CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 8-2025: A 72-Year-Old Woman with Altered Mental Status and Acidemia

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PRESENTATION OF CASE

Dr. David M. Dudzinski: A 72-year-old woman was evaluated at this hospital because of altered mental status.

Five years before the current admission, the patient underwent transurethral resection of a 4-cm papillary transitional-cell carcinoma of the bladder (grade 3 of 3) that had invaded the muscularis propria. She received local radiation therapy, as well as chemotherapy with fluorouracil and mitomycin C. Cytologic examination of the urine performed 3 months before the current admission reportedly showed findings that were suggestive of urothelial cancer.

Two weeks before the current admission, the patient had hematuria with clots, accompanied by dysuria and flank pain. She received a course of oral ciprofloxacin.

Four days before the current admission, cystoscopy revealed evidence of mild radiation cystitis, blood clots, and a new 1.5-cm tumor on the left lateral bladder wall. Results of an analysis of a urine specimen obtained by catheterization are shown in Table 1; cytologic examination revealed high-grade urothelial carcinoma. Bladder fulguration was scheduled.

On the second day after cystoscopy (2 days before the current admission), the patient noted an unintentional weight gain of 2.5 kg during the preceding 2 days. On the third day after cystoscopy, the patient's cardiologist recommended that she add a second daily dose of torsemide and spironolactone to her current regimen. Results of laboratory testing of blood obtained by a home health aide are shown in Table 1.

That night, the patient was agitated and slept without her usual bilevel positive airway pressure device. The next morning, the patient's daughter called emergency medical services when she noticed that the patient had persistent somnolence and altered mental status. The patient was transported to the emergency department of this hospital.

Additional history was obtained from the patient's daughter. The patient had been disoriented for the past few days and had had 2 weeks of hematuria, chills, fatigue, lethargy, progressive dyspnea, and edema in both legs. She had also had

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Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	At Cystoscopy, 4 Days before Current Admission	2 Days before Current Admission	In Emergency Department	On Admission to ICU	Morning of Second Day in ICU	Afternoon of Second Day in ICU
Urine							
Color	Yellow	—	—	—	Brown	—	Yellow
Clarity	Clear	—	—	—	Turbid	—	Turbid
pH	5.0–9.0	5.0	—	—	5.0	—	5.0
Specific gravity	1.001–1.035	1.010	—	—	1.011	—	1.009
Glucose	Negative	Trace	—	—	3+	—	1+
Ketones	Negative	Negative	—	—	Negative	—	1+
Leukocyte esterase	Negative	Negative	—	—	2+	—	1+
Nitrite	Negative	Negative	—	—	Negative	—	Negative
Blood	Negative	3+	—	—	3+	—	3+
Protein	Negative	2+	—	—	1+	—	Negative
Red cells (per high-power field)	0–2	—	—	—	>100	—	>100
White cells (per high-power field)	<10	—	—	—	<10	—	10–20
Bacteria	None	—	—	—	1+	—	1+
Blood							
Hemoglobin (g/dl)	12.0–16.0	—	10.1	8.9	8.5	8.8	—
Hematocrit (%)	36.0–46.0	—	34.0	30.0	29.1	29.9	—
White-cell count (per μl)	4500–11,000	—	9620	12,210	12,690	13,150	—
Platelet count (per μl)	150,000–400,000	—	290,000	248,000	264,000	271,000	—
Sodium (mmol/liter)	135–145	—	137	136	139	139	143
Potassium (mmol/liter)	3.4–5.0	—	4.4	4.7	4.5	4.3	4.0
Chloride (mmol/liter)	98–108	—	90	92	96	94	94
Carbon dioxide (mmol/liter)	23–32	—	33	30	27	22	17
Urea nitrogen (mg/dl)	8–25	—	63	90	89	90	93
Creatinine (mg/dl)	0.60–1.50	—	1.81	3.16	3.18	3.10	3.17
Glucose (mg/dl)	70–110	—	214	203	184	177	230
Anion gap (mmol/liter)‡	3–17	—	14	14	16	23	32
Phosphorus (mg/dl)	2.6–4.5	—	—	—	7.5	7.4	—
Lactate (mmol/liter)	0.5–2.2	—	—	0.7	0.9	0.6	1.1
High-sensitivity troponin T (ng/liter)	0–9	—	—	117	122	—	—

N-terminal pro–B-type natriuretic peptide (pg/ml)	<900	—	—	8812	—	—	—	—
Venous blood pH	7.30–7.40	—	—	7.16	—	—	—	—
Serum osmolality (mOsm/kg)	280–296	—	—	—	—	—	—	349
Arterial blood gases								
Fraction of inspired oxygen	—	—	—	—	0.40	0.40	0.40	0.40
pH	7.35–7.45	—	—	—	7.19	7.18	7.17	7.17
Partial pressure of carbon dioxide (mm Hg)	35–42	—	—	—	87	74	68	68
Partial pressure of oxygen (mm Hg)	80–100	—	—	—	81	89	84	84

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for lactate to milligrams per deciliter, divide by 0.1110.
† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.
‡ The expected anion gap varies relative to the albumin level.

unintentional weight gain. During the previous 6 weeks, the patient had recorded fingerstick blood glucose levels of greater than 230 mg per deciliter (12.8 mmol per liter; reference range, 70 to 100 mg per deciliter [3.9 to 5.6 mmol per liter]), which had been attributed to increased carbohydrate intake. A review of systems had been notable for mechanical falls, right shoulder pain, constipation, and hemorrhoids. She had had no fever, anorexia, known sick contacts, or other neurologic symptoms. She had received two vaccinations against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the previous 9 months.

