Anti-PD1 therapy-associated distal renal tubular acidosis: A case report

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Abstract. Distal renal tubular acidosis (RTA) is a rare adverse reaction to immune checkpoint inhibitors, which only occurs in a small number of cases. To the best of our knowledge, distal RTA caused by sintilimab, a programmed cell death protein 1 (PD-1) inhibitor, has not been previously reported. In the present study, the case of a 62-year-old man with metastatic cardiac carcinoma treated with sintilimab anti-PD-1 therapy was reported. After the fourth administration of sintilimab, the treatment course was interrupted by metabolic hyperchloraemic acidosis with hypokalaemia. Following urine and blood tests, immunotherapy-induced distal RTA was suspected. Treatment with sintilimab and chemotherapy was stopped, and treatment with sodium bicarbonate and potassium citrate was started, which resulted in an adequate response. The present study provides the first case of distal RTA secondary to sintilimab treatment.

Introduction

Programmed cell death protein 1 (PD-1) inhibitors and programed death-ligand 1 (PD-L1) inhibitors can enhance self-immune functions against cancer cells by blocking the binding of PD-1 and PD-L1 (1). PD-1/PD-L1 inhibitors demonstrate high rates of durable clinical responses in multiple types of cancer, such as non-small cell lung cancer and metastatic melanoma (2,3). Widespread use of PD-1 and PD-L1 inhibitors has resulted in an increase in the incidence of immune-related adverse events. The recent literature has demonstrated that PD-1 and PD-L1 inhibitors may affect multiple organ systems, including the skin and cardiovascular, gastrointestinal and endocrine systems (4). Kidney toxicity induced by PD-1 inhibitors occurs in 2-5% of patients treated with immunotherapy (5). Renal tubular acidosis (RTA) comprises a group of disorders in which excretion of hydrogen ions or reabsorption of filtered HCO_3 is impaired, leading to chronic metabolic acidosis with normal anion gap (6). Distal RTA is a rare adverse reaction to PD-1 inhibitors. To the best of our knowledge, distal RTA caused by sintilimab, a PD-1 inhibitor, has not been previously reported. In the present study, a case of distal RTA secondary to sintilimab treatment is presented and the related literature is reviewed to provide a description of distal RTA.

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Case report

A 62-year-old man with a history of cardiac carcinoma with lung, liver and stomach metastasis attended a scheduled oncology visit in August 2022 to the Oncology Department of Hebei General Hospital (Shijiazhuang, China) for the fourth cycle of treatment with the PD-1 inhibitor sintilimab (200 mg every 3 weeks) in combination with oxaliplatin (100 mg every 3 weeks) and albumin-bound paclitaxel (300 mg every 3 weeks). The patient started this regimen 3 months prior to this hospital visit. This visit was 40 days since the third dose of treatment and was delayed because the patient suffered liver injury after the third cycle. At this visit, the patient reported worsening generalized fatigue and progressive weakness. Initial blood samples and blood gas analysis indicated the following: A blood pH value of 7.25; a partial pressure of carbon dioxide (pCO_2) of 21.73 mmHg; a bicarbonate radical (HCO_3^-) level of 9.4 mmol/l; a potassium level of 2.8 mmol/l; a sodium level of 139 mmol/l; a chloride level of 117 mmol/l; an anion gap (AG) of 13; a blood urea level of 5.2 mmol/l; a creatinine level of 111.6 μmol/l (Table I). The patient was diagnosed with metabolic hyperchloraemic acidosis and hypokalaemia, without acute kidney injury (AKI). Sintilimab and chemotherapy treatments were stopped. The patient received a 15% potassium chloride intravenous injection (1.5 g) every day, potassium chloride sustained-release tablets (1 g) three times a day and intravenous sodium bicarbonate (6.25 g) every day for 7 days. On day 7, the blood pH improved to 7.36 and the potassium levels improved to 3.8 mmol/l, but the serum bicarbonate and pCO_2 were still below normal levels (Table I). Given the hyperchloraemic metabolic acidosis with normal AG levels, as indicated by decreased arterial blood pH levels, decreased HCO_3^- levels, decreased pCO_2 levels, increased blood chloride concentrations with hypokalaemia, a urine pH >5.5, urine anion gap >0 (Table I), no diarrhea and normal

Table I. Laboratory values during the hospital admission of the patient.

