

# Case Study: Tea-Colored Urine in a Patient With Diabetic Ketoacidosis

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## Presentation

C.S., a previously healthy 26-year-old Cantonese woman, presented with 6 days of nausea, vomiting, occasional fevers, and nonspecific abdominal pain that progressed to myalgias, polyuria, polydipsia, fatigue, and delirium. She had been asleep in bed for many hours preceding admission. Her only medication was an oral contraceptive, and she did not use herbals or alcohol. Her father had type 2 diabetes.

In the emergency room, she was mildly delirious, hyperventilating, afebrile, and dehydrated. She weighed 133 lb, her pulse was 110 bpm, and her blood pressure was 102/62 mmHg. The physical exam was otherwise normal.

Urinalysis revealed 4+ glucose and ketones, large blood without red blood cells, and no infection. The urine was tea-colored. Plasma glucose was 809 mg/dl, betahydroxybutyrate 6.9 mmol/l, lactate 3.2 mmol/l, sodium 126 mmol/l, potassium 4.9 mmol/l, creatinine 2.2 mg/dl, carbon dioxide 9 mmol/l, leukocytes 24,800/ml, arterial pH 7.06, and partial pressure of arterial carbon dioxide (PaCO<sub>2</sub>) was 15 mmHg. Toxicology screen was negative, phosphate was 3.0 mmol/l, alanine aminotransferase was 299 IU/l, and aspartate aminotransferase was 782 IU/l, with normal bilirubin and alkaline phosphatase levels. Creatine kinase (CK) was 46,305 IU/l. Troponin I peaked at 5.8 ng/ml, but C.S. reported no chest pain, and electrocardiogram showed only sinus tachycardia. Islet cell, insulin, and glutamic acid decarboxylase antibodies were negative. Her hemoglobin A<sub>1c</sub> was 6.7%.

Treating physicians diagnosed diabetic ketoacidosis (DKA) and rhabdomyolysis and initiated intravenous insulin and fluids with bicarbonate. Within 18 hours, C.S. was alert and oriented, and the metabolic abnormalities had been corrected. She was then transitioned to glargine insulin with pre-meal lispro insulin. CK peaked at 51,330 IU/l, but serum creatinine normalized. Blood and urine cultures and serology for acute cytomegalovirus and Epstein-Barr virus infections were negative.

## Questions

1. How often is rhabdomyolysis associated with DKA?
2. What is the mechanism of DKA-mediated muscle injury?
3. Should the management of DKA be modified when there is co-existing rhabdomyolysis?
4. Do patients who present with DKA and rhabdomyolysis have a worse prognosis than patients presenting with DKA only?

## Commentary

Rhabdomyolysis occurs in as many as 50% of patients presenting with DKA or the hyperglycemic hyperosmolar nonketotic syndrome (HHNK) and varies in severity from mildly elevated CK levels with no symptoms to markedly elevated CK with acute renal failure, possibly requiring hemodialysis.<sup>1-3</sup> DKA and HHNK patients with rhabdomyolysis have higher blood glucose concentrations, serum osmolalities, and serum creatinine measurements than do those without rhabdomyolysis.<sup>1-3</sup> However, the mechanism of DKA-mediated muscle

injury is uncertain. Theories include insufficient energy delivery to muscle, hyperosmolar effects, and underlying metabolic defects, such as McArdle's (myophosphorylase deficiency causing glycogen accumulation and reduced muscle ATP generation, usually characterized by fatigue, exercise intolerance, and myalgias).<sup>1</sup>

Although CK measurements are often obtained in older patients to rule out myocardial infarction as a precipitant for DKA, CK levels are not routinely tested in younger patients because their likelihood of myocardial ischemia is low. Furthermore, troponin measurements, which are more specific markers for myocardial injury, are replacing CK testing in many centers. Therefore, rhabdomyolysis associated with DKA may be overlooked, resulting in further complications, such as renal failure.

Nonetheless, rhabdomyolysis is important to diagnose because significant potential complications, such as acute renal failure, may be averted with appropriate therapy. Although controlled clinical trials are lacking, case series and animal data support the use of bicarbonate therapy, aggressive fluid resuscitation, and possibly mannitol infusion in patients with severe rhabdomyolysis to prevent acute renal failure, which may occur in as many as one-fourth of patients with rhabdomyolysis and HHNK.<sup>3-5</sup>

Rhabdomyolysis may also be associated with a high 1-week mortality rate in patients with DKA and HHNK. One report<sup>2</sup> described a fourfold higher 1-week mortality in patients with DKA and rhabdomyolysis compared to

patients with DKA only (38.5 vs. 9.7%). Patients with HHNK and rhabdomyolysis also had a higher mortality rate compared to patients with HHNK only (35.5 vs. 25.4%).