Approximately 7 months before the current admission, the patient had been admitted to this hospital because of somnolence; she had been found to have hypercapnia. She had received bilevel positive airway pressure, antibiotic agents, and diuretic therapy. Her symptoms had been attributed to excessive use of benzodiazepines.

The patient's medical history included asthma and recurrent bronchitis, restrictive lung disease, obstructive sleep apnea, precapillary and postcapillary pulmonary hypertension with right ventricular dysfunction, heart failure with preserved ejection fraction, coronary artery disease, right bundle-branch block, stage 3a chronic kidney disease (baseline creatinine level, 1.3 mg per deciliter [115 mmol per liter]; reference range, 0.6 to 1.5 mg per deciliter [53 to 133 mmol per liter]), hyperlipidemia, hypertension, type 2 diabetes mellitus, gout, gastroesophageal reflux disease, appendectomy, iron-deficiency anemia, osteoarthritis resulting in right total hip replacement and knee arthroscopy, osteoporosis with lumbar compression and previous hip fracture, fibromyalgia, depression, and anxiety.

Medications included oral aspirin, armodafinil, allopurinol, colchicine, dapagliflozin, metformin, melatonin, metoprolol, montelukast, extended-release morphine sulfate, pantoprazole, pravastatin, sertraline, spironolactone, torsemide, and as-needed lorazepam and immediate-release morphine sulfate. The patient also received inhaled fluticasone–salmeterol and mometasone, as-needed supplemental oxygen, and albuterol and ipratropium nebulizers as needed. Cefuroxime, celecoxib, and oxycodone had caused urticaria.

The patient was a retired factory worker and lived with her husband and daughter in the Boston area. She drank wine rarely and did not use tobacco or other substances. Her family history

was notable for breast and stomach cancer in her mother.

On examination, the patient appeared frail and somnolent and was in mild respiratory distress. The temporal temperature was 36.3°C, the heart rate 73 beats per minute, the blood pressure 102/54 mm Hg, the respiratory rate 25 breaths per minute, and the oxygen saturation 96% while she was receiving supplemental oxygen through a nasal cannula at a rate of 4 liters per minute. The weight was 76.0 kg (as compared with 72.3 kg measured 3 weeks earlier); the height was 152 cm, and the body-mass index (the weight in kilograms divided by the square of the height in meters) was 32.9. During the interview, she required frequent redirection, offered brief answers, and followed simple commands. Strength in the arms and legs was symmetric. The lung sounds were diminished in the anterior lung fields, with decreased respiratory efforts and bibasilar crackles. On auscultation, a grade 2/6 systolic murmur was present at the base. There was mild, diffuse abdominal tenderness and 2+ edema in both legs, with mildly diminished pulses that were symmetric. The remainder of the examination was normal.

Blood levels of aspartate aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatase, and calcium were normal, as were the prothrombin time and international normalized ratio; other laboratory test results are shown in Table 1. Blood and urine samples were obtained for culture. Testing for SARS-CoV-2 RNA was negative. Electrocardiography showed sinus arrhythmia and known right bundle-branch block.

Dr. Behrooz Masuodi: A chest radiograph (Fig. 1A) showed low lung volumes, mild interstitial opacities consistent with pulmonary edema, and small bilateral pleural effusions with adjacent atelectasis.

Dr. Dudzinski: The patient received intravenous vancomycin, ceftriaxone, and metronidazole. Bilevel positive airway pressure was initiated. Norepinephrine and bumetanide were administered intravenously.

Four hours after the patient arrived in the emergency department, she was admitted to the intensive care unit (ICU). The temporal temperature was 36.7°C, the heart rate 69 beats per minute, the blood pressure 91/55 mm Hg while she was receiving intravenous norepinephrine, the respiratory rate 20 breaths per minute, and the oxygen saturation 93% while she was receiving bilevel positive airway pressure (inspiratory pressure, 12 cm of water; positive end-expiratory pressure, 5 cm of water; fraction of inspired oxygen, 0.40).

Blood levels of acetaminophen, ethanol, and salicylates were undetectable, and urine toxicology screening was negative. Other laboratory test results are shown in Table 1. A radial arterial catheter and a femoral central venous catheter were placed; measurements of central venous pressure ranged from 8 to 12 cm of water. Bedside cardiac ultrasonography reportedly showed that the left ventricular cavity was small but was functioning normally and that the right ventricle was dilated and hypokinetic.

