Case Report

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

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A R T I C L E   I N F O

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A B S T R A C T

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 empagliflozin 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 up-going 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...
The immediate GRBS showed 218 mg/dl. The oxygen saturation was (Eye opening – 3/4, Verbal response – 3/4, Motor response – 3/4). He was diagnosed as right sided ischemic stroke with UMN type of area. He 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 (blood 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 acetocacetate 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.

Table 1

| 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    | 10³/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 Transf erase (ALT) | 20  | U/L    | 0–35            |
| Aspartate Transf erase (AST) | 23  | U/L    | 0–35            |
| Prothrombin Time     | 13.1   | sec     | 11–13.5         |
| International Normalized Ratio | 1.0  |       | 0.8–1.2         |
| HbA1C                | 13.9%  |         | <5.6%           |
| Random Blood Glucose | 331    | mg/dL   | <140 mg/dL      |

Table 2

| Day of Hospital Admission | GRBS (mg/dl) |
|---------------------------|--------------|
| 1st day                   | 186          |
| 2nd day                   | 103          |
| 3rd day                   | 117          |
| 4th day                   | 145          |
They are used as second-line agents after metformin for the treatment of type 2 diabetes mellitus. They have additional cardio-protective and renoprotective 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 canagliflozin, dapagliflozin, and empagliflozin. Among these drugs, canagliflozin 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.

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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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