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CASE REPORT

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A case report of metformin-associated lactic acidosis

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Key Clinical Message

Metformin-associated lactic acidosis is a rare but serious complication in patients with type 2 diabetes, especially those with multiple health conditions. Prompt recognition and treatment, including potential renal replacement therapy, are crucial for managing severe acidosis and improving patient outcomes.

Abstract

Metformin (MTF) is commonly prescribed as a first-line treatment for diabetes, effectively preventing microvascular and macrovascular complications. However, metformin-associated lactic acidosis is a rare yet severe complication, associated with a mortality rate of up to 50%. We encountered a case involving a 73-year-old woman with type 2 diabetes, mental illness, and hypothyroidism, who developed life-threatening lactic acidosis while on metformin therapy. Upon presenting to the emergency department with complaints of weakness, nausea, and decreased urination for 5 days, she also reported abdominal pain and shortness of breath. Hypotension was noted with a blood pressure of 80/50 mmHg. Initial laboratory results revealed severe acidosis, prompting discontinuation of MTF. Despite resuscitation efforts and vasopressor therapy, severe acidemia persisted, leading to the initiation of renal replacement therapy. Following treatment with continuous renal replacement therapy, her acidemia resolved, and she was discharged from the hospital on the sixth day without complications, with normal kidney function.

KEYWORDS

continuous renal replacement therapy (CRRT), metformin-associated lactic acidosis, multiple health conditions, type 2 diabetes

1 | INTRODUCTION

Diabetes comprises metabolic disorders characterized by elevated blood sugar levels due to insufficient insulin production or cellular resistance to insulin, leading to hypertension and severe complications.[1] Metformin (MTF), a commonly prescribed oral antidiabetic medication, is widely recognized for its efficacy in managing type 2 diabetes.[2] Concerns regarding lactic acidosis limited its use in individuals with impaired kidney function, but recent research suggests that even in mild to moderate renal impairment, MTF levels typically remain therapeutic and

do not significantly raise lactate levels.[3,4] Despite this, metformin-associated lactic acidosis (MALA) can occur, resulting in hemodynamic instability. Treatment primarily involves supportive care to restore acid–base balance, manage concurrent conditions, and, if necessary, discontinue MTF. Patients should be monitored for at least 12 h following overdose for signs of MALA.[5] In this report, we present a case of MALA leading to hemodynamic compromise.

2 | CASE HISTORY AND PRESENTATION

A 73-year-old female patient with a medical history significant for diabetes mellitus for 20 years was managed with MTF 850 mg orally twice a day and glimepiride 4 mg orally once daily, and psychiatric disease, managed with mirtazapine 45 mg orally once daily and quetiapine 100 mg orally twice a day. The patient also has hypothyroidism for the past 3 years, treated with thyroxine 50 mcg orally once daily.

The patient's previous admission to the intensive care unit (ICU) was due to diabetic ketoacidosis (DKA) complicated by acute kidney injury, which required three sessions of hemodialysis. She was diagnosed as having chronic kidney disease (CKD) stage 3 A, and her MTF dose upon discharge was 850 mg orally twice daily, which was appropriate. The patient was discharged in good condition and had no follow-up visits in the past year. There is no history of eye problems or surgery. Laboratory tests included: plasma glucose of 270 mg/dL, PH 7.1, plasma bicarbonate 12 mmol/L, and elevated urine ketones. The baseline estimated glomerular filtration rate (eGFR) was 54 mL/min/1.73 m^2. The reason for continuing high-dose MTF is because the patient lost her follow-up for about 1 year, and her depression might have an effect on that.

She presented to the emergency department (ER) at Omdurman Military Hospital complaining of generalized fatigue, nausea, and decreased urine output for the last 5 days, as well as shortness of breath and abdominal pain for 1 day. In addition, she had a history of relative constipation for the last 10 days. Initial laboratory results revealed a high anion gap metabolic acidosis (baseline anion gap of 19.6 mmol/L). An anion gap blood test checks the acid–base balance of your blood and if the electrolytes in your blood are properly balanced (normal range of anion gap: 12–16 mmol/L). Healthcare providers most commonly use anion gap to identify cases of metabolic acidosis—when you have higher-than-normal amounts of acid in your blood. It is calculated by the following formula: Anion gap $=(Na^+ + K^+) - (Cl^- + HCO_3^-)$.