In the morning of the second day in the ICU, the patient was somnolent. The norepinephrine dose was increased from 5 μg per minute to 14 μg per minute, and vasopressin was started. Overnight, the urine output was recorded at approximately 100 to 150 ml per kilogram per hour, with a net fluid balance of −373 ml from the previous day. Intravenous chlorothiazide and calcium gluconate were administered. The glycated hemoglobin level was 7.5% (reference range, 4.3 to 5.6); the levels of thyrotropin, cortisol, aspartate aminotransferase, and alanine aminotransferase were normal. Other laboratory test results are shown in Table 1.

Dr. Masuodi: Abdominal and pelvic radiographs (Fig. 1B and 1C) showed nondilated bowel loops, a partially healed fracture of the right pubic ramus, and evidence of previous left total hip arthroplasty.

Dr. Dudzinski: In the afternoon of the second day in the ICU, the patient reported diffuse myalgias, and intravenous bumetanide was changed to intravenous furosemide. Over the course of the first 12 hours of the second day, the urine output was 1895 ml, with a total fluid balance of −884 ml. Laboratory test results are shown in Table 1.

Diagnostic and management decisions were made.

DIFFERENTIAL DIAGNOSIS

Dr. Petra Simic: This 72-year-old woman with bladder cancer, right heart failure, stage 3a chronic kidney disease, and type 2 diabetes mellitus who had been taking metformin and dapagliflozin presented with altered mental status and a possible urinary tract infection. She was in shock,

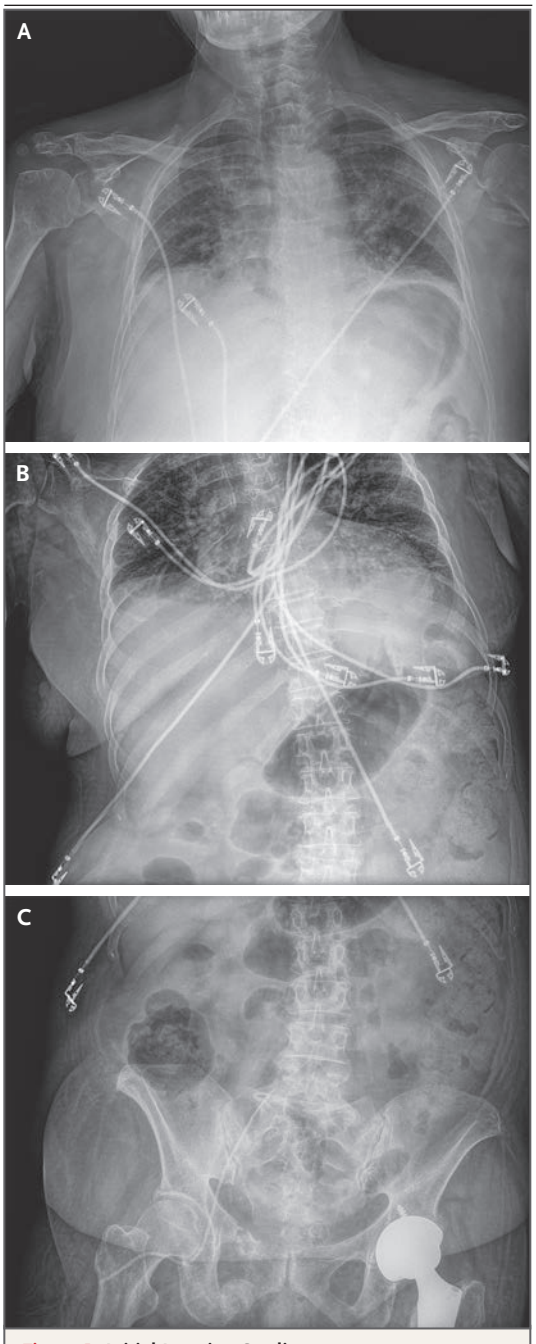


Figure 1. Initial Imaging Studies.

A chest radiograph (Panel A) shows low lung volumes, vascular indistinctness and interstitial opacities that are suggestive of pulmonary edema, and small bilateral effusions with associated bibasilar atelectasis; a prominent stomach bubble is also present. Abdominal and pelvic radiographs (Panels B and C, respectively) show nondilated bowel loops, a partially healed fracture of the right pubic ramus (Panel C), and evidence of previous left total hip arthroplasty.

for which she received vasopressors, and had evidence of organ dysfunction, including delirium, acute-on-chronic kidney failure, hypercapnic and hypoxemic respiratory failure, heart failure, and persistent acidemia. The possible causes of her shock include sepsis (possible urinary tract infection), cardiac dysfunction (peripheral and pulmonary edema), and intravascular hypovolemia (fasting perioperative state, probable reduced oral intake since surgery, and increased doses of diuretics).

