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Case Report

Euglycemic diabetic ketoacidosis in the setting of acute intracerebral hemorrhage

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ABSTRACT

Background: Diabetic ketoacidosis (DKA) is a life-threatening condition among diabetic patients characterized by metabolic anion gap (AG) acidosis of arterial pH <7.30, glucose >250 mg/dL, and positive ketones. The triggers for DKA can be infection, surgery, and, in reported cases, intraparenchymal hemorrhage (IPH). In rare cases of DKA, despite being in active ketoacidosis, glucose levels may be within normal or accepted range. Such a condition is called euglycemic DKA. It has been recently recognized in association with the use of sodium glucose co-transporter-2 (SGLT-2) inhibitors in the treatment of type 2 diabetes.

Case Description: An 83-year-old male taking an SGLT-2 inhibitor (empagliflozin) for type 2 diabetes presented with an IPH. His laboratory studies revealed an elevated AG acidosis, an elevated beta hydroxybutyrate, and serum glucose levels within the acceptable range. Urine studies revealed elevated ketones and glucose. The diagnosis of euglycemic DKA was made, and the patient was treated with insulin and glucose infusions.

Conclusion: Like hyperglycemic ketoacidosis, euglycemic DKA requires prompt recognition and immediate aggressive medical therapy, but the diagnosis can be challenging, and the treatment using insulin in the setting of a normal glucose can be counterintuitive. Euglycemic DKA can often be missed in the setting of blood glucose not being elevated. Prompt recognition and treatment are critical for successful management.

Keywords: Euglycemic diabetic ketoacidosis, Intracerebral hemorrhage, Sodium glucose co-transporter-2 (SGLT-2) inhibitor

INTRODUCTION

Diabetic ketoacidosis (DKA) is a life-threatening state of relative or absolute insulin deficiency defined by hyperglycemia, metabolic acidosis, and elevated ketone concentration in the body.[10] It is commonly seen in patients with type 1 diabetes but can be seen in patients with type 2 diabetes as well.[10] It is considered a medical emergency that requires prompt diagnosis and aggressive medical treatment.[7,10] Diagnosis of DKA may be relatively straightforward when tying together the clinical picture and serologic laboratories, but on rare occasions, such as in euglycemic DKA, serum glucose levels may be normal or within the accepted range. This deviation from the usual triad seen in DKA may lead to delayed diagnosis and treatment of this life-threatening condition. In particular, patients receiving sodium glucose co-transporter-2 (SGLT-2) inhibitors are at risk of developing euglycemic DKA.[6,11,16] Here, we present an 83-year-old male on empagliflozin who developed such a condition in association with an acute intraparenchymal hemorrhage (IPH).

CASE DESCRIPTION

An 83-year-old male with a medical history of anxiety, hyperlipidemia, type 2 diabetes mellitus, hypertension, and glaucoma presented to an emergency department to an outside hospital with a chief complaint of headache and decreased appetite. His home medications at that time were semaglutide, empagliflozin, brimonidine, latanoprost, and atorvastatin. At the outside hospital, a non-contrasted computed tomography (CT) of the head did not reveal an acute process [Figure 1]. Serologic workup from the outside hospital was negative for an acute infection, toxic, or metabolic derangements. He was discharged in stable condition after being given analgesics for his headache.

He presented again to the same emergency department 2 days later after his family members noticed that since discharge, he had worsened mental status and worsening headache; this time also complained of nausea and worsening appetite. On arrival, he was afebrile, blood pressure was 131/99, heart rate was 81, and respiratory rate was 18. Fingerstick glucose was 260 mg/dL, for which he was given two units of insulin aspart. Fentanyl and ondansetron were administered for pain control and nausea. A CT of the abdomen and pelvis due to loss of appetite and nausea was negative for an acute process. Due to encephalopathy and nausea, which was a new feature compared to his prior presentation, a repeat non-contrast CT of the head was obtained, which revealed a new acute left occipital IPH without mass effect or interventricular extension [Figure 2]. On discovery of a new hemorrhage, he was loaded with 2 g of levetiracetam for seizure prophylaxis and was subsequently transferred to our facility in the neurocritical care unit for escalation of care.