Test type	Reference	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 9	Day 11	Day 14
Blood pH	7.35-7.45	7.25	7.29	7.34	7.33	7.31	7.36	7.36	7.40	7.40	7.40
pCO_2 (mmHg)	35-45	21.73	24.88	22.21	19.37	20.90	23.90	30.42	33.21	35.30	37.10
Serum bicarbonate (mmol/l)	22-27	9.4	12.1	11.7	10.0	10.3	13.1	16.7	20.2	23.2	23.6
Anion gap	5-17	13.0	12.5	12.0	9.6	11.3	10.4	13.5	13.7	13.7	10.9
Serum potassium (mmol/l)	3.5-5.3	2.8	2.8	3.7	3.3	3.8	3.5	3.8	3.9	4.5	4.4
Serum sodium (mmol/l)	137-147	139	137	134	137	136	135	135	137	137	138
Serum chloride (mmol/l)	99-110	117	113	112	115	113	110	108	104	103	104
Urine analysis pH	4.5-8	-	7	-	-	7	-	-	-	7	-
Urine anion gap (mEq/l)	>40	-	-	-	23.4	-	-	17.5	-	-	-
Serum blood urea (mmol/l)	3.6-9.5	5.2	-	-	4.8	-	-	3.3	-	3.9	4.0
Serum creatinine (μmol/l)	57-111	111.6	-	-	94.5	-	-	99.9	-	94.2	90.2

Day, days since admission; pCO_2, partial pressure of carbon dioxide; '-', not tested.

AG levels, the patient was diagnosed with distal type I RTA. The patient was treated with potassium citrate (2 g by mouth three times a day) from day 7 to day 12, and on day 12, the pH, pCO_2, HCO_3^-, potassium and chloride levels were within normal limits; therefore, the patient was discharged from the hospital. A month later the patient visited the hospital and an imaging examination found that their disease had progressed; therefore, they switched to a regimen of oxaliplatin (100 mg every 3 weeks) and S-1 (tegafur, gimeracil and oteracil potassium capsules, 60 mg twice a day for 14 days, every 3 weeks). At the time of publication, the patient was still receiving this treatment.

Discussion

Kidney toxicity due to PD-1 inhibitors has been well described and occurs in 2-5% of patients on immunotherapy worldwide (5). Clinically, renal toxicities may present as AKI, proteinuria and dyselectrolytaemia, but acute tubulointerstitial nephritis is the most frequent diagnosis (7). Distal RTA is a rare adverse reaction to PD-1 inhibitors and, to the best of our knowledge, there are currently only 7 cases reported in the literature (Table II) (8-12). Among the 7 patients, 3 patients received treatment with nivolumab, 2 patients received treatment with pembrolizumab, 1 patient received five nivolumab injections and a single injection of pembrolizumab, and 1 patient received treatment with ipilimumab combined with nivolumab, but no reports of RTA caused by sintilimab have been reported. The present study would be the only reported case of distal RTA after treatment with sintilimab.

According to the 7 cases reported in the literature, the time interval from the beginning of PD-1 inhibitor treatment to the occurrence of RTA ranged from 6 weeks to 2 years (8-12). Patients with RTA may have symptoms related to hypokalaemia, such as fatigue and dyspnea, or RTA may be indicated by abnormal laboratory tests. The diagnosis of RTA is mainly based on the results of laboratory examinations, including normal AG levels, decreased arterial blood pH, HCO_3^- and pCO_2 levels, increased blood chloride concentrations with or without hypokalaemia, a urine pH >5.5 and a positive urine anion gap (6). When the patient has the aforementioned abnormalities after use of a PD-1 inhibitor, RTA caused by PD-1 inhibitor treatment should be considered. The time course of RTA onset in the patient of the present study (3 months after the first dose of sintilimab) was consistent with the aforementioned data, and the manifestations and laboratory abnormalities were also similar to the aforementioned cases.

Prompt treatment is important, as the side effects of undiagnosed and untreated distal RTA can be serious, including osteoporosis and respiratory muscle paralysis (13). Conventionally, patients with distal RTA should be treated preferentially with compound citric acid solution (Shohl's solution; containing 140 g citric acid and 98 g sodium citrate, adding water to 1,000 ml) (14). The patient in the present case report was administered potassium citrate, which contains citric acid, after the diagnosis of RTA. All 7 patients in the aforementioned cases improved after receiving treatments with steroids and bicarbonate and potassium supplementation. In the present case, the patient was not treated with steroids since their condition significantly improved after using potassium citrate. The patient was treated with potassium citrate for 5 days and the symptoms gradually improved.

Distal RTA may be caused by the obstructed secretion of H^+ ions in the collecting tubules (15). The function of secreting H^+ ions in the collecting tubules is mainly carried out by type A intercalated cells. CO_2 generates H_2CO_3 under the action of carbonic anhydrase II, which then dissociates into H^+ and HCO_3^- ions (16). An abnormality in the H^+ ion secretion in the distal nephron can simultaneously reduce the degree of urine acidification and the secretion of NH_4^+ ions (17). A large H^+ ion gradient cannot be generated and maintained between the lumen fluid and the peritubular fluid. Therefore, urine cannot be acidified in the case of acidosis. When the urine pH value is >5.5, the net acid output decreases (13).

Major causes of RTA in adults include autoimmune disorders (such as Sjogren's syndrome, primary biliary cirrhosis, autoimmune hepatitis, rheumatoid arthritis and lupus), hypercalciuria (such as hyperparathyroidism and sarcoidosis), drug treatments

Table II. Reported cases of immune checkpoint inhibitor-induced renal tubular acidosis.