During the patient's first two hospital days, her acidosis worsened. She initially presented with acute-on-chronic respiratory acidosis, and despite improvement in the level of partial pressure of carbon dioxide, the pH did not improve, which introduces the possibility of an underlying metabolic acidosis. The anion gap increased from 14 mmol per liter (reference range, 3 to 17) to 32 mmol per liter — a change of 18 mmol per liter. This increase exceeds the decrease in the bicarbonate level from 30 mmol per liter to 17 mmol per liter (reference range, 23 to 32) — a change of 13 mmol per liter — and most likely indicates renal compensation for the respiratory acidosis. The patient had high anion-gap metabolic acidosis, but no apparent non–anion-gap metabolic acidosis was present. In formulating a differential diagnosis, the patient's case centers around the root cause of the key feature — high anion-gap metabolic acidosis.

Approximately 35% of the anion gap is now recognized to originate from Krebs cycle intermediates, which are involved in amino acid, glucose, and triglyceride metabolism.[1] The acronym GOLD MARK[2] provides a useful framework for developing a differential diagnosis for high anion-gap metabolic acidosis in this patient (Table 2).

GLYCOLS AND METHANOL

Ingestion of glycols (such as ethylene glycol and propylene glycol) and methanol can cause high anion-gap metabolic acidosis, but this patient had no history of ingestion of these substances. In addition, ingestion of glycols or methanol causes not only an elevated anion gap but also an elevated osmolar gap. This patient's osmolar gap was 17 mOsm per kilogram, which is lower than the level that would be expected (>20 mOsm per kilogram) if one of these substances were the

cause of high anion-gap metabolic acidosis. Nevertheless, for completeness, measurement of blood levels of glycols and methanol could be considered.

5-Oxoproline

The blood level of 5-oxoproline (pyroglutamic acid) may increase in certain patients who use acetaminophen on a long-term basis and have nutritional deficiencies and chronic kidney disease, and measurement of this level should be considered in this patient's case. However, the presence of an elevated 5-oxoproline level would be unlikely in this case, given that there was no reported acetaminophen use and blood toxicology screening showed an undetectable level of acetaminophen. Because the patient was somnolent and history was obtained from her daughter, I would recommend measurement of the blood 5-oxoproline level, since it can be elevated with long-term acetaminophen use in the absence of acute overdose.[3]

Aspirin

Excessive use of aspirin (acetylsalicylic acid) can cause high anion-gap metabolic acidosis. Although this patient was taking daily low-dose aspirin, the amount of salicylate ingested would not cause high anion-gap metabolic acidosis; moreover, the blood salicylate level was undetectable. These findings make aspirin use an unlikely cause of high anion-gap metabolic acidosis.

Renal Failure

Normally, proximal tubular cells in the kidneys use glutamine, which generates ammonium that is excreted along with hydrogen ions. In patients with renal failure, there is a defect in urinary acidification and accumulation of anion-gap–producing organic acids. However, in patients with acute kidney injury, the anion gap is typically approximately 15 mmol per liter, and in those with chronic kidney disease, 13 to 15 mmol per liter[4]; these levels are consistent with the anion gap of 14 mmol per liter measured in this patient before the current admission. The peak anion gap of 32 mmol per liter in this patient is excessively high for acute kidney injury to be the sole cause of high anion-gap metabolic acidosis. Although ongoing monitoring and treatment of acute-on-chronic kidney failure is critical in this patient's case, other causes of acidosis should be considered.

L-Lactate

Lactic acidosis is another common cause of high anion-gap metabolic acidosis. In patients with type A lactic acidosis, reduced tissue oxygenation shifts metabolism toward glycolysis and lactate production. Type A lactic acidosis usually occurs in patients with conditions such as sepsis, heart failure, and shock, which this patient had. Type B lactic acidosis is not caused by decreased tissue oxygenation but is associated with several features of this patient's case including diabetes, paraneoplastic syndrome, and metformin and beta-agonist use. Of note, this patient's lactate level was normal.

Metformin-associated lactic acidosis should always be considered in patients with metabolic acidosis who are taking metformin. Metformin blocks the mitochondrial electron transport chain and directs glucose toward lactate production. The toxic dose of metformin is approximately 5 g, and in the context of acute kidney injury, it takes approximately two and a half days of therapeutic use for metformin to reach toxic levels in the blood. Subsequently, it can take up to an additional 8 to 12 hours for metformin-associated lactic acidosis to develop.[5,6] Despite the fact that this patient's lactate level remained normal for the initial 28 hours of her hospitalization, measurement of the blood metformin level is advisable.

D-Lactate

D-Lactic acidosis is a rare clinical occurrence and most commonly results from bacterial production associated with short-bowel syndrome, which does not fit with this patient's history. D-Lactic acidosis can occur after ingestion of propylene glycol and occasionally in association with diabetic ketoacidosis.

