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Case of ketoacidosis: Importance of differentiating etiology with respect to treatment course

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Abstract

Ketoacidosis is a metabolic condition that can result from several distinct underlying causes, including but not limited to diabetes, chronic alcohol intake, and starvation. Differentiating between these three forms of ketoacidosis can be diagnostically challenging depending on patient presentation and history. Because diabetic ketoacidosis is most prevalent, and it is a medical emergency that can be life-threatening if left untreated, clinicians may use caution to initially treat for potential diabetic ketoacidosis in more ambiguously presenting patients. Such is this case involving a prediabetic patient with a history of alcohol use disorder, who presents to the emergency department in a hyperglycemic, acidotic state after a four-day period of starvation.

Keywords: Ketoacidosis; Diabetes; Starvation; Alcoholic; Euglycemic; Ketosis.

Introduction

Although ketosis and ketoacidosis are both metabolic conditions resultant from the accrual of ketone bodies, the two conditions are differentiated by the degree of ketone body accumulation and subsequent acid-base status of the patient [1-3]. Ketosis is often a compensatory response by the body to low-carbohydrate states [4]. In this condition, ketone bodies, which by nature are acidic, are increased but insufficient to acidify a patient's blood [2,5]. Thus, it is generally considered a less severe condition than ketoacidosis [2]. Alternatively, the accumulation of ketone bodies in ketoacidosis is enough to decrease blood pH [6]. These terms are not mutually exclusive, as it is possible for ketosis to transition into ketoacidosis [1,2].

When a patient presents with an increased amount of ketone bodies, the leading differential is often tied to diabetes [1,2,6-8]; however, depending on patient history and presentation, etiological ties to chronic alcohol intake and starvation should also be considered [2,4,6,8]. With all three of these etiologies, patients often present with metabolic acidosis with a high anion gap [1,6,8]. However, patients with diabetic ketoacidosis often present more severely, have a history of diabetes, and are hyperglycemic upon presentation [1,5,8]. Exceptions to this may include euglycemic diabetic ketoacidosis in patients who are medicated with sodium-glucose transport protein-2 inhibitors (SGLT2i) [2,4,6-8]; and patients with well-controlled diabetes presenting with acute metabolic acidosis of separate origin [2]. Patients with alcoholic or starvation ketoacidosis are generally euglycemic or hypoglycemic, with patient histories being the key to differentiate one etiology from the other [1,4,5,7]. Although not frequently the case, it is possible for patients with alcoholic or starvation ketoacidosis to present with hyperglycemia [1,5]; and alcoholic ketoacidosis (AKA) often occurs in patients who are also malnourished [1,6]. Furthermore, it is worthy to note that starvation ketoacidosis is less common than its milder form of fasting ketosis [1,2]. Due to these nuances, it may be challenging for clinicians to differentiate between the three etiologies and determine the most appropriate initial treatment upon admission, especially in patients whose histories are more ambiguous or multi-encompassing [1,7].

Several case reports have previously demonstrated this di-

lemma, with patients being initially treated for one etiology in place of the underlying etiology responsible for their condition [1,4,7]. Unfortunately, initial treatment decisions made in the face of this diagnostic challenge have been documented to result in negative consequences, such as iatrogenic hypoglycemia due to initial diabetic ketoacidosis protocol implementation in a patient with alcoholic ketoacidosis [1,5,9]. Some literature strongly supports isolation and treatment of underlying conditions from time of admission [1], whereas others express acceptability for treatment of the most severe potential condition for the possibility that it may otherwise go untreated in a more ambiguously presenting patient [4,8]. Nevertheless, it is important to increase clinician awareness on this subject, as it will ultimately benefit overall patient management.

This case report highlights a patient that can potentially fit the initial criteria for all three aforementioned categories: diabetic, alcoholic, and starvation ketoacidosis. The atypical presentation of this patient, alongside their multifaceted history, is what led to initial diagnostic uncertainty. To the best of our knowledge, this case report is unique for its description of a prediabetic patient with a history of alcohol use disorder, who presents after a four-day period of starvation to the emergency department in a hyperglycemic, acidotic state.

