An Unusual Case of Severe Metabolic Acidosis in MICU: SGLT2 Inhibitor-Associated Diabetic Ketoacidosis

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Patient Presentation

51-year old female presented to the emergency department (ED) for a four day history of nausea, vomiting and generalized weakness

- Lower chest pain x 1 day, worsen by deep breath
- Diffuse abdominal pain
- Denies fever, chills, cough, diarrhea, dysuria
- No recent history of recent travel or ingestion of toxic substances

• Past medical history/past surgical history
  – Type 2 diabetes mellitus / obesity class 3 BMI 53 / hypertension / restless syndrome
  – Cholecystectomy/abdominal hernia repairs x 2

• Home Medications
  – Empagliflozin (SGLT2 inhibitor)
  – Dulaglutide
  – Insulin glargine
  – Others: atorvastatin, trazodone, ropinirole, losartan

• Family / Social history
  – Father has HTN, CAD s/p CABG in 60's
  – Denies alcohol use, tobacco use or recreational drug use
**Physical Exam**

**Vitals:** Temperature 36.7 °C, heart rate 101 beats/min, blood pressure 135/89 mmHg, respiration rate 24 breaths/min and oxygen saturation 97% on room air

**General appearance:** obese, alert, awake, oriented  
**Head/Eyes:** atraumatic, clear cornea, normal conjunctiva/sclera  
**ENT:** dry mucosal membrane, normal pharynx  
**Neck:** supple/no meningismus, no bruit/NL carotids  
**Cardiovascular:** normal capillary refill, normal heart sounds, regular rate and rhythm, normal S1/S2  
**Respiratory:** deep and labored breathing, chest symmetric expansion, no tenderness, clear to auscultation,  
**Abdomen:** soft, non-tender, normal bowel sounds  
**Genitourinary:** no flank pain, no foley  
**Extremities:** moves all, normal capillary refill  
**Musculoskeletal:** normal inspection  
**Neuro/CNS:** alert, oriented X 3, normal speech  
**Skin:** normal color, normal temperature  
**Psychiatry:** normal affect, normal judgment/insight, normal mood
Clinical Data

Other pertinent labs:
- Small serum acetone
- Large urine ketones
- Lactic acid 1.3 mg/dL
- Anion Gap: 20 meq/L
- “Delta-Delta” ratio 0.57

Other pertinent labs:
- Measured serum osmolality 304
- Calculated serum osmolality 287
- Osmolality gap 17
- Serum alcohol <3 mg/L
- B-hydroxybutyrate not available at early phase of assessment and treatment
Hospital Course

Emergency team
- 0.9% saline 2 liters

Hospital medicine team
- Initiated bicarb drip
- Ordered insulin drip
- Consulted Critical Care team

Critical Care team
- Euglycemic diabetic ketoacidosis (DKA) secondary to fatal SGLT2i-induced DKA was highly suspected
- DKA standard of care was initiated with:
  - Intravenous insulin
  - Intravenous fluid
  - Bicarb drip
  - Electrolyte disturbance correction
- ICU course
  - After twenty-eight hours, the patient’s anion gap normalized and intravenous insulin was discontinued

<table>
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<th></th>
<th>28HR</th>
<th>10HR</th>
<th>2HR</th>
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<tbody>
<tr>
<td>ABG PH</td>
<td>7.45</td>
<td>7.13 CL</td>
<td>7.08 CL</td>
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<tr>
<td>ABG PCO2</td>
<td>44</td>
<td>25 L</td>
<td>24 L</td>
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<tr>
<td>ABG PO2</td>
<td>76 L</td>
<td>115 H</td>
<td>112 H</td>
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<tr>
<td>ABG HCO3</td>
<td>30.0</td>
<td>8.2 L</td>
<td>6.9 L</td>
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<tr>
<td>ABG BE</td>
<td>5 H</td>
<td>-19 L</td>
<td>-22 L</td>
</tr>
<tr>
<td>ABG TCO2</td>
<td>31.0 H</td>
<td>9.0 CL</td>
<td>8.0 CL</td>
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<tr>
<td>ABG O2SAT</td>
<td>96</td>
<td>97</td>
<td>96</td>
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<tr>
<td>Anion Gap</td>
<td>12</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>HCT %</td>
<td>36.5</td>
<td>46.4</td>
<td>54.4</td>
</tr>
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At a later date after the patient was discharged home, B-hydroxybutyrate result returned 73 mg/dL (normal 0.2-2.8 mg/dL)

Atypical DKA in this case
- Severe metabolic acidosis
- Near normal serum glucose level
- Very small serum acetone
- B-hydroxybutyrate result not available during initial assessment
DKA Pathophysiology

- DKA results from relative or absolute insulin deficiency combined with counterregulatory hormone excess (glucagon, catecholamines, cortisol, and growth hormone).
  - Both insulin deficiency and glucagon excess are necessary for DKA to develop.

SGLT2 Inhibitor

- SGLT-2 receptor is responsible for 90% of the active glucose reabsorption of the kidney's proximal tubule.
  - By inhibiting this receptor, glucose reabsorption is decreased.
  - Glucose passes into the urine, serum glucose is lowered
- Renal tubular cells from T2DM patients show increased levels of SGLT2, thereby offering a mechanism by which the kidney of a patient with DM achieves its increased ability for glucose reabsorption.

Euglycemic DKA

• Mechanism:
  – decreased release of insulin (due to the lower glucose levels)
  – direct stimulation of glucagon release, and ketogenic effects
• Risk may be higher in:
  – patients undergoing stressful events, such as surgery.
  – with concurrent insulin use
  – patients with lower insulin levels, such as LADA (latent autoimmune diabetes of the adult).
• Due to glucosuria, DKA in these patients is often associated with near normal glucose levels

Mechanisms for Euglycemic DKA


Figure 2: Pathogenesis of SGLT-2 inhibitor-associated EDKA. EGP: endogenous glucose production; TGD: tissue glucose disposal.
**Approach to Better Practice**


- **Clinical manifestations**
  - This type of DKA can be easily missed. Clinicians need to improve awareness to quickly recognize and treat this condition early as it can be fatal.
    - DKA can occur in the setting of relative euglycemia
    - Vigilance for patients with acidosis

- **Testing**
  - Promptly evaluate for urine and/or plasma ketones, any time a SGLT2 inhibitor–treated patient feels unwell regardless of the glucose levels
  - Urine and/or plasma acetone not enough, sometimes plasma acetone normal
  - **Always check B-hydroxybutyrate**

- **Treatment**
  - Discontinue the offending medication
  - DKA standard management
Questions

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