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Case Report

Euglycemic diabetic ketoacidosis in a patient with acute stroke taking sodium glucose co-transporter 2 inhibitor

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ABSTRACT

Introduction: Diabetic Ketoacidosis is characterized by a triad of metabolic acidosis, hyperglycemia, and ketonemia. It is a medical emergency that needs urgent and aggressive management. In some cases, the blood glucose level may be relatively normal. Such a condition is known as Euglycemic Diabetic Ketoacidosis.

Case presentation: We present a case of Euglycemic Diabetic Ketoacidosis, who was initially brought to the emergency room with the features of acute stroke. There was a diagnostic dilemma among the treating physicians due to his relatively normal blood glucose levels while he developed ketoacidosis.

Discussion: Presentation of the patients includes similar to DKA such as nausea, vomiting, malaise, fatigue, and Kussmaul's respiration. The diabetic patients under sodium glucose co-transporter-2 inhibitor therapy may develop it under the setting of different precipitating factors like infection, trauma/surgery, strenuous physical exercise, fasting, alcohol intake and acute vascular events.

Conclusion: Euglycemic DKA is a rare condition and its diagnosis is a challenging task. So, we should always consider it as a differential whenever any diabetic patient shows with increased anion gap metabolic acidosis with or without typical symptoms and signs. Also, we need to be aware to discontinue of SGLT-2 medication during the time of infection, surgery, severe trauma, acute illness and dehydration in the diabetic patients.

1. Introduction

Diabetic Ketoacidosis (DKA) is an acute complication of Diabetes Mellitus. It is defined as the triad of metabolic acidosis, hyperglycemia, and ketonemia. It can occur in both type I and type-II Diabetes Mellitus [1]. It is an endocrine emergency and needs immediate recognition and treatment. However, sometimes, these patients may be relatively euglycemic. Such a condition is referred to as Euglycemic DKA [2]. It was first introduced by Munro et al. The incidence ranges from 2.6% to 3.2% of DKA admissions [3,4].

The diabetic patients receiving sodium glucose co-transporter-2 (SGLT-2) Inhibitor therapy may develop Euglycemic DKA. The underlying precipitating factors are infection, surgery, fasting, alcohol intake, acute vascular events (stroke, myocardial infarction), trauma and prolonged physical exercise [4,5].

Here, we present a case of 64-year-old male with type II Diabetes Mellitus under empaglifozin therapy, who presented in the emergency room with acute stroke and later developed Euglycemic DKA followed by sepsis in Intensive Care Unit (ICU).

2. Case presentation

A 64-year-old male, known case of hypertension, type II diabetes mellitus (DM) under medication for 12 years and a past alcohol consumer presented in the emergency room with complaints of left-sided hemiparesis and right-sided facial deviation, associated with slurring of speech. At presentation, he was conscious with stable vital parameters. On central nervous system examination, he had Broca's aphasia, upper motor neuron (UMN) type VIIth, cranial nerve (CN) palsy, and upgoing plantar reflex on the left side. The power on the left upper limb and left lower limb were 3/5 and 4/5, respectively. The primary investigations at admission are presented on Table 1.

Non-contrast Computerized Tomography (NCCT) head was done which showed infarction over the right hemisphere (temporo-parietal

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Table 1
Baseline laboratory parameters at presentation.

Laboratory tests	Result	Unit	Reference range
Total Leukocytes Count	15.5	10^3/μL	4–11
Neutrophil	65	%	40–80
Lymphocyte	28	%	20–40
Hemoglobin	14.8	g/dl	13–17
Platelet Count	213	10^3/μL	150–450
Urea	41	mg/dl	17–43
Creatinine	1.2	mg/dl	0.7–1.3
Sodium	140	mEq/L	135–145
Potassium	5.1	mEq/L	3.5–5.5
Bilirubin Total	1.1	mg/dl	0.1–1.2
Bilirubin Direct	0.4	mg/dl	0.0–0.2
Alkaline Phosphatase (ALP)	85	U/L	53–128
Alanine Transferase (ALT)	20	U/L	0–35
Aspartate Transferase (AST)	23	U/L	0–35
Prothrombin Time	13.1	sec	11–13.5
International Normalized Ratio	1.0		0.8–1.2
HbA_1C	13.9	%	<5.6%
Random Blood Glucose	331	mg/dL	<140 mg/dL

area). He was diagnosed as right sided ischemic stroke with UMN type of VII[th] CN palsy, and was admitted in the medical ward. His regular antihypertensive (Ramipril 5 mg once daily [OD] and Amlodipine 5 mg once daily [OD]) and antidiabetic medications (Metformin 500 mg OD, Sitagliptin 100 mg OD, Empaglifozin 10 mg OD and Insulin 10 units subcutaneously OD) were continued. Aspirin (75 mg OD) and Statins (10 mg OD) were added. Similarly, his general random blood sugar (GRBS) was also charted since the day of admission, which is presented below under Table 2.