Case presentation

A 62-year-old female presented to the emergency department after collapsing from weakness. Her medical history included prediabetes, rheumatoid arthritis, fibromyalgia, and lung carcinoma, along with a social history of alcohol and tobacco use disorders. She described food and water aversion of four days duration due to intractable nausea, hematemesis, and melenic diarrhea. Reportedly, prior to this time frame, she had still been experiencing nausea and vomiting for two weeks; as well as decreased appetite for approximately nine months post thoracoscopic right upper lobe wedge resection with mediastinal and hilar lymphadenectomy, resulting in unintentional weight loss of 15 pounds.

On arrival to the hospital, the patient's vital signs included: blood pressure 177/92 mmHg; and heart rate 115 bpm. Physical exam was remarkable for 9/10 sharp epigastric pain, diffuse tenderness to palpation of bilateral lower extremities, and a positive hemoccult blood test. Her body mass index was 30.6 kg/m^2. The patient was initially managed using intravenous normal saline, ondansetron, and morphine. Several chemistry (Table 1) and complete blood count (Table 2) panel abnormalities were identified. It was noted that she had electrolyte disturbances, elevated glucose, elevated anion gap, and low bicarbonate values. Additionally, trace ketone level was obtained via urinalysis and small acetone level via bloodwork. Arterial blood gas evaluation obtained pH 7.311 (Table 3). Although the hemoglobin A1C and C-peptide values were not yet available, the constellation of gathered information was agreeable to admission. The leading differential at the time was starvation ketoacidosis. However, due to the lingering possibility of Diabetic Keto Acidosis (DKA), the patient was admitted to the intensive care unit and started on intravenous insulin and fluids (potassium chloride in 5% dextrose and sodium chloride) per DKA protocol.

Her hemoglobin A1C later returned at 6.1%. Following two consecutive negative acetone values and a closed anion gap, DKA protocol was discontinued, and the patient was principally treated for starvation ketoacidosis in the medical surgical unit. Treatment emphasis was placed on increasing caloric intake and balancing electrolyte abnormalities. The patient's epigastric pain, nausea, and appetite continued to improve over the following three days of her hospital stay. During this time, hemoglobin levels remained stable, hematemesis and melenic diarrhea did not recur, and the large anion gap metabolic acidosis had almost entirely resolved. Upon discharge, appointments were scheduled for the patient to follow-up outpatient with their primary care provider in one week, establish care with an endocrinologist in two weeks, and follow up with a gastroenterologist in two weeks regarding the recent occurrence of melenic diarrhea.

Discussion

This case highlights a situation in which there remains uncertainty towards choice of initial treatment protocol, even after diagnostic testing and thorough gathering of patient history. To understand the reasons behind this uncertainty, it is important to address the significance of this patient's presentation. Patient history indicated that the 62-year-old female with ketoacidosis had not ingested adequate food or water for four days prior to admission, resulting in her eventual collapse from weakness. This alone may seem to hint towards starvation as the reason behind her presentation; however, the fact that she also had a history of alcohol use disorder, and a diagnosis of prediabetes, complicated the selection of a leading differential diagnosis.

The patient self-reported during inquiry of her social history at presentation that she was not currently drinking alcohol. It is for this reason that alcoholic ketoacidosis was lower on the list of differential diagnoses. On the other hand, Diabetic Keto-Acidosis (DKA) was more so considered because of the inability to exclude it given the constellation of findings during initial presentation in the emergency department. Hence, due to concerns about the consequences of untreated DKA, the decision was made to treat for this condition initially and monitor with close observation.

It is important to note that this approach to the patient's management yielded positive clinical outcome. Nevertheless, raising awareness regarding the different etiologies of ketoacidosis is important. Furthermore, given the potential for categorial overlap in patient history details or clinical presentation, it is also valuable to highlight the difficulties discerning between the various forms of ketoacidosis. To accomplish this, it is necessary to address the pathophysiology behind ketoacidosis and its different origins, as well as the treatment modalities for each.

Ketoacidosis is a result of the accumulation of ketone bodies, namely acetoacetate and beta- hydroxybutyrate, which are created by the liver via fatty acid oxidation to provide the body with energy in a glucose-deficient state [4]. Ketone body production is triggered by decreased insulin in the body, accompanied by increased glucagon [4]. The reduction of insulin encourages lipolysis, which supplies the liver with available fatty acids for oxidation [6]; this also decreases glucose transport into muscle and adipose tissues to allocate available amounts for the brain [6]. Simultaneously, glucagon serves to induce glycogenolysis, to release stored glucose from the liver [6]. As glucose stores diminis hand production of acidic ketone bodies continues, the

Table 1: Chemistry panel values retrieved post emergency department arrival with reference ranges.