Ketoacidosis

This patient most likely has ketoacidosis, which could be due to either diabetes or starvation. Ketoacidosis involves a decrease in intracellular glucose, which leads to a shift in metabolism toward the production of fatty acids, including the ketones acetoacetate and β-hydroxybutyrate, as vital organ fuel. The use of sodium–glucose cotransporter 2 (SGLT2) inhibitors in persons with diabetes can trigger euglycemic diabetic ketoacidosis in the context of certain stressors such as infection or surgical procedures, which this pa-

Table 2. Approach to Identifying Possible Causes of High Anion-Gap Metabolic Acidosis in This Patient with the Use of the GOLD MARK Acronym.

Cause	Description	Considerations in This Patient	Recommendations in This Patient
G: Glycols	Ethylene glycol and propylene glycol toxicity, typically arising from ingestions	No known ingestion history, and a higher osmolar gap would be expected	Consider measuring blood glycol level
O: 5-Oxoproline	Increased blood level in some patients who use acetaminophen on a long-term basis, typically in the context of renal insufficiency and undernourishment	No report of acetaminophen use, and acetaminophen level undetectable	Consider measuring blood 5-oxoproline level
L: L-Lactate	Elevated level resulting from either type A lactic acidosis (due to reduced tissue oxygenation) or type B lactic acidosis (due to underlying metabolic conditions in the absence of inadequate tissue oxygenation; can be associated with metformin use)	Shock present (associated with type A lactic acidosis), and metformin use reported (associated with type B lactic acidosis), but lactate level not elevated	Monitor blood lactate level; consider measuring metformin level and temporarily discontinuing metformin use
D: D-Lactate	Isomer of L-lactate; elevated level (which can cause D-lactic acidosis) arising in association with short-bowel syndrome, with metabolism of propylene glycol, and occasionally in association with diabetic ketoacidosis	Unlikely	—
M: Methanol	Methanol toxicity	No known ingestion history, and a higher osmolar gap would be expected	Consider measuring blood methanol level
A: Aspirin	Salicylate toxicity	Aspirin use reported, but salicylate not detected on toxicology testing	Temporarily discontinue aspirin use
R: Renal failure	Accumulation of organic acids and ammonium due to impaired urinary acidification	Patient's high anion-gap metabolic acidosis too high to be explained by renal insufficiency alone	Continue to monitor and treat acute-on-chronic kidney failure
K: Ketoacidosis	Accumulation of ketones due to diabetes, starvation, or alcohol use	Euglycemic diabetic ketoacidosis strongly suspected	Evaluate and treat for euglycemic diabetic ketoacidosis; temporarily discontinue use of sodium–glucose cotransporter 2 inhibitor

tient had. SGLT2 inhibitors reduce glucose reabsorption in the proximal tubules of the kidneys, which results in a reduction in the blood glucose level; this reduction in the glucose level leads to decreases in insulin response and intracellular glucose levels, thus propagating euglycemic diabetic ketoacidosis.[7,8] These medications also enhance glycosuria, which contributes to dehydration.

Several features of this patient's presentation support the diagnosis of dapagliflozin-induced euglycemic diabetic ketoacidosis. The presence of 3+ glucose on urinalysis, despite a normal blood glucose level, fits with SGLT2 inhibitor–associated glycosuria. Urinary glucose can be used by some bacteria as a nutrient, which confers a risk of infection. In addition, the pharmacologic effects of dapagliflozin last 2 to 3 days (even as long as 9 days) after discontinuation, given its half-life of 12.9 hours,[9] which contributes to the persistence of euglycemic diabetic ketoacidosis, even after the medication is stopped.

A possible counterargument to the diagnosis of euglycemic diabetic ketoacidosis is the absence of ketones on the patient's first urinalysis. Ultimately, urine dipstick testing showed 1+ ketones. However, the urine dipstick test, which assesses acetoacetate semiquantitatively, can yield false negative or low results. Moreover, SGLT2 inhibitors reduce renal ketone clearance. In contrast, measurement of the blood level of β-hydroxybutyrate offers a more sensitive and direct method to detect ketones. The normal ratio of acetoacetate to β-hydroxybutyrate is 1:3 but shifts to 1:10

in patients with diabetic ketoacidosis.[10] Hence, a markedly high level of β-hydroxybutyrate in the blood during diabetic ketoacidosis may coincide with negative or faintly positive urine dipstick testing.

Metformin blocks the mitochondrial electron transport chain, which guides glucose toward lactate production. In patients taking both dapagliflozin and metformin — particularly those with euglycemic diabetic ketoacidosis — a low intracellular glucose level could impede lactate production, which would promote increased levels of Krebs cycle intermediates and ketone production and would result in a slightly lower lactate level than would otherwise be expected with metformin-induced lactic acidosis (Fig. 2). Concurrent cases of metformin-associated lactic acidosis and euglycemic diabetic ketoacidosis have been documented,[11-13] especially in the context of acute kidney injury. However, those patients had both lactic acidosis and ketoacidosis, whereas this patient did not have an elevated lactate level.