First author, year	PD-1 inhibitor	Dose	Combined medication	Cycles	Time to last administration	Clinical manifestation	Blood pH	CO_2 (mmHg)	HCO_3^- (mmol/l)	AG	K^+ (mmol/l)	Na^+ (mmol/l)	Cl^- (mmol/l)	Urine pH	UAG (mEq/l)	BUN (mg/dl)	Cr (μmol/l)	ANA	Steroid	Prognosis	Immunotherapy rechallenge	(Refs.)
El Bitar *et al*, 2018	Nivolumab	240 mg	NA	4	A few days (not specified in the original text)	Fatigue and weakness	7.21	27	11	10	2.4	137	116	6.5	22	23	147.63	Negative	1 mg/kg/day	Improved	No	(8)
Charmetant *et al*, 2019	Five nivolumab injections and a single injection of pembrolizumab	Nivolumab: 3 mg/kg, pembrolizumab: 2 mg/kg	NA	6	5 days	Fever and maculopapules	7.29	22	11	NA	3.3	NA	113	6.0	36	NA	76.00	Negative	1 mg/kg/day	Improved	No	(9)
Herrmann *et al*, 2020	Pembrolizumab	200 mg	Ibuprofen and omeprazole	4	3 months	NA	7.26	39	16	13	2.8	137	107	6.5	10	27	123.76	NA	40 mg/day	Improved	No	(10)
	Nivolumab	240 mg	PPI	32	NA	Fatigue and loss of appetite	7.25	22	19	11	4.2	144	118	6.3	48	30	440.23	NA	30 mg/day	Improved	No	
	Nivolumab	240 mg	Omeprazole	48 months after omeprazole started	2	NA	7.23	20	16	14	3.9	142	117	6.7	NA	44	231.60	NA	75 mg/day	Improved	No	
Atiq *et al*, 2021	Pembrolizumab	200 mg	NA	5	21 days Change in mental state, fatigue and dyspnea		7.05	23	6	10	3.2	NA	124	6.0	49	47	176.80	NA	40 mg/day	Improved	No	(11)
Doodnauth *et al*, 2021	Ipilimumab and nivolumab	NA	NA	2	A few days (not specified in the original text)	Mental state change, fatigue and anorexia	7.24	24	11	12	3.1	133	110	7.5	40	23	282.88	Negative	1 mg/kg/day	Improved	No	(12)

PD-1, programmed cell death protein 1; HCO_3^-, bicarbonate radical; CO_2, carbon dioxide; K^+, potassium ion; Na^+, sodium ion; Cl^-, chloride ion; UAG, urine anion gap; BUN, blood urea nitrogen; Cr, creatinine; ANA, antinuclear antibody; PPI, proton pump inhibitor; NA, not available in the published paper.

(such as ibuprofen, lithium, amphotericin B and ifosfamide) and other conditions (such as obstructive uropathy and rejection of renal transplants) (12). Although the specific pathological mechanism still requires investigation, acquired distal RTA results from an alteration in the H^+-ATPase or Cl^-/HCO_3^- pump in type A intercalated cells in the collecting duct, and autoimmunity is a frequent cause (9). Among the cases included in the present study review, 3 patients (9,10) underwent a renal biopsy that revealed related manifestations of acute tubulointerstitial nephritis, suggesting that the RTA caused by the PD-1 inhibitor may be immune-mediated. However, the specific pathological mechanism requires further investigation.

Another potential mechanism may be related to the modulation of adenosine by PD-1 inhibitors (10,18). Renal epithelial cells can induce adenosine production when stimulated, and adenosine can activate purinergic type 1 receptors (such as A2A and A2B receptors) to induce vacuolar-type H^+-ATPase (V-ATPase)-dependent H^+ secretion (18,19). PD-1 inhibitors have been demonstrated to synergistically inhibit adenosine signaling through purinergic receptors (18). Therefore, Herrmann *et al* (10) hypothesized that the decrease in V-ATPase expression noted in the patients with distal RTA could be mediated by purinergic receptor inhibition using PD-1 inhibitors. This concept requires further investigation in the future.

Previous studies have demonstrated that the combined use of PD-1 inhibitors and proton pumps may increase the incidence of immune-related adverse reactions caused by PD-1 inhibitors (20,21). Herrmann *et al* (10) reported on 2 patients who had no adverse reaction after using a PD-1 inhibitor for >1 year; however, RTA occurred in these patients after combined use with a proton pump, thus suggesting that proton pump inhibitors should be used cautiously when using PD-1 inhibitors in clinical practice.

In conclusion, RTA caused by PD-1 inhibitors is a rare adverse reaction. Patients with RTA may have symptoms related to hypokalaemia, such as fatigue and dyspnea. Laboratory tests may indicate hyperchloric metabolic acidosis with normal AG, often accompanied by hypokalaemia. Nephrologists and oncologists should be aware of the potentially life-threatening side effect induced by immune checkpoint inhibitors that was reported in the present study.

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

Authors' contributions

XQ drafted the manuscript. BR substantially contributed to the conception or design of the work, and collected important background information. LF and ZD performed interpretation of data and reviewed the manuscript. XQ and BR confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent for publication was obtained by the patient.

Competing interests

The authors declare that they have no competing interests.

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