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A Case of Euglycemic Diabetic Ketoacidosis in Patient with Type 2 DM

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Abstract

Diabetic ketoacidosis (DKA) can cause significant morbidity and mortality in patient with both type 1 and type 2 diabetes mellitus. A subset of DKA cases termed euglycemic diabetic ketoacidosis (EDKA) is characterized by euglycemic (<200 mg/dl), high anion gap metabolic acidosis, and increased plasma ketone concentration. This clinical syndrome is primary related to a general state of starvation, resulting in the development of ketosis while maintaining normoglycemia. It can lead to severe complication, such as extreme dehydration, altered mental status and coma. Early recognition and treatment are essential to avoid this life-threatening complication. EDKA represents approximately 2.6% to 3.2% of total DKA admissions, making it a rare condition. In this case report, a male patient was diagnosed with type 2 DM, 1 week prior to his symptoms and admission in hospital. Despite normal glucose levels at the time of presentation to the ED, he displayed severe acidemia and ketonemia, and was diagnosed with EDKA.

Keywords

Euglycemic DKA, Glucose Level, Acidosis

1. Introduction

Diabetic ketoacidosis (DKA) can cause significant morbidity and mortality in both type 1 and type 2 diabetes mellitus patients. DKA causes an approximate annual hospitalization rate of 6.3% and in hospital case fatality rate of 0.4% [1] [2]. A subset of DKA cases termed Euglycemic Diabetic ketoacidosis (EDKA) is characterized by euglycemic (<200 mg/dl), high anion gap metabolic acidosis, and increased plasma ketone concentration. This clinical syndrome compromises approximately 2.6% to 3.2% of total DKA admissions, making it a rare condition [2] [3].

2. Case Report/Case Presentation

34 years old male patient presented to Emergency Department (ED) with complaints of recurrent vomiting, more than 10 times, and nausea for 2 days. The patient had no fever, chest pain, shortness of breath, diarrhea or constipation. He reported being recently diagnosed with type 2 diabetes mellitus 1 week ago in another facility and started on Semaglutide injections, once a week, and a combination of dapagliflozin/metformin 5 mg/1000mg, twice daily. Patient had received the Semaglutide injections 3 days prior to presenting to the hospital.

On presentation, patient's vital were: temperature 37 C, BP 132/80mmhg, and heart rate 99. Random blood sugar was 145 mg/dl. ECG showed normal sinus rhythm (Figure 1).

On examination:

The patient was nauseated, dehydrated, and looked sick.

Chest was clear, normal breath sounds.

Abdomen soft and lax, generalized tenderness, no rebound tenderness.

Heart s1s2 no added sounds.

CNS unremarkable, GCS 15/15.

The chest X-ray (Figure 2) and abdominal ultrasound were unremarkable.

Blood investigations showed bicarbonate of 11.7 mmol/l, potassium of 5.2 mmol/L, white blood cells count was 15.7. Despite symptomatic treatment, the patient's general status did not improve, with persistent nausea and vomiting. He was admitted as a case of gastritis for medical management. RBS at admission was 164 mg/dl.

After admission, patient abdominal pain improved but he still had persistent vomiting and nausea. BP was oscillating with episodes of hypotension. Venous blood gas (VBG) was repeated and showed PH of 7.0, bicarbonate of 7.7, glucose

