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Case Report

Enfortumab Vedotin-induced Hyperglycemia and Ileal Conduit Reconstruction-induced Metabolic Acidosis

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Abstract

We report a 76-year-old man who was treated for hyperglycemia and metabolic acidosis after chemotherapy with enfortumab vedotin and pembrolizumab administered after his surgery for bladder cancer. He had an approximately 20-year history of diabetes. His body mass index was 18.6, and he received metformin 1000 mg/day, sitagliptin 50 mg/day, mitiglinide 30 mg/day, and voglibose 0.6 mg/day with hemoglobin A1c was approximately 7%. He underwent total cystectomy and ileal conduit reconstruction. After relapse, he received chemotherapy but later developed hyperglycemia and metabolic acidosis. His hyperglycemia was caused by enfortumab vedotin, and metabolic acidosis was attributable to the ileocecal canal. These symptoms should be remembered as important complications of this standard treatment, which prompted this case report.

Key Words: bladder cancer, ileal conduit reconstruction, enfortumab vedotin, hyperglycemia, metabolic acidosis

Abbreviations: HbA1c, hemoglobin A1c; RTA, renal tubular acidosis.

Introduction

Chemotherapy with enfortumab vedotin and pembrolizumab after total cystectomy and ileal conduit reconstruction is expected to become the standard treatment for advanced urothelial carcinomas, including bladder cancer. The existing standard chemotherapy for advanced urothelial carcinoma is platinum-based chemotherapy combined with a PD-1/PD-L1 inhibitor, but the median overall survival with existing chemotherapy is approximately 10 months [1]. Enfortumab vedotin is an antibody–drug conjugate combining a monoclonal antibody targeting nectin-4, a protein detected in 97% of urothelial carcinomas, with a small-molecule drug with microtubule inhibitory activity [2]. In a global phase III trial, enfortumab vedotin significantly prolonged survival compared with the effect of standard chemotherapy in patients with locally advanced or metastatic urothelial cancer previously treated with platinum-based chemotherapy and PD-1/PD-L1 inhibitors, but 6.4% of patients in the same trial experienced hyperglycemia of unknown cause [3]. Ileal conduit reconstruction is the main procedure for urinary tract reconstruction after total cystectomy, and it is associated with metabolic acidosis in 10% to 20% of patients, which is lower than the incidence after conventional reconstruction [4].We describe a case of hyperglycemia and metabolic acidosis after enfortumab vedotin and pembrolizumab therapy and ileal conduit reconstruction for recurrent bladder cancer. This combination regimen could become the standard treatment for advanced urothelial carcinoma, and the diagnosis and findings are discussed.

Case Presentation

A 76-year-old man underwent cystectomy and ileal conduit reconstruction 2 years ago for bladder cancer. His bladder cancer recurred 5 months ago, and he started chemotherapy with a combination of pembrolizumab and enfortumab 4 months ago. His blood glucose levels were measured every month after the start of chemotherapy and ranged from 110 (6.1 mmol/L) to 220 mg/dL (12.2 mmol/L). In addition, the patient was diagnosed with type 2 diabetes when he visited an internist approximately 20 years ago. The patient received medical therapy for type 2 diabetes, most recently with metformin 1000 mg/day, sitagliptin 50 mg/day, mitiglinide 30 mg/day, and voglibose 0.6 mg/day. His hemoglobin A1c (HbA1c) level was generally stable at <7%, being 6.8% in the last measurement 2 months before admission.

Before admission, the patient had an HbA1c level of 8.2%, blood glucose level of 593 mg/dL (32.9 mmol/L), and blood pH of 7.21 in a routine visit. The patient was then admitted to the hospital because it was assumed that pembrolizumab had caused type 1 diabetes, leading to diabetic ketoacidosis.

Diagnostic Assessment

His blood glucose level was 593 mg/dL (32.9 mmol/L), his blood C-peptide was 4.12 ng/mL, and his anti-GAD antibody level was <5.0 U/mL. Because insulin secretory capacity was maintained to some extent and antibodies were negative, the possibility of type 1 diabetes caused by pembrolizumab was dismissed. The patient was prescribed prednisolone 10 mg/day for a skin rash 3 weeks before admission but did not

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actually take the medication until 5 days before admission. Prednisolone was discontinued after hospitalization, but hyperglycemia persisted. Although prednisolone increased blood glucose levels, the effect in this case was considered limited. Therefore, it was assumed that enfortumab vedotin was the cause of hyperglycemia. His acidosis included a normal anion gap, and urinary and blood ketones were not detected, precluding a diagnosis of diabetic ketoacidosis. Because his urinary pH exceeded 5.5 and his urine anion gap was normal, it was assumed that the cause of metabolic acidosis was decreased urinary NH4+ excretion. The findings were similar to those of type 1 renal tubular acidosis (RTA), but potential causes of type 1 RTA including autoimmune disease, drug use, and renal disease were eliminated. Because the patient was elderly at onset, the possibility of hereditary RTA was dismissed. The patient previously underwent ileal conduit reconstruction, and the loss of HCO3− from the intestinal tract was determined to be the cause of metabolic acidosis (Table 1).