On arrival, the patient appeared encephalopathic and was not orientated to the date or place. On visual field testing, he had a right homonymous hemianopsia. He had trouble completing complex commands but had intact strength and sensation throughout. His National Institutes of Health Stroke Scale was a five, scoring two for the level of consciousness questions, one for commands, and two for vision. There were no clinical findings to suggest dehydration, such as increased skin turgor and dry skin, dry mucosal membranes, polydipsia, or decreased urine output. The cardiac workup included an electrocardiogram, which revealed normal sinus rhythm. His serologic workup included a complete blood count with differential, coagulation studies, a complete metabolic panel, a lipid panel, hemoglobin A1c, and a thyroid-stimulating hormone level. All of his serologic laboratory results were unremarkable aside from a hemoglobin A1c of 10.2%, elevated blood urea nitrogen at 23 (normal range 10–20 mg/dL), elevated anion gap (AG) at 17 (normal range 5–15 mmol/L), and a low bicarbonate level at 20 (normal range 22–31 mmol/L). Given the elevated AG and low bicarbonate level, we followed this up with a

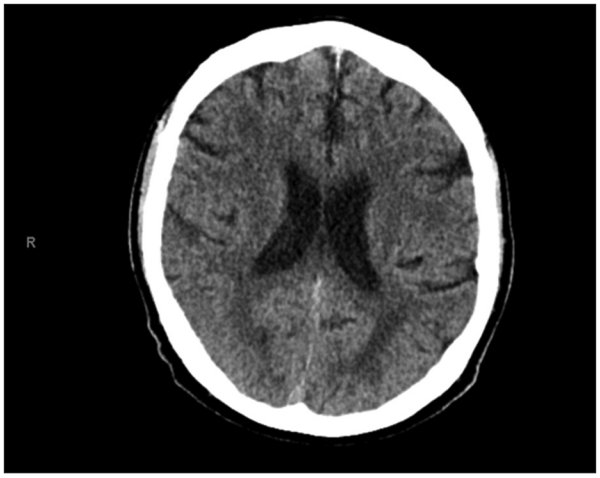

Figure 1: Non-contrast computed tomography of the head during the initial presentation, where there was no evidence of an acute hemorrhage, ischemia, or other processes.

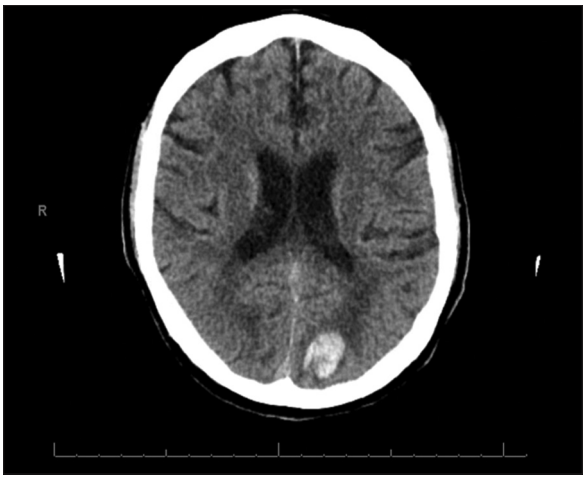

Figure 2: Non-contrast computed tomography of the head 2 days later, which reveals an acute intraparenchymal hemorrhage in the left occipital lobe without associated mass effect or interventricular hemorrhage.

