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A case of Fanconi syndrome as a complication of treatment with a checkpoint inhibitor in a patient with hepatocellular carcinoma

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ABSTRACT

Introduction: Immune checkpoint inhibitors (CPIs) represent novel new cancer immunotherapy agents. The use of nivolumab has been linked with immune mediated acute interstitial nephritis (AIN).

Case Presentation: We present the case of a patients with recurrent hepatocellular carcinoma who developed severe Fanconi syndrome, as evidenced by hyperchloremic metabolic acidosis, hypokalemia, hypophosphatemia, glucosuria, aminoaciduria, 8 months after initiating treatment with nivolumab, without any evidence of acute renal insufficiency.

Conclusion: Clinicians need to be aware of the renal side effects of new novel cancer immunotherapy agents, such as, immune CPIs.

Case Report

Implication for health policy/practice/research/medical education:
Clinicians need to be aware of the renal side effects of new novel cancer immunotherapy agents, such as, immune checkpoint inhibitors.

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Introduction

Immune checkpoint inhibitors (CPIs) represent novel cancer immunotherapy agents. They are used in treating hematological and solid organ malignancies. Immune CPIs are monoclonal antibodies that enhance the body immune reactivity. They include 2 categories of agents; Programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors (1).

PD-1 is a transmembrane protein on the surface of activated T cells, B cells and natural killer cells. It binds to PD ligand 1 (PD-L1) on the surface of tumor cells. This results in tumor cell proliferation and inhibition of tumor cell apoptosis, and downregulation of multiple T lymphocytes functions.

CTLA-4 is a CD28 homolog with a much higher binding affinity for B7 (CD80/86) expressed on antigen presenting cells and thus reduce the magnitude of CD28 costimulatory response and result in inhibition of T cell activation.

The immune CPI monoclonal antibodies either block the interaction between PD-1 on activated T lymphocytes and PD-L1 on tumor cell surface that results in anti-proliferation and tumor apoptosis, or block the interaction of CTLA-4 on T lymphocytes and B7 (CD80/86) on antigen presenting cells that leads to augmented costimulatory pathway activation of effector T lymphocytes. Both scenarios lead to enhanced immune reactivity and may lead to autoimmunity (1).

CPIs have been approved for treatment of a variety of malignancies including melanoma, hepatocellular carcinoma and non-small cell lung cancer (1,2). The FDA has approved several CPIs since 2011. These inhibitors are classified into three categories (Table 1);

1. PD-1 inhibitors target programmed cell death-1 receptor, such as pembrolizumab, nivolumab and

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Table 1. Approved CPIs and their targets and common indications

Checkpoint inhibitor	Target	Market Entry	Common Indications
Pembrolizumab	PD-1	2014	Melanoma, non–small-cell lung cancer
Nivolumab	PD-1	2014	Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma
Cemiplimab	PD-1	2018	Metastatic cutaneous squamous cell carcinoma
Atezolizumab	PD-L1	2016	Non–small-cell lung cancer, urothelial carcinoma
Avelumab	PDL-1	2017	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PDL-1	2017	Urothelial carcinoma
Ipilimumab	CTLA-4	2011	Melanoma

cemiplimab.

2. PD-L1 inhibitors target programmed cell death 1 ligand (PD-L1), such as atezolizumab, avelumab and durvalumab.
3. Monoclonal antibodies that target CTLA-4, such as ipilimumab.

The FDA approved nivolumab for the treatment of advanced non-small cell lung cancer, advanced urothelial bladder cancer, advanced melanoma, advanced head and neck squamous cell cancer, Hodgkin lymphoma, and in select patients with hepatocellular carcinoma who have been treated with sorafenib, and in advanced renal cell cancer and metastatic colorectal cancer (2).

The administration of nivolumab has been linked with immune mediated acute interstitial nephritis (AIN).

We present a case of severe electrolyte imbalance including hypokalemia and hypophosphatemia associated with the use of nivolumab without acute kidney injury (AKI).

Case Presentation

The patient was a 59-year-old man who has a known history of liver cirrhosis due to chronic hepatitis C. On a surveillance liver ultrasound, he was found to have a mass in the right lobe of the liver. The mass was biopsied on 08/07/2015 and he was diagnosed with well-differentiated hepatocellular carcinoma (HCC). The mass measured 1.0 ×1.0 × 1.2 cm and was confirmed with an MRI of the abdomen with and without intravenous (IV) contrast. The mass was resected, and he received no further treatment. A follow up IV contrast enhanced CT scan of the abdomen and pelvis on 01/19/2018 revealed multiple subtle hypodense hepatic lesions mainly in the right hepatic lobe, the largest measuring 1.4 × 1.6 cm. He was diagnosed with recurrent HCC. The patient was started on sorafenib (a vascular endothelial growth factor antagonist) but he experienced adverse cutaneous reactions mainly hand-foot syndrome and pruritus. Sorafenib was discontinued after 5 months and he was started on nivolumab one IV infusion every two weeks. The patient has no history of diabetes mellitus, multiple myeloma, autoimmune disorders or lead poisoning.

