no prior history of hematologic or autoimmune diseases. One month earlier, the patient had undergone "intracanal mass excision and internal fixation" at the Department of Orthopedics, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. Postoperative pathology confirmed clear cell renal cell carcinoma, for which he subsequently underwent a "laparoscopic radical nephrectomy of the right kidney." On January 22, 2024, combination therapy consisting of Toripalimab (240 mg, IV) and Pazopanib (800 mg orally, once daily) was initiated.

Three days before admission, the patient developed a generalized erythematous rash that was partially confluent, accompanied by congestion and swelling of the palpebral and bulbar conjunctiva. Vital signs were stable, but the general condition was poor. Based on clinical manifestations and laboratory findings (**Table 1**), the study considered a diagnosis of TTP. As ADAMTS13 activity testing was unavailable in our institution, plasma exchange was performed twice (2000 mL per session, once daily). High-dose intravenous immunoglobulin (0.4 g/kg), subcutaneous calcium heparin, frozen plasma, cryoprecipitate, and fibrinogen were administered to correct coagulopathy. Meropenem was used for anti-infective therapy, and platelet transfusions were given as needed. Despite these interventions, serial laboratory tests indicated progressive thrombocytopenia and worsening coagulopathy and renal function. His family elected to discontinue treatment and he was discharged. The patient returned to our department on February 21, 2024. Considering the severe immune-related adverse reactions described above, antitumor therapy was suspended. Supportive treatment, including hepatoprotective and renoprotective agents as well as thyroid hormone replacement, was initiated.

On March 10, 2024, the patient developed numbness and weakness in the right upper limb, with the inability to perform fine motor tasks such as buttoning clothes or using chopsticks, accompanied by right shoulder and back pain. He was readmitted to our department. Enhanced MRI of the brain and spine, together with a neurology consultation, revealed progression of vertebral metastases from renal cell carcinoma, causing spinal cord compression and peripheral neuropathy. The treatment regimen was modified to Axitinib (5 mg twice daily). Local radiotherapy was administered to the bone and paravertebral metastatic lesions (6 MV X-ray; PTV 37.5 Gy/2.5 Gy/15 fractions; PGTV 45 Gy/3.2 Gy/15 fractions), in combination with intravenous methylprednisolone (40 mg daily) to reduce edema and with supportive physical rehabilitation. The patient's general condition gradually improved, and he was discharged in stable condition.

Table 1. Laboratory findings

Date	Platelets	Haemoglobin	Creatinine	LDH	Bilirubin	PT	APTT	TT	FIB	Plasma exchange
2024.01.31	68					11.60	33.70	25.60	1.68	
2024.02.01	41	100	477	2244	30.50	12.30	42.10	32.50	1.27	√
2024.02.01						12.80	> 120	> 60	1.01	
2024.02.02	32	104	490	1324	23	12.60	71.20	> 60	0.93	√
2024.02.03	30	98	520	1057	17.50	11.60	76.90	> 60	0.89	
2024.02.20	160				27.70					
2024.02.21	152	99	213	745	44.80	12.20	32.70	19.30	2.22	
2024.02.25	207	92	173		39.80					
2024.02.29	209	98	161		32.10					
2024.03.04	195	93	140		16.80	11.20	31.30	20.90	1.63	
2024.03.13	229	117	108		21.90	11.00	28.50	19.10	2.25	
2024.03.20	151	110	109		14.50					
2024.03.28	140	123	89		23.10					
2024.04.04	110	115	96		23.70	9.90	28.30	18.20	2.77	

Normal reference ranges: Platelets 125–350×109/L; Hemoglobin 130–175 g/L; Creatinine 57–97 μmol/L; LDH 109–245 U/L; Bilirubin 0–23 μmol/L; PT 9.8–12.1 s; APTT 23.3–31.3 s; TT 14–21 s; FIB 1.8–3.5 g/L.

3. Discussion

Although immune checkpoint inhibitors (ICIs) have greatly improved clinical outcomes in cancer patients, they are also associated with an increased incidence of immune-related adverse events (irAEs). Hematologic irAEs caused by ICIs, such as TTP, aplastic anemia, neutropenia, and thrombocytopenia, remain rare and poorly characterized [3]. TTP is a rare but severe thrombotic microangiopathy characterized by a deficiency in the activity of the von Willebrand factor (vWF)-cleaving protease, ADAMTS13. Reduced ADAMTS13 activity leads to the accumulation of ultralarge vWF multimers (UL-vWF) released from endothelial cells, which fail to undergo normal proteolytic cleavage. These UL-vWF multimers can spontaneously bind platelets, promoting microvascular thrombosis and microangiopathic hemolysis, resulting in tissue ischemia, hypoxia, and organ dysfunction. Neurological symptoms, renal impairment, and fever are also commonly observed in affected patients [4].