β-hydroxybutyrate (BOHB) level, which was elevated at 3.65 (normal range 0.0–0.3 mmol/L). The glucose level at the time of the BOHB draw was 120 mg/dL. We obtained a urinalysis (UA) and found that his urine glucose and ketones were >1000 mg/dL and >80 mg/dL, respectively. There were no findings in the UA to suggest infection, and the UA did not reflex on culture. A urine toxicology screen was also negative for recreational drug use. Based on his laboratory results and history of SGLT-2 inhibitor use, we came to the conclusion that he was in euglycemic DKA, and we treated him with 250 cc/h of dextrose 10% (D10) + potassium chloride (KCL) infusion and initiated 1 U/h of insulin drip without an insulin bolus for a goal glucose level of 90–200 mg/dL. He was given a diet and allowed to eat. We monitored his electrolyte status

and BOHB every 4 h and corrected his potassium level as needed. The following morning, his AG closed to 10 mmol/L, and his BOHB level decreased to 0.93 mmol/L and he was transitioned to an insulin sliding scale. After correction of his DKA, his encephalopathy and nausea resolved, with his only neurologic deficit being the visual field cut, which correlated to the IPH found on head imaging.

Regarding his workup and management of his IPH, we kept his blood pressure with a goal systolic blood pressure of <160 mmHg. His 6-h repeat CT head was stable. We also obtained a CT angiogram of the head and neck, which revealed prominent arterial branches in and around the hemorrhage, raising concern for an underlying mass or vascular legion. We followed this up with a magnetic resonance imaging (MRI) of the brain with and without contrast, which revealed an abnormal curvilinear enhancement with a saccular enhancing focus, suggesting an arteriovenous malformation. To confirm the findings on the MRI, we pursued a digital subtraction angiography, which did not appreciate any evidence of an arteriovenous malformation. We attributed his IPH to uncontrolled hypertension, and he was started on lisinopril for long-term blood pressure control.

He was discharged home with home health on hospital day 9, with his semaglutide and empagliflozin being discontinued. Instead, he was started on glargine and lispro with outpatient follow-up with endocrinology. We arranged for an outpatient follow-up with vascular neurology, but he has been lost to follow-up.

DISCUSSION

Our case highlights the need for physicians to be aware that patients who are on SGLT-2 inhibitor therapy presenting with IPH are at risk for developing euglycemic DKA. Euglycemic DKA is a life-threatening medical condition that was first described by Munro *et al*. in 1973 when evaluating a series of 211 patients with DKA from 1964 to 1971.[13] It is defined as euglycemia or mild hyperglycemia (glucose <200 mg/dL), metabolic acidosis (bicarbonate <18 mmol/L, pH <7.3), and ketosis.[1,12] It is a rare form of DKA, with incidence ranging between 2.6 and 3.2% among hospitalized patients with DKA.[9,18] Euglycemic DKA can be precipitated by SGLT-2 inhibitors, but infection, suboptimal therapy, pancreatitis, myocardial infarction, surgery, medication, and cerebrovascular accidents can also cause DKA.[10]

In hyperglycemic DKA, there is reduced insulin concentration (absolute or relative) and an increased concentration of counterregulatory hormones such as catecholamines, cortisol, glucagon, and growth hormone, which lead to a state of hyperglycemia and ketosis. Hyperglycemia is a result of increased gluconeogenesis, increased glycogenolysis, and decreased glucose utilization by peripheral tissues.[10] Increased counterregulatory hormones coupled with insulin deficiency cause the release of free fatty acids into the circulation, leading to unrestricted hepatic fatty acid oxidation to form ketone bodies (β-hydroxybutyrate and acetoacetate), leading to ketonemia and metabolic acidosis.[10]

In euglycemic DKA, insulin deficiency and resistance are milder, and thus, glucose overproduction and underutilization do not play a key role compared to hyperglycemic DKA. However, there is still an increased production of counterregulatory hormones, which result in an increased glucagon/insulin ratio, leading to ketogenesis without a significant impact on hepatic gluconeogenesis and utilization of glucose by peripheral tissues.[1,2,14] This state of euglycemia presents a diagnostic challenge for clinicians, given the low or relatively normal blood glucose levels and the fact that patients may not present with typical signs of DKA, such as dehydration from hyperglycemia.[1,2] This can ultimately lead to a delay in diagnosis and prompt management of these patients. One case series described 13 patients with euglycemic DKA where ketoacidosis was not initially recognized primarily due to the absence of severe hyperglycemia. Due to this, their insulin regimen was not modified, and when patients presented to the hospital in need of acute care, physicians often failed to recognize the DKA in a timely manner, leading to unnecessary workup and treatment.[16] Risk factors for developing euglycemic DKA include decreased carbohydrate intake or starvation, pregnancy, surgery, pancreatitis, sepsis, cocaine abuse, and use of SGLT-2 inhibitors.[1,2,14]