On the basis of the overall findings in this patient, I suspect that a combination of factors — a fasting perioperative status, a possible urinary tract infection, and an outpatient urologic procedure while she was using dapagliflozin — collectively triggered euglycemic diabetic ketoacidosis. To confirm the diagnosis of euglycemic diabetic ketoacidosis, I would obtain a blood sample to measure the β-hydroxybutyrate level. While awaiting this test result, I would administer intravenous insulin and glucose empirically, along with judicious intravenous fluid, given the presence of pulmonary edema.

DR. PETRA SIMIC'S DIAGNOSIS

Euglycemic diabetic ketoacidosis.

DIAGNOSTIC TESTING

Dr. Li Liu: The diagnostic test in this case was measurement of the blood β-hydroxybutyrate level, which was 9.1 mmol per liter (reference value, <0.4). β-Hydroxybutyrate is quantitated by an enzymatic method with the use of β-hydroxybutyrate dehydrogenase on an automated chemistry analyzer. In contrast, the urine dipstick test for ketones is semiquantitative; it involves a test strip on which sodium nitroprusside reacts with acetoacetate to form a purple complex. The analytical sensitivity for acetoacetate is 5 mg per deciliter (0.5 mmol per liter). The test strip does not react with β-hydroxybutyrate, but its reactivity with acetone is approximately 10% of that with acetoacetate.[14]

Ketogenesis involves the reduction of acetoacetate to β-hydroxybutyrate by β-hydroxybutyrate dehydrogenase with the use of NADH cofactor; alternatively, acetoacetate can undergo spontaneous decarboxylation to acetone, a minor ketone component. The ratio of β-hydroxybutyrate to acetoacetate, the two primary ketone bodies in circulation, is dependent on the redox potential (i.e., the ratio of the reduced form of NADH to the oxidized form of NADH) in hepatocellular mitochondria. The excessive β-oxidation of free fatty acids that occurs with diabetic ketoacidosis produces NADH and a reduced mitochondrial redox state in favor of β-hydroxybutyrate production, which results in a β-hydroxybutyrate-to-acetoacetate ratio that ranges from 3:1 to as high as 10:1.[15] The predominance of β-hydroxybutyrate associated with diabetic ketoacidosis and the lack of sensitivity to this compound by the urine dipstick test make measurement of the blood β-hydroxybutyrate level the more accurate diagnostic test for diabetic ketoacidosis.[16,17]

A urine organic acid profile (requested for this patient by the ICU clinicians on admission to evaluate the acidosis before making the clinical diagnosis) showed normal levels of Krebs cycle intermediates but elevated levels of ketone bodies; the β-hydroxybutyrate level was 902 mmol per mole of creatinine, and the acetoacetate level was 246 mmol per mole of creatinine (reference range for both, 0 to 4). These results confirm the diagnosis of ketoacidosis.

LABORATORY DIAGNOSIS

Ketoacidosis.

DISCUSSION OF MANAGEMENT

Dr. Caitlin Colling: Diabetic ketoacidosis is a life-threatening metabolic emergency. This patient's presentation highlights many of the challenges associated with the diagnosis of euglycemic diabetic ketoacidosis. The diagnosis is often delayed

because patients do not have the classic hyperglycemia that serves as a clinical clue to consider a diabetic crisis in the differential diagnosis. In addition, since euglycemic diabetic ketoacidosis is often precipitated by another medical problem, patients (such as this one) often present with a myriad of nonspecific symptoms and complex metabolic abnormalities that must also be evaluated. Thus, the recognition of ketoacidosis is often delayed. Laboratory findings and diagnostic criteria are the same for hyperglycemic (classic) and euglycemic diabetic ketoacidosis and include high anion-gap metabolic acidosis, elevated blood ketone levels, and a reduced blood bicarbonate level. The degree of alteration of mental status helps to distinguish the severity of the diabetic ketoacidosis; mild diabetic ketoacidosis is associated with intact mentation, and stupor or coma is seen with severe diabetic ketoacidosis.

Treatment of euglycemic diabetic ketoacidosis is similar to that used for classic diabetic ketoacidosis. It is focused on the correction of dehydration, hyperglycemia (when present), and electrolyte imbalances, as well as on the identification of any precipitating event.[18]

FLUID MANAGEMENT

Initial fluid therapy aims to expand the intravascular, interstitial, and intracellular volume and restore renal perfusion. The appropriate rate of initial fluid infusion depends on the clinical state of the patient; in patients with hypovolemia but without shock or heart failure, an isotonic fluid such as normal saline is often administered for several hours at a rate of 15 to 20 ml per kilogram of ideal body weight. Of course, in this patient, the clinician would have made a rapid initial decision on the basis of the overall clinical presentation and would have iteratively adjusted the fluid rate, balancing the need for crystalloid solution for treatment of shock with the recognition that the patient already had pulmonary edema, which additional crystalloid solution could have exacerbated. The subsequent choice of fluid replacement is determined by the patient's response to the initial fluid therapy and is guided by the hemodynamic status, the volume status, blood electrolyte levels, and urine output. In general, the use of 0.45% normal saline is appropriate if the corrected sodium level in the blood is normal or elevated; if the corrected sodium level is low, then 0.90% normal saline is used. Fluid replacement should aim to correct the patient's estimated deficits within the first 24 to 48 hours after initiation of therapy.

