New DKA in a geriatric patient on immune checkpoint inhibitor therapy: a case report

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Introduction

Diabetic ketoacidosis is a critical illness requiring early identification and treatment. Diabetic ketoacidosis has no definitive diagnostic criteria but is hallmarked by the presence of hyperglycemia, acidosis and ketones [1]. Diabetic ketoacidosis remains primarily a disease of the young with mortality ranging from 0.65 to 3.3% [1]. Recently, there has been more published concerning atypical diabetic ketoacidosis presentations with normal glucose levels secondary to sodium–glucose cotransporter-2 (SGLT2) inhibitors [1]. Along with hyperosmolar hyperglycemic states, these create diagnostic uncertainty when evaluating older and often more comorbid patients. Here, we present a case of a previously non-diabetic patient presenting to a Canadian tertiary cancer center in diabetic ketoacidosis.

Case

An 87-year-old woman presented to the emergency department (ED) with a multiple day history of nausea and lethargy. Her past medical history included metastatic melanoma and a previous lobectomy for adenocarcinoma. Her only

medication was nivolumab and had completed three cycles in the previous month. She did not have a known history of diabetes or metabolic syndrome. She had no history of previous venous thromboembolism. She denied any vomiting, abdominal pain, dysuria, fever, cough, shortness of breath, or chest pain.

Upon presentation to the ED, her vital signs were heart rate 109, blood pressure 142/53, temperature 35.2 °C, and oxygen saturation of 95% on 3 L by nasal prongs. On physical examination, the patient was tachypneic. She was alert and oriented with Glasgow Coma Scale 15. She did not have any wheeze or crackles on auscultation and no murmurs were identified. She had no peripheral edema or calf tenderness. Her abdomen was soft and non-tender. Her point-of-care glucose was 33 mmol/L.

Rapid venous blood gas testing showed metabolic acidosis and inadequate respiratory compensation with a pH of 6.95, pCO₂ of 25 mmHg and HCO₃ of 5 mmol/L; this prompted the addition of serum ketones. Urea, aspirin, acetaminophen and toxic alcohol levels were not ordered as it was felt to not be in keeping with the patient's presentation. The patient was initially treated with 2 L boluses of ringer's lactate. As laboratory results were pending, the patient was started on a bicarbonate infusion to treat her severe acidemia in the interim. The patient subsequently was found to have an anion gap of 35 mmol/L, glucose of 42.7 mmol/L and positive ketones (Table 1). She was, therefore, diagnosed with diabetic ketoacidosis, given 10 units of insulin glargine subcutaneously and started on an insulin infusion of 0.1 units/kg/h. She was admitted to the intensive care unit and treated with the institutional standardized diabetic ketoacidosis protocol. She was transitioned to subcutaneous insulin the following day and transferred to the ward. She was discharged on post-admission day 5 after diabetes education and home supports were in place. The patient remains

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Table 1 The patient's laboratory values

Laboratory test	Value	Normal Range
Hemoglobin	155 g/L	115–155 g/L
White blood cell count	$20.4 \times 10^9/L$	$3.5\text{--}10.5 \times 10^9/L$
Platelets	$370 \times 10^9/L$	$130\text{--}380 \times 10^9/L$
Sodium	138 mmol/L	135–145 mmol/L
Potassium	5.3 mmol/L	3.5–5 mmol/L
Chloride	100 mmol/L	98–107 mmol/L
Bicarbonate	3 mmol/L	21–32 mmol/L
Anion gap	35 mmol/L	5–12 mmol/L
Creatinine	139 $\mu\text{mol/L}$	22–75 $\mu\text{mol/L}$
Glucose	42.7 mmol/L	4–11 mmol/L
ALT	21 IU/L	17–63 IU/L
ALP	148 IU/L	50–136 IU/L
Bili	< 3 $\mu\text{mol/L}$	3–17 $\mu\text{mol/L}$
Lipase	93 IU/L	73–393 IU/L
Ca	2.5 mmol/L	2.12–2.2 mmol/L
Alb	46 g/L	34–50 g/L
PO ₄	1.94 mmol/L	0.81–1.58 mmol/L
Mg	0.95 mmol/L	0.74–1.03 mmol/L
pH (VBG)	6.95	7.35–7.45
pCO ₂ (VBG)	25 mmHg	35–45 mmHg
HCO ₃ (VBG)	5 mmol/L	21–32 mmol/L
Lactate	4.6 mmol/L	0.5–2.5 mmol/L
Base deficit	28 mmol/L	– 2–3 mmol/L
Serum ketones	Positive	Negative
Troponin	30 ng/L	< 15 ng/L
Urine leukocytes	Negative	Negative
Urine nitrites	Negative	Negative
Urine ketones	Positive	Negative
TSH	2.4 mIU/L	0.34–5.60
Hgb a1c	8.5%	4.8–6%
Cortisol (A.M.)	570 nmol/L	185–624
C-Peptide	40 pmol/L	500–2700 pmol/L