On the fifth day of admission, he suddenly became drowsy with rapid breathing. There was fall in Glasgow Coma scale (GCS) with $E_3V_4M_5$ (Eye opening – 3/4, Verbal response – 4/5, and Motor response – 5/6). The immediate GRBS showed 218 mg/dl. The oxygen saturation was 98% in room air and blood pressure was 120/80 mmHg. On urgent arterial blood gas (ABG) analysis, it showed severe metabolic acidosis (pH: 7.124; HCO_3^-: 4.1; $PaCO_2$: 12.7 mm of HG; PaO_2: 90 mm of Hg; Anion gap: 25 and Lactate: 1.86). Likewise, urine acetone was also positive. Now, there was a dilemma among physicians. This diabetic patient was having high anion gap metabolic acidosis with relatively normal glucose level. Euglycemic DKA, starvation ketosis, alcohol ketoacidosis, lactic acidosis, sepsis, renal failure, and drug overdose (salicylate or tricyclic antidepressants) were close differentials. There was no history of intake of alcohol for many months, so an alcoholic cause was ruled out. The patient was being fed via a nasogastric tube and his bicarbonate level was found to be very low. This rules out the diagnosis of starvation ketosis, in which serum bicarbonate level is usually high. Similarly, renal function test was normal and serum lactic acid level was lower. There was no recent intake of salicylates and antidepressants by the patient. He was under SGLT-2 inhibitor (empaglifozin) for Diabetes for many years. Therefore, this finally led to the diagnosis of Euglycemic DKA. The most probable etiology in this case is acute stroke.

He was given 50 mEq of $NaHCO_3$ stat by intravenous line and again ABG analysis was done which showed mild improvement in ABG (pH: 7.214; HCO_3^-: 5.1; PCO_2: 13; PO_2: 116; and Lactate: 1.71). He was immediately shifted to the high care unit (HCU), where he was given normal saline infusion at 100 ml/hour and 50 mEq stat $NaHCO_3$ which was kept on three times a day afterwards. He was also administered with intravenous antibiotics (piperacillin and tazobactam) 4.5 gm thrice daily for seven days. The regular insulin infusion was started at 2 units/hour and empaglifozin was stopped. As he was still drowsy while in HCU, he was shifted to the intensive care unit (ICU) on the same day.

Table 2
GRBS values during admission in medical ward.

Day of Hospital Admission	GRBS (mg/dl)
1st day	186
2nd day	103
3rd day	117
4th day	145

On the second day of ICU admission, ABG analysis showed that the acidosis had resolved with bicarbonate level on the improving side (13.4 mEq/L) with normal anion gap. On the third day, as GCS was still poor and the patient was tachypneic, he was intubated and mechanically ventilated.

During ICU stay, the DKA was superimposed with sepsis (qSOFA score of 2) (blood pressure; 110/80 mmHg; respiratory rate; 28; GCS: 11/15). He was kept on antibiotics like levofloxacin (750 mg once daily), vancomycin (15 mg/kg/dose every 8 hours), linezolid (600 mg every 12 hours), and colistin (300 mg loading dose followed by 150 mg twice daily as maintenance dose) during the stay. To withdraw from mechanical ventilation, he was kept on spontaneous CPAP (Continuous Positive Airway Pressure) breathing trial, which he passed on the 13th day of ICU stay. Then he was shifted to HCU with the glycemic control target of 110–180 mg/dl. He was kept on Insulin Glargine 10 units subcutaneous once daily and Insulin Aspart 4 units was given subcutaneously before meal thrice daily.

He was stable in HCU with normal vital parameters. He was advised bed side mobilization and chest/limb physiotherapy. Finally, the patient was discharged from the hospital on the 18th day with his regular medication and appropriate counseling.

3. Discussion

Euglycemic DKA is a medical emergency. It occurs in both type-1 and type-2 diabetes mellitus. Diabetic patients under SGLT-2 inhibitor therapy may develop DKA, which is characterized by relative euglycemia (serum glucose <250 mg/dL). This leads to a delay in diagnosis and treatment. Even though hyperglycemia is not severe, euglycemic DKA is a life-threatening condition. It requires early recognition and immediate management as per usual DKA treatment protocol [2,3].

Patient presents with complaints similar to DKA such as nausea, vomiting, malaise, fatigue, and Kussmaul's respiration. Laboratory criteria needed for diagnosis are relative euglycemia (blood glucose <250 mg/dL), increased anion gap metabolic acidosis (blood pH < 7.30, bicarbonate <18 mEq/L) and ketosis. Presence of ketosis can be determined by measuring serum beta-hydroxybutyrate > 3 mmol/L. Alternatively, serum acetoacetate or urine acetone can be used [3,6]. Euglycemic DKA is a diagnosis of exclusion. Before final diagnosis, other possible causes of high anion gap metabolic acidosis should be ruled out, which include alcohol intoxication, lactic acidosis, sepsis, drug overdose (salicylate and tricyclic antidepressants), renal failure and starvation ketosis [4].