Chemistries	Patient's Values	Reference Ranges
Potassium	3.5 mmol/L	3.5-5.5 mmol/L
Sodium	131 mmol/L	133-145 mmol/L
Chloride	96 mmol/L	98-110 mmol/L
Magnesium	2.0 mg/dL	1.6-2.5 mg/dL
Glucose	156 mg/dL	70-99 mg/dL
BUN	33 mg/dL	6-22 mg/dL
CO_2	13 mmol/L	20-32 mmol/L
Creatinine	1.1 mg/dL	0.8-1.4 mg/dL
Albumin	4.1 g/dL	3.5-5.0 g/dL
eGFR	54.3 mL/min/1.73 sq.m.	>60.0 mL/min/1.73 sq.m.
Globulin	4.1 g/dL	2.0-4.0 g/dL
A/G Ratio	1.0	1.1-2.6
Total Protein	8.2 g/dL	6.2-8.1 g/dL
Anion Gap	22.0 mmol/L	3.0-15.0 mmol/L

BUN: Blood Urea Nitrogen; eGFR: Estimated Glomerular Filtration Rate; A/G Ratio: Albumin/globulin Ratio.

Table 2: Complete blood count panel values retrieved post emergency department arrival with reference ranges.

	Patient's Values	Reference Ranges
White Blood Cells	9.1 K/uL	4.0-11.0 K/uL
Red Blood Cells	4.37 M/uL	3.80-5.20 M/uL
Hemoglobin	13.4 g/dL	11.7-16.0 g/dL
Hematocrit	40.4%	35.1-48.0%
Platelet	284 K/uL	140-440 K/uL
Segmented Neutrophils	81%	40-75%
Lymphocytes	16%	20-45%
Monocytes	2%	3-12%

Table 3: Blood gas values quantified via an i-STAT CG8+ cartridge and system.

	Patient's Values	Reference Ranges
Bicarbonate	20.3 mmol/L	22.0-26.0 mmol/L
pH	7.311	7.350-7.450

body progressively develops a high anion gap metabolic acidosis [4].

This is generally what occurs in fasting ketosis as it develops into starvation ketoacidosis (SKA) [1-3]. Susceptible populations may implement the ketogenic/Atkins/South Beach diets, religious fasting, or otherwise may experience post-procedural appetite reduction [2,9]. Risk factors all share in deficient carbohydrate ingestion and eventual exhaustion of reserved glucose stores within 24 hours [2,6]. Once ketoacidosis is achieved, patients may demonstrate symptoms of nausea, vomiting, and lethargy [2,4]; and typically diagnostic tests result in blood pH above 7.3 and serum bicarbonate above 18 mmol/L [2,6]. To combat this type of ketoacidosis, patients may be intravenously hydrated using solutions of dextrose and sodium chloride, with electrolyte replacement as necessary [2,4,7,9]. Insulin infusions and injections are initially avoided because patients experiencing fasting ketosis or SKA synthesize endogenous insulin when carbohydrates are exogenously replenished using dextrose solutions [4,9]; thus insulin administration may result in iatrogenic hypoglycemia [4,9].

With DKA, the primary concern is insulin deficiency [6]; which, when in conjunct with increased glucagon, results in uncontrolled lipolysis, fatty acid oxidation, and generation of ketone bodies [6]. Populations susceptible to this include those with a history of diabetes mellitus [5], with Type 1 being most prevalent [8]. The earliest signs of DKA are polyuria and polydipsia [5]; however, by the time of emergency department presentation, patients often become less alert and incoherent, with many experiencing nausea, vomiting, and abdominal pain [5]. Criteria for diagnosis of DKA include: plasma glucose above 250 mg/dL, elevated serum ketones, blood pH below 7.3, high anion gap, and bicarbonate value below 18 mmol/L [5,8]. Additionally, patients may demonstrate volume depletion and subsequent drops in potassium and phosphate [6]. Although not necessary initially, negative to low C-peptide levels can help support a diagnosis of DKA, since it indicates that the body is not sufficiently synthesizing insulin [3]. To correct for DKA, treatment protocol generally includes administration of: intravenous fluids for rehydration, intravenous or subcutaneous insulin for resolution of ketosis and reduction of glucose levels [8]; with monitoring of: electrolytes, ketones, glucose, and anion gap [8]. Potassium replacement is also important to this protocol [5].