3 | DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS AND TREATMENT

After careful consideration of other causes, MALA in critically ill patients may be suspected in a patient who has received MTF and who has a high anion gap metabolic acidosis, and confirmed when lactate exceeds 5 mmol/L. Generally, the dose that can pose a risk of MALA is more than 2.5 g in a patient with normal renal function. However, if the patient's glomerular filtration range (GFR) is less than 45 mL/min, much lower doses can lead to the development of MALA. Furthermore, MTF should be avoided if the GFR is less than 30 mL/min. The differential diagnosis for this patient included pre-renal acute kidney, acute tubular necrosis (ATN), and Sepsis. Acute Kidney Injury (AKI) was suggested due to generalized fatigue, decreased urine output, and elevated serum creatinine and blood urea levels. Dehydration or hypovolemia was a possibility, indicated by the history of decreased oral intake, relative constipation, and hypotension. Sepsis was another consideration due to the elevated CRP, fever, and tachycardia. The patient was covered with broad-spectrum antibiotics after the cultures were taken, as sepsis was one of the differentials. The presence of an irreducible para-umbilical hernia and mild supra-pubic tenderness pointed towards possible abdominal pathology. Despite the normal echocardiographic findings, heart failure could not be entirely ruled out given the signs of fluid overload and shortness of breath. Metabolic acidosis was indicated by the ABG results showing a low pH, bicarbonate, and elevated lactate. Lastly, the elevated PTH level suggested hyperparathyroidism, which could be primary or secondary.

The investigations for this patient included a thorough assessment involving physical examination, laboratory tests, imaging studies, and other diagnostic procedures. Vital signs revealed a Glasgow Coma Scale (GCS) score of 15/15, drowsiness, temperature of 37.4°C, heart rate of 104 beats/min (regular), blood pressure of 80/50 mmHg, respiratory rate of 32 cycles/min, and oxygen saturation of 94% on room air, with a random blood sugar of 159 mg/dL.

Physical examination noted an irreducible para-umbilical hernia and mild supra-pubic tenderness, with no lower limb edema. Laboratory tests showed a complete blood count with hemoglobin of 12 g/dL, total white blood cells of 9.8×10^9/L, and platelets of 272×10^9/L. C-reactive protein was elevated at 11.8 mg/L (normal range: <5 mg/L). The renal profile indicated elevated blood urea nitrogen and serum creatinine, with normal sodium and potassium values (Table 1).

Additional tests included normal liver function tests (LFTs), arterial blood gases (ABGs) showing pH 7.33,

TABLE 1 Laboratory examinations of the patient.

Patient's tests	Test results	Reference range
Estimated glomerular filtration rate (eGFR)	54 mL/min/1.73 m^2	80–120 mL/min/1.73 m^2
HbA1C	7.4%	4%–5.6%
Baseline anion gap	19.6 mmol/L	12–16 mmol/L
Serum potassium (K^+)	3.6 mmol/L	3.5–5.5 mmol/L
Serum sodium (Na^+)	140 mmol/L	135–145 mmol/L
Serum creatinine	2.6 mg/dL	0.6–1.1 mg/dL
Blood urea nitrogen (BUN)	44 mg/dL	7 and 20 mg/dL

TABLE 2 Arterial blood gases (ABGs) trend during fluid management.

Date	PH (NR 7.35–7.45)	PCO 2 (NR 35–45 mmHg)	PO2 (NR 75–100 mmHg)	HCO3 (NR 22–28 mmol/L)	Lactate (NR <2 mmol/L)
January 19, 2023	7.33	18 mmHg	80 mmHg	13 mmol/L	6.4 mmol/L
January 20, 2023	7.32	19 mmHg	89 mmHg	10 mmol/L	6.0 mmol/L
January 21, 2023	7.23	24 mmHg	90 mmHg	10 mmol/L	4.8 mmol/L
January 22, 2023	7.28	20 mmHg	94 mmHg	8 mmol/L	7.6 mmol/L
January 23, 2023	7.31	22 mmHg	98 mmHg	3 mmol/L	6.9 mmol/L

PCO_2 18 mmHg, PO_2 80 mmHg, HCO_3 13 mmol/L, lactate 6.4 mmol/L (Table 2), and chloride 111 mmol/L. Urine procalcitonin was 0.9 ng/mL, thyroid function tests (TFTs) were normal, coagulation profile was normal, HbA1c was 7.4%, and parathyroid hormone (PTH) was elevated at 311 pg/mL.

Imaging studies included an abdominal ultrasound revealing normal kidneys and multiple gallbladder stones with normal wall thickness, an IVC of 1 cm, normal CT brain and chest scans, and an echocardiogram with an ejection fraction of 64% and normal findings. Blood and urine cultures were also taken for further analysis.

The patient was admitted on continuous renal replacement therapy (CRRT) using continuous venovenous hemodiafiltration (CVVHD) with an ultrafiltration rate of 100 mL/h. Over the following 36 h, the patient's clinical condition improved significantly. Her arterial blood gases (ABGs) showed normalization with a pH of 7.42, bicarbonate (HCO3) of 23 mmol/L, and lactate level reduced to 1.2 mmol/L.

4 | OUTCOME AND FOLLOW-UP

The patient's arterial blood gas (ABG) trends during fluid management revealed a consistent pattern indicative of metabolic acidosis. While the pH levels consistently lingered at the lower end of the normal range, indicating mild acidosis, the partial pressure of carbon dioxide (PCO_2) showed slight elevation, suggestive of a tendency towards respiratory acidosis. Notably, the partial pressure of oxygen (PO_2) remained within the normal range, indicating adequate oxygenation. Bicarbonate (HCO_3) levels fluctuated but generally stayed below the normal range of 22–28 mmol/L, suggesting relatively stable bicarbonate levels. However, lactate levels consistently rose, pointing to ongoing metabolic stress or tissue hypoxia. The patient was diagnosed with a high anion gap metabolic acidosis secondary to metformin-induced lactic acidosis. Consequently, the patient was successfully disconnected from the CRRT machine. She maintained her blood pressure without vasopressor support, had a urine output of 1.2 L/day, and her renal function tests (RFTs) returned to normal levels.

