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Clinical Communications: Adult

METFORMIN-ASSOCIATED LACTIC ACIDOSIS PRESENTING LIKE ACUTE MESENTERIC ISCHEMIA

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☐ **Abstract—Background: Metformin-associated lactic acidosis is a rare but serious complication of taking metformin. Making the diagnosis in the emergency department requires vigilance because the presentation can mimic other diseases. Case Report: We present a case of a patient with diabetes who presented moribund with symptoms and signs consistent with mesenteric ischemia. This diagnosis was seemingly confirmed through computed tomography, and as a result the patient was brought to surgery for emergent exploratory laparotomy. Our patient made a remarkable recovery upon initiation of hemodialysis, demonstrating the need to initiate this life-saving procedure early. Why Should an Emergency Physician be Aware of This?: Metformin levels are rarely available in the setting of the emergency department. Clinicians must remain alert, recognize that imaging studies may be misleading, and consider hemodialysis early in addition to surgical interventions.** © **2019 Elsevier Inc. All rights reserved.**

☐ **Keywords—mesenteric ischemia; metformin; metformin-associated lactic acidosis; lactic acidosis**

INTRODUCTION

We present a case of a 60-year-old woman who arrived to the emergency department with abdominal pain, nausea, vomiting, and diarrhea that was suspected to be caused by severe acute mesenteric ischemia. This case highlights our need as emergency physicians to be vigilant of metformin-associated lactic acidosis (MALA) given the significant benefits of early treatment.

CASE REPORT

A 60-year-old Asian woman with diabetes mellitus taking metformin presented to the emergency department with abdominal pain, nausea, nonbloody vomiting, and diarrhea for 3 days. Her daughter also described progressive confusion over the past 2 days. Her medical history included hypertension and hypercholesterolemia. Additional medications included insulin glargine, acetazolamide, amlodipine, lisinopril, and lovastatin. The patient's daughter reported that her mother was compliant with medications.

Initial vital signs were as follows: blood pressure 105/47 mm Hg, a pulse of 62 beats/min, a respiratory rate of 26 breaths/min, and a temperature of 32.4°C (90.3°F). The physical examination was notable for pallor and diffuse abdominal tenderness without guarding or rebound tenderness. Upon neurologic examination she was obtunded: she did not follow commands, withdrew only to painful stimuli, and intermittently moaned. Examinations of her heart and lungs showed tachycardia with 2 + pulses, and she had no rash.

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Laboratory testing revealed hemoglobin of 6 g/dL (normal 12–16 g/dL), creatinine 8.3 mg/dL (normal 0.5–1.1 mg/dL), blood urea nitrogen 79 mg/dL (normal 2.5–7.1 mg/dL), lactate of 19 mmol/L (normal 0.3–2 mmol/L), and anion gap of 32 (normal 8–16). Serum bicarbonate was undetectable, reading as <5 (normal 24–32). Venous blood gas testing showed severe acidosis with a pH < 6.9 (normal pH 7.31–7.41) and partial pressure of carbon dioxide of <18 mm Hg (normal 38–42 mm Hg). A chest radiograph revealed mild cardiomegaly with no infiltrates or effusions. Bedside ultrasound revealed a small pericardial effusion and good ventricular contractility. An electrocardiogram showed atrial fibrillation with rate of 111 without ST segment and T wave changes.

Coincident with testing, aggressive resuscitation was initiated with broad-spectrum antibiotics (for possible sepsis), saline boluses, and red blood cell transfusions. Despite these interventions her condition acutely deteriorated and she experienced bradycardia followed by pulseless electrical activity. A brief period of advanced cardiac life support ensued including chest compressions, endotracheal intubation, intravenous atropine, and vasopressors. Return of spontaneous circulation was rapidly achieved.