SGLT-2 inhibitors work by inhibiting the resorption of glucose and sodium in the proximal tubules in the kidney, thus promoting urinary glucose excretion and preventing hyperglycemia, as well as decreasing insulin secretion from the pancreas.[10,16] It has been introduced for the management of type 2 diabetes, with proposed advantages being modest weight loss, decreased blood pressure from osmotic diuresis, and loss of glucose in urine.[3,4,16] However, with the introduction of SGLT-2 inhibitors as an option for the treatment of type 2 diabetes, there have been cases of SGLT-2 inhibitor-associated DKAs, including several case reports highlighting the association of SGLT-2 inhibitor use with euglycemic DKA.[13,14,17] This prompted the FDA to issue a warning statement regarding the risk of ketoacidosis while on SGLT-2 inhibitor therapy.[11] More recently, there has been a case report describing euglycemic DKA in a patient with acute ischemic stroke and sepsis who was on an SGLT-2 inhibitor.[15] An increased glucagon/insulin ratio drives the pathophysiology of SGLT-2 inhibitors, precipitating euglycemic DKA due to carbohydrate deficit, usually from glycosuria, which stimulates glucagon secretion and suppression of insulin release. This, in turn, promotes

lipolysis, free fatty acid oxidation in the liver, and the formation of ketone bodies when glycolysis intermediates are unavailable due to low intracellular glucose oxidation.[5,7]

Management of euglycemic DKA involves volume resuscitation, correction of electrolyte derangements, and insulin. It is important to recognize that despite low to normal serum glucose levels, both insulin and glucose must be administered together to correct the metabolic acidosis. This is achieved by initiating dextrose-containing fluid and insulin drip until the correction of ketoacidosis and AG acidosis.[1,2,14] In our patient, we successfully treated his euglycemic DKA with 250 cc/h of D10 + KCL infusion with 1 U/h of insulin drip without an insulin bolus until his AG closed and his BOHB resolved.

Euglycemic DKA is a rare complication among diabetic patients that is often missed due to the deviation in clinical presentation and serologic laboratory findings compared to the more common hyperglycemic DKA. In our patient, his serum glucose level was well within the accepted range for admitted patients and he had no signs of dehydration commonly associated with DKA. Our unique case highlights the importance of recognizing that an acute IPH may be associated with euglycemic DKA in patients on SGLT-2 inhibitor therapy and that correcting the metabolic acidosis requires the co-administration of both glucose and insulin despite normal glucose levels. Hemorrhagic stroke in relation to DKA is not a new phenomenon as it has been reported in pediatric patients, with proposed mechanisms being vascular injury secondary to oxidative stress and proinflammatory states.[5,8] However, we could not find case reports or series describing euglycemic DKA in relation to hemorrhagic stroke in adult and pediatric populations. Based on our literature review, we believe that this is the first description of an acute IPH occurring in association with euglycemic DKA while on an SGLT-2 inhibitor. Physicians should be aware of the risk factors associated with euglycemic DKA, including acute IPH, and keep this on the differential when diabetic patients on SGLT-2 inhibitor therapy present with metabolic acidosis and benign serum glucose levels.

CONCLUSION

Like hyperglycemic ketoacidosis, euglycemic DKA requires prompt recognition and immediate aggressive medical therapy, but the diagnosis can be challenging, and the treatment using insulin in the setting of a normal glucose can be counterintuitive. Euglycemic DKA can often be missed in the setting of blood glucose not being elevated. Prompt recognition and treatment is critical for successful management.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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