5 | DISCUSSION

In this report, the patient with a 20-year history of type 2 diabetes treated with MTF and psychiatric conditions managed with mirtazepine and hypothyroidism for 3 years on thyroxine developed severe lactic acidosis while on MTF treatment. Upon examination complaint of general fatigue, nausea, decreased urination, abdominal pain, shortness of breath, confusion, hypotension with a blood pressure of 80/50 mmHg, and abnormal laboratory findings including a blood gas pH of 7.33, HCO_3 of 13 mEq/L, baseline anion gap of 19.6 mmol/L, and lactate level of 6.4 mmol/L, consistent with severe lactic acidosis.

MTF is widely prescribed for diabetes treatment but is associated with a potential risk of lactic acidosis. It is also

suggested to have preventive effects in various chronic hypoxemic conditions linked to lactic acidosis, including cardiovascular, renal, hepatic, and cancer conditions.[6] However, a recent meta-analysis found limited evidence supporting a significant association between MTF and MALA in patients with stable type chronic kidney disease.[1] in this case, following CRRT, the patient's severe acidosis was stabilized, and discharged without any complications related to acid–base balance or renal function. Although MTF toxicity is uncommon at therapeutic doses, it can be severe at higher doses and may manifest as MALA. Hence, patients and healthcare providers must be mindful of its potential toxicity and the factors that elevate the risk of developing MALA.[5]

Other studies have also reached similar conclusions. However, individuals with severe renal disease, whether chronic kidney disease or acute kidney injury, face a heightened risk of complications from MTF use.[3] Several factors contribute to the development of MALA in patients, including vomiting, diarrhea, kidney injury, high dosage or consumption of MTF, and acute illness leading to tissue hypoxia. MALA development is believed to involve a positive feedback system affecting one or more of these factors. Determining MTF concentrations in patients with MALA can help assess the severity of the condition.[7] In both MALA and another form of lactic acidosis (LAOO), all MALA patients and 31 LAOO patients exhibited severe acidosis (pH <7.0). However, within this subgroup, MALA showed less severe acid–base imbalance compared to LAOO, despite similar disease severity and renal organ failure. Importantly, survival rates were significantly higher in MALA (50%) compared to LAOO (0%). This highlights the significance of aggressive interventions, such as blood transfusions, in treating MALA.[8]

Renda et al. found that the prevalence of MALA is 25.4%.[9] MALA is characterized by excess acid, while renal failure is associated with lower acidity levels. Non-surviving cases of MALA often had comorbidities aside from kidney failure that could have been managed with dialysis.[8] Symptoms of MTF toxicity resemble those of sepsis and gastrointestinal issues, including nausea, vomiting, abdominal pain, and leukocytosis. High lactic acid levels accompanying gastrointestinal symptoms can raise suspicion of mesenteric ischemia.[10] physicians may diagnose lactic acidosis accompanied by gastrointestinal symptoms without recognizing it as MALA.[3] A recent study found that continuous venovenous hemofiltration eliminates MTF less effectively than conventional hemodialysis. Indications for extracorporeal treatment include high lactate levels (>20 mmol/L), low pH (<7.0), shock, inadequate response to standard supportive measures, and decreased level of consciousness.[3] Therefore, continuous hemodialysis may be preferable for patients who are hemodynamically unstable for conventional hemodialysis.

6 | CONCLUSION

This case highlights a rare yet significant complication associated with MTF use, the so-called MALA. The progression from gastroenteritis-induced acute kidney injury to potentially life-threatening MALA, as seen in our patient, underscores the importance of promptly considering this complication in patients presenting with metabolic acidosis and a history of MTF use. Severe metabolic acidosis may necessitate renal replacement therapy regardless of its underlying cause, and the dialyzability of MTF could potentially lead to oversight of this condition. This case shows how effective CRRT is in the management of severe cases, as evidenced by the outcome of our patient. It is crucial to educate both patients and healthcare providers about avoiding MTF in situations predisposing to renal failure, particularly in cases of hypovolemia, to prevent MALA.

AUTHOR CONTRIBUTIONS

Mohammed Taha: Conceptualization; data curation; formal analysis; investigation; validation. **Ayman Azhary:** Conceptualization; data curation; formal analysis; investigation; validation; writing – original draft. **Nooh Mohamed Hajhamed:** Conceptualization; data curation; writing – original draft. **Waleed Azhary Sir Alkhatim:** Conceptualization; investigation; methodology. **Abdullah M. Bakheit:** Investigation; writing – original draft. **Abdallah Elssir Ahmed:** Conceptualization; data curation; formal analysis; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest in this work.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONSENT

Written consent was obtained from the patient for the publication of this case report in accordance with journal's patient consent policy.

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