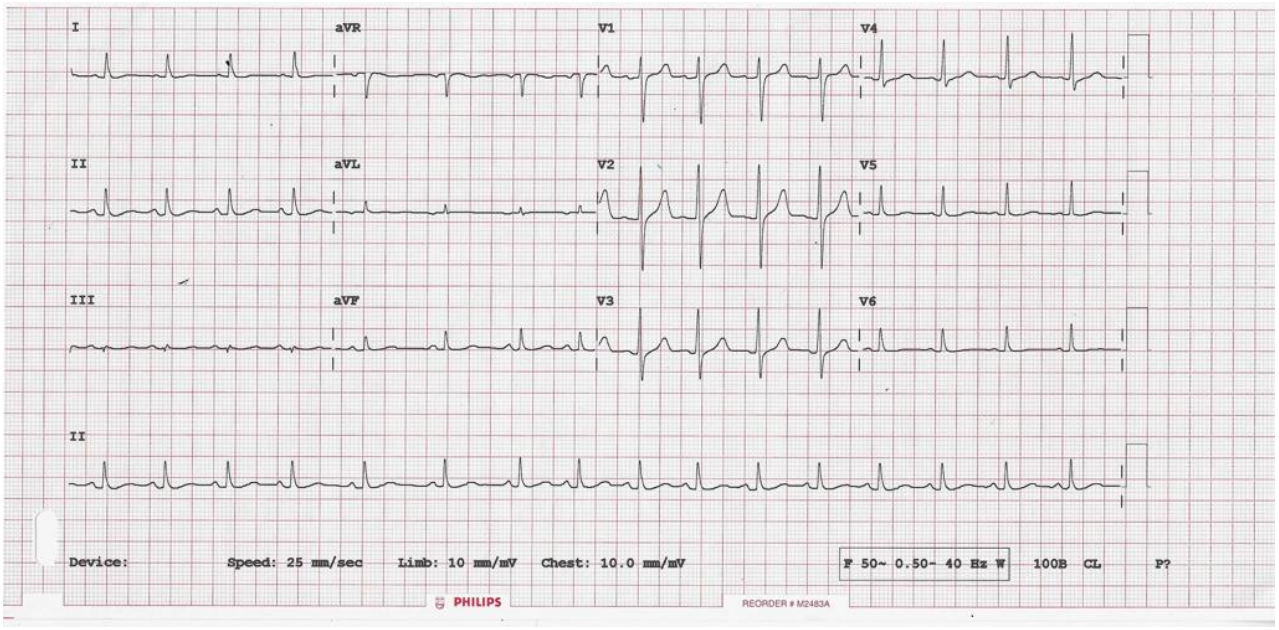

Figure 1. ECG showing sinus rhythm.

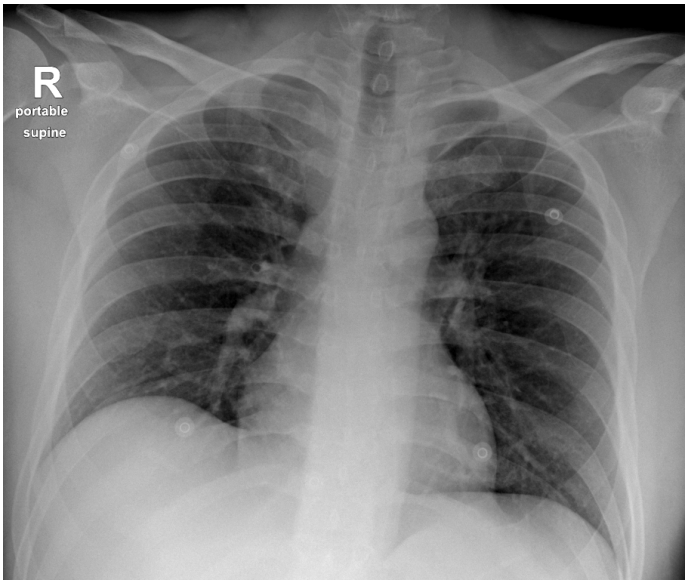

Figure 2. Normal chest X-ray.

234 and CO_2 of 31.5. Urinalysis showed high levels of ketones. The patient was diagnosed with diabetes ketoacidosis (DKA) and shifted to intensive care unit (ICU). Management was started with IV fluids and insulin infusion. HbA1C for this patient was 12.8%.

After diagnoses, endocrinology team was consulted. As per the team, patient C-peptide test, done on another facility before the DKA episode, was inappropriately normal for his extremely high fasting blood sugar (FBS). They advised that further investigations were needed to rule out Type 1 diabetes. Glutamic acid decarboxylase (GAD-65), protein tyrosine phosphate (IA2) and Zinc transporter antibodies 8 (ZINCT8) were requested and were reported as normal.

Patient symptoms improved with treatment, electrolytes and PH normalized. He was classified with severe uncontrolled type 2 diabetes mellitus and DKA. Patient was discharged home on Novorapid insulin, Toujeo insulin and Glucophage. Follow up with diabetic educator and endocrinology team was advised.

3. Discussion

Euglycemic diabetic ketoacidosis (EDKA) is a rare syndrome that can occur in type 1 (T1DM) and type 2 (T2DM) diabetes mellitus [1]. Munro *et al.* presented in 1973 a series of 211 cases of DKA decompensation, of which 37 had severe euglycaemic ketoacidosis. This serious was based on a first description of EDKA as DKA episodes with blood glucose < 300 mg/dl and plasma bicarbonate ≤ 10 mEq/l [2]. In 1993, Jenkins *et al.* reviewed 722 cases of DKA. According to the original criteria proposed by Munro *et al.* studies, Jenkins identified 23 cases of EDKA, around 3.2% of the total. Furthermore, in the study, they adopted a blood glucose level of 180 mg/dl with plasma bicarbonate criteria at ≤10 mEq/l or ≤15 mEq/l. concluding that the incidence of true EDKA was between 0.8% and 1.1% [3].