Values outside of normal range were bolded

ALT alanine aminotransferase, ALP alkaline phosphatase, VBG venous blood gas, pCO₂ partial pressure of carbon dioxide, HCO₃ bicarbonate

insulin-dependent 9 months after her initial presentation with a new diagnosis of type 1 diabetes secondary to her cancer immunotherapy. The patient decided to discontinue immunotherapy due to concern for further complications.

Discussion

Our case demonstrates a new cancer treatment induced diabetes presenting as diabetic ketoacidosis in an elderly patient with no previous history of diabetes.

Immune checkpoint inhibitors are a group of cancer immunotherapies that target cytotoxic T lymphocyte-associated protein-4 (CTLA-4), programmed cell death-1 (PD-1) and PD-ligand 1 (PD-L1) [2]. They have shown great benefit in treating advanced cancers and are fast becoming a more prevalent therapy [3]. The first immune checkpoint inhibitor, ipilimumab, was approved by the FDA in 2011 for melanoma treatment [4]. There are now 7 immune checkpoint inhibitors approved for a multitude of cancers and at different stages of disease [4]. Recent studies have shown a unique risk for immune-related endocrine organ complications in approximately 4–30% of patients with hypophysitis and thyroiditis being most common. A recent systematic review demonstrated diabetes is a life-threatening complication in 1% of patients on immune checkpoint inhibitor therapy [2]. Approximately 50–75% of these patients will first present with diabetic ketoacidosis, and therefore, early recognition and management by emergency physicians is vital [2]. Developing immune checkpoint inhibitor diabetes (ICI-DM) is currently thought to be secondary to pancreas/ β cell inflammation, with 50% of cases developing asymptomatic lipase elevation [2]. The average age of these patients is approximately 65 years old; much older and with more comorbidities than typical diabetic ketoacidosis patients [2, 3]. Currently there are very little data but current estimates are 5.58% of ICI-DM cases result in death, possibly due to the patient population's baseline health [3]. While further research is required to confirm, risk factors for developing ICI-DM seem to be combination therapy, PD-1 or PD-L1 agents and previous autoimmune diseases [2]. Onset of symptoms can range from a few weeks after the first cycle to 1 year, but patients typically present in short time courses with fulminant diabetic ketoacidosis [2]. There also seems to be an increase in prevalence since these medications were introduced from 0.67% in 2015 to 1.83% in 2019 [3]. Furthermore, the incidence of developing ICI-DM is greater than euglycemic diabetic ketoacidosis from SGLT2 inhibitors (< 0.1%) [1].

Management of these patients is typically centered around early diagnosis and treatment with intravenous (IV) insulin [2, 3]. Steroids do not seem to have any added benefit despite the cause being autoimmune-related [2]. Interestingly, the clinician in this case treated the patient with an initial dose of insulin glargine prior to initiating IV insulin therapy. Although there is some evidence for decreased lengths of stay and incidence of rebound hyperglycemia, this has not been tested in immune checkpoint inhibitor diabetic ketoacidosis patients and is not in diabetic ketoacidosis management guidelines [5].

ICI-DM presents a new diagnostic entity that every emergency clinician should be made aware of due its atypical patient population, increasing prevalence and

increased mortality. Due to availability bias, older cancer patients are typically evaluated for infectious, metastatic or prothrombotic etiologies that may delay recognition of diabetic ketoacidosis. Clinicians may attribute the hyperglycemia present to other disease entities, such as sepsis, especially in patients with no prior history of diabetes. Due to its increasing prevalence, unique patient population and increased mortality, awareness of these new immunotherapies is imperative. It is vital for emergency physicians to be aware of this disease entity to allow for early and prompt management.

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Declarations

Conflict of interest No conflict of interest to disclose.

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