Treatment

Insulin therapy was started on admission. His blood glucose levels improved quickly, but his acidosis did not improve. The patient's blood pH normalized after oral sodium bicarbonate therapy (Fig. 1).

Table 1. Laboratory results for the patient

Parameter	Value	Reference values
Biochemical findings		
Sodium, mEq/L	134	138-145
Potassium, mEq/L	3.6	3.6-4.8
Chloride, mEq/L	114	101-108
Blood urea nitrogen, mg/dL	36	8-20
Creatinine, mg/dL	1.06	0.65-1.07
Glomerular filtration rate	53	>90
Glucose, mmol/L	32.9	3.9-7.7
Hemoglobin A1c, %	8.2	4.6-6.2
C-peptide, ng/mL	4.12	0.8-2.5
Anti-GAD antibody, U/mL	<5.0	<5.0
Total ketone bodies, μmol/L	40.9	26-122
Acetoacetate, μmol/L	19.0	13-69
3-hydroxybutyric acid, μmol/L	21.9	≦76
Venous blood gas		
pH	7.21	7.35-7.45
PCO2, mm Hg	29	35-48
HCO3−, mmol/L	11	22-26
Lactic acid, mmol/L	3.6	1.8-1.9
Anion gap	9	10-14
Urinalysis		
pH	7.0	4.8-7.5
Specific gravity	1.010	1.005-1.030
Protein	Positive	
Glucose	Positive	
Ketones	Negative	
Sodium, mEq/L	81	88-285
Potassium, mEq/L	12	17-75
Chloride, mEq/L	78	89-298

Outcome and Follow-up

The patient was discharged on day 16 and continued to take 12 units of insulin degludec/insulin aspart injection and 2 g of sodium bicarbonate. All oral diabetes medications taken before admission were resumed and continued. To date, his HbA1c and pH have remained stable around 7% and 7.4%, respectively.

Discussion

Enfortumab vedotin caused hyperglycemia (≥250 mg/dL or ≥13.9 mmol/L) in 6.4% of patients in an international phase III study [3]. A history of hyperglycemia (38.2%), body mass index ≥ 30 kg/m^2 (29.3%), and pretreatment HbA1c ≥ 6.5% (38.8%) were identified as risk factors for hyperglycemia [3], and pretreatment HbA1c elevation was detected in this patient. Although the mechanism of hyperglycemia is unknown, insulin secretion was not decreased in this patient; thus, it was assumed that hyperglycemia was caused by insulin resistance.

The patient was prescribed 10 mg of prednisolone for a skin rash, which might have contributed, at least in part, to his high blood glucose. However, the patient did not actually take prednisolone until 5 days before admission. Because his HbA1c was 6.8% 2 months before admission and it further increased to 8.2% at the time of admission, we believe that the cause of the hyperglycemia cannot be explained by prednisolone medication alone. Ileal conduit reconstruction is a type of urinary tract reconstruction used in total cystectomy, in which the small intestine is used to create a duct that directs urine. The ureter is connected to that duct, and the contralateral side is connected to the stoma through the abdominal wall. Albeit at lower rates than observed in conventional ureterojejunal anastomosis, metabolic acidosis is reported to occur in 10% to –20% of patients who undergo ileal conduit reconstruction [4], and several cases have been reported in Japan [5]. It is known that metabolic acidosis caused by ileal conduit reconstruction is attributable to urine reabsorption caused by urine retention and residual urine generation in the conduit [6]. When urine accumulates in the intestinal canal, SLC26A3 (Cl−/HCO3− exchange channel), which exists in the luminal membrane of the ileal epithelium, promotes Cl− reabsorption and HCO3− secretion on the ileal epithelium, resulting in HCO3− loss-induced metabolic acidosis [7]. Although the results were similar to those of type 1 RTA, which causes impaired H+ excretion in the distal tubule, this patient did not have collagen disease or other factors that could cause type 1 RTA, and we assumed that the patient had metabolic acidosis caused by ileal conduit reconstruction.