Initial management includes crystalloid fluid resuscitation (preferably balanced solutions like Ringer's Lactate), insulin infusion, intravenous dextrose to avoid hypoglycemia and potassium supplementation if serum potassium is 3.5–5.5 mEq/L. The studies state that administration of bicarbonate is unnecessary even if there is severe acidosis. It is recommended that such patients should be admitted in Intensive Care Unit (ICU), and hourly monitoring of glucose and electrolytes should be done. The underlying etiology should be adequately treated [1–3,5].

The pathophysiology of euglycemic DKA depends on the precipitating factors. The possible causes include recent use of insulin, decreased calorie intake/fasting, heavy alcohol consumption, chronic liver disease, glycogen storage disorders, pregnancy, SGLT-2 inhibitors, cocaine abuse, acute pancreatitis, infection/sepsis, and gastroparesis. All these factors finally result in decreased availability or production of glucose, reduction in insulin secretion, and increased counterregulatory hormones. In this way, a rise in glucagon: insulin ratio ultimately triggers ketogenesis resulting into ketoacidosis [3–5,7].

SGLT-2 inhibitors are newly introduced oral hypoglycemic agents.

They are used as second-line agents after metformin for the treatment of type II diabetes mellitus. They have additional cardio-protective and reno-protective effects. They decrease body weight and blood pressure as well. Therefore, these groups of drugs are most suitable for those who are obese and hypertensive. These include 'Glifozins' as canaglifozin, dapaglifozin, and empaglifozin. Among these drugs, canaglifozin poses the highest risk (hazard ratio = 3.58) of developing DKA. Diabetic patients taking SGLT-2 inhibitors may develop euglycemic DKA in the setting of certain precipitants. The risk is higher for type I Diabetes compared to type II. These drugs act by inhibiting glucose reabsorption in proximal renal tubules, thus causing glycosuria and decreased blood glucose levels. Consequently, counterregulatory hormones are secreted that favor lipolysis and ketogenesis. Moreover, SGLT-2 inhibitors directly act on the kidneys and reduce ketone excretion. They may directly stimulate glucagon secretion from pancreas as well [3,4,6,8].

There are a few cases of euglycemic DKA reported worldwide. Each of them describes different precipitating factors compared to ours. These include pregnancy [9], urinary tract infection [10], surgery [11], dehydration and prolonged fasting [12]. In our scenario, acute stroke was the possible etiology, after which the patient was diagnosed with euglycemic DKA. However, euglycemic DKA induced by SGLT-2 inhibitors in the presence of acute ischemic stroke is seldomly reported in the existing literature. The glycemic level is also variable throughout different studies [10,12]. In our case, the blood glucose was 218 mg/dL. Mumtaz H et al. [10], in his case report of euglycemic DKA, reported that blood glucose in their case was only 84 mg/dL. In a retrospective case series by Menghoum N et al. [12], the glycemia ranged from 112 to 280 mg/dL. This shows that blood glucose level may confuse the treating physicians in diagnosis and treatment. In our case, the presenting symptoms were not typical of DKA. Our patient was admitted in ICU, but then he gradually became drowsy and tachypneic. There were no classical features like nausea, vomiting, abdominal pain, and malaise.

Euglycemic DKA is a rare condition and its diagnosis is a challenging task. Therefore, the treating physicians should always consider this differential diagnosis whenever any diabetic patient shows increased anion gap metabolic acidosis with or without typical symptoms and signs. In addition to that, the underlying etiology should always be looked for and treated. Over and above that, diabetic patients should always be educated regarding this complication before starting SGLT-2 therapy. They should be made aware to discontinue medication during the time of infection/fever, surgery, severe trauma, serious acute illness, and dehydration.

There are some limitations of our study worthy to be mentioned. As the patient was discharged after being stable in the high care unit, we were not able to follow up for further evaluation.

4. Conclusions

Cases of euglycemic DKA with the use of SGLT-2 inhibitors have been reported over the past few years. However, several precipitating factors are being evolved during this period. Acute ischemic stroke can be one of those precipitating factors, which has not been well described in literature. This case report helps us to broaden our understanding of various diagnostic and therapeutic aspects of euglycemic DKA for good functional and neurological outcomes.

Author agreement statement

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We understand that the Corresponding Author is the sole contact for the Editorial process. He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

Ethical approval

This is a case report, therefore, it did not require ethical approval from ethics committee.

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Author statement

Author 1: Led data collection, contributed to writing the case information and discussion.

Author 2: Contributed to the process of original draft preparation and introduction.

Author 3: Revised it critically for important intellectual content, contributed to review and editing.

Author 4: Contributed to literature review and data collection and storage.

Author 5: Contributed to writing the discussion and conclusion.

Author 6: Edited the rough draft into the final manuscript.

Author 7: Contributed to review and editing.

Author 8: The resident physician, who helped in the diagnosis and helped in the discussion section.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal on request.

Registration of research studies

Not applicable.

Provenance and peer review

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Declaration of interest statement

The authors report no conflicts of interest.

Declaration of competing interest

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

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