C.S.'s relative immobilization possibly contributed to the extreme CK elevation. Perhaps she had a Coxsackie virus infection, characterized by fever, nausea, vomiting, myocarditis, rhabdomyolysis, and new-onset diabetes. Unfortunately, we considered this diagnosis when laboratory testing to confirm it was no longer possible.

**Clinical Pearls**

- Rhabdomyolysis occurs commonly in patients presenting with DKA but is usually subclinical
- Patients who present with DKA and severe rhabdomyolysis may have higher short-term mortality rates than patients presenting with DKA only.

- Serum CK is recommended when DKA patients have other risk factors for rhabdomyolysis (prolonged bed rest, significant alcohol consumption, drug use, and toxin exposure) or signs and symptoms of rhabdomyolysis (myalgias, urine dipstick with heme but no red blood cells, or tea-colored urine).
- Consider adding bicarbonate and mannitol to insulin and intravenous fluids when DKA patients present with severe rhabdomyolysis.

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# Case Study: Diabetic Ketoacidosis in Type 2 Diabetes: “Look Under the Sheets”

Brian J. Welch, MD, and Ivana Zib, MD

Diabetic ketoacidosis (DKA) is a cardinal feature of type 1 diabetes. However, there is a strong, almost dogmatic, errant perception by physicians that DKA is a complication that *only* occurs in patients with type 1 diabetes. This is not true. DKA does occur in type 2 diabetes; however, it rarely occurs in the absence of a precipitating event.

**Presentation**

**Case 1**

R.T., a 25-year-old African-American man with type 2 diabetes presented

with a 5-day history of nausea and vomiting. He also reported a 2-week history of polyuria and polydipsia and a 10-lb weight loss. A review of symptoms was pertinent for a 5-day history of persistent lower back pain.

The patient was diagnosed with type 2 diabetes 5 years ago when he presented to a different hospital with symptoms of polyuria, polydipsia, and weight loss. He was given a prescription for a sulfonylurea, which he says he took until his initial prescription ran out 1 month later. He had not taken any other medica-

tion since that time.

Physical examination revealed an afebrile, obese man (BMI 40 kg/m<sup>2</sup>) with prominent acanthosis nigricans, no retinopathy by direct funduscopic exam, and a normal neurological exam, including motor function and sensation. The patient had no tenderness to palpation over the lumbrosacral spine or paraspinal muscles despite his complaint of lower back pain.

The laboratory data showed an anion gap, metabolic acidosis, and hyperglycemia (pH of 7.14, anion gap of 24,

bicarbonate 6 mmol/l, urinary ketones 150 mg/dl, glucose 314 mg/dl) consistent with the diagnosis of DKA. His white blood count was 20,400/ $\mu$ l. Urinalysis demonstrated no evidence of infection. The patient's hemoglobin A<sub>1c</sub> (A1C) was 13.5%.

The patient was admitted and treated aggressively with intravenous fluid and an insulin-glucose infusion. A non-contrast magnetic resonance imaging (MRI) of the lumbosacral spine (L-spine) was obtained because of the patient's persistent complaint of lower back pain. The L-spine MRI results were negative for pathology. However, R.T. reported increasing discomfort and now noted weakness and numbness in his bilateral lower extremities.

Neurology was consulted, and during their assessment, the patient became incontinent and was found to have 0/5 strength in the lower extremities, severely compromised sensation, and decreased rectal tone. A contrast MRI of both the thoracic and lumbar spine was ordered, and the patient was found to have a T10–T12 epidural abscess (Figure 1).

The patient's antibiotic coverage was broadly expanded, high-dose intravenous steroids were initiated, and neurosurgery was urgently consulted. Emergent evacuation of the epidural abscess with laminectomies of T10–T12 was performed without complication.

R.T.'s neurogenic bladder resolved without further intervention. After inten-



**Figure 1. Epidural abscess precipitating DKA in a type 2 diabetic patient.**

sive inpatient rehabilitation, he had 3/5 strength in bilateral lower extremities and was still unable to ambulate.

**Case 2**

S.D., a 39-year-old white man with type 2 diabetes and mild mental retardation, presented with a 3-week history of polyuria and polydipsia, as well as dysuria, left hip pain, and a feeling of incomplete bladder emptying. Because of the severity of his left hip discomfort, the patient required a cane to ambulate.

The patient was diagnosed with type 2 diabetes 4 years ago on the basis of an elevated fasting blood glucose level during a routine medical examination. He was started on oral hypoglycemic agents, but he discontinued them after 1 month because he was unable to pay for them.