Once her condition stabilized and approximately 3 h after presentation she underwent a computed tomography (CT) scan of her abdomen and pelvis without contrast. The CT scan revealed thickened edematous bowel loops involving mostly the proximal bowel segments and ascending colon (Figure 1). Mesenteric ischemia was felt to be the most likely diagnosis because of her symptoms, atrial fibrillation, severe lactic acidosis, and the CT findings of edematous bowel. An emergent exploratory laparotomy revealed retroperitoneal edema as well as edematous pancreas, gallbladder, and small bowel at the base of mesentery. There was, however, no evidence of ischemic bowel, and pulsations were noted in the superior mesenteric artery. This finding may have been caused by inflammation from her significant lactic acidosis compounded by a brief period of hypoperfusion during resuscitation. The abdominal incision was left open in anticipation for possible impending abdominal compartment syndrome because of the edema. With the exclusion of mesenteric ischemia, the presumptive diagnosis of MALA was made and continuous renal replacement therapy was rapidly implemented.

On the second hospital day she was markedly improved, and surgery for closure of the abdominal incision was undertaken without complication. Repeat serum testing revealed normalization of her creatinine (0.9 mg/dL) and lactate (0.9 mmol/L) levels. She was extubated and found to be surprisingly alert and oriented. Her electrocardiogram returned to normal sinus rhythm without acute abnormalities. Our patient confirmed medication compliance and denied metformin overdose. She continued to improve, and on the day of her discharge home (hospital day 6) the metformin level (drawn upon admission) returned as 37 mcg/dL (therapeutic level 1–2 mcg/dL). A cascade of events beginning with gastroenteritis then dehydration and renal impairment likely lead to the development of metformin toxicity.

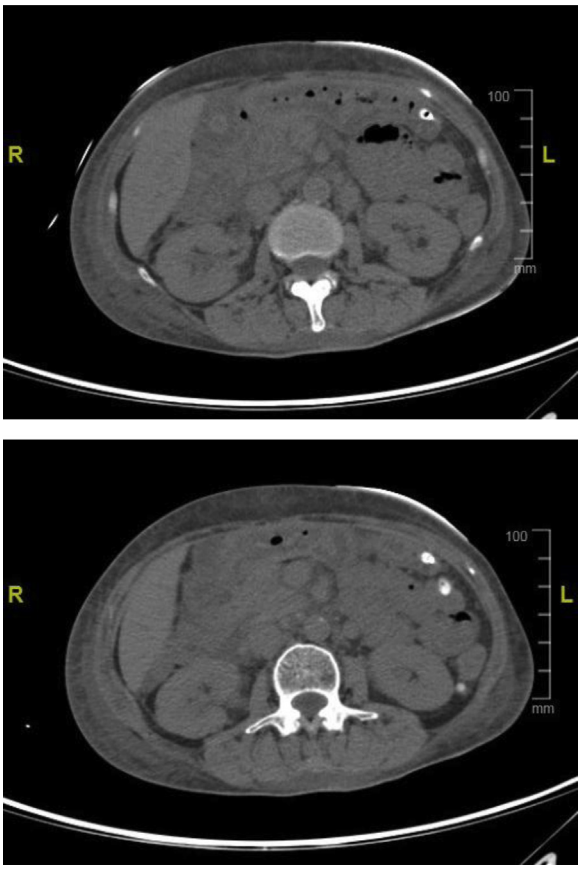

Figure 1. CT of abdomen and pelvis without contrast demonstrating bowel edema.

DISCUSSION

Metformin is one of the most commonly prescribed medications in the world. It is a first-line drug for type 2 diabetes mellitus. Metformin decreases hepatic glucose production and increases peripheral glucose uptake, and it is generally well tolerated. As a medication in the biguanide class it acts by inhibiting mitochondrial respiration in the liver, leading to lactate levels that can build up in the setting of inadequate renal clearance. While lactic acidosis has a broad differential, including sepsis, aspirin toxicity, cardiac failure, and diabetic ketoacidosis, MALA is a rare and dangerous complication of the drug. The mortality of MALA has been reported to be as high as 50% (1). Risk factors for MALA include overdose, renal insufficiency, and hepatic dysfunction. In one case series,

dehydration was the most common precipitating cause (86.4%) (2). The diagnosis of MALA is confirmed with an elevated metformin level in the setting of severe lactic acidosis. Unfortunately, metformin concentrations are not readily available in the emergency department, so a presumptive diagnosis must be made to prevent delays in treatment. Hemodialysis is the basis for treatment in addition to supportive care, and outcomes are enhanced with early implementation (3–8).