The present patient was diagnosed with renal clear cell carcinoma and vertebral metastasis and received combination therapy with Toripalimab and Pazopanib. Five days after treatment initiation, he developed conjunctival congestion and swelling, along with multiple erythematous rashes over the body, some of which were confluent. Thrombotic thrombocytopenic purpura (TTP) was diagnosed, and plasma exchange combined with intravenous immunoglobulin therapy was immediately initiated. Platelet counts gradually increased to normal levels, and the treatment regimen was subsequently switched to Axitinib. The patient had developed a fever three days before admission, which was considered possibly related to the onset of TTP. A markedly reduced ADAMTS13 activity (< 10%) is a key diagnostic criterion for TTP. A limitation of this case was the absence of ADAMTS13 testing to further confirm the diagnosis. Nevertheless, early initiation of plasma exchange and immunoglobulin therapy may have contributed to the favorable clinical outcome. Other therapeutic options

include anti-CD20 (rituximab) and anti-vWF monoclonal antibodies.

The mechanisms underlying ICI-induced irAEs may involve: (1) enhanced T-cell reactivity against shared antigens expressed by tumor and normal tissues; (2) increased production of autoantibodies; and (3) upregulation of proinflammatory cytokines [5]. Pazopanib, a multitarget TKI, exerts antitumor and antiangiogenic effects by inhibiting vascular endothelial growth factor (VEGF) receptors, platelet-derived growth factor receptors, and c-KIT signaling pathways within tumor tissues, thereby improving the prognosis of renal cell carcinoma. Reported adverse effects include thrombocytopenia [6]. Therefore, TTP in this case may have resulted from a synergistic toxic effect of combined ICI and TKI therapy. The mechanism underlying TTP induced by Toripalimab and Pazopanib combination therapy remains speculative. Toripalimab may exacerbate Pazopanib-induced thrombocytopenia by promoting endothelial injury. Activated CD4+ and CD8+ T cells can trigger apoptosis of vascular endothelial cells via the Fas-FasL pathway, leading to microvascular damage and hemorrhage [7].

Apart from drug-induced causes, TTP has also been reported in association with advanced malignancies, often identified during initial diagnosis or recurrence. Approximately 20% of patients with recurrent cancer may develop TTP. The proposed mechanisms include direct invasion of tumor cells into bone marrow, resulting in endothelial damage, excessive release of ultralarge vWF multimers, and subsequent formation of ADAMTS13 autoantibodies and mucin-mediated endothelial injury [8,9]. In our case, TTP did not occur at the initial diagnosis of renal clear cell carcinoma.

With the expanding use of ICIs as adjuvant therapy for multiple malignancies [10,11], the incidence of immune-mediated TTP is expected to rise. Severe TTP poses a life-threatening risk to patients. This case suggests that the combination of Toripalimab and Pazopanib may induce TTP. Clinicians should be aware of the clinical manifestations and initial management strategies for this adverse event. In cases of severe toxicity, prompt discontinuation of therapy is recommended. Future research should focus on optimizing dosage combinations of ICIs and TKIs to maintain efficacy while minimizing adverse effects (**Table 2**).

Table 2. Reported cases of ICI-induced TTP

	Age/Sex	Primary tumor	ADAMTS13	ICI agent	T /d	PE	Drug	Outcome
King *et al*. (2017)	68/F	Melanoma	< 3%	Ipilimumab (CTLA-4)	77 d	√	M+R	Survival
Dickey *et al*. (2019)	60/F	Metastatic NSCLC	< 3%	Pembrolizumab (PD-1)	2 d	√	M	Death
Youssef *et al.* (2018)	42/F	Metastatic RCC	< 3%	Ipilimumab Nivolumab (CTLA-4+ PD-1)	4 d	√	P+R	Survival
Gergi *et al.* (2020)	51/F	Anal SCC	< 9%	Nivolumab (PD-1)	-	-	-	-
Mullally *et al.* (2022)	50/M	Metastatic Melanoma	< 5%	Ipilimumab Nivolumab (CTLA-4+ PD-1)	10 d	√	M	Death
Our case (2024)	50/M	Clear Cell RCC	-	Toripalimab (PD-1)	5 d	√	P	Survival

M: male; F: female; PE: plasma exchange; R: rituximab; M: methylprednisolone; P: prednisone; T: time to onset of platelet decline.

4. Conclusion

This case highlights a rare but serious occurrence of thrombotic thrombocytopenic purpura (TTP) following combination therapy with the immune checkpoint inhibitor Toripalimab and the tyrosine kinase inhibitor Pazopanib in a patient with metastatic renal clear cell carcinoma. Early recognition of characteristic clinical manifestations, such as thrombocytopenia, hemolytic anemia, and rapidly progressive systemic symptoms, combined with prompt initiation of plasma exchange and immunoglobulin therapy, was essential in achieving clinical stabilization. Although ADAMTS13 testing was unavailable, timely intervention likely contributed to the favorable outcome. As the use of ICIs and TKIs continues to expand across malignancies, clinicians should remain vigilant for rare but potentially life-threatening hematologic immune-related adverse events. Optimizing drug combinations and monitoring strategies to balance efficacy and toxicity will be critical in future clinical practice and research.

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Disclosure statement

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