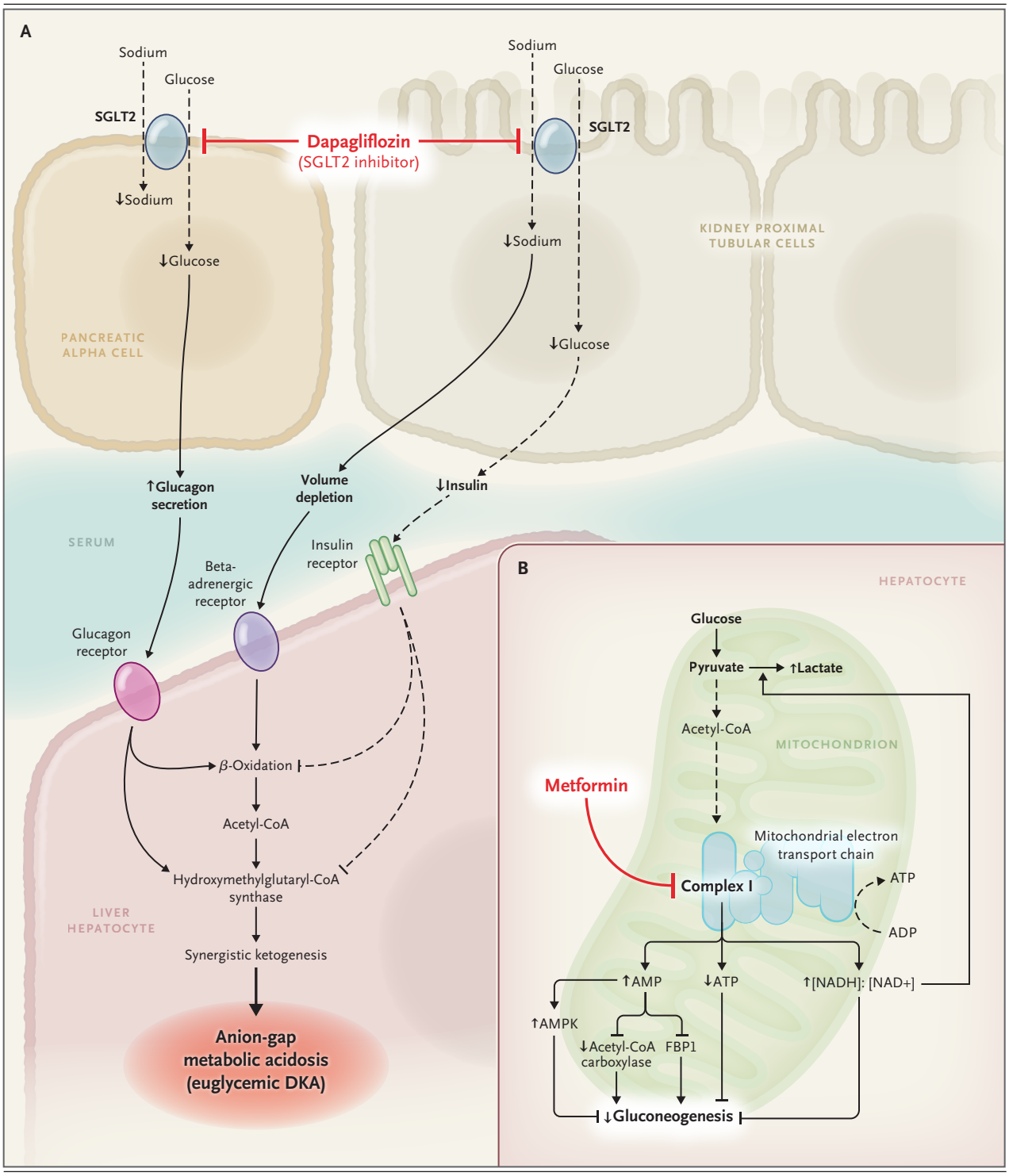
INSULIN AND BLOOD GLUCOSE MANAGEMENT

Insulin is crucial not only to correct hyperglycemia (when present) but also to suppress hepatic ketone production to abrogate ketoacidosis. Insulin is most often administered intravenously, given the short half-life and ease of adjustment of intravenous regular insulin; however, studies have shown that insulin therapy is effective regardless of the route of administration.[19,20] Most often, an initial intravenous dose of regular insulin (0.1 units per kilogram) is used, followed by an infusion at a rate of 0.1 units per kilogram per hour. The rate of insulin infusion is adjusted to decrease the blood glucose concentration by 50 to 75 mg per hour. When the blood glucose level reaches 200 mg per deciliter (11.1 mmol per liter), or in patients with euglycemic diabetic ketoacidosis, the insulin infusion rate may be decreased to 0.02 to 0.05 units per kilogram per hour and dextrose may be added to the intravenous fluids. This patient received an insulin infusion with dextrose for 9 hours at a rate of 0.1 units per kilogram per hour.