The patient received concurrent chemotherapy with enfortumab vedotin and pembrolizumab. Because PD-1 plays an important role in the maintenance of immune tolerance, pembrolizumab, a PD-1 inhibitor, is known to be associated with immune-related adverse effects [8]. The frequency of type 1 diabetes mellitus among immune-related adverse effects caused by pembrolizumab is approximately 0.1%, and although not frequent, it is likely to be severe when it does occur [9]. Therefore, it was necessary to consider the possibility that pembrolizumab caused type 1 diabetes or diabetic ketoacidosis in

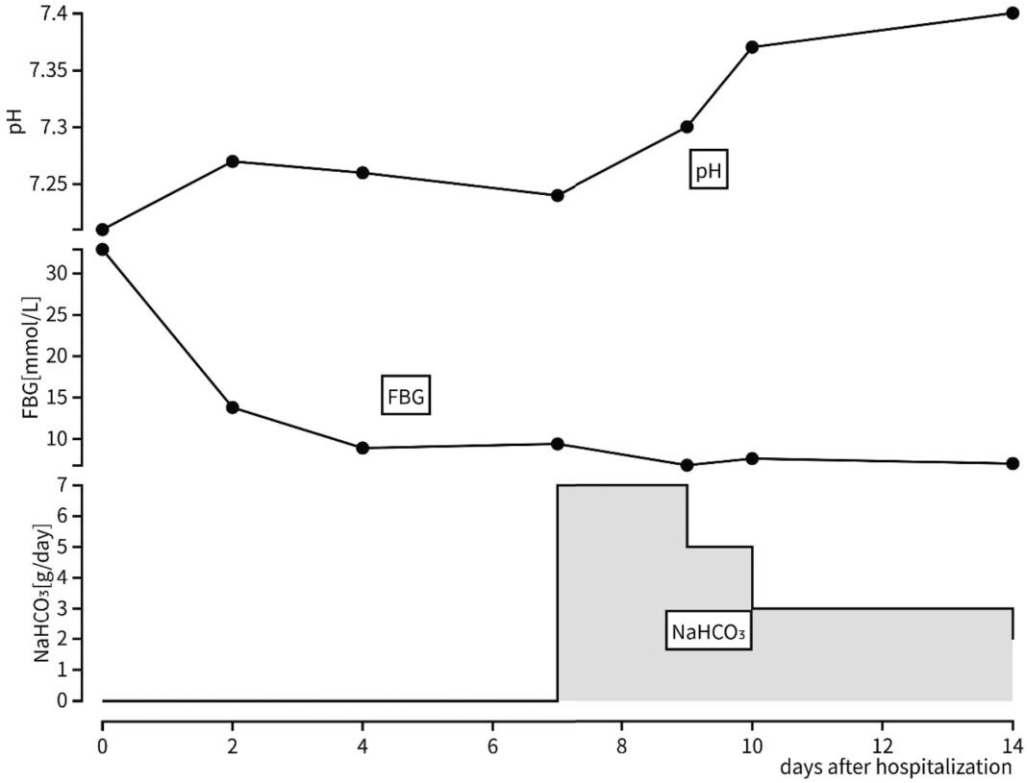

Figure 1. Dose of $NaHCO^3$ and the course of fasting blood glucose (FBG), pH.

this patient. However, there was a normal anion gap on blood gas analysis, and urinary and blood ketones were negative, ruling out diabetic ketoacidosis. His insulin secretory capacity was preserved; therefore, the possibility of type 1 diabetes was dismissed.

Diabetic ketoacidosis is the most common cause of hyperglycemia and metabolic acidosis, but in some cases, hyperglycemia and metabolic acidosis are independent of each other. In fact, in this case, insulin therapy improved the patient's blood glucose level but not acidosis, which required oral sodium bicarbonate. Enfortumab vedotin has proven effective in the treatment of advanced urothelial carcinoma, and its combined use with pembrolizumab is expected to increase in the future. In addition, because of the nature of its use in patients with advanced urothelial carcinoma, enfortumab vedotin is likely to be used more often in patients undergoing urinary tract reconstruction procedures such as ileal conduit reconstruction, and the incidence of hyperglycemia and metabolic acidosis is expected to increase in the future. In addition, it is possible to confuse these symptoms with the development of type 1 diabetes and diabetic ketoacidosis caused by pembrolizumab. These symptoms should be remembered as important complications of this combination treatment for advanced urothelial carcinoma.

Learning Points

- Enfortumab vedotin use after ileal conduit reconstruction may lead to hyperglycemia and metabolic acidosis.
- When enfortumab vedotin and pembrolizumab are used simultaneously, distinguishing the onset of type 1 diabetes with diabetic ketoacidosis from conditions such as those encountered in the present case is challenging.
- Hyperglycemia and metabolic acidosis should be remembered as important complications of this standard treatment.

Contributors

All authors made individual contributions to authorship. T.S., H. Suzuki, and Y.A. were involved in the diagnosis and management of this patient. T.S. drafted the manuscript. H. Sone was responsible for the medical management of the patient and provided oversight. All authors reviewed and approved the final draft.

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Disclosures

The authors have no conflicts of interest to disclose.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Original data generated and analyzed for this case report are included in this published article.

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