On 02/11/2019, eight months since the start of nivolumab he presented to the emergency department with a two-day history of generalized weakness, falls and fatigue. He had difficulty walking and lifting his legs. The patient denied having nausea, vomiting or diarrhea.

His past medical history was significant for chronic obstructive pulmonary disease and extended-spectrum beta-lactamase, *E. coli* UTI in July 2018. Family history was noncontributory. The patient had a 20-pack year smoking history and he drank 2 cans of beer daily. In addition to nivolumab his home medications were fluticasone-vilanterol inhaler, megestrol and pantoprazole.

Physical exam on admission was significant for BP 118/69 mm Hg, HR 92 beats/min, RR 18 per minute, temp 97.8°F, O2 saturation was 96% on room air, weight 57 kg and height 168 cm. The exam was otherwise unremarkable. Hepatosplenomegaly was not noted on exam.

Initial laboratory data: Na 141 meq/L, K 1.7 meq/L, Cl 111 meq/L, CO2 20 meq/L, BUN 15 mg/dL, Cr 0.74 mg/dL, anion gap 10 meq/L, Glucose 122 mg/dL, Ca 9.5 mg/dL, Alb 3.6 g/dL, hemoglobin 15.3 g/dL, Mg 2.3 mg/dL (on day 3), phosphorus 1.2 mg/dL (on day 4).

Urinary studies completed on day 4: 24 hour urine potassium 89 meq, trans-tubular potassium gradient (TTKG) 24.79, 24 hour urine Na was 205 meq, fractional excretion of phosphorus 11%, urine glucose 100 mg/dL, 24 hour urine protein was 1014 mg, urine quantitative amino acid analysis revealed a significant elevation of gamma-aminobutyrate, and minimal to moderate elevations of several other amino acids. He had no paraproteins in serum or urine. Urine volume was 2600 mL per 24 hours. Urinalysis showed a urine pH of 7.0. Arterial blood gas on day 3: pH 7.39, PCO2 25, PO2 75, HCO3 15, BE -8, O2 sat 95% on room air. Further laboratory studies are provided the Table 2.

The patient received aggressive IV and oral replacement of potassium and on hospital day 6 he was discharged

Table 2. Laboratory studies during the patient 6-day hospitalization

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Sodium (mEq/L)	141	141	141	143	144	140
Potassium (mEq/L)	1.7	1.4	2.0	3.0	3.3	3.6
Chloride (mEq/L)	111	112	108	114	114	109
Serum CO2 (mEq/L)	20	18	18	19	21	20
Creatinine (mg/dL)	0.74	0.89	0.87	0.75	0.75	0.65
Calcium (mg/dL)	9.5	8.9	8.7	8.0	8.2	8.6
Phosphorus (mg/dL)				1.2	2.0	2.2

with a potassium level of 3.6 meq/L, CO2 20 meq/L and phosphorus 2.2 mg/dL. Nivolumab was discontinued by his oncologist. His discharge medications included; spironolactone 25 mg daily, potassium sodium phosphate (K Phos Neutral) 250 mg 4 times a day, and potassium chloride 20 meq twice a day.

Eighteen days after discharge his sodium was 145 meq/L, potassium 3.6 meq/L, creatinine 0.8 mg/dL and serum CO2 19 meq/L. The patient has declined follow up in the renal clinic.

This patient's presentation was consistent with acquired Fanconi syndrome (non-anion gap hyperchloremic metabolic acidosis due to proximal renal tubular acidosis (pRTA), hypokalemia, hypophosphatemia, aminoaciduria, and glucosuria) due to the CPI nivolumab. He did not have other conditions that would explain the above findings such as paraproteinemia. He had no prior history of electrolyte problems based on review of prior laboratory studies.

Discussion

The indications for CPIs are expanding for a variety of solid tumors and hematological malignancies. Nivolumab use has been linked with a variety of immune-mediated reactions containing pneumonitis, colitis, hepatitis, endocrinopathies, encephalitis, skin rash, and AIN (2).

The package insert (2) reports immune-mediated nephritis and renal dysfunction in 1.2% of patients; after a median time of 4.6 months. The renal abnormalities led to termination of treatment with nivolumab in 0.3% of patients and to withholding of nivolumab in 0.8% of patients. All patients were treated with high-dose corticosteroids for a median duration of 21 days, resulting in resolution of renal dysfunction in 48% of patients. Re-challenge with nivolumab did not result in recurrence of renal dysfunction.