On physical exam, S.D. was afebrile but tachycardic (heart rate 131 bpm) and hypertensive (blood pressure 192/118 mmHg). General examination revealed a wasted, severely volume-depleted man. Thrush was observed on oropharyngeal exam. Cardiopulmonary and abdominal examinations were unremarkable. The patient had point tenderness on the anterior aspect of his left hip. Rectal examination revealed a non-tender prostate.

The laboratory data showed an anion gap, metabolic acidosis, and hyperglycemia (pH 7.24, bicarbonate 9 mmol/l, anion gap 24, urinary ketones 150 mg/dl, and glucose 322 mg/dl) consistent with the diagnosis of DKA. Urinalysis was remarkable for large blood, 4+ bacteria, and > 400 white blood cells. S.D.'s serum white blood count was 22,200, and his erythrocyte sedimentation rate was 109 mm/hour. His A1C result was 12.6%.

The patient was admitted and treated with intravenous fluids and an insulin-glucose infusion. Cultures were obtained. S.D. was started empirically on ticarcillin/clavulanic acid because of concern for left hip osteomyelitis and complicated urinary tract infection. An

MRI of the left hip was ordered to evaluate for suspected osteomyelitis. Unexpectedly, it revealed left hip myonecrosis and a large loculated prostatic abscess (Figure 2).



**Figure 2. Prostatic abscess precipitating DKA in a type 2 diabetic patient.**

Urology was consulted, and the patient underwent transurethral drainage of the prostatic abscess. Methicillin-sensitive *Staphylococcus aureus* grew from both blood and urine cultures. S.D. was treated with intravenous antibiotics per culture sensitivities. The myonecrosis was treated conservatively.

The patient recovered well. He was started on subcutaneous insulin and discharged home to complete a 2-week course of intravenous antibiotics.

**Questions**

1. What is the mechanism of DKA?
2. Why does DKA occur in type 2 diabetes?

**Commentary**

DKA is a cardinal feature of type 1 diabetes, which has led to the widespread errant perception that it is a complication unique to type 1 diabetes. However, it has been repeatedly reported that DKA does occur in patients with type 2 diabetes.<sup>1-5</sup> Moreover, as the cases presented here illustrate, it can occur even in patients who were previously insulinindependent.

A recent study evaluating 138 consecutive admissions for DKA at a large academic center observed that 21.7% had type 2 diabetes.<sup>6</sup> Nearly 70% of the admissions involved discontinuation of medications, and almost half had an identifiable infection when an intensive search was undertaken.

A review of the mechanism of DKA is important. Ketoacidosis occurs as a function not only of severe insulin deficiency, but also of elevated glucagon levels. Insulin is an anabolic hormone. Severe insulin deficiency results in decreased glucose utilization by muscle and an unregulated increase in lipolysis. This leads to an enhanced delivery of gluconeogenic precursors (glycerol and alanine) to the liver. Furthermore, removal of the normal suppressive effect of insulin causes glucagon elevation.<sup>7,8</sup> Glucagon is a catabolic hormone. Glucagon promotes gluconeogenesis, decreases oxidation of free fatty acids to triglycerides, and promotes hepatic ketogenesis.<sup>9</sup>

Importantly, the concentration of insulin required to suppress lipolysis is only one-tenth of that required to promote glucose utilization.<sup>10</sup> Typically, moderate insulin deficiency (as observed in patients with type 2 diabetes) is associated with sufficient insulin to block lipolysis (and therefore ketoacid formation), but not enough to promote glucose utilization. This leads to hyperglycemia without formation of the ketoacids.

When DKA occurs in patients with type 2 diabetes, the presumed mechanism of ketoacidosis is the combination of relative insulin deficiency and

increased secretion of glucagon (as well as other counterregulatory hormones such as cortisol, catecholamines, and growth hormone) in response to stress from 1) overwhelming infection, 2) infarction of tissue, or 3) other severe illness. The elevated catecholamines further suppress insulin secretion to perpetuate a downward spiral. The increased glucagon-to-insulin ratio causes a mismatch that promotes unregulated lipolysis and proteolysis with subsequent uninterrupted formation of ketoacids.

To summarize, DKA is not a unique feature of type 1 diabetes. Though much more common in type 1 diabetes, it does occur in patients with type 2 diabetes, as illustrated by these case reports. However, it is rare for DKA to occur in type 2 diabetes in the absence of some precipitating event. When DKA occurs in an individual with type 2 diabetes, the clinician should “look under the sheets” and initiate an intensive search for the precipitating factor. Once identified, the trigger should be treated promptly and appropriately.

#### Clinical Pearls

- DKA does occur in type 2 diabetes.
- DKA in type 2 diabetes rarely occurs without a trigger.
- When it does, an intensive search for the precipitating factor should be undertaken.

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