Thrombotic thrombocytopenic purpura associated to dual checkpoint inhibitor therapy for metastatic melanoma

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Abstract

Dual checkpoint inhibitor therapy has known immune-related adverse events. However, checkpoint inhibitor-associated thrombotic thrombocytopenic purpura is very rarely reported. We present a case of a 70-year old man with advanced melanoma, presenting with severe thrombocytopenia, hemolytic anemia with schistocytes and suppressed ADAMTS-13 activity by ADAMTS-13 inhibitors. We discuss differential diagnoses and speculated mechanisms of this obviously therapy-related adverse event, which should be considered by clinicians prescribing these drugs.

Keywords Thrombotic thrombocytopenic purpura · TTP · Acute kidney injury · Checkpoint inhibitor therapy

Dual checkpoint inhibitor therapy (CTLA-4 blocking antibody + PD1 inhibitor) represents the state of the art therapy for advanced melanoma, non-small cell lung carcinoma and renal carcinoma. Common immune-related adverse events of this regimen comprise organ directed autoimmune phenomena as hypophysitis, pneumonitis, hepatitis, colitis, and nephritis. To our knowledge, development of an immune-mediated thrombotic thrombocytopenic purpura (TTP) following ipilimumab alone or in combination with nivolumab was reported only in three cases up to date [1–3].

A 70-year-old man presented as part of a regular control a significant reduction of the platelet count ($7 \times 10^3/\mu\text{L}$, prior $270 \times 10^3/\mu\text{L}$) 18 days after a second combined nivolumab (each administration with 198 mg; 3 mg/kg) plus Ipilimumab (each administration with 66 mg; 1 mg/kg) cycle for metastatic melanoma diagnosed 5 years ago.

The patient presented with impaired physical condition, namely asthenia, muscle weakness and reduced appetite. Blood pressure was 138/85 mmHg, pulse 105 bpm and

oxygen saturation 98%. Clinical examination revealed slowed speech, beginning memory disorders, deteriorated cognition and signs of dehydration. Laboratory results revealed hemolysis by low hemoglobin 10 g/dL; hematocrit 29%, LDH 1312 U/L, haptoglobin < 0.08 g/L, and detection of schistocytes in the blood smear. Additionally, acute kidney injury (creatinine 247 $\mu\text{mol/L}$) and elevated liver enzymes were found (Table 1). Initially he received rehydration with normal saline infusion, one platelet concentrate and dexamethasone (1 mg/kg/body weight) in our intensive care unit. The next day a CT scan confirmed multiple cerebral metastatic lesions with bleedings. Because of the poor prognosis and the dramatically aggravated general condition we decided to waive a plasma exchange in spite of possible TTP. Unfortunately, the patient died on the same day. Later laboratory results confirmed an acquired TTP with ADAMTS 13 deficiency (ADAMTS 13 activity < 5%; ADAMTS 13 inhibitor > 2).

Retrospectively, we postulate a secondary TTP as an immune-related adverse event (irAE) followed by administration of dual checkpoint inhibitor. However, we acknowledge that advanced malignancies can trigger TTP itself [4], strikingly, the temporal parallel of initiation of dual checkpoint inhibition and onset of TTP within weeks is the common characteristic of our and the other reported cases [1–3]. An up-regulation of T-cell immune function may result in TTP as checkpoint inhibitors are associated with exacerbation of underlying autoimmune conditions in up to 50% of patients [5]. A recently published case showed a TTP-like

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Table 1 Laboratory results 18 days before admission and on admission

Test	Before admission	On admission	Reference range
Hemoglobin (g/L)	143	85	120–147
Hematocrit (%)	40	29	40–50
Schistocytes (+/–)	n.d.	+	
Platelets ($\times 10^3/\mu\text{L}$)	255	7	140–360
LDH (U/L)	203	1312	125–220
Total bilirubin ($\mu\text{mol/L}$)	6	63	<21
Haptoglobine (g/L)	n.d.	<0.08	0.4–2.68
Creatinine ($\mu\text{mol/L}$)	67	247	49–90
Direct Coombs's test	n.d.	Negative	
Sodium (mmol/L)	145	140	136–145
Potassium (mmol/L)	3.4	3.1	3.6–5.1
Calcium (mmol/L)	2.45	2.15	2.2–2.5
Phosphate (mmol/L)	n.d.	1.18	0.75–1.52

condition two weeks after administration of nivolumab [3]. In contrast to our case, the authors could not detect an ADAMTS 13 inhibitor and therefore they speculate that the release of multiple inflammatory cytokines hindered the production of ADAMTS 13 [3].

Furthermore, the coexistence of bone marrow metastasis and secondary TTP has been described in retrospective analysis [4] and could have been a differential diagnosis for our patient. Our case presented diffuse bone marrow metastasis, but the normal platelet count prior to checkpoint inhibitor treatment with already metastatic cancer made this association unlikely. However, until now the mechanism of this hematological irAE is not well understood.

Clinicians should consider rare autoimmune hematologic complications like TTP as irAEs when prescribing immune therapy in advanced malignant disease.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Informed consent Informed consent was obtained post mortem from the closest relative (wife).

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