Electrolyte disturbances due to nivolumab have not been widely reported. Most current reports on renal adverse effects of CPIs are focused on AIN with no mention of electrolyte abnormalities. Recently the case of a 58-year-old man with a history of metastatic melanoma was reported who presented with progressive quadriplegia after 10 months of treatment with nivolumab (3). Initial laboratory data showed potassium of 1.7 meq/L, bicarbonate of 9 meq/L chloride of 116 meq/L, sodium of 139 meq/L, serum creatinine of 2.64 mg/dL (baseline: 0.91 mg/dL 3 weeks prior), 24-hour urine potassium of 159 meq/L. Arterial blood gas, magnesium and phosphorus were not reported. A renal biopsy was not done. Nivolumab was discontinued and he was treated with corticosteroids for 4 weeks. Potassium and bicarbonate were replaced. Quadriplegia resolved by the third hospital day. He was discharged with normal creatinine, potassium and bicarbonate. He was then started on pembrolizumab which the patient tolerated well.

Our case is the first report to our knowledge associating nivolumab with multiple electrolyte disturbances without evidence of AKI. Our patient presented with severe hypokalemia and hypophosphatemia. He had evidence of glucosuria, aminoaciduria, and non-anion gap metabolic acidosis. His presentation is consistent with type 2 renal tubular acidosis due to acquired Fanconi syndrome linked with nivolumab treatment. As in other immune injuries linked with nivolumab the lag time between the start of treatment and the injury can be up to several months.

Further work up of the patient excluded other causes of Fanconi syndrome such as paraproteinemia and autoimmune disorders. Moreover, the patient did not have electrolyte abnormalities prior to treatment with nivolumab. These abnormalities were not due to gastrointestinal disorder, alcoholism or use of diuretics. Urinary findings indicate renal wasting of potassium and phosphorus.

Cessation of treatment with nivolumab and aggressive replacement of potassium and phosphorus was sufficient to correct his electrolyte abnormalities. The patient required hospitalization for several days and continuation of oral replacement therapy post discharge. Re-challenge with nivolumab seemed imprudent due to the severity of his electrolyte abnormalities. It is unclear whether a different CPI would result in similar abnormalities. In November 2018 the FDA approved pembrolizumab for

the treatment of hepatocellular carcinoma.

A meta-analysis of 4070 patients (4) enrolled in 8 phase II and III randomized clinical trials identified all-grade immune-related renal toxicity in 0.7% to 6% of patients. The trials utilized different CPIs as a monotherapy or in combination including nivolumab, pembrolizumab and ipilimumab. Treatment with corticosteroids has been utilized in some studies and it resulted in complete resolution of the renal toxicity. Incidence of consequent renal failure was reported in four of the eight studies and it was in the range of 0.3 to 1%. The meta-analysis concluded that CPIs are linked with increased risk of all-grade immune-related nephrotoxicity when compared to control chemotherapy. Electrolyte abnormalities were not reported.

In a case series (5) 13 patients underwent renal biopsy due to CPIs-induced AKI. The patients were on nivolumab, ipilimumab or pembrolizumab. In 12 out of 13 patients the renal biopsy revealed AIN. One patient had acute thrombotic microangiopathy with no evidence of AIN. Median time from the start of treatment with CPIs to AKI was 91 days (range, 21 to 245 days). Most patients were treated with corticosteroids and withholding the CPIs. Four patients required hemodialysis and the rest had partial or complete recovery with corticosteroids. Electrolyte abnormalities were not reported.

Jung et al (6) reported a case of AKI associated with nivolumab. Renal biopsy revealed diffuse tubular injury and immune complex-mediated glomerulonephritis with hump-like subepithelial deposits on electron microscopy. Treatment with nivolumab was discontinued. Renal function returned to baseline after 5 months of corticosteroids and hemodialysis.

A report in the *European Journal of Cancer* (7) detailed the cutaneous, gastrointestinal, endocrine and renal side-effects of anti-PD1 therapy. Electrolyte abnormalities were not reported.

Conclusion

The use of CPIs such as nivolumab is expanding. Clinicians should be vigilant to the potential adverse reactions resulting from this new class of anticancer medications. Patients should be monitored for development of AKI and multiple electrolyte abnormalities especially hypokalemia and hypophosphatemia. The incidence of hypokalemia and hypophosphatemia is unknown. Given the potential severity of these abnormalities we recommend routine laboratory monitoring of renal function and electrolytes in patients on CPIs.

Authors' contribution

All authors contributed in data collection and preparation of the report.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the author. The patient has provided informed consent to publish as a case report.

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