Currently EDKA is characterized by severe metabolic acidosis (arterial pH less than 7.3, serum bicarbonate less than 18 mEq/L) and ketonemia in the presence of blood glucose less than 200 mg/dL [1] [4]. A metanalysis performed by Xiaofang Yu *et al*., reviewed around 156 diabetes ketoacidosis (DKA) cases admited in the medical center in the period of 4 years and identified 4 cases of EDKA with an incidence of 2.6% [5].

EDKA is primary related to a general state of starvation, resulting in the development of ketosis while maintaining normoglycemia. The condition results from the imbalance between insulin and counter-regulatory hormones, associated with a relative or absolute carbohydrate deficit and increased glucagon/insulin ratio [1] [6]. It can lead to severe complication, such as extreme dehydration, altered mental status and coma. Early recognition and treatment are essential to avoid this life-threatening complication. Several triggers have been associated with development of EDKA, such as fasting, anorexia, alcohol abuse, pregnancy, surgery, insulin pump use and now the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors [1] [3].

The newest medication added to the treatment of diabetes mellitus are the SGLT-2 inhibitors. They have been favored due to clinical trials that highlighted reduced number of hospitalizations, protective effect against major cardiovascular adverse events and slower progression of chronic kidney disease [6]. The most used medications from this class are canagliflozin, dapagliflozin, and empagliflozin [6] [7]. The cause of EDKA in individuals on this class of medication is attributed to the osmotic diuresis along with glucosuria, volume depletion and dehydration. Glucagon release is a consequence of the carbohydrate deficit and hypovolemia, increasing glucagon/insulin ratio and trigger ketogenesis with euglycemia [2] [6].

It was evident the increase of published case reports and series about EDKA since the introduction of this inhibitors in the arsenal of drugs against diabetes. However, the accurate incidence rate of EDKA caused by SGLT-2 inhibitors is still unknown [6]. Peters *et al.* analyzed nine patients on ongoing treatment with SGLT-2, they presented with episodes of EDKA or ketosis. None of the type 1 diabetic patients had any prior episodes of DKA other than at the time of diagnosis of diabetes and no type 2 diabetic patient had any history of previous DKA [8].

A metanalysis done by Long *et al.* with 91 published studies about the topic until December 2020, concluded that SGLT-2 inhibitors increase the risk of EDKA by a factor of 7. From the overall DKA admission, 2.6% - 7% of patients were euglycemic, and the cases in insulin-dependent diabetics were correlated to the use of SGLT2 inhibitors in 5% - 12% of cases [4]. A review done by Blau *et al.* on the US FDA Adverse Event Reporting System showed that 71% of the reported cases of EDKA were associated with the use of SGLT2 inhibitor [9].

Warnings that this class of medication can cause DKA have been issued within 3 years of their use worldwide, both by the US Food and Drug Administration (US FDA) and the European Medicines Agency. Still according to the US FDA, the time frame for symptoms development can vary between 1 and 365 days,

with a median time of 43 days [7] [10].

In this study, we present a young male, newly diagnosed diabetes type 2 and started on (Semaglutide) injections and (dapagliflozin/metformin) orally. This oral hypoglycemic medication is a combination of dapagliflozin and metformin. As patient presented with abdominal pain, vomiting to the ED and normoglycemia. After admission, bicarbonate levels were low on blood analysis, RBS was repeated and VBG was done showing signs of DKA.

As highlighted by the previous discussion, euglycemic diabetes ketoacidosis is a rare and commonly missed entity. The normoglycemia parameter often misguides physicians and contributes to the delayed or missed diagnosis. It's also consistent to affirm that a very likely trigger for the present case was the introduction of the dapagliflozin to the treatment regimen. The concomitant use of Semaglutide could also have increased the likelihood of normoglycemia in this patient. After proper diagnosis and treatment, patient improved and was discharged.

4. Conclusion

Euglycemic diabetic ketoacidosis is a challenging diagnosis, not only due to the absence of one of the most important criteria, which is hyperglycemia, but also due to its varied triggers. Knowing the different contexts, and the detailed medical history, including the recent medication used, will allow us to suspect euglycemic diabetic ketoacidosis and begin rapid and adequate treatment of the precipitating cause, as well as aggressive hydration, glucose homeostasis through insulin administration, and the adjustment of electrolyte imbalances. A delay in diagnosing the case will result in increases in-hospital morbidity and mortality. High index of suspension and very detailed medical history will be the cornerstone for early diagnoses and early treatment.

Statement of Ethics

The research was conducted ethically and in accordance with the Declaration of Helsinki. The research committee policies of Dubai Health Authority do not require ethical approval.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Lamiz Tannouri: case presentation, manuscript preparation, literature research.

Shahinaz Gouda: case presentation, manuscript preparation, review.

Youssef Abboud: case presentation, manuscript preparation, review.

Data Availability Statement

All the information generated or analyzed during this study is included in the report. The corresponding author can be contacted for further information.

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