Three previous reports describe patients taking metformin with similar presentations to our patient: nonspecific gastrointestinal symptoms, severe lactic acidosis, and suspicion for acute mesenteric ischemia. All patients underwent nontherapeutic exploratory laparotomy. One patient died because he was too critically ill to undergo hemodialysis. His diagnosis of MALA was made posthumously when the metformin concentration was reported to be 70 mcg/mL (normal 0.5–2.5 mcg/mL) (9), Two other patients received hemodialysis and survived. In the second case, a metformin concentration of 4 mg/L (no range given) supported the diagnosis of MALA (10), while in a third case diagnosis was presumed but not confirmed by metformin level (11). CT of the abdomen and pelvis was done in the third case and only showed dilated bowel loops (11). Our case is unique in that CT imaging revealed bowel wall edema that appeared consistent with mesenteric ischemia. This finding, in addition to her atrial fibrillation that may also have been related to her metformin toxicity (12), led us to initially diagnose her with acute mesenteric ischemia.

Our patient made a remarkable and rapid recovery despite her severe acidosis and cardiorespiratory collapse. Interestingly, complete recovery of patients with MALA complicated by cardiac arrest such as our case has been documented (3,4,7,9,10).

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

Emergency physicians must remain alert while caring for patients who are taking metformin and who present with nonspecific gastrointestinal symptoms or symptoms consistent with acute mesenteric ischemia. Metformin levels may be considered even though the results may be delayed. In the setting of severe lactic acidosis, a presumptive diagnosis of MALA must be considered so that hemodialysis may be initiated early. Aggressive treatment is essential, and recovery may occur despite a moribund presentation.

REFERENCES

1. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: current perspectives on causes and risk. Metabolism 2016;65:20–9.
2. Angioi A, Cabiddu G, Conti M, et al. Metformin associated lactic acidosis: a case series of 28 patients treated with sustained low-efficiency dialysis (SLED) and long-term follow-up. BMC Nephrol 2018;19:77.
3. Bruijstens LA, van Luin M, Buscher-Jungerhans PM, Bosch FH. Reality of severe metformin-induced lactic acidosis in the absence of chronic renal impairment. Neth J Med 2008;66:185–90.
4. Friesecke S, Abel P, Kraft M, Gerner A, Runge S. Combined renal replacement therapy for severe metformin-induced lactic acidosis. Nephrol Dial Transplant 2006;21:2038–9.
5. Lalau JD, Azzoug ML, Kajbaf F, Briet C, Desailloud R. Metformin accumulation without hyperlactataemia and metformin-induced hyperlactataemia without metformin accumulation. Diabetes Metab 2014;40:220–3.
6. Pallavi R, Chaudhari A. Prolonged hemodialysis: an antidote for metformin-associated lactic acidosis. Am J Ther 2016;23: e606–8.
7. Silvestre J, Carvalho S, Mendes V, et al. Metformin-induced lactic acidosis: a case series. J Med Case Rep 2007;1:126.
8. Regolisti G, Antoniotti R, Fani F, Greco P, Fiaccadori E. Treatment of metformin intoxication complicated by lactic acidosis and acute kidney injury: the role of prolonged intermittent hemodialysis. Am J Kidney Dis 2017;70:290–6.
9. Correia CS, Bronander KA. Metformin-associated lactic acidosis masquerading as ischemic bowel. Am J Med 2012;125:e9.
10. Ncomanzi D, Sicat RM, Sundararajan K. Metformin-associated lactic acidosis presenting as an ischemic gut in a patient who then survived a cardiac arrest: a case report. J Med Case Rep 2014;8:159.
11. Ali S, Labuschagne H, Azarov N, Hindi Z, Oud L. Metformin-associated lactic acidosis mimicking ischaemic bowel. BMJ Case Rep 2018;2018, bcr-2017-221686.
12. Boolani H, Shanberg D, Chikkam V, Lakkireddy D. Metformin associated atrial fibrillation - a case report. J Atr Fibrillation 2011;4:411.