The infusion rate of dextrose-containing fluids should be adjusted to allow for ongoing insulin administration and to maintain a blood glucose level of 150 to 200 mg per deciliter (8.3 to 11.1 mmol per liter). In patients with euglycemic diabetic ketoacidosis, infusions of dextrose-containing fluids are often started simultaneously with intravenous insulin, and high infusion rates may be necessary to facilitate ongoing therapy with intravenous insulin. Intravenous insulin therapy is continued until diabetic ketoacidosis has resolved. Frequent blood glucose monitoring is indicated to guide insulin infusion adjustment and prevent hypoglycemia.

POTASSIUM MANAGEMENT

Nearly all patients with diabetic ketoacidosis have a substantial total body deficit of potassium, despite the presence of mild-to-moderate hyperkalemia on presentation. Insulin therapy, correction of acidosis, and volume expansion all reduce blood potassium levels; therefore, ongoing monitoring of the potassium level is warranted. The



goal of treatment is to maintain potassium levels in the normal range. To prevent hypokalemia, potassium replacement is initiated after the blood level falls below the upper limit of the normal range (often at a concentration of 20 to 30 meq of potassium in each liter of infusion fluid). In patients presenting with hypokalemia, potassium replacement is initiated with intravenous fluid therapy, and insulin therapy is delayed until the potassium levels normalize. Because this patient

Figure 2 (facing page). Effects of Dapagliflozin and Metformin on Cellular Metabolism.

As shown in Panel A, inhibition of Slc5A2, also known as sodium–glucose cotransporter 2 (SGLT2), by dapagliflozin in the proximal tubules of the kidneys induces glucosuria and reductions in the blood glucose level and sodium delivery. SGLT2 inhibitors also directly increase glucagon secretion by pancreatic alpha cells. This dual effect leads to a higher blood glucagon level, a lower insulin level, and volume depletion due to diuresis. During periods of organismal stress, these hormonal effects induce a synergistic suppression of hepatic glucose use. Instead, they promote ketogenesis through the increase in lipid β-oxidation and ketogenic enzyme hydroxymethylglutaryl-CoA synthase. Unchecked ketogenesis induces metabolic acidosis through accumulation of acetoacetate and β-hydroxybutyrate without the presence of marked hyperglycemia, a condition known as "euglycemic diabetic ketoacidosis (DKA)." As shown in Panel B, one of the actions of metformin is to inhibit complex I of the mitochondrial electron transport chain, which induces elevations in the cellular ratio of NADH to NAD+ and reduces pyruvate use in the citric acid cycle. This, in turn, leads to a higher rate of conversion of pyruvate to lactate by lactate dehydrogenase, which, if uncontrolled, induces lactic acidosis. AMPK denotes AMP-activated protein kinase, CoA coenzyme A, and FBP1 fructose-1,6-bisphosphatase 1.

presented with a potassium level that was in the normal range, there was no delay in the initiation of insulin therapy.

TRANSITION TO SUBCUTANEOUS INSULIN

Intravenous infusion of insulin is continued until ketoacidosis has resolved, the patient's mental status has improved, and the patient is able to eat. When subcutaneous insulin therapy is indicated, intravenous insulin therapy should overlap with subcutaneous insulin therapy by 1 to 2 hours to prevent recurrence of hyperglycemia or ketoacidosis. In patients who have previously received insulin therapy, the dose of subcutaneous insulin can be guided by their previous insulin doses. A multidose, weight-based regimen is used in patients who have never received insulin therapy.

IDENTIFICATION OF PRECIPITATING FACTORS

It is critical to perform a thorough evaluation for precipitants of diabetic ketoacidosis, since the underlying cause can be life-threatening if it is not treated.[18] The most common precipitating factor is infection, but other factors include discontinuation of insulin therapy, myocardial infarction, cerebrovascular accident, pancreatitis, and new-onset type 1 diabetes. The cause of diabetic ketoacidosis in this patient was SGLT2 inhibitor use in the perioperative state.

FOLLOW-UP

Dr. Dudzinski: In the 9 hours after intravenous insulin therapy was started, the anion gap decreased by more than half, and the arterial pH and bicarbonate levels normalized. Renal function returned to baseline levels. Treatment with metformin and the SGLT2 inhibitor was discontinued indefinitely, and repaglinide was started. Eight weeks later, the patient underwent transurethral resection of the bladder tumor, which was uneventful.

FINAL DIAGNOSIS

Euglycemic diabetic ketoacidosis due to sodium–glucose cotransporter 2 inhibitor use.

This case was presented at the Medicine Case Conference.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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