Less commonly, patients on sodium-glucose transport protein-2 inhibitors (SGLT2i) may present with euglycemic DKA [2,6-8]. In these patients, SGLT2i result in decreased glucose and insulin levels within the body [6]. An increased glucagon/insulin ratio then triggers lipolysis and ketogenesis [6]. Although this is similar to the process for hyperglycemic DKA, this ketoacidosis presents as euglycemic because of the glycosuric action of SGLT2i [6]. Besides euglycemia, this form of DKA presents with severe anion gap metabolic acidosis [2,4]; plasma glucose below 250 mg/dL, and moderate electrolyte disturbances in plasma sodium and potassium [6]. On presentation, patients may report constitutional symptoms, such as nausea or malaise [6]. Treatment for euglycemic DKA caused by SGLT2i is similar to regular DKA protocol as aforementioned, but with the additional withholding of SGLT2 inhibitors while ketones are still present [10].

For Alcoholic Ketoacidosis (AKA), the most vulnerable population is comprised of those who have a history of alcohol use disorder, especially persons known to binge drink [1,5]. The ethanol imbibed is metabolized by the liver, subsequently increasing the ratio of NADH to NAD+ [5,6]. At the same time, inadequate solid and liquid intake due to nausea, vomiting, and abdominal pain results in decreased insulin levels, which in combination with a sympathomimetic state from alcohol withdrawal, triggers abundant lipolysis and ketogenesis [1,5,6]. In the patient, this all culminates into a high anion gap metabolic acidosis [6]; additionally, electrolyte disturbances manifest in the form of reduced plasma magnesium, potassium, phosphate, and sodium [6]. Despite these metabolic changes, patients with AKA are considerably more alert than their DKA counterparts [1,5]. For the treatment of metabolic abnormalities, protocol instructs administration of: intravenous fluids for rehydration [1]; intravenous or intramuscular thiamine to decrease the risk of intensifying any Wernicke's encephalopathy [4], whilst also avoiding lactic acidosis and cardiovascular complications [1,5]. Following thiamine, intravenous dextrose may be administered to combat acidosis [1,5]. Thiamine replenishment is especially important towards the treatment of AKA because chronic alco-

hol intake results in thiamine deficiency due to decreased gastrointestinal absorption [5]. On the other hand, insulin administration must be considered with caution, as these patients are more prone to developing iatrogenic hypoglycemia [9].

Acknowledging the distinct features of these three forms of ketoacidosis, as well as areas of ambiguity, is imperative towards optimization of patient management and outcome [1]. Literature proposes several observed and hypothetical examples of complications, like with those induced by initially treating AKA as DKA [1,6]. Some examples proposed that omission of thiamine administration prior to dextrose may aggravate Wernicke's encephalopathy [1,4], or induce lactic acidosis [7,9]. Another concern includes the initial administration of intravenous insulin resulting in iatrogenic hypoglycemia [1,6]. As with AKA, SKA being initially treated as DKA also has proposed complications, such as refeeding syndrome or iatrogenic hypoglycemia also due to the administration of exogenous insulin [9]. And for DKA, if it is treated as anything other than itself, the probability of fatality increases [9]. Although there exist distinctions between preferred treatment modalities for individual etiologies of ketoacidosis, it is imperative to also acknowledge that various ketoacidoses may coexist, and thus management should be adjusted to address all applicable ketoacidoses accordingly [7].

Aside from optimization of outcomes, a secondary benefit may be cost savings associated with healthcare [8]. Due to the gravity of DKA, many hospitals admit DKA patients to the intensive care unit, as opposed to the medical surgical unit which may cost approximately 2.5 times less per day [8]. Additionally, the administration of intravenous insulin as part of many DKA protocols can cost about 1.5 times more than as-needed subcutaneous insulin [8]. Thereby, hypothetical treatment of AKA or SKA as DKA can result in avoidable overtreatment and the costs that accompany it [8]. For this reason, among others, it may benefit clinicians, patients, and healthcare systems alike to revisit the topic of ketoacidoses and their various origins.

Conclusion

It is important to increase clinician awareness about ketoacidoses and their various etiologies. This insight may result in avoidance of overtreatment and subsequent complications, as well as a reduction of healthcare costs. Nonetheless, clinician capitalization of this opportunity will ultimately benefit patient management.

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